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Multi-modal & multi-scale X-ray analytical imaging to enhance precision medicine

Robert Zboray, Alex Dommann, Antonia Neels

Centre for X-ray Analytics, Department Materials Meet Life, Swiss Federal Institute for Material Science and Technology, Empa

contact: robert.zboray@empa.ch

Content

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- Motivation for using multi-modal X-ray imaging: Clinical vs multi-modal lab CT
- 3D digital histopathology for tissue mapping and phenomics
- Example 1: thyroid carcinomas
- Exmaple 2: intravascular clots
- Conclusions

Clinical CT vs. lab multi-modal μCT

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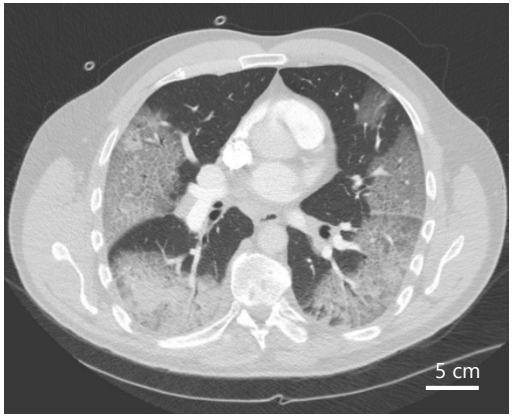
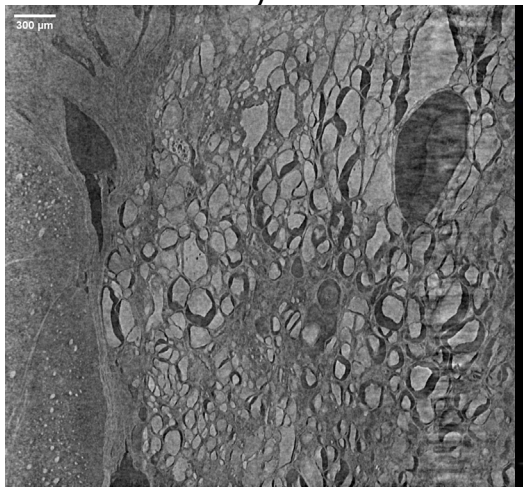
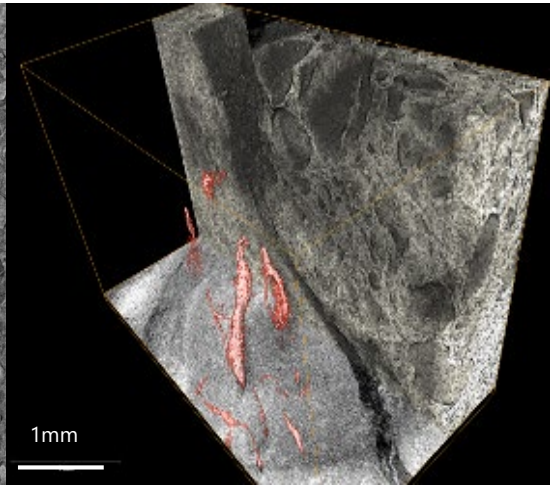


Propagation-based phase-contrast μCT of paraffin-embedded, fixed human thyroid carcinoma





Collaboration with Prof A. Perren, Uni Bern/Inselspital

- Resolution
- Contrast for soft tissue
- Multi-modality

X-ray laboratory multi-modal micro/nano-CT

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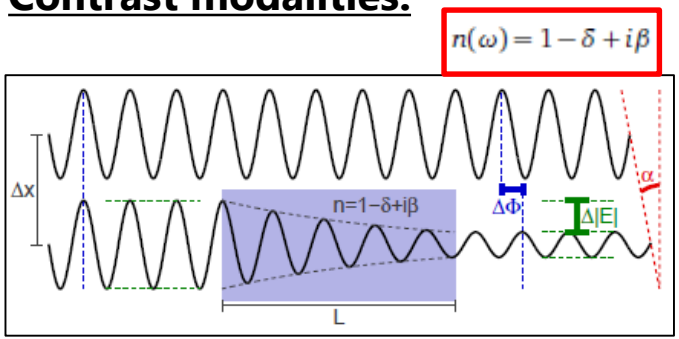
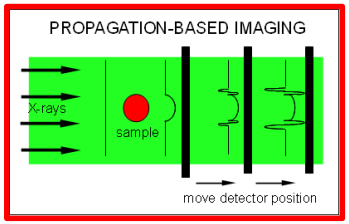
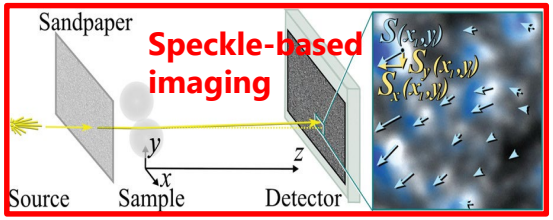
Resolution:

Resolution down to ca. 700 nm!!! ->imaging at cell level

Contrast modalities:







- Phase contrast - small angle refraction $\delta/\beta \sim 10^2$-10^4
- Dark field - ultra small angle scattering sample nano-structure (porosity)

Commercial availability of laboratory nanoCT scanners

What can multi-modal, multi-scale X-ray analytical imaging offer to enhance precision medicine

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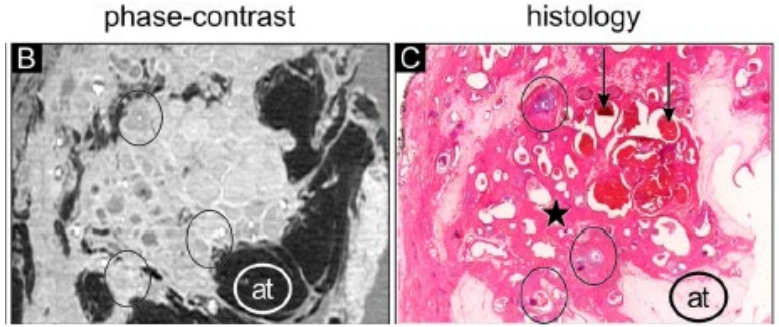
Multi-modal, high resolution tissue mapping with improved contrast and differentiation for soft tissues -> 3D virtual/digital histopathology

K. Hellerhof et al., PLOS One, 2019



- multi-modal data integration -> enhanced clinical diagnostic and decision support
- Spatial and molecular resolution -> deep understanding of the cellular/histological context
- Enables downstream molecular and genetic analysis -> multi-omics screens
- link image-based biomarkers with molecular/biochemical fingerprints.
- Enabling high-throughput tissue phenomics

Project example 1: 3D digital pathology of thyroid carcinomas

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Precision medicine: need for detailed, unbiased 3D info on tissue structure

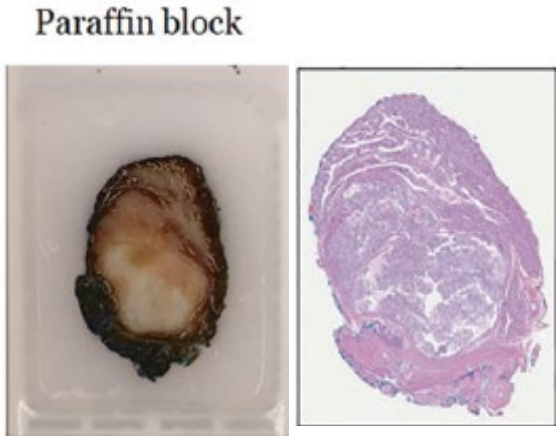
Clinical state of the art, 2D slice histology:

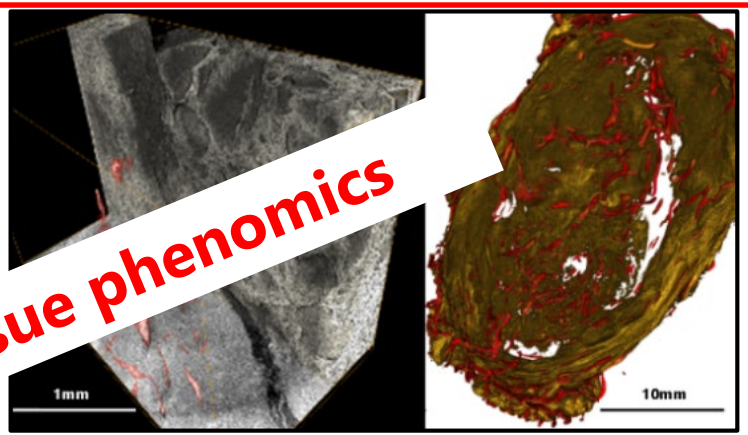
- *invasive histology, slicing*
- *staining (chemicals)*
- *2D (site bias)*

Our approach: advanced 3D X-ray imaging biopsy blocks & TMA

BENEFITS for Precision Medicine:

- *Non-intrusive (virtual slicing/no chemicals)*
- *High-resolution in 3D (intra-tumor heterogeneity, vascularization)*
- *Uncompromised native tissue structures (unstained)*
- *Enabling further downstream analysis and integration in the precision medicine pipeline (omics screen, biochemical)*





Embedding in precision medicine & clinical workflow

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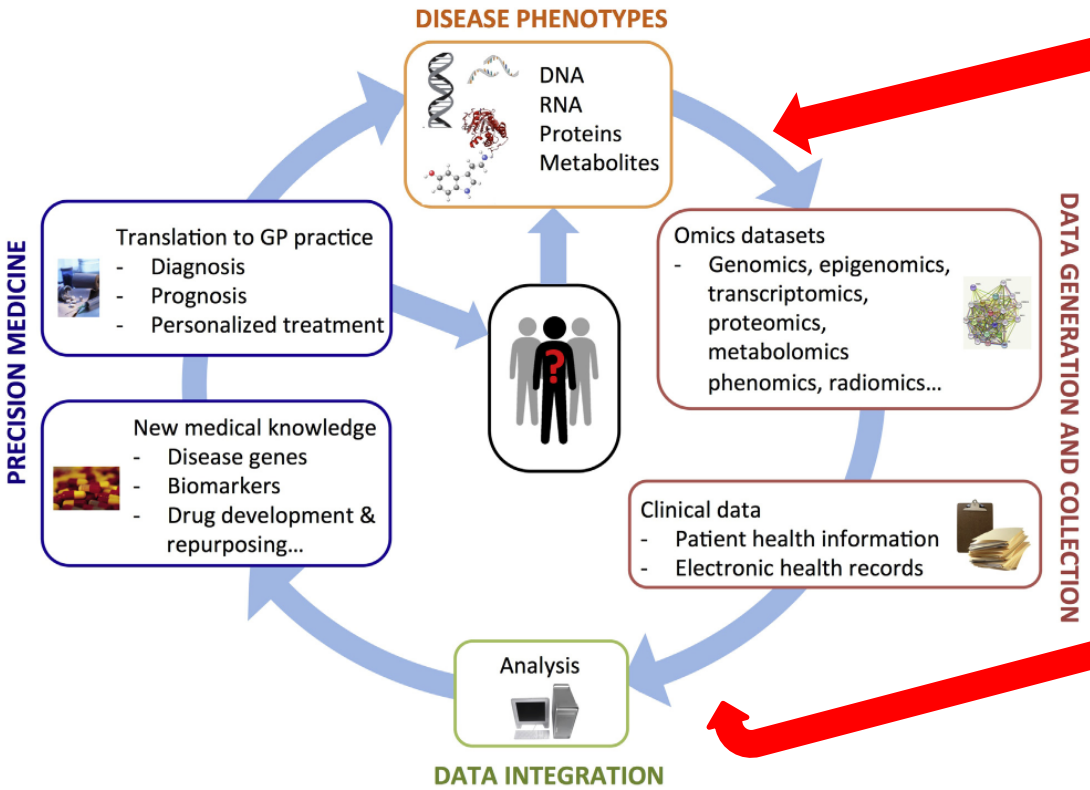
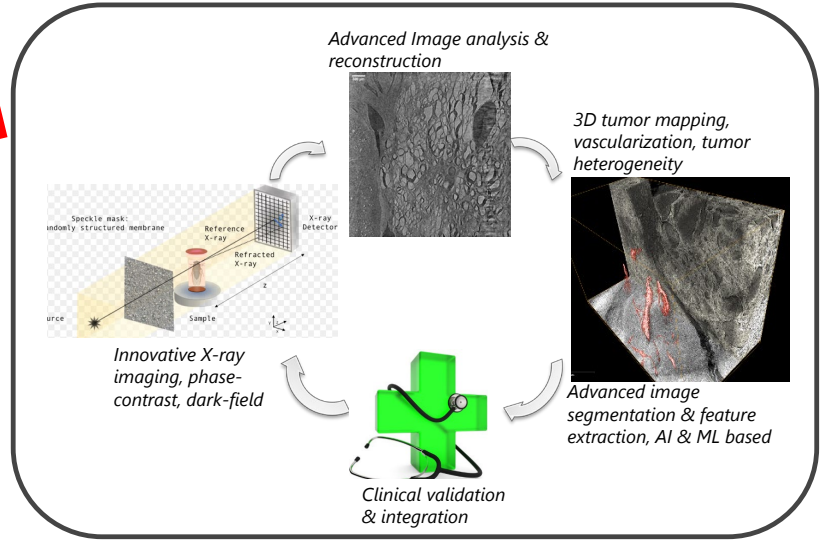
Precision medicine pipe line:



Integration into the clinical/omics workflow:



PHRT Pioneer Imaging Project - Empa

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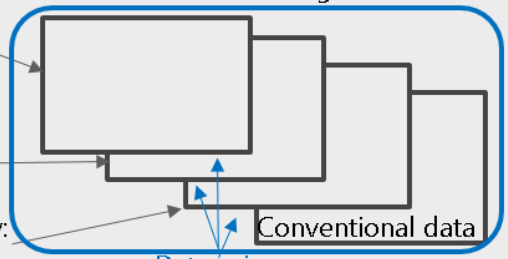
Holistic tissue analysis for precision medicine (long-term vision)

Biopsies

- 2D histoslice microscopy
- molecular path
- biomech
- IHC
- NGS
- ...

Multi-level data integration

- X-ray PCI uCT: 3D, non-invasive
- Omics: geno-, proteo-radio-, ...
- Spectromicroscopy: AFM, Raman



Holistic disease understanding

personalized therapy

Imaging competence hub

Digital twins

ETH zürich

C. Zhang

A. Perren *I. Zlobec*

u b UNIVERSITÄT BERN

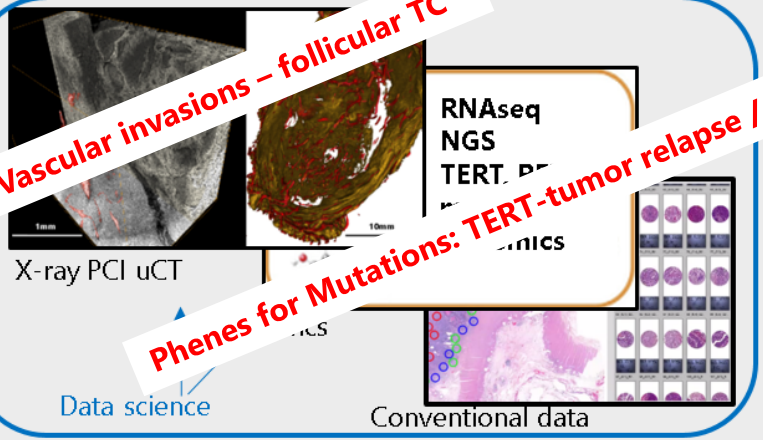
INSELSPITAL

Clinic 2021	Our novelty & clinical implementation	Clinical benefit	Beyond 2023 for PHRT

PIP project: non-invasive 3D thyroid tumor analysis for precision medicine

block

TMA



Capsular/Vascular invasions – follicular TC

Phenes for Mutations: TERT-tumor relapse / RET-inhibitor

Novel 3D ...gy ... tumors

...proved diagnosis, prognosis, stratification

Laying the foundation for the holistic approach

Personalized treatment & follow-up

M. Buljan

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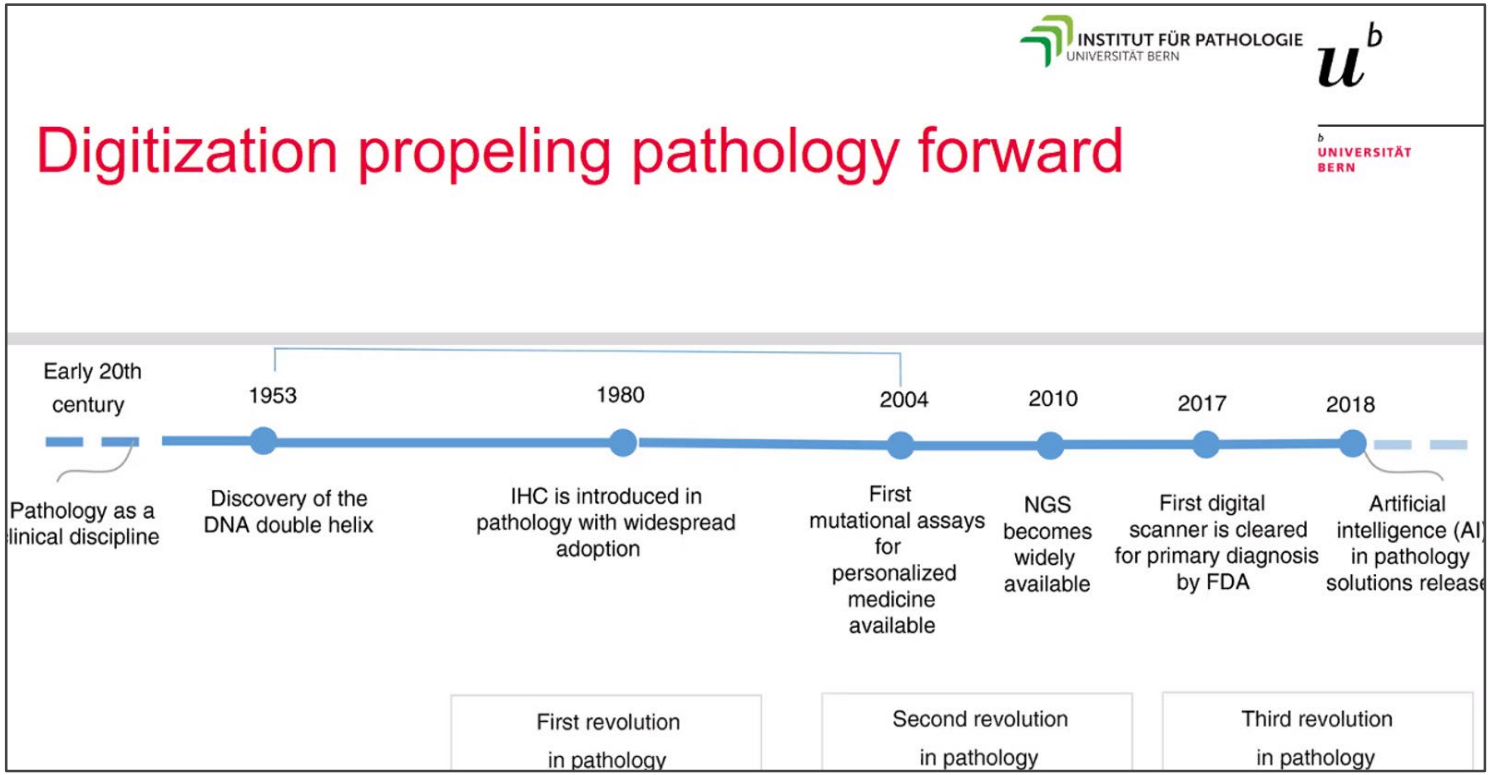
Strategic Focus Area
Personalized Health and Related Technologies

PHRT Pioneer Imaging Project - Empa

A closing remark on our PIP Project:



2023

3D, non-invasive digital pathology

The 4th revolution

Excerpt from CIBM talk of Prof. I. Zlobec

Project example 2: intravascular clots

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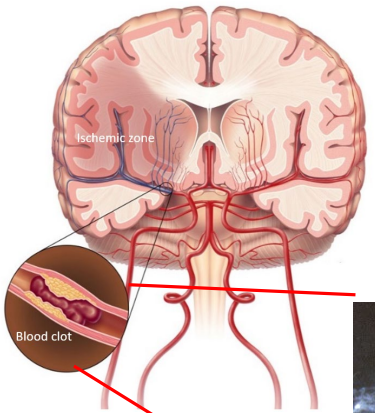
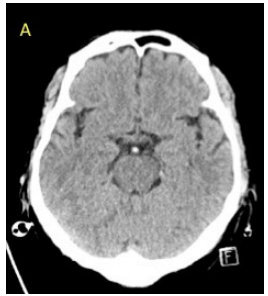
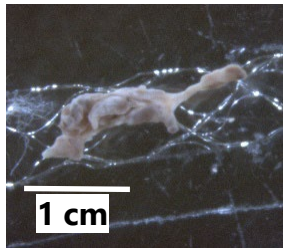
Multi-modal, analytical imaging of thrombi from patients with acute ischemic stroke:







Challenge:
clinical CT/MRI are limited in: resolution, sensitivity, contrast (soft tissue)

Collaboration with Prof K. Lovblad, Uni Geneva/HUG, SNF project

- Clot composition: red / white
- Large variability and complexity in clot composition, biophysical properties
- Steering therapeutic choice: **pharmacological** or **mechanical thromboectomy** (MTB) by stents
- Correlation with clinical CT/MRI
- Multi-level radiomics

Time is brain!:
Neuro degeneration

Project example 2: intravascular clots

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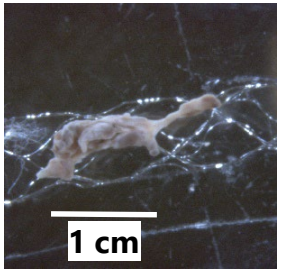
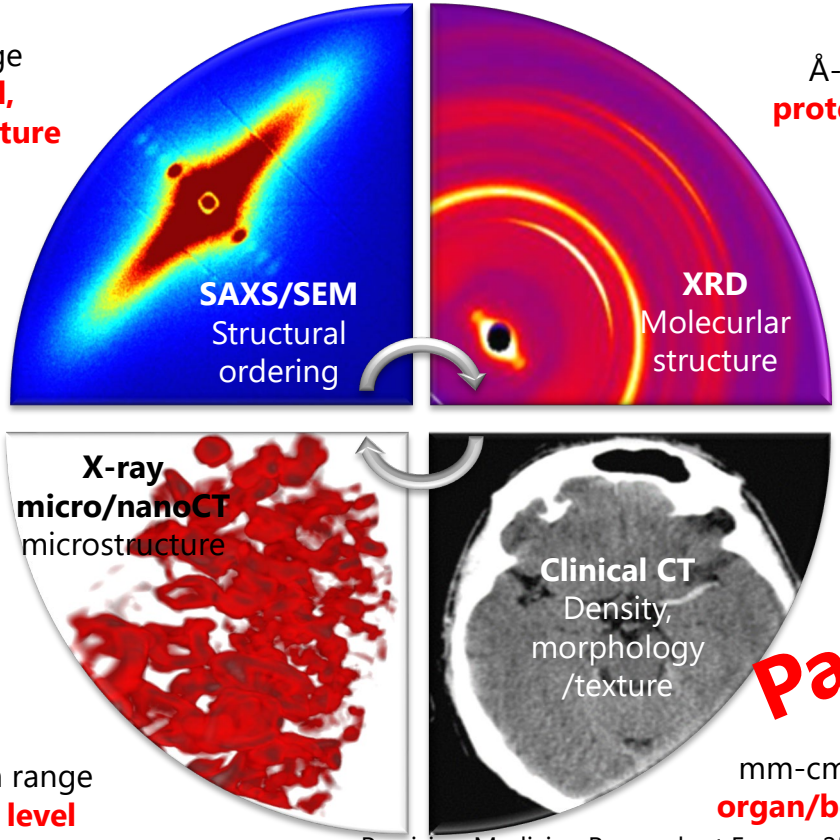
Our approach: Multi-level & multi-modal imaging and ML (radiomics)



nm range
cell level, nano structure

Å-range
protein level



sub um-mm range
tissue /cell level

mm-cms range
organ/body level

- Large variability and complexity in clot composition
- Clot composition influences biophysical/ mechanical properties -> success of recanalization
- Choice of stent type -> MTB outcome

Patient specific treatment

3D digital histopathology of the blood clot

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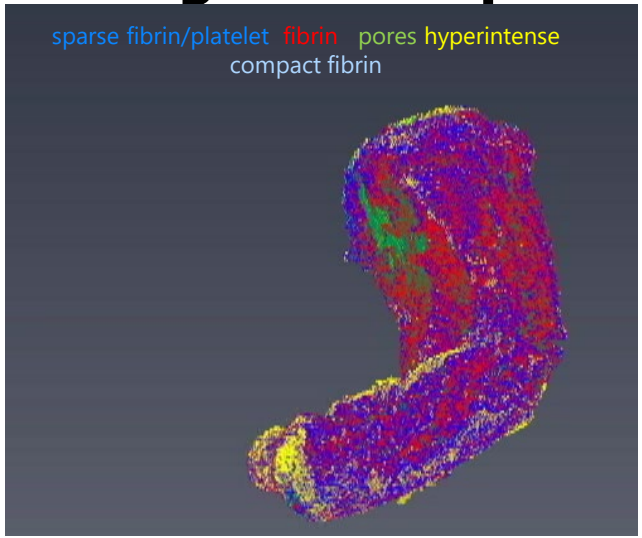

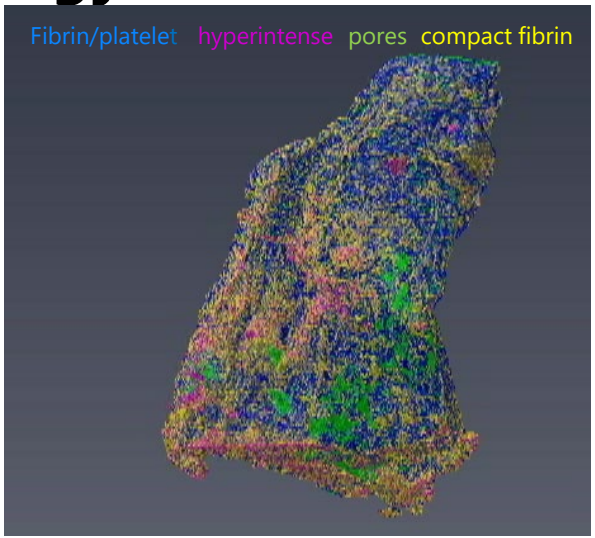

UNIVERSITÉ DE GENÈVE
HUG Hôpitaux Universitaires Genève

K. Lovblad

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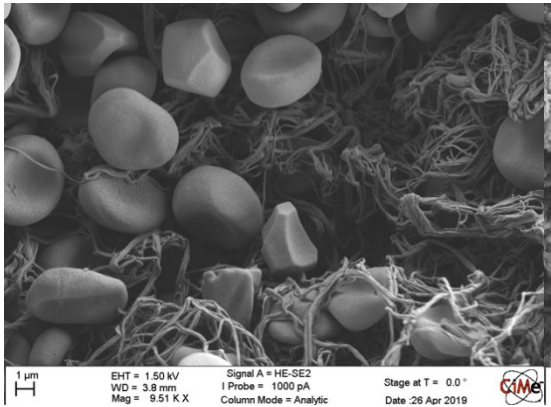
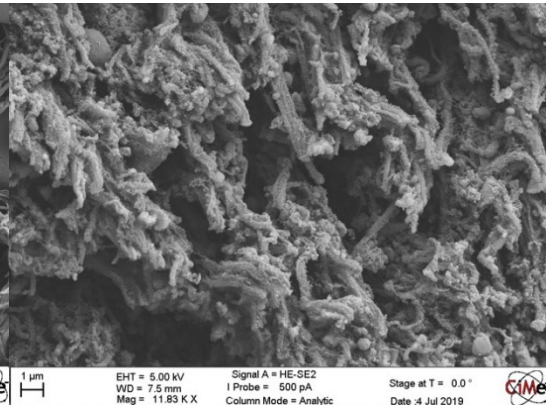
S. Saghamanesh





Cross validation by SEM

3D digital histopathology of the blood clot cont'd

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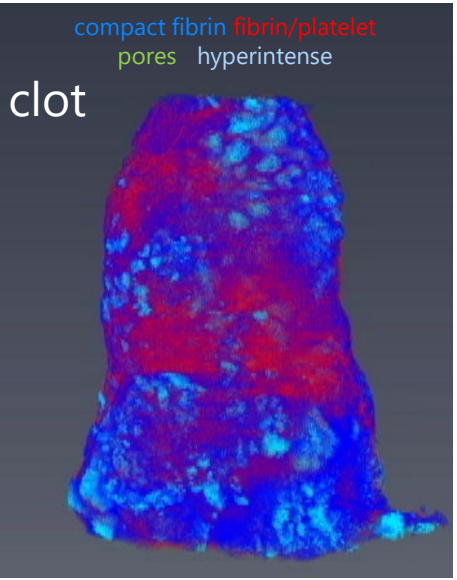
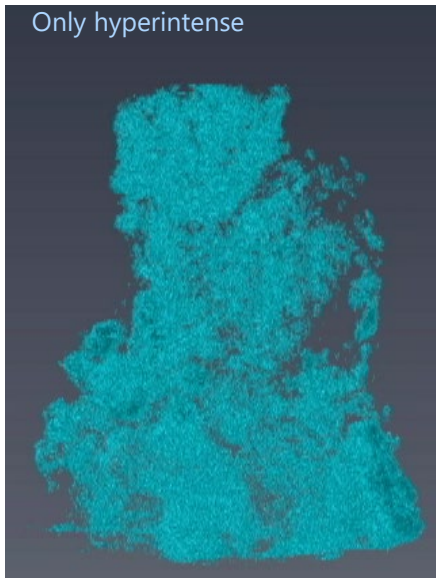
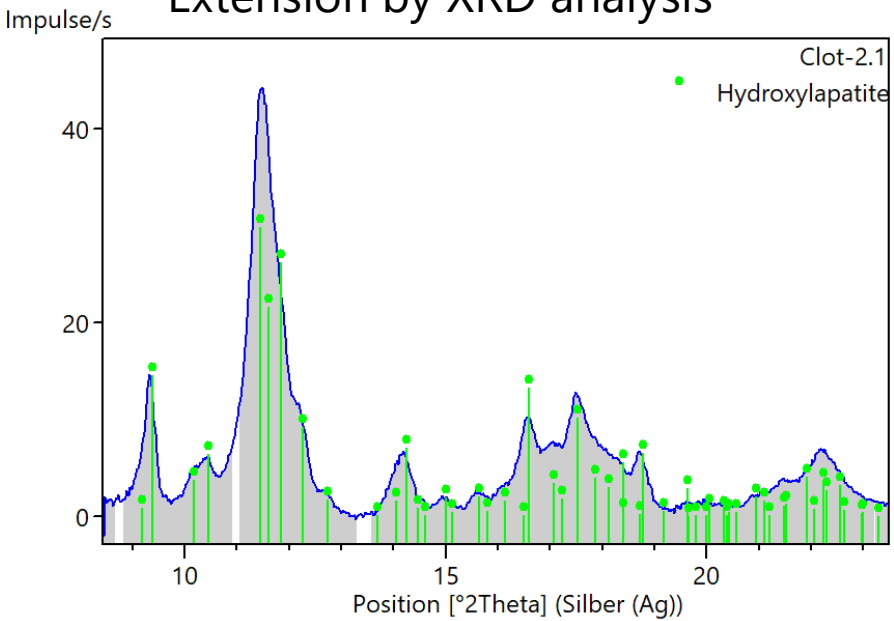




Extension by XRD analysis



For the Clot 2.1 sample (blue diffraction curve), indexing revealed hydroxyapatite $Ca_{10}(OH)_2(PO_4)_6$ (PDF-Nummer: 96-901-1093, COD data base). No additional crystalline phases are present.

PHRT TechTransfer project blood clots 2: flow chart

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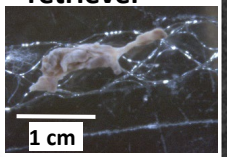
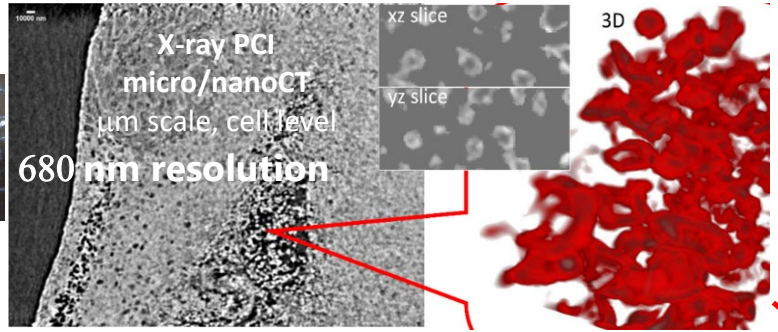
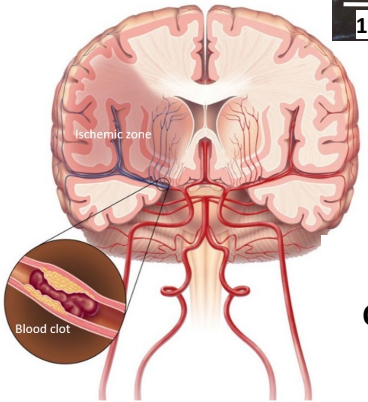
Blood clot 3D histology by micro/nano CT

Blood clot in stent retriever

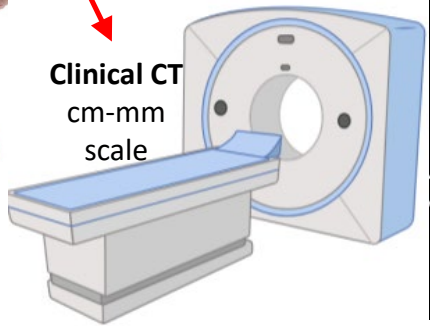


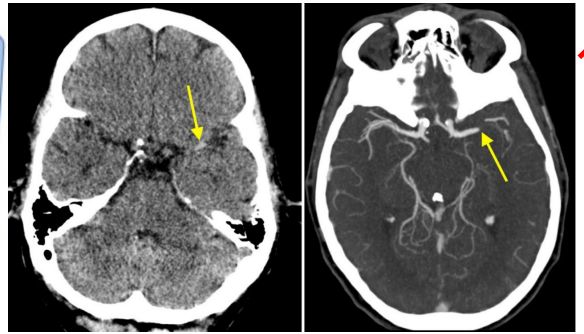




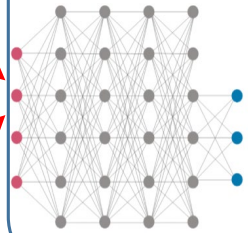
Multi-level radiomics across scales: clinical CT vs. microCT

Clinical CT
cm-mm scale





Radiomics model



ML

Improved:

- **Clot composition prediction**
- **MTB outcome prediction**
- **Personalized treatment**

Conclusions

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- Multi-scale multi-modal X-ray analytical imaging techniques open up unprecedented new opportunities for analyzing biopsies & soft tissue samples for precision medicine
- Due to commercial availability of lab devices, the integration into the clinical workflow is within reach
- Non-invasive, 3D digital histopathology combined with ML methods enables high throughput tissue analysis (whole biopsy blocks, TMAs, blood clots) down to cellular level.
- Natural embedment into a holistic tissue analysis with multi-level data integration workflow including downstream genetic and molecular analysis

Thank you for your attention!

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Acknowledging my group at CXA:

The CXA team at Empa: