

SLS Symposium on

X-ray Imaging for Medicine

Tuesday, November 8, 2011

10:00 to 12:15, WBGB/019

10:00 Genetic-Studies on Bone using Synchrotron-based Tomography

K. Mader, P. Schneider, D. Ruffoni, T. Kohler, L.R. Donahue, R. Müller, and M. Stampanoni

10:30 Small-angle X-ray scattering of carious human teeth

H. Deyhle, O .Bunk and B. Müller

11:00 Coffee

11:15 The progression of Alzheimer's disease revealed by differential phase contrast imaging of amyloid plaques in the brain of a transgenic mouse model

B. R. Pinzer, M. Cacquevel, P. Modregger, S. A. McDonald, J. C. Bensadoun, T. Thuering, P. Aebischer and M. Stampanoni

11:45 Differential Phase Contrast Mammography

Z. Wang, C. David, E. Rössl, M. Trippel, R.A. Kubik-Huch, G. Singer, M. K. Hohl, N. Hauser, M. Stampanoni

Genetic-Studies on Bone using Synchrotron-based Tomography

K. Mader(1,2), P. Schneider (3), D. Ruffoni (3), T. Kohler (3), L.R. Donahue(4), R. Müller(3), and M. Stampanoni(1,2)

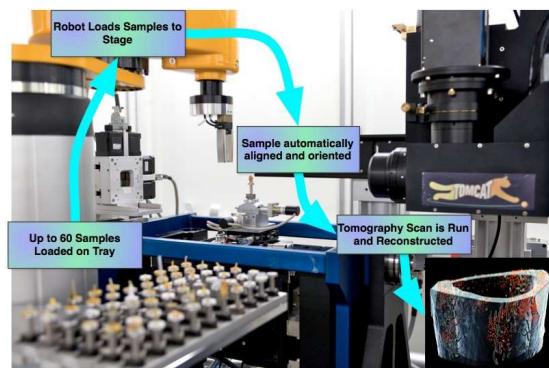
(1) Swiss Light Source, Paul Scherrer Institut, Villigen, Switzerland

(2) Institute of Biomedical Engineering, University and ETH Zürich, Zürich, Switzerland

(3) Institute for Biomechanics, ETH Zürich, Zürich, Switzerland

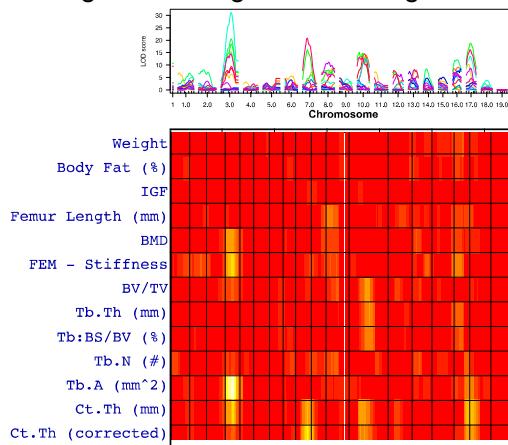
(4) The Jackson Laboratory, Bar Harbor, ME, USA

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Developments at the TOMCAT Beamline at the Swiss Light Source optimizing and automating measurement and reconstruction [1] have enabled studies with more than 1000 samples with a high degree of reproducibility and data quality. Genetic-scale phenomics studies require thousands of samples in order to have an adequate sampling across genome and statistical significance in the results found. Because the calcite-crystal in bone absorbs x-rays so strongly and the other

biological tissues so weakly, bone makes a perfect candidate for a synchrotron-based genetic study, specifically cortical bone, which has structures at the micron-level [2], that are presumed to play an important role in femoral neck fracture. This extremely debilitating fracture is curiously inexplicable through loss in bone mineral density, normally the single most important material factor. We thus establish a map of the murine genome attributing regions (quantitative trait loci) to measured morphological phenotypes. This map provides a basis for identifying candidate genes for further study and insight into the growth and regulation of cortical bone.



The statistically determined regions of the mouse genome (x-axis) correlated with the named phenotype (rows/y-axis). Color indicates strength of correlation on logarithmic scale

[1] K. Mader, F. Marone, G. Mikuljan, A. Isenegger, and M. Stampanoni. 2011. "High-throughput, fully-automatic, synchrotron-based microscopy station at TOMCAT." *Journal of Synchrotron Radiation*.

[2] K. Mader, P. Schneider, D. Ruffoni, G. H. van Lenthe, J.-Ph. Thiran, R. Müller and M. Stampanoni. Automated, high-throughput, multi-scale assessment of bone morphology and bone competence. Proc. 6th World Congress of Biomechanics, Singapore, Singapore, August 1-6, IFMBE Proceedings, 31(3):841-843, 2010

Small-angle X-ray scattering of carious human teeth

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Spatially resolved small-angle X-ray scattering based on synchrotron radiation combines the quantitative assessment of nanometer-sized components using scattering with the real-space imaging by means of scanning. The method allows to study the organization of biological specimens in the sub-micrometer range over extended areas. Bacterial attacks on teeth, known as caries, are known to damage the enamel, the dentin and the cementum through the production of acidic species that dissolve the ceramic tooth components. Destroyed tooth structures do not fully regenerate, although re-mineralization of small carious lesions occurs under optimized dental hygiene in dentin has been observed [1]. It has however been hypothesized, based on electron microscopy images, that the organic components, in particular the collagen, may remain unaffected [2].

We investigated the effect of caries-induced damages on the inorganic and organic nanoscopic components in human teeth. Collagen, the main organic component in dentin, yields a characteristic scattering peak around 67 nm, which can be extracted from the total scattering signal, allowing to obtain information solely related to the collagen. We investigated several 200 to 500 μm -thin tooth slices with focus on orientation and abundancy of the nanometer-sized tooth components. The bacterial processes dissolve the ceramic components in enamel and dentin but the dentinal collagen network remains practically unaffected with respect to its abundance and orientation in early stages of caries and in parts of extended carious lesions.

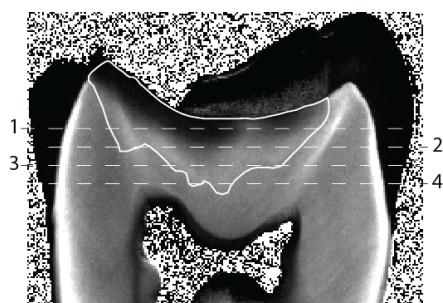
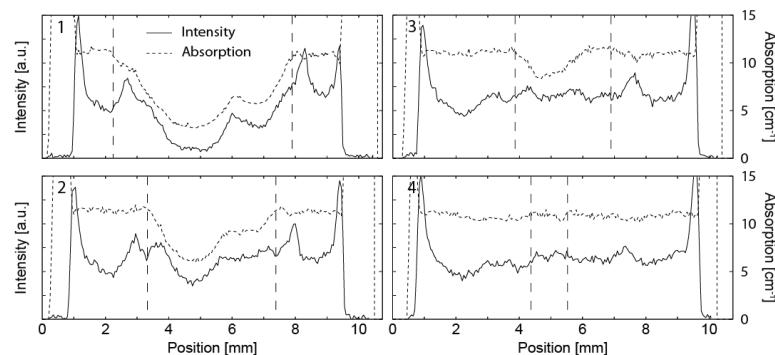


Fig 1. Intensity of the collagen-related signal across one carious tooth slice: The line plots according to the dashed lines in the image quantitatively show the changes in collagen scattering signal intensity (solid line) and specimen absorption (dotted line). The higher concentration of collagen fibrils near the dentin-enamel junction produces the prominent feature.



[1] KK. Mäkinen, *Int. J. Dent.* **2010**, 981072 (2010)

[2] Ohgushi K, Fusayama T. *J. Dent. Res.* **54**, 1019 (1975).

The progression of Alzheimer's disease revealed by differential phase contrast imaging of amyloid plaques in the brain of a transgenic mouse model

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Alzheimer's disease (AD) is characterized by two microscopic pathological features: the extracellular amyloid plaques and the intracellular neurofibrillary tangles. Both lesions accumulate in the brain of AD patients and are used to validate the diagnosis *post mortem*. Structural modifications of the brain tissue start to appear decades before the occurrence of the neurological symptoms. Therefore, there is a great interest in imaging this pathology in the living patient in order to facilitate the diagnosis as well as to measure the progression of the disease. In clinics, positron emission tomography (PET) allows quantification of the amyloid pathology at a spatial resolution on the order of several millimeters, and is used to obtain an overview of the plaque distribution. To image single plaques, which measure mostly between 10 and 40 μm in humans, histological sectioning followed by immunostaining of the amyloid plaques is still the method of reference.

With the very high sensitivity to variations in electron density of the X-ray grating interferometer at the TOMCAT beamline, we were able to image single plaques in a mouse model of AD over the entire brain, with a pixel size of 7.4 μm . The 5xFAD mouse model was chosen because it shows a similar size distribution of amyloid plaques as in humans. The good signal-to-noise ratio of the measurements allowed for an automated segmentation of amyloid plaques in pre-selected regions of interest, for example the cerebral cortex, which yields complete structural information of the distribution of the plaques. Classical parameters such as the plaque load, defined as the mean fraction of plaque area over cortex area in several brain slices, can be easily assessed, including the spatial variation along the cortex. In addition, three-dimensional parameters such as the size distribution of plaques can be extracted. First results concerning the evolution of the plaque load over time matched well with previous studies. Detailed data about the distribution of plaques will not only help to better understand the evolution of AD or the effects of drugs, but also to develop reliable markers for current non-invasive clinical imaging techniques.

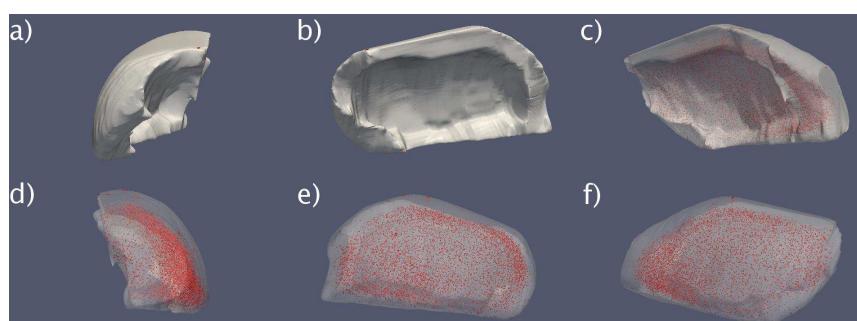


Figure 1: Distribution of amyloid plaques (red spots) within the cerebral cortex (gray) of a 70 weeks old transgenic mouse. The cortical region of interest was defined manually, while the plaques were segmented using automated thresholding. In a) and b), the cortex is shown as opaque.

Differential Phase Contrast Mammography

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Phase contrast and scattering-based X-ray imaging can potentially revolutionize the radiological approach to breast imaging because they are intrinsically capable of detecting subtle differences in the electron density of a material and of measuring the effective integrated local small-angle scattering power generated by the microscopic density fluctuations in the specimen. The emerging grating-based X-ray interferometry can simultaneously generate differential phase contrast (DPC) and scattering signals of the sample, as well as the conventional absorption signal, and therefore is believed as a promising method for better breast cancer screening and diagnosis. Recently, our research team presented the first investigation of native, non-fixed whole breast samples including regular breast tissue and breast cancer formations. In this pioneering work we designed, constructed and operated a differential phase contrast mammography (mammoDPC) demonstrator based on a conventional X-ray source and measured whole native breast specimen directly after mastectomy, which is very close to the clinical routine. The results demonstrate that this technique can indeed provide additional and useful information to complement and improve the diagnostic process in the clinical setting.

