Bio-medical imaging using synchrotron radiation

MARTIN.BECH@MED.LU.SE MEDICAL RADIATION PHYSICS

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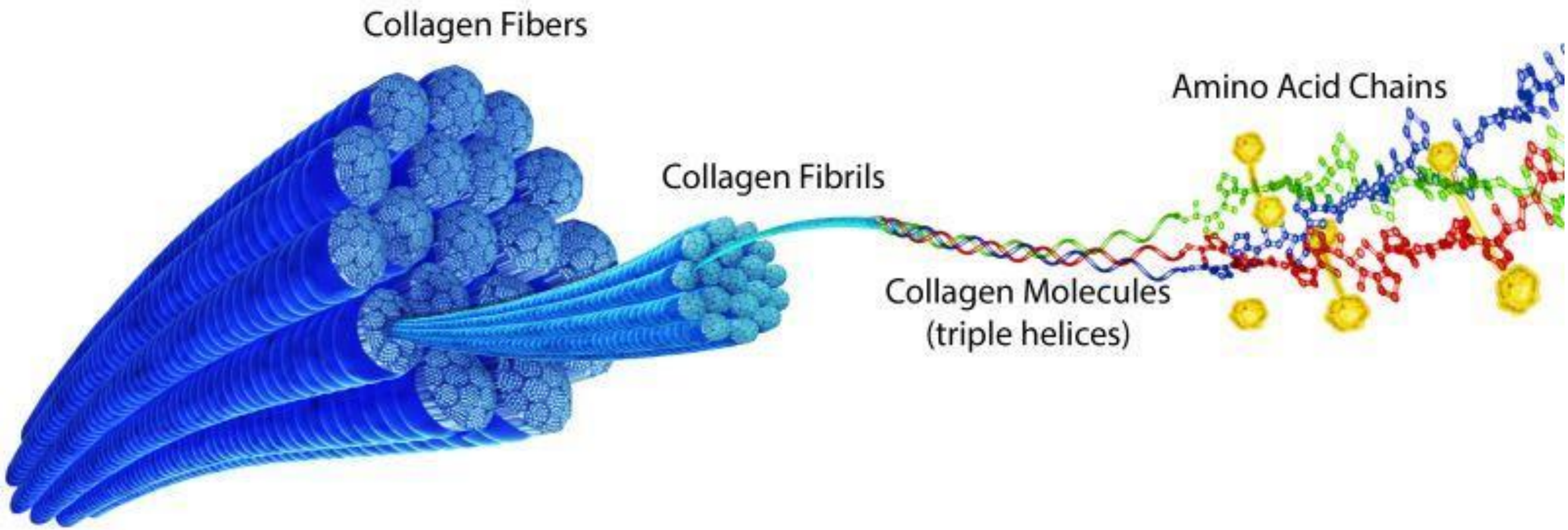
Outline

» What is phase contrast imaging and dark-field imaging?

» Why are these new imaging modalities good for bio-medical imaging?

» Future prospects of phase-contrast imaging?

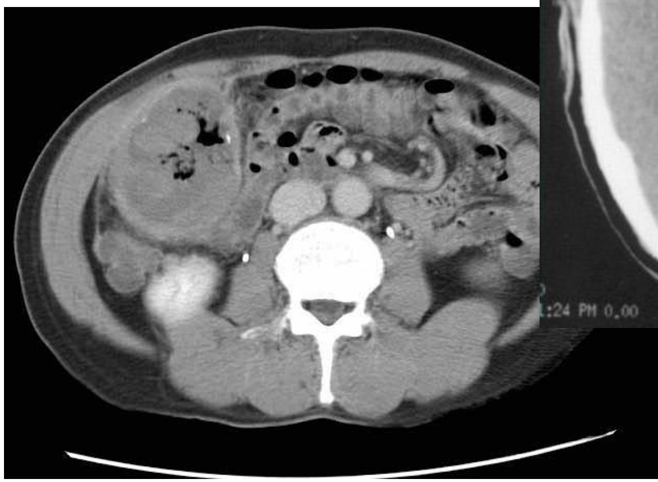
Biology can best be understood if studied at different length and time scales



High Contrast / Low Contrast

First x-ray image
made by Röntgen in 1896

Modern x-ray image today



Synchrotron-based phase contrast micro-CT

Electron accelerator, highly parallel X-rays

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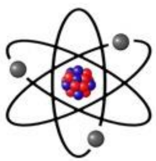
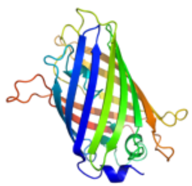
Medicine at different length scales

MicroMAX BioMAX coSAXS NanoMAX MedMAX I MedMAX II

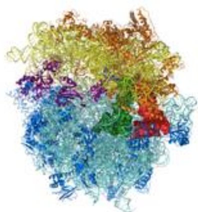
10^{-10} m 10^{-9} m 10^{-6} m



Atoms



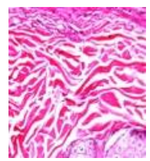
Biomolecules



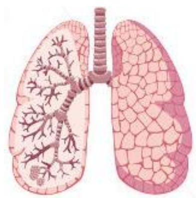
Molecular complexes

Micro-structures

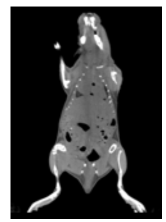
Cells



Tissues



Organs



Animals

Molecular Medicine/Drug Design

Cellbiology

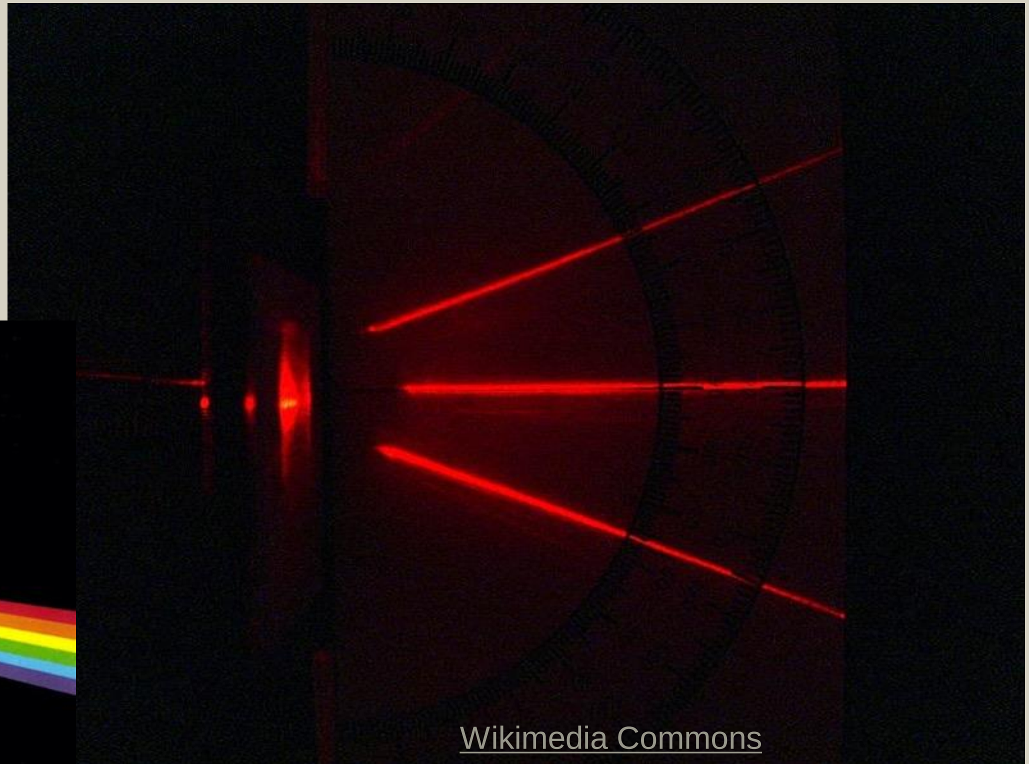
Disease models

Phase contrast and dark-field imaging

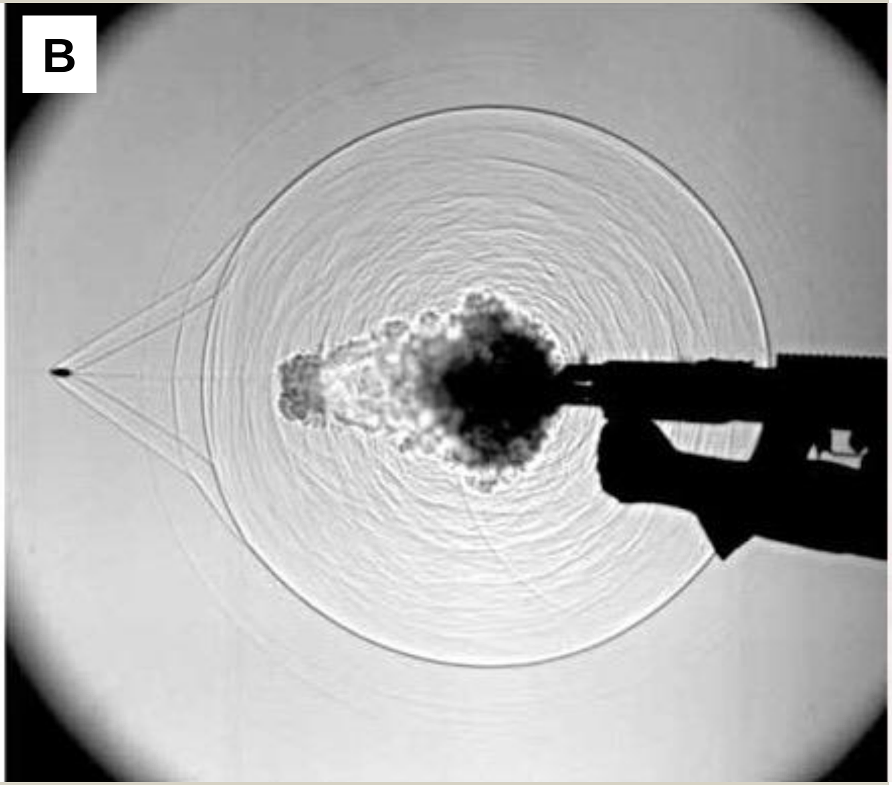
Analogy – Visible Light

» Diffraction

» Refraction



Analogy – Visible Light



Images by Gary S. Settles, Penn State Gas Dynamics Lab

Phase contrast imaging

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Röntgen was also looking for refraction…

W. C. RÖNTGEN

ÜBER EINE NEUE ART VON STRAHLEN

ERICHTE
GESELLSCHAFT ZU WÜRZBURG
) JAHRGANG 1896, S. 10

ITGEN
HAFT DIE ERSTE MITTEILUNG
TEN STRAHLEN VOR

UCK
HRIGEN BESTEHENS
MEDIZINISCHEN
ZU WÜRZBURG

T 1849 VON
A. v. KÖLLIKER · F. RINECKER · J. SCHERER · R. VIRCHOW
UND ANDEREN

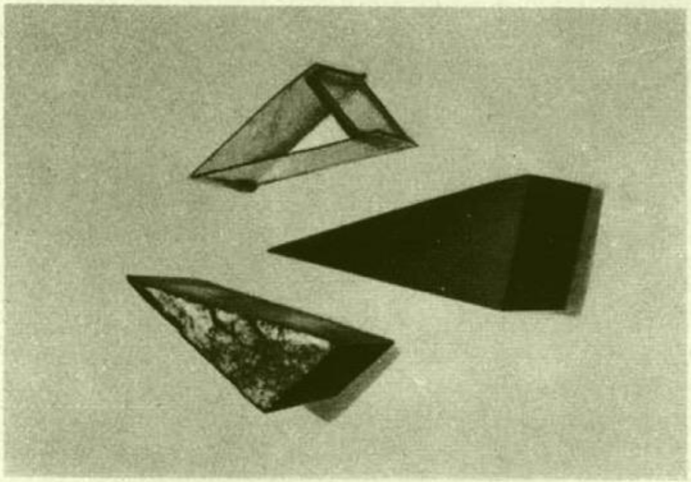

Bild 5. Prismen aus Hartgummi und Aluminium und Hohlprisma aus Glimmerplättchen wurden auf die horizontale Bleiplatte von Bild 4 gesetzt; etwaige Ablenkung der Strahlen hätte auf diese Weise erkennbar werden müssen (vgl. Abschnitt 7).

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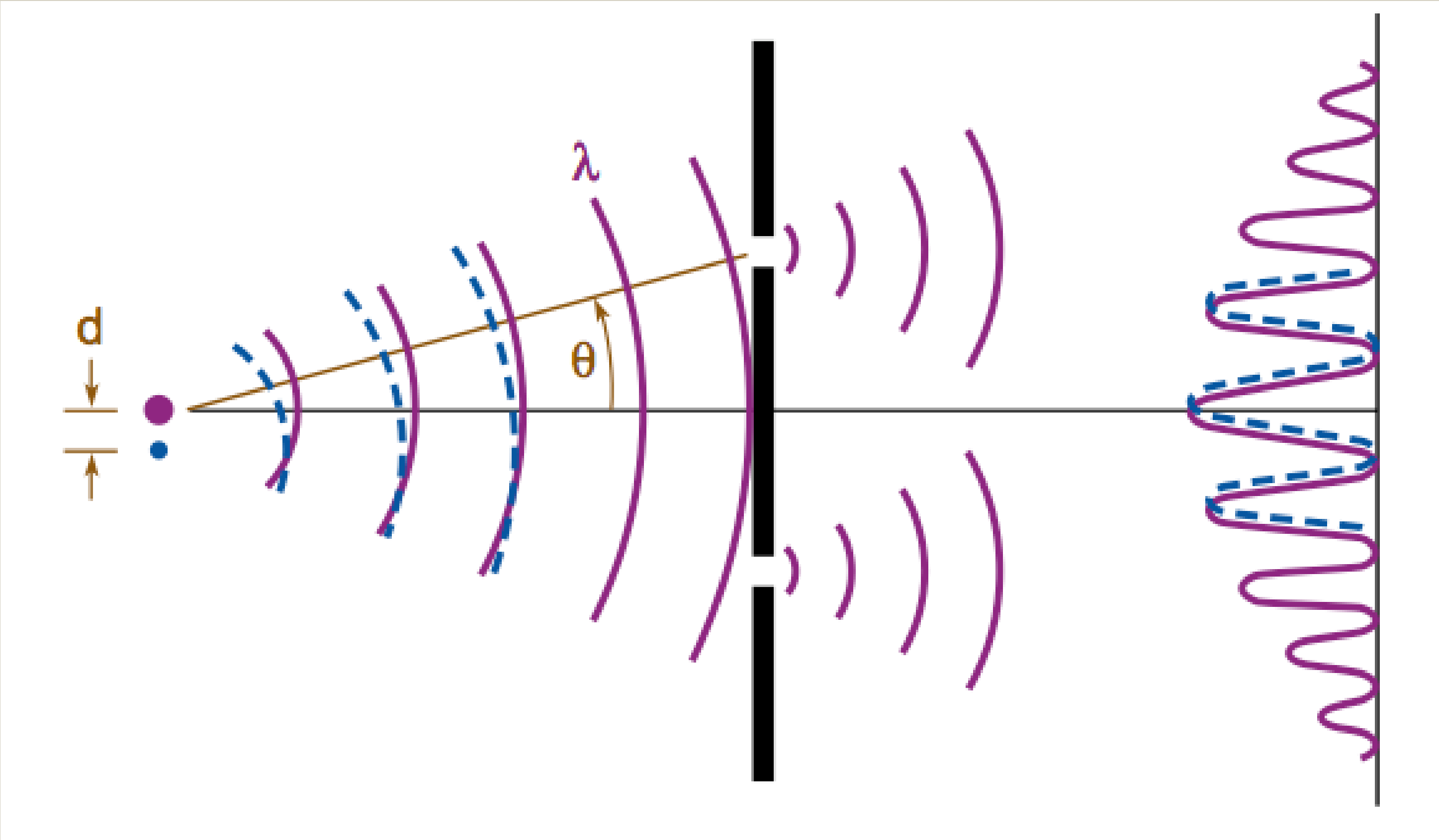
Coherence

» Ability to interfere due to particle/wave duality



Near-field versus far-field

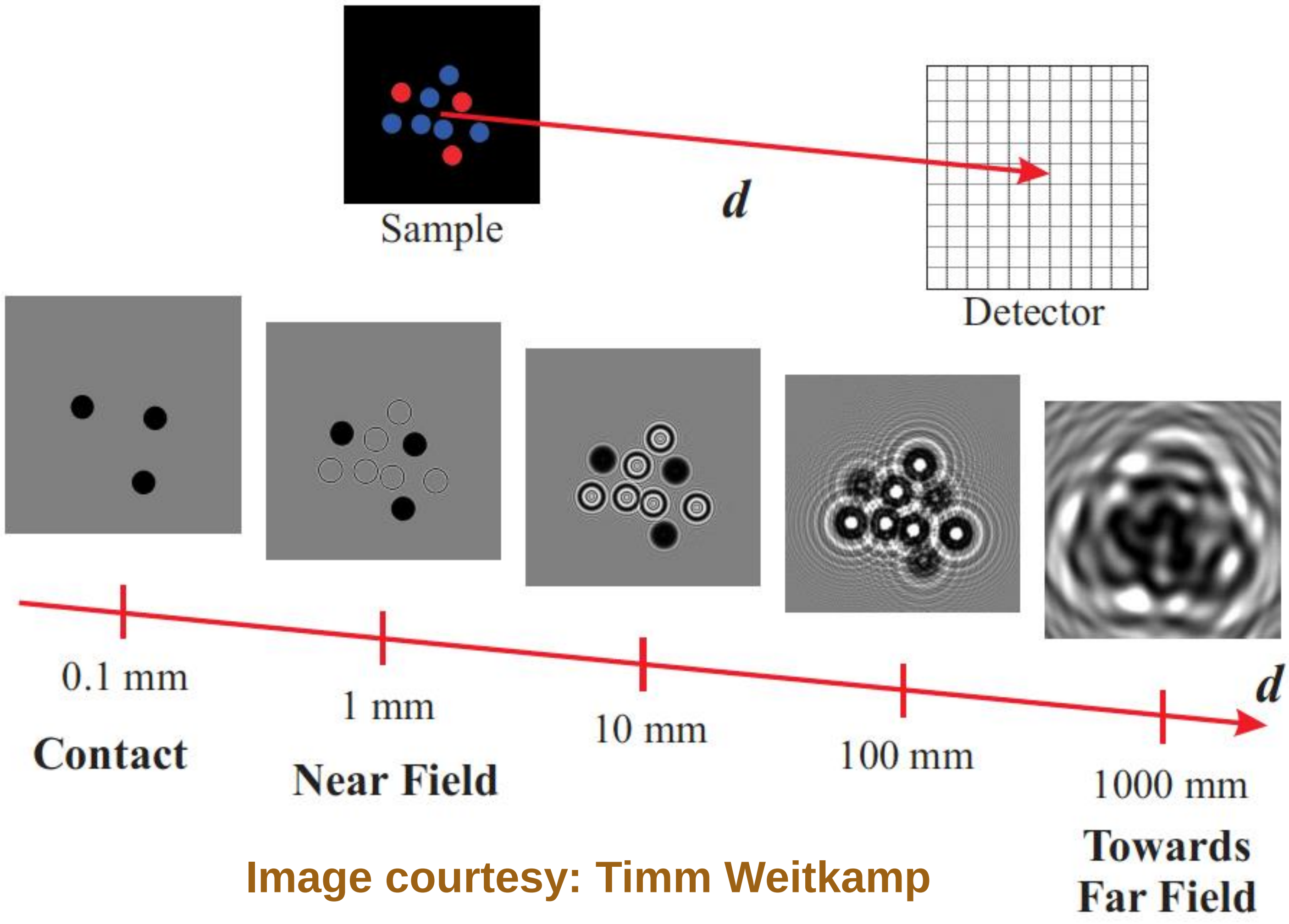


Image courtesy: Timm Weitkamp

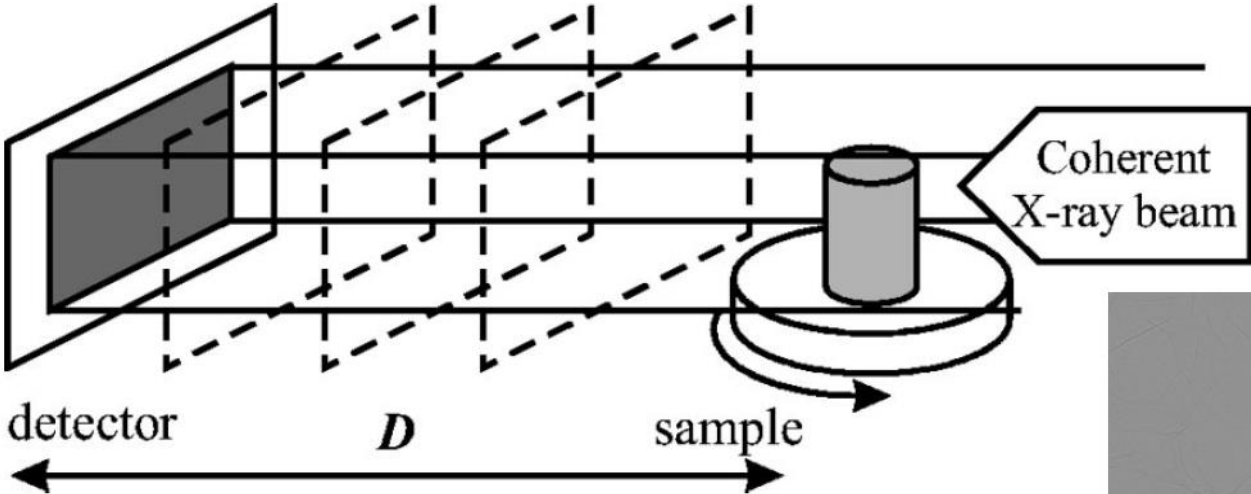
Wave propagation for beginners

Wave propagation regimes: **Fresnel number:** $F = \frac{a^2}{\lambda Z}$

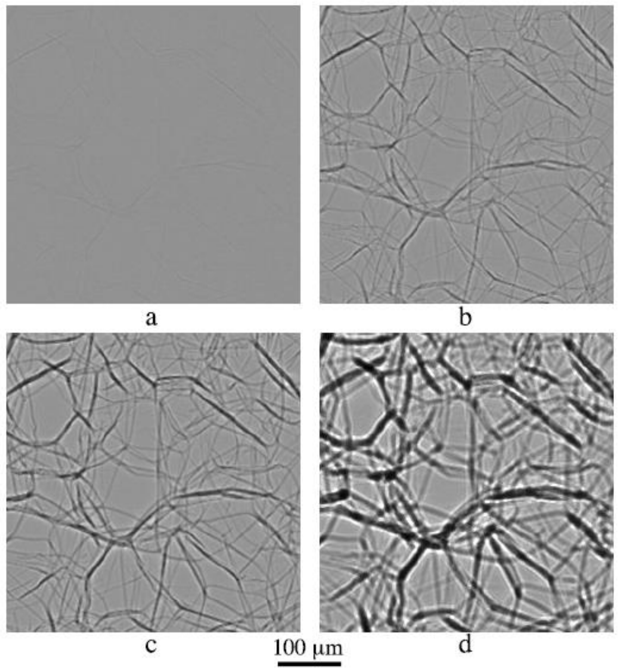
a = "resolution", λ = wavelength, Z = propagation distance

For $\lambda = 10^{-10}$ m		a	Z
- Contact regime	F >> 1	1 mm	10 cm
- Near field regime (Fresnel)	F ~ 1	1 µm	10 cm
- Far field regime (Fraunhofer)	F << 1	1 nm	10 cm
- Near field regime (Fresnel)	F ~ 1	1 mm	10 km
- Near field regime (Fresnel)	F ~ 1	1 µm	10 cm
- Near field regime (Fresnel)	F ~ 1	1 Å	1 Å

Holotomography



Polystyrene foam.
P. Cloetens 1999



Outline

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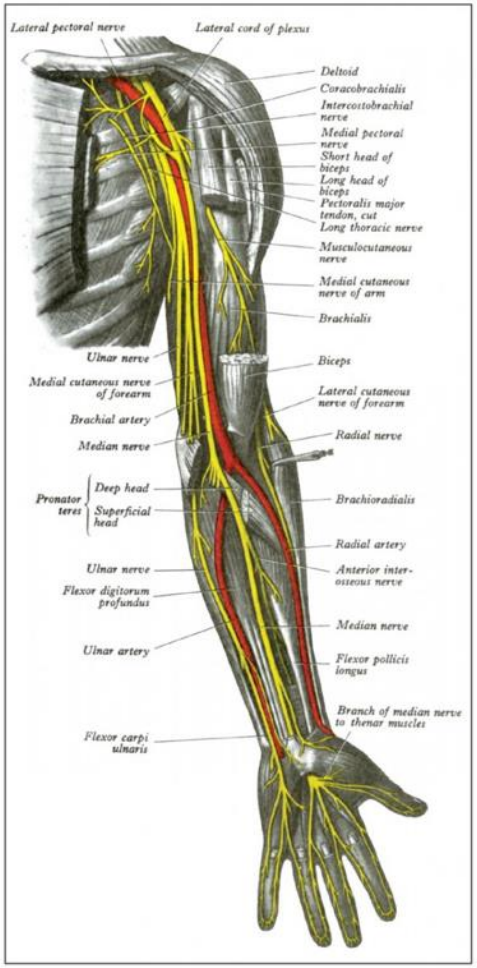
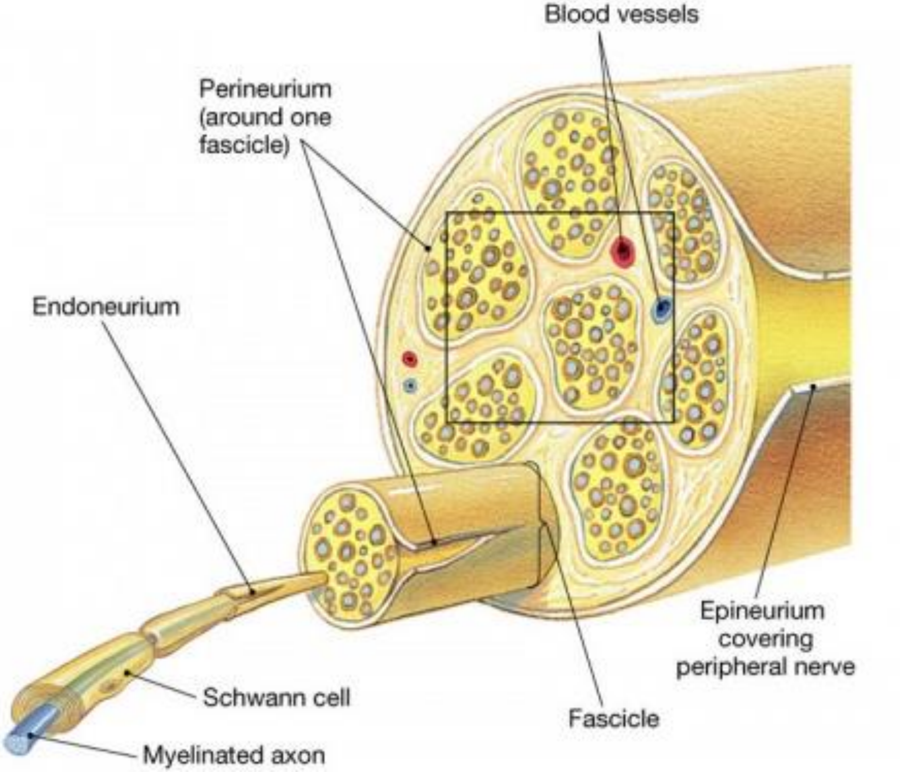
- » Why are these new imaging modalities good for bio-medical imaging?
- » Future prospects of phase-contrast imaging?

Selected Application

3D IMAGING BY NANO HOLOTOMOGRAPHY

Zoom tomography of biopsies from human peripheral nerves





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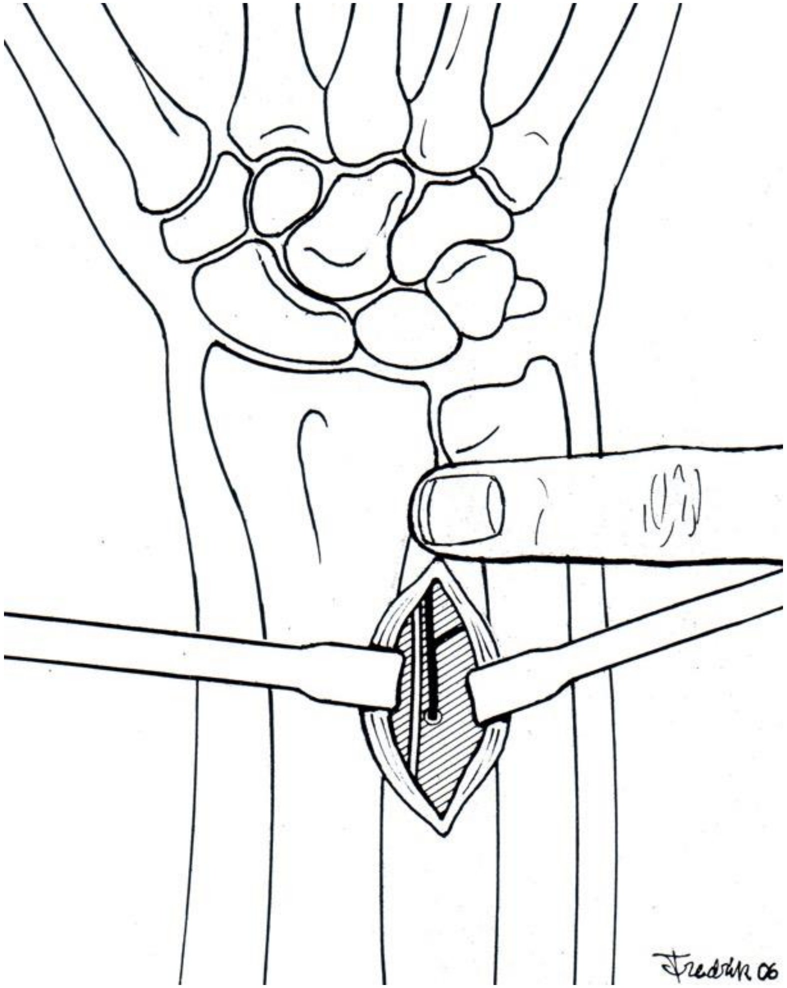
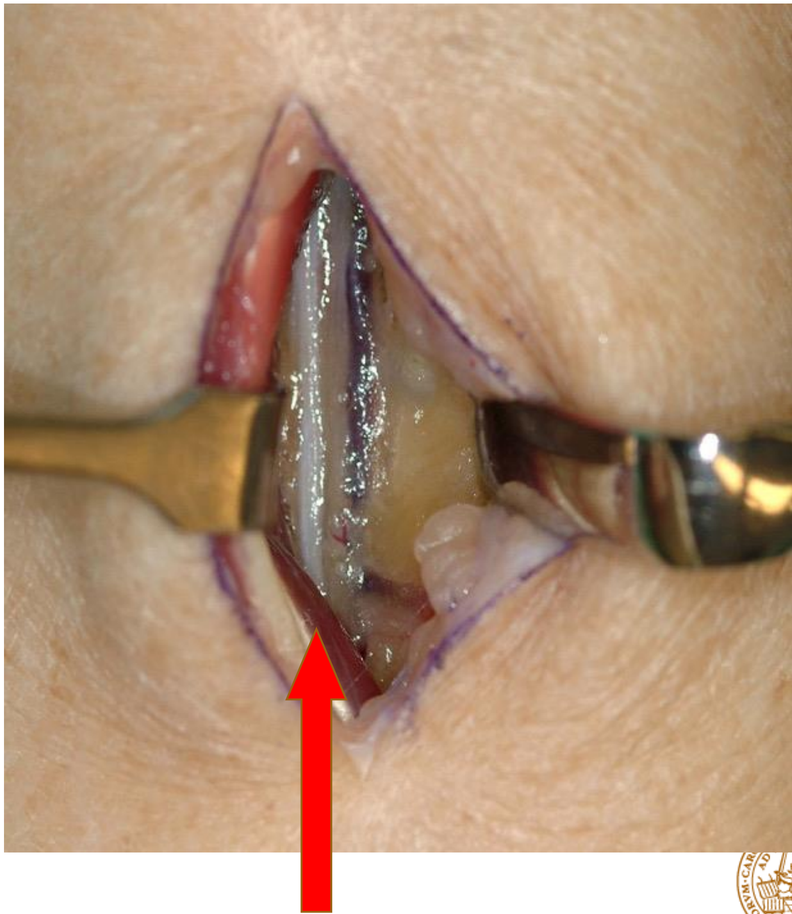
PIN biopsy method





Posterior interosseus nerve

Collaboration Niels Thomsen and Rayaz Malik

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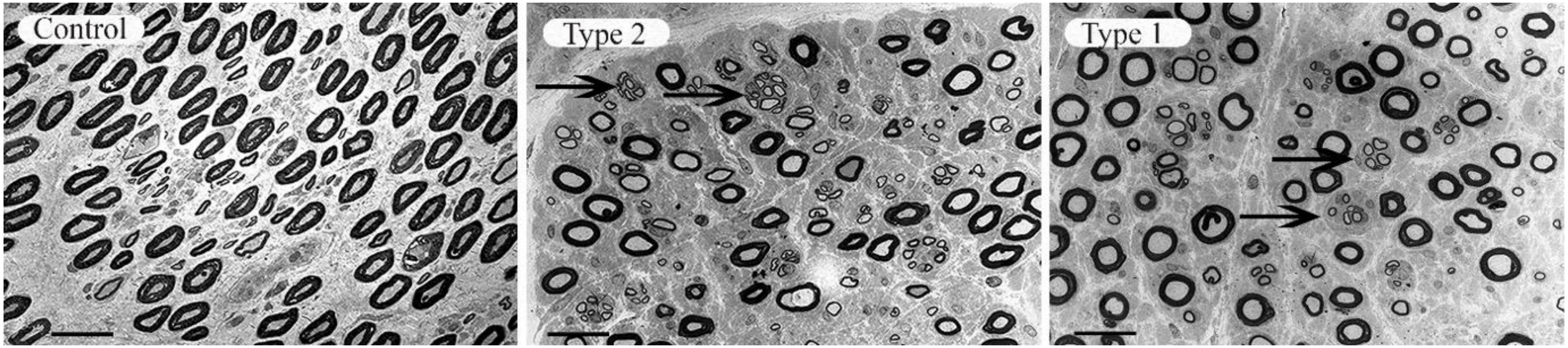
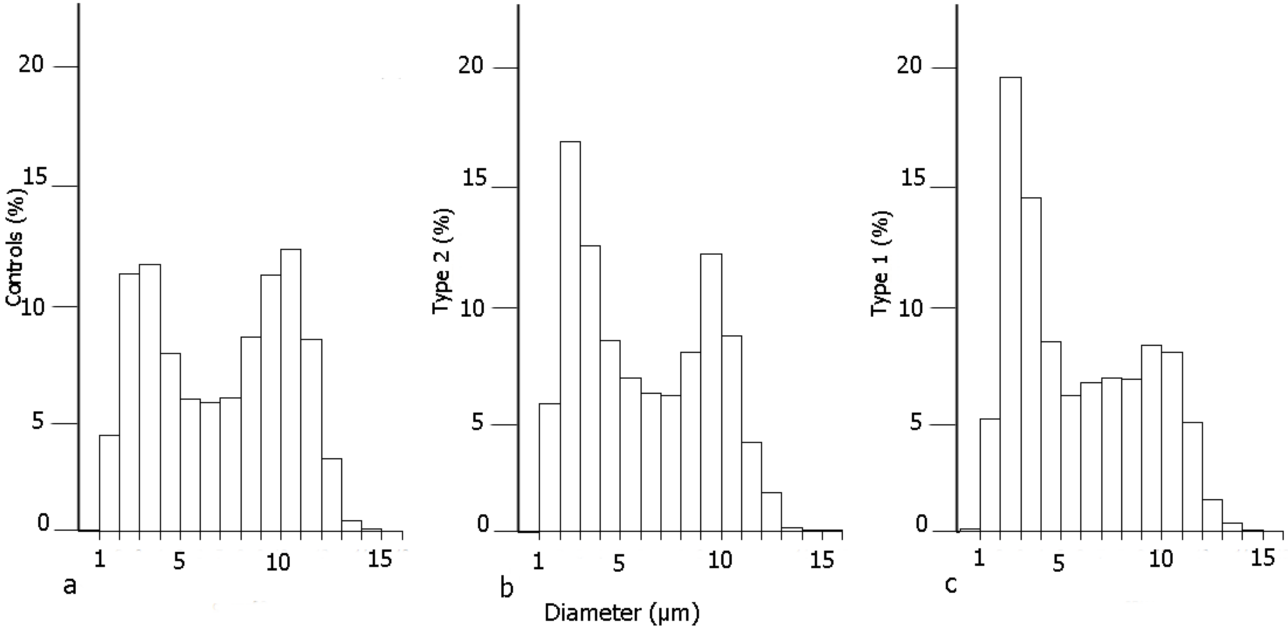
Diabetic Neuropathy – nerve fiber distribution





Posterior interosseous nerve – upper extremity

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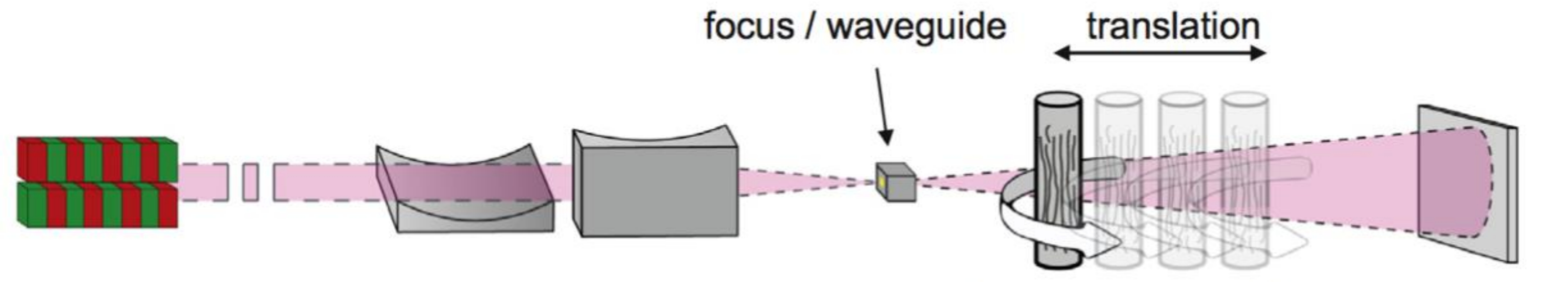
Nano tomography @ synchrotron



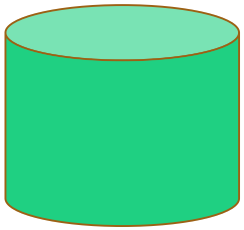
Myelinated mouse nerves studied by X-ray phase contrast zoom tomography

M. Bartels [a], M. Krenkel [a], P. Cloetens [b], W. Möbius [c,d], T. Salditt [a,d,*]

[a] *Institut für Röntgenphysik, Georg-August-Universität Göttingen, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany*
[b] *ESRF – The European Synchrotron, 38043 Grenoble, France*
[c] *Max-Planck-Institut für Exp. Medizin, Hermann-Rein-Straße 3, 37075 Göttingen, Germany*
[d] *Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany*

Journal of Structural Biology 192 (2015) 561–568

Synchrotron Nano CT versus 3D Electron microscopy

Technique	Resolution	Field of View	Acquisition Time	Other
Synchrotron Imaging	75 nm	~150 µm 	Hours	Non destructive
3D Electron microscopy	In plane: ~ 5-20 nm Slice-wise: ~ 50+ nm	 **Abdollahzadeh et al. 2019 ~15 x 15 x 15 µm^3**  **Lee et al. 2019 48 x 36 x 20 µm^3**	Days	Destructive Artifacts in different slices Need for alignment of 2D images

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Nano-Tomography at ID-16NI, ESRF

Three-dimensional architecture of human diabetic peripheral nerves revealed by X-ray phase contrast holographic nanotomography

L.B. Dahlin[1,2], K.R. Rix[3], V.A. Dahl[4], A.B. Dahl[4], J.N. Jensen[4], P. Cloetens[5], A. Pacureanu[5], S. Mohseni[6], N.O.B. Thomsen[2], M. Bech[1]

Affiliation: [1]Lund University, Lund, Sweden; [2] Skåne University Hospital, Malmö, Sweden; [3]Copenhagen University, Blegdamsvej 17, 2100 Copenhagen, Denmark; [4]Technical University of Denmark, Lyngby, Denmark; [5]ESRF, Grenoble, France; [6]Linköping University, Linköping, Sweden; **martin.bech@med.lu.se**

Scientific Reports *(2020) 10:7592*
https://doi.org/10.1038/s41598-020-64430-5

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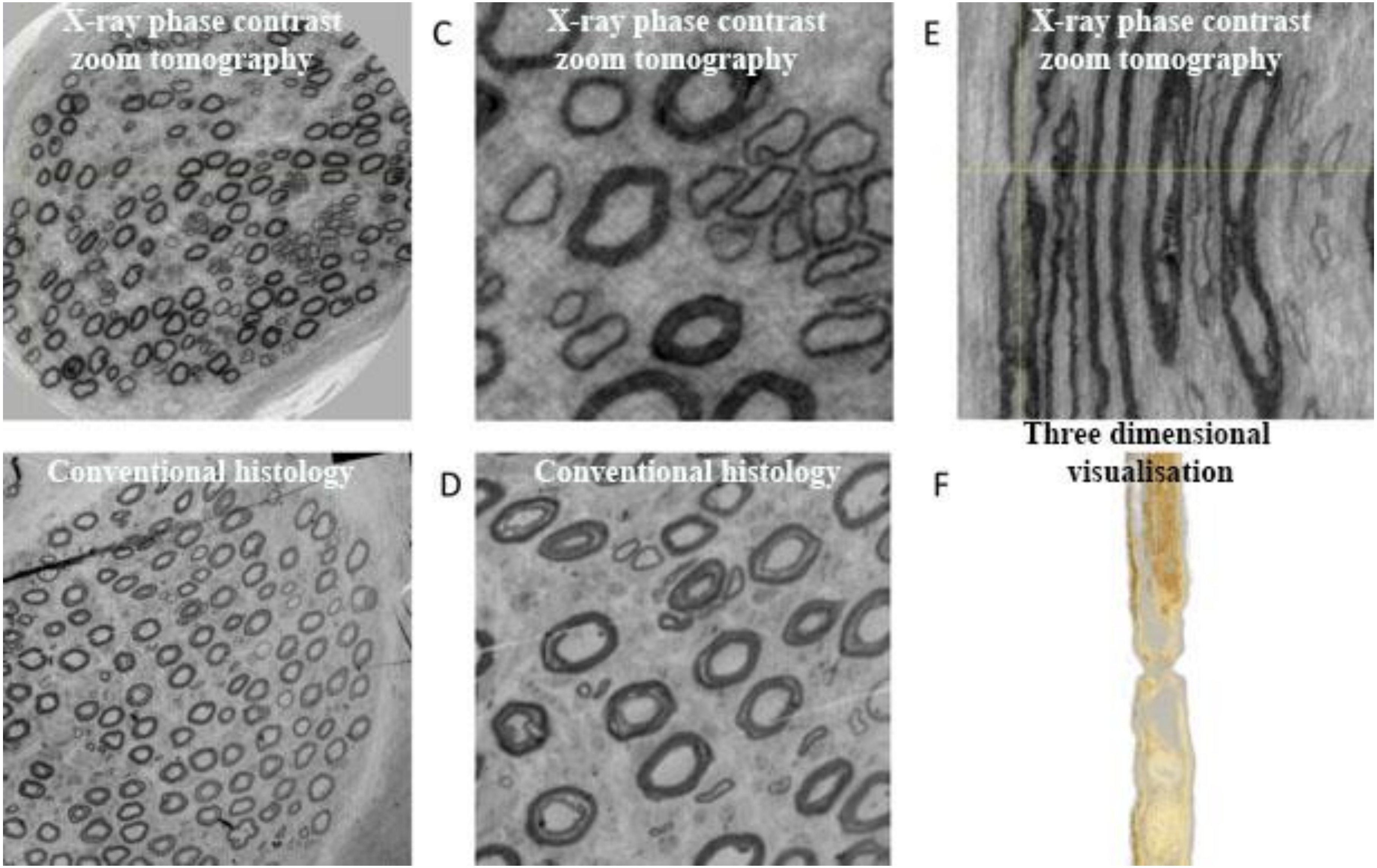
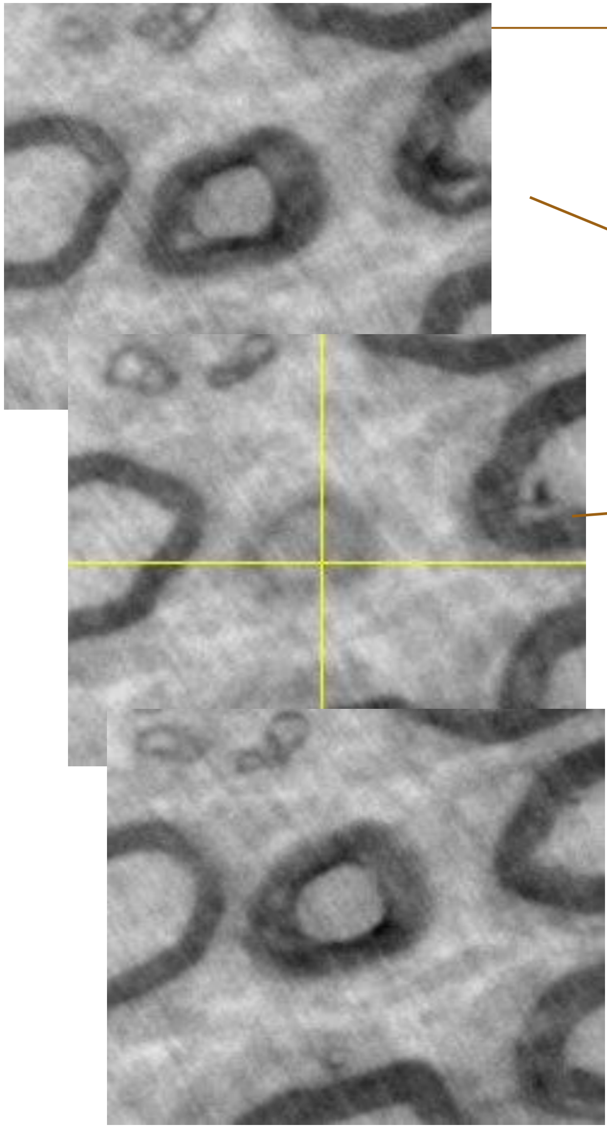
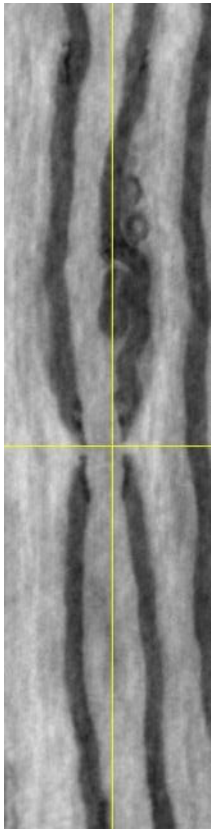
X-ray phase contrast zoom tomography

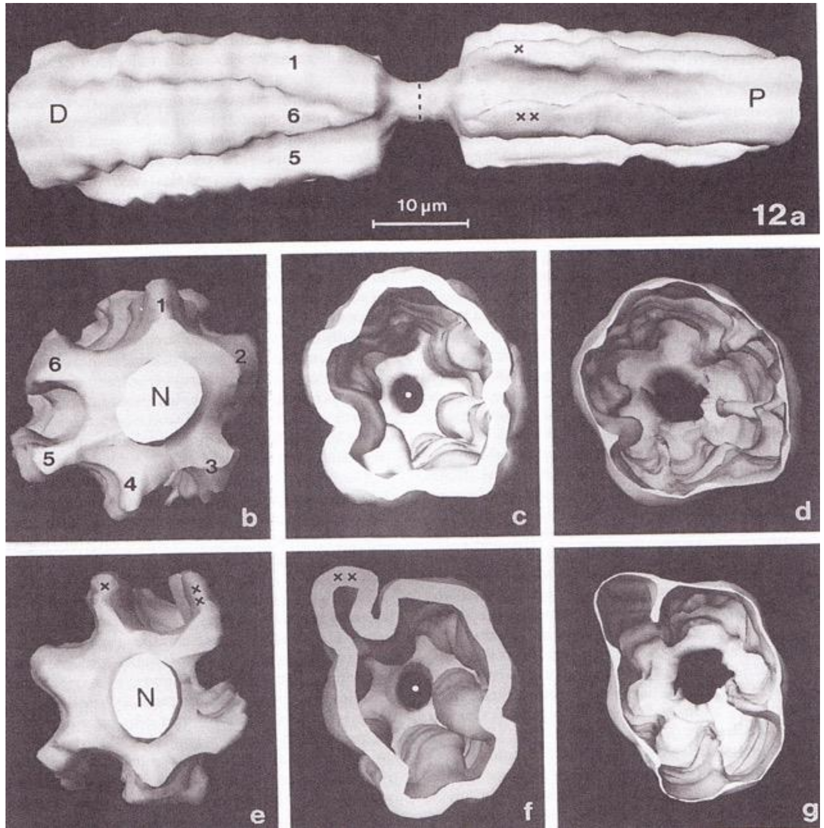


Node of Ranvier

Node of Ranvier – myelinated nerve fiber with myelin deleted







Berthold et al 1990

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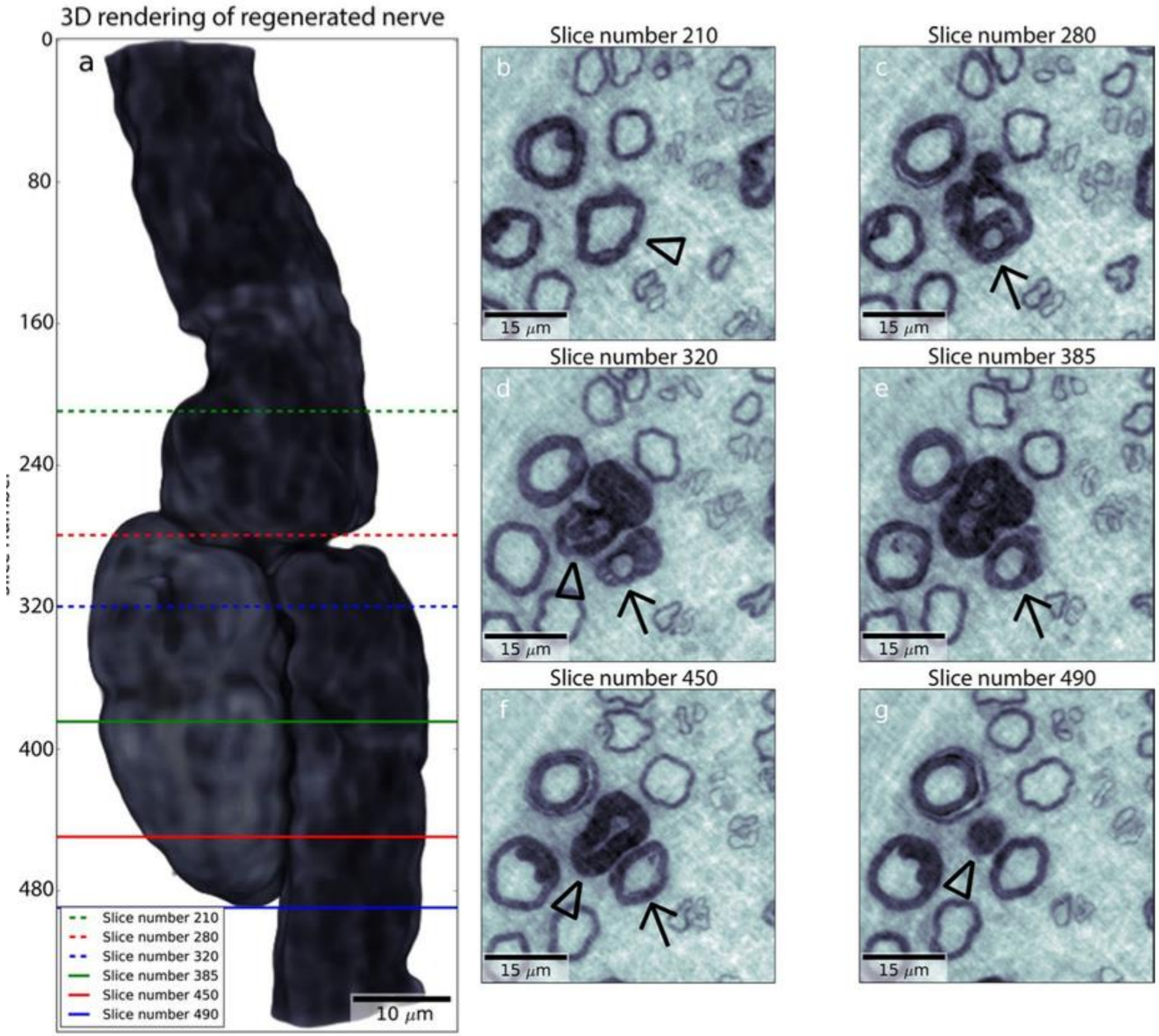
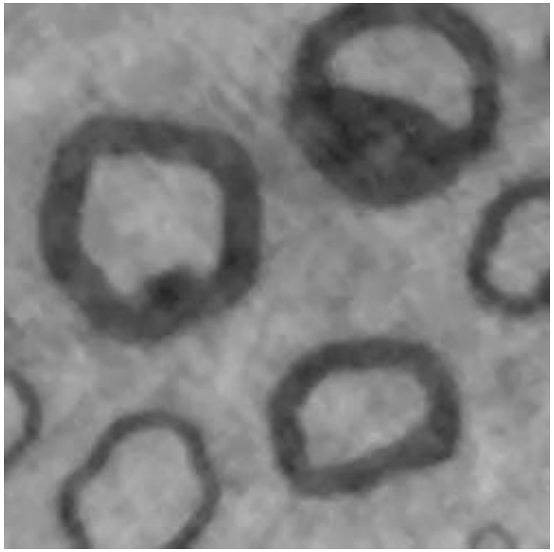
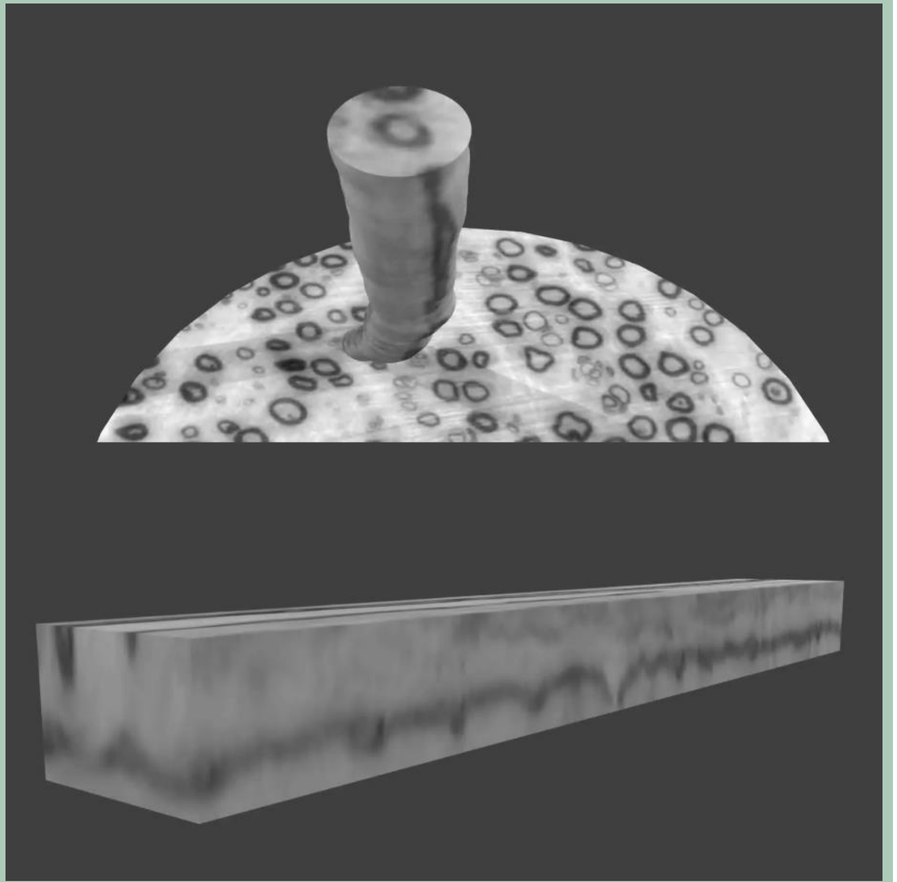
Regeneration – the birth of an axon





Data segmentation

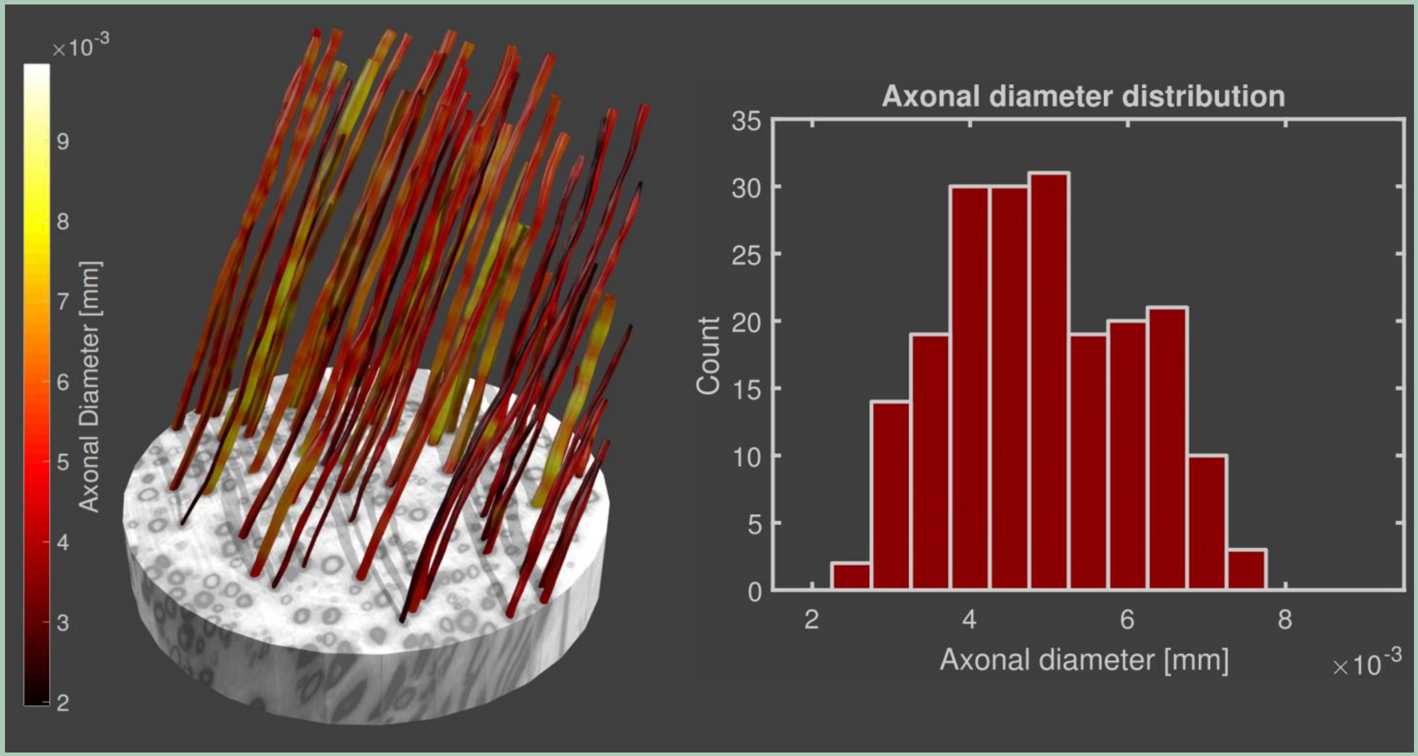
» Extraction of both inner and outer surface



Dahl, V. A., Trinderup, C. H., Emerson, M. J., & Dahl, A. B. (2018) Content-based Propagation of User Markings for Interactive Segmentation of Patterned Images. IEEE Transactions on Image Processing. 2018

Data analysis by Hans Martin Kjer

Morphology: Axonal diameter



Data analysis by Hans Martin Kjer, DTU

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Quantitative data extraction

Data: Hand Nerve Biopsies, ESRF, Lars Dahlin et al.

Data ID	#Fiber	#Node of Ranvier	Axonal volume [mm^3] X10^{-3}	Myelin volume [mm^3] X10^{-3}	Length of fibers tracked [mm]
NT32	246	45	1.29	2.97	54.75
NT45	240	28	1.2	2.84	55.13
NT46[#]	380	58	1.9	4.5	87.33
NT53[#]	447	90	1.56	5.3	101.96
NT2	188	84	1.36	2.42	50.28
NT14	186	47	0.92	2.02	40.79
NT16	130	30	0.59	1.43	31.59
NT23	245	57	1.03	2.42	58.26
NT132	158	20	0.23	0.76	28.86
NT5	308	63	1.9	2.76	65.86
NT18	162	37	0.89	2.19	37.87
Sum:	2690	559	12.87	29.61	612.89

Outline

- » What is phase contrast imaging and dark-field imaging?
- » Why are these new imaging modalities good for bio-medical imaging?
- » Future prospects of synchrotron phase-contrast imaging?

Outlook: Bio-medical Imaging and pre-clinical implementation

Bio-imaging at different length scales

Protein crystallography — Coherent diffractive imaging — Nano/Micro tomography

10^{-10} m — 10^{-9} m — 10^{-6} m

Atoms — Biomolecules — Molecular complexes — Micro-structures — Cells — Tissues — Organs — Animals

Slide courtesy: Tomas Lundqvist

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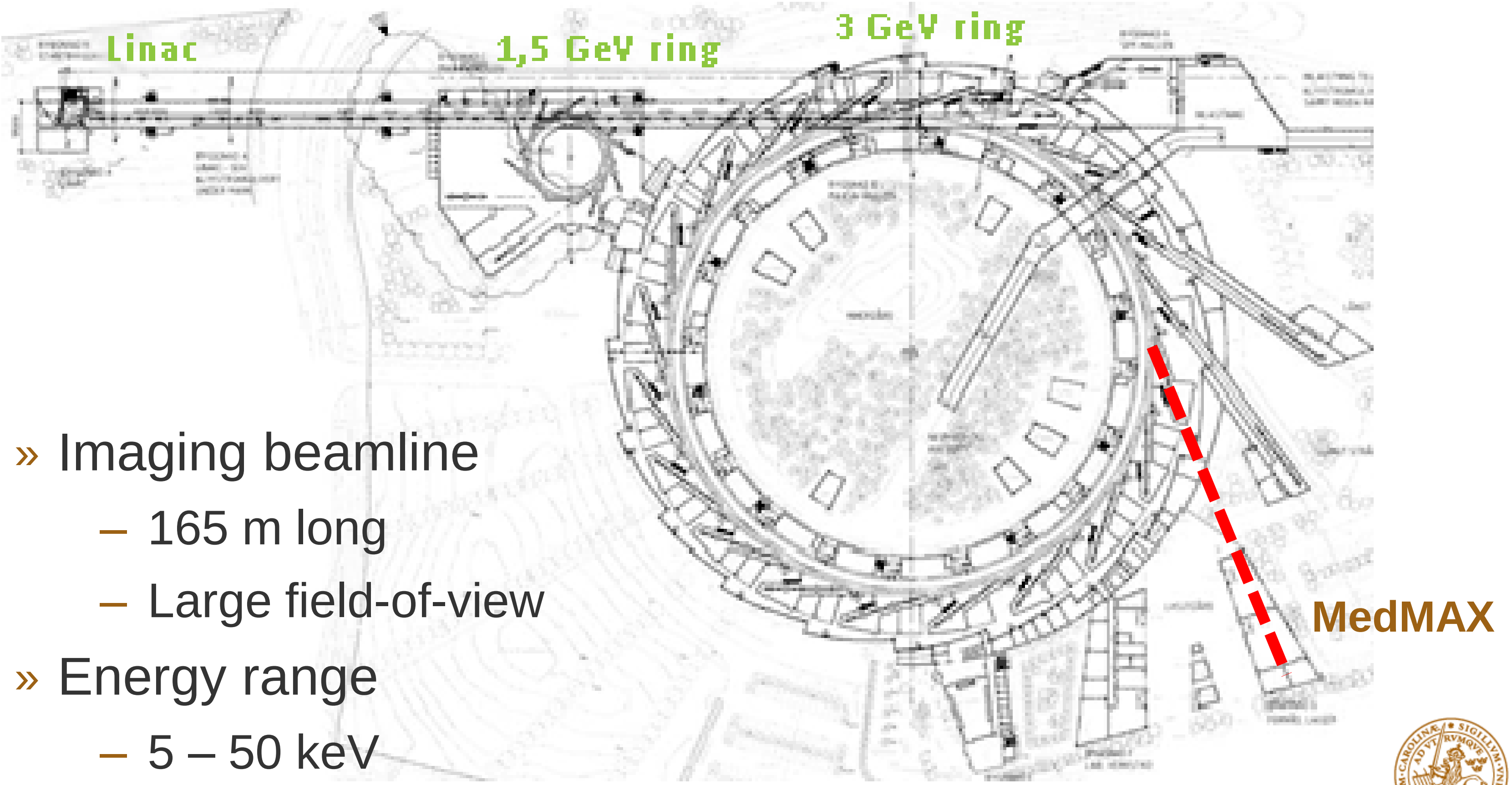
MedMAX – for biomedical imaging



- Imaging beamline
  - 165 m long
  - Large field-of-view
- Energy range
  - 5 – 50 keV

Technical scope for Biomedical beamline, MedMAX

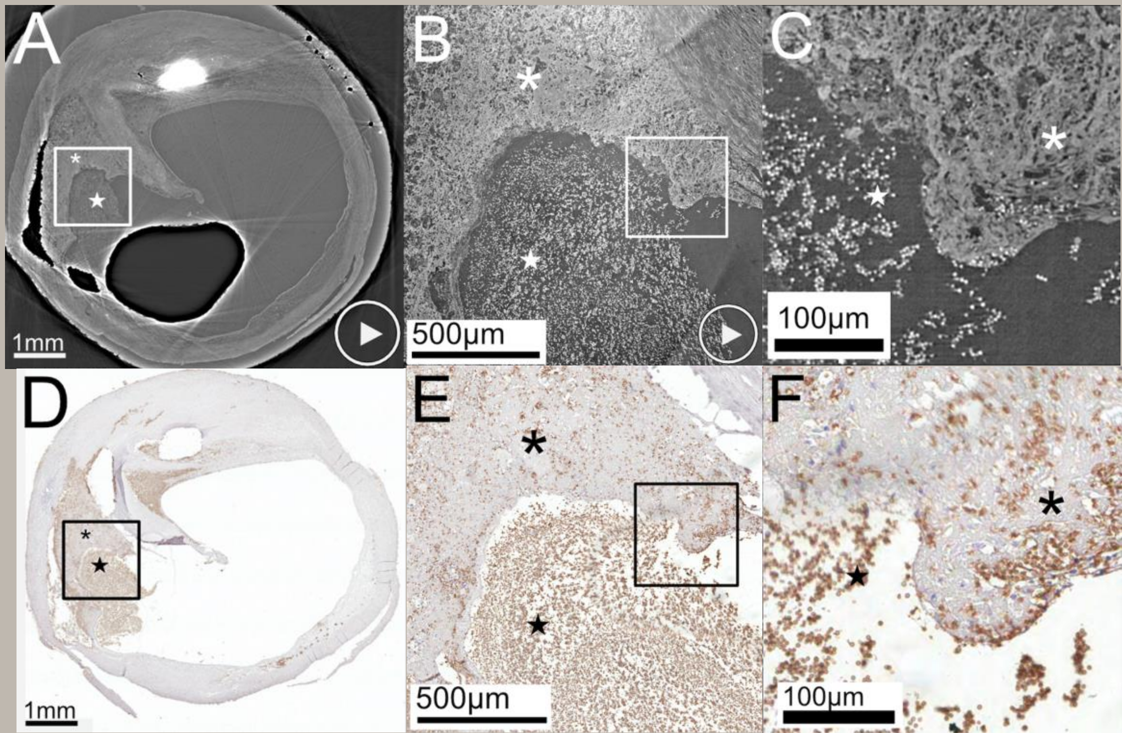
36 **Chapter 3. Technical solutions**

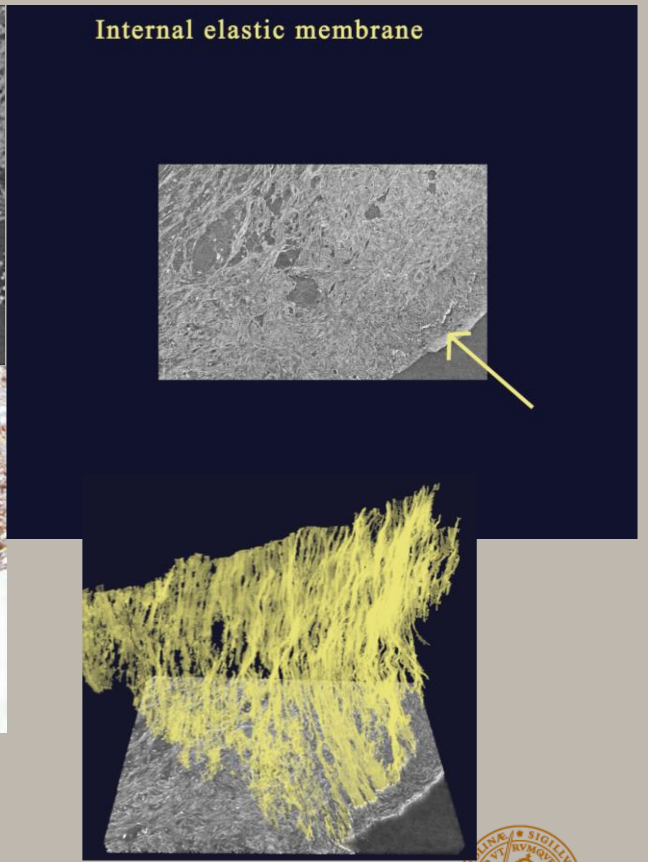
Specifications	nanotomo	microtomo	in-vivo tomo
Distance from source [m]	135	150	165
X-ray energy	12,24,36 keV	12-40 keV	20-40 keV
Beam size at sample	0.05-0.2 mm	1-2 mm	20-50 mm
Beam modes	Focused	Parallel	Expanded
X-ray bandwidth	$10^{-4} - 10^{-2}$	10^{-2}	$10^{-4} - 10^{-2}$
Flux at sample @25keV [ph/s]	$10^{12} - 10^{13}$	$5x10^{15}$	$10^{13} - 10^{14}$
3D spatial resolution	100-300 nm	1-2 μm	5-30 μm
Trademarks	nano-scale phase tomography and spectroscopy of cells, bacteria and biologic material	fast ex-vivo and in-vivo micrometer scale imaging of tissues and selected organ regions.	in-vivo imaging of whole organs in small animals, low-dose longitudinal studies

Table 3.1: The design goals in terms of beam parameters at the sample position and instrument performance

Conceptual design report

Imaging with synchrotron x-rays





Truong et al. (2022) Sub-micrometer morphology of human atherosclerotic plaque revealed by synchrotron radiation based µCT—A comparison with histology. PLOS ONE 17(4): e0265598.

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Thank you for your attention

- Lund University
- Region Skåne
- Medicon village

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