MASR 2015

Medical Applications of Synchrotron Radiation

5-9 October 2015

ESRF Grenoble & Villard de Lans, France

Conference Booklet

website:http://www.esrf.fr/masr2015 info: masr2015@esrf.fr

MASR 2015

5th - 9h October 2015

Venue: ESRF and Villard de Lans

TABLE OF CONTENTS

Chairmen's Welcome

With great pleasure the Grenoble synchrotron radiation community welcomes you to the eight Medical Applications of Synchrotron Radiation (MAR2015) conference jointly organized by the European Synchrotron Radiation Facility and the Centre Hospitalière Universitaire, Grenoble, France, with the strong support of the COST Action TD1205 (SYRA3).
The conference will be held in Grenoble and Villard de Lans from Monday 5th to Thursday 8th October followed, on Friday 9th October, by a session dedicated to the Working Group Meetings of the COST Action.

Following the spirit of the previous meetings, the main scope of MASR2015 is to provide a lively forum establishing interdisciplinary communication channels between the synchrotron radiation facilities/programs worldwide and physicians, physicists and biologists involved in the present day medical research at synchrotrons, as well as with more conventional techniques related to the synchrotron radiation research topics.

MASR2015 is the 8th in a series of workshops and conferences initially organized in Daigo, Ibaraki Prefecture, Japan (1992) then in Haga, Hyogo Prefecture, Japan (1997), in Grenoble, France (2001), Trieste, Italy (2004), Saskatoon, Canada (2007), Melbourne, Australia (2010), and eventually Shanghai, China (2012).

We trust that the congress and the social events will offer opportunities for fruitful discussions as well as the possibility to initiate new friendship, collaborations and joint projects.

We thank you for your participation and look forward to seeing you in Grenoble!

Alberto Bravin, ESRF Grenoble

François Estève, CHU Grenoble

Scientific Advisory Committee

Sam Bayat	Université de Picardie Jules Vernes
Martin Bech	Lund, MAX IV
Caterina Biscari	Alba Synchrotron, Barcelona
Dean Chapman	University of Saskatchewan
Paola Coan	Ludwig Maximilians Universität München
Jeffrey Crosbie	RMIT university, Melbourne
Avraham Dilmanian,	NSLS, Stony Brook University Medical Center
Michael Grotzer	Universität Zürich
Daniel Häusermann	Australian Synchrotron
Marie Jacquet	Labo de L'Accélérateur Linéaire Université Paris-Sud
Ralf Menk	Elettra Synchrotron
Atsushi Momose	University of Tokyo
Carmel Mothersill	McMaster University, Ontario
Uwe Oelfke	Institute of Cancer Research, London
Alessandro Olivo	UCL, London
Franz Pfeiffer	Technische Universität München
Christophe Rau	Diamond Light Source
Anatoly Rozenfeld	University of Wollongong
Marco Stampanoni	Swiss Light Source
Giuliana Tromba	Elettra Synchrotron
Stefan Vogt	APS
Tiqiao Xiao	Shanghai Institute of Applied Physics, CAS
Lisa Xu	Shanghai Jiaotong University
Naoto Yagi	Spring-8/JASRI

Local Organizing Committee

Jean-François Adam	CHU, INSERM
Sylvain Bohic	CHU, INSERM
Elke Bräuer-Krisch	ESRF
Alberto Bravin	ESRF
Isabelle Combe	ESRF
Antoine Depaulis	INSERM
Hélène Elleaume	CHU, INSERM
François Estève	CHU, INSERM
Géraldine Le Duc	ESRF
Anne-Françoise Maydew	ESRF
Jean-Luc Ravanat	CEA Grenoble
Michel Renier	ESRF
Herwig Requardt	ESRF
Raphaël Serduc	CHU, INSERM

Keynote Speakers

- **Jacques Balosso** is a Professor specialised in cancerology-radiotherapy, expert in cancers of the digestive system, at the Grenoble hospital.
- **Uwe Oelfke** is a Professor combining recent developments in cancer biology, cancer therapeutics and medical physics in order to improve radiotherapy treatment and planning, at the Institute of Cancer Research in London
- **Sandro Olivo** is a professor in applied physics in the department of Medical Physics & Biomedical Engineering at UCL IRIS at the University College London
- **Maximilian Reiser** is a Professor of radiology, chairman of the department of clinical radiology, and dean of medicine at Ludwig Maximilians University of Munich
- **Andrey Solovyov** is a Professor at MBN Research Center UG at Frankfurt Innovation Center of Biotechnology GmbH
- **Han Wen** is a Doctor, Senior Investigator at the Laboratory of Imaging Physics at the National Heart, Lung and Blood Institute in the US.

Conference Venue

Monday 5th October 2015: ESRF Grenoble

The first Day of the MASR 2015 Conference will take place at the European Synchrotron Research Facility (ESRF), located on the EPN campus (www.epn-campus.eu) **in Grenoble.**

Detailed travelling information is available on the EPN Campus pages: http://www.epn-campus.eu/practical-info/travelling-to-epn-science-campus/.

Note that tramway B stops at 'Grenoble Presqu'île' (10mn's walk to ESRF) and goes to downtown Grenoble. The timetable is available on www.tag.fr. Look for tramway line B.

The registration fees include coffee breaks, lunches and dinners.

Accommodation is not included in the registration fees, so participants should reserve a hotel in Grenoble for Sunday night.

Participants of the first day will be transferred by bus from ESRF to Villard-de-Lans for the rest of the MASR 2015 conference.

Tuesday 6th October to Friday 9th October: Villard de Lans

How to reach Villard-de-Lans from Grenoble?

The MASR2015 conference will organize transportation by bus from Grenoble on Monday evening, bus will depart from the ESRF at **20:00**.

On Thursday morning, bus transportation will also be provided from Villard-de-Lans to Grenoble railway and bus stations; departure will be at **8.45 am** and on Friday afternoon departure will be at **4.30 pm**.

The "Transisère Bus Line 5100" can be used for your convenience between Grenoble and Villard-de-Lans (the timetable can be downloaded from Internet or from the Gare Routière)
http://www.transisere.fr/ftp/documents_CG38/FH_21050901_5100-5110.pdf

The bus station (*Gare routière)* in Grenoble is just next to the train station (*Gare SNCF)*:

Taxi

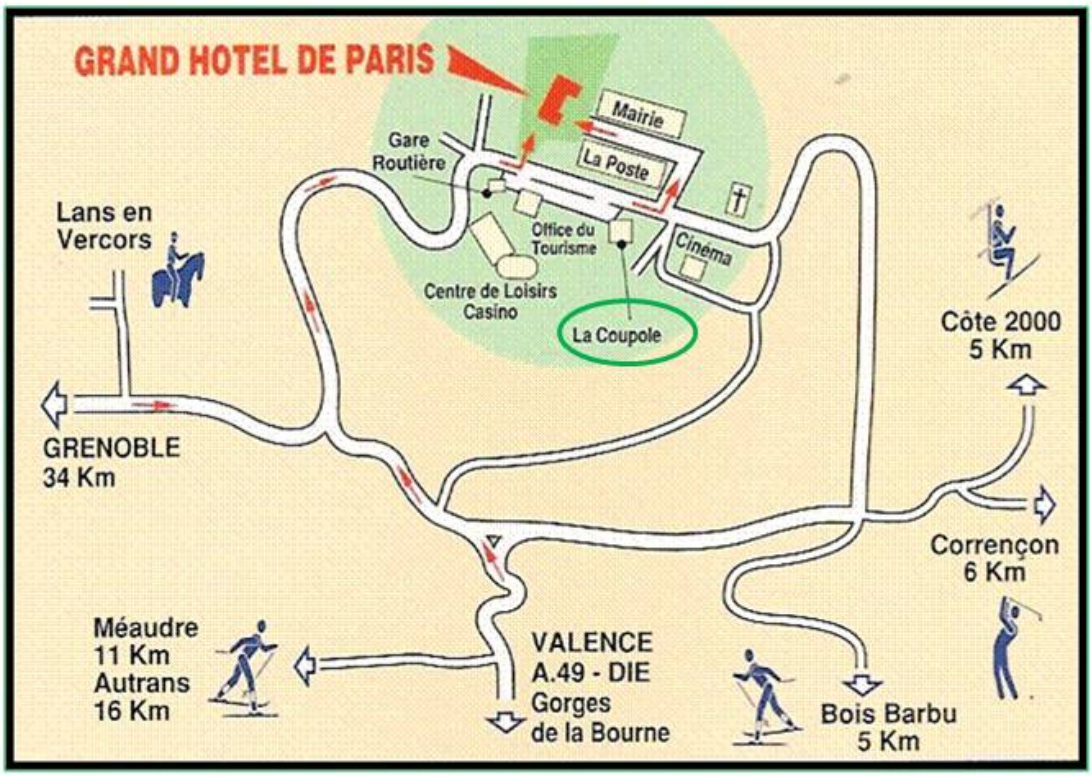
For a taxi service from Grenoble to Villard-de-Lans, you can contact Altitude Taxi at Altitude-taxi@orange.fr / +33 6 85 42 40 66.

Cost per journey: 65 € (day) / 85 € (night) for up to 4 passengers.

Conference location in Villard-de-Lans

The events (oral presentations, poster session, social events) will be divided between the auditorium *La Coupole* and the Grand Hôtel de Paris.

From the *Gare routière de Villard-de-Lans*, you can walk to the *Coupole* where the MASR 2015 conference will be held, they are very close to each other.



Street view of the Coupole:

Practical Information

Practical Information

Time zone

In October France is on summer time which is GMT + 2.

Climate

October being a transitional period, a large variety of weather conditions and temperatures can be experienced in Grenoble and Villard-de-Lans.

Due to its location at ~1000m of elevation, Villard-de-Lans is somewhat colder: average minimal and maximal temperatures are 6.6°C and 18.6°C, respectively. Although unusual for the season, snow falls are not impossible.

Money

The currency in France is the Euro. Other currencies are usually not accepted in hotels, restaurants and shops. Popular foreign currencies can be changed in banks (open Monday to Friday).

Tax: VAT is 20% on most articles and is usually included in the displayed price.

Credit cards: Visa and Mastercard are accepted almost everywhere, and can be used to get cash from ATMs. Other cards may be accepted in major establishments. Traveler's cheques are not widely used and will probably need to be exchanged in a bank.

Many ATMs can be found in Grenoble city centre. There are 5 ATMs in Villard-de-Lans city centre.

Electricity

AC 230V 50 Hz. European sockets. Adapters can be bought in airports, large supermarkets, or electronics shops.

Insurance

The organizers cannot accept any liability or responsibility for death, illness, or injury to the person, or for loss of or damage to the belongings of participants and accompanying persons which may occur during, before, or after the conference. Participants are advised to make arrangements in respect of health and travel insurance.

Phone numbers

MASR 2015 contact during the conference:
+33 6 88 38 71 06 and +33 6 88 38 71 12

General emergencies (from any European mobile phone): 112

General assistance will be available all week long to help you with travel arrangements, *etc*...

A notice board will be set at the entrance of the *Coupole* to give you the latest updates about the conference.

Certificates of participation

Certificates will be provided to all attendees during registration.

Meals

Lunch on Monday 5th October will be taken at the ESRF restaurant. During the conference, meals will be served in the *Grand Hôtel de Paris*, unless otherwise stated. All meals are included in the conference registration fees.

The conference dinner will take place on Wednesday evening. Transportation will be arranged from Villard de Lans to Lans en Vercors, where the conference dinner will take place.

Conference Programme

PROGRAMME

Monday, 5th October – ESRF Grenoble

10:00	*Welcome coffee and opening of registration*	
10:30 – 12:30	Beamline Visit	**Guided by the ID17 team**
12:30 – 13:30	*Lunch at the ESRF-ILL onsite restaurant*	
13:30	Registration continues	
14:00 – 14:15	Welcome by the Chairmen, Alberto Bravin and François Estève	
14:15 – 14:30	Welcome by Jean Susini, ESRF Director of Research	
Special Presentations		
14:30 – 15:15	Biomedical applications of nanoimaging	**P. Cloetens,** ESRF, France
15:15 – 16:00	Ultra-high dose-rate, FLASH irradiation increases the differential response between normal and tumor tissue and allows minimization of lung fibrosis in mice	**V. Favaudon,** Institut Curie-Recherche, Orsay, France,
16:00 – 16:15	*Tea & coffee break*	
16:15 – 17:30	Mini-clips posters	
17:30 – 19:30	Wine & cheese	
20:00	*Bus to Villard de Lans*	

Session 1, Chair person: P. Coan		
08:45– 09:20	**Keynote Presentation:** Limits and strengths of today's clinical radiology: where the research should focus on	**M. Reiser,** LMU, Germany
09:20– 09:40	Tomographic in-vivo study of lung physiology at the micrometer scale	**G. Lovric,** PSI, Switzerland
09:40 – 10:00	X-ray Specks – Ultra low dose in vivo imaging of lung structure and function	**M. Kitchen,** Monash Univ., Australia
10:00 – 10:30	*Coffee & Tea break*	
Session 2, Chair person: R. Mokso		
10:30 – 10:50	High-speed multi-modal x-ray imaging of airway surfaces for in vivo testing of treatment effectiveness	**K. Morgan,** Monash Univ., Australia
10:50 – 11:10	Investigating cystic fibrosis lung disease using synchrotron phase contrast imaging at CLS BMIT beamline	**X. Luan,** University of Saskatchewan, Canada
11:10 – 11:30	X-ray synchrotron interferometric measurement of eye lens media: evidence of a stepped gradient lens	**B. Pierscionek,** Kingston University, UK
11:30 – 11:55	**Facility Report:** Achievements and perspectives in medical applications at the PSI-TOMCAT beamline (Title to be confirmed)	**M. Stampanoni,** PSI and ETH, Switzerland
11:55 – 12:30	**Facility Report:** Biomedical phase-contrast imaging at MAX-IV	**M. Bech,** Lund University, Sweden
12:30 – 14:00	*Lunch at the Grand Hôtel De Paris*	

Session 3, Chair person: D. Chapman		
14:00 – 14:35	**Keynote Presentation:** Is relaxing the coherence requirements a necessary step to enable a clinical translation of X-ray phase contrast imaging?	**A. Olivo,** University College London, UK
14:35 – 14:55	3D imaging of neuron system and vascular network in mouse spinal cord for the investigation of neurodegenerative diseases	**A. Cedola,** CNR-Institute of Nanotechnology, Italy
14:55 – 15:15	Diffusion-Convection Interaction as a cause of uneven gas distribution in rabbit lung	**S. Bayat,** Univ. de Picardie Jules Vernes, France
15:15 – 15:35	Demonstrating the benefits of beta-blockers in hypertensive diabetic heart disease with synchrotron microangiography	**J. Pearson,** Monash Univ., Australia
15:35 – 16:00	*Coffee & Tea break*	
Session 4, Chair person: E. Brun		
16:00 – 16:20	Low dose phase-contrast breast tomography with synchrotron radiation at Elettra: first images	**R. Longo,** INFN Trieste, Italy
16:20 – 16:40	The application of Synchrotron free propagation phase contrast CT in preclinical asthma research	**C. Dullin,** University Medical Center Göttingen, Germany
16:40 – 17:00	3D quantification of microvascular regeneration after spinal cord injury in rat model by SRμCT	**Y. Cao,** Xiangya Hospital, China
17:00 – 17:20	*Coffee & Tea break*	
Session 5, Chair person: L. Porra		
17:20 – 17:40	Spectral K-edge subtraction imaging of bone-seeking elements	**A. Panahifar,** University of Saskatchewan, Canada
17:40 – 18:00	Synchrotron Radiation Computed Tomography with combined high spatial and temporal resolutions	**M. Ruat,** ESRF, France
18:00 – 18:20	Spatiotemporally resolved In vivo X-ray imaging studies of morphological dynamics, and of tissue and cell movements during biological processes	**T. Baumbach,** KIT, Germany
	Poster Session at the Grand Hôtel de Paris	
	Dinner at the Grand Hôtel de Paris	

Session 1, Chair person: R. Menk		
08:45– 09:20	**Keynote Presentation:** From nano particles to nanometric far-field interferometers - collaborations between beamlines and x-ray tubes	**H. Wen,** NHLBI, NIH, USA
09:20– 09:40	A single-image retrieval method for fast and low-dose applications of edge illumination X-ray phase-contrast imaging	**P. Diémoz,** UCL London, UK
09:40 – 10:00	Dark-field imaging dependence on energy and sample granularity: from synchrotron to X-ray tubes using a single photon-counting detector	**S. Gkoumas,** PSI, Switzerland
10:00 – 10:30	*Coffee & Tea break*	
Session 2, Chair person: X. Jiang		
10:30 – 10:50	Cartilage and soft tissue imaging using X-rays - Propagation-based phase-contrast CT of the human knee in comparison to clinical imaging techniques and histology	**T. Geith,** Klinikum der Universität München, Germany
10:50 – 11:10	Multiple energy synchrotron biomedical imaging system	**B. Bassey,** University of Saskatchewan, Canada
11:10 – 11:30	Towards medical applications of grating interferometer at SLS	**Z. Wang,** PSI, Switzerland
11:30 – 11:50	X-ray dark-field imaging (XDFI) optics and its application to medicine	**M. Ando,** Tokyo Uni of Science, Japan
11:50 – 12:15	**Facility Report:** The Australian synchrotron imaging and medical beamline: Facility update	**D. Häusermann,** Australian Synchrotron, Australia
12:15 – 12:40	**Facility Report:** Biomedical imaging @ Elettra: the SYRMEP beamline	**G. Tromba,** Elettra, Italy
12:40 – 14:00	*Picnic Lunch*	
14:00 – 17:00	**Networking Activity / Hiking**	
Session 3, Chair person: A. Stevenson		
17:00 – 17:20	Edge illumination dark-field imaging: applications with conventional X-ray sources, achromaticity and high energy implementations	**M. Endrizzi,** UCL London, UK
17:20 – 17:40	High-resolution subcellular imaging at the ESRF new nanoimaging beamline: deciphering intracellular targets of anticancer drugs in breast cancer cells	**F. Fus,** ESRF, France
17:40 – 18:00	Shedding light on the safety of ultrasound imaging/therapy using Analyzer Based X-ray Imaging	**Z. Izadifar,** University of Saskatchewan, Canada
18:00 – 18:20	Quantitative phase contrast computed tomography of large biomedical samples in the hard X-ray domain	**S. Gasilov,** KIT, Germany
18:20 – 18:40	Quantitative retrieval of absorption, refraction and scattering with Analyzer Based Imaging utilizing a novel three image algorithm	**F. Arfelli,** INFN, Italy
19:30	*Conference Gala Dinner*	

Session 1, Chair person: J. A. Laissue		
08:30– 09:05	**Keynote Presentation:** Multiscale understanding and modelling of radiation biodamage	**A. Solov'yov,** MBN Research Center, Germany
09:05– 09:25	Dose thresholds for destroying hypoxic tumor and stromal cells with microbeam radiotherapy	**A. Jamshidi-Parsian,** Univ. of Arkansas for Medical Science, USA
09:25 – 09:45	The Munich Compact Light Source – The potential for x-ray microbeam irradiations at a compact synchrotron	**K. Burger**, TUM, Germany
09:45 – 10:05	Can computer modelling of the microvasculature help understanding the MRT tissue sparing?	**A. Merrem,** Institute of Cancer Research, Germany
10:05 – 10:30	*Coffee & Tea break*	
Session 2, Chair person: E. Bräuer-Krisch		
10:30 – 10:50	Synchrotron microbeam radiation - a new promising anti-angiogenic strategy for cancer treatment	**V. Djonov,** University of Bern, Switzerland
10:50 – 11:10	Radiotherapy by photoactivation of iron nanoparticles and Mössbauer effect	**P. Gimenez,** INSERM/ESRF, France
11:10 – 11:35	**Facility Report:** Achievements and perspectives in medical applications at the ESRF – ID17 beamline	**A. Bravin,** ESRF, France
11:35 – 12:00	**Facility Report:** Achievements and perspectives in medical applications at Shanghai synchrotron (Title to be confirmed)	**T. Xiao,** Shanghai Institute of Applied Physics, China
12:00 – 12:25	**Facility Report:** BMIT Facility at the Canadian Light Source, biomedical applications and future plans	**T. Wysokinski,** University of Saskatchewan, Canada
12:25 – 14:00	*Lunch at the Grand Hôtel De Paris*	

Session 3, Chair person: C. Ceresa		
14:00 – 14:35	**Keynote Presentation:** MRT – Solved problems and unmet challenges to establish a new paradigm in radiation therapy	**U. Oelfke,** Institute of Cancer Research, UK
14:35 – 14:55	Fluorescent nuclear track detector technology – high resolution imaging tool for photon and charge particle dosimetry and spectroscopy	**M. Akselrod,** Oklahoma State University, USA
14:55 – 15:15	Characterisation of a synthetic diamond detector for experimental dosimetry in MRT	**J. Livingstone,** Australian Synchrotron, Australia
15:15 – 15:35	*In vivo* dosimetry for synchrotron stereotactic radiation therapy	**D. Reynard,** ESRF, France
15:35 – 16:00	*Coffee & Tea break*	
Session 4, Chair person: F. Estève		
16:00 – 16:35	**Keynote Presentation:** Synchrotron Radiation Therapy: ongoing development and long term prospect	**J. Balosso,** CHU Grenoble, France
16:35 – 16:55	Medical physics issues in contrast-enhanced synchrotron stereotactic radiotherapy clinical trials.	**J.F. Adam,** INSERM/ESRF, France
16:55 – 17:15	Multi-strip silicon sensor for beam array monitoring in Micro-beam Radiation Therapy	**N. Pacifico,** University of Bergen, Norway
17:15 – 17:35	*Coffee & Tea break*	
Session 5, Chair person: S. Wiebe		
17:35 – 17:55	The use of theranostic gadolinium-based nanoprobes to improve radiotherapy efficacy.	**G. Le Duc,** ESRF, France
17:55 – 18:15	The Eclipse™ treatment planning system for microbeam radiotherapy trials at the Australian Synchrotron	**J. Crosbie,** RMIT, Australia
18:15 – 18:35	Quantitative characterisation of the white/ pink X-ray beam at the Australian Synchrotron Imaging & Medical Beamline (IMBL)	**A. Stevenson,** CSIRO, Australia
18:35	Discussion	
	Dinner at the Grand Hôtel de Paris	

WG1	Radiation Biology	Chair: C. Mothersill Vice Chairs: V. Djonov, J Hopewell	
08:30– 08:50	Abscopal and bystander effects following exposure of rodent brains to synchrotron medical microbeam irradiation		**C. Mothersill,** McMaster University, Canada
08:50– 09:10	Synchrotron X-ray Pencil beam Irradiation as Boost after Whole Brain Irradiation		**E. Schültke,** Rostock University Medical Centre, Germany
WG2	Treatment of tumours using MRT and SSRT, including improved drug delivery	Chair: M. Grotzer Vice Chair: J.A. Laissue	
09:10 – 09:30	Synchrotron microbeam radiotherapy evokes a different tumor immunomodulatory response to conventional radiotherapy		**J. Crosbie,** RMIT, Australia
09:30 – 09:50	The development of a proton-beam grid radiotherapy		**T. Henry,** Stockholm University, Sweden
09:50 – 10:10	Multifunctional gold nanoparticles for image-guided microbeam radiation therapy		**S. Roux,** Université de Franche-Comté, France
10:10 – 10:30	*Coffee & Tea break*		
10:30 – 10:50	The minipig experiment: a last major milestone prior clinical trials in MRT		**E. Bräuer-Krisch,** ESRF, France
10:50 – 11:10	MRT for pet animals: Normal organ tolerance for MRT of the rabbit nose and jaws		**J.A. Laissue,** University of Bern, Switzerland
WG3	Dosimetry and treatment planning for small fields and microbeams	Chair: E. Bräuer-Krisch Vice Chair: U. Oelfke	
11:10 – 11:30	Online 3D measurement of SSRT beams		**Y. Arnoud,** UJF Grenoble France
11:30 – 11:50	The development of a clinical protocol for microbeam-grid radiation therapy		**A. Siegbahn,** Stockholm University, Sweden
11:50 – 12:10	Conformal imaged guided MRT for multiple port treatment and first results on 4D dose calculations in MRT including tissue motion		**M. Donzelli,** ESRF, France
12:10 – 13:30	*Lunch at the Grand Hôtel De Paris*		

WG4	Emerging applications of microbeams	Chair: A. Depaulis Vice Chair: M. Jacquet
13:30 – 14:00	Liquid-metal-jet X-ray tube technology	**T. Tuohimaa,** Excillum, Stockholm, Sweden
14:00 – 14:30	Potential of compact Compton sources in the medical field	**M. Jacquet,** CNRS Orsay, France
14:30 – 15:00	General Disscussion	
End of Work Group Meetings		
15:00 – 16:00	Restricted to COST SYRA3 Management Committee (MC) Separate Agenda provided to MC members	

16:30: Bus departure to Grenoble

cost
EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

Syra3

Speakers' Abstracts

In order of appearance

Biomedical applications of X-ray nano-imaging

P. Cloetens[1], A. Pacureanu[1], Y. Yang[1], J.C. da Silva[1], S. Bohic[1,2], F. Fus[1], M. Hubert[1,3], M. Langer[1,4], L. Weber[1,4]

[1]ESRF – The European Synchrotron, 38043 Grenoble, France, [2]INSERM U-836 Team 6, Grenoble, France, [3]Univ. Grenoble Alpes – CEA/LITEN, Grenoble, France, [4]Univ. de Lyon, INSERM U1044; Lyon, France **cloetens@esrf.eu**

X-ray nano-imaging is a valuable tool for the 3D characterization of the morphology and the elemental composition of biological specimens such as organelles, cells, tissue and model organisms, in their native state. The new nano-imaging beamline ID16A-NI of the ESRF combines coherent imaging techniques and X-ray fluorescence microscopy at the ultimate spatial resolution. This enables unprecedented quantitative studies for biological sciences.

High-brilliance X-ray beams focused down to nanometer sizes open new possibilities to tackle major challenges in biology and biomedical sciences. The Nano-Imaging beamline ID16A-NI aims at the quantitative 3D characterization at the nanoscale of the morphology and the elemental composition of specimens in their native state through the combination of coherent imaging techniques and X-ray fluorescence analysis. Coherent imaging techniques map quantitatively the electron density distribution in the sample. Three such techniques are used and actively developed at ID16A-NI: magnified phase nano-tomography [1], far-field ptychography [2] and near-field ptychography [3]. Complementary to coherent imaging techniques, X-ray fluorescence analysis maps the (trace) element distribution by scanning the specimen through the X-ray nanoprobe. To study metal based drugs, X-ray fluorescence is particularly suited to identify the intracellular compartments targeted by these compounds as a main step towards explaining the drug action mechanisms. In correlative microscopy, X-ray fluorescence analysis and magnified phase imaging are combined to obtain quantitative maps of metal concentration in whole cells [4]. A spatial resolution of a few tens of nm in both imaging methods has been demonstrated at discrete energies of 17keV and 33.6keV. The next big challenge consists in adding a cryogenic environment, crucial to get as close as possible to the native state in life science applications without radiation damage. The final goal for the beamline after Phase II of the ESRF Upgrade Program, which will provide a factor 20 more photon intensity and transverse coherence, is to reach a focus size of 10nm and pave the way to dynamical studies.

References

[1] - M. Langer, A. Pacureanu, H. Suhonen, Q. Grimal, P. Cloetens, and F. Peyrin, "X-ray phase nanotomography resolves the 3D human bone ultrastructure", PLoS One **7**, e35691 (2012).

[2] - B. Enders, M. Dierolf, P. Cloetens, M. Stockmar, F. Pfeiffer, P. Thibault, "Ptychography with broad-bandwidth radiation", Appl. Phys. Lett. **104**, 171104 (2014).

[3] - M. Stockmar, P. Cloetens, I. Zanette, B. Enders, M. Dierolf, F. Pfeiffer, and P. Thibault, "Near-field ptychography: phase retrieval for inline holography using a structured illumination", Scientific Reports **3**, 1927 (2013).

[4] - E. Kosior, S. Bohic, H. Suhonen, R. Ortega, G. Deves, A. Carmona, F. Marchi, J.F. Guillet, and P. Cloetens, "Combined use of hard X-ray phase contrast imaging and X-ray fluorescence microscopy for sub-cellular metal quantification" J. Struct. Biol. **177**, 239 (2012).

Ultra-high dose-rate, FLASH irradiation increases the differential response between normal and tumor tissue and allows minimization of lung fibrosis in mice

V. Favaudon[1], C. Fouillade[1], M.-C. Vozenin[2]

[1] Institut Curie, Inserm U 612/U 1021, Bâtiments 110-112, Centre Universitaire, 91405 Orsay Cedex, France.
[2] Laboratoire de Radio-Oncologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Suisse
vincent.favaudon@curie.fr

Submillisecond pulses of radiation have been shown to generate less exchange chromosomal aberrations [1, 2] and a smaller extent of delayed cell death [3, 4] than continuous irradiation delivered at conventional dose-rate. This prompted us to determine whether and how pulsed irradiation affects the response of normal and tumor tissues *in vivo*.

With this goal in mind female C57BL/6J mice aged 10 weeks were given a single dose of 4.5 MeV electrons in bilateral thorax exposure either at a high (≥ 60 Gy/s, beam-on time ≤ 0.5 s, *FLASH*) or conventional dose-rate (0.03 Gy/s, beam-on time ≥ 500 s, *CONV*) using the *Kinetron* linear electron accelerator established in the Research Division of Institut Curie at Orsay. Irradiated lungs were removed at suitable times for histological and IHC or IF determination of apoptosis (< 24 h), DNA damage repair (≤ 1 week) and fibrosis (> 8 weeks). The antitumor potential of both radiation modalities was compared using human tumor xenografts in Swiss nude mice (HBCx-12A, HEp-2) and an orthotopically implanted, syngeneic lung carcinoma in C57BL/6J mice (TC-1 Luc+).

Fibrogenesis in the CONV group started as early as 8 weeks pi and progressively worsened, resulting in dense intraparenchymal fibrosis at 24 weeks pi with thickening and reorganization of alveolar septa, intense collagen deposition and activation of the TGF-□eta/Smad cascade. In contrast, no histological signs of pulmonary fibrosis were observed in the 17 Gy FLASH group; as much as 30 Gy FLASH was necessary for mice to develop lung fibrosis as intense as after 17 Gy CONV. FLASH elicited a dramatic reduction of vascular apoptosis. The skin was also spared by FLASH irradiation, yet well-delimited hair depigmentation restricted to the irradiated area was observed. ATM activation in the lung parenchyme did not depend very much on whether radiation was given as CONV or FLASH whilst FLASH was significantly less efficient than CONV in inducing foci of the phosphorylated forms of H2AX, Chk1, 53BP1 Rad51 and Ki67. Last but not least, FLASH was as effective as CONV in the repression of tumor growth.

Taken together, these results show that FLASH irradiation selectively spares normal tissue without loss of the antitumor activity, suggesting that dose escalation in the FLASH mode might allow complete eradication of tumors and reduce the occurrence and severity of early and late complications affecting normal tissue after radiotherapy. A putative lead to explain this new paradigm will be discussed.

References

[1] Prempree et al. Int J Radiat Biol 15: 571 (1969)
[2] Schmid et al. Radiother Oncol 95: 66 (2010)
[3] Ponette et al. Int J Radiat Biol 76: 1233 (2000)
[4] Fernet et al. Int J Radiat Biol 76: 1621 (2000)

Limits and Strengths of Today's Clinical Radiology: Where the Research Should Focus on

M.F. Reiser

Department of Radiology, Ludwig- Maximilians-University, Munich
Maximilian.reiser@med.uni-muenchen.de

During the past decades and years, we witnessed enormous developments and improvements in medical imaging, which had far- reaching impact on healthcare. The introduction of computed tomography (CT) and magnetic resonance imaging (MRI) was ranked among the 10 most important innovations in medicine in the 20th century.

Recently, major advances in were made which greatly enhanced efficacy of imaging modalities, e.g. multi- slice CT, multi- parametric MRI and hybrid imaging allowing the seamless combination of different modalities, such as PET-CT. The challenges for diagnostic imaging mirror those the whole healthcare system is confronted with: 1. Containment of costs which have soared in all societies due to demographic development, 2. Chronic diseases which are associated with modern life- style and environmental conditions as well as longevity of people and 3. Disparities of healthcare among countries and societies.

In order to cope with these challenges of healthcare a paradigm shift is noted in diagnostic imaging which includes contributions to "precision medicine". Precision medicine signifies the personalized assessment and therapy of a particular patient. This also includes to avoid any measures which may harm the patient and to employ minimally invasive therapies instead of open surgery and guidance with modern imaging modalities are key for precise targeting. The potential long-term effects of ionizing radiation, notably induction of cancer have to be respected and dose reduction is urgently needed.

Both in research and patient care biomarkers are searched for which allow for assessment of risk factors, early detection and precise assessment of a particular manifest disease. Moreover, biomarkers to allow appraisal of prognosis are searched for. Current imaging research is focussed on imaging biomarkers which can be combined to a radiomic assessment. For that purpose a combination of multi-parametric imaging data is employed and morphologic features, functional information and texture analysis are utilized to obtain specific information concerning prognosis and therapy response.

While the results of imaging used to be communicated according to the visual impression of the observer they have to be expressed in a quantitative and reproducible manner as they are used as imaging biomarkers. A major obstacle is the limited reproducibility and comparability among the equipment provided by different vendors.

References

[1] – J.C. Waterton and L. Pylkkanen: Qualification of imaging biomarkes for oncology drug development. Eur J Cancer **48** (4): 409-415 (2012).
[2] - European Society of Radiology: White paper on imaging biomarkers. Insights Imaging **1**(2): 42-45 (2010)
[3] – E.A. Eisenhauer, P.Therasse, J Bogaerts et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer **45** (2): 228-247 (2009).
[4] – A.R. Padhani, and A.A. Khan:Diffusion-weighted (DW) and dynamic contrast- enhanced (DCE) magnetic resonance imaging (MRI) for monitoring cancer therapy. Target Oncol 5(1):39-52 (2010).
[5] – P.M. Bossuyt, J.B. Reitsma, D.E. Bruns et al: Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Radiology **226** (1):24-28 (2003)

Tomographic *in-vivo* study of lung physiology at the micrometer scale

G. Lovric[1,2], F. Arcadu[1,2], I. Vogiatzis Oikonomidis[1,3], J.C. Schittny[3], M. Roth-Kleiner[4], R. Mokso[1], and M. Stampanoni[1,2]

[1]Swiss Light Source, Paul Scherrer Institute, 5234 Villigen, Switzerland
[2]Institute for Biomedical Engineering, University and ETH Zurich, 8092 Zurich, Switzerland
[3]Institute of Anatomy, University of Bern, 3012 Bern, Switzerland
[1]Clinic of Neonatology, University Hospital of Lausanne (CHUV), 1011 Lausanne, Switzerland
goran.lovric@psi.ch

Recent advances in synchrotron-based X-ray imaging techniques proved to reach micrometer resolutions and thus opened completely new insights into micrometer-scale biology [1,2]. However, combining high spatial with temporal resolution, especially considering radiation dose, still remains a challenging task [3]. Moreover, currently established methods in 3D lung imaging have been unsuccessful in answering still open questions in lung physiology, such as the question about how lungs inflate and deflate at a microscopic level [4]. We demonstrate for the first time in-vivo tomographic imaging of lungs with pixel sizes down to about one micrometer and at localized dose rates permitting terminal in-vivo experiments. We identify temporal resolution (in our case with single exposure times of a few ms) as the main current limitation towards µm-resolution in-vivo tomography and observe strong differences in septal thicknesses between in-vivo and ex-vivo lung tissue. We find for the first time direct evidence supporting a heterogeneous distension pattern at the level of alveoli (see Figure 1), rather than the often-hypothesized alveolar recruitment [5]. To the best of our knowledge, the highest resolution in in-vivo lung imaging achieved at a synchrotron has been reported by Sera et al. [6] imaging lungs with pixel sizes of about 12 µm, while our technique represents an improvement in spatial resolution by a factor of four.

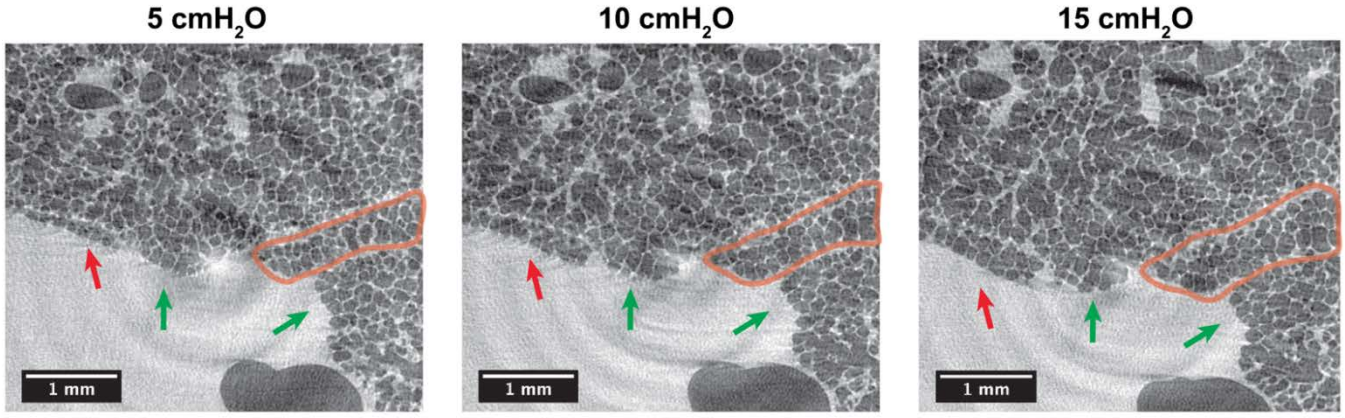


Figure 1: Tomographic slices of rats lungs at different breath-hold peak-inspiratory pressures. The marked area indicates the region of biggest stretching (approximate change in diameter from 350µm to 450µm, the green arrows indicate regions that are very little changed upon intubation, while the red arrows show a region where new alveolar structures appear, which however originate from "deeper" slices.

References

[1] - J. Moosmann, A. Ershov, V. Altapova *et al.*, Nature, **497** (7449) 374 (2013).
[2] - R. Mokso, D. A. Schwyn, S. M. Walker *et al.*, Sci. Rep. **5** (8727), 2015.
[3] - G. Lovric, S.F. Barré, J.C. Schittny *et al.*, J. Appl. Cryst. **46** (4), 856 (2013).
[4] - G. C. Smaldone & W. Mitzner, J. Appl. Physiol., **113**(12), 1945 (2012).
[5] - S. P. Albert, J. DiRocco, G. B. Allen *et al.*, J. Appl. Physiol. **106**(3), 757 (2009).
[6] - T. Sera, H. Yokota, K. Fujisaki *et al.*, Phys. Med. Biol. **53**(16), 4285 (2008)

X-ray Specks – Ultra low dose in vivo imaging of lung structure and function

M.J. Kitchen[1], G.A. Buckley[1], A.F.T. Leong[1], R.P. Carnibella[2], A. Fouras[2], M.J. Wallace[3], and S.B. Hooper[3]

Affiliation: [1]School of Physics and Astronomy, Monash University, Melbourne, Clayton, Victoria, Australia. [2]Department of Mechanical and Aerospace Engineering, Monash University, Clayton, Victoria, Australia. [3]The Ritchie Centre, MIMR-PHI Institute of Medical Research and the Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia.

marcus.kitchen@monash.edu

Respiratory health is directly linked to the structural and mechanical properties of the airways. For studying respiratory development and pathology, the ability to quantitatively measure airway dimensions and changes in their size during respiration is highly desirable. Real-time imaging of the terminal airways with sufficient contrast and resolution during respiration is currently not possible [1]. Phase contrast X-ray imaging can render the lungs highly visible as a result of the strong phase gradients imparted on the wavefield by the many air/tissue interfaces. For propagation-based phase contrast X-ray imaging, the lungs are rendered highly visible as a speckled intensity pattern [2] (Fig. 1). Recently we have shown that these speckle patterns can provide quantitative measures of lung air volume and the dimensions of the airways *in vivo* [3,4]. Those methods require some image-based *a priori* information to be known about the airways, such as the absolute lung air volumes to measure airway dimensions [4]. Herein a method requiring no *a priori* information will be presented for measuring lung airway dimensions in small animals from a single propagation-based phase contrast X-ray image, thereby requiring minimal radiation. We demonstrate that Fourier space quantification of the speckle texture can be used to statistically measure airway dimensions at the alveolar scale, with measurement precision finer than the spatial resolution of the imaging system. Using this technique we discovered striking differences in developmental maturity in the lungs of rabbit kittens at birth.

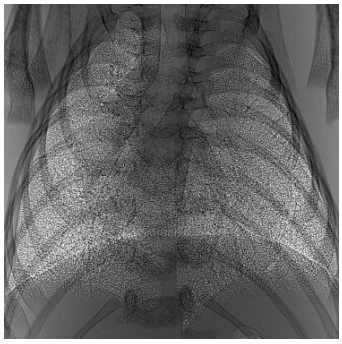


Figure 1. Propagation-based phase contrast X-ray image, revealing the lungs as a speckled intensity pattern.

References

[1] Fouras, A., M.J. Kitchen, S. Dubsky, et al., J. Appl. Phys., 2009. 105(1): 102009.

[2] Kitchen, M.J., D. Paganin, R.A. Lewis, et al., Phys. Med. Biol., 2004. 49(18): 4335-48.

[3] Leong, A.F.T., D.M. Paganin, S.B. Hooper, et al., Opt. Express, 2013. 21(23): 27905-23.

[3] Leong, A.F.T., G.A. Buckley, D.M. Paganin, et al., Biomed. Opt. Express 2014. 5: 4024-38.

High-speed multi-modal x-ray imaging of airway surfaces for *in vivo* testing of treatment effectiveness

K.S. Morgan[1,2], M. Donnelley[3-6], N. Farrow[3-6], P. Cmielewski[3-6], D. Paganin[1], Y. Suzuki[7], A. Takeuchi[7], K. Uesugi[7], N. Yagi[7], K. K. W. Siu[1] and D. Parsons[3-6]

[1]School of Physics, Monash University, Clayton, Australia, [2]Institute of Advanced Study, Technische Universität München, Garching, Germany, [3]Respiratory and Sleep Medicine, Women's and Children's Hospital, Adelaide, Australia, [4]Robinson Research Institute, [5]School of Paediatrics and Reproductive Health, [6]Centre for Stem Cell Research, University of Adelaide, Australia, [7]SPRing-8\RIKEN, Hyogo, Japan

kaye.morgan@monash.edu

In vivo phase contrast x-ray imaging (PCXI) is proving to be a powerful technique in the study of soft tissue structure, biomedical function and treatment response. High-speed imaging presents additional challenges, particularly at high magnification, where biological movement can easily result in motion blur. This often means that images can only be captured using a single short exposure, particularly in cases where the dynamics are irreversible (e.g. for assessing treatment effect). Therefore propagation-based PCXI is often used to capture dynamics, providing strong contrast in the lungs, but limited sensitivity to different types of soft tissue in projection.

This project applied PCXI to monitor the surface of murine airways *in vivo* and measure the effectiveness of treatments for cystic fibrosis. An effective treatment should increase the depth of the airway surface liquid (ASL), so that inhaled particles can be transported out of the lungs by ciliary beating.

In order to achieve the required imaging speed and sufficient sensitivity to differentiate the airway surface liquid from underlying tissue, we developed a single-grid method of phase contrast imaging [1]. This technique places a grid upstream of the sample and analyses sample-induced distortions in the grid image to retrieve differential phase contrast images in both directions [2]. The resulting differential images have successfully resolved the airway surface liquid and tracked treatment-induced changes with time *ex vivo* [3] and *in vivo* [4]. Our most recent work has placed the grid across part of the field of view to capture both propagation-based PCXI (PB-PCXI) and single-grid PCXI (SG-PCXI) in the same image (see Fig. 1), enabling simultaneous measurement of particle transit speed [5] and ASL depth [3-4].

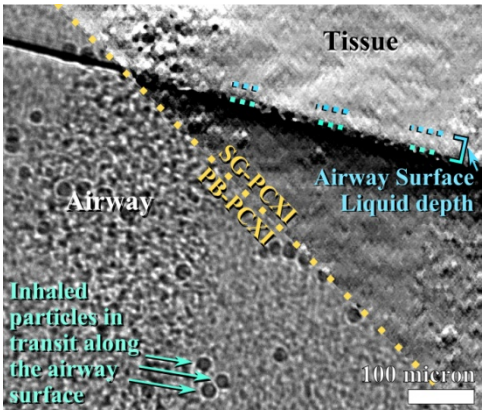


Figure 1: A reconstructed 60ms exposure of the airway, captured with a single grid over the upper right of the image to provide differential contrast by single-grid (SG)-PCXI and edge enhancement by propagation-based (PB)-PCXI in the bottom left.

These image sequences will use both measures to non-invasively provide immediate feedback on the effectiveness and effect duration of new cystic fibrosis treatments, accelerating treatment development.

References

[1] K. S. Morgan, D. M. Paganin and K. K. W. Siu, Optics Express **19**, 19781 (2011).
[2] K. S. Morgan, P. Modregger, S. C. Irvine, S. Rutishauser, V. A. Guzenko, et al., Optics Letters **38**, 4605 (2013).
[3] K. S. Morgan, M. Donnelley, D. M. Paganin, A. Fouras, N. Yagi, Y. Suzuki et al., PLoS ONE **8**, e55822 (2013).
[4] K. S. Morgan, M. Donnelley, N. Farrow, A. Fouras, N. Yagi, K. Uesugi, R. C. Boucher, K. K. W. Siu, D. W. Parsons, American Journal of Respiratory and Critical Care Medicine **190**, 469 (2014).
[5] M. Donnelley, K. S. Morgan, K. K. W. Siu, A. Fouras, et al., Journal of Synchrotron Radiation **21**, 768-773 (2014).

Investigating cystic fibrosis lung disease using synchrotron phase contrast imaging at CLS BMIT beamline

X. Luan[1], D. Chapman[2], J.P. Ianowski[1]

Affiliation: [1]Department of Physiology and [2]Anatomy & Cell Biology, University of Saskatchewan

Cystic Fibrosis (CF) is the most common, fatal genetic disease in Caucasian populations in Europe and worldwide. CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. CF can affect many body system, but CF lung disease is currently the source of most morbidity and mortality in CF patients. Unfortunately, the events leading from CFTR mutation to CF lung disease are not fully understood, and there is controversy on the primary defect responsible for CF lung disease pathogenesis. This gap in our understanding of CF lung disease makes the development of new and effective treatments more difficult.F patients always suffer from the repeated cycles of infection and inflammation, mucus accumulation, and airway remodeling, which lead to the blockage of air flow in their lung (1, 2, 3). The pathogenesis of CF lung disease still remain a mystery since the study model limitation. However, the development in the last several years of new CF swine (4) that develop lung disease that recapitulates in human has allowed researchers to study the function and anatomy of the lung before the onset of chronic symptoms that irrevocably alter the biology of the lung.

One of the biggest challenges to study the development of CF lung and to follow the longitudinal process is the lack of a non-invasive experimental technique with adequate spatial and temporal resolutions to measure the anatomical and physiological changes in the lung structure. Conventional imaging methods lack adequate definition and contrast to observe the soft tissue structure including lung; however, the synchrotron phase contrast imaging (PCI) can be used to image the airspace in the lung (5). Our objective is to develop an experimental method for investigating the biological and anatomical changes in the upper and lower airways and tracking the possible longitudinal differences in the CF lung disease.

Recently, we develop a synchrotron-based phase-related imaging method to examine ASL secretion response to inhaled bacteria relevant to CF in the upper airway of live swine. Our result indicates that bacteria (*P. aeruginosa*) trigger ASL secretion in live swine, which involved toll-like receptor 5-mediated immune response. And it also suggests that this bacteria-triggered ASL secretion is CFTR-dependent; this response would be missing in CF airway, which leads to innate defense failure against bacteria and further results in chronic infection and inflammation. Moreover, our result suggests that synchrotron-based PCI has the potential to investigate the physiological changes in the distal airway of live swine. The preliminary data show synchrotron-based PCI projection and CT can detect the small airways (less than 300 um in diameter) in swine lung.

References

[1] B.W. Ramsey, et al., Am J Respir Crit Care Med 185(8), 887 (2012).
[2] R.S. Baltimore, et al., Am Rev Respir Dis 140(6), 1650 (1989).
[3] R. Hamutcu, et al., Am J Respir Crit Care Med 165(8), 1172 (2002).
[4] C.S. Rogers, et al., Am J Physiol Lung Cell Mol Physiol 295(2), L240 (2008).
[5] D.W. Parsons, et al., J Anat 213(2), 217 (2008).

X-ray synchrotron interferometric measurement of eye lens media: evidence of a stepped gradient lens

B.K. Pierscionek[1], M.Hoshino[2], N. Yagi[2], M. Bahrami[1], A.Augousti[1] J. Regini[3], K. Uesugi[2]

Faculty of Science, Engineering and Computing, Kingston University London, Kingston-upon-Thames, KT1 2EE, UK,[1] Japan Synchrotron Radiation Research Institute (SPring8), Sayo, Hyogo, Japan, [2] School of Optometry and Vision Sciences, Cardiff University, Cardiff, UK [3].
b.pierscionek@kingston.ac.uk

The eye lens is a major refracting element of the eye responsible for a third of the refractive power and for adjusting the power of the eye for different focal distances. With age and some chronic systemic diseases, the lens can lose transparency and if the opacification becomes sufficiently detrimental to affect sight, it is deemed to be a cataract. The nature of lens transparency remains little understood. It is known that the eye lens has a gradient of refractive index created by the constituent proteins. How the gradient alters with age and as cataract starts to form depends on alterations in the proteins and requires a method that can make measurements in three dimensions and detect the subtle variations in refractive index in intact lenses. Lens samples from animal and human lenses set in a physiologically balanced gel were subjected to analysis of refractive index using an X-ray Talbot interferometer [1] constructed at the bending magnet beamline at the SPring-8 synchrotron. The monochromatic X-ray beam passed through a Si(111) double crystal monochromator and two transmission gratings, a phase and absorption grating [1]. The absorption grating was shifted with a Piezo stage to achieve fringe scans. An X-ray imaging detector acquired an image of the sample. Phase shifts were calibrated against solutions of known concentration and refractive index was calculated from equations relating phase shifts, protein concentration and refractive index [1].

The refractive index profile varies in different species from a steep parabolic profiles in a mouse lens to a profile better fitted with a higher order function as seen in the human lens which has a gradient in the periphery and a constant refractive index in the central, nuclear regions. In all species examined, there were fluctuations in the refractive index profile. In some lenses, such as porcine and murine, these deviations from a smooth profile were at similar distances on either side of the optic axis [2]. In the human they have been linked to distinct features seen in living lenses [3]. The assumption that the refractive index is smooth appears to be incorrect. The fluctuations in the gradient appear to be akin to steps and could be manifestations of lens growth, which occurs by layers of cells growing over existing tissue, or may be features that are important for lens optical quality. In either case they have significance for design of intraocular lenses which are used to replace the lens after cataract surgery and which to date have been unable to replicate the image quality provided by the biological lens.

References

[1] A. Momose, Jpn. J. Appl Phys.**44**, 6355-6367 (2005).
[2] M. Hoshino, K. Uesugi, N. Yagi, S. Mohri, J. Regini and B. Pierscionek,.PLoS One **6**, e25140 (2011).
[3] M. Bahrami, M. Hoshino, B. Pierscionek, N. Yagi, J. Regini and K. Uesugi, Exp. Eye Research **124**, 93-99 (2014)

Achievements and perspectives in medical applications at the PSI-TOMCAT beamline

M. Stampanoni[1,2] on behalf of the whole TOMCAT team

[1]Swiss Light Source, Paul Scherrer Institut, CH-5232 Villigen,
[2]Institute for Biomedical Engineering, ETH and University of Zürich, CH-8092 Zürich, **stampanoni@biomed.ee.ethz.ch**

The TOMCAT beamline of the Swiss Light Source operates multiple imaging end-stations, covering three orders of magnitude in spatial resolution (0.1-10 um) and enabling dynamical 3D acquisitions within a fraction of a second. The talk presents the latest achievements obtained in terms of instrumentation development and results, with particular emphasis on (bio)-medical applications. I will review some of the technical challenges which have been addressed in the recent past enabling dynamical, tomographic microscopy of flying insects [1,2] or the alveolar visualization of the breathing mouse lung [3]. Our future works will focus on the further optimization of the acquisition protocols for ultrafast imaging (introducing the GigaFROST [4] detector to users), as well as the continuous development of grating-based interferometry methods [5] and applications [6-9].

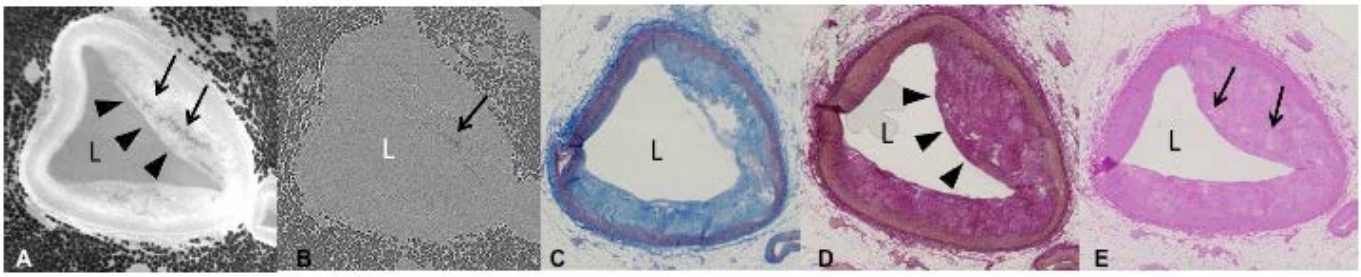


Figure 1 : Pathologic intimal thickening according to the modified AHA classification system**.** Phase contrast imaging **(A)** demonstrates pathologic intimal thickening with extracellular lipid accumulations (A, arrows) in the thickened intima (A, arrowheads) in the absence of a necrotic core. Pathologic intimal thickening is fundamental for the development of advanced atherosclerotic plaque stages while still being considered stable. In the corresponding absorption images **(B),** the lumen of the vessel and some of the lipid components (arrow) are depicted, whereas the layers of the vessel are only poorly definable. Histopathology with Masson`s trichrome **(C)**, Elastic van Gieson **(D)**, Hematoxylin and Eosin stainings **(E)** confirmed the presence of a markedly thickened intima (D, arrowheads) with lipid deposits (D, arrows) and the absence of a necrotic core. L = vessel lumen. Figure adapted from Ref. [9].

References

[1] Walker, Schwyn, Mokso et al., *In Vivo Time- Resolved Microtomography Reveals the Mechanics of the Blowfly Flight Motor*, Plos Biology **12** (3) (2014).
[2] Mokso, Schwyn, Walker et al., *Four-dimensional in vivo X-ray microscopy with projection-guided gating*, Sci Rep-Uk **5** (2015).
[3] Lovric, ETH Zürich, 2015.
[4] Mokso, Theidel, Schmidt et al., presented at the 12th International Conference on Synchrotron Radiation Instrumentation, New York, 2015 (unpublished).
[5] Peter, Modregger, Fix et al., *Combining Monte Carlo methods with coherent wave optics for the simulation of phase-sensitive X-ray imaging*, Journal of Synchrotron Radiation **21**, 613 (2014).
[6] Bonanno, Coppo, Modregger et al., *Ultra-high-resolution 3D imaging of atherosclerosis in mice with synchrotron differential phase contrast: a proof of concept study*, Sci Rep-Uk **5** (2015).
[7] Weber, Robert, Ksiazek et al., *Living-Engineered Valves for Transcatheter Venous Valve Repair*, Tissue Eng Part C-Me **20** (6), 451 (2014).
[8] Trachet, Fraga-Silva, Piersigilli et al., *Dissecting abdominal aortic aneurysm in Ang II-infused mice: suprarenal branch ruptures and apparent luminal dilatation*, Cardiovasc Res **105** (2), 213 (2015).
[9] Winklhofer, Peter, Tischler et al., *Diagnostic Accuracy of Quantitative and Qualitative Phase-Contrast Imaging for the Ex Vivo Characterization of Human Coronary Atherosclerotic Plaques*, Radiology (Ahead of Print), 141614.

Biomedical phase-contrast imaging at MAX-IV

M. Bech[1], K. Paulsson[2], L. B. Dahlin[3], R. Mokso[4]

[1]Medical Radiation Physics, Dep. of Clinical Sciences Lund, Lund University, Lund, Sweden
[2]Hand Surgery, Dep. of Clinical Sciences Malmö, Lund University, Malmö, Sweden
[3]Department of Clinical Genetics, Bio-Medical Centre, Lund University, Lund, Sweden
[4]MAX IV Laboratory, Lund University, Lund, Sweden
martin.bech@med.lu.se

Phase-contrast x-ray imaging has recently been proven to give improved contrast in soft tissue samples. In particular with highly brilliant synchrotron radiation, different approaches with coherent x-rays can give very good contrast with resolution ranging from micrometers to a few tens of nanometers. This is an excellent tool for studying three-dimensional morphology in a non-destructive way.

At the MAX IV laboratory in the northern part of Lund, a synchrotron is under construction and will be ready for the first scientific experiments in 2016 [1]. One of the beamlines planned at the MAX IV laboratory is the MedMAX beamline for biomedical and preclinical imaging [2].

Here we will present the current state of the MedMAX beamline project, the plans for future phase-contrast imaging possibilities, and give examples of applications in the fields of biology and medical research.

Current design plans include the options of having a combined undulator/wiggler source, and two end stations. The experimental station will allow high flux and high resolution imaging, with an additional option to allow a larger field-of-view for medium resolution low-dose imaging.

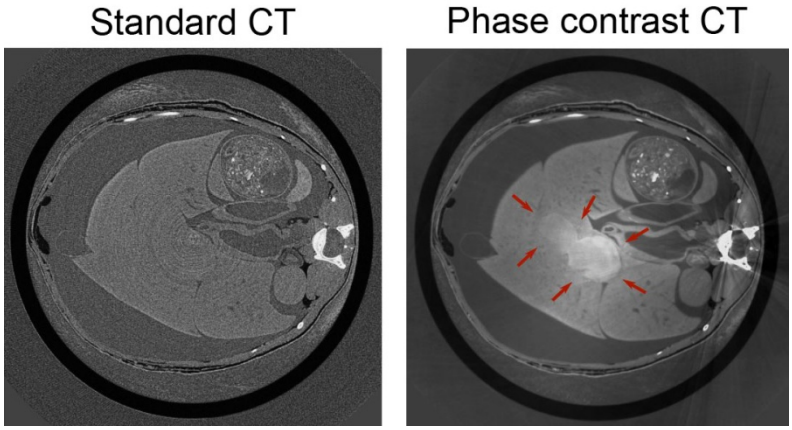


Figure 1: Example of enhanced image quality in soft tissue using x-ray phase-contrast imaging

References

[1] www.maxlab.lu.se/maxiv
[2] www.maxlab.lu.se/medmax

Is relaxing the coherence requirements a necessary step to enable a clinical translation of X-ray phase contrast imaging?

A. Olivo[1,2,*], P.C. Diemoz[1,2], M. Endrizzi[1], C.K. Hagen[1], A. Astolfo[1], F.A. Vittoria[1,2], A. Zamir[1], G. Kallon[1], D. Basta[1], T.P. Millard[1], P.R.T. Munro[1], L. Rigon[3], F. Arfelli[3], R. Longo[3], D. Dreossi[4], R. H. Menk[4], G. Tromba[4], P. Delogu[5,6], A. Vincenzi[7], R. Bellazzini[6,7], U.H. Wagner[8], C. Rau[8], I.K. Robinson[2,9], P. De Coppi[10], P. Coan[11,12], A. Bravin[12]

Affiliations: [1]Department of Medical Physics and Biomedical Engineering, UCL, WC1E 6BT London, UK; [2]Research Complex at Harwell, Harwell Oxford Campus, OX11 0FA Didcot, UK; [3]Department of Physics, University of Trieste, Via Valerio 2, 34127 Trieste, Italy; [4]Sincrotrone Trieste SCpA, S.S. 14 km 163.5, 34012 Basovizza, Trieste, Italy; [5]Dipartimento di Fisica, University of Pisa, Largo B. Pontecorvo 3, 56127 Pisa, Italy; [6]INFN, Pisa Section, Largo B. Pontecorvo 3, 56127 Pisa, Italy ; [7]PIXIRAD Imaging Counters s.r.l., c/o INFN Pisa, Italy; [8]Diamond Light Source, Harwell Oxford Campus, OX11 0DE Didcot, UK; [9]London Centre for Nanotechnology, WC1H 0AH London, UK; [10]Institute of Child Health, UCL, London WC1N 1EH, UK ; [11]Faculty of Physics and Department of Clinical Radiology, Ludwig Maximilians University, 85748 Garching, Germany; [12]European Synchrotron Radiation Facility, 38043 Grenoble, France; [*]**a.olivo@ucl.ac.uk**

While X-ray phase contrast imaging (XPCI) is now widely used at synchrotrons where it has become a reference research tool [1], its translation into clinical and other mainstream applications has so far encountered significant difficulties [1, 2]. It was indeed known since the beginnings [e.g. 3] that coherence (especially spatial) was one of the most significant requirements for XPCI to work, which seemed to make either synchrotron radiation or at the very least microfocal sources necessary. One significant step forward was achieved through opportunely designed source collimation systems, which created arrays of mutually incoherent, but individually coherent sourcelets [4, 5]; this enabled for the first time the use of spatially incoherent sources. However, restrictions in the emitted flux and limitations related to the construction, handling and alignment of the required optical elements created significant obstacles in terms of practical translation.

Among non-specialized communities and some parts of industry, this seems to have generated the false assumption that translating XPCI into clinical applications might be impossible. To counteract this dangerous belief, the community must react by a) improving the translatability of coherent methods and b) developing incoherent approaches [e.g. 6].

This talk focuses on b), and will demonstrate that 1) incoherent approaches can be adapted to standard environments without affecting the phase sensitivity or the capacity to retrieve quantitative information; 2) they are extremely flexible and allow e.g. the use of asymmetric masks and multiple ways to implement CT approaches and/or retrieve dark-field information; 3) they yield significant advantages also when used with coherent sources like synchrotrons. A series of relevant medical applications (breast, extremities, regenerative medicine and others) will be used to support the above claims.

References

[1] A. Bravin, P. Coan and P. Suortti, Phys. Med. Biol. **58**, R1 (2013)
[2] A. Olivo and E. Castelli, Riv. Nuovo Cimento **37**, 467 (2014)
[3] A. Snigirev, I. Snigireva, V. Kohn, S. Kuznetsov and I. Schelokov, Rev. Sci. Instrum. **66**, 5486 (1995)
[4] F. Pfeiffer, T. Weitkamp, O. Bunk and C. David, Nat. Phys. **2**, 288 (2006)
[5] R. Lanza, B. Horn and A. Damato, International Patent **WO 09/058976** (7 May 2009)
[6] P.R.T. Munro, K. Ignatyev, R. Speller and A. Olivo PNAS **109**, 13922 (2012)

3D imaging of Neuron System and Vascular Network in mouse spinal cord for the investigation of neurodegenerative diseases

Inna Bukreeva[1], Michela Fratini[1,2], Gaetano Campi[3], Raffaele Spanò[4], Valentina Petrosino[5], Francesco Brun[6], Giuliana Tromba[7], Peter Modregger[8] , Herwig Requardt[9], Ranieri Cancedda[5], Antonio Uccelli[6], Nicole Kerlero de Rosbo[6], Alberto Bravin[9], Maddalena Mastrogiacomo[5], Alessia Cedola[1*]

1. Institute of Nanotechnology-Laboratory of Soft and Living Matter-CNR c/o Physics Department at 'Sapienza' University, Piazzale Aldo Moro 2, 00185 Rome, Italy
2. Department of Physic, University of Roma TRE, via della Vasca Navale, Rome, Italy
3. Institute of Crystallography-CNR, Monterotondo, Rome, Italy
4. Department of Experimental Medicine, University of Genova & AUO San Martino - IST, Largo R. Benzi 10, 16132 Genova, Italy.
5. Department of Neuroscience, Ophthalmology and Genetics, University of Genoa,Largo Daneo 3,16132 Genoa-Italy.
6. Department of Engineering and Architecture, University of Trieste, Via A. Valerio, 10, 34127 Trieste, Italy.
7. Elettra – Sincrotrone Trieste S.C.p.A, S.S. 14 km 163.5 in Area Science Park – Basovizza, Trieste, Italy.
8. Swiss Light Source, Paul Scherrer Institut, 5232 Villigen, Switzerland & Centre d'Imagerie BioMedicale, Ecole Polytechnique Federale de Lausanne, 1015 Lausanne, Switzerland.
9. European Synchrotron Radiation Facility, 71 Avenue des Martyrs, 38043 Grenoble, Cedex France

The investigation of Neuronal System (NS) and Vascular Network (VN) in mouse spinal cord is a basis for the research on neurodegenerative diseases. X-ray Synchrotron Phase-Contrast Tomography (XSPCT) allows the simultaneous 3D investigation of NS and VN, at scales spanning from millimeters to hundreds of nanometers. We obtained 3D images of NS and VN of an ex-vivo mouse spinal cord with one single XSPCT measurement. This result has been obtained without the use of contrast agent and without any special sample preparation or sectioning. We image the 3D distribution of the micrometric nerve fibers, axon-bundles, neuron soma, and vascular and capillaries network.

The focus of the present work is the pre-clinical study of neurodegenerative disease: By XSPCT we study the spinal cord from mice with experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis. In particular we compare healthy samples, untreated samples and sample treated by i.v. injection with mesenchymal stem cells, a subset of adult progenitor cells with immunomodulatory and neuroprotective properties, which ameliorate EAE and are being considered as alternative therapy for *neurological diseases*. The comparison leads to the relationship between blood-spinal cord-barrier impairment and neuroinflammation, and how this relationship is affected by treatment with mesenchymal stem cells.

Diffusion-Convection Interaction as a cause of uneven gas distribution in rabbit lung

S. Bayat[1], L. Broche[1, 2], L. Degrugilliers[1], L. Porra[3], A. Wexler[4], M. Paiva[5] and S. Verbanck[5]

[1]Université de Picardie Jules Verne & Amiens University Hospital – Amiens/FR, [2]European Synchrotron Radiation Facility – Grenoble/FR,[3]University of Helsinki – Helsinki/FI, [4]University of California Davis/USA
[5]University Hospital UZ Brussels Brussels/BE, **email: bayat.sam@chu-amiens.fr**

Interaction between convection and diffusion has been suggested theoretically to play a role in the uneven distribution of gases in the mammalian lung. Here we present the first direct experimental demonstration of this process *in vivo*. The experiments were performed in 4 anesthetized and mechanically ventilated New-Zealand White rabbits (2.9 ± 0.1 kg). We used K-edge subtraction imaging to simultaneously image the distribution of xenon within the airspaces at 350 µm resolution [1] at 1.15 s intervals during a slow Xe inhalation. Synchrotron images of a right rabbit lung obtained immediately post-mortem at 47 µm pixel size were segmented, and custom software was used to extract the branching structure of conducting airways [2]. The resulting tree structure included 7175 branching airways, feeding 3843 terminal acinar units. We simulated gas transport in this tree structure using a previously described transport equation [3], and imposing at the model entrance, the Xe flows recorded during the imaging experiments (Figure 1-A, lower panel).

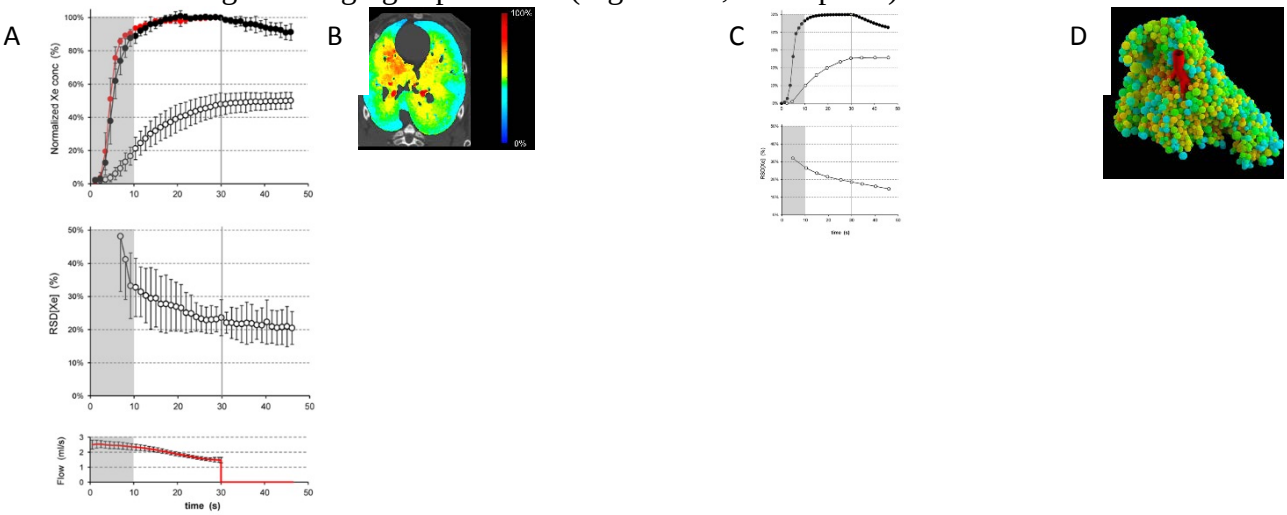


Figure 1: **A.** experimental Xe concentration vs. time in a representative image slice of the right lung (**B**); red curves are the conditions of Xe concentration and flow at the model entrance; **C:** Corresponding simulations showing that very similar curves are obtained by solving the differential equation of diffusive and convective gas transport (3) in the bronchial tree structure (**D**), without any parameter fitting.

Both the degree of peripheral Xe heterogeneity during inhalation and it's very slow equilibration during breath hold, are the direct result of the diffusion-convection interaction. These data provide the first *in vivo* demonstration of the concept of diffusion-convection interaction in the mammalian lung.

References

[1] - Bayat, S. et al. Anesthesiology 2013;119: 89-100
[2] - Verbanck, S. et al. J Appl Physiol 1993;75 :441-451
[3] - Lee, D.Y. et al. Anat Rec 2008;291 :916-926

Demonstrating the benefits of beta-blockers in hypertensive diabetic heart disease with synchrotron microangiography

J.T. Pearson[1], A.J. Edgley[1,2], Y-C. Chen[1], H. Thambyah[1], H. Tsuchimochi[3], T. Inagaki[3], M. Waddingham[2], D.J. Kelly[2], K.Umetani[4], M. Shirai[3]

Australian Synchrotron and [1]Department of Physiology and Monash Biomedical Imaging Facility, Monash University, Melbourne [2]St Vincent's Hospital, University of Melbourne, [3]National Cerebral & Cardiovascular Center, Japan, [4]SPring-8/JASRI. Email: james.pearson@monash.edu

Hyperinsulinemia and sympathetic overactivation have been suggested to play a role in the salt sensitivity of blood pressure as insulin resistance is strongly associated with hypertension in patients [1]. The Goto-Kakizaki (GK) rat is a non-obese model of type-2 diabetes that has basal hyperinsulinemia and insulin resistance for much of its young adult life. The aims of this study were 1) to investigate if chronic exposure to a high salt diet causes coronary endothelial dysfunction and an early onset of the decline in coronary flow reserve (assessed by dobutamine infusion), and 2) determine if these changes in vascular function and high blood pressure are prevented to a greater extent by β-adrenoceptor blockade with carvedilol (vasodilating β-blocker [2]) over metoprolol treatment.

We used synchrotron contrast microangiography (iodine K-edge 33.2keV) to compare arterial vessel internal diameters (30-350 μm) and vessel number in Wistar (Wi, control group) and GK rats following chronic exposure to either a normal chow diet or high salt chow diet (6% NaCl) with normal drinking water or β-blocker (metoprolol 6mg/kg/day or carvedilol 3mg/kg/day) for 8 weeks. Imaging was performed during baseline conditions and subsequently during administration of vasodilators (acetylcholine, SNP), followed by infusion of dobutamine (DOB), a β-adrenergic agonist (8μg/kg/min for 5 min) before and after NOS/COX blockade with L-NAME and sodium meclofenamate. We found that β-blocker treatment improved endothelium-mediated vasodilator responses and response to a cardiac stress test (DOB) in GK rats (Fig.1). In particular, with microangiography we show that blocking activation of the sympathetic nervous system preserved perfusion of the microvessels (4th order vessels) to improve cardiac function in pre-diabetic rats. These findings help to establish an underlying factor in heart failure.

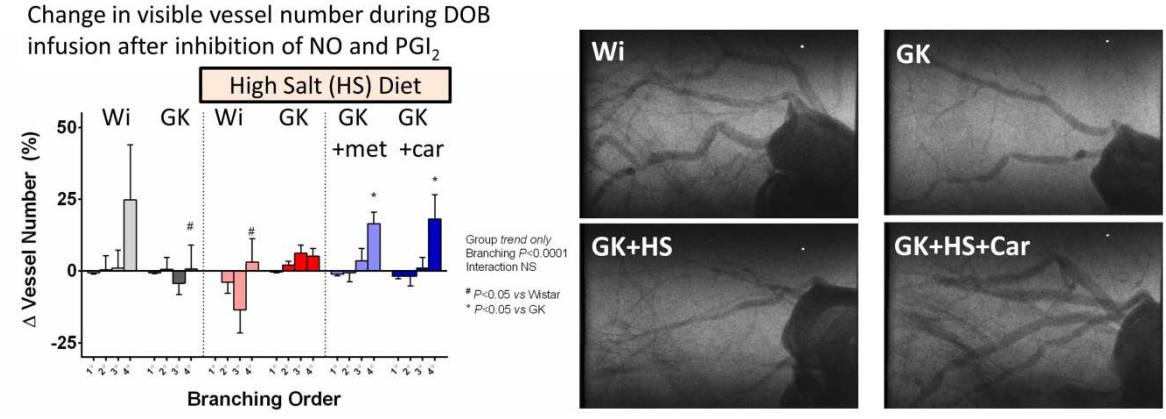


Figure 1: Change in vessel number from baseline during dobutamine infusion following inhibition of nitric oxide and prostaglandins. Typical angiograms of Wistar and GK rats on a normal chow diet and a GK rat on high salt diet (normal drinking water) or GK rat on high salt diet with carvedilol treatment.

References

[1] M.S. Yatabe, J. Yatabe et al. American Journal of Clinical Nutrition **92**, 77-82 (2010).
[2] G.L. Bakris. Journal of Managed Pharmacy Care **13**(5), S9-S12 (2007).

Low dose phase-contrast breast tomography with synchrotron radiation at Elettra: first images

R. Longo[1,2*], F. Arfelli[1,2], R. Bellazzini[3,7], A. Brez[3,7], F. Brun[4,9], P. Delogu[6,7], F. Di Lillo[8], D. Dreossi[9], V. Fanti[10], C. Fedon[1,2], B. Golosio[5], N. Lanconelli[11], G. Mettivier[8], M. Minuti[3,7], P. Oliva[5], M. Pinchera[3,7], L. Rigon[1,2], P. Russo[8], A. Sarno[8], G. Spandre[3,7], G. Tromba[9], F. Zanconati[12]

Affiliation: [1]Department of Physics, University of Trieste, Trieste, Italy [2]INFN Sezione di Trieste, Trieste, Italy [3]PiXirad Imaging Counters srl, Pisa, Italy, [4] Department of Engineering and Architecture, University of Trieste, Trieste, Italy, [5]University of Sassari & INFN Sezione di Cagliari, Sassari, Italy, [6] Department of Physics, University of Pisa, Pisa, Italy [7]INFN Sezione di Pisa, Pisa, Italy [8]Department of Physics, University of Napoli & INFN Sezione di Napoli, Italy [9]Elettra-Sincrotrone Trieste S.C.p.A, Basovizza, Trieste, Italy [10]Department of Physics, University of Cagliari & INFN Sezione di Cagliari, Italy [11]Department of Physics and Astronomy, University of Bologna & INFN Sezione di Bologna, Italy [12]Cytodiagnosis and Histopathology Clinical Operational Unit, University of Trieste, Trieste, Italy

***renata.longo@ts.infn.it**

The aim of the SYRMA-CT collaboration is to set-up a new clinical trial of Phase Contrast breast CT with Synchrotron Radiation (SR) at the SYRMEP beamline of Elettra, the SR laboratory in Trieste (Italy). In order to combine high image quality and low delivered dose a number of innovative elements will be merged: a novel CdTe single photon counting detector [1], state-of-the-art CT reconstruction algorithms, phase map reconstruction. To perform an accurate exam optimization, a Monte Carlo model has been developed for the dose calculation.

In this study CT scans of objects with dimensions and attenuation similar to human breast and two breast tissue specimens were acquired. The average glandular doses were in the range of those delivered in the cone-beam breast CT clinical studies (5 - 20 mGy [2]) while the isotropic spatial resolution $(0.120\ \text{mm})^3$ was higher. Due to the spatial coherence of the SR beam and the distance between sample and detector, the images contain not only absorption but also phase information from the samples so a phase-retrieval algorithm was applied [3]: the signal-to-noise ratio of the reconstructed slices increased significantly while the contrast remained about the same. Applying SART reconstruction technique [4] the quality of low dose images (5mGy) is comparable in spatial resolution and noise to the quality of images obtained with a 4 times higher dose.

These first results indicate that the clinical breast CT with SR is feasible and promising. The upgrade of the SYRMEP radiology area is in progress and the clinical protocol is under discussion.

References

[1] - Bellazzini R, Spandre G, Brez A, Minuti M, Pinchera M and Mozzo P *J Instrum* **8** C02028 (2013)

[2] – Zhao B, Zhang X, Cai W, Conover D and Ning R *Eur. J. Radiol.* **84** 48-53 (2014)

[3] - Paganin D, Mayo SC, Gureyev TE, Miller PR and Wilkins SW *J. Micros.* **206** 33-40 (2002)

[4] - Gordon R, Bender R, Herman GT *Journal of Theoretical Biology* **29** 471-481 (1970)

The application of Synchrotron free propagation phase contrast CT in preclinical asthma research.

C. Dullin[1], E. Larsson[2,3,4] A. Markus[1], F. Alves[1,6] and G. Tromba[2]

[1]University Hospital Goettingen, Germany, [2]Eletrra-Sincrotrone Trieste Italy, [3]Linköping University, Sweden, [4]University Trieste, Italy, [6]Max-Plank Institute for experimental Medicine Goettingen, Germany,
christian.dullin@med.uni-goettingen.de

Background: Asthma is a common burden of public health affecting more than 300 Mio. people worldwide. Its underlying pathomechanisms are still not completely understood [1] and existing therapies are far from being optimal. It is a disease, which involves the whole immune system and can therefore only be studied in living organisms such as mouse models. Anatomical hallmarks of asthma such as airway obstruction, reduced lung tissue elasticity and swelling of the airway walls present only mild alterations of the lung structure, rendering their quantification challenging. Nevertheless, in order to evaluate novel asthma therapy concepts a reliable screening platform is of great demand, which in combination with the smallness of the lungs in preclinical mouse models calls for a high resolution 3D imaging technique.
Perspectives & Results: Synchrotron free propagation in-line phase contrast CT in combination with single distance phase retrieval algorithm has already been proven to deliver detailed high contrast 3D data sets of mouse lungs [2]. Here we demonstrate the benefits of this technique applied in asthma mouse models generating data sets with an at least 10 fold increased contrast-to-noise ratio than absorption based CT. Furthermore, in combination with a special sample preparation scheme that allows to mimic in-vivo conditions of the lung as close as possible, we show that phase contrast CT enables the characterization and quantification of structural alterations within the lung of asthma models of different severity compared to treated mice and healthy controls. All studies have been performed at the SYRMEP beamline of the Italian Synchrotron Light Source "Elettra" and were verified by lung function measurement and histological analysis. Moreover, the gain in image quality in phase contrast CT has allowed to exploit labeled macrophages as specific tracer to localize inflammatory sites in combination with a detailed anatomical depiction of the lung [3]. We will demonstrate that this approach reveals significant differences in the biodistribution of these injected macrophages in asthmatic lung tissue compared to healthy controls. This, up to the knowledge of the authors, presents the first study combining functionalized contrast with phase contrast CT within mouse lungs.
Conclusion: Synchrotron radiation based phase contrast CT has therefore been the base to established a mouse lung screening platform to characterize asthma models of different severity and at different time points during the course of the disease as well as to monitor therapy effects.

References

[1] S. S. Braman, "The Global Burden of Asthma," p. 4S–12S, Jul. 2006.
[2] M. J. Kitchen, "Phase contrast X-ray imaging of mice and rabbit lungs: a comparative study," pp. 1018–1027, Nov. 2005.
[3] C. Dullin, S. dal Monego, E. Larsson, S. Mohammadi, M. Krenkel, C. Garrovo, S. Biffi, A. Lorenzon, A. Markus, and J. Napp, "Functionalized synchrotron in-line phase-contrast computed tomography: a novel approach for simultaneous quantification of structural alterations and localization of barium-labelled alveolar macrophages within mouse lung samples," *J. Synchrotron Radiat.*, vol. 22, no. 1, pp. 0–0, 2015.

3D quantification of microvascular regeneration after spinal cord injury in rat model by SRμCT

Hu, Jianzhong [1]; Li, Ping[1]; Zhou, Yuan[1]; Cao, Yong[1]; Wu, Tianding[1]; Lu, Hongbin*[2]

[1]Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China
[2]Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
* Corresponding author: **hongbinlu@hotmail.com**

Introduction: Acute spinal cord injury (SCI) is a devastating event involving the central nervous system. Local vascular reaction and ischemia occurred within the spinal cord are thought to be the most important issues in the SCI process. Therefore, investigation of the three-dimension (3D) pathological changes of microvasculature in the SCI process may provide our further insight into the pathological changes of SCI and aid in novel therapeutic strategy development. In this study, we analysed the 3D microarchitecture changes after SCI using synchrotron radiation micro-CT (SRμCT) in rats.

Methods: Twenty-eight SD male rats were employed for this study, where twenty-four SD rats were subjected to the modified Allen's weight impacting to induce SCI while the other four rats undergoing laminotomy as the sham group. T10 cord samples were harvested at 1, 3, 7, 14 and 28 day post injury. The 3D vasculature of spinal cord was determined by SRμCT and quantitatively analyzed by USIS software.

Results: (1) 3D morphology change of the spinal cord microvasculature in the natural healing process after SCI was clearly visualized. (2) Quantitative analysis on 3D images of the injured spinal cord revealed a significant decrease in the number of vascular networks. This was especially relevant to vessels with a diameter under 40 μm. (3) Vascular length was reduced significantly at 24 h post injury compared to the sham group ($p < 0.01$), followed by a gradual increase at 3, 7 day post-injury, and peaked up a plateau at 14 day post-injury. However, the length of vessels failed to reach the normal level at 28 days post-injury, but the neurologic function had also recovered. Compared to the sham group, the density of vascular segments were increased significantly at 1 day after injury ($p < 0.01$) and gradually reduced thereafter. By contrast, the density of vascular nodes were reduced significantly at 24 h post injury ($p < 0.01$), and gradually increased thereafter.

Conclusion: In this study, we successfully delineated the quantitative indicators of 3D microvasculature changes after SCI using SRμCT for the first time. These quantitative parameters of microvasculature post injury will conduce to a better understanding of the pathomorphology of SCI. In addition, it may also provide a standard method for evaluation of the treatment efficacy after SCI.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171698 and No. 81371956). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

Spectral K-edge Subtraction Imaging of Bone-Seeking Elements

[1]A. Panahifar, [2]N. Samadi, [3]T. Swanston, [4]M.J. Pushie, [1, 5]L.D. Chapman, [1]D.M.L. Cooper

Departments of [1]Anatomy and Cell Biology, [2]Biomedical Engineering, [3]Archaeology and Anthropology, [4]Geological Sciences, University of Saskatchewan, [5]Canadian Light Source, Canada, **a.panahifar@usask.ca**

Introduction: The physiological process of bone turnover (*i.e.*, remodeling) lies at the root of many diseases such as osteoporosis, osteoarthritis, bone cancers, *etc*. In order to better understand the role of remodeling in bone diseases, we combined anatomical imaging of bone with functional imaging of new bone formation/turnover at high resolution, after dynamic labeling with non-radioactive barium in rats. Barium, similar to calcium, when bioavailable will incorporate into the hydroxyapatite mineral of newly forming bone. To visualize spatial localization of barium tracer in bone we used dual energy spectral K-edge subtraction (SKES) technique to acquire projection and computed tomography (CT) data.

Methods: Two groups of healthy male rats of either 1 month-old (n=5) (*i.e.*, developing skeleton) or 8 month-old (n=5) (*i.e.*, skeletally mature) were dosed orally with barium chloride for 4 weeks (Ba^{2+} 33 mg/Kg/day). After euthanasia, barium distribution in the bone was evaluated in projection and CT mode by SKES technique (100 µm) at the BioMedical Imaging and Therapy (BMIT) bending magnet beamline at the Canadian Light Source (CLS). The SKES technique, unlike traditional KES, does not require separate imaging of the sample below and above the K-edge energy of the desired element (barium, 37.441 KeV) as the bent Laue monochromator used in this system provides a narrow spectrum of 275 eV energy range enabling imaging both energies simultaneously [1].

Results: The image acquisition for projectional SKES was approximately 30 seconds for isolated limbs (10-12 cm length) and the measured absorbed radiation dose was 0.75 mGy. Short term exposure to barium at the experimented low concentration led to its incorporation predominantly in newly forming bone such as the trabecular surfaces of articular joints (Figure). A previous preliminary study suggested that a larger bioavailable dose, whether as a result of prolonged exposure or higher dosage, may change the deposition pattern to wide spread uptake throughout the bone, both in the trabecular and cortical bone. Barium was also detected in the gastrointestinal tract as its excretion route.

Conclusion: The SKES method produces high resolution images (micron level) far better than nuclear medicine (*e.g.*, SPECT: 0.5-1 cm). The traditional KES method, while being highly effective for *ex vivo* samples [2], is not ideal for *in vivo* imaging due to the necessity of holding the animal perfectly still for two successive scans. Whereas the SKES method scans both energies simultaneously, minimizing the motion artefact. Therefore, it has great potential, after barium administration, for a rapid scout scanning of live animals for variety of diagnostic applications such as detection of bone metastasis in cancer animal models.

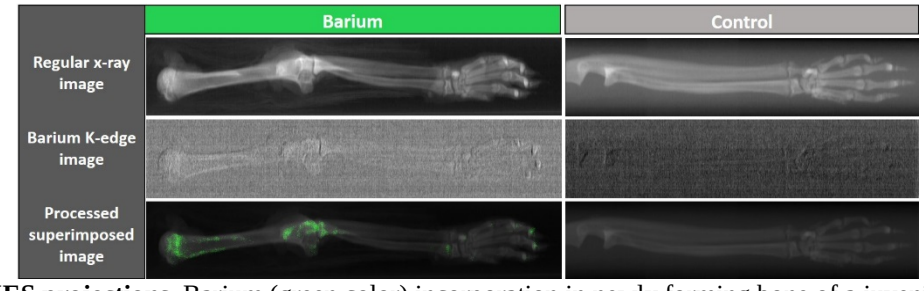


Figure: **SKES projections.** Barium (green color) incorporation in newly forming bone of a juvenile rat (left).

References

[1] - Y. Zhu, N. Samadi, M. Martinson, L.D. Chapman, *et al.* Phys. Med. Biol., **59**: 2485-2503 (2014).
[2] - D.M.L. Cooper, L.D. Chapman, Y. Carter, A. Panahifar, *et al.* Phys. Med. Biol., **57**: 5777-86 (2012).

Synchrotron Radiation Computed Tomography with combined high spatial and temporal resolutions

M. Ruat[1], J.F. Adam[2], C. Nemoz[3], D. Reynard[2], P. Deman[4], T. Brochard[3], C. Ponchut[1]

[1]ESRF-The European Synchrotron, Grenoble, FRANCE, **marie.ruat@esrf.fr** ; [2]INSERM U836, Grenoble Institute of Neuroscience, UJF, Grenoble, FRANCE, **adam.jeanfrancois@gmail.com, dimitri.reynard@esrf.fr** ; [3]ESRF ID17 Medical Beamline, Grenoble, FRANCE, **nemoz@esrf.fr, brochard@esrf.fr** ; 4 Department of Oral Biological and Medical Sciences, University of British Columbia, Vancouver, CANADA, **deman.pierre@gmail.com**

Studying the hemodynamics in brain is of particular interest for the diagnosis, the understanding and the management of pathologies such as ischemia [1], tumors [2], and traumas [3]. For malignant glioma, it has been shown that perfusion parameters are correlated to the tumor aggressivity [4], and can be used for the treatment outcome prognosis [5]. Quantitative measurements have to be compared between various imaging days and between patients. Synchrotron Radiation Computed Tomography (SRCT) is the gold standard to measure in vivo contrast agent concentrations with high accuracy and precision owing to the characteristic of the beam and performances close to theoretical limits: high flux, nearly parallel and monochromatic x-ray beams [6,7]. In addition to being quantitative, SRCT [8] could be greatly improved with both a high temporal and spatial resolution, which we assumed would be combined using the Maxipix-CdTe detector under development at ESRF [9]. This detector features a monolithic 1 mm thick single crystal CdTe sensor (99% efficient at energies up to 60 keV) hybridised to a matrix of 3x1 Timepix chips, giving a total area of 768x256 pixels at 55 µm pitch (45 x 15 mm2). Its tomographic spatial resolution is of 0.06x0.06x0.06 mm3. The high efficiency of the detector as well as its background noise suppression enabled low dose imaging (200mGy/s). Monochromatic X-rays at 35 and 51 keV were used. 360° tomography images have been taken over 2s, 6s, and 60s. Reconstruction of the tomographic slices was conducted using PyHST package developed at ESRF. A software extension has been developed to correct for defective or unstable pixels. The results were compared to images acquired with the reference 1D germanium detector. We have successfully retrieved iodine contrast agent quantification for both steady-state protocol and dynamic contrast-enhanced perfusion imaging, with phantoms. In vivo SRCT imaging in rats bearing brain tumors also proved successful, following up the iodine uptake for 25 minutes. We foresee low dose high resolution volumic perfusion measurements, relying on enhanced frame rates and synchronization accuracy as well as improved image reconstruction techniques.

References

[1] Klotz E, et al., European Journal Of Radiology. 1999; 30: 170-84.
[2] Eastwood JD, et al., Neuroradiology. 2003; 45: 373-6.
[3] Wintermark M, et al., Radiology. 2004; 232: 211-20.
[4] Roberts HC, et al., AJNR Am J Neuroradiol. 2000; 21: 891-9.
[5] Cao Y, et al., International Journal Of Radiation Oncology Biology Physics. 2006; 64: 876-85.
[6] Adam, J. F., H. Elleaume, et al., Journal Of Cerebral Blood Flow And Metabolism 23(4): 499-512 (2003).
[7] Adam, J. F., C. Nemoz, et al., Journal Of Cerebral Blood Flow And Metabolism 25(2): 145-153 (2005).
[8] Le Duc G. et al., European Radiology 10 : 1487-1492 (2000).
[9] Ruat M and Ponchut C, IEEE Trans. Nucl. Sci. 59(5): 2392-2401 (2012)

Spatiotemporally resolved In vivo X-ray imaging studies of morphological dynamics, and of tissue and cell movements during biological processes

T. Baumbach[a,b], A. Ershov[b], T. Faragó[a], R. Heine[a], L. Helfen[a,c], R. Hofmann[a], T. van de Kamp[a,b], J. Kashef[a,b], J. Moosmann[a,b], T. dos Santos Rolo[a], P. Vagovič[a,d], F. Xu[a,c], Y. Yang[a,c]

Affiliation: [a]ANKA / Institute for Photon Science and Synchrotron Radiation, Karlsruhe Institute of Technology, Germany, [b]Laboratory for Applications of Synchrotron Radiation, Karlsruhe Institute of Technology, Germany, [c]European Synchrotron Radiation Facility, France, [d]Center for Free-Electron Laser Science, DESY, Germany

tilo.baumbach@kit.edu

The talk will focus on developments at KIT in the context of current challenges in biotechnology and life sciences, where state-of-the-art X-ray imaging techniques provide spatiotemporally resolved information about micro-structure and its evolution during technological and biological processes.

X-ray laminography has been developed for multiple-contrast imaging in extended objects [1-4], permitting in situ and in operando studies. It enables scanning of complete entities with medium resolution, and zooming into region of interests with high resolution down to 50nm and correlation of various scanning and full field contrast mechanisms [5-8], as will be demonstrated by examples of bat wings, bacteria films and lung tissue under nanotoxicological stress.

An important issue is the development of dose-efficient imaging methods, which enable the visualization of soft tissue, in order to facilitate in vivo and in vitro investigations, e.g. for developmental biology, functional morphology, nano-toxicology and tissue engineering. The opaqueness of many organisms impedes in vivo investigation by light microscopy. In combination with optical flow algorithms, 4D phase-contrast µCT allows following of spatiotemporal movements, e.g. in order to observe tissues and individual cells during embryonic development [9, 10]. To investigate fast structure dynamics with feature sizes in the micron range and with high temporal resolution, we designed X-ray cine-tomography [11]. The technique enables e.g. new insights into the physiology of small animals by tracking the 4D dynamics of anatomical features as demonstrated by the analysis of screw-and-nut type weevil hip joints [12].

Further development will require an increase in dose-efficiency. Promising routes here include improvement of single-distance phase retrieval at large propagation distances, as well as the use of diffraction based magnifying optics combined with single photon counting detectors [13-16].

References

[1] L. Helfen *et al.*, APL 86 (2005);
[2] L. Helfen *et al.*; APL 94 (2009);
[3] D. Hänschke *et al.*, APL 101 (2012);
[4] Y. Cheng *et al.*, Soft Matter (2014);
[5] T. Tian *et al.*, APL 99 (2011);
[6] T. Morgeneyer *et al.*, Acta Materialia 69 (2014);
[7] V. Altapova et al., Opt Express 20 (2012);
[8] F. Xu et al., PloS ONE 7 (2012);
[9] J. Moosmann *et al.*, Nature 497 (2013);
[10] J. Moosmann *et al.*, Nat Protoc 9 (2014);
[11] T. dos Santos Rolo *et al.*, PNAS 111 (2014);
[12] T. van de Kamp *et al.*, Science 333 (2011).
[13] R. Hofmann *et al.*, Opt Express 19 (2011);
[14] J. Moosmann *et al.*, Opt Express 19 (2011);
[15] P. Vagovič *et al.*, J Synchrotron Rad 20 (2013);
[16] E. Hamann *et al.*, IEEE Trans Med Imaging (2014)

From nano particles to nanometric far-field interferometers - the romance between beamlines and x-ray tubes

H. Wen

NHBI, Imaging Physics Laboratory, Betheseda, USA

wenh@nhlbi.nih.gov

In the past half century the potential of x-ray phase-sensitive imaging to reveal hidden information at low radiation doses inspired steady development of new techniques and applications. From an overview of current imaging techniques I will focus on two examples of the latest developments - a simple technique capable of imaging nano particles, and a highly sensitivity technique for low-dose biomedical applications.

A single-image retrieval method for fast and low-dose applications of edge illumination X-ray phase-contrast imaging

P.C. Diémoz[1,2,*], C.K. Hagen[1], M. Endrizzi[1], F. Vittoria[1,2], U.H. Wagner[3], C. Rau[3], I.K. Robinson[2,4], P. Coan[5], A. Bravin[6], A. Olivo[1,2]

Affiliations: [1]Department of Medical Physics and Biomedical Engineering, UCL, WC1E 6BT London, UK; [2]Research Complex at Harwell, Harwell Oxford Campus, OX11 0FA Didcot, UK; [3]Diamond Light Source, Harwell Oxford Campus, OX11 0DE Didcot, UK; [4]London Centre for Nanotechnology, WC1H 0AH London, UK; [5]Faculty of Physics and Institute for Clinical Radiology, Ludwig Maximilians University, 85748 Garching, Germany; [6]European Synchrotron Radiation Facility, 38043 Grenoble, France; [*]**p.diemoz@ucl.ac.uk**

The efficient translation of X-ray phase-contrast imaging from synchrotron facilities to table-top setups has been a long-standing goal since the introduction of such methods, and has been the subject of intensive research efforts in recent years. A widespread availability of phase-contrast imaging in normal laboratories and clinical settings would indeed greatly expand the range of applications that could be targeted, especially in the biomedical field. In this context, the edge illumination (EI) technique has been shown to have the potential to bridge this gap, thanks to the simplicity of its experimental setup, the robustness to mechanical instabilities and its low coherence requirements [1-3].

In order to effectively enable its implementation for biomedical purposes, the acquisition procedure must fulfil specific requirements: 1) be fast, especially for CT and dynamic studies, 2) simple, e.g. require the smallest number of movements of the optical elements – ideally none, 3) enable a low-dose implementation, which is important for small-animal imaging and an essential requirement for clinical applications.

We present here a method based on the EI principle that appears well suited to this aim [4]. Contrary to existing retrieval methods for EI [2,3], which require as input two images acquired in different configurations of the setup, the proposed approach can retrieve the object phase from a single image, thus significantly simplifying the acquisition procedure and reducing data collection times. The method makes the assumption of a quasi-homogeneous object, which has been extensively used in the field of free-space propagation and demonstrated to be applicable to a broad class of biomedical samples.

The proposed method is experimentally demonstrated using both planar and tomographic acquisition geometries. Extension from monochromatic synchrotron radiation to polychromatic beams typical of laboratory setups is also illustrated. Besides showing the high stability of the method with respect to noise, we demonstrate how this approach enables low-dose imaging on a variety of biomedical specimens. Importantly, the developed approach is also suited to other differential phase techniques, such as grating interferometry and analyzer-based imaging, and should thus find application in several areas of research using both synchrotron and laboratory setups.

References

[1] - A. Olivo and R. Speller, Appl. Phys. Lett. **91**(7), 074106 (2007).
[2] - P.R.T. Munro, K. Ignatyev, R. Speller and A. Olivo, PNAS **109**, 13922 (2012).
[3] - P.C. Diemoz *et al.*, Appl. Phys. Lett. **10**3, 244104 (2013).
[4] - P.C. Diemoz *et al.*, J. Synchrotron Radiat., in press.

Dark-field imaging dependence on energy and sample granularity: from synchrotron to X-ray tubes using a single photon-counting detector

S. Gkoumas[1], Z. Wang[1,2], P. Villanueva-Perez[1], G. Tudosie[3], T. Donath[3], C. Brönnimann[3], M. Stampanoni[1,2]

[1]Swiss Light Source, Paul Scherrer Institut, Villigen 5232, Switzerland, [2]Institute for Biomedical Engineering, ETH Zurich, Zurich 8092, Switzerland, [3]Dectris Ltd., Baden 5400, Switzerland, **spyridon.gkoumas@psi.ch**

Over the last few years X-ray grating interferometry is gaining increasing popularity as a phase imaging technique as it offers two main attractive attributes. Firstly, it provides the attenuation, differential phase and dark-field complementary contrast images from the same acquisition data set. Secondly, with the addition of a source grating (G_0), which provides the necessary spatial coherence by creating a Talbot-Lau arrangement, the technique can be used with table-top X-ray tube setups.
The latest generation of single-photon counting detectors offers unique characteristics such as large active area, zero dark noise, high frame rates, small pixel size and adjustable energy thresholds. These features are highly desirable for synchrotron experiments but can also prove crucial for X-ray table-top setups. Moreover, novel room temperature semiconductor sensor materials such as Cd(Zn)Te can provide two dimensional detectors of high quantum efficiency (> 90% for an interferometer of 25 keV design energy).
The aim of this study is to exploit the features of novel single-photon counting detectors and in combination with X-ray grating interferometry imaging explore the potential of achieving structural discrimination between samples of different granularity.
The work presented in this study can be split in two parts. In the first part we examine the visibility reduction or so called “dark-field” signal as a function of energy and sample structural characteristics. The experiments were carried out at the SLS TOMCAT beamline, using the coherence provided by a Si <111> crystal. The energies used range from 16 keV up to 37 keV in 3 keV intervals. Each sample studied consists of single diameter microspheres in water. The two materials of microspheres studied were SiO_2 and polystyrene, each of 2, 6 and 10μm diameter spheres.
In the second part we aim at transferring the synchrotron experiment to a table-top micro-focal X-ray tube Talbot grating interferometer, by exploiting the energy threshold feature of a high-Z sensor, single-photon counting detector such as the Pilatus 3X 300K CdTe detector. By acquiring images of the microsphere samples at increasing energy thresholds and by creating energy bins of 3 keV width we attempt to emulate the synchrotron experiment.
Finally, by cross-comparing the synchrotron and X-ray tube experiments to theoretical calculations we evaluate the sample structural information and the potential of structural sample separation by such a table-top experiment, using a single-photon counting detector in binned threshold mode.

Cartilage and soft tissue imaging using X-rays - Propagation-based phase-contrast CT of the human knee in comparison to clinical imaging techniques and histology

A. Horng[1], E. Brun[2,3], A. Mittone[1,2,3], S. Gasilov[3], L. Weber[3,4], T. Geith[1], S. Adam-Neumair[5], S. Auweter[1], A. Bravin[2], M. Reiser[1], P. Coan[1,3]

[1]Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, Germany, [2]European Synchrotron Radiation Facility (ESRF), Grenoble, France, [3]Department of Physics, Ludwig-Maximilians University, Garching, Germany, [4]Phelma, Institut National Polytechnique de Grenoble (INPG), Grenoble, France, [5]Institute of Anatomy, Ludwig-Maximilians University, Munich, Germany

annie.horng@med.uni-muenchen.de, Tobias.Geith@med.uni-muenchen.de

Objectives: This study evaluates high-resolution tomographic X-ray phase-contrast imaging (PCI) in whole human knee joints for the depiction of soft tissue with emphasis on hyaline cartilage [1]. The method is compared to conventional computed tomography (CT), synchrotron radiation absorption based CT, and magnetic resonance imaging (MRI).

Material and Methods: After IRB-approval, two cadaveric human knees were examined at the European Synchrotron Radiation Facility (biomedical beamline, ESRF/France) using an X-ray beam of 60 keV, a detector with a 90mm² field-of-view and a pixel size of 46x46µm². PCI-CT images were reconstructed with the filtered backprojection algorithm and the Equally Sloped Tomography method. Image quality and tissue contrast were evaluated and compared in all modalities and with histology.

Results: PCI provides visualization of altered cartilage regions invisible in absorption CT with simultaneous high detail of the underlying bony abnormalities. The delineation of surface changes is similar to 3T-MRI using cartilage-dedicated sequences. PCI-CT presents soft tissue contrast surpassing conventional CT with a clear discrimination of ligamentous, muscular, neural and vascular structures. Additionally, PCI images show cartilage and meniscal calcifications that are not perceptible on conventional CT nor MRI.

Conclusions: PCI-CT may facilitate a more complete evaluation of the human knee joint by providing concurrent comprehensive information about cartilage, the underlying subchondral bone and their changes in osteoarthritic conditions.

References

[1] A. Horng, E. Brun, A. Mittone, S. Gasilov, L. Weber, T. Geith, S. Adam-Neumair, S. Auweter, A. Bravin, M. Reiser, P. Coan "Cartilage and soft tissue imaging using X-rays - Propagation-based phase-contrast CT of the human knee in comparison to clinical imaging techniques and histology". Investigative Radiology, 49(9), 627-34 (2014).

Multiple Energy Synchrotron Biomedical Imaging System

B. Bassey, M. Martinson[1], N. Samadi[2], G. Belev[3], C. Karanfil[4], D. Chapman[3, 5]

Physics and Engineering Physics, University of Saskatchewan, Saskatoon, Canada,
[1]Physics and Engineering Physics, University of Saskatchewan, Saskatoon, Canada,
[2]Biomedical Engineering, University of Saskatchewan, Saskatoon, Canada,
[3]Canadian Light Source, Saskatoon, Canada,
[4]Physics, Muğla Sıtkı Koçman University, Muğla, Turkey,
[5]Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, Canada,
bassey.bassey@usask.ca

Imaging has revolutionized the practice of health care since the discovery of x-rays by Roentgen. It is pervasively used for screening, diagnosis, and monitoring of the treatment of disease. The continual drive to improve and expand the amount of information extracted from various imaging modalities has led to the use of multiple x-ray photon energies in computed tomography clinical systems [1]. The interest in multiple energy imaging (MEI) is not only with the use of laboratory x-ray source but also with synchrotron x-ray source [2]. The continuous spectrum available from synchrotron light facilities provides a nearly an ideal source for MEI. For biological subjects a MEI system that can extract multiple endogenous or induced contrast materials as well as water and bone images would be ideal. A novel MEI system, which prepares a focused polychromatic x-ray, has been developed at the Biomedical Imaging and Therapy (BMIT) bend magnet beamline at the Canadian Light Source. The MEI system is made up of a cylindrically bent Laue single (5, 1, 1) silicon crystal monochromator and an area detector. Depending on the crystal's bent radius and the horizontal beam width of the filtered synchrotron radiation (20 to 50 keV) used, the size and spectral range of the focused beam prepared vary. For example, with a bent radius of 95 cm and a 50 mm wide beam, a 0.5 mm wide focused beam of spectral range 27 keV to 43 keV was obtained. This spectral range covers the k-edges of iodine (33.17 keV), xenon (34.56 keV), cesium (35.99 keV), and barium (37.44 keV); some of these elements are used as biomedical and clinical contrast agents. Using the developed MEI system, a test subject composed of iodine, xenon, cesium, and barium along with water and bone were imaged and their concentrations successfully extracted. The MEI system, its operation, the measurements performed including dose rate to the test subject, and the possible biomedical applications will be presented.

References

[1] - J. Fornaro, S. Leschka et al., Insights into Imaging **2**,149 (2011).
[2] - K. Ham and L.G. Butler, Nucl Instrum Meth B. **262**, 117 (2007).

Towards medical applications of grating interferometer at SLS

Z. Wang[1,2], M. Kagias[1,2], C. Arboleda[1,2], S. Gkoumas[1], M. Abis[1,2], M. Buechner[1,2], S. Cartier[1], I. Jerjen[1], K. Jefimovs[1] and M. Stampanoni[1,2]

[1]Swiss Light Source, Paul Scherrer Institut, Villigen 5232, Switzerland, [2]Institute for Biomedical Engineering, ETH Zurich, Zurich 8092, Switzerland, [3]Dectris Ltd., Baden 5400, Switzerland, **zhentian.wang@psi.ch**

Originating from Synchrotron, hard X-ray phase contrast imaging (PCI) [1] has been recognized as a promising technique for medical imaging due to high soft tissue sensitivity and potential dose reduction. Numerous efforts have been made to transfer this technique to (pre-) clinical applications with the emerging of Talbot-Lau grating interferometer and coded aperture method, both allows effectively sensing phase and scattering information of the sample on X-ray tube sources. Successful and promising applications have been demonstrated for both radiography and tomography.

In this work, we present the recent developments at SLS towards medical imaging applications of grating interferometer PCI. We will give a comprehensive introduction of the still ongoing phase contrast mammography project, which demonstrated that phase contrast imaging could provide superior image quality over conventional absorption-based imaging for mammography [2, 3], as well as additional, valuable diagnostic information such as volumetric breast density [4] and microcalcification classification [5]. Towards *in vivo* phase contrast mammography, we will report the latest progress on the development of a Talbot-Lau grating interferometer equipped on a Philips Micro-dose mammography system, featuring a slit-scanning data acquisition mode [6].

Towards phase contrast CT for medical applications, high energy grating interferometer becomes a necessary but poses demanding challenges on fabricating high aspect ratio absorption grating. We report here our progress and experiment results on the high energy PCI using edge-on illumination grating configuration [7] together with single photo counting CdTe detector. This configuration overcomes the current fabrication limits and allows a large field of view under divergent beam.

For clinical applications of the grating interferometer, the employment of the absorption grating G2 constitutes a major obstacle because of the fabrication difficulties and it reduces the flux and dose efficiency. Together with the detector group of Paul Scherrer Institut, we propose a G2-less, single shot PCI method using a direct conversion detector with single photon sensitivity and charge integrating capability. The new detector features a physical pixel size suitable for medical imaging but can achieve micrometer resolution by exploiting the charge sharing effect. The proposed approach allows the absence of G2 without comprising the sensitivity and spatial resolution of the grating interferometer.

References

[1] - Bravin, A. et al., *Phys. Med. Biol.* **58** (2013): R1-R35.

[2] - Stampanoni, M. et al., *Invest. Radiol.* **46** (2011): 801-806.

[3] - Hauser, N. et al., *Invest. Radiol.* **49** (2014): 131-137.

[4] - Wang, Z. et al., *Phys. Med. Biol.* **60** (2015): 4123-4135.

[5] - Wang, Z. et al., *Nat. Commun.* **5** (2014): 3797.

[6] - Arboleda, C., et al., *Opt. Express* **22**, (2014): 15447.

[7] – Thuering, T., et al., *Sci. Rep.* **4** (2014): 5198.

X-ray dark-field imaging (XDFI) optics and its application to medicine

M. Ando, R. Gupta[1], S. Ichihara[2], X. Jiang[3], G. Jin[4], J.-K. Kim[5], H. Kim[5], G. Li[6], J.-H. Lim[7], K. Mori[8], N. Sunaguchi[9], Y. Sung[1], Y. Suzuki[4], T. Yuasa[10]

Research Institute of Science and Technology, Tokyo University of Science, Noda, Japan, [1]Massachusetts General Hospital, Boston, USA, [2]Nagoya Medical Center, Nagoya, Japan, [3]Beijing Advanced Sciences and Innovation Center, CAS, Beijing, China, [4]Kyushu Institute of Technology, Kitakyushu, Japan, [5]Catholic Univ. of Daegu, Daegu, Korea, [6]Beijing Synchrotron Radiation Facility, IHEP, CAS, Beijing, China, [7]Industrial Technology Convergence Center, Pohang Accelerator Laboratory, Pohang, Korea, [8]Graduate School of Information Science, Nagoya Univ., Nagoya, Japan, [9]Faculty of Science and Technology, Gunma University, Kiryu, Japan, [10]Grad. School of Science and Engineering, Yamagata University, Yonezawa, Japan, **msm-ando@rs.noda.tus.ac.jp**

Since 2002 we have been developing X-ray optics, dubbed X-ray Dark-Field Imaging (XDFI) [1], which comprises an asymmetrically-cut monochromator-collimator (MC), a Laue type angle analyser (LAA), and a specimen located between the two (Figure 1). In most cases 35keV has been chosen as the X-ray

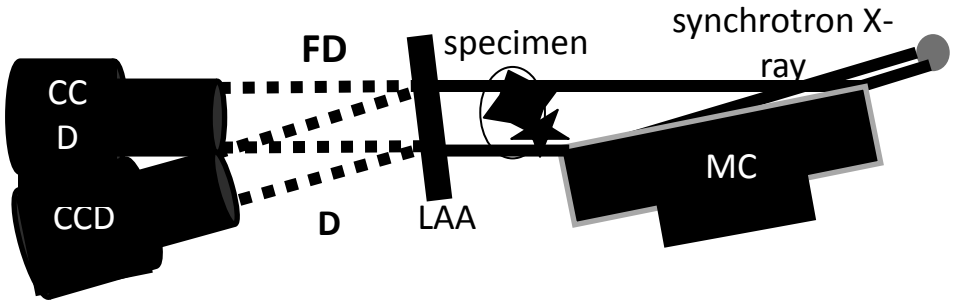


Figure 1: XDFI optics comprising MC (monochromator), specimen and LAA (Laue angle analyzer). Pre-monochromated synchrotron radiation is well collimated by MC that illuminates specimen; refracted x-rays are angularly analyzed by LAA. FD and D will be imaged simultaneously by CCD'S.

energy because of its low absorption and high transmission through biological tissue of interest. The diffraction index of the optics is matched to the (440) silicon crystal plane because of its narrower angular width and sharper angular resolution. Thickness of LAA has been selected so that the X-ray intensity of the beam along the forward diffraction (FD) becomes zero at the Bragg angle while the intensity along the diffraction (D) direction reaches a maximum at precisely the same angle. This gives the highest dynamic range and imaging contrast when measuring the refraction produced by different specimens. We have tested this imaging system for diagnosing breast cancer in the projection domain (i.e., 2D). In 2005, we developed tomographic reconstruction algorithm to demonstrate 3D imaging from 2D projection data [2]. Endoscopy algorithms [3] applied to the 3D tomographic reconstructions of phase contrast images enabled virtual ductoscopy of high-grade ductal carcinoma in situ in 2008 [4]. In addition to 2D, 3D, and endoscopic evaluation of phase data, we have developed a variety of other algorithms for data manipulation and image quality improvement have been developed. These include elimination of artifacts arising from bone and/or calcification [5] and tomographic reconstruction from a limited number of views using compressed sensing. To date, a variety of human internal organs such as breast tissue, arteries, articular cartilage, eye ball have been imaged with the spatial resolution of 10 [6,7]. In order to truly achieve non-invasive X-ray pathology and to replace or augment conventional staining-based pathology, even higher spatial resolution is needed. As predicted by the Takagi-Taupin theory [8], further boost in spatial resolution can be achieved with the order of 2-3 um by thinning the LAA. The ultimate objective of XDFI is to bring such advanced imaging in routine clinical practice both for pathologic evaluation of ex-vivo tissue as well as patient imaging. Enlargement of FOV for clinical view has been initialized by introducing CZ-Fz silicon single crystal.

References [1] M. Ando et al, Jpn. J. Appl. Phys. **41**, L1016 (2002). [2] A. Maksimenko et al, Appl. Phys. Lett. **86**,124105-1(2005). [3] K. Mori et al, IEICE TRANS. INF. & SYST. **79-D**: 809 (1996). [4] S. Ichihara, M. Ando, A. Maksimenko, T. Yuasa, H. Sugiyama, E. Hashimoto, K. Yamasaki, K. Mori, Y. Arai and T. Endo, Virchows Archiv **451**, 41 (2008). [5] N. Sunaguchi, T. Yuasa, M. Ando, Appl. Phys. Lett. **103** 143702-1 (2013). [6] M. Ando et al, European Radiology **23**, 3021 (2013). [7] M. Ando et al, Application of Synchrotron Radiation by World Scientific Publishing in press (2015). [8] Y. Suzuki, Y. Chikaura and M. Ando, J. Appl. Phys. **110** 084902-1 (2011).

The Australian Synchrotron Imaging and Medical Beamline: Facility update

D. Häusermann

Imaging and Medical Beamline, Australian Synchrotron, 800 Blackburn Road, Clayton, Victoria 3168, Australia,
daniel.hausermann@synchrotron.org.au

The Imaging and Medical Beamline (IMBL) opened for users in October 2012 with 50% of the available beamtime for users and 50% for development and commissioning. This ratio is now 75-25 and will be 90-10 in 2016. The source to sample distance can be up to 135m and the beam size up to 4cm x 50cm (white and monochromatic). The IMBL operates in 3 modes. Mode 1 for high dose step-and-shoot (SaS) microbeam radiation therapy (MRT) at 20m, Mode 2 for high speed computed tomography (CT) and dynamic MRT (DynMRT) with vertical microbeams at 35m, Mode 3 for high resolution imaging and CT at 135m in the satellite (SAT) building. The IMBL has an extensive research infrastructure for *in vivo* studies with animals ranging from rodents to sheep and these studies use all 3 Modes.

Two years ago we set 30 June 2015 as the milestone for completing the projects funded by the National Health and Medical Research Council. We capitalized AU$1.4M into labour and embarked on an ambitious design and implementation programme. Despite the aggressive timeline and technical challenges we reached our objectives: The completion of assigned projects on schedule with two longer term developments for delivery in 2016: The Patient Positioning System (PPS) and a high efficiency clinical detector (total budget of AU$1.5M). The main projects are listed below. They will be presented with scientific results from recent experiments.

- Front end upgrade and BPSmart - an intelligent beamline protection EPICS application
- Fast shutters for imaging and radiotherapy
- 7 detectors covering a wide range of field of view, resolution, efficiency and speed
- Streamlined SaS MRT setup for high throughput *in vivo* and cell irradiation
- Dedicated setup for DynMRT of cells and rodents (commissioned *in vivo* in June 2015 – Figure 1)
- Image guided DynMRT using fast monochromatic to white beam switching
- Validated Patient Safety System for DynMRT
- Dosimetry instrumentation and high accuracy spectral calculation
- Dedicated fast-CT setups with dual detector stage
- Versatile sample positioning stage for small animals
- LAPS: Robotic positioning system for large animals (Figure 2)
- PPS: Contract placed for delivery in 2016
- Clinical detector prototype

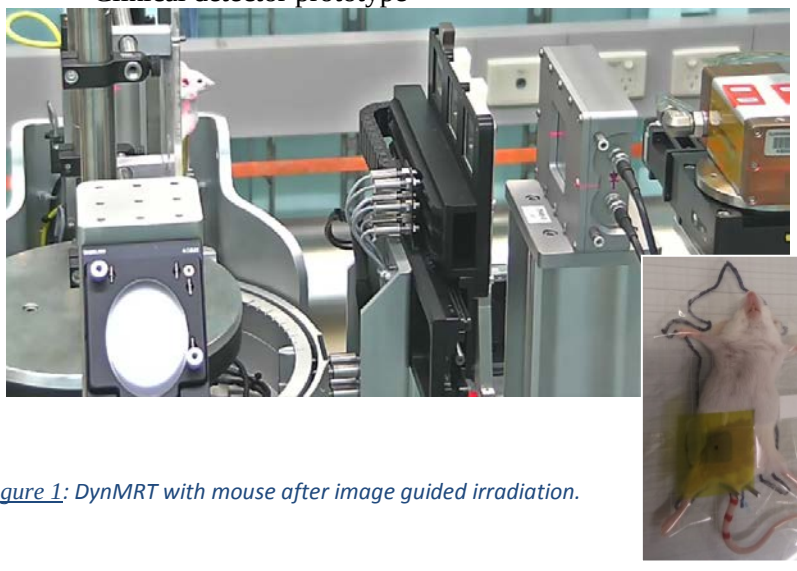


Figure 1: DynMRT with mouse after image guided irradiation.

Figure 2: LAPS in the IMBL SAT building.

Biomedical Imaging @ Elettra: Status Report of the SYRMEP beamline

G. Tromba
On behalf of the SYRMEP Collaboration

Elettra – Sincrotrone Trieste, Basovizza (Trieste), Italy

The SYnchrotron Radiation for MEdical Physics (SYRMEP) beamline at the Elettra light source in Trieste (Italy) has several years of activity in the field of bio-medical imaging.
The beamline is equipped with two imaging stations for users' experiments (with monochromatic and white/pink beam) and a radiological facility for mammography studies on patients.
Biomedical research has been developed following three main directions: clinical mammography, imaging of small animals, high resolution imaging of tissue specimens, organs, biomaterials, etc. Propagation Based phase contrast imaging and Analyzer Based Imaging are routinely applied for different users' experiments.

After completing the clinical protocol of 2D mammography with SR, future plans go in the direction of a new clinical trial of breast CT that combines the potential of Propagation Based (PB) phase contrast imaging with the use of a new CdTe single photon counting detector. The most relevant issue for this purpose regards the optimization of the reconstruction workflow including the pre-processing steps, like the phase retrieval, the reconstruction algorithm and the post-processing.
The beamline is well suited for imaging of small animals and some feasibility studies demonstrated also the possibility to face the *in-vivo* phase. As an example, in this framework, a very challenging application concerns the development of a protocol for morphologic and functional imaging of asthmatic mice.
Computed micro-tomography (microCT), either in PB and in absorption mode, is extensively applied for regenerative medicine purposes to evaluate the morphological structure of tissue engineering scaffolds and to assess their bio-integration, highlighting the new bone formation and the neo-vascularization.
For many of the above mentioned experiments, phase retrieval algorithms are applied to enhance the visibility of the different sample phases prior to the quantitative analysis. New modalities, based on the use of staining procedures, to further increase the image contrast, have been also experienced.

To address the users' request, a new user-friendly software suite has been developed in-house to support absorption and propagation based phase contrast microCT studies by offering single distance phase retrieval pre-processing, filtered back projection and other reconstruction algorithms suitable for low-dose or fast CT, where a reduced number of noisy projections is acquired.

The talk will give an overview of the latest achieved results, highlighting the development programs and the main research perspectives.

Edge illumination dark-field imaging: applications with conventional X-ray sources, achromaticity and high energy implementations.

M. Endrizzi[1,*], F. A. Vittoria[1,2], P. C. Diemoz[1,2], C. K. Hagen[1], A. Zamir[1], G. Kallon[1], D. Basta[1], T. P. Millard[1], P. Delogu[3,4], A. Vincenzi[5], R. Bellazzini[4,5], I. K. Robinson[2,9] and A. Olivo[1,2]

[1]Department of Medical Physics and Biomedical Engineering, UCL, WC1E 6BT London, UK;
[2]Research Complex at Harwell, Harwell Oxford Campus, OX11 0FA Didcot, UK;
[3]Dipartimento di Fisica, University of Pisa, Largo B. Pontecorvo 3, 56127 Pisa, Italy;
[4]INFN, Pisa Section, Largo B. Pontecorvo 3, 56127 Pisa, Italy ;
[5]PIXIRAD Imaging Counters s.r.l., c/o INFN Pisa, Italy;
[6]London Centre for Nanotechnology, WC1H 0AH London, UK;
[*]**m.endrizzi@ucl.ac.uk**

Edge Illumination (EI) [1] is a non-interferometric hard-X-ray imaging technique capable of the quantitative retrieval of the absorption, refraction and ultra-small-angle scattering properties of the sample [2, 3]. It can be adapted for use with synchrotrons, as well as conventional rotating anode [4] and microfocus [5] sources, making it compatible with a variety of environments. Here we focus on the implementation of dark-field imaging with laboratory-scale experimental set-ups. We discuss how the retrieval algorithm can be adapted in the case of non-ideal optical elements [6]. Due to current fabrication limits and desired compatibility with large field of view and high angular acceptance, this situation becomes practically inevitable when high-energy X-ray spectra are used. In addition, we also report on the experimental demonstration of EI's achromaticity. By using an energy-resolved single-photon counting detector we measured the illumination function, describing the sensitivity of the imaging system, across the entire spectrum of a rotating anode, molybdenum target X-ray source. To a large extent, the illumination function remains constant across the energy range investigated, ensuring that the full broadband of a conventional X-ray tube is simultaneously exploited for generating contrast. Moreover, a comprehensive analysis of the influence of a polychromatic spectrum on the retrieval of transmission, refraction and dark-field images is presented, along with a correction algorithm enabling the recovery of quantitative images [8]. The theory is validated on experimental data from a laboratory-scale implementation of the beam-tracking approach [9]. This is also compared to the result obtained by using existing retrieval algorithms, showing that these can cause significant bleeding of the attenuation signal into the dark-field channel, resulting in incorrect interpretation of the experimental data.

References

[1] A. Olivo et al., Med. Phys. **28**, 1610–1619 (2001).
[2] P.R.T. Munro, K. Ignatyev, R. Speller and A. Olivo, PNAS **109**, 13922 (2012).
[3] M. Endrizzi et al., Appl. Phys. Lett. **104**(2), 024106 (2014).
[4] A. Olivo and R. Speller, Appl. Phys. Lett. **91**(7), 074106 (2007).
[5] M. Endrizzi et al., Opt. Lett. **39**(11), 3332–3335 (2014).
[6] M. Endrizzi and A. Olivo, J. Phys. D: Appl. Phys. **47**(50):505102 (2014).
[7] M. Endrizzi et al., Opt. Express *under review*
[8] F.A. Vittoria et al., Appl. Phys. Lett. *under review*
[9] F.A. Vittoria et al., Appl. Phys. Lett. **104**, 134102 (2014).

High-resolution subcellular imaging at the ESRF new nanoimaging beamline: deciphering intracellular targets of anticancer drugs in breast cancer cells

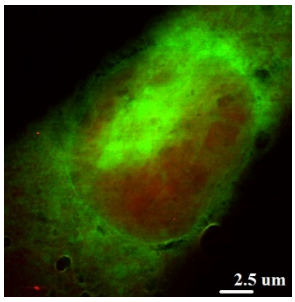
Florin Fus[a,b], Peter Cloetens[a], Siden Top[c], Yang Yang[a], Alexandra Pacureanu[a], Julio Cesar da Silva[a], Anne Vessière[c], Gérard Jaouen[c], Sylvain Bohic[a,b]

[a] ESRF, Grenoble, France, [b] INSERM, U836, Grenoble, France, [c] Sorbonne Universités, UPMC Univ Paris 06, UMR 8232, IPCM, Paris, France

Introduction and Objectives

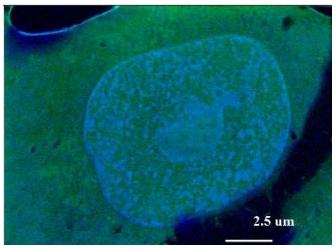
The new state-of-the-art beamline ID16A-NI at ESRF offers unique capabilities for X-ray imaging at nanometer scale delivering a highly coherent, very intense nanofocused beam (> $5\ 10^{11}$ ph/s at $\Delta\lambda/\lambda \sim 10^{-2}$) at high energies (~20nm at 17kev). It is particularly well suited for the investigation of biological samples at high resolution, e.g. the detection and quantification of trace elements [2], such as metals in metal-based drugs in cancer treatment. Triple negative breast cancer tumors, responsible for a high rate of mortality, are a major challenge for breast oncologists since no targeting therapy is currently available for them. Jaouen's group has developed [1] ferrocenyl metal-based drug candidates that can target both hormone-dependent and independent breast cancer cells at low nM range showing encouraging anticancer effects. Our aim is to identify the targeted intracellular compartments where these compounds are active as a main step towards explaining their action mechanisms.

Methods



Osmium derivatives of the ferrocenyl based drug were imaged in MDA-MB-231 breast cancer cell line using both X-ray fluorescence and phase imaging. Various sample preparation techniques were explored. First chemically fixed cells were imaged in 2D (fluorescence at 50 nm and phase imaging at 10 nm pixel size) to reveal the quantitative elemental distribution. Then we imaged 200 nm thin sections prepared by high pressure freezing for fixation followed by cryo-substitution and resin embedding. Finally X-ray fluorescence tomography scans of the entire cells were performed at 150 nm step size.

Results and Conclusions



The 2D fluorescence maps of entire cells consistently revealed a pattern of high Os concentration alongside the nuclear membrane, localization further confirmed by the 3D fluo-tomography data. This work confirms the potential to reveal structural information at unprecedented resolution.

Fluorescence maps of breast cancer cells at 50 nm pixel size. Up: Zn (red) and Os (green). Down: 200 nm section, Cl (green), P (blue)

References

[1] Hillard, E. A.; Vessieres, A.; Jaouen, G., Ferrocene Functionalized Endocrine Modulators as Anticancer Agents. In *Medicinal Organometallic Chemistry*, Jaouen, G.; Metzler-Nolte, N., Eds. Springer Verlag, 2010; Vol. 32, pp 81-118.

[2] Bohic S. et al., Biomedical applications of the ESRF synchrotron-based microspectroscopy platform, Journal of Structural Biology, 177 (2012) 248-258

Shedding light on the safety of ultrasound imaging/therapy using Analyzer Based X-ray Imaging

Zahra Izadifar[1], George Belev[2], Paul Babyn[3], Dean Chapman[1, 2]
[1]University of Saskatchewan, [2]Canadian Light Source, [3]Royal University Hospital, **email: zai206@mail.usask.ca**

The observation of ultrasound generated cavitation bubbles deep in tissue is very difficult. The development of an imaging method capable of investigating cavitation bubbles in tissue would improve the efficiency and application of ultrasound in the clinic. The spatial distribution of cavitation bubbles, driven by 0.8835 MHz therapeutic ultrasound system at output power of 14 Watt, have been observed in water using a synchrotron x-ray imaging technique, Analyzer Based Imaging (ABI). The cavitation bubble distribution was detected by repeated application of the ultrasound and imaging the water tank. The spatial frequency of the cavitation bubble pattern was evaluated by Fourier analysis. Acoustic cavitation was imaged at four different locations through the acoustic beam in water at a fixed power level.

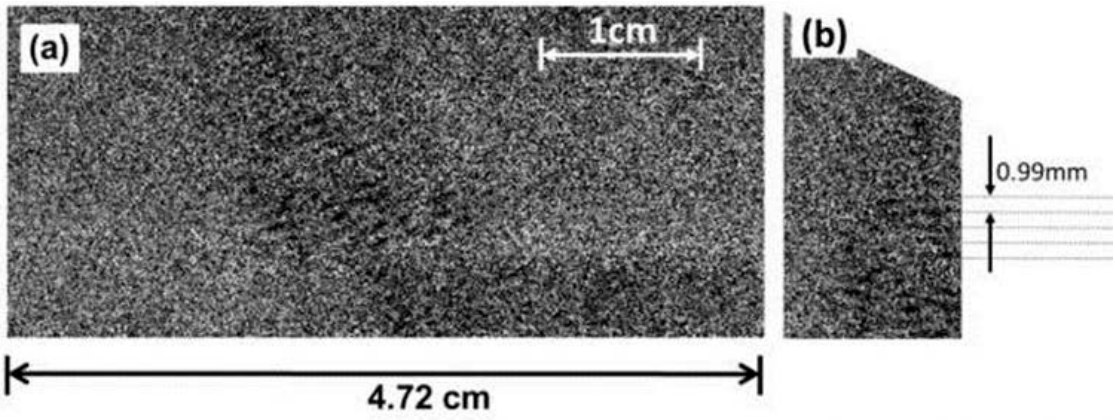


Figure 1: Vertical scan of the whole ultrasound beam of a therapeutic ultrasound system below the tip of the probe at 0.8835 MHz and 14 W (a) the sequence form of cavitation bubbles' location with approximately same intervals between sequences (b).

Quantitative phase contrast computed tomography of large biomedical samples in the hard X-ray domain

S. Gasilov, A. Mittone[1], S. Grandl[2], A. Horng[2], A. Mirone[1], A. Bravin[1], and P. Coan[2,3]

ANKA synchrotron radiation facility, KIT, Eggenstein, Germany, [1]European synchrotron radiation facility, Grenoble, France, [2]Institute for Clinical Radiology, LMU Hospital, Munich, Germany, [3]Faculty of Physics, LMU Munich, Garching, Germany, **sergei.gasilov@kit.edu**

In this work we study approaches for an accurate 3D reconstruction of the hard X-ray index of refraction of biological tissues, which are located inside large and complex biomedical samples. We discuss and demonstrate the unique capability of phase contrast computed tomography (CT) of depicting anatomical and pathological details that are poorly visualized in conventional absorption based radiology. As examples, two challenging radiological cases are considered: the detection of cancer in whole human breasts (thickness up to 10 cm), where the involved tissue have very similar attenuation properties and thus are difficult to be distinguished, and imaging of osteoarthritic animal joints for the examination of fine changes in the cartilage tissue, which is highly radiotransparent.

Experiments were performed at the biomedical beamline (ID17) of the European Synchrotron Radiation Facility at photon energies above 50 keV. This beamline has a number of unique properties, which make it very suitable for the X-ray phase-contrast imaging applications. We have employed the analyzer-based crystal technique to acquire differential phase contrast projections. In order to utilize state of the art CT algorithms in the data reconstruction, we developed a method for the integration of the refractive index gradient vector field [1], and also suggested a regularized phase retrieval algorithm [2]. We found that in combination with an iterative CT algorithm [3] both methods can produce better images than the conventionally used filtered backprojection algorithm with a specialized Hilbert filter function. In all cases, the quality of refractive-based CT images was significantly better than the absorption-based CT images, while the dose delivered to the sample during the CT scan was several times smaller.

We believe that refraction based CT is one of the most promising applications of the X-ray phase-contrast imaging. Proposed methods can be used to retrieve 3D distribution of the refractive index from differential phase images obtained with analyzer-based, grating interferometry, and coded aperture experiments and can find applications in biomedical imaging and material science.

References

[1] – S. Gasilov, A. Mittone, E. Brun, *et al.*, Opt. Express **22**, 5216 (2014).
[2] – S. Gasilov, A. Mittone, A. Horng, *et al.*, Opt. Express **23**, 13294 (2015).
[3] – A. Mirone, E. Brun, E. Gouillart, *et al.*, Nucl. Instr. and Meth. B **324**, 41 (2014).

Quantitative retrieval of absorption, refraction and scattering with Analyzer Based Imaging utilizing a new three image algorithm

F. Arfelli[1,2], A. Astolfo[3], L. Rigon[1,2], R.H. Menk[4]

[1]Department of Physics, University of Trieste, Trieste (Italy)
[2]INFN Sezione di Trieste, Trieste (Italy)
[3]Department of Medical Physics and Biomedical Engineering, UCL, London (UK)
[4]Elettra-Sincrotrone Trieste S.C.p.A, Basovizza, Trieste (Italy)
*arfelli@ts.infn.it

In the last decades different x-ray phase contrast based methods have been developed for improving the image quality and exploiting a novel contrast source forms. As thoroughly discussed in [1] and the references cited within, free space propagation, analyzer based imaging (ABI) and grating based imaging (interferometric and non-interferometric methods) have been extensively applied in various field from material science to biomedical and medical imaging.
One of the main goal of these methods is not only the visibility enhancement of low contrast details in low absorbing sample, but the retrieval of quantitative complementary information of the physical peculiarities of the sample in terms of x-ray absorption, refraction and scattering properties. The latter can be also be considered as ultra-small-angle scattering or multiple refraction effect which turns in dark field images, that very recently attract attention of this research community.
In contrast to multiple images approach [2], in ABI several algorithms and strategies have been developed to extract this information with a reduced number of acquired images in order to lower acquisition time and delivered dose. A minimum of three input images has to be acquired to extract these three parametric images applying a dedicated image processing on a pixel basis is applied. These modalities can be extended from planar images to computed tomography.
Different phase contrast imaging methods have been utilized at the medical beamline SYRMEP of the synchrotron radiation facility Elettra (Trieste, Italy) and a particular effort was carried out on ABI and diffraction enhanced imaging (DEI) [3] studies.
In particular we have developed algorithm methods for DEI where second order Taylor expansion approaches in combination with three image acquisitions are utilized to extract the three parametric images under certain conditions and limitations [4].
To overcome the limitations due the Taylor approximation we have developed a new three image method based on a Gaussian analytical algorithm capable of exploring a wider range of refraction and scattering angles that occur for instance in biological samples. The robustness of the algorithm allows precise assessment of quantities such as refraction angle and ultra-small-angle scattering. In order to assess the capability of the algorithm it has been verified on simulated images and has been applied experimentally to phantoms and to biological samples producing excellent results at biocompatible radiation doses.

References

[1] - Bravin et al., Phys. Med. Biol. **58**, R1–R35 (2013)
[2] - Wernick et al., Phys. Med. Biol., **48**, 3875 (2003)
[3] - Chapman et al., Phys. Med. Biol., **42**, 2015 (1997)
[4] - Rigon et al., Appl. Phys. Lett., **90**, 114102 (2007)

Multiscale understanding and modelling of radiation biodamage

E. Surdutovich[1, 2], A.V. Solov'yov[2]

[1]Department of Physics, Oakland University, Rochester, Michigan 48309, surdutov@oakland.edu
[2]MBN Research Center, Altenhöferallee 3, D-60438 Frankfurt, Germany, solovyov@mbnresearch.com

The multiscale approach to the molecular level assessment of radiation damage in biological targets consequent to irradiation by ions was designed in order to qualitatively and quantitatively describe the effects that take place when energetic ions interact with living tissues, e.g. the Relative Biological Effectiveness (RBE) of radiation [1]. A road towards the understanding physical aspects of ion-beam cancer therapy on the molecular level revealed that this problem has many temporal, spatial, and energy scales, while the main events leading to the cell death happen on a nanometer scale. The multiscale approach is interdisciplinary, phenomenon-based and, having started some years ago, passed several milestones making discoveries on different scales, for review see [1]. Thus, in addition to the traditional pathways of biodamage often related to secondary electrons and free radicals production in cells after irradiation, the multiscale approach also considers a new efficient pathway of DNA damage caused by the nanoscopic shock waves created by the strong local heating in the vicinity of the ion tracks due to the energy deposited by ions [1, 2]. It allows also to evaluate radio-sensitisation effects caused by metal nanoparticles and other radio-sensitising molecular species [3]. This work is especially active now within the currently running European project ITN-ARGENT [4].

The multiscale approach for various irradiation modalities is currently under development.

References

[1] E. Surdutovich, A.V. Solov'yov, Eur. *Phys. J. D, Colloquium paper,* v.68, p.354-(1-30) (2014) [2] P. de Vera, R. Garcia-Molina, I. Abril, A.V. Solov'yov, Physical Review Letters **110**,148104 (2013)
[2] E. Surdutovich, A. Yakubovich, and A.V. Solov'yov, *www.nature.com / Scientific reports*, **3**, 1289 (2013)
[3] A.V. Verkhovtsev, A. V. Korol, A.V. Solov'yov, Physical Review Letters, **114,** 063401 (2015)
[4] http://www.itn-argent.eu/

Dose Thresholds for Destroying Hypoxic Tumor and Stromal Cells With Microbeam Radiotherapy

R.J. Griffin[1], A.J. Parsian[1], Ruud P.M. Dings[1], Nathan A. Koonce[1]

[1] Department of Radiation Oncology, Radiation Biology Division, University of Arkansas for Medical Sciences, Little Rock, AR 7223 USA

jamshidiazema@uams.edu

Although microbeam therapy has been shown to be highly potent at in-beam peak doses of hundreds of Gy, there is interest to use lower doses for clinical safety and to reduce possible normal tissue effects. However, the existence of hypoxia in many solid tumors targeted with microbeam therapy may promote the survival and expansion of cells in the beam when doses are in the range of up to 100 Gy. Furthermore, we have obtained recent evidence that radiation-induced bystander effects are muted or completely absent in our working model of spatial fractionated radiotherapy. We have recently reported on the existence of hypoxic blood vessels and endothelial cells in various tumor models (1). In addition, our recent studies on stereotactic radiotherapy suggest that vascular damage and subsequent indirect tumor cell killing plays an important role in the overall tumor response to high dose conventional radiotherapy (2). Therefore, it was of interest to understand what level of hypoxic radioprotection occurs by using clonogenic analysis in vitro as a first step to characterize what role hypoxia plays in microbeam therapy. Murine endothelial cells (2H11) and a human lung carcinoma cell line (A549) were incubated in aerobic or hypoxic (0.5% oxygen) environments overnight and then exposed to 10-100 Gy x-ray irradiation. We found that endothelial cells had an oxygen enhancement ratio of 3.0 or greater until approximately 50 Gy, while the tumor cells had an OER of 2-2.5 at doses between 20-50 Gy. After these dose thresholds, the hypoxic protection was rapidly lost. This is one of the first reports to our knowledge on the possible protective effects of hypoxia on micro-beam relevant doses of radiation. Further work on characterizing the tissue damage created in hypoxic vs oxic tumor volumes using microbeams is warranted since the protection in 3-dimensional tissue may be even greater than in broad beam, 2-dimensional in vitro studies and various cell types that comprise the tumor may have distinct thresholds for protection and varying levels of bystander effects, or lack thereof due to hypoxia.

1. Koonce N, Raleigh, J, Dings RPM, Griffin RJ Detection of vascular hypoxia as a cancer theranostic. PlosOne. 2015.

2. Song CW LY-J, Griffin RJ, Park I, Koonce NA, Hui S, Kim M-S, Dusenbery KE, Sperduto PW, Cho LC. Indirect tumor cell death after high dose hypo-fractionated irradiation: implications for SBRT and STS. Int J Radiat Onc Biol Phys 2015.

The Munich Compact Light Source – The potential for X-ray microbeam irradiations at a compact synchrotron

K. Burger[1,2,3], E. Eggl[1,2], C. Jud[1,2], M. Dierolf[1,2], B. Gleich[2], K. Achterhold[1,2], K. Ilicic[3], T.E. Schmid[3], J.J. Wilkens[1,3], and F. Pfeiffer[1,2]

[1]Lehrstuhl für Biomedizinische Physik, Physik-Department, Technische Universität München, Garching, Germany,
[2]Institut für Medizintechnik, Technische Universität München, Garching, Germany,
[3]Department of Radiation Oncology, Technische Universität München, Klinikum rechts der Isar, München, Germany
Karin.Burger@tum.de

Recently, the first compact synchrotron x-ray source based on inverse Compton scattering has been installed at the TUM Institute for Medical Engineering (IMETUM), delivering brilliant quasi-monochromatic x-rays tunable from 15 to 35 keV with a flux up to $1x10^{10}$ ph/s.

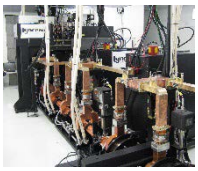


Figure 1: The Munich Compact Light Source developed by Lyncean Technology (ca. 5x2 m^2).

At the Munich Compact Light Source (MuCLS) two endstations will be available: one dedicated to x-ray imaging, e.g. phase-contrast computed tomography [1,2,3] and tensor tomography using a larger field of view and a second one closer to the source, where micro-CT, near-field ptychography, as well as microbeam radiation therapy can benefit from a higher photon flux.
In the last decade, microbeam radiation therapy has attracted attention as it permits to treat tumours with extremely high dose beamlets while sparing healthy skin tissue. Additionally, a higher therapeutic index has been reported as the damage induced by the microbeams affects the tumorous vasculature stronger than the mature vasculature of normal tissue [4]. Requiring a high dose rate, this therapy method has so far been mainly investigated at large synchrotron facilities where patient treatment is highly complex [5]. Therefore, the MuCLS offers great potential to advance x-ray microbeam radiation therapy towards clinical application. In order to demonstrate the feasibility of microbeam production, we will report on the potential of microbeam irradiations at the MuCLS. Tumor cells can be irradiated with spatially separated beamlets created by a multislit collimator and evaluated for cell survival by standard protocols.
Starting from this benchmark experiment, the clinical potential of microbeam radiation therapy will be further explored in animal studies. In parallel to therapy and imaging measurements, the technical components of the MuCLS will be improved in order to achieve, e.g. higher flux and stability.

Supported by DFG Cluster of Excellence: Munich-Centre for Advanced Photonics.

References

[1] S. Schleede et al., PNAS, **109**(44), 17880-17885 (2012)
[2] K. Achterhold et al., Sci. Rep., **3**, 1313 (2013)
[3] E. Eggl et al., PNAS **112**(18) 5567-5572 (2015)
[4] D. N. Slatkin et al., Med. Phys.**19**(6) 1395–1400 (1992)
[5] M. Renier et al., Eur. J. Radiol. **68**(3) 147-150 (2008)

Can Computer Modelling of the Microvasculature help Understanding the MRT Tissue Sparing?

A. Merrem[1], S. Bartzsch[2], J. Laissue[3], U. Oelfke[2]

[1]Max Planck Institute for biophysical chemistry, Göttingen, Germany, [2]ICR, The Institute Of Cancer Research, London, United Kingdom, [3]University of Bern, Switzerland, **Contact: amerrem@gwdg.de**

Although the reasons for the unusually high normal tissue sparing in microbeam radiation therapy (MRT) are not yet completely known, increasing evidence underpins an important role of the vasculature (e.g. [1]). Most likely various factors come into play, e.g. rapid healing of micro-lesions, immune reactions and regeneration originating from the low dose regions. In this study we developed a computer model of a vascular system and simulated the effects of microbeam and broad beam exposure.

The cerebral cortical vascular and capillary network was simulated in a constrained constructive optimization based algorithm [2] by taking various physiological parameters into account [3, 4]. Assuming broad beam and microbeam dose distributions, the damage to the vasculature was calculated by modelling the vessels' radio-sensitivity based on cell survival curves. Thus to each vessel connecting two nodes in the vascular network was assigned a certain probability to be destroyed after radiation exposure. We quantified the damage by different end points, e.g. average cell to vessel distance.

Our simulations reproduced a tissue sparing effect of microbeams when compared to broad beams (Figure 1). At the same integrated dose a higher peak to valley dose ratio (PVDR) inferred a higher vascular damage. We attribute this effect to a convex dose-response relationship. Furthermore we found that the radiation effects depend on the network morphology. In particular the distribution of vessel radii appears to be crucial. This could be an explanation for the differential response of tumours and normal tissue.

The model did not take into account repair mechanisms, the immune system or any bystander signalling effects. Nonetheless our simulations support a factor of 3 in radiosensitivity between broad beam and microbeam irradiations for the same integrated dose. We therefore suggest considering a geometrical contribution to the MRT tissue sparing effect.

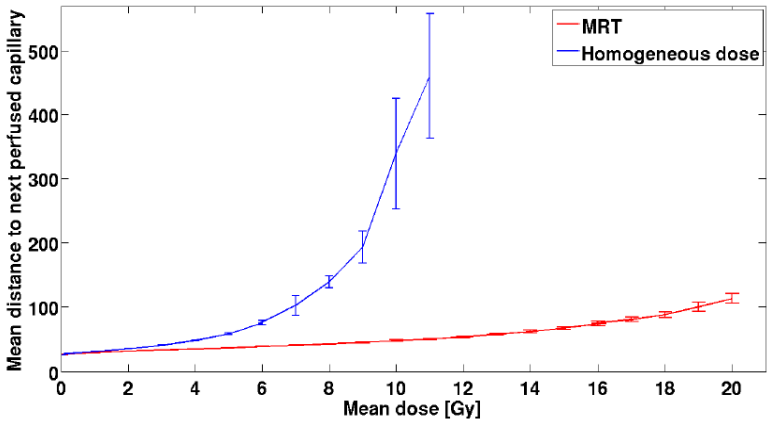


Figure 1: The mean distance of cells to the next perfused capillary after MRT and broad beam irradiation

References

[1] A. Bouchet, et al., International Journal of Radiation Oncology*Biology*Physics, **78,** 1503 (2010)
[2] G. Hamarneh and P. Jassi, Computerized Medical Imaging and Graphics **34**, 605, (2010).
[3] B. Weber, et al., Cerebral Cortex **18,** 2318, (2008).
[4] H. Duvernoy, et al., Brain Research Bulletin **7,** 519, (1981).

Synchrotron Microbeam Radiation
A New Promising Anti-Angiogenic Strategy for Cancer Treatment

Valentin Djonov, Daniel Brönnimann; Marine Potez; *Elke Braeuer-Krisch, Jean Laissue, Audrey Bouchet

Institute of Anatomy, University of Berne, Switzerland
*ESRF - Experiments Division, Grenoble, France. **Email: djonov@ana.unibe.ch**

Background: The results from preclinical and especially clinical trials applying different anti-angiogenic strategies for cancer treatment are rather disappointing. The conceptually new approach, using synchrotron microbeam radiation therapy (MRT), has been applied in different animal models to destroy the immature (new formed) and the tumor vasculature.

Method: We employed the zebrafish caudal fin regeneration model to study the effects of microbeams on the vasculature *in vivo* by comparing mature and immature, i.e. newly formed blood vessels. The anti-angiogenic efficacy of the MRT has been confirmed in orthotopic 9L, gliosarcoma and M16 melanoma models.

Results: Applying a correlative microscopic approach by combining *in vivo* observation with morphological investigation and high resolution micro-angiography the following events have been documented: In the regenerating vasculature of the zebrafish fin, 2-3h after MRT, endothelial cells revealed intracellular vacuolization and appeared swollen and partially disrupted. Severe blood flow perturbation up to complete vascular occlusion has been recorded 6h after MRT. Electron microscopy revealed endothelial cells with disrupted luminal surfaces; the lumen was often engorged with leukocytes and macrophages. At this time point the capillary plexus adopted a striated metronomic pattern, with alternating destroyed and intact zones corresponding to the beam paths. In contrast to the severe changes within the newly formed, immature vessels, the old, i.e. mature vessels remained perfused and structurally intact.
The morphologic alterations of immature vessels of the investigated irradiated tumors resembled closely those described in immature vessels of zebrafish. Due to the vascular toxicity caused by MRT, the intratumoral vessel density estimated by micro-angiography was dramatically reduced after treatment. In contrast, the normal blood vessels from the surrounding normal tissues were barely affected by MRT. As a consequence the tumor progression was significantly reduced with no detectible effects on the normal brain.

Conclusions: The vascular toxicity induced by MRT depends on the stage of capillary maturation and appears in the first hours/days after irradiation. Newly formed, immature (tumor) capillaries are highly sensitive to MRT, in contrast to mature vessels of the surrounding normal tissue that are barely affected. A single short MRT application decreased the tumor growth and increased significantly the survival of the animals and this without apparent effects in the normal tissue. The selective vascular damage mediated by MRT could serve in creating new and more efficient anti-angiogenic treatment strategies against cancer and angioproliferative vascular diseases.

Radiotherapy by Photoactivation of Iron Nanoparticles and Mössbauer effect

P. Gimenez[1, 2], H. Elleaume[1], JL. Ravanat[2]

[1]INSERM U836, GIN, ESRF, [2] INAC/SCIB/LAN CEA Grenoble, Univ. Grenoble Alpes, **paul.gimenez@esrf.fr**

The Mössbauer effect [1], the resonant and recoil-free absorption and subsequent re-emission of γ rays by Mössbauer isotopes (e.g. ^{57}Fe) leads to the emission of many Auger electrons (a single Auger event is comparable to more than 10^5 photon absorption events). These high LET electrons can induce clustered DNA damages (including Double Strand Breaks (DSB) and Locally Multiple Damaged Sites (LMDS)) if emitted in the direct vicinity of DNA.
Dose (in J/kg) enhancement using Mössbauer effect has been first described *in vitro* by Mills et al. [2]. Since then, several studies have obtained conflicting results. The divergence of the data is mainly due to stringent experimental conditions mandatory to get Mössbauer resonance: photon energy of 14.4 keV (for ^{57}Fe), crystalline network of the atom…

Since Synchrotron radiation properties are well suited for Mössbauer resonance (high fluence and precise control on the irradiation energy), we propose to evaluate the efficiency of iron nanoparticles (NPFe) enriched in ^{57}Fe to enhance dose deposition during radiotherapy. A sharp increase is expected in presence of nanoparticles.

A preliminary experiment has been carried out at the European Synchrotron Radiation Facility ID18 (Mössbauer-dedicated beamline). Under irradiation at 14.4 keV (delta E = 0.65 meV), NPFe (synthesized as Choi described previously [3]) embedded in agarose gel produce a Nuclear Inelastic Scattering spectrum giving a density of phonon states similar to bulk iron as measured by Handke [4]. This result indicates that Mössbauer interactions can happen at room temperature in NPFe in a material with tissue-like rigidity.

In parallel to this study, dose-enhancement produced by the photoelectric effect was also evaluated. F98 rodent glioma cells incubated with NPFe and irradiated at various monochromatic energies on the Beamline ID17 (30 to 80 keV) present a decreased survival rate due to photoelectrons produced by the interactions of low energy radiations with heavy atoms.

We observed by ICPMS a very high concentration of the same alginate-coated magnetite nanoparticles in F98 rat glioma cells after 24h of incubation, up to a hundred of pg/cell. Those results have been confirmed by a 2D-X Ray microfluorescence experiment at the ID16B Beamline of the ESRF, showing high concentration of nanoparticles around the nucleus.

To conclude, the performed experiments refine our comprehension of the physics of Mössbauer interactions, as well as confirm the theoretical basis for its application to enhance radiotherapy efficacy, and provide nanoparticles suitable to continue the study.

References

[1] - R. L. Mössbauer, Z. Physik **151**, pp. 124-143 (1958).
[2] - Mills *et al.*, Nature **336**, pp. 787-789 (1988).
[3] - Choi *et al.*, Radiation Oncology **7**, 184 (2012).
[4] – Handke *et al.*, PRL B **71**, 144301 (2005).

Achievements and perspectives in medical applications at the ESRF-ID17 beamline

A. Bravin[1] on behalf of the whole ESRF-ID17 team

[1]European Synchrotron Radiation Facility, BP220 F-38043 Grenoble
bravin@esrf.fr

The ID17 biomedical beamline of the ESRF is dedicated to applications in biomedical imaging, radiation biology and radiation therapy; its operation covers multiple scales, going from cells to humans. Several ancillary laboratories serve users in the cultivation of cells, small animals care and management and post-irradiation analysis. X-rays originates from two wiggler sources installed in the ESRF storage ring; the wigglers (respectively of 125 mm and 150 mm period) can operate simultaneously to provide an intense, quasi laminar beam. The beamline operates two experimental hutches: the MRT station, located at 38-50 m from the source and the imaging-therapy station at 145-157 m. At the MRT hutch both polychromatic (up to ~350 keV) and monochromatic (33-120 keV) beams are made available to users; monochromatic beams are delivered to the second hutch covering the energy range 20-200 keV.

The MRT station has been developed to perform preclinical experiments using extremely intense, spatially fractionated, quasi parallel X-ray beams, delivered by a single or multiple ports. Thanks to an in-house developed image guidance system, these beams can be delivered to the target with submillimetric precision. The user programs include the evaluation of tissue sparing and potential therapeutic use of microbeams to treat tumors [1-3] or central nervous system pathologies [4-5].

The second station hosts experiments profiting of the other peculiarity of ID17, i.e. the possibility to deliver intense, quasi monochromatic and wide (up to ~ 150 mm) beams, in a broad energy range. These beams are used to develop innovative radiation therapy strategies [6-8], to irradiate patients recruited within the Stereotactic Synchrotron Radiation Therapy clinical trials program [9] and to perform in-vitro and in-vivo high resolution medical imaging, using dual energy or propagation-, analyzer- and coded aperture-based phase contrast imaging techniques. Detection systems having pixel sizes covering the range 3.5 - 350 micron are available to the user community to fit with the experimental requirements. The imaging programs include functional lung imaging [10], neuroimaging [11] and the development of techniques for low dose / high resolution computed tomography [12-14].

[1] A. Bouchet et al. *Radiother Oncol. 2013 Jul;108(1):143-8*
[2] A. Bouchet et al. *International Journal of Cancer 2015 1;136(11):2705-16*
[3] E. Schültke et al. *PLoS ONE 8(1): e54960 (2013)*
[4] B. Pouyatos et al. *Neurobiol Dis. 2013 Mar;51:152-60*
[5] P. Romanelli et al. *PLoS ONE 8(1): e53549*
[6] P. Deman P et al. *Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):e693-700*
[7] F. Taupin et al. *Physics in Medicine and Biology 2015; 60(11):4449-4464*
[8] C. Ceresa et al. *Anticancer Res. 2014 Oct;34(10):5351-5*
[9] M. Renier et al. *European Journal of Radiology 68S (2008) S147-S150*
[10] S. Bayat et al. *Anesthesiology. 2013 Jul;119(1):89-100*
[11] M. Fratini et al. *Scient. Rep 5: 8514*
[12] A. Horng et al. *Investigative Radiology, 2014 Sep;49(9):627-34*
[13] P. C. Diemoz et al. *Physical Review Letters 2013, 110, 138105*
[14] Y. Zhao et al. *PNAS 2012, November 6, vol. 109, no. 45, 18290–18294*

X-ray biomedical imaging and its applications at SSRF

Tiqiao Xiao, Honglan Xie, Biao Deng, Guohao Du, Rongchang Chen, Yanan Fu, Han Guo, You He, Guanyun Peng, Yuqi Ren, Yudan Wang, Yanling Xue, Guangzhao Zhou

Shanghai Institute of Applied Physics, Chinese Academy of Sciences, No.239 Zhangheng Road, 201204 Shanghai, China, **Email: tqxiao@sinap.ac.cn**

The X-ray imaging beamline (BL13W1) at SSRF aims at developing and evaluating the effectiveness of SR-based imaging techniques in planar or CT modalities, which found extensive applications in biomedical research [1,2]. In recent years (2012, 2013, 2014), 66 groups of biomedicine users, coming from 20 universities, 6 institutes and 11 hospitals, located in 10 provinces of China, carried out their experiments at BL13W1 with 68 publications in total. The main biomedical X-ray imaging methods include micro-tomography, local CT imaging and quantitative imaging [1,3]. Some of the typical medical applications will be presented. The SR-μCT is utilized to evaluate the bone regeneration and vessel formation of medical engineering materials of a rabbit [4, 5]. Biodegradation control by brushite coating on Mg-Nd-Zn-Zr alloy for mandibular bone repair, is also investigated[6]. Functional in vivo imaging of cerebral lenticulostriate artery is carried out[7]. Three-Dimensional Structure of Dermal Tissues were nondestructively obtained and analyzed by phase contrast micro-CT[8]. Morphology and function investigation on pharmacy are also pushed forward[9]. New imaging methods, including dynamic CT based on monochromatic beam[10], X-ray fluorescence CT[11] and stereo imaging with three X-ray beam are under developing, which will bring new chance for biomedical research.

References

[1] Xiao, T. Q., Xie, H. L., Deng, B., Du, G. H.,Chen, R. C.,The progresses of X-ray imaging methodology and its applications at Shanghai synchrotron radiation facility, Acta Optica Sinica 34(1) 1000015514(2014)

[2] Chen, R., Liu, P., Xiao, T.,Xu, L. X., X-ray Imaging for Non-destructive Microstructure Analysis at SSRF, Adv. Mater. DOI: 10.1002/adma.2014029565712(2014)

[3] Wenhao Chen , Yudan Wang, Huiqiang Liu, Biao Deng, Yushuang Yang, and Tiqiao Xiao, Pseudo-global tomography for local micro-computed tomography with high-brightness synchrotron X-rays, Chinese Optics Letters 12(2), 023401(2014)

[4] Jing Zhang, Xiaoyu Ma, Dan Lin, Hengsong Shi, Yuan Yuan, Wei Tang, Huanjun Zhou, Han Guo, Jiangchao Qian, Changsheng Liu, Magnesium modification of a calcium phosphate cement alters bone marrow stromal cell behavior via an integrin-mediated mechanism, Biomaterials. 53,Pages 251-264 (2015)

[5] Cao, L., Wang, J., Hou, J., Xing, W.,Liu, C., Vascularization and bone regeneration in a critical sized defect using 2-N,6-O-sulfated chitosan nanoparticles incorporating BMP-2, Biomaterials. 35(2) 684-6985617 (2014)

[6] Xingmin Guan, Meiping Xiong, Feiyue Zeng, Bin Xu, Lingdi Yang, Han Guo, Jialin Niu, Jian Zhang, Chenxin Chen, Jia Pei, Hua Huang, and Guangyin Yuan, Enhancement of Osteogenesis and Biodegradation Control by Brushite Coating on Mg–Nd–Zn–Zr Alloy for Mandibular Bone Repair, ACS Applied Materials Interfaces 6: 21525-21533 (2014).

[7] Xiaojie, Lin ; Peng, Miao ; Zhihao, Mu ; Zhen, Jiang ; Yifan, Lu ; Yongjing, Guan ; Xiaoyan, Chen ; Tiqiao, Xiao ; Yongting, Wang ; Guo-Yuan, Yang, Development of functional in vivo imaging of cerebral lenticulostriate artery using novel synchrotron radiation angiography, Physics in Medicine and Biology 60 1655 (2015)

[8] Jiang Y, Tong Y, Xiao T, Lu S., Phase-Contrast Microtomography with Synchrotron Radiation Technology: A New Noninvasive Technique to Analyze the Three-Dimensional Structure of Dermal Tissues. Dermatology 225(1):75-80(2012).

[9] Xianzhen Yin, Haiyan Li, Zhen Guo, Li Wu, Fangwei Chen, Marcel de Matas, Qun Shao, Tiqiao Xiao, Peter York, You He, Jiwen Zhang, Quantification of Swelling and Erosion in the Controlled Release of a Poorly Water-Soluble Drug Using Synchrotron X-ray Computed Microtomography, The AAPS Journal 15 1025-1034(2013)

[10] L. Xu, R. Chen, G. Du, H. Xie and T. Xiao, Fast X-ray micro-tomography for low-Z materials, JINST, doi:10.1088/ 1748-0221/10/03/C03010:1-9(2015)

[11] Biao Deng, Guohao Du, Guangzhao Zhou, Yudan Wang, Yuqi Ren, Rongchang Chen, Pengfei Sun, Honglan Xie and Tiqiao Xiao, 3D elemental sensitive imaging by full-field XFCT, Analyst, DOI: 10.1039/c4an02401j(2015).

BMIT Facility at the Canadian Light Source, biomedical applications and future plans

T. W. Wysokinski[1], G. Belev[1], D. Miller[1], A. Webb[1], N. Zhu[1], L. D. Chapman[1,2], D. Cooper[2]

[1] Canadian Light Source, Saskatoon, SK, Canada, [2] Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, SK, Canada, **bmit@lightsource.ca**

The BioMedical Imaging and Therapy (BMIT) facility located at the Canadian Light Source, provides synchrotron-specific imaging and radiation therapy capabilities [1-5]. There are two separate endstations used for experiments currently: the Bending Magnet (BM) beamline POE-2 endstation that was opened for general user program in 2011 and the Insertion Device (ID) beamline SOE-1 endstation that started general user program in 2015. Core research programs include human and animal reproduction, cancer imaging and therapy, spinal cord injury and repair, cardiovascular and lung imaging and disease, bone and cartilage growth and deterioration, mammography, developmental biology, gene expression research as well as the introduction of new imaging methods.

The bending magnet beamline 05B1-1 (See Fig. 1) is designed for X-ray imaging and irradiation experiments primarily in animals ranging in size from insects to mice to small dogs and cats, as well as tissue specimens including plants. The monochromatic spectral range spans 15–40 keV, and the beam is more than 200 mm wide in the experimental hutch. In addition users have access to filtered white beam which can be used for imaging, irradiation, and X-ray instrumentation development experiments. Several different imaging modalities can be used at the BM beamline. In addition to standard absorption X-ray imaging with both monochromatic and polychromatic X-rays, users have access to synchrotron imaging modalities such as K-edge subtraction imaging (KES), phase contrast imaging (PCI) and analyser based imaging (ABI) both in projection and CT modes. This is mainly accomplished through having a number of detectors and utilizing a flexible set-up strategy. Experimental geometry can be varied as needed, including sample-to-detector distance up to 6 meters.

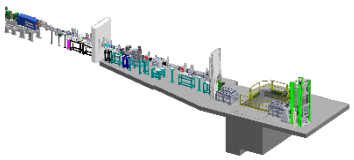


Figure 2 Model of the 05B1-1 Beamline

The insertion device beamline 05ID-2 SOE-1 endstation is designed for imaging and therapy research in animals, with the current focus on medium size animals such as piglets, rabbits, dogs and sheep. The monochromatic spectral range spans 25 to 140 keV, and the beam is more than 220 mm wide in the experimental hutch.
The second endstation (POE-2) of the ID beamline will provide access to white beam in the future for therapy and irradiation experiments.

BMIT facility provides unique in North America synchrotron-specific imaging capabilities that have proven to be powerful tools for visualization of soft tissue. Several different X-ray detectors are available with resolutions ranging from 2 μm to 200 μm. With the opening of the ID beamline the established imaging program will extend to higher energies (up to 140 keV) and a higher capacity positioning system (up to 450 kg).

References

Chapman LD, (2007) CLSI Doc. No. 26.2.1.1 Rev. 0.A
Chapman LD, (2006) CLSI Doc. No. 26.2.1.2 Rev. 0
Wysokinski TW et al. (2007) NIM A 582:73-76
Wysokinski TW et al. (2013) J. Phys: Conf Ser 425: 07
Wysokinski TW et al. (2015) NIM A 775:1-4

MRT – Solved problems and unmet challenges to establish a new paradigm in radiation therapy

U. Oelfke and S. Bartzsch

ICR/RMH London – **uwe.oelfke@icr.ac.uk**

The fascinating idea of utilizing grids of spatially modulated radiation beams for a broadening of the therapeutic window in radiation therapy dates back to early experimental evidence in the 1960s. However, despite enormous research efforts over the last 50 years, mostly focussed on technology development and creation of a growing pool of favourable pre-clinical biological data, no clinical trials to demonstrate the superior efficacy of micro-beam therapy (MRT) have been launched yet.

Admittedly, the technical challenges for a reliable and safe delivery of exorbitant high doses with astronomical dose rates when compared to conventional radiation therapy are enormous and there were many of them, ranging from the geometrical accuracy for the fabrication and placement of collimator systems, the design of safe beam monitoring and control systems, the build of new radiation detectors with extreme spatial and temporal resolution to the formulation of dosimetry protocols, dose algorithms and treatment planning software. However, almost all of these challenges were addressed within the recent decade by efforts spearheaded by ESRF and collaborators, who currently form the COST action initiative.

However, as natural with the introduction of any potentially step-changing technology into clinical work there remains a number of problems to be solved. The most prominent one is to unlock the dominant biological mechanism responsible for the differential radiobiological effect of MRT between healthy tissues and tumours. There is a number of valuable hypothesis being discussed, but the experimental efforts lack guidance from any serious modelling. Currently our insights are quite limited and far from being convincing to the general community of oncology. A better understanding of the underlying mechanism of MRT will also enable the further systematic enhancement of the clinical effect achievable by grid-optimization or combined treatments with radio-sensitizers or chemotherapy. Other challenges to be discussed are the identification of the most promising treatment site and the development of an integrated, non-cyclotron based treatment technology platform.

Fluorescent Nuclear Track Detector technology – high resolution imaging tool for photon and charge particle dosimetry and spectroscopy

M. S. Akselrod[1,2], J. B. Bartz, E[1,2], V. V. Fomenko[1], and E. Bräuer-Krisch[3]

[1] Landauer, Inc., Crystal Growth Division, 723 ½ Eastgate St., Stillwater, OK 74074, USA
[2] Oklahoma State University, Physics Department, Stillwater, OK 74078, USA
[3] ESRF-The European Synchrotron, 71 Avenue des Martyrs, 38043 Grenoble, France

The next technological breakthrough in tools for medical dosimetry, radiobiology and radiation protection was achieved with Fluorescent Nuclear Track detectors (FNTD) [1] that has some important advantages in imaging and quantitative measuring of photon, neutron, and high energy heavy charge particles (HCP) fields. New detectors are made of luminescent carbon- and magnesium-doped aluminum oxide single crystals (Al_2O_3:C,Mg) having complex luminescent aggregate defects. FNTD imaging instrumentation [2] is based on confocal laser scanning fluorescent microscopy and novel image processing technique. The results of experiments in synchrotron microbeam radiation therapy [3], neutron detection, LET spectroscopy of HCPs, fragmentation, 2D and 3D imaging of particles will be presented. Special attention will be dedicated to the possible use of FNTDs as a radiobiology research tool and QA tool in radiotherapy [4].

Crystals. Al_2O_3:C,Mg crystals have high concentration of single and double oxygen vacancies associated with impurities and forming aggregate defects with unique optical properties. These color centers undergo radiochromic transformation which remains thermally stable up to 600ºC and are insensitive to ambient light. FNTDs do not require chemical etching before imaging. Images of tracks are obtained in fluorescent contrast and the readout can be repeated multiple times without erasure. If needed FNTDs can be erased and reused after bleaching with pulsed UV laser light.

Radiological characteristics: The main advantage of FNTDs is their ability to image individual ions and even delta electrons with diffraction limited resolution. At low fluences and doses individual 3D track image reconstruction and spectroscopic LET measurements were demonstrated. At higher doses a special "analogue" image processing algorithm involving dual color fluorescent imaging is applied for radiation dose measurements.

Commercial FNTD reader: Two varieties of fully automatic table-top FNTD readers for routine neutron dosimetry and advanced radiobiology research were developed. The readers allow one to load up to 200 detectors on a tray, to read their engraved IDs and automatically scan and process 3D stacks of fluorescent images for track reconstruction.

[1] M.S. Akselrod, and G.J. Sykora, *Fluorescent Nuclear Track Detector technology - a new way to do passive solid state dosimetry*, Radiat. Meas.(2011) **46** 1671-1679.
[2] M.S. Akselrod, V. V. Fomenko, J. A. Bartz and T. L. Haslett, *Automatic Neutron Dosimetry System Based on Fluorescent Nuclear Track Detector Technology*, Radiat. Prot Dosim. (2014), **161**(1-4) 86–91.
[3] J.A. Bartz, G.J. Sykora, E. Bräuer-Krisch, M.S. Akselrod, *Imaging and dosimetry of synchrotron microbeam with aluminum oxide fluorescent detectors*, Radiat. Meas., **46** (2011) 1936-1939
[4] S. Greilich, J.-M. Osinga, M. Niklas, F.M. Lauer, G. Klimpki, F. Bestvater, J.A. Bartz, M.S. Akselrod, O. Jäkel, *Fluorescent nuclear track detectors as a tool for ion-beam therapy research*, Radiat. Meas. (2013) **56** 267-272.

Characterisation of a Synthetic Diamond Detector for Experimental Dosimetry in MRT

J. Livingstone[1], J. –F. Adam[2,3,4], A. W. Stevenson[1,5], C. J. Hall[1], D. Pelliccia[1,6] and D. Häusermann[1]

[1]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria, Australia
Jayde.Livingstone@synchrotron.org.au
[2]Université Joseph Fourier, Grenoble, France
[3]INSERM U836, Team 6, Grenoble, France
[4]ID17, European Synchrotron Radiation Facility, Grenoble, France
[5]CSIRO Manufacturing Flagship, Clayton South, Victoria, Australia
[6]School of Applied Sciences, RMIT University, Melbourne, Victoria, Australia

Microbeam radiation therapy (MRT) is a preclinical treatment under development on the Imaging and Medical Beamline (IMBL), Australian Synchrotron. It uses spatially fractionated x-ray microbeams with a width of 50 μm and 400 μm pitch. The x-ray beam, which has a mean energy of approximately 100 keV in the treatment enclosure, is generated by a wiggler source and collimated by a tungsten multislit collimator. Preclinical studies on other synchrotron beamlines have previously demonstrated preferential tumour damage and sparing of surrounding normal tissue [1-3]. A synchrotron source is necessary to produce the high dose rates, high dose gradients and minimal beam divergence required for MRT to maintain a highly collimated, spatially fractionated array of microbeams. The ratio between the dose in the microbeams and the dose between the microbeams, known as the peak-to-valley dose ratio (PVDR) is thought to be of therapeutic importance, with the valley dose believed to be a primary factor influencing the normal tissue tolerance [3]. It is thus important to be able to perform absolute dosimetry and accurately measure the PVDR.

Dosimetry for MRT is challenging due to the inherent beam properties of MRT. Small field sizes and large dose gradients can produce large uncertainties caused largely by the partial volume effect. Additionally, a number of dosimeters exhibit energy dependence for keV x-rays and ion recombination effects at high dose rates. The PTW microDiamond detector has been identified as a potential MRT dosimeter due to its small 2.2 mm × 1 μm cylindrical sensitive volume. The purpose of the study was to characterise the microDiamond detector in broadbeam and microbeams to determine its suitability for MRT dosimetry. The energy dependence has been investigated and characterised and the dose rate dependence was found to be minimal over the dose range 1—600 Gy. Preliminary measurements of microbeam profiles and PVDR were also promising. Measurements will be repeated using the recently commissioned dedicated MRT system to optimise the procedure with a view towards developing an absolute dosimetry protocol. Results will be discussed in the presentation.

References

[1] – J. A. Laissue, et al., *Int. J. Cancer*, **78**, 654—660 (1998).
[2] – A. Bouchet, et al., *Int, J. Radiat. Oncol.Biol. Phys.***78**, 1503—1512 (2010).
[3] – R. Serduc, et al. *Phys. Med. Biol.*, **53**, 3609—3622 (2008).

In vivo dosimetry for Synchrotron Stereotactic Radiation Therapy

D. Reynard[1], H. Elleaume[1], T. Brochard[2], J.F. Adam[1]
[1]INSERM U836, Grenoble Institute of Neuroscience, UJF, Grenoble, FRANCE
h.elleaume@esrf.fr
adam.jeanfrancois@gmail.com
dimitri.reynard@esrf.fr
[2]ESRF ID17 Medical Beamline, Grenoble, FRANCE
brochard@esrf.fr

The first clinical study of therapeutic applications of Contrast-Enhanced Synchrotron Stereotactic Radiation Therapy (SSRT) is underway since June 2012 at the European Synchrotron Radiation Facility (ESRF). The phase I-II clinical trial is designed to test the feasibility and safety of SSRT through a dose escalation protocol. So far, 10 patients suffering from brain metastasis of medium to small volume have already been treated using this modality. A localized dose enhancement is obtained due to higher photoelectric effect rate in the target and is directly related to the amount iodine located in a given voxel of tissue (about 10% per mg/mL of iodine). The 3D iodine content in a given patient is derived from the 3D CT acquisition obtained during the dosimetry CT procedure and associated treatment planning [1] . *In vivo* dosimetry (i.e., experimental dosimetry in real time during the treatment) would be a serious added value to the project, in terms of online dose monitoring and quality assurance. It is challenging to perform *in vivo* dosimetry with the currently available conventional clinical techniques [2] . Entrance measurements using semiconductor detectors lead to significant incoming beam perturbations (medium energy x-rays) whereas it's complicated to set-up portal imaging techniques, as the iodine content is not taken into account. The idea is to measure the iodine fluorescence X-rays yield emitted from the target during the irradiation. This can be achieved using spectrometry techniques and iodine K_α peaks analysis. Our first approach consists in developing a 0D model with a CZT detector pointing on the irradiation isocenter to characterize the relationship between peak contents and average iodine concentration obtained in the tumor during irradiation [3]. Fluorescence from iodine tubes of different concentrations (0.5 to 20 mg/mL) were acquired in air and inserted into an anthropomorphic radiosurgery phantom. The same setup has been recently used on the last patient treated in SSRT at the ESRF. The detector was pointing the isocentre and the spectra were recorded during the three irradiation incidences.

The iodine concentration was plotted *versus* the number of counts in the fluorescence channel for the tubes in air. We notice a non-linearity in the curve due to self-absorption [4]. Concerning the signal obtained in patients, it should be furthered analyzed in order to retrieve the concentration. For this purpose, simulations should be used, using a priori information from the dosimetry CT scans.. A potential improvement of the technique would be its transfer to a 3D modality using a pixelated spectrometric detector.

References

[1] L. Obeid,*et al. J. Cereb. Blood Flow Metab.*, vol. 34, no. 4, pp. 638–45, Apr. 2014.
[2] B. Mijnheer,et al. *Med. Phys.*, vol. 40, no. 7, p. 070903, Jul. 2013.
[3] A. M. Rene Van Grieken, "Handbook of X-Ray Spectrometry, Second Edition,." [Online].
[4] C. Hall, *J. Instrum.*, vol. 8, no. 06, pp. C06007–C06007, 2013.

Synchrotron Radiation Therapy: ongoing development and long term prospect

J. Balosso

University Grenoble Alpes, Grenoble, France. **JBalosso@chu-grenoble.fr**

Therapeutic applications of the Synchrotron Light (SL) are becoming a reality. As an experimental radiotherapy, the present principles of use remain rather close to the classical radiotherapy performed in oncology. For instance, the very first human application of SL, the ongoing SSRT trial (stereotactic synchrotron radiation therapy), is mostly mimicking stereotactic arctherapy and is applied to the same patients than those treated at the hospital [1].
However, this is only a transitory step allowing to go progressively from well known situations to more innovative ones.

This presentation will address, first, the starting points of the different types of SL clinical study applications we could develop with the present type of patients we are recruiting at ESRF, namely pauci-brain-metastatic patients. Early medical exploration of SSRT and of MRT (micro beam radiotherapy) [2] will be described.

Then, as a second generation of study, the first possibilities to address real orphan diseases able to be alleviate or hopefully cured by SL will be described. This could be particular forms of meningioma, very resistant life threatening epileptic conditions [3], diffuse brain micrometastatic evolution, etc. These rare diseases could be a reason for multicentric recruitment of the patients and for attractive international collaborations.

Finally very innovative applications combining different possibilities, specific to SL, will be described as narrow spectra high dose rate therapy with nanoparticles for large target volumes; or very high dose rate “white” SL delivered as micro beams for small target volumes, both being fractionated.

These items are presented as an introduction and an invitation for imagination and creativity about the use and the applications of SL, which is still in its infancy. From the selection of the most useful and applicable procedures could come more narrow definitions of specific machines [4] devoted to produce either monochromatic X ray or huge dose rate X ray beams or both!

References

[1] - Brauer-Krisch E, et al., Medical physics aspects of the synchrotron radiation therapies: Microbeam radiation therapy (MRT) and synchrotron stereotactic radiotherapy (SSRT), Physica Medica (2015), http://dx.doi.org/10.1016/j.ejmp.2015.04.016

[2] - Bravin A, et al., SYRA3 COST Action - Microbeam radiation therapy: Roots and prospects, Physica Medica (2015), http://dx.doi.org/10.1016/j.ejmp.2015.06.002

[3] - Studer F, et al., Synchrotron X-ray microbeams: A promising tool for drug-resistant epilepsy treatment, Physica Medica (2015), http://dx.doi.org/10.1016/j.ejmp.2015.04.005

[4] - A. Variola et al., The ThomX project status, prepress WEPRO052, 5th International Particle Accelerator ConferenceIPAC’14 (Dresden, Germany, 15 - 20 june 2014).http://www.umr-lams.fr/spip.php?article169

Medical physics issues in Contrast-enhanced Synchrontron Stereotactic Radiotherapy Clinical Trials

J.F. Adam[1,2], M. Vautrin[1], D.Reynard, G. Galisot[1], L. Obeid[1], A. Tessier[3], Y. Prezado[4], M. Renier[5], C. Nemoz[5], T. Brochard[5], E. Spasic[6], J.F. Le Bas[1,2], H. Elleaume[1], P. Berkvens[5], J. Balosso[1,2], F. Estève[1,2],

[1]Grenoble Institut des Neurosciences - Université Joseph Fourier - INSERM U836-6, Grenoble, France, [2]Centre Hospitalier Universitaire de Grenoble, Grenoble, France,
[3]Centre Hospitalier Régional d'Annecy, Annecy, France,
[4]Unité Imagerie et Modélisation en Neurobiologie et Cancérologie, UMR 8165, CNRS, Orsay, France, [5]European Synchrotron Radiation Facility, European Synchrotron Radiation Facility, France
[6] CEA, LIST, Laboratoire de Mesures Optiques, Gif-sur-Yvette, France
adam@esrf.fr

Introduction: The first clinical study of therapeutic applications of Contrast-Enhanced Synchrotron Stereotactic Radiation Therapy (SSRT) is underway since June 2012 at the European Synchrotron Radiation Facility (ESRF) and at the University Hospital (CHU) in Grenoble (France). This phase I-II clinical trial is designed to test the feasibility and safety of SSRT through a dose escalation protocol. Two years after the start of the trial, this study has already included ten patients suffering from few brain metastases of medium-to-small volume. The treatment is based on stereotactic irradiations using high-flux quasi-parallel monochromatic medium energy x-ray beams (80 keV). The irradiation is performed, in presence of iodinated contrast agent, previously introduced in the tumor. At these energies, a localized dose enhancement occurs in the target, due to increased photoelectric absorption. This differential effect is due to a difference in the photons interactions mechanisms in the target volume where the contrast agent leaks from the capillaries when compared to the healthy brain where the iodine concentration remains negligible. The moderate kinetic energy photoelectrons deposit their energy over a submillimetric distance, in the close vicinity to the heavy atoms; whereas Compton scattering predominates in the surrounding healthy tissues. Consequently, the radiation becomes more penetrating, and hence interesting, for treating deep-seated tumors. The medical physics developments, which have been performed for this innovative technique, will be discussed in this presentation.

Methods: A dedicated treatment room has been built at the ESRF medical beamline. The patient is seating on an armchair with his head tightly maintained by the same stereotactic frame used at the CHU for complimentary irradiations. A dedicated treatment planning system was adapted to SSRT specificities. The synchrotron beamline geometry was modeled. The dosimetry is based on parallelized Monte Carlo simulations of low-medium energy electrons and polarized photons transport in presence of high-Z material. Dedicated quality assurance protocols were implemented. The treatments plans and absolute dosimetry[1] are validated with measurements performed in a dedicated water tank as well as in solid water with and without bone slabs. A 2D dosimetry technique is being developed in anthropomorphic phantoms using EBT3 gafchromic films. *In vivo* dosimetry based on optically stimulated luminescence (Al_2O_3 crystals) has been tested. The contrast agent uptake has been previously studied on 12 patients which received an intravenous bolus of iodinated contrast agent (40 mL, 4 mL/s), followed by a steady-state infusion (160 mL, 0.5 mL/s) in order to ensure stable intratumoral amounts of iodine during the treatment[2]. Absolute iodine concentrations and quantitative perfusion maps were derived from 40 multi-slice dynamic conventional CT images of the brain (recruitment day) or from quantitative synchrotron radiation CT (treatment day). For three of these patients, iodine concentrations reached in the tumor were compared between the recruitment day and the treatment day (~10 days interval).

Results & Discussion: The SSRT procedure includes the i.v. injection of iodinated contrast agent (400 mg/ml nominal concentration) followed by the monochromatic irradiation in the next minutes, with 1 to 10 beams. The post-infusion mean intratumoral iodine concentration (over thirty minutes) reached 1.94 ± 0.12 mg/mL (200 mL of contrast injected). Reasonable correlations were obtained between these concentrations and the permeability surface area product and the cerebral blood volume. Iodine concentrations were reproducible leading to dose errors in the radiotherapy standards. In this first clinical trial phase, the patients receive a fraction of the treatment by SSRT (5 or 7 Gy), while the remaining of the treatment is delivered by standard stereotactic irradiation at the CHU (6 or 4 Gy and 2 x 11Gy). All patients were in good general condition.

References:

1. Dosimetry protocol for the forthcoming clinical trials in synchrotron stereotactic radiation therapy (SSRT). (Y. Prezado et al.) *Med. Phys.* **38**, 1709-1717 (2011).
2. Absolute perfusion measurements and associated iodinated contrast agent time course in brain metastasis: a study for contrast-enhanced radiotherapy (L. Obeid et al.) *Journal of Cerebral Blood Flow & Metabolism* **34**, 638-645 (2014).

Multi-strip silicon Sensor for Beam Array Monitoring in Micro-beam Radiation Therapy

A.Kok[1], E. Alagoz[2], A. Bravin[3], I. Cornelius[4], E. Brauer-Krisch[3], P. Fournier[4], T-E Hansen[1], M. Lerch[4], E. Monakhov[5], J. Morse[3], M. Petasecca[4], M. Povoli[5], H. Requardt[3], A. B. Rosenfeld[4], D. Roehrich[2], H. Sandaker[6], M. Salome[3], B. Stugu[2]

Affiliation: [1]SINTEF MiNaLab, Department of Microsystems and Nanotechnology, Norway **angela.kok@sintef.no**
[2]Department of Physics and Technology, University of Bergen, Norway
[3]European Synchrotron Radiation Facility, Grenoble, France
[4]Centre for Medical Radiation Physics, University of Wollongong, Australia
[5]Centre for Material Science and Nanotechnology, University of Oslo, Norway
[6]Department of Physics, University of Oslo, Norway

Silicon radiation sensors that are developed in a well-established technology can easily be coupled to their associated readout electronics to provide a real time on-line irradiation monitoring, which can benefit many newly emerging radiation therapies. One promising technique is the Micro-beam Radiation Therapy (MRT) [1]. MRT features a highly collimated array of X-ray beams. Each beam is of between 25 and 100 μm wide, separated by between 100 and 400 μm. The array delivers an extremely high dose to the tumour cells, and irradiation dose rates as high as 20 kGy/s. The spatially fractionated beams have shown a different effect between the tumour vasculature and the normal tissue vasculature, inducing hypoxia in certain tumour models [2]. Prior to the clinical trials of this new therapy, a new on-line monitoring system must be developed for a real-time beam monitoring as well as dosimetry quality assurance. Due to the extremely high dose rate and the microscopic dimensions of the micro-beam, designs and sensor configuration must be specific for the unique requirements for the MRT. Within the Silicon-based 3D Mini- and Microdosimetry (3DMiMic) collaboration, new devices for the MRT beam monitoring and on-line dosimetry using advanced fabrication techniques are currently being developed. The first prototypes have been successfully fabricated, which were designed specifically to tackle the required high spatial resolution and high dose rate of the MRT. The completed sensors were tested at the biomedical beam-line ID17 at the European Synchrotron Radiation Facility (ESRF) where MRT is currently being developed. The experimental data demonstrated their potential suitability as part of a beam monitoring system. In addition, detailed device studies were also carried out using an X-ray microprobe, also at the ESRF which aim to identify design and fabrication parameters for future optimisation. This presentation will give an overview of the research and development in the 3DMiMic collaboration where experimental results of the first prototypes will be discussed.

References

[1] – E. Brauer-Krisch, et al., "Effects of pulsed, spatially fractionated microscopic synchrotron X-ray beams on normal and tumoral brain tissue", Mutation Resaerch Vol. 704, (2010) pp.160-166

[2] A. Bouchet et al., "Synchrotron microbeam radiation therapy induces hypoxia in intracerebral gliosarcoma but not in the normal brain ", Radiotherapy and Oncology 108 (2013) 143-148.

The use of Theranostic Gadolinium-based Nanoprobes to Improve Radiotherapy Efficacy.

G. Le Duc[1], S. Dufort[2,3], M. Salomé[1], V. Bentivegna[1], Montigon O[4], L. Sancey[5], C.Verry[6], E. Bräuer-Krisch[1], H. Bernard[1], C. Caloud[7], D. Colliat[1], H. Requardt[1], S. Roux[8], O.Tillement[4].

Affiliation: [1]ESRF, X ray Imaging group, 71, Avenue des Martyrs, Cédex 9, F 38043 Grenoble cedex 9, [2]CR INSERM / Université Joseph Fourier U823, Institut Albert Bonniot, F 38706 La Tronche Cedex, [3] Nano-H S.A.S, 2 Place de l'Europe, F 38070 Saint Quentin-Fallavier , [4]UMS "IRMaGe" Unité IRM 3T Recherche CHU Grenoble - CS 10217, F 38 043 Grenoble Cedex 9, [5]Institut Lumière Matière, UMR 5306 CNRS-UCBL, Université Claude Bernard Lyon 1, F 69622 Villeurbanne Cedex, [6]Service de Radiothérapie, Hôpital A. Michallon, Centre Hospitalier Universitaire de Grenoble, CS 10217, F 38043 Grenoble cedex 9, [7]Charles Rivers Lab, BP 0109, F 69592 L'Arbresle, [8]Institut UTINAM, UMR 6213 CNRS-UFC, Université de Franche-Comté, 25030 Besançon Cedex, France.

leduc@esrf.fr

Ultrasmall gadolinium-based nanoparticles (GBN, hydrodynamic diameter < 5 nm) were recently developped. Since they are designed for combining renal clearance, magnetic resonance imaging (MRI) and radiosensitization, these nanoparticles appear as attractive agents for image-guided radiotherapy. Their efficiency to improve the survival time of tumor bearing animals rests on the possibility to determine, from the data collected by MRI, the delay between the irradiation and the intravenous injection of GBN. The attempts to determine this delay were assessed by combining MRT experiments in parallel with MRI and it provided unexpected results. In this talk, we will summarize these results that were achieved through the long term project MD606 (ANR Theraguima) at the ESRF including survival curves of animals as a function of (i) the time delay between injection and irradiation, (ii) the combination between nanoparticles and temozolomide and (iii) the comparison with the radiosensitization issued by the use of Gd chelates instead of GBN. Additionally, the biodistribution of the GBN within the tumor will be presented through MRI results and XRF results (ID21). On going experiments are now focused on the comparison between the efficiency of the GBN using MRT and in parallel a 6MeV irradiator at the local hospital.

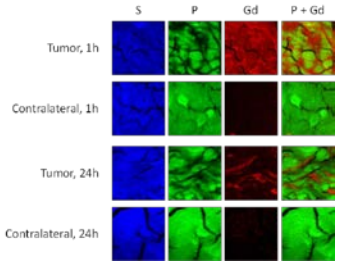


Figure 1: XRF maps of S, P, Gd elements and overlay of Gd and P maps of ROIs in the tumor and the contralateral region from the brain of 9LGS bearing rats sacrificed 1h and 24h after intravenous injection of GBN. Field of view 50 × 50 µm^2, 0.5 µm step size.

The Eclipse™ treatment planning system for Microbeam Radiotherapy trials at the Australian Synchrotron

C.M. Poole[1], P.A.W. Rogers[2], J.C. Crosbie[1]

[1]School of Applied Sciences, RMIT University, Melbourne, VIC 3001, Australia
[2]University of Melbourne Department of O&G, and Royal Women's Hospital, Parkville, VIC 3052, Australia

Before clinical trials of synchrotron microbeam radiotherapy (MRT) on humans can occur, a computerised treatment planning system (TPS) to calculate the dose distribution in the patient must be developed and validated. To satisfy this requirement, we use a research licenced version of the Eclipse™ TPS from Varian Medical Systems. This research license allows for customised dose calculation algorithms to be integrated with the clinical work-flows in Eclipse™ that are typical to modern radiotherapy.

Our treatment planning system is designed for the dynamic MRT modality that has been developed for the Imaging and Medical Beamline (IMBL) at the Australian Synchrotron. It represents an ideal simulation of this treatment delivery, uses a pencil beam convolution algorithm for dose calculation, and allows for the design of customised conformal masks. For the treatment itself, the white beam is collimated to a 30 mm wide and 1 mm high field which illuminates the MRT collimator, which in turn produces 50 um wide vertical microbeams separated at 400 um center-to-center. The sample and a mask is then dynamically swept through this array of microbeams, producing a dose of radiation in the sample that is conformal to the mask aperture.

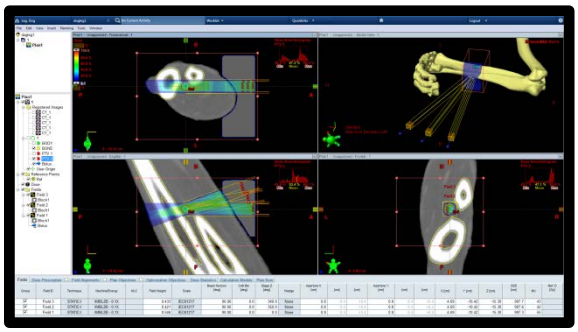


Figure 1: A screenshot of the Varian Eclipse TPS, customised to calculate dose for MRT.

Dose calculation considers the sample geometry derived from conventional CT data, custom bolus structures, standard and custom conformal masks, and multiple fields. Digitally reconstructed radiographs are also produced for online image guidance. Beam configurations and sample stage motions are limited so as to reflect the actual limits on the beamline. We have compared the output from the MRT TPS to measurements on the beamline[1], and documented our experiences in using it for planning the delivery of known doses to samples.

References

[1] - J.C. Crosbie, et al. Medical physics 40.6 (2013).

Quantitative Characterisation of the white/ pink X-ray beam at the Australian Synchrotron Imaging & Medical Beamline (IMBL)

A. W. Stevenson[1,2], J. C. Crosbie[3], C. J. Hall[1], D. Häusermann[1] and J. E. Lye[4]

[1]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria, Australia
Andrew.Stevenson@synchrotron.org.au
[2]CSIRO Manufacturing Flagship, Clayton South, Victoria, Australia
[3]School of Applied Sciences, RMIT University, Melbourne, Victoria, Australia
[4]ARPANSA, Yallambie, Victoria, Australia

A critical early phase for any synchrotron beamline involves detailed testing, characterisation and commissioning; this is especially true of a beamline as ambitious and complex as the Imaging & Medical Beamline (IMBL) at the Australian Synchrotron [1-3]. IMBL staff and expert users have been performing precise experiments aimed at quantitative characterisation of the primary white/ pink X-ray beam, with particular emphasis placed on the wiggler insertion devices (IDs), the primary-slit system and any *in-vacuo* and *ex-vacuo* filters.

We will describe our findings from these studies. Such results will benefit IMBL users in the future, especially those for whom detailed knowledge of the X-ray beam spectrum (or "quality") and flux density is important. This information is critical for radiotherapy and radiobiology users, who need to know (to better than 5%) what X-ray dose or dose rate is being delivered to their samples.

We have accounted for various correction factors associated with ionisation-chamber (IC) dosimetry, e.g. recombination, electron-loss effects. A new and innovative approach has been developed in this regard, which provides confirmation of key parameter values such as the magnetic field in the wiggler and the effective thickness of key filters. IMBL commenced operation in December, 2008 with an Advanced Photon Source (APS) wiggler as the (interim) ID. A superconducting multi-pole wiggler (SCMPW) was installed and operational in January, 2013. Results are presented for both of these IDs.

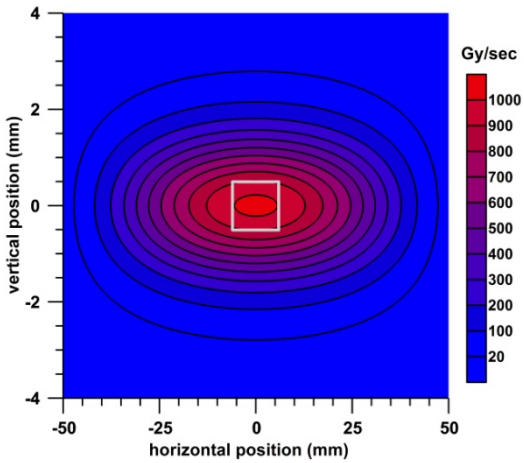


Figure 1: Dose-rate distribution for the SCMPW 3.00T case. The *in-vacuo* filters 0.45mm graphene, $15\sqrt{2}$ mm HD graphite, and $2\sqrt{2}$ mm Cu, and the fixed filters consisted of: 74mm He path, 1.8m air path, 0.35mm Be window, and 38μm Al foil. Note that the horizontal and vertical scales are quite different. The small grey rectangle represents 12mm (H) × 1mm (V). Other relevant parameter values were: 3.032GeV, 200mA, 22.3m from the source. Emittance effects were included. Component distributions were calculated from 1 to 999keV in steps of 2keV. The calculation steps were 0.1mm horizontally and 0.01mm vertically.

References

[1] – A. W. Stevenson, et al., *J.Synch.Rad.*, **17**, 75-80 (2010).
[2] – A. W. Stevenson, et al., *J.Synch.Rad.*, **19**, 728-750 (2012).
[3] – J. C. Crosbie, et al., *Med.Phys.*, **40**, 062103 (9pp) (2013).

Abscopal and bystander effects following exposure of rodent brains to Synchrotron Medical Microbeam Irradiation

[1*]C Mothersill, [1]C. Fernandez-Palomo, [2]E. Schultke, [1]C. Seymour

[1]Medical Physics, McMaster University, Hamilton, Canada
[2]Department of Radiotherapy, Rostock University Medical Center, Rostock, Germany
*Corresponding author. **Email: mothers@mcmaster.ca**

The question of whether the bystander effect and the abscopal effect are the same is unclear. Our experimental system enables us to address this question by allowing irradiated organisms to partner with unexposed individuals. Organs from both animals and appropriate sham and scatter dose controls are tested for expression of a variety of relevant endpoints such as calcium flux, role of 5HT, reporter assay cell death and proteomic profile. The results show that membrane related functions of calcium and 5HT are critical for true bystander effect expression. Inhibition of these functions prevents inter-animal transmission of signals. Our original inter-animal experiments used fish species whole body irradiated with low doses of x-rays, which prevented us from addressing the abscopal effect question. Data which are much more relevant in radiotherapy are now available for rats which received high dose local irradiation to an implanted right brain glioma. The data were generated using quasi parallel microbeams at the biomedical line at the European Synchrotron Radiation Facility in Grenoble France. This means we can directly compare abscopal and "true" bystander effects in a rodent tumour model. Analysis of right brain hemisphere, left brain and urinary bladder in the directly irradiated animals and their unirradiated partners strongly suggests that bystander effects (in partner animals) are not the same as abscopal effects (in the irradiated animal). Furthermore, the presence of a tumour in the right brain alters the magnitude of both abscopal and bystander effects in the tissues from the directly irradiated animal and in the unirradiated partners which did not contain tumours, meaning the type of signal was different.

Synchrotron X-ray Pencilbeam Irradiation as Boost after Whole Brain Irradiation

F. Jaekel[1], E. Bräuer-Krisch[2], H. Requardt[2], H. Blattmann[3], J. Laissue[4], G. Hildebrandt[1], E. Schültke[1]

[1]Department of Radiooncology, Rostock University Medical Center, Südring 75, 18059 Rostock, Germany, [2]Biomedical Beamline ID 17, ESRF, 3 Avenue des Martyrs, 38000 Grenoble, France, [3]Niederwiesstr.13C, 5417 Untersiggenthal, Switzerland, [4]University of Bern, Switzerland, **elisabeth.schueltke@med.uni-rostock.de**

Background:

Based on a clinically established concept of boost irradiation for patients with multiple brain metastases and the reported experience with clinically used grid therapy as well as with irradiation schedules using monoplanar microbeam irradiation (MRT) as boost in preclinical studies, we have conducted first experiments using irradiation with synchrotron X-ray pencilbeam irradiation as boost after a conventional X-ray broad beam irradiation schedule. The aim of this first experiment was to assess normal tissue tolerance to such recently developed pencilbeams [1].

Materials and methods:

We have used both cell culture and *in vivo* experiments in tumour-free mice to explore cell and tissue responses to a conventional X-ray irradiation schedule with pencilbeam boost, compared to either the conventional schedule alone or the pencilbeam boost alone and to untreated controls. As means of analysis we have used cell survival curves, colony assays, and immunocytochemistry stains looking at reactive oxygen species and DNA damage.

The experiments are under way at the time point of abstract submission. First results will be presented in poster form at the MASR 2015 meeting.

References:

[1] – E. Schültke et al., PLoS ONE **8(1)**, e54960 (2013).

Synchrotron microbeam radiotherapy evokes a different tumor immunomodulatory response to conventional radiotherapy

Y. Yang[1], A. Swierczak[2], M Ibahim[1], P. Paiva[1], L. Cann[1], A. W. Stevenson[3,4], J. C. Crosbie[5], R. L. Anderson[2], and Peter A. W. Rogers[1]

[1]University of Melbourne Dept of Obstetrics & Gynaecology, The Royal Women's Hospital, Parkville, Victoria, Australia
[2]Division of Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[3]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria, Australia
[4]CSIRO Manufacturing Flagship, Clayton South, Victoria, Australia
[5]School of Applied Sciences, RMIT University, Melbourne, Victoria, Australia, **Jeffrey.Crosbie@rmit.edu.au**

Synchrotron microbeam radiation therapy (MRT) is a novel form of radiotherapy that has potential for clinical application. Several studies have shown in pre-clinical models that synchrotron MRT achieves equivalent tumor control to conventional radiotherapy (CRT) but with significantly reduced normal tissue damage. The current study compares the intratumoral immune responses following CRT and MRT.

A new analysis of published gene array data from mammary tumors exposed to either CRT or synchrotron MRT was performed to identify the intratumoral immune response signature. The myeloid cell infiltrate into tumors and tumour cytokine profiles after CRT and MRT were assessed. There are marked differences in the immune response signature in tumors exposed to CRT compared to synchrotron MRT. CRT induced marked increases in tumor-associated macrophages and neutrophils whilst there were no increases in these populations following MRT. Cytokines analyses demonstrated major differences between the two forms of radiation. Increased levels of CCL2 by immunohistochemistry in tumors subjected to CRT, but not to MRT were noted. In conclusion; this study demonstrates that MRT evokes a different immunomodulatory response in tumors compared to CRT.

Title: The development of a proton-beam grid radiotherapy

T. Henry[1] , E. A. Siegbahn[1]

[1] Medical Radiation Physics, Stockholm University, email: **thomas.henry@fysik.su.se**

Radiation therapy with grids has in the past normally been carried out with photon beams [1]. The grid method is used as an attempt to exploit the clinical finding that normal tissue can tolerate higher doses as the irradiated volumes become smaller. In this work we studied the possibilities to perform proton-beam grid therapy with millimeter-wide proton beam elements by performing Monte Carlo simulations of dose distributions produced in a human phantom.

The Monte Carlo calculations were performed using Topas [2] version 1.0-b12 in a 20x20x20 cm^3 water tank. The beam grids (each containing 16 proton beams arranged in a 4x4 square matrix) were aimed towards cubic target volumes of different sizes centred at a selected depth in water. A total of 4 grid angles were used (2x2 opposing grids) for the treatment simulations in which the target was cross-fired in an interlaced manner to create a nearly homogeneous dose distribution (with a high minimum dose) as illustrated in Figure 1. A beam size of 3 mm (full-width at half-maximum) was used as it was found to provide a suitable compromise between beam thinness, peak to entrance dose ratio, and transversal dose fall-off both at the entrance side and at the peak.

Dose distributions were calculated for the following beam element center-to-center (c-t-c) separations (inside the grids): 6, 8 and 10 mm. The mean, minimum and maximum doses in the target were then compared. Transversal dose profiles at the entrance, before the target and inside the target were plotted to study the impact of the c-t-c distance on the peak-to-valley dose ratios (Figure 2). By interlacing beam grids incident from several directions, a cubic and nearly homogeneous dose distribution could be achieved while maintaining the grid structure of the dose distribution close to the target. The main results of these calculations are summarized in Table 1. The c-t-c distance has a significant impact on the relative dose inside and outside of the target and on the peak-to-valley dose ratio. The results in this work indicate that, from a dosimetric point of view, it is possible to use grids containing millimeter-sized proton beams for grid treatments.

Figure 1. Interlacing 4 proton beam grids in a cubic target

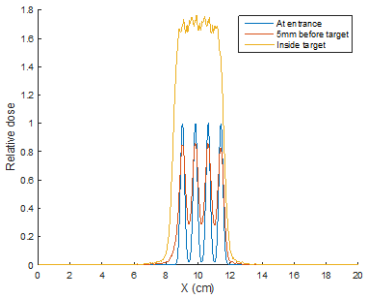


Figure 2. Lateral profiles at different depths for a c-t-c of 8 mm

References

[1] - Mohiuddin, M, Fujita M, Regine WF, Megooni AS, Ibbott GS, Ahmed MM. High-dose spatially-fractionated radiation (GRID): A new paradigm in the management of advanced cancers. Int J Radiat Oncol Biol Phys. 1999;45:721–727

[2] - Perl J, Shin J, Schumann J, Faddegon B, Paganetti H. TOPAS: an innovative proton Monte Carlo platform for research and clinical applications. Med Phys. 2012 Nov; 39(11):6818-37

Multifunctional Gold Nanoparticles for Image-Guided Microbeam Radiation Therapy

G. Laurent[1], G. Jimenez Sanchez[1], C. Alric[2], C. Bernhard[3], S. Dufort[4], R. Bazzi[1], E. Bräuer-Krisch[5], H. Requardt[5], F. Boschetti[6], F. Lux[2], F. Denat[3], G. Le Duc[5], O. Tillement[2], S. Roux[1]

[1] Institut UTINAM, UMR 6213 CNRS-Université de Franche-Comté, Besançon; [2] Institut Lumière Matière, UMR 5306 CNRS – Université de Lyon, Villeurbanne; [3] ICMUB, UMR 6302 CNRS- Université de Bourogne, Dijon; [4] nano-H SAS, Saint-Quentin Fallavier; [5] ID17 Biomedical Beamline, ESRF, Grenoble; [6] CheMatech SAS, Dijon

stephane.roux@univ-fcomte.fr

Owing to their large range of properties which can be accurately tuned by the chemical composition, the shape and the dimensions, multifunctional nanoparticles appear as promising candidates for image-guided therapy. For achieving this goal, we developed the synthesis of gold nanoparticles which are designed for combining multimodal imaging (magnetic resonance imaging (MRI), scintigraphy (SPECT), ultrasound imaging (echography) and X-ray imaging) and radiotherapy [1-5].

Ultrasmall gold nanoparticles were synthesized by reducing gold salt in presence of various highly hydrophilic dithiolated polyaminocarboxylate ligands (linear (DTDTPA) and macrocyclic (TADOTA, TADOTAGA) ligands). They are composed of a gold core (mean diameter of ~ 2.5 nm) encapsulated within an organic shell of ligands (DTDTPA, TADOTA or TADOTAGA). The gold core is expected to provide a strong X-ray absorption whereas the ligands of the organic shell were chosen for their propensity to entrap gadolinium ions (for MRI) and radionuclides (for SPECT).

Since the passive accumulation of the gold nanoparticles in the tumor depends on the nature of the ligands, the possibility to follow up the gadolinium chelate-coated gold nanoparticles by MRI is therefore very useful for determining the most opportune delay between intravenous injection and irradiation. Owing to the radiosensitizing effect of the gold core, the combination of microbeam radiation therapy (MRT) and gold nanoparticles based MRI contrast agents led to a great increase in lifespan of the 9L gliosarcoma-bearing rats in comparison to non-treated animals and animals treated only by MRT [5].

Finally, this study demonstrated that gadolinium chelate-coated gold nanoparticles exhibit a real potential for image-guided microbeam radiation therapy.

Acknowledgment / References

We wish to thank the “Agence Nationale de la Recherche” for the financial support (ANR 2011 NANO 017), the region Franche-Comté for the doctoral grant (GJS) and the ESRF Biomedical Beamline.

[1] P.-J. Debouttière *et al*., *Adv. Funct. Mater.* **2006**, *16*, 2330–2339.
[2] C. Alric *et al*., *J. Am. Chem. Soc.* **2008**, *130*, 5908–5915.
[3] D. R. Arifin *et al*., *Radiology* **2011**, *260*, 790–798.
[4] C. Alric *et al*., *Nanoscale* **2013**, *5*, 5930-5939.
[5] I. Miladi *et al*., *Small* **2014**, *10*, 1116-1124.

The minipig experiment: a last major milestone prior clinical trials in MRT?

E. Bräuer-Krisch[1], R. Serduc[2]
on behalf of the scientific collaboration towards clinical trials in MRT

Affiliation: [1]European Synchrotron Radiation Facility, Grenoble, France
[2]Inserm, U836, Grenoble, F-38043, France

Microbeam Radiation Therapy (MRT) has made considerable advances in all domains over the last 2 decades. By now, we have a better understanding of the underlying biological processes and in particular solid proof by scientists from different laboratories of the extraordinary normal tissue sparing of MRT as well as its differential effect between the tumour vasculature and the normal tissue vasculature, inducing hypoxia in preclinical tumour models when high-dose, spatially fractionated microbeams are applied in preclinical research[1]. Further milestones include the development of a dosimetry protocol, benchmarking of Monte Carlo dose calculations using several high resolution dosimeters, the development of a treatment planning system and the development of a MRT Patient Safety system to control dose delivery at high dose rates around 8000 Gy/sec.
Prior a successful translation of the biological findings into an optimized treatment plan for humans, larger animals than rodents should be treated in MRT, which is one of the aims of the veterinary trials. A realistic scenario for a clinical trial phase I could be an MRT treatment delivered as a boost in order to delay tumor growth and increase the lifespan. The plan to irradiate landrace pigs in such a regim using 3 x 11Gy as in conventional RT in 1 week compared to 2 x 11Gy plus 1 MRT irradiation at 11 Gy in the valley at the tumour site is being proposed. This project represents one of the last steps towards clinical application of MRT where microbeam radiation therapy would be applied as a relevant and efficient therapeutic boost for brain tumor management.

A phase I clinical trial should first demonstrate the normal tissue tolerance in humans applying a simple cross-fired microbeam array from a maximum of 3 ports prior moving to more sophisticated irradiation geometries. Such potentially interesting irradiation geometries could keep the normal tissue at very low dose values applying a large centre to centre distance of 1200 µm, and in combination with a horizontal microbeam dose delivery from several ports, tumor control could be improved using intersperced beams to deliver a radiotherapeutic relevant valley dose only at the tumour site at tighter ctc spacing.

References

[1] – A. Bouchet et al., "Synchrotron microbeam radiation therapy induces hypoxia in intracerebral gliosarcoma but not in the normal brain" Radiotherapy and Oncology 108 (2013) 143-148

MRT for pet animals: Normal organ tolerance of the rabbit nose and jaws; preliminary data

J.A. Laissue[1]*, G. Le Duc[2], E. Bräuer-Krisch[2], H. Mathieu[3], S. Barré[4], H. Blattmann[5], R. Serduc[3,6], S.Bartzsch[7], V. Djonov[4], H. Bernard[2], C. Caloud[2], M. Economou[4]

[1]University of Bern, Bern Switzerland [2]European Synchrotron Radiation Facility, Grenoble, France [3]Université Joseph Fourier, Grenoble Institut des Neurosciences, UMR-S836, Grenoble, France, [4]Institute of Anatomy, University of Bern, Switzerland, [5]Niederwiesstrasse 13C, Untersiggenthal, Switzerland, [6]INSERM, U836,Grenoble, France, [7]The Institute of Cancer Research, Physics, Sutton, United Kingdom

*** laissue@pathology.unibe.ch**

To test the normal organ tolerance of a Microbeam Radiation Therapy for squamous cell carcinoma of the nasal plane of pet animals, the nose and jaws of six New Zealand albino rabbits were irradiated laterally by a 30mm wide and 26mm high array of 50 micron wide quasiplanar beamlets, spaced 400 micron on center. The entrance doses were 200Gy, 330Gy, and 500 Gy. All the rabbits survived, were followed up, examined by MRI on day 431 post irradiation, and then culled. After perfusion fixation, microtomograms of the irradiated parts of the head were done. We did not detect signs of osteoradionecrosis of the jaws; however, at EDs of 330 Gy and 500 Gy some dental lesions occurred.

Online 3D measurement of SSRT beams

Y. Arnoud[1], R. Delorme[1], R. Fabbro[1,2], J-F. Adam[3]

Affiliation: [1]LPSC/CNRS/UJF/Grenoble INP UMR5821, [2]ANR-11-LABX-0063/ ANR-11-IDEX-0007, [3]Grenoble Institut Neurosciences, unité INSERM U836, **yannick.arnoud@lpsc.in2p3.fr**

Introduction: Beam control is a key factor during treatment delivery, especially when dose rate reaches very high levels while patients are being treated. A transmission detector, located ahead to the patient is being developed by the DAMe group of the LPSC. This detector aims at recording in real time and in 2D the properties of intensity modulated radiotherapy beams in the framework of conventional radiotherapy external beam treatments. It consists in an array of ionisation chambers, read by in-house designed electronics. While being developed, some instabilities in the detector global response where noticed, that could be beam related or detector related. In order to characterise the intrinsic detector response, we studied the temporal behaviour of the detector response under the ID17 Synchrotron stereotactic radiotherapy (SSRT) beam line, which presents an ideal stability.

Material and Methods: Two measurement sessions were performed. First to test the stability of the clinical designed prototype; second to test a specific designed prototype for the ID17 beam line which aims at increasing the transparency of the detector. Proof of concept was done using the specific prototype perpendicular to the beam for a 2D fluence measurement, and then parallel to the pencil beam for a 1D fluence measurement minimizing the beam perturbation.

Results:
The first measurement session gave very promising results. The clinical detector stability was as good as the reference ionisation plane chambers used for beam quality control, adding an extra 2D measurement on the geometrical beam characteristics. It showed no saturation although it was primarily designed for conventional radiotherapy beams, with a much lower dose rate.
It appears that such a detector (sensitive device and electronics) could be adapted from its initial conventional RT goal to SSRT quality control applications. With a simple adapted prototype, we showed that a measure of 1D beam intensity seems feasible while passing the thin beam between the two electrode plans, minimizing the attenuating matter before the patient. Nevertheless, the detector is working better when the beam is interacting perpendicularly to it. Furthermore, the detector transparency is homogeneous enough to use the detector perpendicular to the beam.

Conclusion:
These results lead to a collaboration involving both the equipe 6 GIN, INSERM unit U836, and the radiotherapy team from the Grenoble Public Hospital in order to study the detector response under conventional RT beams and SSRT beams. The goal of the study is to adapt the detector to the ID17 beam line and to compute from the detector response the dose delivered to the patient being treated for high grade gliomas, both under conventional clinical beams (most of the delivery sessions) and under SSRT (some delivery sessions).

A further evolution would consist in modifying the sensitive device while keeping the same readout electronics in order to measure the microbeams intensity in real time, providing additional information for quality assurance of treatments.

The development of a clinical protocol for microbeam-grid radiation therapy

E. A. Siegbahn[1], T. Henry[1], G. Mondlane[1], and A. Valdman[2] and

Affiliation: Stockholm University [1], Karolinska Institutet[2], email: **albert.siegbahn@fysik.su.se**

Microbeam grid therapy (MRT) has thus far mainly been suggested for brain treatments in children. The prescribed peak doses in the MRT pre-clinical trials have usually been very high, e.g. 625 Gy. In the work here presented, we are analysing the factors of importance for the dose prescription with the future human clinical trials in mind. We are assuming that MRT with a crossfiring geometry is used since this has been the most commonly used setup in the pre-clinical trials. This mode of irradiation is more similar to radiosurgery (RS) than to radiotherapy (RT) since the aim is not just to traverse the target with microbeams, as in the unidirectional approach, but to increase the damage to the target by (1) overlapping the lower valley doses and (2) decreasing the geometric separation between the microbeam peak doses.

We searched the literature to obtain information about which doses that would be sufficient for achieving local control of common disease treated today in the clinic with RS. A single-fraction dose of approximately 25 Gy to the periphery of the target has been found to be sufficient to control a wide range of tumors [1]. The most feared sequela in the brain is radiation necrosis, the risk for which has been shown to increase with the brain volume receiving doses larger than 10 Gy. Moreover, there is a danger that the developing brains in children may be damaged with doses as low as 0.1 Gy, which has been shown to sometimes cause cognitive difficulties later in life [2]. There is also a certain risk that RT treatments will produce a radiation-induced cancer, the probability of which is assumed to rise linearly with dose up to doses of a few Gy. The cancer induction risk is also more important for children due to, among other things, their longer life expectancy.

Biological models, used to predict the risks of certain endpoints in standard RT are not directly applicable to MRT since they do not consider the spatial distribution of the dose, but only the sum of the doses to individual volumes. In these models the tissue damage is assumed to be completely uncorrelated, spatially. The tolerance doses for microbeam grid irradiations have in the past been determined in *in vivo* studies for a few endpoints. When the microbeams are closely separated, the valley doses increase rapidly and the damage to cells created by one microbeam may affect the chance of cellular repair in an adjacent microbeam path. This "bystander" damage will probably have to be determined empirically from case to case for the narrower beam separations which are approaching one microbeam width in distance.

Based on our work, we suggest that the prescribed dose for crossfired MRT is assigned to the minimum target dose. A delivered dose in the range of 12 Gy to 40 Gy, depending on the type of disease treated and the diameter of the target, should be sufficient to treat most types of common disease which could be indications for MRT. This means a reduction of the microbeam peak doses, compared to what has been used in the MRT preclinical trials so far. It must also be emphasized that the valley doses given to normal tissue in between the microbeams should be as low as possible to prevent severe side effects. Therefore, we suggest a 1-2 Gy maximum dose limit for valley doses in the healthy brain (in the part which is far from the target) for the initial human clinical trials with single fraction MRT treatments. The preliminary calculations done in this work indicate that the cancer induction risk may be reduced with MRT compared to standard RT, depending on the dose prescription. This is due to the high frequency of cell kill in the high-dose microbeam paths which are reducing the importance of new mutations (known to increase the cancer risk) in these subvolumes. In between the microbeams paths, the valley dose can be kept at a low level which means fewer mutations.

[1] B. Lippitz, et al, Cancer Treat Rev 40 48-59 (2014). [2] - ICRP 118, "Statement on Tissue Reactions", (2012).

Conformal imaged guided MRT for multiple port treatment and first results on 4D dose calculations in MRT including tissue motion

M. Donzelli[1], E. Bräuer-Krisch[1], U. Oelfke[2]

Affiliation: [1]European Synchrotron Radiation Facility, Grenoble, France
[2]Institute of Cancer Research, London, United Kingdom
donzelli@esrf.fr

Organ motion has not been an issue in microbeam radiation therapy (MRT) as long as research was carried out in small samples, such as cell cultures and rodents. But the future treatment of human brains - in cancer therapy or radio surgery - using microbeam radiation is affected by the cardiosynchronous tissue pulsation. This pulsation, having an amplitude in the order of 100 µm, induces a translation and blurring of the initially plane-parallel microbeam pattern.

Monte Carlo calculations for different microbeam reference dosimetry configurations and dose rates show significant changes under certain conditions compared to the static case. The affected indicators include peak dose, peak-to-valley dose ratio (PVDR), microbeam width, spacing, and penumbra.

Preliminarily it can be concluded that under the effect of organ movement high dose rates become even more important in the application of microbeam radiation, unless more sophisticated irradiation geometries will be developed.

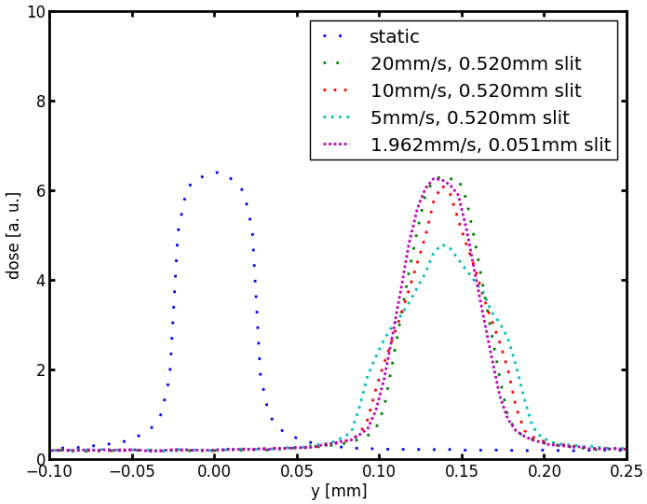


Figure 1: Microbeam profiles affected by organ motion in dependence of the scan speed and the vertical slit size compared to a microbeam in standard configuration.

Liquid-metal-jet X-ray tube technology

T. Tuohimaa[1]

[1] Excillum AB, Torshamnsgatan 35, 164 40 Kista, **tomi.tuohimaa@excillum.com**

The power and brightness of electron-impact micro-focus X-ray tubes have long been limited by thermal damage in the anode. This limit is overcome by the liquid-metal-jet anode (MetalJet). This is possible due to the regenerative nature of this anode and the fact that the anode is already molten, which allows for significantly higher e-beam power density than on conventional solid anodes.

Over the last years, the MetalJet technology has developed from prototypes into fully operational and stable X-ray tubes, such as the MetalJet D2 seen in Fig. 1, running in many labs over the world. Key applications include X-ray diffraction and scattering but also advanced X-ray imaging such as phase-contrast imaging.

This presentation will review the current status of the technology.

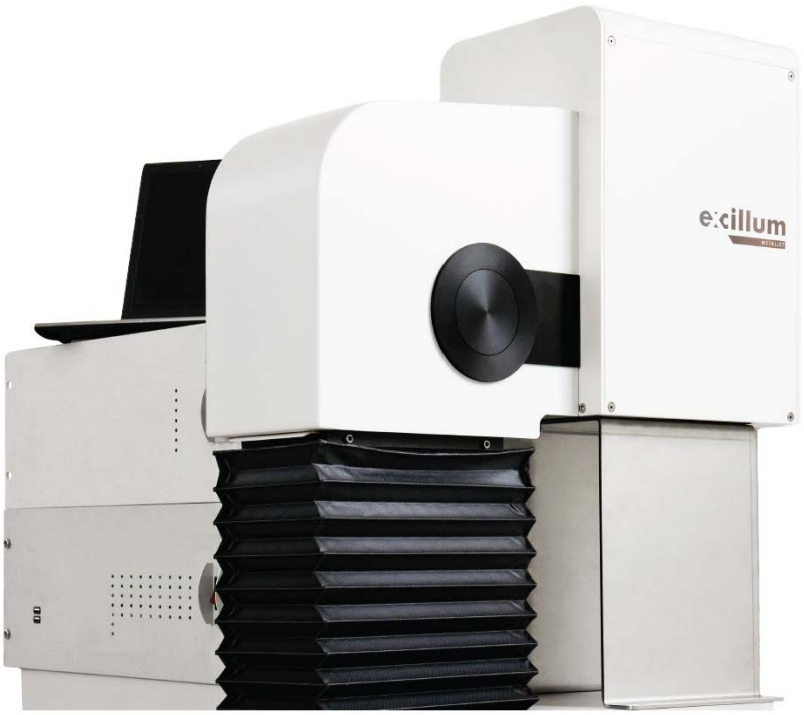


Figure 3 : *The MetalJet D2 X-ray tube*

Potential of Compact Compton sources In the Medical Field

M. Jacquet
CNRS, Orsay, France. **mjacquet@lal.in2p3.fr**

Since the exceptional development of high power femtosecond lasers in the last fifteen years, the interest in Compton X-ray sources becomes very important. In particular projects aiming to provide a laboratory-size source of high power and high quality are in full development over recent years.
Compton sources are based upon inverse Compton scattering of laser light against high energy electrons. In term of integrated emitted flux and brightness the most ambitious projects can be placed near the second generation radiation facilities with the very important advantage of the compactness (~100 m^2) and so the possibility to be integrated in a laboratory, a museum or a hospital. In addition to their compactness and their high flux, Compton sources should have the possibility to adjust the energy of the Compton photons and to produce high energy X-ray (20-100 KeV). This makes possible a wide range of studies requiring intense monochromatic or "pink" beams at various X-ray energies. A whole series of researches using analysis techniques previously reserved to synchrotron facilities should now become accessible and feasible in a laboratory environment.
After a short presentation of basic principles of a Compton compact source (CCS), the key parameters needed to produce a high quality beam will be highlighted and the current high flux CCS projects in the world briefly presented. From the specifications of the French project ThomX, the potential of applications of CCS will be discussed in the biomedical field (imaging, therapy, adjuvants tests).

List of Posters

By alphabetical order

List of Posters

Posters' Abstracts

By alphabetical order

P1

Role of parenchymal interdependence in the short-term dynamics of recruitment/derecruitment in injured lung: a modelling study

L. Broche[1, 2], A. Tannoia[3], M. Pellegrini[3], S .Derosa[3], A. Sindaco[3], J.B Borges[4], L. Porra[5], A. Larsson[4], G. Hedenstierna[4], A. Bravin[1], G. Perchiazzi[3], A. Wexler[6], S. Verbanck[7], J.A. Bates[8], S. Bayat[2]

[1]European Synchrotron Radiation Facility – Grenoble/FR **broche@esrf.fr**, [2]Université de Picardie Jules Verne & Amiens University Hospital – Amiens/FR, [3]University of Bari – Bari/IT, [4]Uppsala University Hospital –Uppsala/SE, [5]University of Helsinki – Helsinki/FI, [6]University of California Davis/USA, [7]University Hospital UZ Brussels Brussels/BE, [8]University of Vermont Burlington/USA

In this study, we propose a computational model that simulates recruitment/derecruitment (R/D) in a realistic structure of the injured rabbit right lung, based on phase contrast synchrotron CT imaging.

Methods: The lung was imaged 3 times at approx. 100 s intervals at baseline and after injury. The regional distribution of R/D was analyzed by subtracting subsequent volumetric images following image-segmentation and registration [1]. Synchrotron images of the rabbit right lung were also obtained immediately post-mortem, branching structure was segmented with a custom made software [2] (Fig.1-right). We implemented a computational model [3], in which each airway of the bronchial tree and acinar unit has an opening and closing critical pressure and speed. The model was modified to include mechanical interdependence between neighboring acini; at each time point, opening and closing pressures of a given unit depended on the state (open/closed) of the surrounding units.

Results: The model mimicked alternating R/D of neighboring lung units (Fig. 1-right) over short time scales, similar to our previous experimental findings, under ventilation in PC mode (Fig. 1-left). This behavior was accurately reproduced by the computational model only when parenchymal interdependence was included.

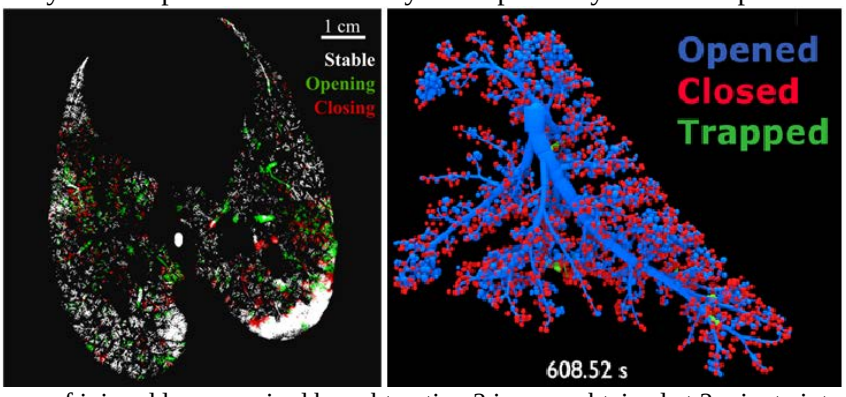


Figure 1: Left: R/D maps of injured lung acquired by subtracting 2 images obtained at 2 minute intervals (green: opening, red: closing, white: stable). Right: Injured lung model in a realistic airway tree.

Conclusion: Our data show that alternating R/D of neighboring lung units occur because airway and terminal lung unit opening/closure are dynamic phenomena determined by opening and closing speeds, and that mechanical interactions exist between neighboring terminal lung units. These findings provide further insight into the biophysics of the injured lung under mechanical ventilation.

References:

[1] Broche L et al. Am J Respir Crit Care Med 2014;189:A5024
[2] Lee, D.Y. et al. Anat Rec (Hoboken) 2008;291 :916-926
[3] Ma B. et al. Annals of Biomedical Engineering 2010:38(11) :3466–3477

Chronic intermittent hypoxia accelerate coronary microcirculatory dysfunction in young insulin resistant Goto-Kakizaki rats

Y-C. Chen,[1] T. Inagaki,[2] Y. Fujii,[2] D.O. Schwenke,[3] A.J. Edgley,[1,4] K. Umetani,[5] Y. Zhang,[4] D.J. Kelly,[4] M. Yoshimoto,[2] H. Tsuchimochi,[2] H. Nagai,[6] I. Kuwahira,[7] R.G. Evans,[1] M. Shirai,*[2] J.T. Pearson,*[1,8,9]

[1]Department of Physiology, Monash University, Melbourne, Australia, [2]National Cerebral and Cardiovascular Center Research Institute, Suita, Japan, [3]Department of Physiology – HeartOtago, University of Otago, Dunedin, New Zealand, [4]St Vincent's Hospital, University of Melbourne, Melbourne, Australia, [5]Japan Synchrotron Radiation Research Institute, Harima, Japan, [6]Departments of Clinical Laboratory Medicine and Forensic Medicine, University of Tokyo, Tokyo, Japan, [7]Department of Pulmonary Medicine, Tokai University Hospital, Tokai University, Tokyo, Japan, [8]Monash Biomedical Imaging Facility, Melbourne, Australia, [9]Australian Synchrotron, Melbourne, Australia. **Email: ycche17@student.monash.edu**

Sleep apnea syndrome (SAS) is a sleep disorder characterised by repeated episodes of apnea during sleep [1]. SAS and intermittent hypoxia (IH) have been shown to induce oxidative stress and activation of inflammatory mediators, which impair vascular endothelial function and promote atherogenesis [2,3] Long-term insulin resistance also leads to endothelial dysfunction [4,5]. Therefore it is of interest to determine whether the effects of exposure to chronic IH exposure and insulin resistance are synergistic.

In the current study, we tested the hypothesis that the onset of coronary vascular dysfunction in young insulin resistant rats (Goto-Kakizaki, GK) is accelerated by medium term exposure to a severe level of chronic IH. We therefore investigated the effects of IH (21-4% O_2, normocapnia, 40 cycles/h, 8 hr per day) for 4 weeks in 16 week old male GK rats and aged matched Wistar control rats. Coronary endothelial function was assessed using microangiography with synchrotron radiation. We found that vessel dilation mediated by endothelium-derived hyperpolarisation was reduced in microvessels of GK rats (Fig 1a), and that diabetes increased the media-lumen ratio in the resistance vessels in IH treated GK rats (Fig 1b). Therefore, IH increased structural and functional remodelling to small coronary arteries and large arterioles (100-200 μm) in insulin resistant rats.

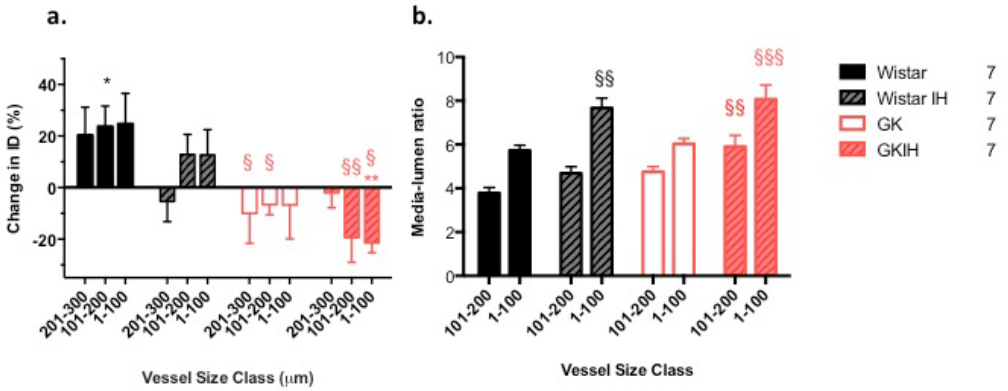


Figure 1: (a) Change in vessel internal diameter categorized by size class, in the four groups with ACh infusion post blockade. (b) Media lumen ratio in microvessels in four groups. Values expressed as mean ± SEM. (§ p<0.05, §§ p<0.01 §§§ p<0.001 vs. Wistar; * p<0.05, ** p<0.01, *** p<0.001 vs. baseline ID)

References

[1] Punjabi, N.M. Proceedings of the American Thoracic Society **5**(2), 136-143 (2008).
[2] Kohler, M. and J.R. Stradling. Nature Reviews Cardiology **7**(12), 677-685 (2010).
[3] Wang, Z., et al. PloS one **8**(3), e58078 (2013).
[4] Stühlinger, M.C. et al. Jama **287**(11), 1420-1426 (2002.).
[5] Balletshofer, B.M. et al. Circulation **101**(15), 1780-1784 (2000).

P3

The dynamic x-ray micro-tomography with monochromatic beam

Rongchang Chen, Guangzhao Zhou, Liang Xu, Guohao Du, Biao Deng, Honglan Xie and Tiqiao Xiao

Shanghai Institute of Applied Physics, Chinese Academy of Sciences, Shanghai 201204, China.
Email: rcchen@sinap.ac.cm, tqxiao@sinap.ac.cn

With the availability of third generation Synchrotron Radiation (SR) sources, SR-μCT has evolved as an increasingly accepted and utilized technique for quantitative characterizing the 3D internal structure of samples in different research fields [1, 2]. In the last decades, the spatial resolution of SR-μCT increased sharply with the rapid development of detector techniques. However, the low temporal resolution of SR-μCT limits its application fields, such as investigating the dynamic phenomena.

The filtered back projection (FBP) algorithm, a typical CT reconstruction algorithm of SR-μCT, requires high completeness of projection data. It will no doubt decrease the temporal resolution of SR-μCT. In order to speed up SR-μCT, two fast micro-CT imaging systems based on compressed sensing (CS) theory [3, 4] and equally sloped tomography (EST) [5] have been developed at the X-ray imaging and biomedical application beamline (BL13W1) [6-8] of SSRF. Compare with FBP algorithm, both two algorithms can obtain comparable results, by utilizing a fraction of FBP project number, with FBP algorithm ones using full set of FBP project number. These will no doubt achieving higher time resolution and simultaneously reducing the dose delivered to the samples that is especially beneficial in medical applications such as *in-vivo* CT investigations. Beside, both two algorithms allow for the accurate reconstruction of images using incomplete and undersampled SR-μCT data that open its applications such as for flat samples.

Both imaging systems were validated using experimental data collected at BL13W1, equipped with air-bearing rotation stage and Hamamatsu flash 4.0 detector. The results demonstrate that the CS-CT algorithm yields good reconstruction accuracy for incomplete and undersampled data, and it is capable of performing sub-second temporal resolution dynamic SR-μCT. The EST algorithm can achieve 75% dose reduction for *in-vivo* micro-CT and high pressure (samples in the diamond-anvil cell) micro-CT with incomplete data.

References

[1] R. C. Chen,R. Longo,L. Rigon,F. Zanconati,A. De Pellegrin,F. Arfelli,D. Dreossi,R. H. Menk,E. Vallazza,T. Q. Xiao,E. Castelli, Phys. Med. Biol. **55**, 4993 (2010)
[2] R. C. Chen,L. Rigon,R. Longo, Opt. Express **21**, 7384 (2013)
[3] D. L. Donoho, IEEE. T. Inform. Theory **52**, 1289 (2006)
[4] L. Xu,R. Chen,G. Du,H. Xie,T. Xiao, J. Instrum. **10**, C03010 (2015)
[5] J. W. Miao,F. Forster,O. Levi, Phys. Rev. B **72**, (2005)
[6] H. Xie,B. Deng,G. Du,Y. Fu,Y. He,H. Guo,G. Peng,Y. Xue,G. Zhou,Y. Ren,Y. Wang,R. Chen,Y. Tong,T. Xiao, J. Instrum. **8**, C08003 (2013)
[7] R. C. Chen,P. Liu,T. Q. Xiao,L. X. Xu, Adv. Mater. **26**, 7688 (2014)
[8] T. Q. Xiao,H. L. Xie,B. Deng,G. H. Du,R. C. Chen, Acta Optica Sinica **34**, 100001 (2014)

P4

Investigation of Energy and Dose Dependence of High-Resolution Dosimetric Materials for Microbeam Radiation Therapy

Authors: F. Chicilo[1], G. Okada[2], G. Belev[3], T. Wysokinski[3], A. Edgar[4], D. Chapman[3], S. Kasap[2]

Division of Biomedical Engineering, University of Saskatchewan, Saskatoon, SK, Canada[1],
Department of Electrical and Computer Engineering, University of Saskatchewan, Saskatoon, SK, Canada[2].
Canadian Light Source Inc., Saskatoon, SK, Canada[3],
School of Chemical & Physical Sciences & MacDiarmid Institute, Victoria University of Wellington, New Zealand[4].

Microbeam radiation therapy (MRT) is a promising cancer therapy technique based on the irradiation of a tumor by high-dose narrow microbeams (typical width of 10 - 20 μm) that are closely spaced (with a typical separation of 500 μm). One of the difficult hurdles in the clinical use of microbeams arises from the measurement of the dose distribution. The dose at the center of a microbeam is extremely large, on the scale of several hundreds of grays (Gy), while the valley between each planar beam must be below a critical limit, typically less than twenty Gy. Currently, there are no existing detectors that can achieve both very high spatial resolution and a large dynamic range of measured dose. Our initial work has led to promising results in the development of samarium doped glasses and glass-ceramics where the conversion of Sm^{3+} to Sm^{2+}, induced by the irradiation serves as a measurement of dose delivered. The two ions have distinctly different photoluminescence (PL) signatures, which means that we can separate the Sm^{3+} and Sm^{2+} PL signals and hence use the PL signal from converted Sm^{2+} ions, through suitable calibration, to measure the delivered dose. In our findings, we have shown that these new dosimetric glass-ceramic materials are fast and erasable, thus demonstrating the potential for future applications [1]. In our current work, we have been concentrating on developing materials with close to tissue equivalent properties that will allow for the same dynamic range and spatial resolution, as well as investigating the dose rate and energy dependence, which were previously not considered. Using the BMIT beamline at the CLS, we have investigated the energy dependence of fluoroaluminate samples and found a strong correlation between the energy of the incident x-ray beam and the measured signal while the dose rate and total measured dose from an ionization chamber were kept constant. This experiment was repeated by keeping a constant energy and modifying the dose rate and the results were noticeable. Since the success of MRT relies on using energies around 90-100 keV and high dose rates, the complete characterization of samarium doped glass detectors is critical in properly assessing the dose delivered to a patient. Our research has found that conversion in samarium doped glasses is an excellent method for recording both high and low doses with high resolution and the present work continues to characterize this promising new material further for MRT applications by examining the dependence of the sensor responsivity on dose, dose rate and the average x-ray photon energy. We discuss the results in terms of radiation induced defects in the glass structure and the role these defects play in the conversion efficiency of Sm^{3+} to Sm^{2+}.

[1] G. Okada, J. Ueda, S. Tanabe, G. Belev, T. Wysokinski, D. Chapman, D. Tonchev, and S. Kasap. “Samarium-Doped Oxyfluoride Glass-Ceramic as a New Fast Erasable Dosimetric Detector Material for Microbeam Radiation Cancer Therapy Applications at the Canadian Synchrotron” *J. Am. Ceram. Soc.*, 97[7] 2147-2153 (2014)

Functional and microstructural studies of the rat somatosensory cortex by synchrotron X-ray microbeams and micro-CT imaging

A.G. Zippo[1], V. Del Grosso[1,2], G. Bertoli [1], A. Bravin[2], P. Coan[2,3], A. Mittone[2], M. P. Riccardi[4] , H. Requardt[2], and G.E.M. Biella[1]

1. IBFM, CNR, Segrate (Milan) Italy; 2. ESRF, Grenoble, France; 3. Ludwig-Maximilian Universitaet, Muenchen, Germany; 4. University of Pavia, Centro Arvedi, Italy

In previous studies from our laboratory using simultaneous massive electrophysiological recordings from the thalamus and the somatosensory cortex, it appeared that chronic pain affects (i) the capacities of groups of neurons to effectively communicate between them and (ii) to integrate the different tasks simultaneously running in the brain. In pioneering tests, performed at ESRF (ID17), seven X-ray microbeams (MB) (100 μm wide, spaced of 350 μm and depositing a dose of 200 Grays) were delivered over the somatosensory cortex of control rats and of chronic pain rat models [1]. This strategy had the aim to artificially generate segregated islets of cortex. Along our hypothesis this operation would have enriched the reduced dynamics of the cortex by multiplying the independent somatosensory regions thus increasing the adaptativity of the thalamo-cortical circuitry [2]. Comparing the behavioural, electrophysiological and anatomical data from Control, Chronic Pain non-irradiated and Chronic Pain irradiated rats, the results showed that Chronic Pain irradiated rats exhibited behavioural and electrophysiological parameters ($p < 0.01$) statistically comparable to those from the Control rats and thus significantly different from Chronic Pain non-irradiated rats. The further step has been to propose to get deeper in the micro-architectural anomalies potentially nested in the cortical microscopic texture hosting the neuron-glia-vessel matrices. The interpretation of these results lives on the fact that the synaptic activities transmit the neuronal messages not only from one neuron to the other, but also to the nearby astrocytes that in turn are faced over the microvessels membranes. Messages from neurons to vessels, regulating their diameters are mainly driven by astrocytic intermediation. The reorganization of the neural substrate, as it happens in chronic pain, should involve deep microvascular rearrangements with potential backward effects. A preliminary micro-CT imaging analysis focused on micro-architectural alignments among neurons, astrocytes and cortical microvessels has been performed in control rats to establish a reference case for further observations on Chronic Pain models.

References

[1] - A.G. Zippo, R. Storchi, M. Valente, G. Caramenti and G. E. M. Biella, “Neural Substrates of Chronic Pain in the Thalamocortical Circuit”, Nature Precedings, http://hdl.handle.net/10101/npre.2011.6548.1, (2011)

[2] Clune J, Mouret JB, Lipson H (2013) The evolutionary origins of modularity. Proceedings of the Royal Society B. 280: 20122863

[3] A.G. Zippo et al. Functional impairments of the somatosensory thalamocortical circuit in rat models of chronic pain. In preparation

Hydrated electron yield enhancing by Gd nanoparticles under X-rays beams: an in-line fluorescence study

I. Denden[1], P. Gimenez [2], H. Elleaume[3], J.L. Ravanat[2], G. Baldacchino[1]

[1] CEA Saclay IRAMIS/LIDYL-LFP, [2] CEA Grenoble INAC/LAN, [3] ESRF Grenoble, **ibtihel.denden@cea.fr**

Nanoparticles can be used to enhance the effect of the dose delivered by the ionizing beam in cancer therapy. [1][2] In this framework, we have studied the formation of hydrated electrons yield formation under X-ray beams in the presence of NP by using resazurin molecule in de-aerated water. The method lays on the detection of resorufin (RN) fluorescence. This species is the product of the resazurin reduction by hydrated electron. Fluorescence spectroscopy is performed in line with X-ray beam using real-time emission detection and a 532nm-CW laser as an excitation source. Experiments were performed at the ESRF synchrotron in the biomedical ID17 room with an X-ray energy ranging between 45 keV and 90 keV, around the K-edge of Gd. The results show an increase of the resorufin yield formation in the presence of Gd nanoparticles. Furthermore, the RN radiolytic yield increases with the increase of Gd nanoparticles concentration. We further demonstrated that resazurin reduction depends on the dose rate. As shown in the figure below, the concentration of RN at a fixed absorbed dose increases at lower dose rates. For the future work, we intend to repeat this experiment by irradiating with high-energy electrons and alpha particles.

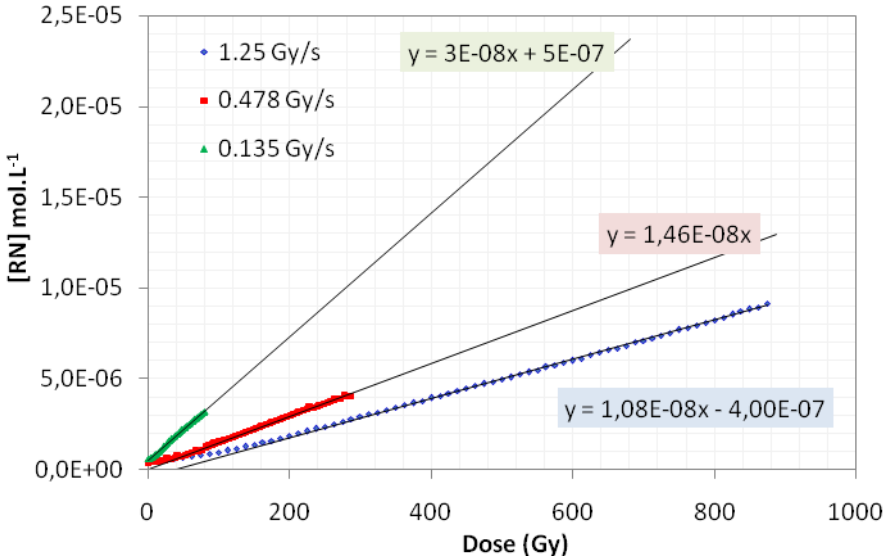


Figure: Effect of the dose rate on resorufin formation under X-ray beam as a function of the absorbed dose. Resazurin concentration = $5x10^{-4}$M, Energy = 80 keV.

References

[1] – M. Y. Chang, A. L. Shiau, Y. H. Chen, C. J. Chang, H. H-W Chen and C. L. Wu. Cancer Science. **99(7)**, 1479, (2001).

[2] – A. Mesbahi. Reports of pratical Oncology & Radiotherapy. **15(6)**, 176, (2010).

X-ray fluorescence computed tomography at SSRF

Biao Deng*, Guohao Du, Guangzhao Zhou, Yudan Wang, Yuqi Ren, Rongchang Chen, Pengfei Sun, Honglan Xie, Tiqiao Xiao**

Shanghai Institute of Applied Physics, Chinese Academy of Sciences
*E-mail:dengbiao@sinap.ac.cn; **E-mail:tqxiao@sinap.ac.cn

X-ray fluorescence computed tomography (XFCT) is a stimulate emission tomography that allows nondestructive reconstruction of elements distribution in the sample. XFCT system was established in the X-ray imaging (BL13W1) at Shanghai Synchrotron Radiation Facility (SSRF) [1-4]. And ordered subsets expectation maximization (OSEM) algorithm has been introduced into XFCT to speed up the data acquisition process and improve the imaging accuracy. Generally, XFCT is done by scanning a pencil-beam across the sample. This paper presents a feasibility study of full field XFCT (FF- XFCT) for 3D elemental imaging. The FF-XFCT consists of a pinhole collimator and X-ray imaging detector with no energy resolution. A prototype imaging system was set up at the Shanghai Synchrotron Radiation Facility (SSRF) for imaging the phantom. The first FF-XFCT experimental results are presented. The cadmium (Cd) and iodine (I) distributions were reconstructed. The results demonstrate FF-XFCT is fit for 3D elemental imaging and the sensitivity of FF-XFCT is higher than conventional CT system[5].

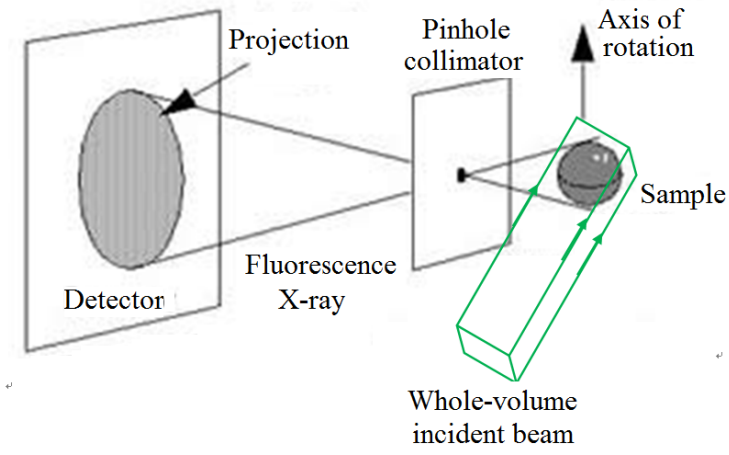


Fig. 1. The sketch of FF-XFCT with pinhole collimator.

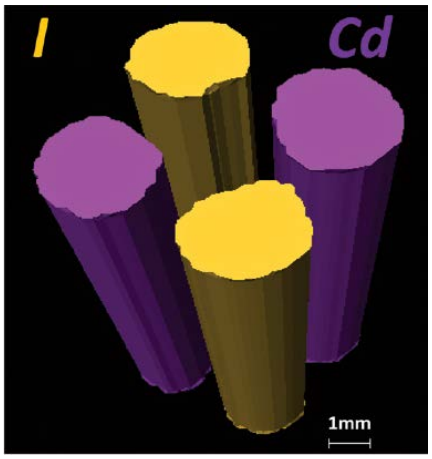


Fig. 2 3D cadmium and iodine imaging.

References

[1] Biao Deng, Qun Yang, et al. ***Chin. Phys.C***. 35(2011)402-404
[2] Qun Yang, Biao Deng, et al. ***J. Syn. Rad.*** 19(2012)210-215
[3] Biao Deng, Qun Yang, et al. ***NIMB.*** 305 (2013) 5–8
[4] Qun Yang, Biao Deng, et al. ***XRS.*** 43(2014)278-285
[5] Biao Deng, Guohao Du, et al***, Analyst,*** 2015, 140, 3521–3525

P8

X-*Tream* Dosimetry at the Australian Synchrotron

A. Dipuglia[1], P. Fournier[1], I. Cornelius[1,2], M. Petasecca[1], A. Stevenson[2,3], C. Hall[2], D. Hausermann[2], A.B. Rosenfeld[1], M.L.F. Lerch[1]

Affiliation: [1]Centre for Medical Radiation Physics, University of Wollongong, Australia
ad150@uowmail.edu.au
[2]Imaging and Medical Beamline, Australian Synchrotron, Australia
[3] Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia

Microbeam Radiation Therapy (MRT) uses synchrotron generated X-rays to deliver a treatment dose at a very high dose rate via physically collimated planar, parallel array of microbeams. The synchrotron X-ray beam in hutch 1B of the Imaging and Medical Beamline (IMBL) at the Australian Synchrotron is spatially fractionated by a tungsten/kapton multislit collimator (MSC) resulting in beam dimensions of either 25 or 50 μm FWHM microbeams with center to center spacing of 200 μm. Through the use of these beam dimensions the dose volume effect is evident and results in a tissue sparing effect. One consequence of this effect is an observed healthy tissue sparing whilst maintaining tumor control [1]. Due to the high dose rate and complex structure of the radiation field, current traditional dosimeters are not optimal for ensuring patient safety immediately pre-treatment as they either lack the required high spatial resolution, or real-time readout required. The X-*Tream* dosimetry system, is a new system based on the use of a Silicon Strip Detector (SSD) with real time readout and high spatial resolution, and has been developed at the Centre of Medical and Radiation Physics (CMRP) at the University of Wollongong, Australia [2]. Preliminary dosimetric measurements at the Australian Synchrotron, for both broad beam and microbeams, were investigated using the X-*Tream* system coupled with the silicon strip detector. These measurements were taken after calibration using a Pinpoint ionization chamber (PTW 31014), at the Imaging and Medical Beam Line (IMBL) at the Australian Synchrotron (AS), for both water and solid water phantoms using a variety of field sizes. The Peak to Valley Dose Ratios (PVDR), which are vital dosimetry parameters in the Quality Assurance (QA) in MRT were acquired and evaluated at a variety of depths for two different microbeam dimensions and will be presented in this poster coupled with the microbeam profiles.

References

[1] - Dilmanian, F. A., Button, T. M., Duc, G. L., Zhong N., Pea, L. A., Smith, A. L., … &Rosen, E. M. (2002) Response of rat intracranial 9l gliosarcoma to microbeam radiation therapy. *Neuro Oncol* 4(1), 26-38

[2] - Lerch, M. L. F., Petasecca, M., Cullen, A., Hamad, A., Requardt, H., Bräuer-Krisch, E., ...& Rosenfeld, A. B. (2011). Dosimetry of intensive synchrotron microbeams. *Radiation Measurements*, *46*(12), 1560-1565.

P9

Assessing particle mucociliary transit in excised sheep trachea

M. Donnelley[1-4], K. Morgan[5], N. Farrow[1-4], C. Hall[6], R. Acres[6], D. Parsons[1-4]

[1]Respiratory and Sleep Medicine, Women's and Children's Hospital, Adelaide, SA
[2]Robinson Research Institute, [3]School of Paediatrics and Reproductive Health, [4]Centre for Stem Cell Research, University of Adelaide, South Australia
[5]School of Physics, Monash University, Clayton, Victoria
[6]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria
martin.donnelley@adelaide.edu.au

Introduction: Cystic fibrosis (CF) airway disease is caused by an improperly functioning ion channel in the airway epithelium and results in impaired mucociliary transport (MCT), the mechanism that moves inhaled particles along the airway surface out of the lungs. CF mice are a limited model because they do not exhibit human-like lung pathophysiology. Our group is interested in using newly developed CF animal models, such as the CF pig, that display human-like lung disease. A recent study has demonstrated differences in MCT between CF and normal pig airways, however, that study used a human clinical CT setup combined with large (350 μm dia x 25 μm thick) tantalum discs as MCT markers. The aim of this study was to establish the utility of synchrotron phase contrast x-ray imaging (PCXI) to quantify MCT in a large animal airway at high spatial and temporal resolution.

Materials and methods: PCXI was performed on the Imaging and Medical Beamline (IMBL) at the Australian Synchrotron. Five freshly-excised normal adult sheep tracheae were cut into 3-5 segments (~3 cartilage rings each). Samples of 100 μm dia high refractive index (HRI) glass particles (Corpuscular, NY, USA) were delivered to each segment using a Dry Powder Insufflator™ (PennCentury, PA). Samples were placed on the X-Y stage with temperature and humidity maintained at physiological levels. A sample to detector distance of 250 cm was used. Images of the trachea (effective pixel size of 16 μm, field of view of ~ 16.6 mm x 14 mm, and an exposure length of 1 sec) were captured from two directions (dorsal/ventral and lateral) using the Ruby detector. In some segments, after baseline imaging was performed an Aeroneb nebuliser was used to deliver aerosolised hypertonic or isotonic saline to test the effects of altered airway surface hydration. Custom image tracking software was used to tag particles, and calculate particle transit rates.

Results: HRI bead MCT was visible in all tracheal segments examined, except for one that was deliberately imaged ~24 hours after excision. Beads moved in the direction of preferential MCT, including vertically up the tracheal wall when oriented against gravity. Beads tended to organise and aggregate into long strings, and appeared to move in favoured MCT tracts, with beads moving circumferentially towards the ventral tracheal surface. Further MCT analyses are ongoing.

Conclusions: This experiment demonstrated that the wide beam at the IMBL is suitable for imaging MCT in *ex vivo* tissue samples. With increased flux and reductions in exposure length live imaging of intact large animals such as sheep and pigs should be possible.

Acknowledgements: Studies supported by the WCH and Cure4CF Foundations. Experiments performed under proposal AS151/IMBL/8993. MD is supported by a MS McLeod Postdoctoral Fellowship and KM by an ARC DECRA.

P10

Image-guided conformal MRT at the ESRF beamline ID17

M. Donzelli[1], E. Bräuer-Krisch[1], C. Nemoz[1], T. Brochard[1], U. Oelfke[2]

Affiliation: [1]European Synchrotron Radiation Facility, Grenoble, France
[2]Institute of Cancer Research, London, United Kingdom

Moving from preclinical trials in microbeam radiation therapy (MRT) towards applications in larger organisms demands a better control of the treatment geometry. For the treatment of non-superficial tumours with irradiations from multiple ports the peak entrance dose is limited by the normal tissue tolerance at shallow depth.

To optimise normal tissue sparing, an image-guidance protocol has been developed which allows an accurate and precise irradiation of deep-seated tumours, according to a CT-based treatment plan. The positioning of the patient is based on external fiducial markers which can easily be detected on both, CT images for treatment planning and X-ray projection images taken prior to the treatment for a correct alignment.

As a result, the irradiation field size can be reduced to the actual tumour shape for each port, thus lowering the amount of irradiated normal tissue and increasing the peak-to-valley dose ratio (PVDR) which in turn increases the normal tissue radiation tolerance.

A low dose, in-vivo X-ray projection imaging technique using synchrotron-generated pink beam has been optimised for this purpose. The resulting dose to the patient was assessed with two different ionisation chambers and corrected for the highly inhomogeneous imaging beam.

Results:
Realistic experiments with an anthropomorphic head phantom, employing a full chain starting from CT-imaging for treatment planning down to the irradiation, show a maximum deviation from the targeted point of less than 2 mm. For an improved protocol, even less than 1 mm of misalignment is possible. In the first case, the rotational error is smaller than 2°.
The imaging dose is in the range of diagnostic reference levels for comparable human head radiographs.

Conclusion:
The beamline ID17 of the ESRF is technically ready to accurately apply conformal image-guided MRT treatments including combinations of multiple beam ports.

Ref.: M. Donzelli et al. ‘Conformal image-guided Microbeam Radiation Therapy at the ESRF biomedical Beamline ID17’, to be submitted to Medical Physics

Cardiosynchronous brain motion artefacts in MRT: a Monte Carlo study

M. Donzelli[1], E. Bräuer-Krisch[1], U. Oelfke[2]

Affiliation: [1]European Synchrotron Radiation Facility, Grenoble, France
[2]Institute of Cancer Research, London, United Kingdom
donzelli@esrf.fr

Organ motion has not been an issue in microbeam radiation therapy (MRT) as long as research was carried out in small samples, such as cell cultures and rodents. But the future treatment of human brains - in cancer therapy or radio surgery - using microbeam radiation is affected by the cardiosynchronous tissue pulsation. This pulsation, having an amplitude in the order of 100 µm, induces a translation and blurring of the initially plane-parallel microbeam pattern.

Monte Carlo calculations for different microbeam reference dosimetry configurations and dose rates show significant changes under certain conditions compared to the static case. The affected indicators include peak dose, peak-to-valley dose ratio (PVDR), microbeam width, spacing, and penumbra.

Preliminarily it can be concluded that under the effect of organ movement high dose rates become even more important in the application of microbeam radiation, unless more sophisticated irradiation geometries will be developed.

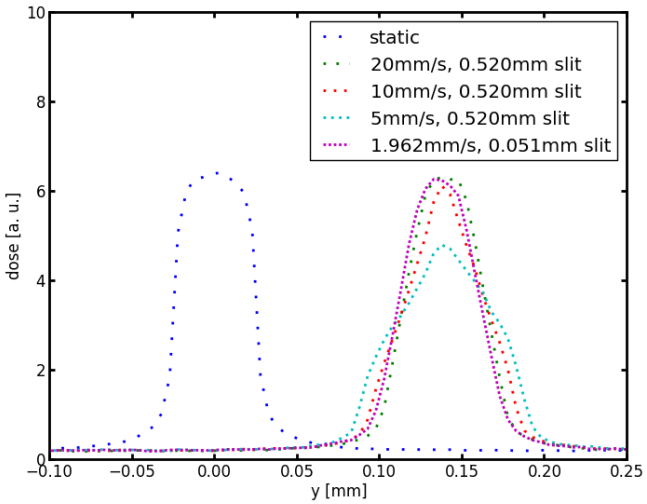


Figure 1: Microbeam profiles affected by organ motion in dependence of the scan speed and the vertical slit size compared to a microbeam in standard configuration.

P12

Three-dimensional reconstruction and visualization of lumbar facet joint in rats model by SR-μCT

Hu,JianZhong[1];Zhang,Yi[1];; Cao, Yong[1]; Lu,HongBin[2*] ;Duan,ChunYue[1*]
1 Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
2 Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
* Co-Corresponding author: hongbinlu@hotmail.com; 93448157@qq.com

INTRODUCTION: There has been increasing interest in the study of three-dimensional (3D) morphology of lumbar facet joint (LFJ). However, its morphology investigation is currently constrained in two-dimensional (2D) using the conventional method, which only provides 2D information of the complex structure and does not represent the 3D forms that precisely reflect the nature of the LFJ. In this study, we demonstrated a novel imaging technique and assessed its feasibility for 3D visualization of LFJ in a rat model using synchrotron radiation micro-tomography (SRμCT).

METHOD: Five normal rat LFJs were harvest and prepared for SRμCT measurement. After SRμCT scanning, the corresponding samples were re-embedded for tissue histologic studies. The histomorphology data were compared with the results obtained from SRμCT imaging.

RESULTS: The 3D microstructure of lumbar facet joint was successfully obtained via SRμCT. After image segmentation, the micro morphology of the cartilage and subchondral bone in LFJ were also vividly visualized and could be rendered in 3D. Additionally, without application of any stain, the morphology of the cartilage of the LFJ in SRμCT was consistent with the images of the histomorphological observations.

CONCLUSIONS: These results indicate that SRμCT is an excellent tool in addition to conventional histomorphological analyses and opens a new dimension for 3D morphological investigations of the LFJ microstructure and its alteration during degeneration process, and it could help to evaluate the efficiency of therapeutic strategies on rejuvenation of the degeneration of LFJ.

ACKNOWLEDGEMENT: This work was supported by the National Natural Science Foundation of China (No. 81301522). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

Mammography with Synchrotron Radiation: dose and diagnostic comparison of a clinical study report

C. Fedon[1], L. Rigon[1*], F. Arfelli[1], M. Borelli[2], D. Dreossi[3], E. Quai[4], M. Tonutti[5], G. Tromba[3], M. A. Cova[5], R. Longo[1]

[1]Università degli Studi di Trieste, Dip. Fisica and Istituto Nazionale di Fisica Nucleare, Trieste (Italy)
[2]Università degli Studi di Trieste, Dip. Scienze della Vita, Trieste (Italy)
[3]Sincrotrone Trieste SCpA, Trieste (Italy)
[4]IAEA, Vienna (Austria)
[5]Azienda Ospedaliero Universitaria "Ospedali Riuniti", Trieste (Italy)
[*]luigi.rigon@ts.infn.it

Mammography with Synchrotron Radiation (MSR) has been performed at the SYRMEP (SYnchrotron Raditioan for MEdical Physics) beamline at Elettra synchrotron in Trieste, Italy [1]. The clinical study involved 71 female patients (age range 41-82), who received a doubt diagnosis at conventional Digital Mammography (DM). Partial results, limited to 49 patients, were already discussed in [1]. The work presented hereby is based on the whole patients cohort and shows the synergy between Mean Glandular Dose (MGD) reduction and diagnostic performances. The image quality analysis was presented in [2].

Using the statistical tool of generalized linear model, the BI-RADS scores are related to the final diagnosis. The results obtained for MSR and DM are shown in Figure 1: nineteen patients that after DM were associated to BI-RADS score 4 (i.e. suspicious abnormalities) were moved to BI-RADS score 1 (10/19), score 2 (1/19) and score 3 (6/19) after MSR. Moreover, good results were found for all those patients with a dense breast (category 3-4), whose diagnosis appears difficult at DM (black dots on Figure 1).

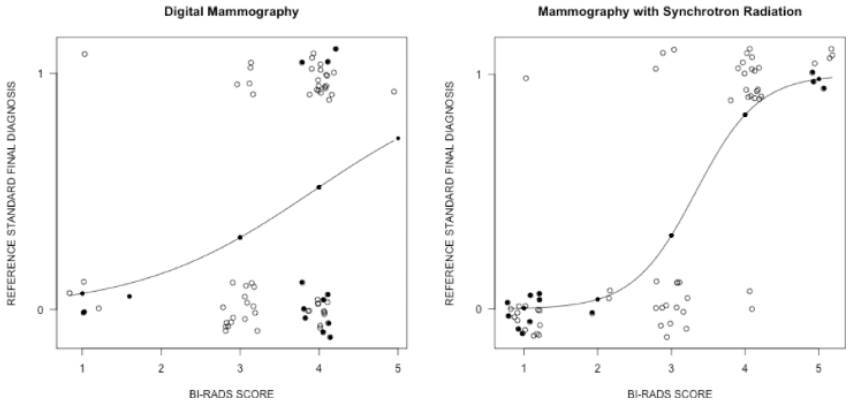


Figure 1: Generalized linear model applied to DM data (on the left) and to MSR data (on the right): the solid line is the fit model, each dot is a patient (in black those who have a dense breast of category 3 or 4). On ordinate the reference final diagnosis (i.e. biopsy or follow up) is shown: 0 means healthy, 1 means sick.

An average 42% reduction of MGD is observed in MSR compared to the DM due to the fact that monochromatic SR has no low-energy components, unlike conventional x-ray spectra.

References

[1] – E. Castelli et al. *Radiology* **250(3)**, 684-94 (2011)
[2] – R. Longo et al. *Phil. Trans. R. Soc.* **372** (2014)

P14

Breast CT with Synchrotron Radiation: dosimetric approach to the first clinical trial

C. Fedon[1*], F. Di Lillo[2], G. Mettivier[2], P. Russo[2], F. Arfelli[1], G. Tromba[3] and R. Longo[1]

[1]Università degli Studi di Trieste (Italy) and Istituto Nazionale di Fisica Nucleare Trieste (Italy)
[2]Università di Napoli Federico II (Italy) and Istituto Nazionale di Fisica Nucleare Napoli (Italy)
[3]Sincrotrone Trieste SCpA, Trieste (Italy)
*christian.fedon@ts.infn.it

The aim of SYRMA-CT project is to perform the first clinical study of phase contrast breast CT at the SYRMEP beamline at Elettra Synchrotron (Italy). In order to combine high image quality and low delivered dose a number of innovative elements will be merged: a novel CdTe single photon counting detector, state-of-the-art CT reconstruction algorithms, phase map reconstruction. Due to the laminar shape of the Synchrotron Radiation (SR) beam, acquisition from a breast volume requires multiple rotations of the patient on the patient support. The breast volume under investigation will be selected during the exam initialization and it will be covered collecting several CT scans at different vertical positions: the expected scan number is in the range 10-20 (3-6 cm height).
In this presentation the Monte Carlo code (based on GEANT4 software), developed for the SYRMA-CT dosimetry, is presented, including its experimental validation (Fig. 1). Since the definition of the mean glandular dose (MGD) assumes that the whole breast is exposed to the x-rays, this parameter is not applicable here, thus an extension has to be defined. The Slice Average Glandular Dose (SAGD), defined as the average dose value in the slice volume irradiated, and Total Average Glandular Dose (TAGD), calculated as the average dose in the whole breast in the slice volume irradiated, are introduced. The goal of this study is to create a database of normalized glandular dose (DgN) values (e.g. in [1]) as a function of monochromatic energy for several breast glandularity and diameters: according to the energy suitable for the clinical exams, the SAGD and TAGD are evaluated using the DgN coefficients and the air-kerma measured by the two ionizing chambers of the mammography facility of the SYRMEP beamline.

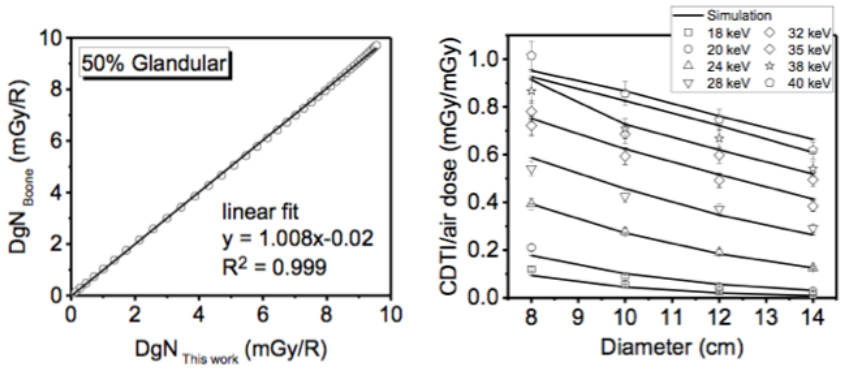


Figure 1: Left graph shows the comparison of DgN coefficients with literature [1]; the right graph shows Monte Carlo data and the experimental values of the CTDI as a function of the PMMA sample diameter.

References

[1] – J. M. Boone *Med. Phys.* **29** 869-875 (2002)

P15

Silicon based Single Strip Detector for dosimetry applications in Microbeam Radiation Therapy

P. Fournier[1], I. Cornelius[1,2], S. Bartzsch[3], E. Bräuer-Krisch[4], M. Petasecca[1], J.F Adam[5], H. Requardt[4], T. Brochard[4], C. Nemoz[4], A.B. Rosenfeld[1], M.L.F. Lerch[1]

Affiliation: [1]Centre for Medical Radiation Physics, University of Wollongong, Australia **pf891@uowmail.edu.au**
[2]Imaging and Medical Beamline, Australian Synchrotron, Australia
[3]Institute of Cancer Research, London, England
[4]European Synchrotron Radiation Facility, Grenoble, France
[5] INSERM U836, Team 6, Grenoble, France

Microbeam Radiation Therapy (MRT) is a novel irradiation technique based on the use of plane parallel arrays of microbeams (MBs). The beam spatial fractionation is produced by a multislit collimator (MSC) (50 μm FWHM MBs spaced by 400 μm). Such beam dimensions permit to take advantage of the dose volume effect which will result in the sparing of the healthy tissue while maintaining a detrimental effect on the tumor. A 3rd generation synchrotron X-ray source is required for MRT for several reasons: the low beam divergence allows the production of plane parallel MBs, the high dose rates ensure fast irradiation times thus avoiding any blurring of the MBs with cardiosynchronous motion [1] and the energy spectrum in the range 27-600 keV [2] provides sharp beam penumbra. As for any radiotherapy treatment involving radiations, pre-treatment Quality Assurance (QA) is required for MRT but remains a challenging task due to the high spatial resolution and the radiation resistance properties required from the dosimeter. To meet the challenge, the Centre for Medical Radiation Physics has developed the Single Strip Detector (SSD), a high resolution detector based on an epitaxial layer of silicon, especially for MRT dosimetry purposes [3]. The SSD potential has been evaluated for different types of QA on the ID17 biomedical beamline at the European Synchrotron Radiation Facility (ESRF). Peak to Valley Dose Ratios and Output Factors, two important dosimetry parameters in MRT, have been measured and compared to MC simulations results. The SSD has also been used for the alignment of the MSC using a method based on the in-air measurements of the MBs profiles. Finally, the energy dependence of the SSD has been evaluated and will be presented in this poster.

References

[1] - Bräuer-Krisch, Elke, et al. "Effects of pulsed, spatially fractionated, microscopic synchrotron X-ray beams on normal and tumoral brain tissue."*Mutation Research/Reviews in Mutation Research* 704.1 (2010): 160-166.
[2] - Martínez-Rovira, I., et al. "Development and commissioning of a Monte Carlo photon beam model for the forthcoming clinical trials in microbeam radiation therapy." *Medical physics* 39.1 (2012): 119-131.
[3] - L Lerch, M. L. F., et al. "Dosimetry of intensive synchrotron microbeams."*Radiation Measurements* 46.12 (2011): 1560-1565.

P16

From Synchrotron Radiation to the most recent breakthroughs in Clinical Regenerative Dentistry

A.Giuliani[1], S.Mazzoni[1], A.Manescu[1], M. Langer[2], C.Mangano[3], A.Barone[4], G. Tromba[5], B.Barboni[6], A.Piattelli[7], G.Papaccio[8]

[1]Università Politecnica delle Marche, Dip. di Scienze Cliniche e Odontostomatologiche, Ancona, Italy, **a.giuliani@univpm.it,** [2]Creatis, INSA-Lyon, Université CB Lyon & European Synchrotron Radiation Facility, [3]University of Insubria, Dept. of Morphological and Surgical Sciences, Varese, Italy, [4] Università di Pisa, Dipartimento di Chirurgia, Pisa, Italy, [5]Elettra - Sincrotrone Trieste S.C.p.A., Basovizza, Trieste, Italy, [6] Università degli Studi di Teramo, Department of Comparative Biomedical Sciences, Teramo, Italy, [7] University of Chieti, Department of Oral Medicine and Pathology, Chieti, Italy, [8]Secondo Ateneo di Napoli, Dipartimento di Medicina Sperimentale, Napoli, Italy,

In recent years there has been an increasing interest in a novel approach to evaluate human bone biopsy specimens by means of synchrotron micro-tomography (SCT)[1]. Using SCT, bone regeneration subsequent to grafting hosting sites with different types of biomaterials (with or without stem cells seeding) is recently explored. Evaluation of the amount of bone formed is usually based on histomorphological data obtained from one or several histological sections; however, conventional histological evaluation and corresponding histomorphometric measurements provide only 2D information with the consequent risk that the selected sections do not properly represent the entire bone biopsy specimen.

Furthermore, if the regenerative potential of neighbouring tissues with different morphology (alveolar process, unmineralized extracellular matrix involvement, regenerated vessels, etc.) on a defect or space to regenerate is not clearly verified or unknown, 3D analysing methods like high resolution SCT are indicated to explore dynamic and spatial distribution of regenerative phenomena in such complex anatomic structures [2]. Traditionally, SCT is conducted in absorption mode in medical applications. Homogeneous materials with a low attenuation coefficient (like collagen, unmineralized extracellular matrix, vessels, nerves, etc.) or heterogeneous materials with a narrow range of attenuation coefficients (like the case of heterologous bone scaffolds or for graded mineralized bone - such as that created by regeneration process deriving from engrafted stem cells) produce insufficient contrast for absorption imaging. For such materials, the imaging quality can be enhanced through the use of phase contrast tomography (PCT)[3]. In addition, whereas PCT is based on a single distance between the detector and the sample, holotomography (HT) involves imaging at several distances, then combining the phase shift information to generate 3D reconstructions. HT is helpful when the material of interest has very small variations in attenuation coefficients, which lead to unsatisfactory imaging results even with phase contrast techniques [4].

In the present lecture the most recent breakthroughs in Clinical Regenerative Dentistry will be shown, demonstrating the unique capabilities of the SCT in offering not only an advanced characterization of different biomaterials (to understand the mechanism of their biological behaviour as bone substitute) but also to investigate the growth kinetics of regenerated bone in different dental implants retrieved from humans.

Implant survival, bone regeneration, graft resorption, neo-vascularization and morphometric parameters (including anisotropy and connectivity index of the structures) were evaluated by microCT and HT at different times from implantation or grafting in human bone defects.

These innovative techniques allowed not only the visualization and quantification of mineralized tissues, but showed also the eventual presence and distribution of vascularization. This is of paramount importance and demonstrates that X-Ray phase tomography and holotomography appear to be important ways to investigate the cellular events involved in bone regeneration and represent promising tools for future clinical investigations of the cranio-facial tissues.

References

[1] - R. Cancedda, A. Cedola, A. Giuliani , V. Komlev, S. Lagomarsino, M. Mastrogiacomo, F. Peyrin and F. Rustichelli, Biomaterials **28(15),** 2505-2524 (2007).

[2] - A. Giuliani, V. Komlev, and F. Rustichelli. In: Innovative Technological Materials, by Skrzypek, Jacek J.; Rustichelli, Franco, ISBN 978-3-642-12058-9. Springer-Verlag Berlin Heidelberg, 2010, p. 123.

[3] - A. Manescu, A. Giuliani, S. Mazzoni, S. Mohammadi, G. Tromba, F. Diomede, N. Zini, A. Piattelli, and O. Trubiani, Accepted on 15th Apr 2015 by Journal of Periodontal Research - Manuscript ID JRE-11-14-2872.R2.

[4] – A. Giuliani, A. Manescu, M. Langer, F. Rustichelli, V. Desiderio, F. Paino, A. De Rosa, L. Laino, R . D'Aquino, V. Tirino, and G. Papaccio, G. Stem Cells Translational Medicine **2**, 316-324 (2013).

Edge illumination x-ray phase contrast computed tomography: Recent developments and new applications

C.K. Hagen[1,2], P.C. Diemoz[1], M. Endrizzi[1], A. Zamir[1], F.A. Vittoria[1], A. Olivo[1]

Affiliation: [1]Department of Medical Physics and Biomedical Engineering, University College London, Malet Place, London WC1E 6BT, United Kingdom, [2]**charlotte.hagen.10@ucl.ac.uk**

X-ray phase contrast imaging, especially in combination with computed tomography, has become an important tool for the non-destructive study of biomedical specimens, which often do not provide sufficient image contrast in purely attenuation-based radiography. While phase-based methods are nowadays used routinely at synchrotrons, their usage in standard research labs is still limited. This is mainly due to the fact that only a small number of phase-based methods allow a straightforward adaptation with commercially available, non-specialized x-ray equipment. Among these is the edge illumination method, which, due to its independence from spatial and temporal coherence, is naturally suited to both synchrotron and laboratory environments. The edge illumination method is highly phase sensitive [1], dose efficient [2] and based on a simple experimental setup (see Fig. 1). Recently, it has been combined with the principles of computed tomography, allowing the reconstruction of 3D, fully quantitative phase maps [3].

This talk will give an overview of recent developments of tomographic edge illumination x-ray phase contrast imaging. First, we will discuss different experimental setups, including the "scanning" implementation typically used at synchrotrons [Fig. 1(a)] and the "full-field" implementation normally used in combination with lab-based sources [Fig. 1(b)]. We will briefly describe phase retrieval and image reconstruction procedures. In addition, approaches for fast and low dose imaging will be presented, based on the concept of reverse projection and single-shot methods. Finally, new applications in the biomedical field will be reviewed, including regenerative medicine and tissue engineering.

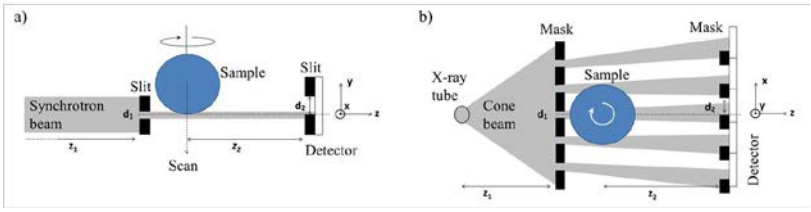


Figure 1: a) Synchrotron ("scanning") implementation of the edge illumination method: a beam is collimated by a first slit, while a second slit in front of the detector stops half of the beam, allowing the remaining half through. This "edge illumination" configuration is the sensing mechanism for refraction-induced beam displacements. A 2D image can be obtained by scanning the sample through the setup. b) Laboratory ("full-field") implementation, in which the slits are replaced by two apertured masks, repeating the edge illumination configuration over the entire field of view. No scanning is required to obtain a 2D image.

References

[1] – P.C. Diemoz *et al*, Phys. Rev. Lett. 110(13): 138105 (2013).
[2] – A. Olivo *et al*, Med. Phys. 40(9): 090701 (2013).
[3] – C.K. Hagen *et al*, Med. Phys. 41(7): 070701 (2014).

P18

X-Ray imaging detectors for the IMBL at the Australian Synchrotron

:

Chris Hall[1], Daniel Hausermann[1], Anton Maksimenko[1], Andrew Stevenson[1,2], James Pearson[1,3], Jayde Livingstone[1]

[1] Imaging and Medical Beam line, Australian Synchrotron, Clayton, Victoria, Australia (**chris.hall@synchrotron.org.au**)
[2] CSIRO Manufacturing Flagship, Clayton South, Victoria, Australia
[3] Monash University, Monash Biomedical Imaging, Clayton, Victoria, Australia

The Australian Synchrotron Imaging and Medical Beam Line (IMBL) provides Australia with an unrivalled facility for x-ray imaging and radiotherapy research, covering a wide range of applications in disease studies, treatments, and revealing physiological processes. The clinical research drivers for IMBL rely on the facility's ability to support moderate spatial, and high contrast resolution imaging.
The beam line provides a maximum source to sample distance of 140 m which when coupled to a high field wiggler source yields an exceptionally wide beam, with sufficient coherence for exploiting phase contrast imaging. IMBL operates with a superconducting multi-pole wiggler and can deliver a 40 cm wide beam, 4 cm high at the patient position in furthest experiment enclosure. Imaging is performed in the photon energy range 15-150 KeV with either monochromatic or polychromatic radiation.
The wide variety of demands for x-ray imaging using IMBL cannot be covered with a single detector system. After assessing the experiments most likely to be performed during the first few years of operation, a list of seven detector tasks were specified. These were based on the demands for photon beam energy, imaging speed, field of view, and spatial resolution. The demands were broadly covered by the following categories: low energy (20-35 keV), medium energy (35-70 keV), high energy (70-150 keV), high resolution (10 micron), medium resolution (50 micron), low resolution (100 micron), and high frame rate (> 30fps) and low frame rate (< 10 fps).

- High resolution material imaging and CT of small objects at low energies
- Medium resolution biomedical imaging and CT at medium and high energies
- Medium resolution material CT, and biomedical imaging with fast frame rates
- Large field alignment for therapy with polychromatic beam
- Portal imaging for therapy and biomedical imaging at fast frame rate
- Wide field, medium resolution high energy imaging
- Very wide field medium resolution imaging and CT at high energies

The first six tasks have been covered with six different detectors, the last being left for future development. This presentation describes these detectors and discusses the competing demands from the science on the technology of the systems.

References

[1] C. Hall et al., 'Detectors for the Imaging and Medical Beam Line at the Australian Synchrotron', JInst **8** C06011 (2013) doi:10.1088/1748-0221/8/06/C06011

P19

Combined SRCT and FXCT

C. J. Hall[1], Robert Acres[1]

[1]Imaging and Medical Beam line, Australian Synchrotron, Clayton, Victoria, Australia (chris.hall@synchrotron.org.au)

One of the goals in developing synchrotron radiation x-ray CT (SRCT) for biomedical specimens is to allow particular tissues and cell types to be marked in the images. This is equivalent to the staining in histology, which allows researchers to visualise and measure tissue structure and biochemical processes within the specimen. Some progress in this idea in SRCT is being made using a variety of contrast agents [1]. These provide image contrast by altering the natural x-ray attenuation of the marked tissue. For instance iodine compounds, phosphor-tungstic acid, and various nanoparticles are popular in the SRCT community. However there are limits to the usefulness of these attenuation altering techniques. Often high concentrations of potentially disruptive chemicals are required with reduced compatibility for in-vivo studies.

Another image highlighting technique which might prove more sensitive, is biomedical x-ray fluorescence imaging. This technique is exploited on x-ray fluorescence microscopy (XFM) beam lines around the world to great effect. In this case usually endogenous elemental markers are visualised. We would like to develop a lower resolution, but wider field of view means of 3-D fluorescence imaging compatible with SRCT.

At the previous MASR a beam modulation technique was proposed to allow fluorescence CT (FXCT) and SRCT data to be collected simultaneously [2]. This work resulted in proof of concept modelling and a simple experiment test system. Results showed promise but that further work was required to refine the technique. During the study the technique was found to fail when more than one point source of fluorescence was present in the object.

Since seminal papers on the subject were published in 2008, there has been significant activity in the signal processing community on Compressive Sensing (CS). These ideas have been proven for imaging at optical and infra-red wavelengths. The most well-known is arguably the 'Single Pixel Camera' [3]. They have also caused a lot of excitement in the medical imaging community. However, to date not much has been published on using CS in SR x-ray imaging. We believe CS imaging techniques suit SRCT and may overcome the issues in combining SRCT and FXCT. Our previous work was based on using a single fixed pattern coding mask to modulate the illuminating beam. We have now shown that CS helps improve the reconstruction in this case, and it suggests better modulation strategies.

In this paper we present recent data which demonstrates the reconstruction of low resolution iodine fluorescence maps of realistic phantoms, from data collected on a single point detector during a CT scan on IMBL.

References

[1] - Pauwels et al, 'An exploratory study of contrast agents for soft tissue visualization by means of high resolution X-ray computed tomography imaging', Journal of Microscopy, Vol. 250, Pt 1 2013, pp. 21–31, doi: 10.1111/jmi.12013

[2] - C. Hall, 'Combined x-ray fluorescence and absorption computed tomography using a synchrotron beam', 2013, Journal of Instrumentation. doi:10.1088/1748-0221/8/06/C06007

[3] - S. S. Walsh et al, 'Fast full-color computational imaging with single-pixel detectors' , Optics Express, Vol. 21, Issue 20, pp. 23068-23074 (2013), doi:10.1364/OE.21.023068).

P20

In-line Phase-Contrast Microcomputed Tomography: New Application for In Vivo Imaging of Cortical Bone Remodeling of the Rat Forelimb

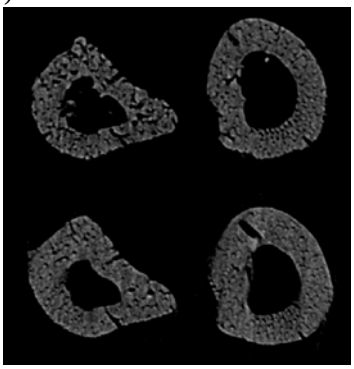
K. Harrison[1], G. Belev[2], N. Zhu[2], M. A. Webb[2], I. Pratt[1], D. Cooper[1]

[1] Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, SK, Canada
[2] Canadian Light Source, Saskatoon, SK, Canada

Basic Multicellular Units (BMUs) are groups of cells responsible for turnover of bone known as 'remodeling'. In cortical bone this is achieved through the localized osteoclastic resorption of a cylindrical space of tissue followed by concentric osteoblastic infilling by new tissue. With increasing age, this balance between bone resorption and formation shifts, resulting in increased cortical porosity and increased risk of developing bone degenerative diseases such as osteoporosis. A central hypothesis regarding BMU spatio-temporal behavior is that all remodeling events are targeted [1] or 'steered' [2] towards areas of microdamage. Due to a lack of three-dimensional (3D) analytical techniques, the majority of what is currently known regarding BMU behavior is *ex vivo* and two-dimensional in nature. It is imperative, however that BMUs be imaged in their natural 3D environment to fully appreciate factors that affect their morphology and spatio-temporal behavior [3] therefore, a means to track their progression over an extended period of time at a safe radiation dose in a live animal is crucial.

X-ray micro-CT and Synchrotron Radiation (SR) micro-CT are commonly employed, *in vivo*, for 3D analyses of trabecular bone microarchitecture in living animals and more recently, for cortical bone porosity, *ex vivo*. However, both micro-CT and SR micro-CT share the limitation that in general, improving resolution by a factor of 2 increases radiation dose by a factor of 16 to maintain image quality [4]; a characteristic particularly problematic for imaging small scale cortical bone morphology in a living animal. Using the BioMedical Imaging and Therapy (BMIT-BM; 0581-1) bending magnet beamline at the Canadian Light Source (CLS) synchrotron, our group tested in-line phase contrast micro-CT as a safe *in vivo* longitudinal protocol for live animal imaging. Key advantages of phase contrast over absorption based imaging are: 1) images derived from the refractive indices of an object's internal structures [5] can be optimized by increasing the object-to-detector distance to produce contrast [6; 7] and 2) by imaging at higher X-ray energies where absorption is lower, dose is potentially decreased while resolution is maintained [6]. Each rat's right forelimb was scanned, *in vivo*, on two separate occasions at two week intervals to identify the effects of radiation dose and the ability to visualize cortical porosity. Two different radiation dose levels (2 Gy and 3 Gy), at a voxel size of 12µm and a 90 cm target-to-detector distance was used for all *in vivo* scanning. Results have shown that at both radiation doses, cortical porosity was visualized and matching of consecutive scans for the purpose of tracking BMU progression within the bone of an individual animal is achievable (Figure 1). Secondly, daily monitoring of all the rats did not reveal any overt signs of radiation sickness and post-scan, *ex vivo* high resolution (5 µm) micro-CT will reveal any radiation effects on bone microarchitecture. Imaging of live animals provides direct and novel *in vivo* evidence of BMU behavior in relation to microdamage in 3D. Further development of such methodology promises to advance our understanding of fundamental bone biology which will enhance the efficacy of drug and physiological therapies for degenerative diseases such as osteoporosis.

Figure 1: Matched SR micro-CT (11.8 µm; 2 Gy) scans of a rat forelimb. Scan 2 (bottom row) was carried out 2 weeks after the first scan (top row) on the same rat.



References

[1] R. B. Martin, Bone, 30(1), 8-13 (2002).
[2] R. B. Martin, Bone, 40, 1574-1580 (2007).
[3] D.M.L. Cooper et al., The Anatomical Record, 288A, 806-816 (2006).
[4] N. Ford et al., Medical Physics, 2869-2877 (2003).
[5] Arfelli et al., Physics in Medicine and Biology, 2845-2852 (1998).
[6] S.A. Zhou & A. Brahme, Physica Medica, 129-148 (2008).
[7] Pratt et al., Physics in Medicine and Biology. 211-232 (2015).

Dual energy computed tomography for element analysis based on K-shell absorption edge using the LEBRA PXR

Y. Hayakawa, K. Hayakawa, M. Inagaki, T. Kaneda[1], K. Nakao, K. Nogami, T. Sakae[1], T. Sakai, Y. Takahashi[2], T. Tanaka

Inst. of Quantum Sci. , Nihon Univ., Narashinodai 7-24-1, Funabashi 274-8501, Japan;
email: **yahayak@lebra.nihon-u.ac.jp**
[1]Nihon Univ. School of Dentistry at Matsudo, Sakaecho-Nishi, 2-870-1, Matsudo 271-8587, Japan
[2]Inst. of Mater. Struct. Sci., KEK-PF, Oho 1-1, Tsukuba 305-0801, Japan

The Laboratory for Electron Beam Research and Application (LEBRA) in Nihon University has been regularly providing a coherent X-ray beam based on parametric X-ray radiation (PXR). The characteristics of the PXR X-rays allow us to carry out diffraction-enhanced imaging (DEI), despite the cone beam with mrad order of the aperture angle [1]. This suggests the possibility of application to a further advanced imaging system similar to stereoscopic/triscopic imaging conducted at third-generation SR facilities [2]. In addition, the crossing beams with either energy with respect to the absorption edge of a specific element can be formed by taking advantage of the spatial chirp in the PXR beam profile. Due to the existence of the absorption edge, it is possible to observe the dual X-ray absorption image with drastically changed contrast for the same object.
Figure 1 shows the schematic illustration of the imaging system. Also shown is a typical image of a polypropylene tube filled with the epoxy resin containing small polyethylene fragments that were colored with $SrTiO_3$, which were taken by adjusting the PXR center energy to the Sr K-shell edge of 16.1keV. Although the X-ray flux of the PXR source is far lower than those of SR sources, the high stability of the X-ray beam has allowed the dual-energy computed tomography (DE-CT) that required several hours of a measurement time. The three dimensional distribution of Sr in the light medium has been successfully reconstructed from the projection images obtained by the imaging system.

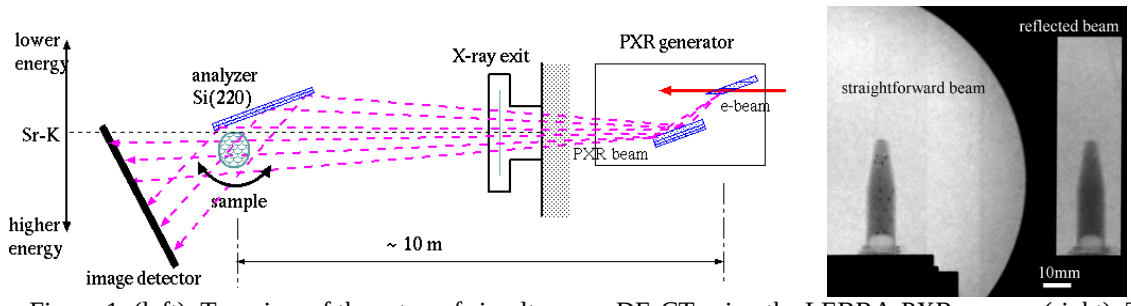


Figure 1: (left): Top view of the setup of simultaneous DE-CT using the LEBRA-PXR source; (right): The typical projection raw image obtained by this imaging system at the energy of Sr K-shell absorption edge.

References

[1] – Y. Hayakawa, Y. Takahashi, T. Kuwada, et al., J. Instrumentat. **8**, C08001 (2013).
[2] - M. Hoshino, T. Sera, K. Uesugi, N. Yagi, J. Instrumentat. **8**, C05002 (2013).

P22

Three-dimensional imaging of morphological changes to the microvasculature in the rat spinal cord after injury

Hu, JianZhong[1*]; Cao, Yong[1]; Wu, Tianding[1]; Lu, HongBin[2]

1 Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
2 Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
* Corresponding author: **jianzhonghu@hotmail.com**

Introduction: Research studies on the three-dimensional (3D) morphological alterations of the spinal cord microvasculature after injury provides insight into the pathology of spinal cord injury (SCI). Knowledge in this field has been hampered in the past by imaging technologies that provided only two-dimensional (2D) information on the vascular reactions to trauma. The aim of our study is to investigate the 3D microstructural changes of the rat spinal cord microvasculature upon injury using synchrotron radiation micro-tomography (SRμCT).

Method: SD rats were subjected to the modified Allen's weight impacting to induce an SCI model. The imaging acquisition was performed at Shanghai Synchrotron Radiation Facility (SSRF) in China.

Results: This technology provides high-resolution 3D images of microvasculature in both normal and injured spinal cords, and the smallest vessel that was detected is approximately 7.4 μm. Moreover, we optimized the 3D vascular visualization with color coding and accurately calculated quantitative changes in vascular architecture after SCI. Compared to the control spinal cord, the damaged spinal cord vessel numbers decrease significantly after injury. Furthermore, the area of injury did not remain concentrated at the epicenter; rather, the signs of damage expanded rostrally and caudally along the spinal cord in 3D. The observed pathological changes were also confirmed by histological tests.

Conclusion: These results prove that SRμCT is an effective technology platform for imaging the pathological changes in small arteries in neurovascular disease and for evaluating therapeutic interventions.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171698 and No. 81371956). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

P23

3D digital anatomical characteristic of the spinal cord Microvasculature in rat model by SRμCT

Hu, JianZhong[1*]; Cao, Yong[1]; Wu, Tianding[1]; Ni, Shuangfei[1]; Lu, HongBin[2]

1 Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.

2 Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.

* Corresponding author: **jianzhonghu@hotmail.com**

Introduction: Study of the normal arrangement of spinal cord microvasculature would broaden our understanding of the underlying variation during the pathological process that associate with spinal cord vascular disease. However, the unique and complicated 3D microvasculature of spinal cord makes the vessel visualization and analysis difficult. Synchrotron radiation micro-tomography (SRμCT), a high-resolution 3D imaging technique has been developed and provide us platform to investigate the 3D morphology of small blood vessels.

Method: We present clear framework for 3D characteristic labeling of the spinal cord microvasculature using synchrotron radiation micro-tomography (SRμCT). The image post-processing method including the segmentation, skeletonization, vectorization and final visualization were also used for analyzing the 3D data obtained from SRμCT.

Results: The main vessel and their minor branches were automatic segmented and labeled with characterized colors, and rendering in multi perspective. The local and related features of the vessel segment, such as the diameter, length and connectivity, were also obtained.

Conclusions: This imaging technique allows us to obtain further insight into the angioarchitecture of the spinal cord and study its alteration under various pathological conditions in small animal models.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171698 and No. 81371956). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

P24

Low-dose phase-based X-ray imaging techniques for *in-situ* soft tissue engineering assessment

Zohreh Izadifar[1], Ali Honaramooz[1], Sheldon Wiebe[2], George Belev[3], Daniel Chen[1], Dean Chapman[1,3]

[1]University of Saskatchewan, [2]Royal University Hospital, [3]Canadian Light source, Canada z**ohreh.izadifar@usask.ca**

With the progression of tissue engineering technology towards repairing damaged tissues and organs in human patients, non-invasive monitoring techniques are required for assessing the success of the repair process. The conventionally used evaluation techniques mainly include *ex vivo* biochemical analysis that are invasive, destructive, not applicable to patient assessments, and not economically efficient for longitudinal *in vivo* animal studies. Non-invasive visualization of soft tissues and low density tissue engineering materials is particularly challenging due to their negligible X-ray attenuation in conventional X-ray imaging and their weak radio frequency signal in magnetic resonance imaging (MRI). Phase-based X-ray imaging techniques that use X-ray refraction-based contrast mechanisms offer great potential for visualization of soft tissues as well as synthetic micro-/macrostructures employed in tissue engineering therapeutic strategies. In this study, the capability of three main phase-based X-ray imaging techniques, computed tomography (CT)-diffraction enhanced imaging (DEI), CT-analyzer based imaging (ABI), and CT-phase contrast imaging (PCI) were investigated and compared for non-invasive, *in situ* soft tissue engineering assessment applications. Different aspects of these techniques such as level of macro-/micro-structural features visualization, radiation dose, scan time, and the ease of implementation were investigated and analyzed to asses these methods for longitudinal *in vivo* animal studies. Juvenile pig joints implanted with low density engineered scaffolds in the knee cartilage were imaged at 40 keV X-ray energy at the Biomedical Imaging and Therapy (BMIT) beamline at the Canadian Light Source (CLS). To optimize the techniques for live animal studies, different low-dose imaging strategies of reduced projection-CT, region-of-interest and lower resolution imaging were adopted and reduced the radiation dose to a reasonable range comparable to clinical CT scans (effective dose of 0.3-10 mSv). The effectiveness of the low-dose imaging strategies in maintaining the desired image information and microstructural details was demonstrated using a clinically relevant image quality scoring system. CT-ABI delivered the smallest radiation dose and PCI provided the shortest scan time. CT-DEI retained more contrast than ABI and PCI when low-dose imaging strategies were adopted for substantial decrease of radiation dose and scan time.

P25

Synchrotron X-ray Pencilbeam Irradiation as Boost after Whole Brain Irradiation

F. Jaekel[1], E. Bräuer-Krisch[2], H. Requardt[2], H. Blattmann[3], J. Laissue[4], G. Hildebrandt[1], E. Schültke[1]

[1]Department of Radiooncology, Rostock University Medical Center, Südring 75, 18059 Rostock, Germany, [2]Biomedical Beamline ID 17, ESRF, 3 Avenue des Martyrs, 38000 Grenoble, France, [3]Niederwiesstr.13C, 5417 Untersiggenthal, Switzerland, [4]University of Bern, Switzerland, **felix@m20a.de**

Background:

Based on a clinically established concept of boost irradiation for patients with multiple brain metastases and the reported experience with clinically used grid therapy as well as with irradiation schedules using monoplanar microbeam irradiation (MRT) as boost in preclinical studies, we have conducted first experiments using irradiation with synchrotron X-ray pencilbeam irradiation as boost after a conventional X-ray broad beam irradiation schedule. The aim of this first experiment was to assess normal tissue tolerance to such recently developed pencilbeams [1].

Materials and methods:

We have used both cell culture and *in vivo* experiments in tumour-free mice to explore cell and tissue responses to a conventional X-ray irradiation schedule with pencilbeam boost, compared to either the conventional schedule alone or the pencilbeam boost alone and to untreated controls. As means of analysis we have used cell survival curves, colony assays, and immunocytochemistry stains looking at reactive oxygen species and DNA damage.

The experiments are under way at the time point of abstract submission. First results will be presented in poster form at the MASR 2015 meeting.

[1] – E. Schültke et al., PLoS ONE **8(1)**, e54960 (2013).

P26

Image characters of lung cancer phantom under the simulative clinical condition performed with in-line imaging and DEI

JIANG Xiaoming, LI Gang[1], CHEN Yu[1], ZHANG Jie[1], LI Kun[1], Masami Ando [2]

Beijing Advanced Sciences and Innovation Center, CAS, Beijing, China, [1]Beijing Synchrotron Radiation Facility, IHEP, CAS, Beijing, China, [2]Research Institute of Science and Technology, Tokyo University of Science, Noda, Japan,
jiangxm@ihep.ac.cn

The lung cancer has the highest mortality rate in all cancers, and its morbidity becomes higher and higher in recently years all over the world. It is the leading death cause of all cancers in the world according to the statistics of WHO in 2008. Early diagnosis is crucial for successful treatment and to increase the survival rate since about 70% of the lung cancer can be cured in this stage. By now the medical tomography is the most simple and widely used method to screening the lung cancer although its dose is too high to screen health people. The sensitivity, specificity and accuracy of PET-CT is much higher than tomography, but it is not a suitable method for the lung cancer screen among commom people due to its high dose and high false positive rate.

Hard X-ray phase contrast imaging is a potential method to screen the early lunge cancer among the health pepole due to its high sensitivity to soft tissue and its low does if using high energy X-ray. We studied the imaging characters of lung cancer phantoms by synchrotron hard X-ray phase contrast imaging experiment (in-line, DEIand XDEI) and Monte Carlo simulation, under the simulative clinical condition as chest projection imaging during physical examination. The imaging experiments are performed at SSRF (in-line imaging), BSRF (DEI imaging) and PF (XDFI imaging), and the Monte Carlo simulation is focused on DEI with 1mm lung cancer and 10cm thickness lung under different X-ray energy, 20keV, 35keV, 60keV. The phase retrial, neighbour average filtering, neighbour mean square root filter are used to improve the visibility of the lung cancer phantoms. The details of the phantoms and the imaging experiment, and the imaging characters under different conditions will be presented.

The preliminary conclusions are:

(1)Synchrotron hard X-ray in-line holography imaging is a potential screen method of the small lung cancer in its early stage with better sensitivity and lower dose than the traditional medical methods.

(2) The overlap of the images of normal lung tissues has the notable negative influence to the visuality of the small lung cancer phantoms but can be overcome partially.

Position Visualisation Methods for the Eight-degrees of Freedom, High Capacity Kappa Goniometer

Graham Kerr[1], D. Miller[1], M. Bree[1], G. Belev[1], N. Zhu[1], A. Webb[1], T.W. Wysokinski[1]

Affiliation: [1]Canadian Light Source Inc. Saskatoon SK Canada
graham.kerr@lightsource.ca

The Micro-beam Radiation Therapy (MRT) lift, used at the BioMedical Imaging and Therapy beamline (BMIT) [1-5] at the Canadian Light Source, is a robotic positioning and scanning system which provides precise sample positioning and a large range of motion. The MRT lift has eight degrees of freedom, often resulting in movement directions and paths which are difficult for a user to predict. A dynamic three dimensional model of the MRT lift has been created utilizing SolidWorks software and visual basic dot net code. The model acts as a server, receiving positions from the MRT lift control software and outputting high resolution images of the lift's desired position in real time. The images allow a user to perform quick visual checks of the MRT lift, reducing collision potential and alignment time. Additionally, the MRT lift and beam positions can be compared, further reducing alignment time. It is also possible to add simplified human or animal models to the stage of the lift model, allowing for visualisations of a sample's region of interest. No specialized user training is required to interpret the images output by this model, which is well suited for the variety of medical and veterinary users at the BMIT facility. The methodology of the MRT lift model is to save time by providing images which do not require a technical background to interpret.

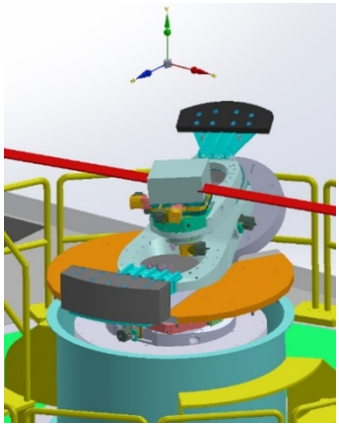


Figure 1: MRT lift visualization produced by dynamic model.

References

[1] Chapman LD, (2007) CLSI Doc. No. 26.2.1.1 Rev. 0.A
[2] Chapman LD, (2006) CLSI Doc. No. 26.2.1.2 Rev. 0
[3] Wysokinski TW et al. (2007) NIM A 582:73-76
[4] Wysokinski TW et al. (2013) J. Phys: Conf Ser 425: 07
[5] Wysokinski TW et al. (2015) NIM A 775:1-4.

P28

X-ray fluorescence microscopy and other spectroscopies for radiology and therapy

W. M. Kwiatek, J. Czapla-Masztafiak, M. Lekka, J. Lekki, E. Lipiec, J. Miszczyk, Cz. Paluszkiewicz, A. Panek, A. Wiecheć

Institute of Nuclear Physics, Polish Academy of Sciences, Krakow, Poland
wojciech.kwiatek@ifj.edu.pl, joanna.czapla@ifj.edu.pl, malgorzata.lekka@ifj.edu.pl, janusz.lekki@ifj.edu.pl, ewelina.lipiec@ifj.edu.pl, justyna.miszczyk@ifj.edu.pl, czeslawa.paluszkiewicz@ifj.edu.pl, agnieszka.panek@ifj.edu.pl, anna.wiechec@ifj.edu.pl

Natural radioactivity, cosmic radiation, nuclear industry (including military applications) and medical diagnostics as ionizing radiation have the influence on human health. It is well known that ionizing radiation can cause damages to DNA which is important in cell proliferation. Therefore it is very important to learn about the mechanisms of radiation damage and its far-off effects. In addition, in order to improve diagnostic methods it is essential to develop rapid and sensitive methods of such a damage detection.

Ionizing radiation at high dose can cause damage to cells and DNA, leading to cell death, while the low doses of radiation may cause mutations that increase the risk of cancer. Therefore, the DNA molecule is a main subject of this study. The various methods have been applied to investigate DNA chemical structure, properties, and conformation. Those methods include X-ray fluorescence, the atomic force microscopy (AFM), molecular spectroscopy: infrared and Raman spectroscopies. Among these methods only AFM can provide information on the level of individual atoms, but such highly localized information is restricted only to the surface of a sample. However, combining AFM with Raman spectroscopy, the TERS (Tip Enhanced Raman Spectroscopy) spectrum can be recorded which will provide nanoscale spectroscopic image of the sample. The X-ray fluorescence will provide elemental distribution while XAS gives distribution of chemical compounds which can be supported by FTIR imaging obtained with the use of nanoIR apparatus.

During the lecture, various spectroscopic imaging techniques will be discussed and possible applications of X-rays, nanoIR, Raman, FTIR and AFM will be presented.

Acknowledgements
The research has been supported by the Małopolska Regional Operational Programme 2007 – 2013
.

P29

Monte Carlo Study on Analyser Crystal Based Imaging of a Homogeneous Object inside Multi-Scattering Material

LI Kun, JIANG Xiaoming, CHEN Yu, LI Gang,

Institute of High Energy Physics, Chinese Academy of Science, jiangxm@ihep.ac.cn

Human lung consists large numbers of alveoli, which would refracted x ray passes through many times randomly, and thus have some very distinct properties in X-ray imaging. In order to investigate the feasibility of using analyzer crystal based imaging as a early stage lung cancer screening method, Monte Carlo method is adopted to simulate the imaging of specimens consists large numbers of micro spheres which contains a small tumour inside (as small as 4mm). After Gaussian Curve Fitting process, comparing to absorption based imaging, analyzer crystal based imaging show its own strength and weakness in the imaging of multi-scattering material. Verification experiments are also conducted, and backs the simulation well.

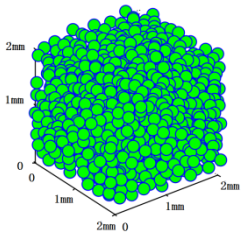


Figure 1: Part of the specimen used in simulation

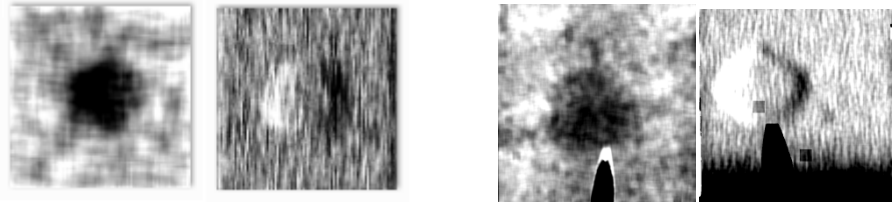


Figure 2: Result of simulation and experiment. In each set of images, the left image is ultra small angle scattering image, and the right image is refraction image.

References

[1] Chapman, Dean, et al. "Diffraction enhanced x-ray imaging." *Physics in medicine and biology* 42.11 (1997): 2015.

[2]- Khromova, A. N., et al. "Monte Carlo simulation of X-ray multiple refractive scattering from fine structure objects imaged with the DEI technique." *Nuclear Science Symposium Conference Record, 2004 IEEE*. Vol. 6. IEEE, 2004. [2] - J.D. Watson and F.H.C. Crick, Nature **171**, 737 (1953).

P30

Role of fibroblasts in breast cancer metastasis studied by FTIR microspectroscopy and x-ray fluorescence microscopy

X. Liu[1,2,] and S. Kumar[1,2]

Canadian Light Source Inc. [1] Anatomy and cell biology, University of Saskatchewan, Saskatoon, Canada [2]
Xia.liu@lightsource.ca, saroj.kumar@lightsource.ca

Breast cancer represents a global health problem because of its highest rates of incidence and being the second leading cause of mortality in women[1]. Surgery is the primary treatment in the majority cases, however around 50% of these cases will develop metastatic diseases which lead to mortality. The mechanism involved in the progression of breast cancer towards metastasis remains poorly understood. It has been proposed that the stroma, in particular, reactive fibroblasts of microenvironment around cancer cells plays important role in development of metastatic diseases[2,3]. FTIR microspectroscopy could be able to probe the differences, at molecular level, bewteen normal and reactive stroma[4]. Chemically specific x-ray fluorescence microscopy is able to reveal the distribution of metal ions inside of the single cells with high lateral spatial resolution. To understand the role of fibroblasts playing in the metastatic progression, we characterized its biochemical structure changes and metal ions distribution upon cancerous stimulation inside individual cells using synchrotron based FTIR microspectroscopy and x-ray fluorescence microscopy. New biomarkers have been discovered by comparing the stimulated fibroblasts with normal ones, which will provide insight to early diagnosis of breast cancer. The associated metal ions distribution changes are able to potentially guide future drug development for better treatment strategies

References

[1]- R. Siegel, J. Ma, Z. Zou, A. Jemal, CA: A Cancer Journal for Clinicians, 64, 9 (2014)
[2]-A. Sadlonova, D.B. Bowe, Z. Novak, S. Mukherjee, V.E. Duncan, G.P. Page, A.R. Frost, Cancer Microenvironment, 2, 9 (2009)
[3]- I.I. Patel, D.A. Shearer, S.W. Fogarty, N.J. Fullwood, L. Quaroni, F.L. Martin, J. Weisz, Cancer Biology & Therapy, 15, 1 (2014)
[4]-S. Kumar, T.S. Shabi, E. Goormaghtigh, Plos One, 9, e111137 (2014)

P31

Analysis of Fe, Cu and Cu/Zn in human prostate cell using synchrotron X-ray microfluorescence mapping

R.G. Leitão[1], C. A. N. Santos[2], A. Palumbo Jr.[3], P. V. R. Souza[4], C. G. L. Canellas[5], M. J. Anjos[1, 5], L. E. Nasciutti[3], R. T. Lopes[1].

[1]Nuclear Instrumentation Laboratory, Federal University of Rio de Janeiro, 21941-942, Rio de Janeiro, RJ, Brazil.
ricardo@lin.ufrj.br

[2] Biotechnology Laboratory – Bioengineering – DIPRO, National Institute of Metrology, Standardization and Technology, Xerém., Duque de Caxias, RJ, Brazil.

[3] Department of Histology and Embryology, Federal University of Rio de Janeiro, RJ, Brazil.

[4] Department of Urology, Andarai General Hospital, 20541170, Rio de Janeiro, RJ, Brasil

[5] Physics Institute, Stated University of Rio de Janeiro, RJ, Brazil.

Micro X-Ray Fluorescence (μXRF) is a non-destructive technique very often used in biological investigations to obtain information regarding the elemental distribution in tissue and cell samples. Diseases of the prostate gland such as Prostate Cancer (PCa) and Benign Prostate Hyperplasia (BPH) are the most frequent health problems in men after middle age. In this context, the aim of this work was to investigate the distribution of Fe and Cu using synchrotron X-ray microfluorescence (SRXRF) in cell spheroids in benign prostate hyperplasia (BPH) and prostate cancer (DU145) supplemented with Zinc and to analyze the influence on intensity of Fe, Cu and Cu/Zn after Zinc supplementation. The SRμXRF measurements were performed at the XRF beam line at the Synchrotron Light National Laboratory (Campinas, Brazil). The results showed non-uniform distribution of Fe and Cu in all the spheroids analyzed. It was possible observed that intensity of Fe, Cu and Cu/Zn was changed with the Zn supplementation. Therefore, the Zn supplementation changes the metabolic of prostate cell.

P32

Study of human prostate cancer cell lines supplemented whit Zn by synchrotron X-ray microfluorescence

R.G. Leitão[1], K.M.J. Rocha[1], E.G.Oliveira-Barros[2], M.A. Oliveira[2], C.G.L. Canellas[3], M.J. Anjos[1, 3], L.E. Nasciutti[2], R.T. Lopes[1]

[1]Nuclear Instrumentation Laboratory, Federal University of Rio de Janeiro, 21941-942, Rio de Janeiro, RJ, Brazil.
ricardo@lin.ufrj.br
[2] Institute of Biomedical Sciences, Federal University of Rio de Janeiro, RJ, Brazil
[3]Physics Institute, Stated University of Rio de Janeiro, RJ, Brazil

Prostate cancer is the most frequently diagnosed form of noncutaneous cancer in men. Prostatic epithelial cells have a unique capability of accumulating high levels of zinc and previous studies indicate that zinc may have a protective effect by inhibiting prostate tumor cell growth and inducing apoptosis. Recent studies identified ZIP1 (SLC39A1) as responsible for the rapid uptake and accumulation of physiologically effective zinc in prostate cells. The distribution and local chemical environment of metals and non-metals in tissues and cells is the most fundamental knowledge of any kind of organism. Synchrotron-based X-ray microfluorescence (SRμXRF) is a powerful technique for the mapping of elemental distributions at a subcellular level. This study investigated Zn distribution in prostate cancer (DU145 and PC3) cell spheroids and analyzed the different response to Zinc supplementation by 24 h and 48 h using synchrotron X-ray microfluorescence (μSRXRF). We evaluated in this study the cell growth, cell death and the expression of ZIP1. The SRμXRF measurements were performed at the XRF beam line at the Synchrotron Light National Laboratory (Campinas, Brazil). The results by SRμXRF showed non-uniform Zn distribution in all the spheroids analyzed. It was possible observed that Zn intensity were changed with the Zn supplementation. These results suggest that Zinc affecting cell growth and cell death. Therefore, the Zn supplementation changes the metabolic of prostate cancer cell.

P33

Application of SR-μCT to Evaluate the Effects of Low-intensity pulsed ultrasound on bone-tendon junction healing after inflammatory stage

Hongbin Lu[1], Huabin Chen[1], Feifei Liu[1], Cheng Zheng[1, 2], Jingyong Zhou[1], Daqi Xu[1], Jianzhong Hu[3]*

1 Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China
2 Sports Medicine & Rehabilitation Center, Wuhan Sports University, Wuhan, Hubei, PR China
3 Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China
* Corresponding author: **jianzhonghu@hotmail.com**

Introduction: The aim of this study was to quantitatively evaluate the effects of low-intensity pulsed ultrasound (LIPUS) on bone–tendon junction (BTJ) healing process after inflammatory stage using synchrotron radiation micro computed tomography (SR-μCT).

Methods: Twenty four mature female New Zealand rabbits with partial patellectomy were used to establish a BTJ injury model, and randomly divided into LIPUS treatment and placebo control groups at the initial 2 weeks postoperatively (20 min/day). The patella-tendon complexes were harvested at week 4, 8 and 16 postoperatively and prepared for SR-μCT scanning at X-ray imaging and biomedical application beamline (BL13W1) of Shanghai Synchrotron Radiation Facility in China. The projection images were captured by a CCD detector with 3.25 μm resolution. The three dimensional images of BTJ were acquired by VG Studio Max.

Results: The LIPUS treatment promoted dense and irregular woven bone formation at week 8, which was characterized by higher bone volume fraction, number and thickness of new trabecular bone but lower separation than that of control group, whereas there was on significant differences between this two groups at week 4.

At week 16, LIPUS group contained mature lamellar bone with higher bone volume fraction and thicker trabeculae than that of control group; however, there was no significant difference in separation and number of the new trabecular bone.

Conclusion: This study reveals that after inflammatory stage, LIPUS treatment is able to promote the BTJ healing process in a rabbit model by enhancing new trabecular bone formation and remodeling. The SR-μCT could be applied for a useful three dimensional visualization technique to quantitatively evaluate the microarchitecture change of new bone formation in BTJ.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171699 and No. 84172072). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

P34

Characterization of Ca and Zn Spatial Distributions at the Fibrocartilage Zone of Rabbit Patella-Patellar tendon Insertion: A SR-μXRF Study

Hongbin Lu*[1], Can Chen[1], Zhanwen Wang[1], Cheng Zheng[1], Yong Cao[2], Jianzhong Hu[2]

[1]Department of Sports Medicine, Research Center of Sports Medicine, Xiangya Hospital, Central South University, PRC
[2]Department of Spine Surgery, Research Center of Sports Medicine,Xiangya Hospital, Central South University, PRC
*Corresponding author; E-Mail: **hongbinlu@hotmail.com**

Introduction: The tendon attaches to bone through a functionally graded fibrocartilage zone, plays a pivotal role in mediating load transfer between tendon and bone. Fibrocartilage zone is a distinct tissue type and could be histologically divided into uncalcified fibrocartilage (UF) and calcified fibrocartilage (CF) using the tidemark (TM). Ca and Zn play vital roles in the normal growth, mineralization and repair of the fibrocartilage zone of patella-patellar tendon insertion (PPI), yet the spatial distributions of Ca and Zn at the fibrocartilage zone and its distribution-function relationship are not totally understood. In this study, the synchrotron radiation micro X-ray fluorescence analysis (SR-μXRF) in combination with backscattered electron imaging (BEI) were employed to characterize the distributions of Ca and Zn at the fibrocartilage zone of PPI.

Methods: (1) Sample Preparation: Five PPI of healthy mature rabbits were embedded with polymethylmethacrylate and cut sagittally with a thickness of 10 μm. (2) BEI and Histology: A SEM (what's SEM) was utilized to acquire a series of BEI images of PPI at 40~150 magnifications to define different tissue regions of fibrocartilage at SR-μXRF maps. The sections adjacent to those used for SR-μXRF were stained by H&E to study the general morphology of the PPI. (3) SR-μXRF: Ca and Zn at the fibrocartilage zone of PPI were detected using SR-μXRF at BL15U1, SSRF, China.

Results: The unique distribution of Ca and Zn at the fibrocartilage zone of the PPI were clearly mapped by SR-μXRF. We found that the distribution of Ca and Zn at the fibrocartilage zone of the PPI were inhomogeneous. A significant accumulation of Zn was exhibited in the transition region between UF and CF. The highest Zn content (3.17 times of that of patellar tendon) was in the TM of fibrocartilage zone. The Ca content began to increase near the TM and increased exponentially across the CF region toward the patella. The highest calcium content (43.14 times of that of patellar tendon) was in the transitional zone of CF region and the patella, approximately 69 μm from the location with the highest Zn content.

Conclusion: SR-μXRF provides us an advanced tool for tracing element distribution at the fibrocartilage zone of the PPI with high spatial resolution and high sensitivity. Spatial distributions of Ca and Zn at the fibrocartilage zone of the PPI were firstly characterized by SR-μXRF combination with BEI.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171699 and No. 84172072). The authors would like to thank all the staffs for their kind assistances in the experiment at BL15U1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

P35

Investigating abnormal airway surface liquid secretion in cystic fibrosis airway using synchrotron phase contrast imaging

X. Luan[1], D. Chapman[2], J.P. Ianowski[1]

Affiliation: [1]Department of Physiology and [2]Anatomy & Cell Biology, University of Saskatchewan
xil496@mail.usask.ca

Cystic Fibrosis (CF) is the most common, fatal genetic disease in Caucasian populations in Europe and worldwide. CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. CF can affect many body system, but CF airway disease is currently the source of most morbidity and mortality in CF patients. Unfortunately, the events leading from gene mutation of CFTR to airway disease are not fully understood, thus, complicating the development of effective treatment.

Normal airways are protected from inhaled bacteria by a complex immune defense system; and airway surface liquid (ASL) plays an important role in the airway defence (1). However, in CF airways, host defence seems to be compromised, and it has been suggested that abnormal ASL secretion may contribute to CF airway disease (2, 3). However, ASL secretion mechanism, or the differences between normal and CF airway, has never been directly tested *in vivo*.

One of the biggest challenges to study ASL secretion *in vivo* is the lack of a non-invasive experimental technique with adequate resolution to measure the liquid layer that may be as several micrometer thick. Conventional imaging methods lack adequate definition and contrast to observe the ASL layer in intact airways; however, the synchrotron phase contrast imaging (PCI) can be used to detect the ASL layer in the trachea (4). Recently, we develop a synchrotron-based phase-related imaging method to measure the height of ASL layer and to examine ASL secretion response to bacteria relevant to CF in live swine. Our objective is to study the possible protective ASL secretion mechanisms in the upper airway of swine *in vivo* and how this response may be altered in CF

We instilled bacteria *(Pseudomonas aeruginosa*)-laden and bacteria-free agarose beads in the trachea of one week old swine, 3-5 kg, and we further measured the ASL secretion response. Our results indicated that there are two separate CFTR-dependent mechanisms of ASL secretion that protect the airway from bacterial infection. a) Bacteria-triggered ASL secretion in live swine, which involved toll-like receptor 5-mediated immune response. Our result also suggested that this *P. aeruginosa*-triggered ASL secretion is CFTR-dependent; this response would be missing in CF airway, which leads to innate defense failure against bacteria and further results in chronic infection and inflammation. b) Spontaneous ASL secretion in live swine. This basal ASL secretion was also mediated by CFTR anion channel. The spontaneous ASL secretion may perform a housekeeping airway defense against inhaled pathogen.

In the future, we will test the role of CFTR anion channel on ASL secretion in the airways of newly developed CF swine *in vivo*.

References

[1] E.R. Lillehoj and K.C. Kim, Arch Pharm Res 25(6), 770 (2002).
[2] R.C. Boucher, J Intern Med 261(1), 5 (2007).
[3] A.R. Berkebile and P.B. Jr McCray, Int J Biochem Cell Biol 52, 124 (2014).
[4] X. Luan, et al., Proc Natl Acad Sci U S A 111(35), 12930 (2014).

P36

New copper organic complexes as radioprotective and potential anticancer agents

M.H. Malakyan[1,2], V.A. Ayvazyan[1], E.A. Arakelova[1], G.V. Tsakanova[1], V.J. Tonoyan[2]

[1]Institute of Molecular Biology NAS RA, [2]Scientific Centre of Radiation Medicine and Burns MH RA,
ritamalakyan@email.com

There is a continual interest worldwide to screen for non-toxic radioprotectors that can be used against harmful effects of radiation in both occupation and therapeutic settings. Despite extensive work done in this field, not a single compound has emerged so far as an effective non-toxic radioprotector for practical purposes. It is desirable to have globally effective pharmaceuticals that could be easily taken orally without any undue side effects prior to a suspected or impending nuclear/radiological event. Taking into account the role of essential metalloelements in tissue maintenance and functions, as well as the roles of essential metalloelement-dependent enzymes in responding to injury, metal-containing compounds are considered as worth for screening of effective radioprotectors. Among the numerous reports on therapeutic use of transition metals' organic complexes a certain place occupy data on radiation protection and radiation recovery with copper(II) chelate complexes. The aim of our study was to investigate the radioprotective effects of new aromatic amino acid Schiff base Cu(II) complexes containing isomeric pyridinecarboxaldehydes as aldehyde component of the Schiff base. White rats were exposed to X-ray irradiation at LD100/30 and LD50/30 after preliminary subcutaneous or oral administration of the copper(II) complexes at 10 and 40 mg/kg doses 1 or 24 hour prior to exposure. Radioprotective activities of the compounds were evaluated by the determination of animal survival during 30-day post-irradiation period, as well as cytogenetic, immunological, hematological, biochemical and biophysical analyses were performed on days 3, 7, 14, 21 and 28 after irradiation at LD50/30. The results obtained demonstrate that the most active were (3-pyridinecarboxaldehyde-Tyrosine)$_2$Cu and (3-pyridinecarboxaldehyde-Tryptophan)$_2$Cu, which increased the survival of lethally irradiated animals up to 40-50%, as well as (2-pyridinecarboxaldehyde-Tryptophan)$_2$Cu, (4-pyridinecarboxaldehyde-Histidine)$_2$Cu and (3-pyridinecarboxaldehyde-Phenylalanine)$_2$Cu, which provided 80-100% survival in case of LD50/30 irradiation dose level. The results obtained showed that these metallocomplexes reveal high antioxidant activity, stimulate the activities of enzymes of endogenous antioxidant defense system, regulate the levels of biomarkers of the organism immune system, apoptosis and inflammation upon irradiation. Moreover, they possess no cytotoxic and genotoxic activity, reveal anti-inflammatory and immunomodulatory effects. Based upon the results obtained we concluded that these compounds may be considered as a new generation of highly efficient multifunctional radioprotectors that can be used not only in prevention and treatment of radiation-induced injury, but also in cancer therapy, especially as agents that have a dual action of protecting normal tissue and sensitizing cancer cells at medical interventions, which envisage radiation exposure of patients - radiotherapy of tumors, radiological examinations, etc.

P37

Phase Preserving Beam Expander for Biomedical X-ray Imaging

M. Martinson[a], N. Samadi[b], B. Bassey[a], A. Gomez[c] and D. Chapman[acd]

[a]Physics & Engineering Physics, University of Saskatchewan, [b]Biomedical Engineering, University of Saskatchewan, [c]Canadian Light Source, [d]Anatomy & Cell Biology, University of Saskatchewan
mercedes.m@usask.ca

The BioMedical Imaging and Therapy beamlines at the Canadian Light Source are used by many researchers to capture phase-based imaging data. These experiments have so far been limited by a small vertical beam size, requiring vertical scanning of biological samples in order to image their full vertical extent. Previous work has been done to develop a Bent Laue Beam Expanding Monochromator [1] for use at these beamlines, however the first attempts exhibited significant distortion in the diffraction plane, increasing the beam divergence and eliminating the monochromator's usefulness for phase-related imaging techniques. Recent work [2] has been done to more carefully match the polychromatic and geometric focal lengths in a so-called “magic condition” that preserves the divergence of the beam and enables full-field phase-based imaging techniques. The new experimental parameters, namely asymmetry and Bragg angles, were evaluated by analysing knife-edge and in-line phase images to determine the effect on beam divergence in both vertical and horizontal directions, using the beamline's flat Bragg double-crystal monochromator as a baseline. The results show that by using the magic condition, the difference between the two monochromator types is less than 10% in the diffraction plane. Phase fringes visible in test images of a biological sample demonstrate that this difference is small enough to enable in-line phase imaging, despite operating at a sub-optimal energy for the wafer and asymmetry angle that was used.

References

[1] M. Martinson, N. Samadi, G. Belev, B. Bassey, R. Lewis, G. Aulakh, D. Chapman, Development of a bent Laue beam-expanding double-crystal monochromator for biomedical X-ray imaging, Journal of Synchrotron Radiation, 21 (2014) 479-483.
[2] M. Martinson, N. Samadi, B. Bassey, A. Gomez, D. Chapman, Phase-preserving beam expander for biomedical X-ray imaging, Journal of Synchrotron Radiation, 22 (2015) 801-806.

3-D Dosimetry for MRT using optical CT

C.M. McErlean[1], E. Bräuer-Krisch[2], J. Adamovics[3], S.J. Doran[1]

[1]Institute of Cancer Research, UK, [2]ESRF, France, [3]Rider University, USA **cmcerlean@icr.ac.uk**

As microbeam radiation therapy (MRT) irradiation geometries become more complex there is a clear need for a dosimeter capable of producing 3-D information, in addition to existing high-resolution planar techniques. Optical computed tomography (CT) has been shown to provide excellent 3-D visualisation of MRT irradiations [1,2]. However, initial measurements of the peak-to-valley dose ratio (PVDR) were significantly lower than expected values from Monte Carlo simulation [3].

Here we report experiments investigating the cause of this underestimation. Three cylindrical samples of the PRESAGE® radiochromic dosimeter were irradiated with microplanar arrays with different peak doses and field sizes. The samples were scanned using a modified version of the optical CT system described in [1] and reconstructed with voxel size (5.2 μm)^3. Fig.1 shows optical CT measurements of PVDR were all roughly 30% of the expected values from Monte Carlo simulation [3]. The linear trend indicates that the error is systematic and is not due to dynamic range or noise problems as it is consistent for different peak doses and field sizes. A simple simulation of our system suggests that a true resolution of 10μm is required to measure the peak value of a 50μm beam profile within 1% error. Using a knife-edge method, we measured the resolution of our system over an extended depth-of-field (DOF). The results showed that the maximum spatial resolution giving a DOF large enough to cover the entire sample was (21.5±0.5)μm. This resolution is insufficient for quantification of peak dose, however there is clear potential to measure the valley dose, which is four times wider than the peak and is arguably, in terms of patient safety, the most important biological factor.

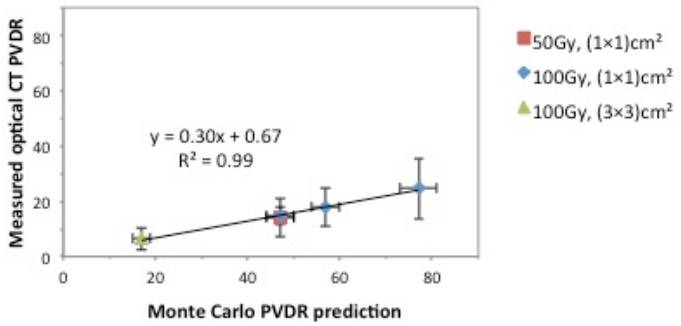


Figure 1: Comparison of PVDR measured with optical CT and MC for samples with different peak doses (50 and 100 Gy) and field sizes (1×1 and 3×3 cm^2).

References

[1] S. J. Doran *et al.*, Phys. Med. Biol. **58**, 6279 (2013).
[2] E. Bräuer-Krisch *et al.*, Physica Medica **31(6)**, 568 (2015).
[3] I. Martínez-Rovira *et al.*, Phys. Med. Biol. **55**, 4375 (2010).

P39

SR-EBRT: Synchrotron Radiation External Beam rotational Radiotherapy for breast cancer

P. Russo, G. Mettivier, F. Di Lillo, A. Sarno

Dipartimento di Fisica, Università di Napoli *Federico II*, Napoli, Italy and INFN, Sezione di Napoli, Napoli, Italy
mettivier@na.infn.it

Computed Tomography systems dedicated to X-ray imaging of the breast (Breast CT, or **BCT**) for cancer screening and diagnosis have been developed by several research groups to overcome the limit of screening mammography due to the spatial overlap of tissue structures [1]. In these scanners, the woman is laying prone on a table with an opening, and each breast, in pendant position, hanging freely through the hole, is imaged separately. In 2012, the UC Davis group [2] proposed the inclusion in the BCT platform of a system for image-guided external beam radiotherapy (**EBRT**). They proposed the use of the rotational summation of a suitably collimated X-ray beam from a 320-kVp orthovoltage X-ray tube to deliver the therapeutic dose, instead of the typical 6-MV photon beam with breast tangential fields produced by a clinical linear accelerator. Advantages are expected for dose reduction to non-breast organs, possibility of real-time imaging, absence of patient repositioning error in fraction dose delivery, reduced cost of the procedure. We propose to implement EBRT in breast cancer therapy, using a synchrotron radiation (SR) beam and dedicated setup for irradiating the pendant breast of the woman in prone position (SR-EBRT). The possibility to have, at the ESRF facility, of a monochromatic synchrotron radiation beam with energy 60 keV or higher, makes it possible to investigate the realization at ESRF of a therapeutic station for treatment of solid breast tumors. The same platform could be adopted for BCT (to e.g. about 60 keV) as well as for breast EBRT on the same setup; in this case BCT would be used for tumor 3D localization and beam centering, prior to the radiotherapy. In order to obtain a validation of this technique we developed a dedicated Geant4 Monte Carlo simulation code. This code was validated by comparison with literature data and measured data in the case of a polychromatic x-ray beam. Simulations to study optimal energy and geometry in monochromatic setup report an optimal beam energy of 175 keV and the possibility to realizing “dose-painting”. An example is shown in figure 1. We have shown that a monochromatic energy lower than the average beam energy (178 keV) tested in [3], can be used for SR-EBRT, with a skin spearing factor (dose to the skin divided by dose to the tumor) close to that of orthovoltage EBRT at 320 kV (about 10%).

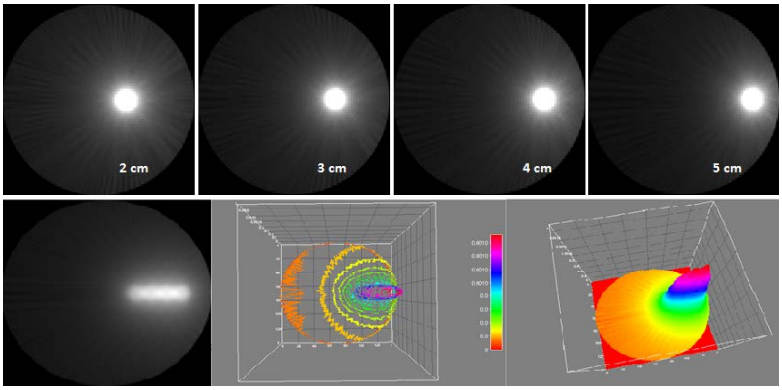


Figure 1: (Upper row) Dose distribution in the central slice of the 14-cm-diameter polyethylene phantom for a 300-kVp rotating source in off-center irradiation. The source was shifted radially by 1, 2, 3 and 4 cm from the centre of the phantom. (Bottom row) Sum of all the dose distribution and corresponding 3D representations [3].

References

A. Sarno, G. Mettivier, P. Russo, Med. Phys. **42,** 2786-2804 (2015)
N.D. Prionas, S.E. McKenney, R.L. Stern, and J.M. Boone, Int. J. Rad. Oncol. Biol. Phys. **84**, 533–539 (2012).
P. De Lucia, MSc. Thesis in Physics, Un iversity of Naples Federico II (2015).

P40

An approximate single image method for fast hard X-ray refractive index CT

A. Mittone[1, 2, 3], S. Gasilov[4], A. Bravin[2], and P. Coan[1, 3]

[1] Department of Physics, Ludwig Maximilians University, Garching 85748, Germany, [2] European Synchrotron Radiation Facility (ESRF), Grenoble 38043, France, [3] Department of Clinical Radiology, Ludwig Maximilians University, Munich 81377, Germany, [4] ANKA Synchrotron Radiation Facility, Karlsruhe Institute for Technology, Eggenstein 76344, Germany, **alberto.mittone@esrf.fr**

X-ray refraction-based computer tomography (CT) is a well-established method for nondestructively and accurately investigating an object. A novel method, based on an estimation of the absorption of the sample is here presented [1]. It allows the extraction of the refraction signal by using a single set of differential phase projections.

In order to perform the 3D reconstruction of the index of refraction, two or more tomographic sets of differential phase projections are normally required, leading to an increase of the acquisition time and of the delivered dose. These data sets can be obtained by using different X-ray phase-contrast imaging methods like the analyzer-based imaging, the interferometric and the coded aperture techniques. To extract the refraction component of the signal (i.e. the differential phase), the acquired sets of raw phase-contrast images are then combined together by means of specific algorithms.

To test the validity and the accuracy of our method, we applied it to the CT imaging of a thick excised human breast using the analyzer based imaging technique. The suggested approach considers a Gaussian curve as approximation of the analyzer crystal rocking curve similarly to other algorithms. If a homogenous sample composition can be assumed, then it is possible to analytically calculate the sample's absorption signal with good approximation and, as a consequence, to reduce the number of unknowns in the retrieval problem to one. In this way, the refraction signal can be extracted using a single set of images. The retrieved refraction component may then be used in combination with the gradient filtered back-projection algorithm to obtain a full 3D reconstruction of the index of refraction of the sample under investigation. The results were compared with the ones derived with the extended diffraction enhanced imaging algorithm [2], which instead needs two sets of differential phase projections to separate the refraction and the absorption components. From a quantitative point of view this method shows an accuracy in distinguishing between the different tissues similar to that obtained with standard algorithms; besides, it shows the advantage of a reduction of the acquisition time and dose delivered by a factor of two.

References:

[1] Mittone, A et al 2015. A single-image method for x-ray refractive index CT. *Phys. Med. Biol*. 60 3433.

[2] Hu, C. et al., 2008. Comparison of refraction information extraction methods in diffraction enhanced imaging. *Optics Express*, 16(21), p.16704.

P41

A Novel Method of Synchrotron Radiation Renal Microangiography in *In Vivo* Rat

Ken Miya[1], Shonosuke Matsushita[2], Kazuyuki Hyodo[3], Chiho Tokunaga[1], Hiroaki Sakamoto[1], Taro Mizutani[1], Yuji Hiramatsu[1]

[1]University of Tsukuba, Tsukuba, Japan; [2]Tsukuba University of Technology, Faculty of Health Science, Tsukuba, Japan; [3]Photon Factory, High Energy Accelerator Research Organization (KEK), Tsukuba, Japan

Email: ken-miya@hotmail.co.jp

Background:

Real-time in vivo renal microangiography is considered useful for investigation of renal physiology. However, conventional X-ray is not capable of visualizing structures smaller than 200 μm [1], making it difficult to fully elucidate the structure of nephrons.

Method:

The study was performed at the High Energy Accelerator Research Organization (KEK) PF BL-14C beam line facility, Tsukuba, Japan. An asymmetrically cut silicon crystal was used to select the monochromatic beam by expanding the synchrotron radiation (SR) vertically. The imaging energy was 33.21 KeV, which is 40 eV above the iodine K-edge. X-rays transmitted through a subject were recorded with a CCD camera. Two-dimensional images with a pixel size of 9 μm were obtained. The exposure time was fixed to 50 ms, with a maximum acquisition rate of 3 images/s. Male Wistar rats were anesthetized, and a catheter was inserted via laparotomy into the descending aorta with its tip placed above the renal arteries. The rats were paralyzed with a neuromuscular blocking agent and mechanically ventilated. An inorganic iodine contrast medium was injected via the catheter.

Results:

Afferent arterioles with a diameter of approximately 20 μm and glomeruli with a diameter of approximately 170 μm were visualized without exteriorizing the kidneys.

Conclusion:

The method is expected to be useful in elucidating renal physiology and pathology.

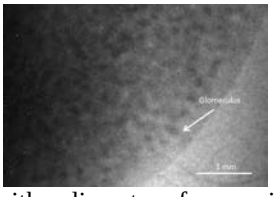


Figure 1: A glomerulus with a diameter of approximately 170 μm (arrow).

References

[1] Shirai M, Schwenke DO, Tsuchimochi H, Umetani K, Yagi N, Pearson JT. Synchrotron radiation imaging for advancing our understanding of cardiovascular function. Circ Res 112: 209-221, 2013.

MedMAX: The future of biomedical imaging at MaxIV

R.Mokso[1,2], M. Bech[3], T. Lundqvist[2]

[1]MaxIV Laboratory, Lund University, Lund, Sweden, **rajmund.mokso@maxlab.lu.se**
[2]Swiss Light Source, Paul Scherrer Institute, Villigen, Switzerland
[3]Department of Medical Radiation Physics, Lund University

Visualizing fast micrometer-scale internal movements of small animals is a key challenge for studies in functional anatomy, physiology and biomechanics [1]. In-vivo X-ray imaging is routinely performed down to a spatial resolution of several tens of micrometers. However, combining high spatial with sub-second temporal resolution still remains a challenging task [2]. In particular, breaking the 10 μm barrier is very difficult due to the radiation dose deposited in the tissue and the severe motion artifacts [3]. We address this challenge in the concept of the Biomedical Imaging beamline, MedMAX, at the new MaxIV storage ring. MedMAX will in particular be optimized for time resolved micrometer resolution tomography using the information encoded in the refraction of X-rays traveling through the sample. We present the concept focused on dose-optimized in-vivo imaging of small animals and insects.

References

[1] - S. M. Walker, D. A. Schwyn, R. Mokso, M. Wicklein, T. Müller, M. Doube, M. Stampanoni, H. G. Krapp, G. K. Taylor, PLoS Biol. **12**, e1001823 (2014).
[2] - R. Mokso, F. Marone, S. C. Irvine, M. Nyvlt, D. Schwyn, K. Mader, G. K. Taylor, H. G. Krapp, M. Skeren, M. Stampanoni, J. Phys. D. Appl. Phys. **46**, 494004 (2013).
[3] - G. Lovric, S. F. Barré, J. C. Schittny, M. Roth-Kleiner, M. Stampanoni, R. Mokso, J. Appl. Crystallogr. **46**(4), 856 (2013).

P43

Subpixel X-ray phase imaging using synchrotron radiation

Presenting author underlined, in Times 12, centred, as in the following:
P.R.T. Munro[1], A. Olivo[1]

Department of Medical Physics and Biomedical Engineering, University College London, UK, **p.munro@ucl.ac.uk**

We have previously demonstrated a method of performing phase and absorption retrieval using synchrotron radiation using the edge illumination setup depicted in Figure 1 [1]. This retrieval method assumes that that phase gradient of the sample is constant within the transmitting region of the pre-sample mask. Recently, however, we have developed a formalism which allows the detector pixel's signal, which we assume to detect all photons propagating through the transmitting region of the detector mask, to be calculated as:

$$I \propto \int_{-\frac{P}{2M}}^{\frac{P}{2M}} K(z_{od}\alpha(\xi) + M\xi, \Delta P)\mathrm{d}\xi$$

Where *K* is the so-called generalised detector sensitivity function which takes into account source size and pixel cross-talk, a is the refraction angle and $M=(z_{so}+z_{od})/z_{so}$. Using this formalism it is possible to show that sub-pixel information about samples can be obtained, so long as the projected phase of the sample remains smooth within the transmitting region of the pre-sample mask. This concept is most easily understood in the case of negligible absorption as is shown in Figure 1. In particular, the red ray represents the ray, refracted by the largest angle, to reach the detector. It is thus possible to extract both $\Delta\xi$ and α from the same measurement since they are not independent. We have demonstrated how using this corrected method leads to a better agreement with the analytic phase gradient of cylindrical fiber of radius 100μm and refractive index $1\text{-}10^{-6}$. We will show how this method may be used to improve the resolution and sensitivity of images acquired using synchrotron radiation.

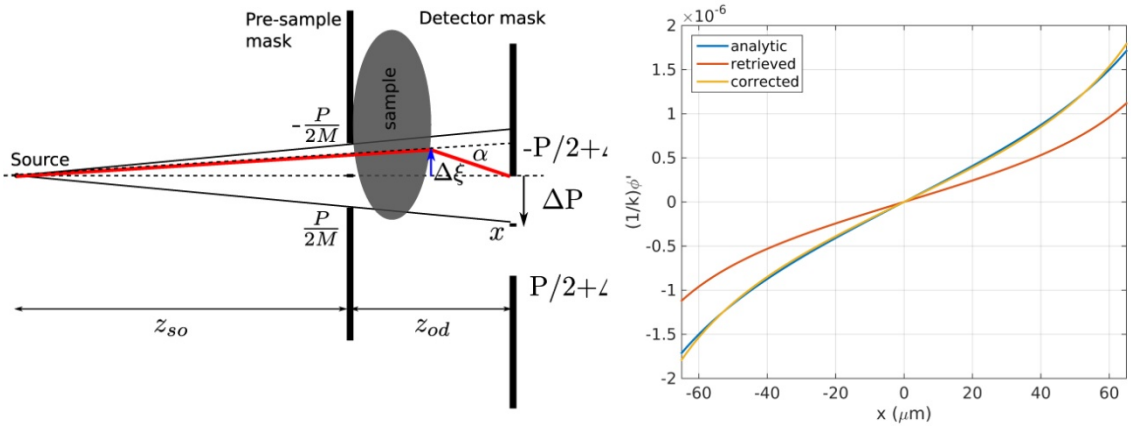


Figure 1: (left) The schematic of the imaging setup and (right) a numerical example of phase gradient retrieved using the original and corrected methods.

References

[1] – P.R.T. Munro, K. Ignatyev, R.D. Speller and A. Olivo, Proc. Nat. Acad. Sciences USA **109**, 13922 (2012)

Live small animal lung phase-contrast x-ray velocimetry: Optimising imaging rates

R.P. Murrie[1], D.M. Paganin[1], A. Fouras[2], K.S. Morgan[1,3]

[1]School of Physics and Astronomy, Monash University, Clayton, Victoria, Australia
[2]Division of Biological Engineering, Monash University, Clayton, Victoria, Australia
[3]Institute of Advanced Study, Technische Universität München, Garching, Germany
rhiannon.murrie@monash.edu

Phase contrast x-ray imaging (PCXI) allows us to image soft tissue at high resolution by exploiting the differences in refractive indices between different materials. This technique is particularly effective for imaging the lungs, as the refractive index difference between the air in the alveoli and the surrounding lung tissue is significant, and results in a high quality edge-enhanced image of the airways. This edge enhancement effect for multiple alveoli results in a characteristic speckle pattern [1], which can be used to track the movement of the lungs during inhalation and exhalation. This is a technique known as x-ray velocimetry (XV), and reveals the local motion and flow of air through the lungs and airways, thus improving our ability to identify regional areas of disease during the natural breathing cycle [2, 3]. This in turn promotes earlier and more accurate diagnosis of chronic lung diseases, and allows us to expand research into treatment development through direct, real-time, high-resolution visualisation of lung dynamics.

Here we investigate the optimal imaging speed to capture the lung motion *in-vivo* in small animals using XV. This optimisation balances the noise inherent in a short exposure with the motion blur that results from a long exposure, over a range of velocities. As XV has, up until now, primarily been performed on synchrotron sources, but as we move toward imaging in a clinical setup, we will consider results from both a synchrotron and laboratory x-ray source via simulation and experimental data.

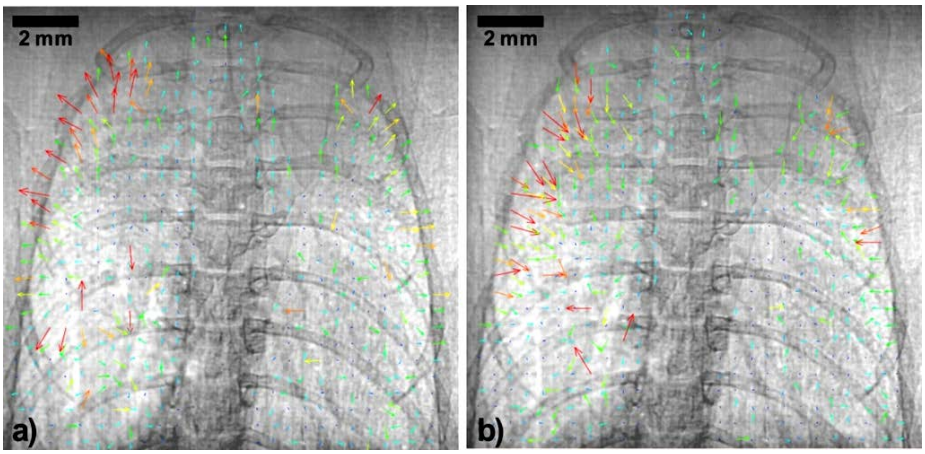


Figure 1: X-ray velocimetry of a mouse lung imaged *in-vivo* at the Australian Synchrotron during (a) inhalation and (b) exhalation.

References

[1] Kitchen, M. J., Paganin, D., Lewis, R. A., Yagi, N., Uesugi, K. & Mudie, S. T. (2004). *Phys. Med. Biol.* **49**, 4335-4348
[2] Dubsky, S., Hooper, S. B., Siu, K. K. W. & Fouras, A. (2012). *J. R. Soc. Interface* **9**, 2213-2224.
[3] Fouras, A., Allison, B. J., Kitchen, M. J., Dubsky, S., Nguyen, J., Hourigan, K., Siu, K. K., Lewis, R. A., Wallace, M. J. & Hooper, S. B. (2012). *Ann. Biomed. Eng.* **40**, 1160-1169

P45

Synchrotron Microtomography Approach for Determination of *Rhodnius prolixus'* Digestive Volume

G. Sena[1], A. Almeida[2], L. Nogueira[3], D. Braz[1], M. Gonzalez[4], P. Azambuja[5], J. Soares[3], G. Tromba[6], R. Barroso[3]

[1]COPPE/Federal University of Rio de Janeiro, [2]State University Centre of West Zone, [3]Lab of Applied Phys to Biomed and Environmental Sci/Physics Institute/State University of Rio de Janeiro, [4]Fluminense Federal University, [5]Oswaldo Cruz Institute, Brazil, [6]Elettra-Sincrotrone Trieste ScpA, Italy. **liebertrj@gmail.com**

Advancements in microtomography (μCT) have made possible fine resolution of internal morphology of very small insects. μCT has been used to quantify insect tracheal system dimensions [1], however has never been used to quantify *Rhodnius prolixus* structures, the most important insect vector of *Trypanosoma cruzi*, the etiologic agent of Chagas' disease. Studies have been shown that μCT provides an excellent tool for 3D reconstruction of *Rhodnius prolixus* [2] and slices analysis showed that variation in size of the digestive system of *Rhodnius prolixus* can be noted in different times after feeding [3]. In this work the digestive system volume of *Rhodnius prolixus* was measured using synchrotron μCT.

The microtomographic images were obtained using the new experimental setup which was recently made available at the SYRMEP beamline of ELETTRA (Trieste, Italy). A 2μm resolution was achieved in the μCT images. A 25-μm thick single crystal of cerium-doped lutetium–aluminum garnet ($Lu_3Al_5O_{12}$) scintillator screen (Crytur, Czech Republic) was coupled to an air-cooled 16 bit CCD camera (Photonic Science, KAI 4022M CCD, 2048 x 2048 full frame, 2x2 μm^2 pixel size, 7x7 mm^2 field of view) via a visible light microscope optics (LEICA).

In order to understand the behavior of the digestive structures [Figure 1], three different groups of *Rhodnius prolixus* were used. One group was fed with defibrinated rabbit blood and was sacrificed 10 days after feeding, another group was sacrificed 4 days after feeding and the last one remained unfed. The digestive system volume of each group showed relevant different values. Understanding the behavior of digestive system can provide a new view of the *Rhodnius prolixus* digestive apparatus and will help understand the mechanism of blood digestion by *Rhodnius prolixus* and its interaction with the agent of Chagas' disease, *Trypanosoma cruzi*, the parasite which grows within the insect's digestive system.

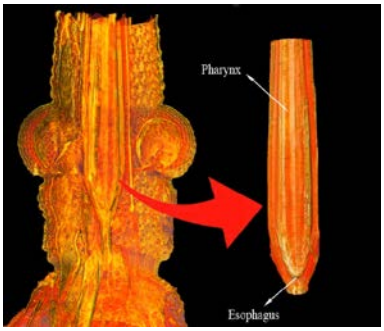


Figure 1: Longitudinal section of *Rhodnius prolixus* head (left). Detail of the pharynx and esophagus.

References

[1] - R. K. Shahaa, J. R. Vogt, Arthropod Structure & Development **42** 437-442 (2013)
[2] - A. P. Almeida, D. Braz, JINST **8** C07004 (2012).
[3] - G. Sena, A. P. Almeida, J. Phys.: Conf. Ser. **499** 012018 (2014).

P46

Ecdysis Period of *Rhodnius prolixus* Head Investigated by Phase Contrast Synchrotron Microtomography at the Brazilian Synchrotron Laboratory

G.Sena[1], A. Almeida[2], L. Nogueira[3], D. Braz[1], M. Gonzalez[4], P. Azambuja[5], R. Barroso[3]

[1]COPPE/Federal University of Rio de Janeiro, Brazil, [2]UEZO/State University Centre of West Zone, Brazil, [3]Lab of Applied Physics to Biomedical and Environmental Sciences/Physics Institute/State University of Rio de Janeiro, Brazil, [4]Department of General Biology/Federal University Fluminense, Brazil, [5]Laboratory of Biochemistry and Physiology of Insects/Oswaldo Cruz Institute/FIOCRUZ, Brazil **liebertrj@gmail.com**

Microtomography using synchrotron sources is an useful tool in biological imaging research since the phase coherence of synchrotron beams can be exploited to obtain images with high contrast resolution [1-2]. This work uses phase contrast synchrotron microtomography (μCT) in the study of *Rhodnius prolixus* head, the insect vector of Chagas' disease, which accounts for about 12,000 deaths per year. The control of insect vector is the most efficient method to prevent this disease and studies have shown that the use of triflumurom, a chitin synthesis inhibitor, disrupts chitin synthesis during larval development, being an alternative method against insect pests [3]. The aim of the present work was to investigate the biological effects of treatments with triflumuron in the ecdysis period (the moulting of the *R. prolixus* cuticula) using the new imaging beamline IMX at Brazilian Synchrotron Light Laboratory (LNLS, Campinas-SP).

Nymphs of *Rhodnius prolixus* were taken from the Laboratory of Biochemistry and Physiology of Insects, Oswaldo Cruz Foundation, Brazil. Different doses of triflumurom were applied directly to the ventral surface of the abdomen of the insects immediately after feeding. The insects were sacrificed 27 days after feeding (intermoulting period) and fixed with glutaroldeydhe. The results obtained from the new setup at LNLS showed the internal structures of the insects in the ecdysis period (Figure 1) what has never been shown before with this technique, with a final resolution of 2 μm. The images revealed the behavior of the moulting as a result of the administration of triflumurom.

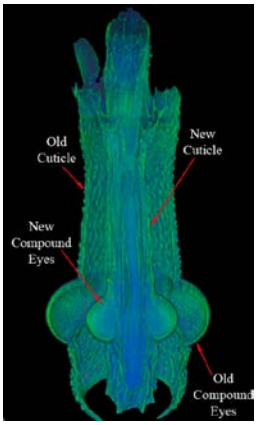


Figure 1: Longitudinal section of *R.prolixus* head in the ecdysis period.

References

[1] - A. P. Almeida, D. Braz, Radiat Phys Chem **95** 243-246 (2014).
[2] - A. P. Almeida, D. Braz, JINST **8** C07004 (2012).
[3] - C. B. Mello, D. Mendonça-Lopes, Mem. Inst. Oswaldo Cruz **103** 8 (2008).

P47

Optimization of the reconstruction workflow for clinical application of low-dose phase contrast CT in breast imaging.

S.Pacilè[1,2,*], F.Brun[1,2], C. Dullin,[3] Y.I. Nesterest,[4] D.Dreossi,[1] M.Tonutti,[5] F.Stacul,[5] D.Lockie,[6] F.Zanconati,[7] A.Accardo,[2] T.E.Gureyev[4,8,9] and G.Tromba[1]

[1]Elettra - Sincrotrone Trieste S.C.p.A., Basovizza (Trieste), Italy
[2]Department of Engineering and Architecture, University of Trieste, Trieste, Italy
[3]Department of Diagnostic and Interventional Radiology, University Hospital Göttingen, Göttingen, Germany
[4]Commonwealth Scientific and Industrial Research Organisation, Melbourne, Australia
[5]AOU - Trieste Hospital, Department of Radiology, Trieste, Italy
[6]Maroondah BreastScreen, Melbourne, Australia
[7]Department of Medical Science-Unit of Pathology, University of Trieste, Trieste, Italy
[8]School of Physics and Astronomy, Monash University, Clayton, VIC, Australia
[9]School of Science and Engineering, University of New England, Armidale, NSW, Australia
***serena.pacile@elettra.eu**

In this work we present the results of a feasibility study of low dose tomographic mammography using in-line phase contrast.
The aim of the study is to investigate the reconstructed image quality as a function of different image processing operations.
Detailed evaluation and optimization of computed tomography workflows have been carried out using combinations of several advanced image reconstruction algorithms with different pre-processing and post-processing steps. Special attention was paid to the effect of phase retrieval on the diagnostic value of the reconstructed images. A number of objective image quality indices have been applied for quantitative evaluation of the results, and these were compared with subjective assessments of the same images by three experienced radiologists and one anatomo-pathologist.
The proposed methodology was applied to a specially designed test object and two different tissue samples obtained from mastectomies, belonging to different clinical contexts.
All datasets presented in this study were acquired at the SYnchrotron Radiation for MEdical Physics beamline of the ELETTRA synchrotron light source (Basovizza - Trieste, Italy) at a X-ray energy of 32 keV using a Dalsa Argus CCD TDI detector. Due to its general approach, the method can be applied to other experimental setups at different energies and using other kind of detectors.
The outcomes of this study provide practical guidelines for the optimization of image processing workflows in synchrotron radiation propagation-based phase-contrast mammo-tomography.

P48

Towards the reconstruction of the mouse brain vascular networks with high- resolution synchrotron radiation X-ray tomographic microscopy

A. Patera[1,2], A. Astolfo[1], K. S. Mader[1,3], M. Schneider[4,5], B. Weber[5], M. Stampanoni[1,3]

[1]Swiss Light Source, Paul Scherrer Institute, Villigen, Switzerland, **alessandra.patera@psi.ch**
[2]Centre d'Imagerie BioMedicale, Ecole Polytechnique Federale de Lausanne, 1015 Lausanne, Switzerland
[3]Institute of Biomedical Engineering, University and ETH Zürich, Switzerland
[4]Computer Vision Laboratory, ETH Zurich, Sternwartstrasse 7, 8092 Zurich, Switzerland
[5]Institute of Pharmacology and Toxicology, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

Brain vessels play an important role in the process of maintaining normal brain function. An in-depth knowledge of the vascular structure and topology is essential for better understanding the pathophysiological cerebral processes. Currently, the architecture of the cerebral vasculature is documented at 100 μm [1] resolution for human brain and about 10 μm for mouse brain. More recently, Micro-Optical Sectioning Tomography has shown potential in imaging the vessel network of an entire mouse brain with a voxel resolution of $0.35\times0.4\times2.0$ μm^3 [2]. However, the destructive nature of the technique avoids the potential options of *in-viv*o imaging. Within the context of the Human Brain Project (HBP), we use synchrotron radiation X-ray phase-contrast tomographic microscopy at the Swiss Light Source of the Paul Scherrer Institute (Switzerland) as a key technology for reconstructing, in a non-destructive way, the entire vascular system of the mouse brain at 1 μm resolution. More specifically, we use the tomographic configuration equipped with PCO.Edge detector and 10× objective, thus yielding a pixel size of 0.65 μm. The mouse brain is infused with 50% indian ink and kept in glue to ensure the stability of the sample. In a preliminary experiment, a sub-volume covering an axial area of 5.1×7.5 mm^2 over 1 cm^3 sample is acquired with 5×6×2 scans and a total scanning time of 9 hours at 25 keV. After reconstruction, the Fourier transform-based phase correlation method [3] is successfully applied to compute translational offsets between the sub-volumes. A main challenge of the experiment is related to the amount of data to be handled and analysed. After stitching, a volume of $5.1\times7.5\times2.8$ mm^3 consists of 188 GB. To fully reconstruct the complete cerebrovascular network of the mouse brain, we estimate a final total reconstructed volume of approximatively 7 TB. To address this challenge, we extend the method in order to work on several scans by enabling the use of many machines in parallel, thus allowing the stitching and analysis of such large datasets. At this point, these pioneering efforts are pointing towards new horizons in the investigation of large biological samples with 3D high spatial resolution.

References

[1] - Lauwers F, Cassot F, Lauwers-Cances V, Puwanarajah P, Duvernoy H. Morphometry of the human cerebral cortex microcirculation: general characteristics and space-related profiles. Neuroimage. 2008 Feb 1; **39** (3): 936-48 (2008).
[2] - Xue S, Gong H, Jiang T, Luo W, Meng Y, et al. Indian-Ink Perfusion Based Method for Reconstructing Continuous Vascular Networks in Whole Mouse Brain. PLoS ONE **9**(1): e88067 (2014).
[3] - Preibisch, Stephan, Stephan Saalfeld, and Pavel Tomancak. Globally optimal stitching of tiled 3D microscopic image acquisitions. Bioinformatics (Oxford, England) **25** (11): 1463–5 (2009).

P49

Development of an image guidance protocol for MRT at IMBL

D. Pelliccia[1,2], J. Livingstone[2], D. Häusermann[2] and J.C. Crosbie[1]

[1]School of Applied Sciences, RMIT University, Melbourne, Victoria, Australia
daniele.pelliccia@rmit.edu.au
[2]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria, Australia

Microbeam radiation therapy (MRT), using X-rays generated by a synchrotron facility, is a novel, preclinical form of radiotherapy that shows promise of providing a major advance in cancer control if successfully translated to clinical practice. To generate MRT, the synchrotron beam (mean energy of 100keV) is segmented by a collimator into a lattice of microbeams, usually 25-50 μm wide (see e.g. [1-2]). The beams have minimal divergence and are spaced at regular intervals of 200-400μm. Typical radiation doses are 300-1000Gy in the microbeams (peak dose), and 5-20Gy in the valley between the beams. This dose is delivered in milliseconds.

We describe the developments in image guidance for the MRT station for preclinical small animal trials on the Australian Synchrotron Imaging and Medical Beamline (IMBL). The purpose of image guidance in clinical radiotherapy is to guarantee precise control of the radiation field to accurately deliver the prescribed dose to the target and not its surroundings. As such, a valid protocol must be able to generate live images of the patient and register these with existing treatment plan developed for the patient prior to the arrival at the synchrotron. Data obtained from image guidance will inform decisions about patient positioning. An imaging modality based on modification of the wiggler gap to produce a low intensity, low energy imaging beam was proposed at the ESRF [3]. On the IMBL however, the wiggler field cannot be easily changed and an alternative approach was developed.

Our double-crystal Laue monochromator produces a 20mm vertical offset between the diffracted monochromatic beam and the transmitted pink beam. Either beam can be selected by moving a slit. *In-vacuo* filtering (upstream of the monochromator) is chosen to select the pink (treatment) beam with a mean energy of 95keV. The monochromator is then aligned to select an imaging energy of 50keV. After imaging, the sample and the relevant beamline components are translated into the pink beam for treatment without changing the beam filtration or monochromator settings.

Preliminary results indicate that the proposed approach is viable and permits the fast imaging and subsequent alignment of targets with very good accuracy.

References

[1] - E. Brauer-Krisch et al., Mutat. Res. **704**, 160 (2010).
[2] - J.C. Crosbie et al., Int. J. Radiat. Oncol. Biol. Phys. **77,** 886 (2010).
[3] - R. Serduc et al., J. Synchrotron Rad. **17**, 325 (2010).

Microdosimetry for Microbeam Radiation Therapy using Gafchromic films: comparison between a Zeiss microscope and a Microdensitometer

P. Pellicioli[1], S. Bartzsch[2], M. Donzelli[1], P. Fournier[3], E. Bräuer-Krisch[1]

[1]ESRF, European Synchrotron Radiation Facility, Grenoble, France
[2]ICR, the Institute of Cancer Research, London, United Kingdom
[3]CMRP, Centre for Medical Radiation Physics, University of Wollongong, Australia
Contact: paolo.pellicioli@esrf.fr

High resolution absolute dosimetry is still a challenge in Microbeam Radiation Therapy (MRT). Monte Carlo (MC) calculated dose deviates up to 10% from the quantitative dose measurements. Despite improvement in MC calculation, including a phase space file [1] and further improvement [2][3], we are still above the 3% difference for benchmarking of a TPS which is typically required for clinical trials. Gafchromic films are promising dosimeters in MRT with a resolution of few µm. In the past, a Microdensitometer was used to read out films but it is sensitive to individual adjustments and measurements lack reproducibility. A modified Zeiss optic microscope has therefore been purchased by the ESRF. This new microscope is expected to give more reliable results than the Microdensitometer and in much less time.

A series of Gafchromic films were exposed to MRT synchrotron radiation in a solid water phantom. Both, the modified Zeiss optic microscope and the Microdensitometer were used to read out the films. For microscope measurements, an Image Protocol has been especially developed using MatLab software to analyse the acquired images.

In this poster, we will present the direct comparison between the dose measurements obtained with the Zeiss microscope and the Microdensitometer. In addition, a direct comparison of these data with MC dose calculations is reported. These results include a) the evaluation of peak and valley dose for different field configuration and b) the measurement of the Output Factors (OF) for microbeam sizes down to 25µm.

References

[1] Martínez-Rovira, Sempau, and Prezado: Development and commissioning of a Monte Carlo photon beam model for the forthcoming clinical trials in microbeam radiation therapy, Medical Physics, Vol. 39, No. 1, January 2012
[2] Stefan Bartzsch, Michael Lerch, Marco Petasecca, Elke Bräuer-Krisch, Uwe Oelfke“Influence of Polarisation and a source model for dose calculation in MRT”, Medical Physics 2014
[3] Bartzsch, S., Lott, J., Welsch, K., Bräuer-Krisch, E., Oelfke, U. “Micrometer-resolved Film Dosimety Using a Microscope in Microbeam Radiation Therapy (MRT) submitted 2015 Medical Physics

P51

Three Dimensional Speciation Imaging: A Feasibility Study at the Selenium K-edge

P. Qi[1], I. Pickering[2], G. George[2], L. D. Chapman[3]

[1]Biomedical Engineering, [2]Geological Sciences, [3]Anatomy & Cell Biology
University of Saskatchewan **peng.qi@usask.ca**

Elements form the basis of all living systems. It is the bonding or chemical state of those elements that define their roles in those systems. Obtaining a 3D image of chemical forms of an element within a living system would be insightful for many health research areas. X-ray Absorption Spectroscopy (XAS) can derive chemical form information, based on absorption near the absorption edge profile of an element. The near edge absorption structure gives speciation information while structure farther from the edge gives information about local environment around the element. Though powerful, these methods are challenging to apply to 3D objects [1, 2] because of the extra dimension that the energy scan about the absorption edge adds to the data acquisition process. There are several systems which provide an angularly dispersed energy range that improves the efficiency of data acquisition, but suffer somewhat with insufficient energy resolution. Meanwhile, K-edge Subtraction Imaging (KES) can reveal the 3D distribution of an element, but traditionally with no chemical information. These systems typically use transmission or Laue monochromators. Recently we have developed Laue monochromators which have improved focal and energy dispersive properties sufficient for XAS studies [3]. This work presents results showing the feasibility of 3D speciation imaging with our monochromator and analysis algorithms using Se in a living plant system as a tractable test case. Future studies will apply our methods to biomedical systems.

References

[1] Pickering IJ, Prince RC, Salt DE, George GN (2000) Quantitative, Chemically Specific Imaging of Selenium Transformation in Plants. PNAS 97:10717-10722.

[2] Pickering IJ, Wright C, Bubner B, Ellis D, Persans MW, Yu EY, George GN, Prince RC, Salt DE (2003), Chemical form and distribution of selenium and sulfur in the selenium hyperaccumulator Astragalus bisulcatus, Plant Physiol. 131 1460 – 1467.

[3] Zhu Y, Samadi N, Martinson M, Bassey B, Wei Z, Belev G, Chapman D (2014) Spectral K-Edge Subtraction Imaging. Phys Med Biol. 59 (10) 2485-2503

Changes in regional distribution of gas and blood volumes within a single respiratory cycle

[1,2]L. Porra, [3]M. Wallin, [3]M. Hallbäck, [4,5]L. Broche, [1]P. Suortti, [2]A. Sovijärvi, [6]F. Petak, [7]W. Habre and [5]S. Bayat

[1]Department of Physics, P.O. Box 64, FIN-00014 University of Helsinki, Finland, [2]Helsinki University Central Hospital, Finland [3]MAQUET Critical Care AB, Sweden, [4]European Synchrotron Radiation Facility, France, [5]University of Amiens, France, [6]University of Szeged, Hungary, [7]Geneva University Central Hospital, Switzerland

Email: liisa.porra@helsinki.fi

Background: Regional lung function depends on the amount of capillary blood that interfaces with alveolar air, and both parameters dynamically change during the respiratory cycle. Although the spatial distribution of regional blood (V_B) and gas (V_G) within the lung has previously been assessed, their dynamic changes during the respiratory cycle have not been directly quantified.

Methods: K-edge subtraction (KES) imaging with synchrotron radiation is a unique method for simultaneous imaging of structure and function of lungs. This method allows imaging of regional gas spaces as well as regional blood volumes using inhaled xenon or iodine in the blood as contrast agent [1]. KES-CT imaging and a post-gating reconstruction sequence was used to quantitatively image regional V_G, tissue density and V_B in 6 anaesthetized rabbits *in vivo*. Images were repeatedly collected during ventilation and inhalation of 70% Xe, or iodine infusion. Data were acquired in 2 different axial chest positions, at zero or positive end-expiratory pressure (ZEEP/PEEP), and tidal volumes (VT; volume of one breath).

Results and conclusions: Serial images showing the dynamic changes in gas and blood volume during the respiratory cycle were obtained. Changes in the V_G and V_B during ventilation are shown in the Figure. The dynamics of V_G and V_B were affected both by tidal volume and PEEP. This study shows for the first time, the relation between regional blood and gas volume during the respiratory cycle.

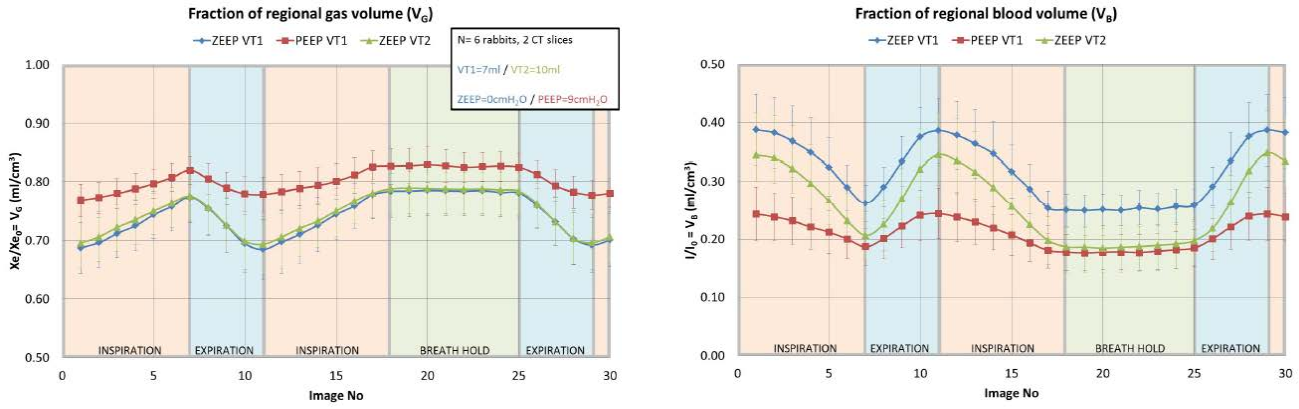


Figure 1: Relative lung gas and blood volumes during 2 successive respiration cycles

References

[1] L. Porra et al., Critical Care Medicine 39(7), 1731 (2011).

P53

Progress Report on the SSRT clinical trials conducted at the ESRF

M. Renier[1], J.F. Adam[2], C. Nemoz[1], Th. Brochard[1], P. Berkvens[1], A. Bravin[1], G. Berruyer[1], H. Elleaume[3], J. Balosso[2], J.F. LeBas[2], F. Estève[3,4]

[1]European Synchrotron Radiation Facility, Grenoble, France, [2]University Joseph Fourier, Radiotherapy, Grenoble, France, [3]Inserm U836 E6, Grenoble Institute of Neurosciences, Grenoble, France , [4]University Joseph Fourier, Grenoble Institute of Neurosciences, Grenoble, France **Contact email: renier@esrf.fr**

Clinical trials are currently being conducted at the ESRF with two types of approaches for the treatment of high-grade brain tumours: 1- one method irradiates the tumours with monochromatic X-rays in the energy range dominated by the photo-electric effect, and 2- the second method, called Micro-beam Radiation Therapy (MRT), and targeting spontaneous tumours in pets, uses an array of very intense, poly-energetic micro-beams (typically 50 microns wide, separated by 400 microns). The first method called Stereotactic Synchrotron Radiation Therapy (SSRT) will be presented in this poster.

The current clinical trials program benefits from the ID17 Biomedical beamline setup that had been developed for intravenous coronary arteries imaging. A total of 65 human patients (2000 to 2003) were imaged during that period. A specially designed Patient Positioning System (PPS) had been constructed for clinical trials. Intense monochromatic laminar beams ranging from 25 to 180 keV, and 150 mm wide, 4-5 mm height are available.

The SSRT principle combines two cumulative effects. The first one is a local dose enhancement produced by the presence of heavy atoms in the tumour, mainly due to the increased interaction with the monochromatic synchrotron radiation at 80 keV. Pre-clinical tests conducted over a decade have favoured the use of iodine (k-edge = 33 keV) and of platinum compounds, the latter commonly used as anti-cancer agents (k-edge = 78 keV).
The second effect, or stereotactic effect, is obtained from the accumulation of the dose deposited in the tumour from up to 10 different coplanar entry ports, whilst the dose deposited in the healthy tissues is kept below the tolerance. Furthermore, the tumours are irradiated through conformal collimators.
Obviously, in addition of guaranteeing the value of the dose delivered and at the exact target location, one of the main concerns is to guarantee the patient safety during the irradiation and during the 3-D X-ray image guidance procedures performed prior to the irradiation. To this end, a redundant Patient Safety System (PASS) is controlling all the parameters in real-time and would interrupt the beam in less than 4 ms in any case of reaching preset limit values.

The first SSRT patient has been treated at the ESRF in June 2012, and at the University Hospital (CHU) in Grenoble. Three to six patients have been and will be treated each year during 6 years to complete this Phase I/II of the clinical trials protocol which aims to prove 1- the technical feasibility of the project, 2- the tolerance by the patient (no unexpected side-effect!), and 3- the patient acceptance of anti-cancer treatment by synchrotron radiation.

P54

Internalization of iron nanoparticles by tumor associated macrophages for the improvement of tumor treatment

S. Reymond[1, 2, 3, 4], P. Gimenez[1, 2, 3, 4, 9], R. Serduc[1, 3], J. Arnaud[5], J.-P. Kleman[6], V. Djonov[7], W. Graber[7], J.A. Laissue[7], J.-K. Kim[8], S.-J. Seo[8], J.-L. Ravanat[4, 9, 10], H. Elleaume[1, 2, 3, 4]

[1]INSERM, U836, Grenoble, France; [2]Université Joseph Fourier, Grenoble Institut des Neurosciences, UMR-S836, Grenoble, France; [3]European Synchrotron Radiation Facility, Grenoble, France; [4]LabEx PRIMES Lyon, France; [5]CHU Grenoble, France; [6]IBS Grenoble, France; [7]University of Berne, Bern, Switzerland; [8]Catholic University of Daegu, Daegu City, Korea; [9]INAC/SCIB LAN CEA-Grenoble, France;
[10]Université de Grenoble - **sreymond@esrf.fr**

Rationale: An alternative approach for the improvement of radiotherapy consists in increasing differentially the radiation dose between tumors and healthy tissues using nanoparticles (NPs) that have been beforehand internalized into the tumor. These high-Z NPs can be photo-activated by monochromatic synchrotron X-rays, leading to a local dose enhancement delivered to the neighboring tumor cells [1]. This enhancement is due to secondary and Auger electrons expelled from the NPs by the radiations. In order to carry the NPs into the tumor center, macrophages are currently under study for their phagocytosis and diapedesis abilities [2]. In this study, we characterized J774A.1 macrophages' internalization kinetics and subcellular distribution of iron NPs.

Methods: Three aspects of internalization were examined: first, the *location of internalized NPs* in cells was determined using J774A.1 macrophages and F98 glioblastoma cells from ATCC. After a 24h incubation with iron NPs, the cells were washed and fixed for imaging. Optical microscopy was performed after cell slicing. Then, the *iron intake* after a 24h incubation with NPs was characterized for the two types of cells using ICP-MS. Finally, the *internalization dynamics* were studied: F98 internalizing NPs were observed by live phase-contrast microscopy imagining. Besides, NPs were injected in 96-well plates where J774A.1 were grown. Each hour, 4 wells were washed and absorbance, *i.e.* the iron mass retained in cells, was measured at 450 nm using a plate reader.

Results: F98 tumor cells and J774A.1 macrophages are both able of endocytosing NPs: we measured ~61±10 pg of internalized iron per macrophage compared with ~33±5 pg per tumor cell (initial iron concentration: 0.3 mg/mL in culture medium). F98 internalizing NPs for 10 hours showed some stress signs during the first minutes after the NPs injection, but behaved like F98 control cells during the rest of the experiment. Finally, we determined that the internalization kinetics for J774A.1 had a six-hour saturation typical time.

Conclusion: Macrophages seem to be promising vectors for NPs, being able to endocytose and retain in their cytoplasm larger quantities of NPs than tumor cells. Our following studies will attempt to shed light on their other potential abilities as "Trojan Horses".

References

[1] – F. Taupin *et al.*, Phys Med Biol **60**, 11 (2015).
[2] – J. Choi *et al.*, Biomaterials **33**, 16 (2012).

P55

An energy dispersive bent Laue monochromator for K-edge subtraction imaging

N. Samadi[1], Y. Zhu[2], M. Martinson[3], B. Bassey[3], G. Belev[4], A. Gomez[4], D. Chapman[4]

[1]Biomedical Engineering, University of Saskatchewan, Saskatoon, Canada, [2] McCaig Inst for Bone and Joint Health, University of Calgary, Calgary, Canada, [3]Physics and Engineering Physics, University of Saskatchewan, Saskatoon, Canada,[4]Canadian Light Source, Saskatoon, Canada, **nazanin.samadi@usask.ca**

K-Edge Subtraction (KES) is a powerful synchrotron imaging method that allows the quantifiable determination of a contrast element (i.e. iodine) and matrix material (usually represented as water) in both projection imaging and computed tomography [1]. With living systems, a bent Laue monochromator is typically employed to prepare imaging beams above and below the contrast element K-edge which focus at the subject location and subsequently diverge onto a detector. Conventional KES prepares the two beams by utilizing a splitter that blocks approximately 1/3 of the vertical beam size to prevent "edge crossing" energies beyond the monochromator (Figure 1).

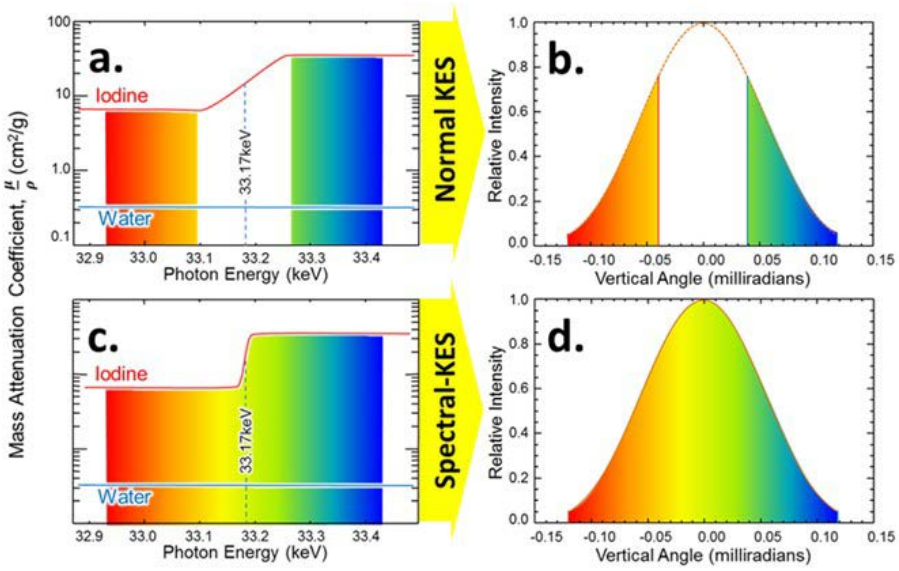


Figure 4 Iodine absorption edge (a & c) and vertical synchrotron beam profile (b & d) for a conventional bent Laue system (a & b) and Spectral-KES (c & d). Note that fully 1/3 of the beam in the conventional system is removed to avoid edge crossing energies which is not the case for Spectral- KES.

A bent Laue monochromator has been developed with very good focal and energy dispersive properties for KES. Approximately 4% of the vertical beam profile is involved in "edge crossing" energies, thus no splitter is employed. The beam can be narrowed vertically allowing a smaller crossover angle than a splitter based system, minimizing artifacts. The combination of good spatial resolution, energy dispersive properties, flux and a unique approach to data analysis make this system nearly ideal for KES [2].

Some of the relevant details of the monochromator will be discussed, especially the focal and energy dispersive properties, as well as, some details of artifacts caused by the beam focusing at the sample location. Example images of the beam and the object images will be presented as well.

References

[1] – See, for example, P. Suortti, W. Thomlinson, *et al.* A bent Laue crystal monochromator for angiography at the NSLS Nucl. Instr. Meth. Phys. Res. A 269 639–48 (1988).

[2] - Y. Zhu, N. Samadi, *et al.* Spectral K-edge subtraction imaging. Phys. Med. Biol., **59**: 2485-2503 (2014).

P56

Reduced Side Effects in Normal Tissue by MRT and Proton Minibeam Radiotherapy

Schmid T.E.[1], Girst S.[2], Bartzsch S.[3], Oelfke U.[3], Bräuer-Krisch E.[4], Bravin A.[4], Greubel C.[2], Reindl J[2]., Ilicic K[1]., Walsh D[1]., Multhoff G.[1], Dollinger G.[2], Wilkens J.J.[1]

1Klinikum rechts der Isar, Technische Universität München, Munich, Germany.
2Universität der Bundeswehr München, Neubiberg, Germany.
3German Cancer Research Center (DKFZ), Heidelberg, Germany and The Institute of Cancer Research, Sutton, United Kingdom.
4European Synchrotron Radiation Facility, Grenoble Cedex, France.

Purpose: MRT (Microbeam Radiation Therapy), a spatially fractionated radiotherapy at the European Synchrotron Radiation Facility (ESRF), uses an array of microscopically thin and nearly parallel synchrotron-generated X-ray beams. A different approach using focused proton minibeams spreading out into the tumor was recently established at the ion microprobe SNAKE in Munich. Our aim was to investigate if microbeam irradiations with micrometer sized X-ray and proton beams can minimize the risk of normal tissue damage in radiotherapy and to elucidate the biological normal tissue sparing effects.

Methods: Our investigations using MRT in proton minibeams were performed in an *in vitro* human skin tissue model which were irradiated with a mean dose of 2 Gy over the irradiated area either with parallel synchrotron-generated X-ray beams at the ESRF and with 20 MeV protons at the ion microbeam SNAKE in Munich in four different irradiation modes: homogeneous field, parallel lines (ESRF only) of 50 µm width, separated by 400 µm, spots of 50x50 μm^2 set by a 500x500 μm^2 matrix and spots of 180x180 μm^2 set by a 1800x1800 μm^2 matrix. In an *in vivo* experiment, 20 MeV protons were administered to the right ear of 2-3 months old, female Balb/c mice, using an average dose of 60 Gy in a field of 7.2 x 7.2 mm^2 in the central part of the ear, in two irradiation modes, homogeneous and minibeams. The 4 x 4 minibeams of 180 x 180 μm^2 size were set in a distance of 1.8 mm, resulting in a dose of 6,000 Gy in the channels, but with negligible dose in between.

Results: In the *in vitro* experiment the resulting cell viability of homogenuous irradiation in relation to unirradiated controls was 39.7±0.5% for protons and 38.9±4.4% for X-rays. Irrespectively of the size and distances of the channels, the cell viability was significantly lower with homogeneous irradiation compared to MRT or proton minibeam irradiation. No significant differences were observed with synchrotron X-rays vs. protons. In the *in vivo* study, ear swelling and skin reactions were monitored for 90 days following irradiation. No ear swelling or other skin reaction were detected after the minibeam irradiations, while significant ear swelling (up to 4-fold), erythema and desquamation developed in homogeneously irradiated ears 3-4 weeks after irradiation.

Conclusion: Our data show that normal tissue irradiation using parallel synchrotron-generated X-ray beams as well as minibeam proton irradiation maintained higher cell viability and lower genetic damage compared to conventional homogenous irradiation.

Supported by the DFG-Cluster of Excellence ‘Munich-Centre for Advanced Photonics’.

References

Girst S, Marx C, Bräuer-Krisch E, Bravin A, Bartzsch S, Oelfke U, Greubel C, Reindl J, Siebenwirth C, Zlobinskaya O, Multhoff G, Dollinger G, Schmid TE, Wilkens JJ. Improved normal tissue protection by proton and X-ray microchannels compared to homogeneous field irradiation. Phys Med. 2015 doi:10.1016/j.ejmp.2015.04.004.

P57

X-ray microtomography and fluorescence study of human embryo hands at 11-21 weeks of development

R.A.Senin, S.V.Saveliev[1], V.E.Asadchikov[2], A.V.Buzmakov[2], D.A.Zolotov[2], V.I.Gulimova[1]

NRC "Kurchatov institute", [1]Research Institute of Human Morphology, [2]Shubnikov Institute of Crystallography of RAS
senin_ra@nrcki.ru

The research of differentiation of skeletal elements for human embryos hands at 11-21 week of development was done. The need of usage of multiple energies of x-ray is shown for objects separation and 3D reconstruction. Independent accumulation of the extracellular matrix elements is found. It is shown that the cartilage germs of metacarpus and carpus are starting accumulate matrix elements a few weeks later than phalanges of differencing fingers and forearm bones. It is found that fast embryonic grow of a hand follows as a result of grow in pre epiphyseal zones of diaphyses. The distal parts of phalanges and nail bed are collecting calcium and phosphorus, that leads to their arrested development [1,2,3].

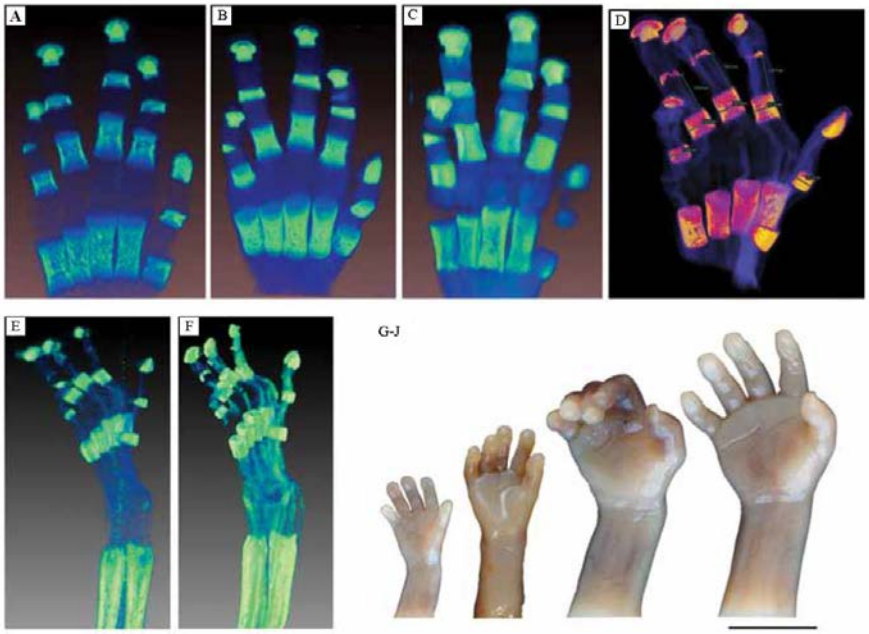


Figure 1. The results of microtomography and optical images of specimens. A-D – Tomographic reconstruction of 13.5 week old embryo hand; A- MoK_α line, B- 13 keV SR, C- CuK_α line, D - x-ray fluorescence setup Xradia Versa XRM-500; E-F – 15.5 weeks old embryo hand, E- CuK_α, F- MoK_α.G-J – Embryo hands a 11,13.5, 18 and 21 weeks old embryo hands. Scale bar for optical images – 10 mm.

References

[1] – S.V.Saveliev, V.E.Asadchikov, A.V.Buzmakov, D.A.Zolotov, V.I.Gulimova, R.A.Senin. X-ray microtomography and X-ray -fluorescence analysis of human fetal hand during 11-21 weeks of de velopment. Journal of Clinical and experimental morphology, **1**(13) 2015 , (pp.38-42) (*in Russian).*

[2] - Buzmakov, A., Chukalina, M., Nikolaev, D., Schaefer, G., Gulimova, V., Saveliev, S., ... & Asadchikov, V. (2013, July). Computed microtomography and x-ray fluorescence analysis for comprehensive analysis of structural changes in bone. In Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE (pp. 2340-2343). IEEE.

[3] - Asadchikov, V. E., Senin, R. A., Blagov, A. E., Buzmakov, A. V., Gulimova, V. I., Zolotov, D. A., ... & Kovalchuk, M. V. (2012). Comparison of the data of X-ray microtomography and fluorescence analysis in the study of bone-tissue structure. *Crystallography Reports*, ***57***(5), 700-707.

P58

Synchrotron x-ray microtransections: a new treatment for epileptic seizures arising from eloquent cortical areas

B. Pouyatos[1,2,3], C. Nemoz[4], T. Chabrol[1,2], M. Potez[1,2], E. Bräuer[4], L. Renaud[5,6], K. Pernet-Gallay[1,2], F. Estève[1,2], O. David[1,2], P. Kahane[1,2,7], J.A. Laissue[8], A. Depaulis[1,2] and R. Serduc[1,2]

[1] INSERM, U836, Grenoble, F-38043, France
[2] Université Joseph Fourier, Grenoble Institut des Neurosciences, UMR-S836, Grenoble, F-
[3] Synapcell S.A.S – Bâtiment Biopolis – 5 avenue du Grand Sablon, La Tronche, France.
[4] ESRF, Grenoble, France
[5] CNRS; CE2F PRIM UMS3537; Marseille, France
[6] Aix Marseille Université; Centre d'Exploration Fonctionnelle et de Formation; France
[7] Neurology Department, Michallon Hospital; France
[8] University of Bern, Switzerland

Synchrotron-generated X-ray (SRX) microbeams deposit high doses to submillimetric targets whilst minimizing irradiation of neighboring healthy tissue. We developed a new radiosurgical method which demonstrably transects cortical brain tissue without affecting adjacent regions. This non-invasive method mimicks surgical multiple subpial transections and similarly prevents epileptic seizure propagation into non-resectable and/or eloquent brain regions. We made such image-guided microtransections in the left somatosensory cortex in a rat model of generalized epilepsy using high interlaced radiation doses (820Gy) in thin (200µm) parallel slices of tissue. This procedure, targeting the brain volume from which seizures arise, altered the horizontal propagation of abnormal neuronal activities for 9 weeks, as evidenced by a decrease of seizure power and the coherence between tissue slices in comparison to the contralateral cortex. The brain tissue sited between transections stayed functionally and histologically normal, while the irradiated micro-slices remained devoid of myelin and neurons two months after irradiation. This pre-clinical proof of concept highlights the translational potential of non-invasive SRX transections for treating epilepsies that are not eligible for resective surgery.

P59

Synchrotron X-ray boost delivered by Microbeam Radiation Therapy improves glioma control after conventional fractionated X-ray therapy

Audrey Bouchet*, Marine Potez[†,††], Mélanie Flaender[†,††], Laura Schaad*, Claire Rome[†,††], Régine Farion[†,††], Jean A. Laissue*[$], Michael Grotzer***, Valentin Djonov*, Elke Brauer[†††], Hélène Elleaume[†,††], Emmanuel Brun and Raphaël Serduc[†,††]

[*] Institute of Anatomy, group tomographic and clinical anatomy, University of Bern, Baltzerstrasse 2, CH-3000 Bern 9 Switzerland
[†] INSERM, U836, Grenoble, F-38043, France
[††] Université Joseph Fourier, Grenoble Institut des Neurosciences, UMR-S836, Grenoble, F-38043, France
[†††] ESRF, Grenoble, F-38043, France
[$] University of Bern, Hochschulstrasse 4, CH-3012 Bern, Switzerland
*** Department of Oncology, University Children's Hospital of Zurich, Switzerland

Synchrotron microbeam radiation therapy (MRT) is an alternative treatment modality for brain tumors which uses synchrotron light. MRT relies on the spatial fractionation of the incident X-rays which allows high dose delivery to tumors (hundreds of Gy in the microbeam paths) without inducing severe damages to normal tissues. Because temporal fractionation is the standard radiotherapy protocol for brain tumors, the aim of this work was to evaluate the efficiency of MRT delivered as a boost after a temporally fractionated broad beam (BB) irradiation sequence to palliate F98 glioma bearing rats.

Rats were irradiated by 3 temporally fractionated BB irradiations at 6 Gy, then by 2 temporally fractionated synchrotron BB or MRT at 8 Gy. *In vivo* tumor follow up were performed by MRI. *Ex vivo* cell cycle analysis was made by FACS and the tissue responses were characterized by immunohistochemistry.

MRT induced significant and prolonged tumor cell cycle arrest compared with BB exposures. MRT stopped the tumor growth during 4 weeks and significantly increased the median survival time compared with the BB group. These results show for the first time the relevance of MRT as a radiation boost delivered after BB irradiation, suggesting that MRT is a realistic and more efficient alternative for brain tumor treatment when applied in a hypo-fractionated schedule.

Characterisation of the double-crystal Laue monochromator (DCLM) at the Australian Synchrotron Imaging & Medical Beamline (IMBL)

A. W. Stevenson[1,2], A. Maksimenko[1], C. J. Hall[1] and D. Häusermann[1]

[1]Imaging and Medical Beamline, Australian Synchrotron, Clayton, Victoria, Australia
Andrew.Stevenson@synchrotron.org.au
[2]CSIRO Manufacturing Flagship, Clayton South, Victoria, Australia

A key X-ray optical component of the Imaging & Medical Beamline (IMBL) at the Australian Synchrotron [1,2] is the double-crystal Laue monochromator (DCLM). The DCLM was supplied by IDT, is located at 16m from the source (a superconducting multi-pole wiggler insertion device), and enables X-ray energies to be selected from 20 to 130keV. The two crystals are 1mm thick Si, both of which can be bent (either concave or convex). The 311 reflection can be used, rather than the standard 111 reflection, in the case of higher X-ray energies.

We will present various results which demonstrate the utility and performance of the DCLM, principally in the context of X-ray imaging and tomography. Calculations of the monochromator's reflectivity and bandpass will be compared with experimental results. The issue of harmonic contamination and the effect of very high absorbed-power density for the (cooled) 1st Si crystal will be discussed. These will include the presentation of experimental data collected as a function of ring current, from less than 1mA to the standard 200mA, in order to assess the importance of 1st-crystal distortions, i.e. the 'heat bump'.

Figure 1: Left: DCLM on the IMBL, Australian Synchrotron. Right: schematic of one of the Si crystals.

References

[1] – A. W. Stevenson, et al., *J.Synch.Rad.*, **17**, 75-80 (2010).
[2] – A. W. Stevenson, et al., *J.Synch.Rad.*, **19**, 728-750 (2012).

P61

Radiosurgery of epilepsy using synchrotron x-ray microbeams

F. Studer[1], R. Serduc[1], B. Pouyatos[2], E. Bräuer-Krisch[3], F. Estève[1,4], A. Depaulis[1,4]

[1]Grenoble Institut des Neurosciences, INSERM U836, 38000 Grenoble, France, [2]SynapCell SAS, 38700 La Tronche, France, [3]European Synchrotron Research Facility, Biomedical beamline ID17, Grenoble, France, [4]CHU de Grenoble, 38000 Grenoble, France, florian.studer.88@gmail.com

Epilepsy is one of the most important neurological diseases. It concerns about 1% of the population worldwide. Despite the discovery of new molecules, one third of epileptic patients are resistant to anti-epileptic drugs and among them only a few can benefit from resective surgery. In this context, radiotherapy is an interesting alternative to the other treatments and several clinical devices have been developed (*e.g.*, Gamma Knife®). The European Synchrotron Radiation Facility offers the possibility to develop new methods of radiosurgery and to study their antiepileptic effects [1]. We showed recently a decrease of seizures after *Interlaced Microbeam Radiotherapy* (IntMRT) of the somatosensory cortex, known as the seizure generator, in the GAERS genetic model of absence epilepsy [2]. These antiepileptic effects were stable over 4 months with low tissular and functional side-effects. The irradiated pyramidal neurons still displayed their physiological activity but did not synchronize anymore. We also obtained a lasting suppression of seizures after IntMRT of the dorsal hippocampus in a mouse model of mesiotemporal lobe epilepsy. However, an important variability of antiepileptic efficiency was observed probably due to the small size of the targeted structure. We now develop IntMRT cortical transections based on the technique called Multiple Subpial Transections developed by Franck Morrel [3]. Such transections induce a significant reduction of the seizure power all over the irradiated hemisphere of GAERS for several weeks and need now to be tested on models of refractory epilepsy. The aim is to implement this approach to non-human primates, before moving to clinical trials.

References

[1] Serduc R, Bräuer-Krisch E, Siegbahn EA, Bouchet A, Pouyatos B, Carron R et al. (2010) High-precision radiosurgical dose delivery by interlaced microbeam arrays of highflux low-energy synchrotron X-rays. *PLoS ONE*

[2] Pouyatos B, Serduc R, Chipaux M, Chabrol T, Bräuer-Krisch E, Nemoz C et al. (2013) Synchrotron x-ray interlaced microbeams suppress paroxysmal oscillations in neuronal networks initiating generalized epilepsy. *Neurobiol. Dis*

[3] Morrell F, Whisler WW, Bleck TP. (1989) Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. *J Neurosurg*

P62

Evaluation of fundamental characteristics of carbon ion beams for use in Microbeam radiation therapy with Monte Carlo simulations

T. Tsubouchi, E. A. Siegbahn[1],

Department of Radiation Oncology, Osaka University Graduate School of Medicine,
JSPS Research Fellow,
[1]Department of Physics, Stockholm University,
e-mail:tsubouchi@radonc.med.osaka-u.ac.jp

Background: Microbeam radiation therapy (MRT) is being performed by using a set of highly collimated, narrow rectangular X-ray beams spaced by 1 mm or less. The tolerance of normal tissue to these microbeams has been found to be higher than to broad X-ray beams[1]. The distance between the microbeams and the lateral peak-to-valley dose ratio (PVDR) are important therapeutic parameters and are related to the biological effects[2]. The aim of this study was to evaluate the characteristics of a single microbeam of carbon ions and also the lateral PVDRs for grids of such beams.

Material & Method: In order to simulate the properties of single carbon microbeams, e.g. the FWHM at the position of the Bragg peak in a water phantom, we used the PHITS Monte Carlo simulation code. The shape of simulated carbon microbeams were rectangular and the sizes were 1 cm * 0.1 cm, 1 cm * 0.01 cm, and 1 cm * 0.001 cm. Various incident beam energies were considered.
We also calculated the spread-out Bragg peak and investigated the lateral PVDRs as a function of depth. Finally, we studied the irradiation of a hypothetical target, located in a water phantom, with two opposing grids of carbon microbeams (Fig. 1). A tumor target at the depth of about 10 cm in the phantom was assumed. The size of target is about 1 cm^3 (Fig. 1).

Results: We established the relationships between energy of carbon microbeams and FWHM at the position of the Bragg peak and between the incident beam size and the FWHM at the Bragg peak. We also determined how the lateral PVDRs varied as a function of depth.

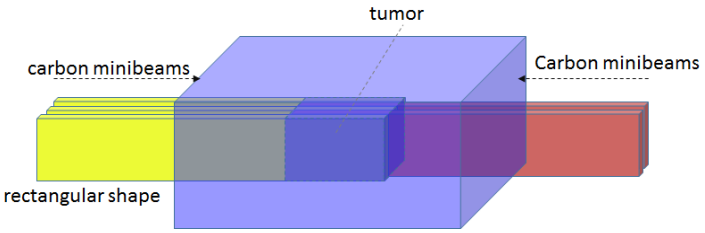


Figure 1: The design of calculation geometry with the two-directional carbon beam grid

References

[1] - E. A. Siegbahn, J. Stepanek, E. Brauer-Krisch, and A. Bravin, Med. Phys. 33 (9), September 2006.
[2] – M. Klodowska, P. OLko and M.P.R. Waligorski, Physica Medica (2015).

P63

Live Animal Imaging Program at BMIT facility at the Canadian Light Source

M.A. Webb[1], G. Belev[1], D. Miller[1], N. Zhu[1], M. Gibbons[2], J. Alcorn[2], T.W. Wysokinski[1]

[1]Canadian Light Source Inc. Saskatoon SK Canada
[2]University of Saskatchewan, Saskatoon SK Canada
adam.webb@lightsource.ca

The BioMedical Imaging and Therapy (BMIT) facility provides synchrotron-specific imaging and radiation therapy capabilities [1-5]. There are two separate end-stations used for experiments: the Bending Magnet (BM) 05B1-1 beamline [3] and the Insertion Device (ID) 05ID-2 beamline [4-5]. The design of the facility centres on the potential for human and animal studies and related applications. Currently focus is on small animal projects.

The live animal imaging program at the BMIT facility at the Canadian Light Source has been developing and continues to grow. It is expected to become a large portion of the user activity as numerous groups work towards the goal of live animal studies. The beamline provides basic support and has been improving the facilities available. For example, there have been changes to the lab to allow for longer rodent housing and improved housing during measurements. Remote control of heat lamps and of flow rate for gas anaesthesia allow a veterinarian or animal care person to make adjustments without interrupting the imaging. A zone bypass option gives rapid access to the enclosure if intervention is needed. Integration of user equipment such as heart/breathing monitoring and ultrasound equipment with the beamline systems can be used for gating control of imaging.

Future improvements will be done with consultation with University veterinarians and the user groups. Collaborations with the nearby VIDO-InerVac and the Western College of Veterinary Medicine (WCVM) are possible and they also provide expertise with farm animals. An important goal of the beamline is the integration of project specific equipment with the beamline allowing for flexibility in the user program and extensibility of the beamline while maintaining a high standard of animal care and research quality.

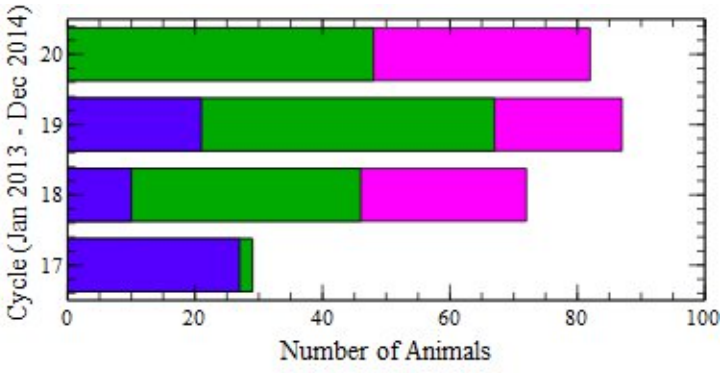


Figure 1: Animals imaged at BMIT (blue: Mouse, green: Rat, purple: Piglet).

References

[1] Chapman LD, (2007) CLSI Doc. No. 26.2.1.1 Rev. 0.A
[2] Chapman LD, (2006) CLSI Doc. No. 26.2.1.2 Rev. 0
[3] Wysokinski TW et al. (2007) NIM A 582:73-76
[4] Wysokinski TW et al. (2013) J. Phys: Conf Ser 425: 07
[5] Wysokinski TW et al. (2015) NIM A 775:1-4.

P64

Regularized phase retrieval algorithms for X-ray phase tomography of 3D bone cell culture analysis

Loriane Weber[1,2], Max Langer[1,2], Peter Cloetens[2] and Françoise Peyrin[1,2]

[1] Creatis, Université de Lyon, CNRS UMR5220, Inserm U1044, INSA-Lyon, Université Lyon 1, Villeurbanne, France
[2] The European Synchrotron Radiation Facility (ESRF), Grenoble, France, **loriane.weber@creatis.insa-lyon.fr**

Regenerative medicine is receiving increased interest. In the field of bone tissue engineering, a recurrent problem is to select efficient association of scaffolds and bone cells to maximize bone formation. Sensitive imaging modalities are required to quantify both cells and mineralized tissue. To this aim, X-ray phase contrast imaging is an attractive modality since it offers three orders of magnitude higher sensitivity than conventional radiology. In-line phase contrast imaging consists in letting a spatially coherent beam propagate after passing through a sample [1]. Projections are acquired at several angles, for several sample-to-detector distances. The phase can be extracted from projections using a so-called phase retrieval algorithm. A tomographic reconstruction algorithm is then applied to these phase projections to obtain a 3D-map of the refractive index in the object.

In this work, we compare several phase retrieval methods based on different priors [3, 4, 5] in porous bone scaffolds seeded with bone forming cells.

These algorithms not only enable to discriminate bone cells, newly formed bone and scaffolds, but quantify the volume and density of the calcified fraction, as well as the volume of extra-cellular matrix generated by the bone cells, by thresholding the refractive index maps. Further, the use of heterogeneous object algorithms enabled quantification of the refractive index of the soft tissue compartment, as well as segmentation of osteoblasts trapped in the pre-bone matrix, which was not possible using standard μCT.

References

[1] A. Snigirev, I. Snigireva, et al., Rev Sci. Instrum., vol. 66, no. 12, p. 5486 (1995).
[2] D. Paganin, S. C. Mayo, et al., J. Microsc., vol. 206, no. 1, pp. 33–40 (2002).
[3] M. Langer, P. Cloetens, and F. Peyrin, IEEE TIP, vol. 19, no. 9, pp. 2428–36 (2010).
[4] M. Langer, P. Cloetens, et al., Opt. Lett., vol. 37, no. 11, pp. 2151–3 (2012).
[5] M. Langer, P. Cloetens, et al., Philos. Trans. R. Soc. A, vol. 372, no. 2010, p. 20130129 (2014).

P65

ID source for biomedical imaging and therapy programs at 3-rd generation synchrotrons – technical constraints

Tomasz W. Wysokinski, L. Dean Chapman, Denise Miller, George Belev
Canadian Light Source, Saskatoon, SK, Canada, **bmit@lightsource.ca**

Biomedical research programs at 3-rd generation 3 GeV synchrotrons require a unique radiation source that can provide a wide beam fan with high critical energy and high dose rates. At 3 GeV machines a high field superconductive (SC) wiggler is the only practical solution in order to match the flux and spectrum of beamlines located at 6 and 8 GeV machines. BMIT's 4.3 Tesla superconductive wiggler is one of the first of the new family of the wigglers designed specifically for such imaging and therapy programs. Design requirements were defined in 2005 [1-2], manufacturing started in 2006, and the wiggler was installed in November of 2007 [3-5].

Smaller 3 GeV synchrotrons are very compact, thus the distance from the source to the first optical component (Be or diamond window) is short -- for the BMIT ID beamline, it is less than 12 metres. This translates into very high power density transmitted by the first optical component, which can reach as much as 80 W/mm^2. The critical energy (E_c) at 3 GeV machines, even with a high field wiggler, is much smaller than at 6 GeV machines using conventional wigglers. For example at BMIT E_c=24 keV while at ESRF ID-17 it is 35 keV. The end result is that when trying to match the flux at higher energies, the 3 GeV machines produce effectively more heat-load from low energy X-ray absorption, with the same total power emitted from the source.

The spectrum and the photon flux depend on the operating magnetic field of the wiggler. In the case of SC wigglers, the field can change more than twofold. This change affects the position of the SR beam and an additional corrective coil system is required for unrestricted changes of the field. To reduce the Ohmic heatload in the cold area of the wiggler the current is split between several power sources. This complicates the operation of the wiggler, as strict synchronization in current levels between the power supplies is required. SC wigglers can be designed to operate as effectively zero boil-off machines between the maintenance periods, so the actual operating costs are primarily defined by cost of the maintenance of the compressors and cryocoolers and the cost of electricity and cooling water.

In the case of BMIT ID, several modifications to original external hardware and to the power supplies' controls were implemented to address the air leaks into the He space and to provide the ability to change the field of the wiggler during normal operation without affecting other research groups. The ramping look-up table was enhanced to include more points and effectively to reduce the possibility of current mismatch between the points.

4 T SC wigglers are optimized for the existing 3 GeV rings and can provide effective flux required for both therapy and imaging experiments within 25-140 keV spectral range span. If higher energy levels are required, the wigglers could be upgraded with Nb_3Sn Superconducting wires which will however significantly increase the cost of the wiggler.

References

[1] Sitnikov A, (2005) CLSI Doc. No. 5.8.25.5 Rev. 0
[2] Chapman LD, (2007) CLSI Doc. No. 26.2.1.1 Rev. 0.A
[3] Khrushchev SV et al. (2009) NIM A 603:7-9
[4] Wysokinski TW et al. (2013) J. Phys: Conf Ser 425: 07
[5] Wysokinski TW et al. (2015) NIM A 775:1-4

P66

Investigation on the relationship between morphology and active ingredient of Chinese medicinal materials based on X-ray quantitative micro-tomography

Y.L. Xue[1], Z.T. Liang[2], P.F. Sun[1], Z.Z. Zhao[2], T.Q. Xiao[1]

[1]Shanghai Institute of Applied Physics, Chinese Academy of Sciences, 201204, Shanghai, China
[2]School of Chinese Medicine, Hong Kong Baptist University, Hong Kong Special Administrative Region
Email: ylxue@sinap.ac.cn; tqxiao@sinap.ac.cn

Identification and quality evaluation of Chinese medicinal materials(CMMs) is the foundation of traditional Chinese medicines. The current quality evaluation method is to measure the effective components by different means, such as chromatography, spectral method etc., which usually need very strict operation procedures, and always last a long process. What's more, additional chemical reagents are required, which may result in structure information loss or fake image. Owing to the high spatial coherence, high flux density and unique penetrating characters of synchrotron radiation X-ray beam, synchrotron radiation X-ray imaging can achieve in situ, nondestructive research on CMMs without any sample preparation[1,2]. In this study, we intend to establish the relationship between morphology and active ingredients of CMMs, in ordor to develop a new method to simplify the quality evaluation of CMMs based on morphological information directly. In this presentation, ginseng is selected as sample, the localization of the main active components--ginsenosides are studied by means of laser microdissection and ultra high performance liquid chromatography-mass spectrometry (UPLC-MS). The measurement results of the active components showed that ginsenosides are mainly distributed in cork, followed by cortex, phloem and xylem respectively(cork, cortex and phloem are at the outside of the cambium, xylem is at the inside)[3]. Then, synchrotron radiation X-ray quantitative micro-tomography at Shanghai Sychrotron Radiation Facility is employed to achieve the 3D mophology information of gensing samples, and quantify the volume of the different tissues in the main root of four kinds of ginsengs. The results showed that the higher the grade of ginseng, the larger the volume ratio of tissues outside the cambium to that inside the cambium. This result is confirmed by the ginsenosides quantity which is measured by laser microdissection and UPLC-MS. Therefore, synchrotron radiation X-ray quantitative micro-tomography is expected to be a simple, rapid and nondestructive method for quality asessment of CMMs.

This work is supported by the National Natural Science Foundation of China grant 11475248 and 11105213.

References

[1] - Y.L. Xue, T.Q. Xiao, L.H. Wu, C. Chen, R.Y. Guo, G.H. Du, H.L. Xie, B. Deng, Y.Q. Ren and H.J. Xu, Acta Physica Sinica **59**, 5496(2010).
[2] - L.L. Ye, Y.L. Xue, L.H. Ni, H. Tan, Y.D. Wang and T.Q. Xiao, Journal of Instrumentation **8**, C07006(2013).
[3] - Z.T. Liang, Y.J. Chen, L. Xu, M.J. Qin, T. Yi, H.B. Chen and Z.Z. Zhao, Journal of Pharmaceutical and Biomedical Analysis **105**, 121(2015).

P67

High-resolution tomographic microscopy of intramedullary arteries in rat spinal cord: comparison of absorption and phase contrast imaging using synchrotron radiation

Cao, Yong[1]; Hu, JianZhong[1*]; Wu, Tianding[1]; Zhou Yuan[1], Li, Dongzhe[1], Ni, shuangfei[1], Lu, HongBin[2]

1 Department of Sports Medicine and Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
2 Department of Spine Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, PR China.
* Corresponding author: **jianzhonghu@hotmail.com**

Introduction: Numerous spinal cord circulatory disorders have substantial involvement of small vessel lesions. Early detection of the small vessels leads to effective diagnosis and treatment of the diseases. However, such small vessels involved are beyond the detection limit of the currently existing traditional imaging techniques.

Method: Here, the x-ray absorption contrast imaging (ACI) and phase contrast imaging (PCI) base on the novel developed synchrotron radiation (SR) were combined to detect the images of intramedullary arteries in the spinal cord from which the 3D structure and distributions of vasculature could also be analyzed. The results of these two imaging model were qualitatively and quantitatively compared.

Results: Both ACI and PCI based on synchrotron radiation successfully visualized the intramedullary arteries of the spinal cord. Couple with the micro-computed tomography, the high-resolution 3D physiologic arrangement of the entire intramedullary artery network at the micrometer scale in rat spinal cord was obtained, and related vessel morphology of the central sulcus artery is also studied.

Conclusions: The detection of intramedullary arteries by PCI relies no application of contrast agent caused less dose imparted to the specimen is an ideal imaging method and provide a new way for evaluating pathologic changes in small vessels and clarify their role in neurovascular disorders.

Acknowledgement: This work was supported by the National Natural Science Foundation of China (No. 81171698 and No. 81371956). The authors would like to thank Tiqiao Xiao and other staffs for their assistances in the experiment at BL13W1 of Shanghai Synchrotron Radiation Facility (SSRF) in China.

P68

Developing a compact microbeam radiation therapy system using the carbon nanotube field emission X-ray source array

Lei Zhang, Christy Inscoe, Hong Yuan, Yueh Lee, Jianping Lu, Sha Chang, and Otto Zhou

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA
Corresponding email addresses: **leiz@email.unc.edu** and **zhou@email.unc.edu**

Microbeam radiation therapy (MRT) is a novel and experimental cancer treatment modality that has received accumulating focus and emphasis worldwide in recent years. It uses arrays of quasi-parallel radiation beams that are up to a few hundred microns wide and separated by several times of its beamwidth. Extensive preclinical studies at ESRF and several other national synchrotron facilities have demonstrated that microbeams with doses of several hundreds of Gy are well tolerated by healthy brain tissues but cause preferential damage in tumor. As the effort now moves towards large animal and clinical trials, there are eminent needs to develop compact and economically-viable microbeam irradiators for MRT radiobiology research and clinical installation eventually.

Our group has recently developed the first laboratory-scale microbeam irradiator using the carbon nanotube (CNT) field emission X-ray source array technology [1-2]. The CNT source array technology allows optimization of the anode focal spot shape and size, and therefore overcomes the obstacles of producing high flux microbeam radiation using conventional X-ray tubes. The first CNT-MRT prototype has been systematically characterized and is capable of generating orthovoltage radiation with all essential characteristics of MRT dose distribution. An on-board micro-CT is incorporated in the system design, and dedicated image-guidance protocols have been developed for accurate dose delivery [3]. Preliminary studies with tumor bearing small animals have been carried out using the CNT-MRT prototype and have shown encouraging therapeutic effects in terms of tumor local control and survival time extension [4].

Several advantages make CNT-MRT an attractive alternative as a clinical microbeam delivery system. In addition to its compactness, the CNT X-ray source array is electronically controlled with instantaneous beam response, which allows for physiologically gated microbeam delivery [5]. By synchronizing the microbeam radiation exposure with the cardiac or respiratory signals, motion-induced beam blurring and positioning errors could be largely minimized. Besides, the CNT source array affords great flexibility in source design in terms of number of sources and configurations. Multi-arrays of microbeams cross-firing at the brain tumor target simultaneously can be achieved with a ring-shaped system design [6]. Such design could improve the dose deposition in tumor, and also alleviate the problematic skin damage caused by high dose kilovoltage radiation. With ongoing development and optimization, this nanotechnology-based compact MRT system has shown promise as a research tool for revealing the therapeutic mechanism of MRT, and offers a potential pathway for clinical translation.

References

[1] - O. Zhou and S. Chang, US Patent No. 8,600,003.
[2] - M. Hadsell, J. Zhang et al., Applied Physics Letters **103**, 183505 (2013).
[3] - L. Zhang, H. Yuan et al., Physics in Medicine and Biology **59**, 1283-1303 (2014).
[4] - H. Yuan, L. Zhang et al., Radiation Research, Aug (2015).
[5] - P. Chtcheprov, L. Burk et al., Medical Physics **41**(8), 081705 (2014).
[6] - L. Zhang, H. Yuan et al., Expert Review of Anticancer Therapy **14** (12), 1411-1418 (2014).

BioMedical Imaging and Therapy (BMIT) Facility Update

N. Zhu[1], G. Belev[1], D. Miller[1], M.A. Webb[1], T.W. Wysokinski[1]

[1] Canadian Light Source, Saskatoon, SK, Canada
bmit@lightsource.ca

The BioMedical Imaging and Therapy (BMIT) facility at the Canadian Light Source provides a world class facility with unique synchrotron specific imaging and therapy capabilities [1-5]. It is used to study diverse problems in human medicine, veterinary medicine, agriculture, and other biomedical areas. The facility is comprised of 05ID-2 and 05B1-1 beamlines and supporting laboratories.

The bend magnet beamline, 05B1-1, will test and validate new ideas in imaging and therapy for eventual translation to BMIT's insertion device beamline 05ID-2. Currently, there is one endstation (experimental hutch) in each beamline. The 05B1-1 beamline is 28.5 meters in length and has a monochromatic spectral range from 8 to 40 keV. Its maximum load capacity is 50 kg. The 05ID-2 beamline is 55 meters in length and has a monochromatic spectral range from 25 to 140 keV. Its maximum load capacity is 450 kg. There are several supporting laboratories built at the BMIT facility including a small animal preparation room, a large animal preparation room, a mechanical workshop, and a computer laboratory for imaging data processing. Additionally, there is a new life sciences laboratory operated next to the BMIT facility.

A number of different imaging modalities are available at the BMIT facility. The 05B1-1 beamlines can host K-edge subtraction, diffraction enhanced imaging, multiple image radiography, in-line phase contrast imaging, and regular absorption imaging in both projection and CT modes of operation, while the 05ID-2 beamline only provides in-line phase contrast imaging, and regular absorption imaging in both projection and CT modes so far. More than ten different x-ray detector systems are available at the BMIT facility. They provide adequate coverage for the available x-ray energy range (8-140 keV), for different resolution (from 2 to 200 μm) and speed requirements, and are able to image objects of very different sizes.

References

[1] Chapman LD, (2007) CLSI Doc. No. 26.2.1.1 Rev. 0.A
[2] Chapman LD, (2006) CLSI Doc. No. 26.2.1.2 Rev. 0
[3] Wysokinski TW et al. (2007) NIM A 582:73-76
[4] Wysokinski TW et al. (2013) J. Phys: Conf Ser 425: 07
[5] Wysokinski TW et al. (2015) NIM A 775:1-4.

P70

Optimization of in-line phase contrast imaging setup for *in vivo* visualization of hydrogel scaffolds in nerve tissue engineering applications

N. Zhu[1], A. Rajaram[2], A. Olubamiji[2], D.J. Schreyer[3], T.W. Wysokinski[1], G. Belev[1], X.B. Chen[2,4]

[1] Canadian Light Source Inc., University of Saskatchewan, Saskatoon, SK S7N 2V3, Canada

[2] Division of Biomedical Engineering, University of Saskatchewan, Saskatoon, SK S7N 5A9, Canada

[3] Department of Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, SK S7N 5E5, Canada

[4] Department of Mechanical Engineering, University of Saskatchewan, Saskatoon, SK S7N 5A9, Canada

Ning.zhu@lightsource.ca

Synchrotron-based in-line Phase Contrast Imaging (in-line PCI) technique has great potential in soft tissue engineering applications [1]. It is able to detect fine features in weakly absorbing tissues and low density scaffolds, which are invisible in conventional radiographs due to the weak X-ray attenuation of the samples. Optimization of sample-to-detector distance (SDD) on specific tissue engineering samples is of great importance in in-line PCI to clearly visualize detailed features due to the fact that the effect of the sizes of the X-ray source and the pixels of the detector cannot be ignored [2]. In the present study, in-line PCI combined with computed tomography (CT) was used for non-invasive *in vivo* visualization of nerve tissue scaffolds. The experiments were conducted at the 05B1-1 beamline at the Biomedical Imaging and Therapy (BMIT) facility at the Canadian Light Source (CLS) [3]. An alginate hydrogel porous scaffold was implanted at the site of transection of the left sciatic nerve in rats. The animals were sacrificed after 2 days survival, and the hindlimbs with the scaffold-implants were imaged. The images were recorded by a beam monitor AA-60 (HAMAMATSU) coupled to a camera C9300 (HAMAMATSU). The variation of the edge contrast based on the same sample is discussed at the X-ray energy of 30 keV with different SDD (40cm, 1.52m, 4.6m, and 6.2m). The results show that the edge-enhanced contrast makes the edges of hydrogel scaffolds and soft tissues detectable at SDD more than 1.52 m. But edge blur and noises in the images become more obvious when increasing the distance, especially at 6.2 m. The images obtained from the scan at 1.52 m of SDD show better image quality when compared with others and it is good for *in vivo* visualization of nerve tissue scaffolds. The imaging parameters discussed in this study will also be helpful in optimizing the setup of in-line PCI for other soft tissue scaffold imaging applications.

References

[1] N. Zhu, X.B. Chen, et al., Journal of Biomimetics Biomaterials and Tissue Engineering 7, 81 (2010).

[2] Q.J. Jia, Y. Chen, et al., Chinese Physics C **36**, 267 (2012).

[3] T.W. Wysokinski, et al., Nuclear Instruments and Methods in Physics Research A **582**, 73 (2007).

List of participants

Name	Laboratory	Country	Email
Jean Francois ADAM	Universite Joseph Fourier	FRANCE	adam.jeanfrancois@gmail.com
Mark AKSELROD	Landauer Inc	USA	makselrod@landauerinc.com
Masami ANDO	Photon Factory - KEK	JAPAN	msm.ando@rs.noda.tus.ac.jp
Fulvia ARFELLI	Universita di Trieste	ITALY	fulvia.arfelli@trieste.infn.it
Jacques BALOSSO	CHU Grenoble	FRANCE	jbalosso@chu-grenoble.fr
Giacomo BARBONE	ESRF	FRANCE	giacomo.e.barbone@gmail.com
Stefan BARTZSCH	Institute of Cancer Research	UNITED KINGDOM	s.bartzsch@dkfz.de
Bassey BASSEY	University of Saskatchewan	CANADA	bassey.bassey@usask.ca
Tilo BAUMBACH	Karlsruhe Institute of Technology	GERMANY	tilo.baumbach@kit.edu
Sam BAYAT	Universite de Picardie Jules Verne	FRANCE	Bayat.Sam@chu-amiens.fr
Martin BECH	University of Lund	SWEDEN	martin.bech@med.lu.se
Helene BERNARD	ESRF	FRANCE	hbernard@esrf.fr
Gabriele BIELLA	Consiglio Nazionale delle Ricerche	ITALY	gembiella@gmail.com
Sylvain BOHIC	INSERM U836 - ESRF	FRANCE	bohic@esrf.fr
Audrey BOUCHET	University of Berne	SWITZERLAND	abouchet38@gmail.com

Name	Laboratory	Country	Email
Elke BRAEUER-KRISCH	ESRF	FRANCE	brauer@esrf.fr
Alberto BRAVIN	ESRF	FRANCE	bravin@esrf.fr
Ludovic BROCHE	ESRF	FRANCE	broche@esrf.fr
Emmanuel BRUN	INSERM U836 - ESRF	FRANCE	emmanuel.brun@esrf.fr
Karin BURGER	Klinikum rechts der Isar - TU Muenchen	GERMANY	Karin.Burger@tum.de
Inna BURKEEVA	CNR-IFN	ITALY	innabukreeva@yahoo.it
Charlene CALOUD	ESRF	FRANCE	Charlene.caloud@esrf.fr
Yong CAO YONG	Xiangya hospital of Central South University	CHINA	caoyong1912@163.com
Crister CEBERG	University of Lund	SWEDEN	crister.ceberg@med.lu.se
Alessia CEDOLA	Universita di Roma La Sapienza - CNR	ITALY	alessia.cedola@cnr.it
Cecilia CERESA	University of Milan-Bicocca	ITALY	cecilia.ceresa1@unimib.it
Dean CHAPMAN	Canadian Light Source	CANADA	dean.chapman@usask.ca
Anne Marie CHARVET	ESRF	FRANCE	charvet@esrf.fr
Yi Ching CHEN	Monash University	AUSTRALIA	peggy.chen@monash.edu
Rongchang CHEN	Shanghai Institute of Applied Physics	CHINA	rongchang.chen@gmail.com

Name	Laboratory	Country	Email
Farley CHICILO	University of Saskatchewan	CANADA	chicilo@gmail.com
Paola COAN	Ludwig-Maximilians University	GERMANY	paola.coan@physik.uni-muenchen.de
Isabelle COMBE	ESRF	FRANCE	isabelle.combe@esrf.fr
Jeffrey CROSBIE	RMIT University	AUSTRALIA	jeffrey.crosbie@rmit.edu.au
Denis DAUVERGNE	LPSC (ex ISN)	FRANCE	denis.dauvergne@lpsc.in2p3.fr
Veronica DEL GROSSO	ESRF	FRANCE	veronica.del-grosso@esrf.fr
Biao DENG	Shanghai Institute of Applied Physics, CAS	CHINA	dengbiao@sinap.ac.cn
Antoine DEPAULIS	INSERM - UJF	FRANCE	antoine.depaulis@ujf-grenoble.fr
Paul Claude DIEMOZ	University College London	UNITED KINGDOM	p.diemoz@ucl.ac.uk
Salvatore DI MARIA	CTN, Instituto Superio Tecnico	PORTUGAL	salvatore@ctn.ist.utl.pt
Valentin DJONOV	Institute of Anatomy	SWITZERLAND	djonov@ana.unibe.ch
Martin DONNELLEY	University of Adelaide	AUSTRALIA	martin.donnelley@adelaide.edu.au
Mattia DONZELLI	ESRF	FRANCE	donzelli@esrf.fr
Christian DULLIN	University Medical Center Goettingen	GERMANY	christian.dullin@gmail.com
Hélène ELLEAUME	INSERM - CHU Grenoble	FRANCE	helene.elleaume@gmail.com

Name	Laboratory	Country	Email
Marco ENDRIZZI	University College London	UNITED KINGDOM	m.endrizzi@ucl.ac.uk
Francois ESTEVE	INSERM U836 - ESRF	FRANCE	esteve@esrf.fr
Christian FEDON	Sincrotrone Trieste S.C.p.A	ITALY	christian.fedon@ts.infn.it
Melanie FLAENDER	INSERM U836 - ESRF	FRANCE	melanie.flaender@gmail.com
Pauline Helene FOURNIER	University of Wollongong	AUSTRALIA	pauline.fournier.pf@gmail.com
Florin Gica FUS	ESRF	FRANCE	florin.fus@gmail.com
Sergey GASILOV	ANKA Angstroemquelle GmbH	GERMANY	sergei.gasilov@gmail.com
Tobias GEITH	Ludwig-Maximilians-University Hospital Munich	GERMANY	tobias.geith@med.uni-muenchen.de
Paul GIMENEZ	CEA Grenoble - INAC	FRANCE	paul.gimenez@cea.fr
Spyridon GKOUMAS	Paul Scherrer Institute	SWITZERLAND	spyridon.gkoumas@psi.ch
José María GÓMEZ ROS	CIEMAT	SPAIN	jm.gomezros@ciemat.es
Michael GROTZER	University of Zurich	SWITZERLAND	Michael.Grotzer@kispi.uzh.ch
Kim HARRISON	University of Saskatchewan	CANADA	kharrison226@hotmail.com
Daniel HAUSERMANN	Australian Synchrotron	AUSTRALIA	Daniel.Hausermann@synchrotron.org.au

Name	Laboratory	Country	Email
Yasushi HAYAKAWA	Nihon University	JAPAN	yahayak@lebra.nihon-u.ac.jp
Thomas HENRY	Karolinska Institute	SWEDEN	thomas.henry@ki.se
Guido HILDEBRANDT	Rostock University Medical Center	GERMANY	Guido.Hildebrandt@uni-rostock.de
Mark HILL	University of Oxford	UNITED KINGDOM	mark.hill@oncology.ox.ac.uk
John W. HOPEWELL	Churchill Hospital	UNITED KINGDOM	john.hopewell@gtc.ox.ac.uk
Richard Peter HUGTENBURG	University of Wales - Swansea	UNITED KINGDOM	r.p.hugtenburg@swansea.ac.uk
Zahra IZADIFAR	University of Saskatchewan	CANADA	zai206@mail.usask.ca
Zohreh IZADIFAR	University of Saskatchewan	CANADA	zohreh.izadifar@usask.ca
Marie JACQUET	IN2P3-CNRS - Universite Paris-Sud 11	FRANCE	mjacquet@lal.in2p3.fr
Felix JAEKEL	Rostock University Medical Center	GERMANY	felix.jaekel@uni-rostock.de
Azemat JAMSHIDI-PARSIAN	University of Arkansas for Medical Sciences	USA	jamshidiazema@uams.edu
Xiaoming JIANG	Institute of High Energy Physics (CAS)	CHINA	jiangxm@mail.ihep.ac.cn
Jianzhong JIANZHONG HU	Xiangya hospital of Central South University	CHINA	jianzhonghu@hotmail.com
Jani Petteri KEYRILAINEN	Turku University Hospital	FINLAND	jani.keyrilainen@tyks.fi

Name	Laboratory	Country	Email
Jong-Ki KIM	Catholic University of Daegu	KOREA	jkkim@cu.ac.kr
Marcus KITCHEN	Monash University	AUSTRALIA	Marcus.Kitchen@monash.edu
Youri KOUBYCHINE	Universidad Politecnica de Catalunya - UPC	SPAIN	iouri.koubychine@upc.edu
Wojciech M. KWIATEK	Institute of Nuclear Physics	POLAND	wojciech.kwiatek@ifj.edu.pl
Jean Albert LAISSUE	University of Berne	SWITZERLAND	laissue@pathology.unibe.ch
Max LANGER	CNRS UMR 5515 - INSA 502	FRANCE	max.langer@esrf.fr
Anders LARSSON	Uppsala University	SWEDEN	anders.larsson@surgsci.uu.se
Geraldine LE DUC	ESRF	FRANCE	leduc@esrf.fr
Gang LI	Institute of High Energy Physics (CAS)	CHINA	lig@ihep.ac.cn
Xia LIU	Canadian Light Source	CANADA	xia.liu@lightsource.ca
Jayde LIVINGSTONE	Australian Synchrotron	AUSTRALIA	Jayde.Livingstone@synchrotron.org.au
Renata LONGO	Universita di Trieste	ITALY	renata.longo@ts.infn.it
Ricardo LOPES	Federal University of Rio de Janeiro	BRASIL	ricardo@lin.ufrj.br
Goran LOVRIC	Paul Scherrer Institute	SWITZERLAND	Goran.Lovric@gnudo.com
Hongbin LU	Xiangya hospital of Central South University	CHINA	hongbinlu@hotmail.com

Name	Laboratory	Country	Email
Xiaojie LUAN	University of Saskatchewan	CANADA	xil496@mail.usask.ca
Margarita MALAKYAN	Institute of Molecular Biology	ARMENIA	ritamalakyan@email.com
Mercedes MARTINSON	Canadian Light Source Inc.	CANADA	mercedes.m@usask.ca
Anne-Francoise MAYDEW	ESRF	FRANCE	maydew@esrf.fr
Kadda MEDJOUBI	Synchrotron Soleil	FRANCE	kadda.medjoubi@synchrotron-soleil.fr
Ralf Hendrik MENK	Elettra - Sincrotrone Trieste	ITALY	ralf.menk@elettra.trieste.it
Andreas MERREM	MPI fuer Biophysikalische Chemie	GERMANY	amerrem@gwdg.de
Giovanni METTIVIER	Universitario Monte Santagelo	ITALY	mettivier@na.infn.it
Alberto MITTONE	ESRF	FRANCE	alberto.mittone@esrf.fr
Ken MIYA	University of Tsukuba	JAPAN	ken-miya@hotmail.co.jp
Peter MODREGGER	Paul Scherrer Institute	SWITZERLAND	peter.modregger@gmail.com
Rajmund MOKSO	Lund University	SWEDEN	rajmund.mokso@maxlab.lu.se
Kaye MORGAN	Monash University	AUSTRALIA	kaye.morgan@monash.edu
Carmel MOTHERSILL	McMaster University	CANADA	mothers@univmail.cis.mcmaster.ca

Name	Laboratory	Country	Email
Peter MUNRO	University College London	UNITED KINGDOM	p.munro@ucl.ac.uk
Rhiannon MURRIE	Monash University	AUSTRALIA	rhiannon.murrie@monash.edu
Christian NEMOZ	ESRF	FRANCE	nemoz@esrf.fr
Liebert NOGUEIRA	State University of Rio de Janeiro	BRASIL	liebertrj@gmail.com
Uwe OELFKE	Institute of Cancer Research	UNITED KINGDOM	Uwe.Oelfke@icr.ac.uk
Alessandro OLIVO	University College London	UNITED KINGDOM	aolivo@medphys.ucl.ac.uk
Serena PACILE'	Elettra - Sincrotrone Trieste	ITALY	serena.pacile@elettra.eu
Arash PANAHIFAR	University of Saskatchewan	CANADA	a.panahifar@usask.ca
Alessandra PATERA	Paul Scherrer Institut	SWITZERLAND	alessandra.patera@psi.ch
James PEARSON	Australian Synchrotron	AUSTRALIA	james.pearson@monash.edu
Paolo PELLICIOLI	ESRF	FRANCE	paolo.pellicioli@mail.polimi.it
Qi PENG	University of Saskatchewan	CANADA	peng.qi@usask.ca
Barbara PIERSCIONEK	Kingston Univresity London	UNITED KINGDOM	B.Pierscionek@kingston.ac.uk
Liisa PORRA	University of Helsinki	FINLAND	liisa.porra@helsinki.fi

Name	Laboratory	Country	Email
Maximilian REISER	Ludwig-Maximilians University	GERMANY	maximilian.reiser@med.uni-muenchen.de
Michel RENIER	ESRF	FRANCE	renier@esrf.fr
Herwig REQUARDT	ESRF	FRANCE	requardt@esrf.fr
Benjamin RESTAUT	ESRF	FRANCE	benjamin.restaut@esrf.fr
Solveig REYMOND	ESRF	FRANCE	solveig.reymond@esrf.fr
Dimitri REYNARD	INSERM U836 - ESRF	FRANCE	dreyelinerz@gmail.com
Nazanin SAMADI	Canadian Light Source Inc.	CANADA	Nazanin.samadi@usask.ca
Carlo SANTINI	Universita di Camerino	ITALY	carlo.santini@unicam.it
Thomas SCHMID	Klinikum rechts der Isar - TU Muenchen	GERMANY	t.e.schmid@lrz.tu-muenchen.de
Elisabeth SCHULTKE	Rostock University Medical Center	GERMANY	elisabeth.schueltke@med.uni-rostock.de
Roman SENIN	NRC Kurchatov Institute	RUSSIA	senin_ra@nrcki.ru
Raphael SERDUC	INSERM U836 - ESRF	FRANCE	raph.serduc@gmail.com
Erik Albert SIEGBAHN	Karolinska Institutet	SWEDEN	albert.siegbahn@ki.se
Andrey SOLOVYOV	MBN Research Center gGmbH	GERMANY	solovyov@mbnresearch.com
Evgeny SOZONTOV	NRC Kurchatov Institute	RUSSIA	esozontov@yahoo.com
Marco STAMPANONI	Paul Scherrer Institute	SWITZERLAND	marco.stampanoni@psi.ch

Name	Laboratory	Country	Email
Andrew STEVENSON	Australian Synchrotron	AUSTRALIA	Andrew.Stevenson@ synchrotron.org.au
Xavier STRAGIER	Eindhoven University of Technology	NETHERLANDS	X.F.D.Stragier@TUE.NL
Florian STUDER	INSERM - UJF	FRANCE	florian.studer.88@gmail.com
Bjarne STUGU	University of Bergen	NORWAY	bjarne.stugu@ift.uib.no
Pekka SUORTTI	University of Helsinki	FINLAND	pekka.suortti@helsinki.fi
William THOMLINSON	University of Helsinki	FINLAND	william.thomlinson@gmail.com
Francesco TISATO	CNR - ICIS	ITALY	tisato@icis.cnr.it
Michael TRIPPEL	University Hospital Freiburg	GERMANY	Michael.Trippel@uniklinik-Freiburg.de
Giuliana TROMBA	Elettra - Sincrotrone Trieste	ITALY	giuliana.tromba@elettra.trieste.it
Toshiro TSUBOUCHI	Osaka University	JAPAN	tsubo19860503@gmail.com
Tomi TUOHIMAA	EXCILLUM AB	SWEDEN	tomi.tuohimaa@excillum.com
Alexander VALDMAN	Karolinska Institute	SWEDEN	alexander.valdman@karolinska.se
Janne VIGNERO	Katholieke Universiteit Leuven	BELGIUM	janne.vignero@kuleuven.be
Zhentian WANG	Paul Scherrer Institute	SWITZERLAND	zhentian.wang@psi.ch
Adam WEBB	Canadian Light Source	CANADA	adam.webb@lightsource.ca

Name	Laboratory	Country	Email
Loriane WEBER	CNRS UMR 5515 - INSA 502	FRANCE	lweber@esrf.fr
Han WEN	NHLBI	USA	wenh@nhlbi.nih.gov
Sheldon WIEBE	University of Saskatchewan	CANADA	Sheldon.Wiebe@usask.ca
Michael WRIGHT	Varian Medical Systems, Inc.	USA	michael.wright@varian.com
Tianding WU	Xiangya hospital of Central South University	CHINA	tiandingwu@hotmail.com
Tomasz WYSOKINSKI	Canadian Light Source Inc.	CANADA	Tomasz.Wysokinski@lightsource.ca
Tiqiao XIAO	Chinese Academy of Science	CHINA	tqxiao@sinap.ac.cn
Yanling XUE	Shanghai Institute of Applied Physics, CAS	CHINA	ylxue@sinap.ac.cn
Lei ZHANG	University of North Carolina at Chapel Hill	USA	leiz@email.unc.edu
Ning ZHU	Canadian Light Source	CANADA	ning.zhu@lightsource.ca

My notes

Sponsors

THANK YOU!

MASR 2015

MASR 2015

	Monday, 5 October	Tuesday, 6 October	Wednesday, 7 October	Thursday, 8 October	Friday, 9 October	
08:00-08:30				Session 1 - Chair J. Laissue	Working Group 1	08:00-08:30
08:30-09:00		Session 1 - Chair P. Coan	Session 1 - Chair R. Menk	Keynote presentation: A. Solov'yov	C. Mothersill	08:30-09:00
09:00-09:30		Keynote presentation: M. Reiser	Keynote presentation: H. Wen	A. Jamshdidi-Parsian	E. Schültke	09:00-09:30
09:30-10:00		G. Lovric	P. Diémoz	K. Burger	Working Group 2	09:30-10:00
10:00-10:30	Registration opens	M. Kitchen	S. Gkoumas	A. Merrem	J. Crosbie	10:00-10:30
10:30-11:00		Coffee & tea break	Coffee & tea break	Coffee & tea break	T. Henry	10:30-11:00
11:00-11:30	Beamline visit guided by the ID 17 team	Session 2 - Chair: R. Mokso	Session 2 - Chair: X. Jiang	Session 2 - Chair E. Bräuer-Krisch	S. Roux	11:00-11:30
11:30-12:00		K. Morgan	T. Geith	V. Djonov	Coffee & tea break	11:30-12:00
12:00-12:30		X. Luan	B. Bassey	P. Gimenez	E. Bräuer-Krisch	12:00-12:30
12:30-13:00	Lunch at the ESRF-ILL onsite restaurant	B. Piersionek	Z. Wang	A. Bravin	J.A. Laissue	12:30-13:00
13:00-13:30		M. Stampanoni	M. Ando	T. Xiao	Working Group 3	13:00-13:30
13:30-14:00	Registration continues	M. Bech	D. Häusermann	T. Wysokinski	Y. Arnoud	13:30-14:00
14:00-14:30		Lunch: Grand Hôtel de Paris	G. Tromba	Lunch: Grand Hôtel de Paris	A. Siegbahn	14:00-14:30
14:30-15:00	Welcome: J. Susini	Session 3 - Chair D. Chapman	Picnic Lunch	Session 3 - Chair C. Cesera	M. Donzelli	14:30-15:00
15:00-15:30	Special presentations	Keynote presentation: A. Olivo		Keynote presentation: U. Oelfke	Lunch: Grand Hôtel de Paris	15:00-15:30
15:30-16:00	P. Cloetens	A. Cedola	Networking Activity Hiking	M. Akselrod	Working Group 4	15:30-16:00
16:00-16:30	V. Favaudon	S. Bayat		J. Livingstone	T. Tuohimaa	16:00-16:30
16:30-17:00	Mini-clips posters	J. Pearson		D. Reynard	M. Jacquet	16:30-17:00
17:00-17:30		Coffee & tea break	Session 3 - Chair: A.	Coffee & tea break	Discussions	17:00-17:30
17:30-18:00	Wine & cheese event: onsite restaurant	Session 4 - Chair: E. Brun	M. Endrizzi	Session 4 - Chair F. Estève	End of Working Group Meetings	17:30-18:00
18:00-18:30		R. Longo	F. Fus	Keynote presentation: J. Balosso	Restricted to COST SYRA 3 Management Committee	18:00-18:30
18:30-19:00		C. Dullin	Z. Izadifar	J.F. Adam	Bus leaves for Grenoble	18:30-19:00
19:00-20:00		Y. Cao	S. Gasilov	N. Pacifico		19:00-20:00
	Bus to Villard de Lans	Coffee & tea break	F. Arfelli	Coffee & tea break		
		Session 5 - Chair: L. Porra		Session 5 - Chair S. Wiebe		
		A. Panahifar	Conference Gala dinner	G. Leduc		
		M. Ruat		J. Crosbie		
		T. Baumback		A. Stevenson		
		Poster Session		Discussions		
		Dinner: Grand Hotel de Paris		Dinner: Grand Hôtel de Paris		