Life Science at the First Ultimate Storage Ring MAX IV, Lund, Sweden

Uwe Mueller

MAX IV – A dream for a long time came true

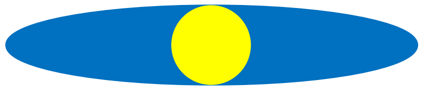
Architects 3D model

MAX IV

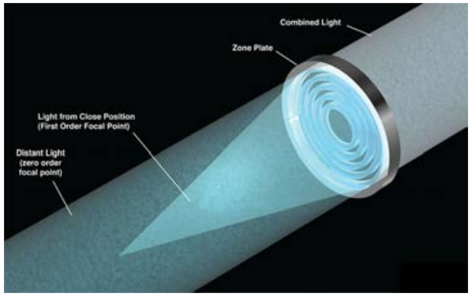
Why do we need novel photon sources ?

Source parameter

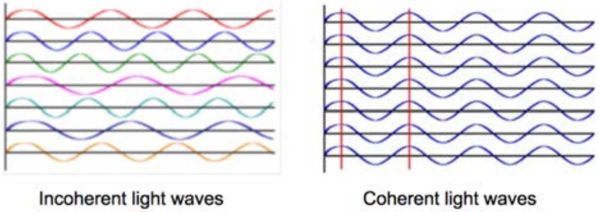
- Reduced X-ray beam size at low divergence and high photon flux:
  - To match smaller samples
  - To increase the spacial resolution (spectroscopic nanoprobes)
  - Advantageous for almost every experiment



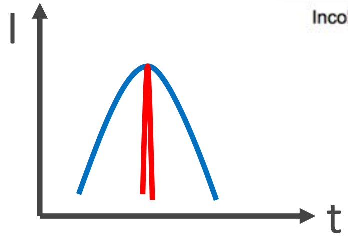
- More symmetrical horizontal and vertical emittances (round beam)
  - H-V symmetric optics (zoneplates, CRL-focusing))
  - More flexibility in optics design



- Coherent x-rays
  - Better imaging possibilities (creating a uniform wavefront)
  - Nanofocussing
  - Ultra high flux



- Fs-pulses
  - Sampling of fast dynamics
  - Radiation damage free observations

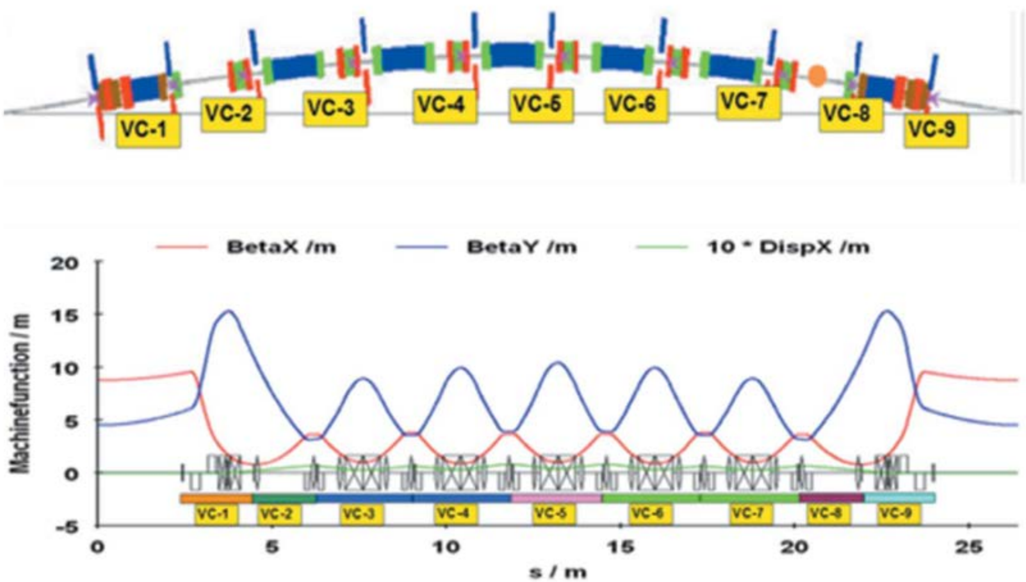


How to build a low emittance ring ?

How to minimize emittance?

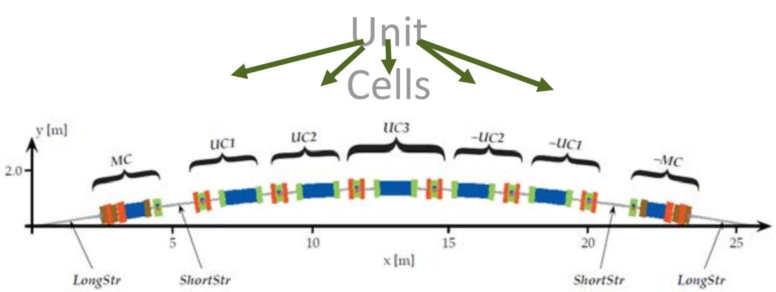
- Reduce dispersion and beta function in bend magnets, achieved by refocusing beam ‘inside’ bending magnets -> need space
-> too expensive

- ‘Split’ bending magnets -> multi bend achromats → how?

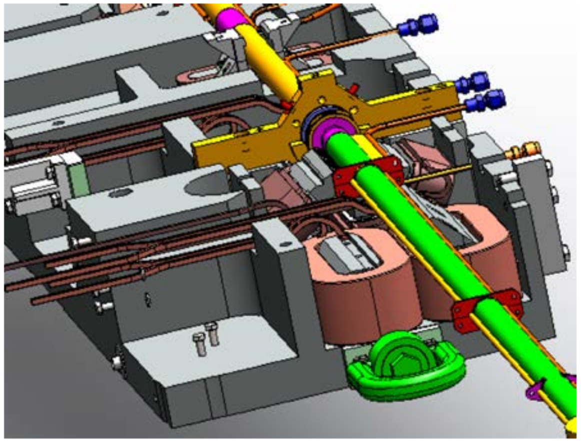


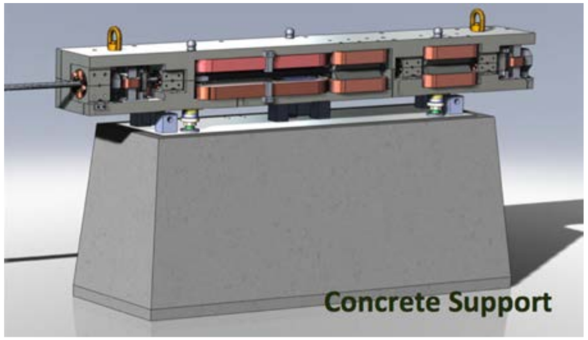
7-bend achromat magnet lattice of MAX IV

Novel magnet lattice technologies



- Emittance: 200 -330 pmrad
- Max. current: 500 mA



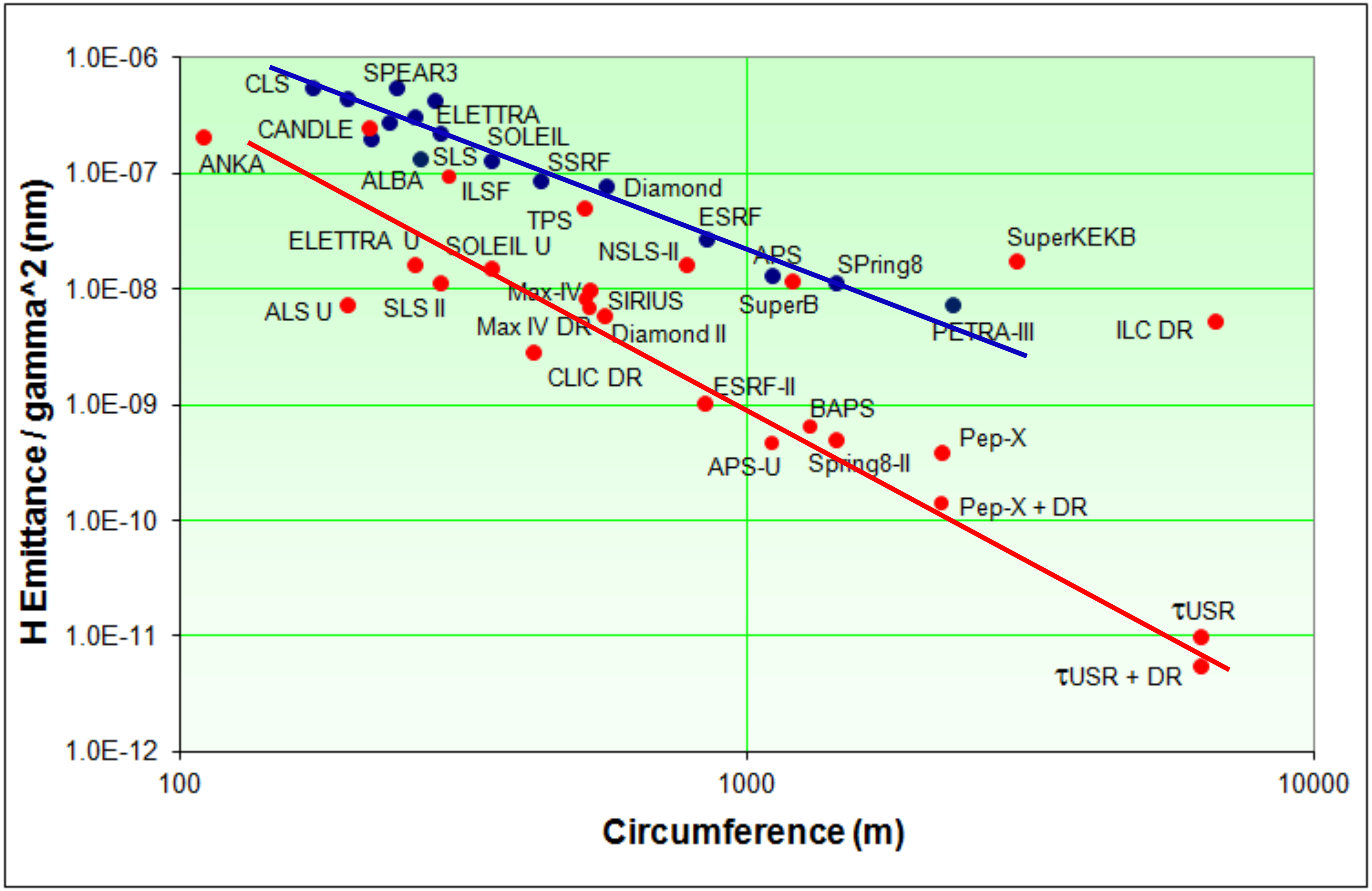


Compact magnet and vacuum technology

Courtesy S. Leemans

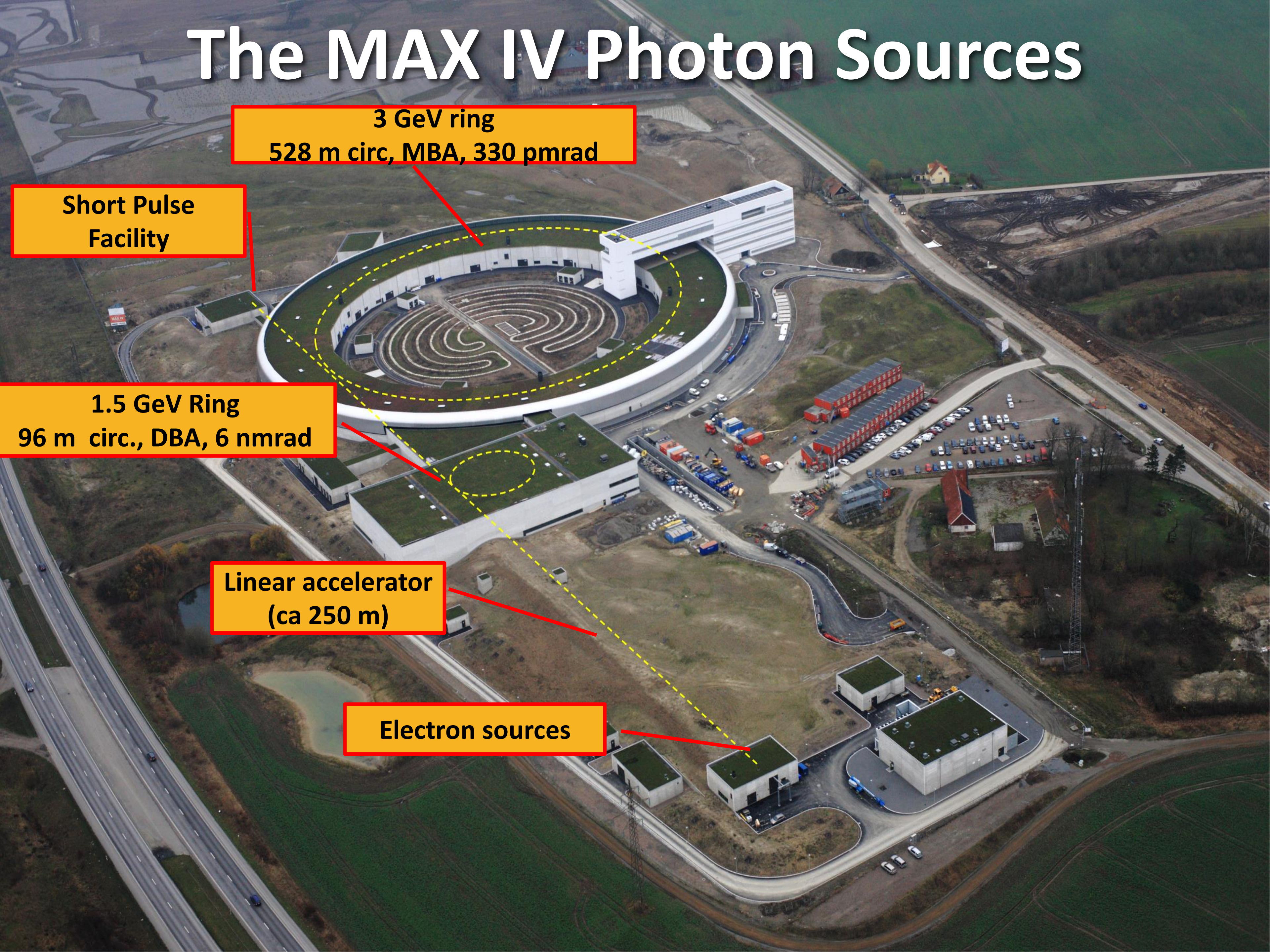
MAX IV

New storage rings in the future



R. Bartolini

The MAX IV Photon Sources



MAX IV Beamlines

3 GeV Ring

NanoMAX
Nano-focus & coherence

DanMAX
Imaging & diffraction

Balder
EXAFS & RIXS

ForMAX
Wood based material

CoSAXS
SAXS & coherence

BioMAX
Protein structure

MicroMAX
Protein structure

VERITAS
Excitations in solids & liquids

HIPPIE
Operando spectroscopy

SoftiMAX
X-ray microscopy & coherence

1.5 GeV Ring

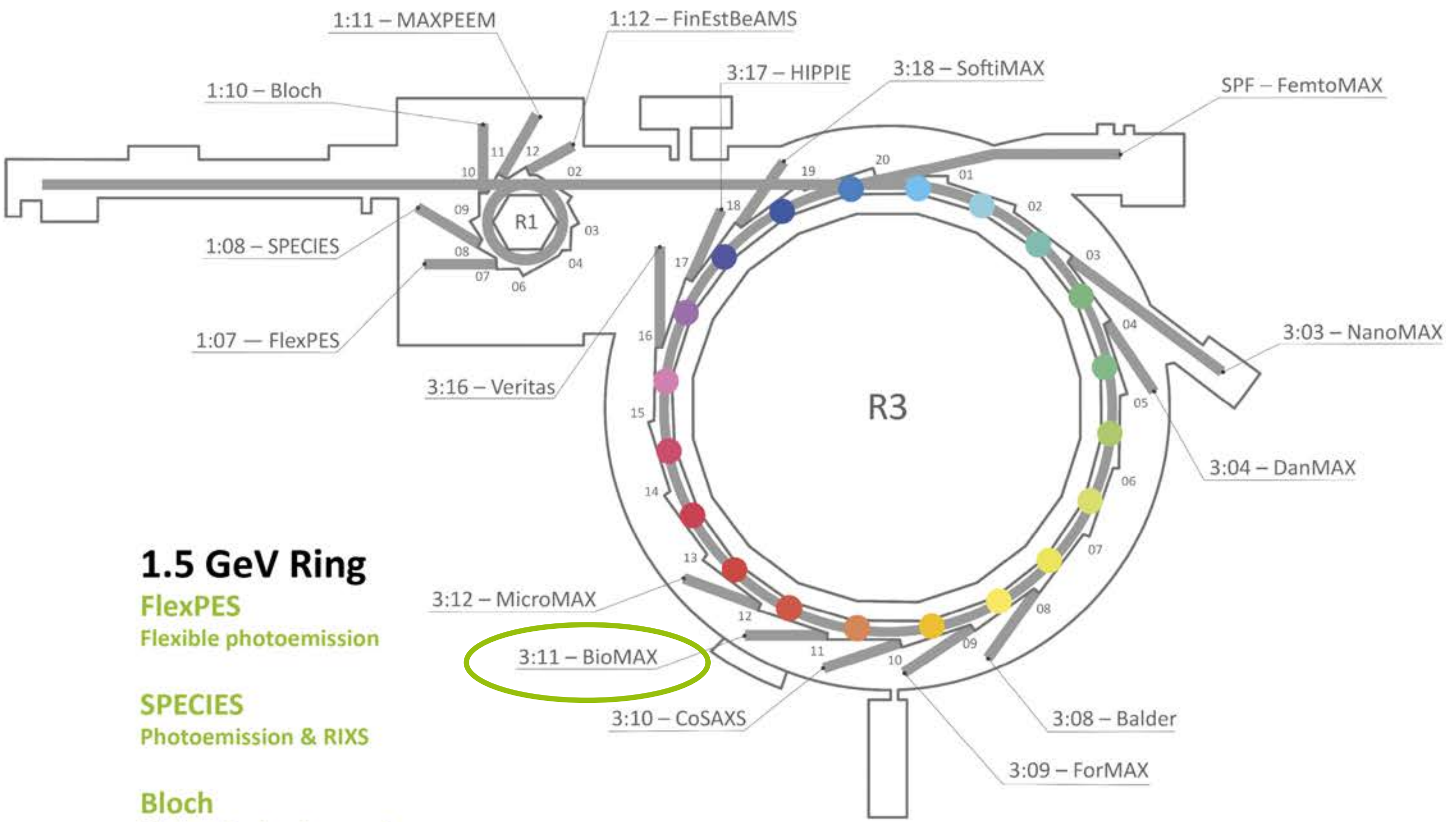
FlexPES
Flexible photoemission

SPECIES
Photoemission & RIXS

Bloch
Electronic structure surfaces

MAXPEEM
Microscopy of surfaces

FinEstBEAMS
Gas phase & luminescence

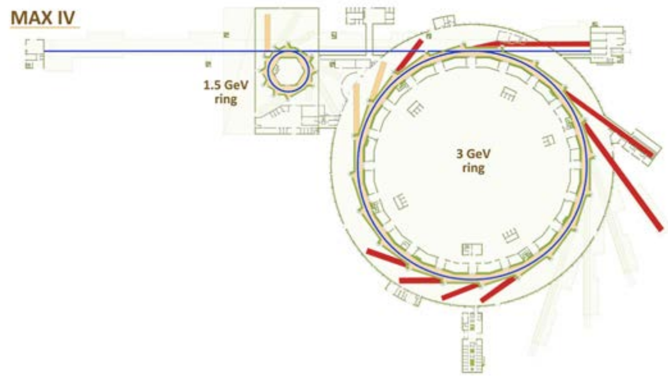


3 GeV Linac

FemtoMAX
Ultra-fast diffraction & spectroscopy

Legend (status autumn 2019):
User operation
Commissioning
Construction

Life science at different length scales

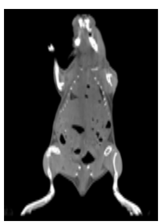


Imaging
MedMAX II
MedMAX I
NanoMAX
SoftiMAX

Diffraction
coSAXS
BioMAX
MicroMAX

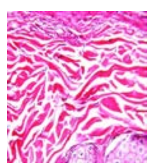
Spectros-copy
FemtoMAX
Balder

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



Animals

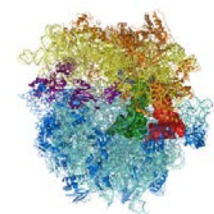
Organs



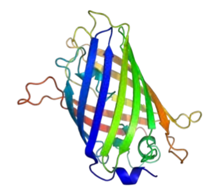
Tissues

Cells

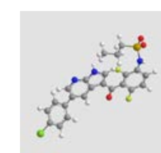
Micro-structures



Molecular complexes



Biomolecules

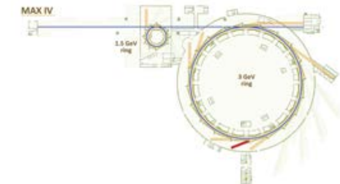


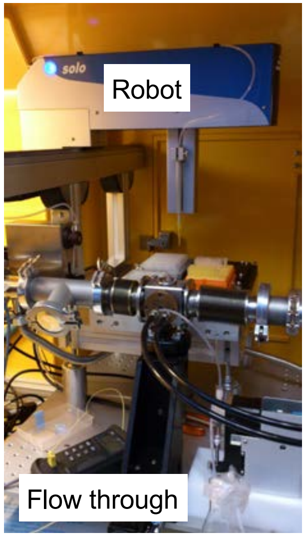
Atoms

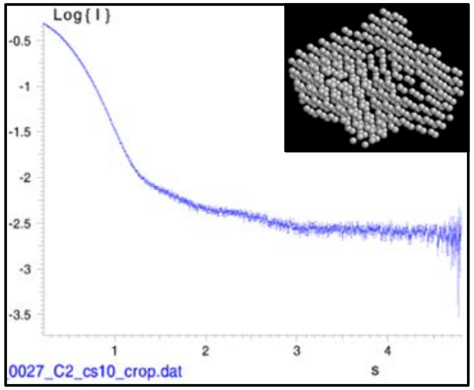
Disease models
Histopathology
Cell Biology
Molecular Medicine/Chemical Biology

MAX IV

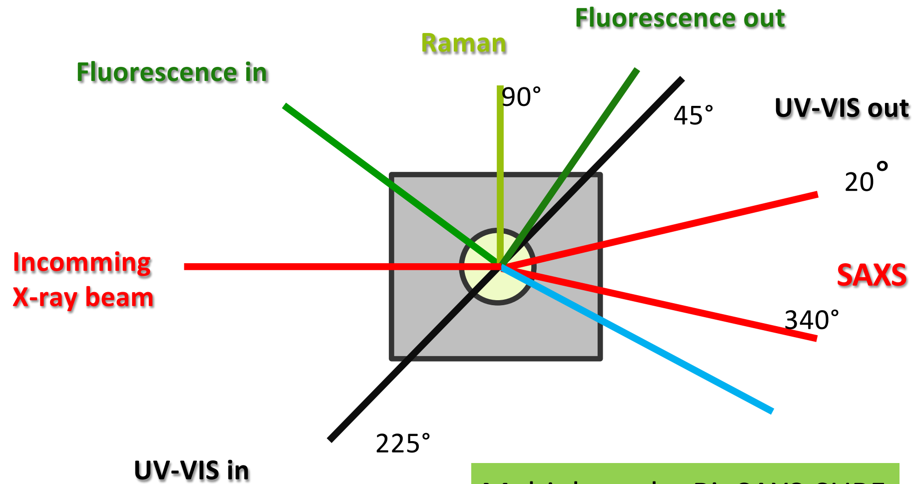
coSAXS-BioSAXS





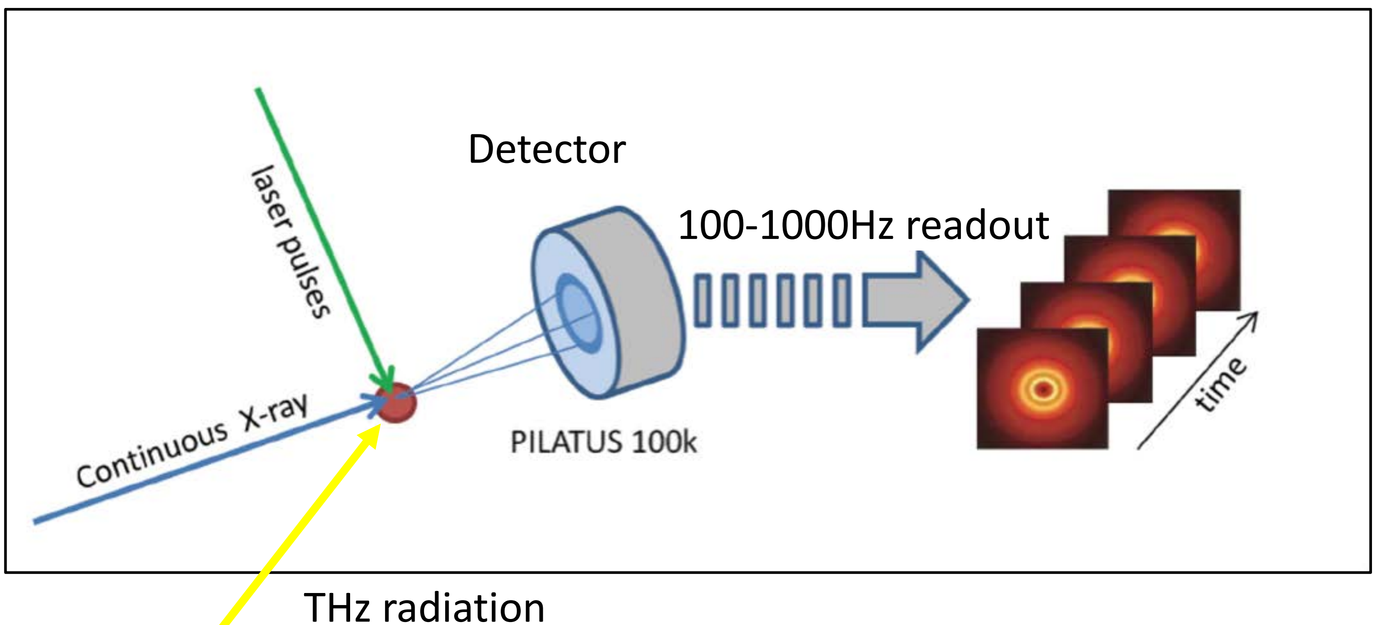


Static BioSAXS



Multiple probe BioSAXS-SURF

CoSAXS-LU-SWING (Soleil)



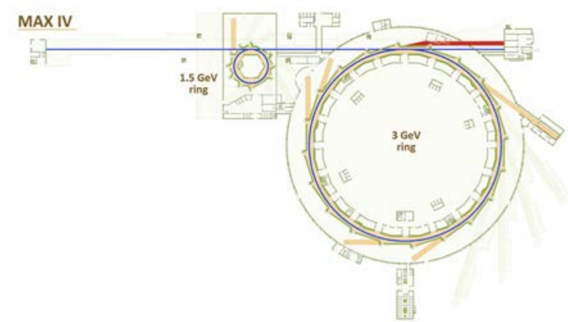
Dynamic BioSAXS
Conformational changes

CoSAXS-FemtoMAX
Lübeck University-EMBL/Ham.

MAX IV

FemtoMAX

Jörgen Larsson, email: **Jorgen.Larsson@fysik.lth.se**



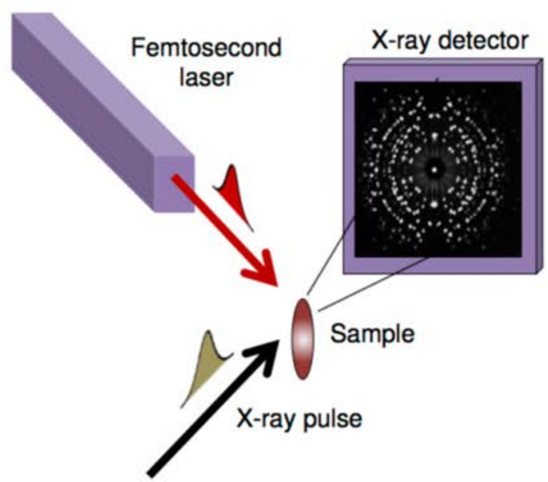
Aim:

Study of ultrafast chemical reaction, dynamics of biomolecules

Probes:

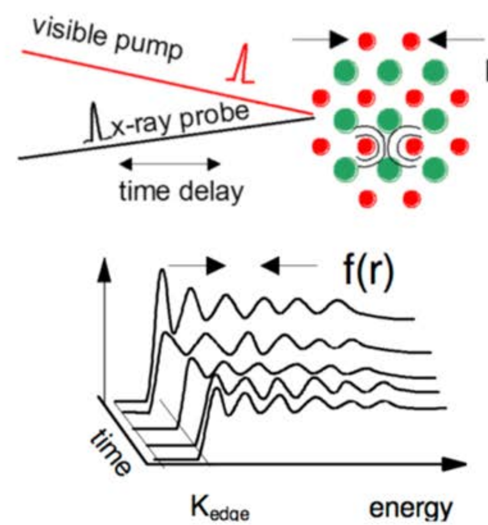
- Fs –Laser
- X-ray
- Ps –THz probe

Time-resolved x-ray diffraction



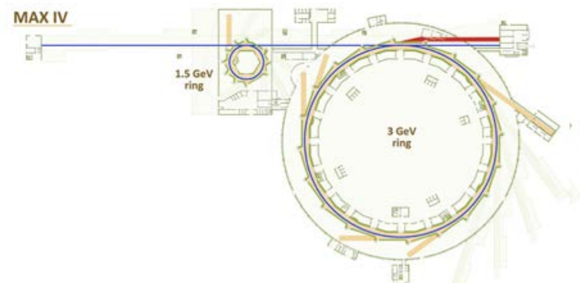
Phase-transitions, phonons in ordered systems

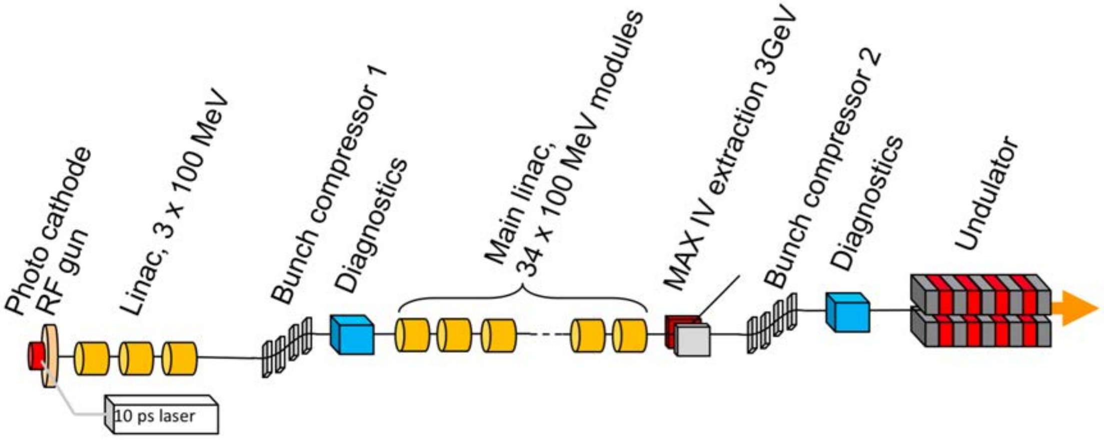
Time-resolved EXAFS



Complex disordered materials

FemtoMAX



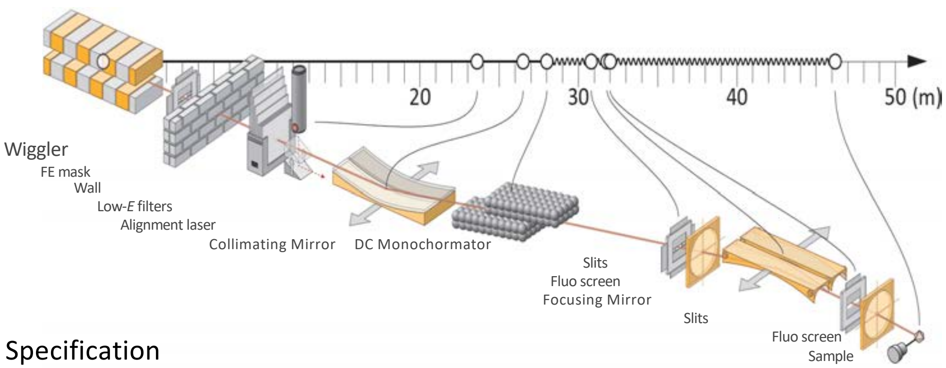


Beamline schematics

10m long FemtoMAX ivu

	Electrons	Photons
Energy	3 GeV	2-20 keV
Emittance	e_N~ 2.5 mmRad	
Beam size in undulator	100 μm FWHM	100 μm FWHM
Pulse duration	100 fs FWHM	100 fs FWHM
Energy spread/Bandwidth	1.5%	1% with multilayer mono
Charge/Flux	100 pC/pulse	10^7 ph/pulse at 6 keV

Balder



Specification

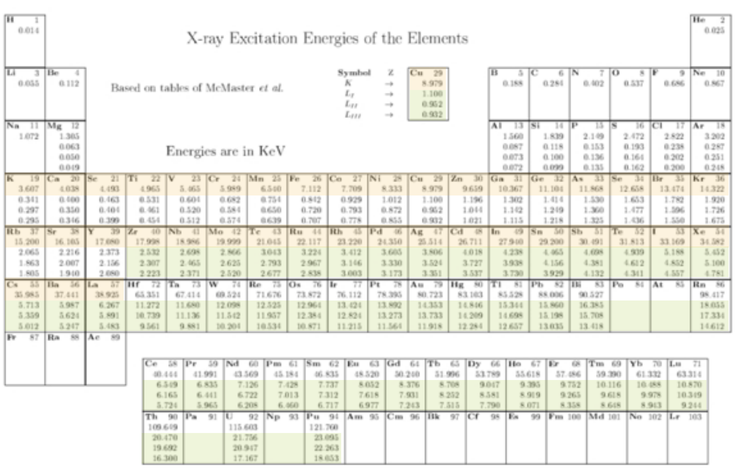
Energy range: *2.4 - 40 keV (S to La K-edges)*

Flux: *10^{12}-10^{13} photons/s*

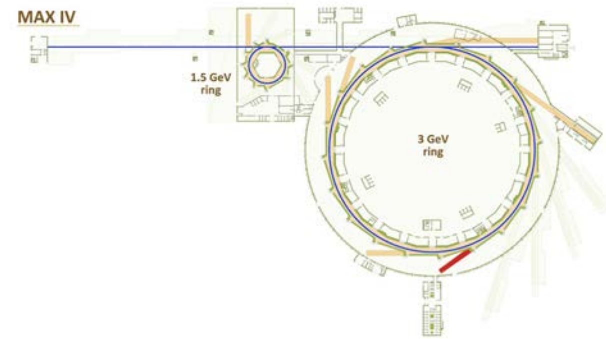
Beam spot size: *focused ~100 x 100 µm^2 or*
defocused V ~0.1-2mm x H ~ 2-9mm

Suitable for time resolved studies (sub-sec) and dilute, radiation sensitive samples.

2.4 – 40 keV = sample with elements



Important in biology: S, Ca, V, Mn, Fe, Co, Ni, Cu, Zn, Se, Mo



XAS/XES

- Elegant probe for element speciation in biological and environmental samples.
- Element-specific structural information.
- Detailed information on metal centers in proteins.

Sample environment for bio

4-300 K closed cycle cryostat: multiple samples, variable volume 10-200 µl, mapping inside -*MAX IV design*
Liquid flow cell
Electrochemistry cell

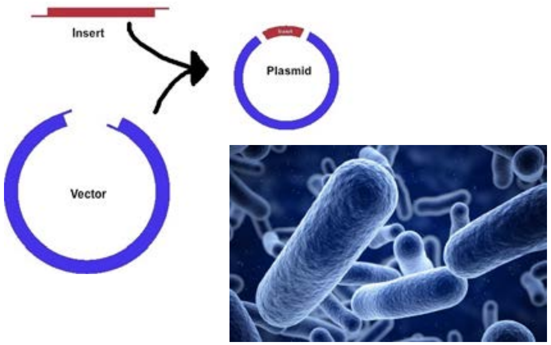
BioXAS/XES goals

- To measure XAS and XES on small dilute samples of metalloproteins without X-ray damage.
- To measure real-time changes in the metal coordination during biocatalysis (*in situ* BioXAS).
- To have high throughput data acquisition on multiple samples.

Timeline

First X-rays autumn 2016 – commissioning
First users during 2017

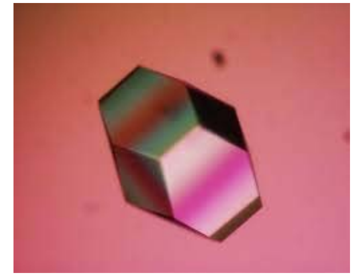
Macromolecular crystallography -Principle



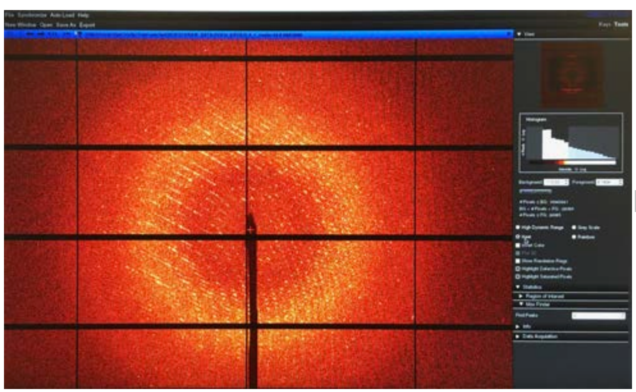
Heterologous or native expression in host cells (E.Coli, insect cells, etc.)

Highly purified protein in mg quantities

Protein crystallization

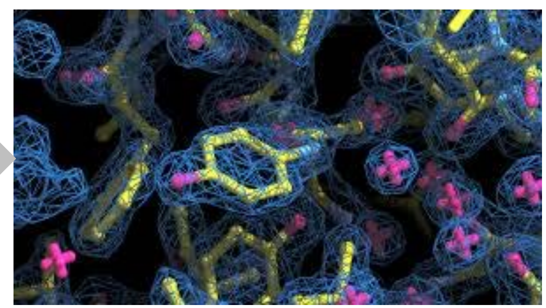


Single, diffracting protein crystal



Complete diffraction experimental data-set at high resolution

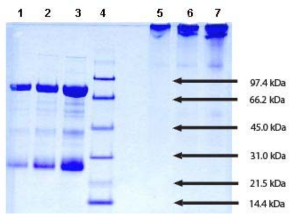
Phase problem



Interpretable electron density

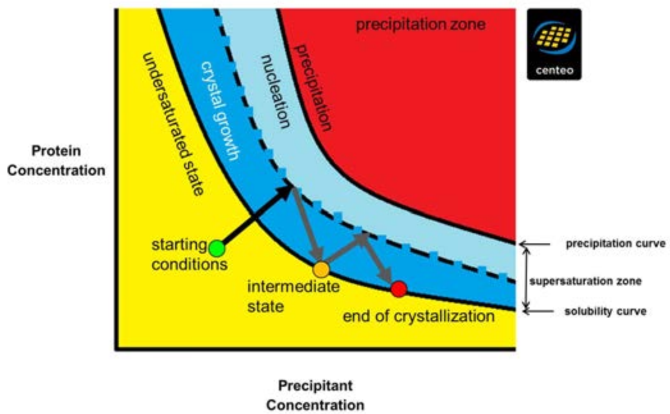
Final structure model

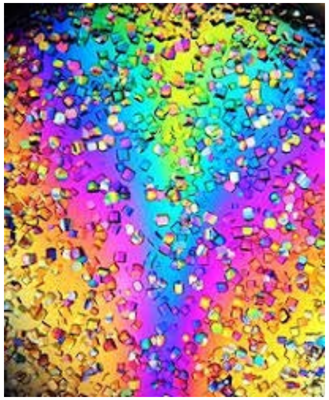
Macromolecular crystallography -Crystallization

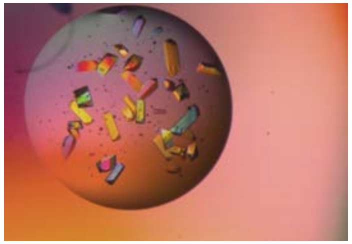


Requirements:

- Concentrated, highly pure and monodisperse sample

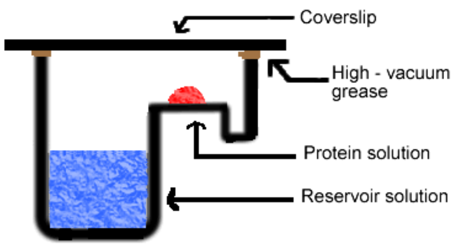




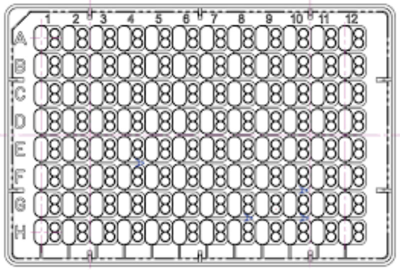


Protein crystals, 5-100 µm size

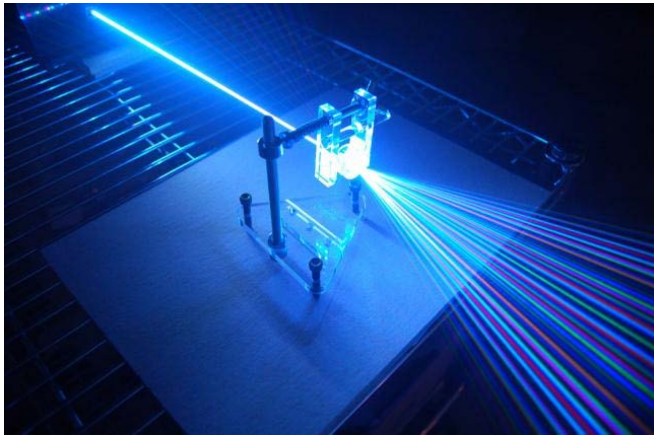
Vapor diffusion



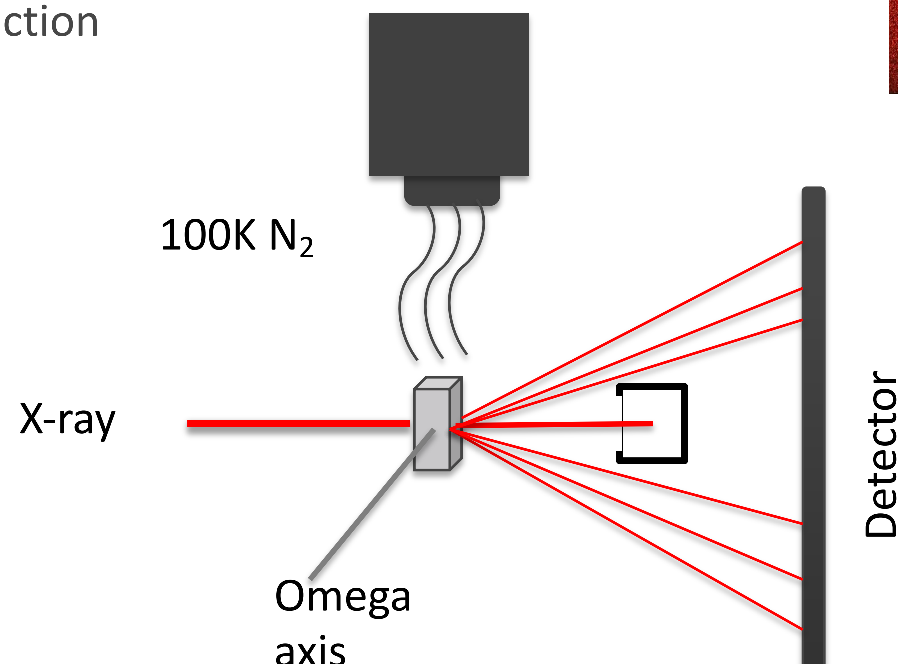
96 well crystallization plate

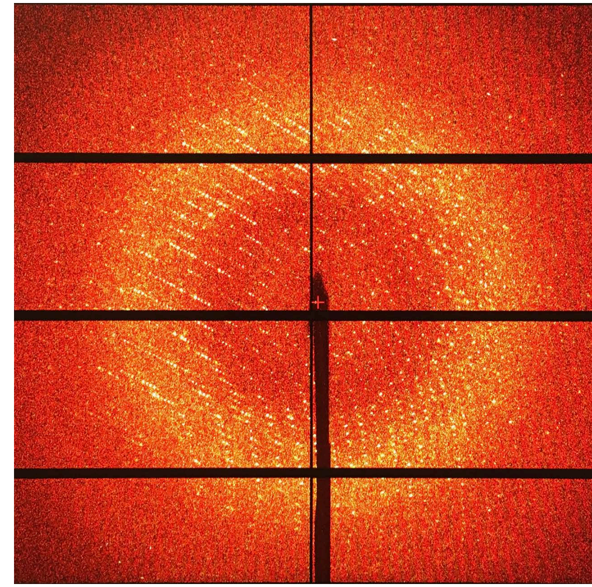


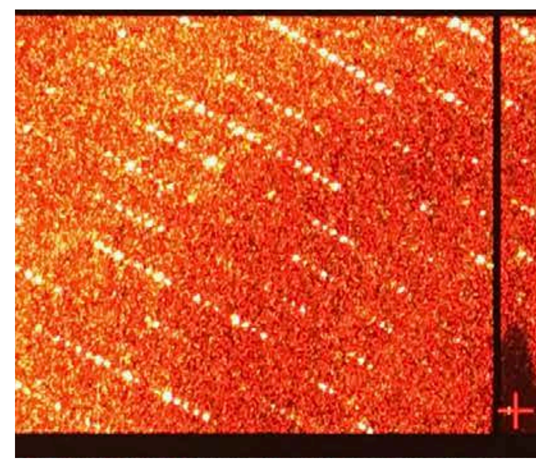
Macromolecular crystallography –Diffraction



Visible light diffraction



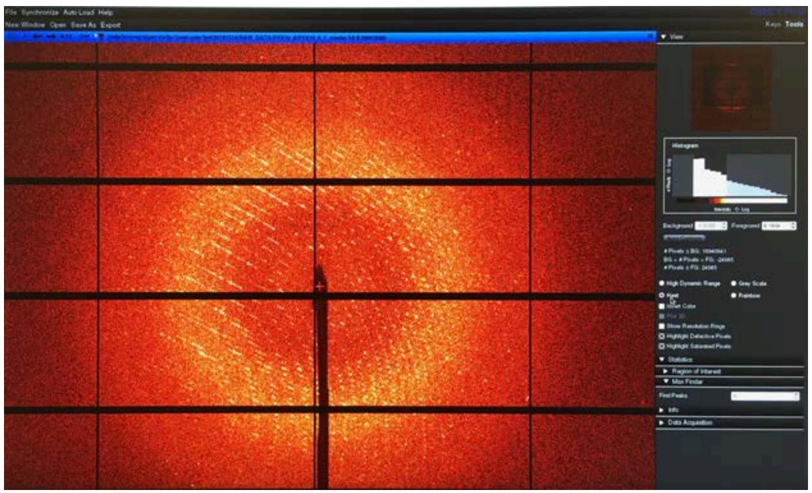


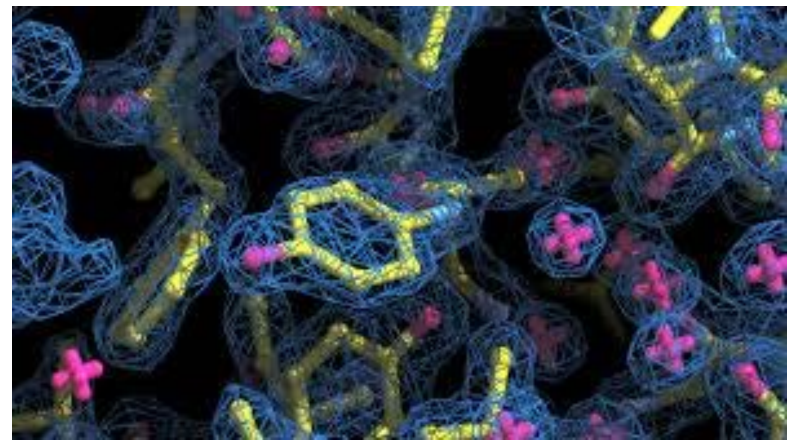


X-ray diffraction

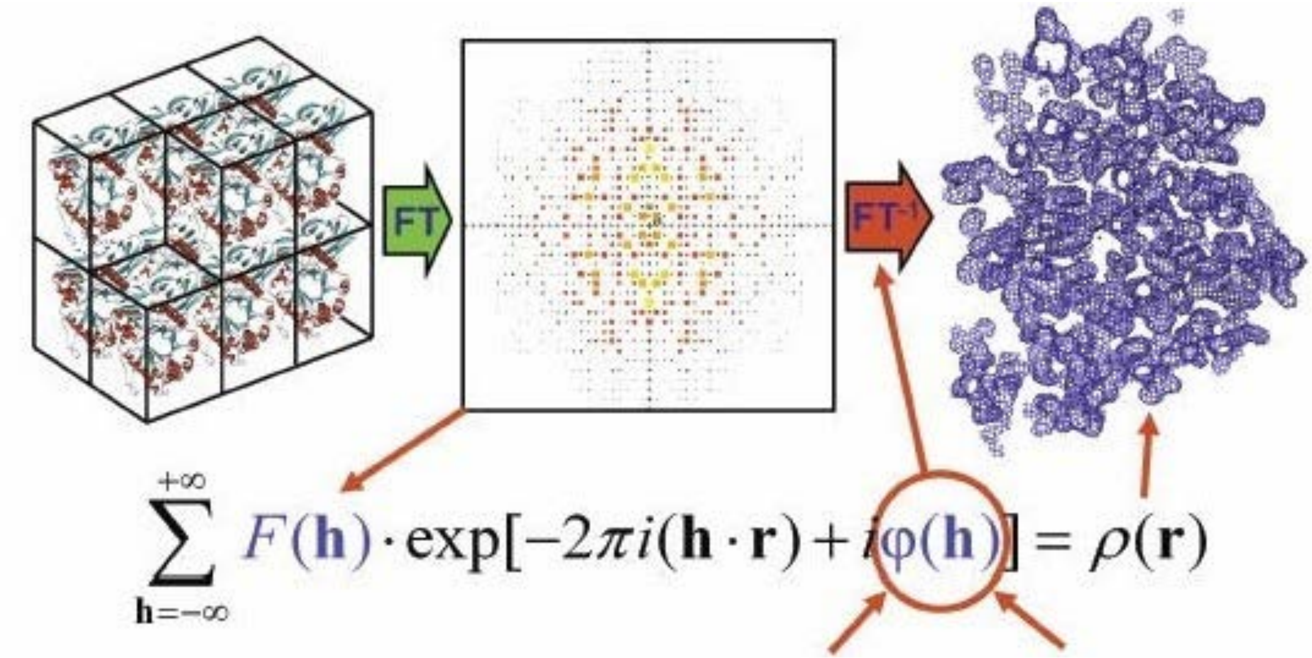
MAX IV

Macromolecular crystallography –Phase problem





Macromolecular crystallography –Phase problem



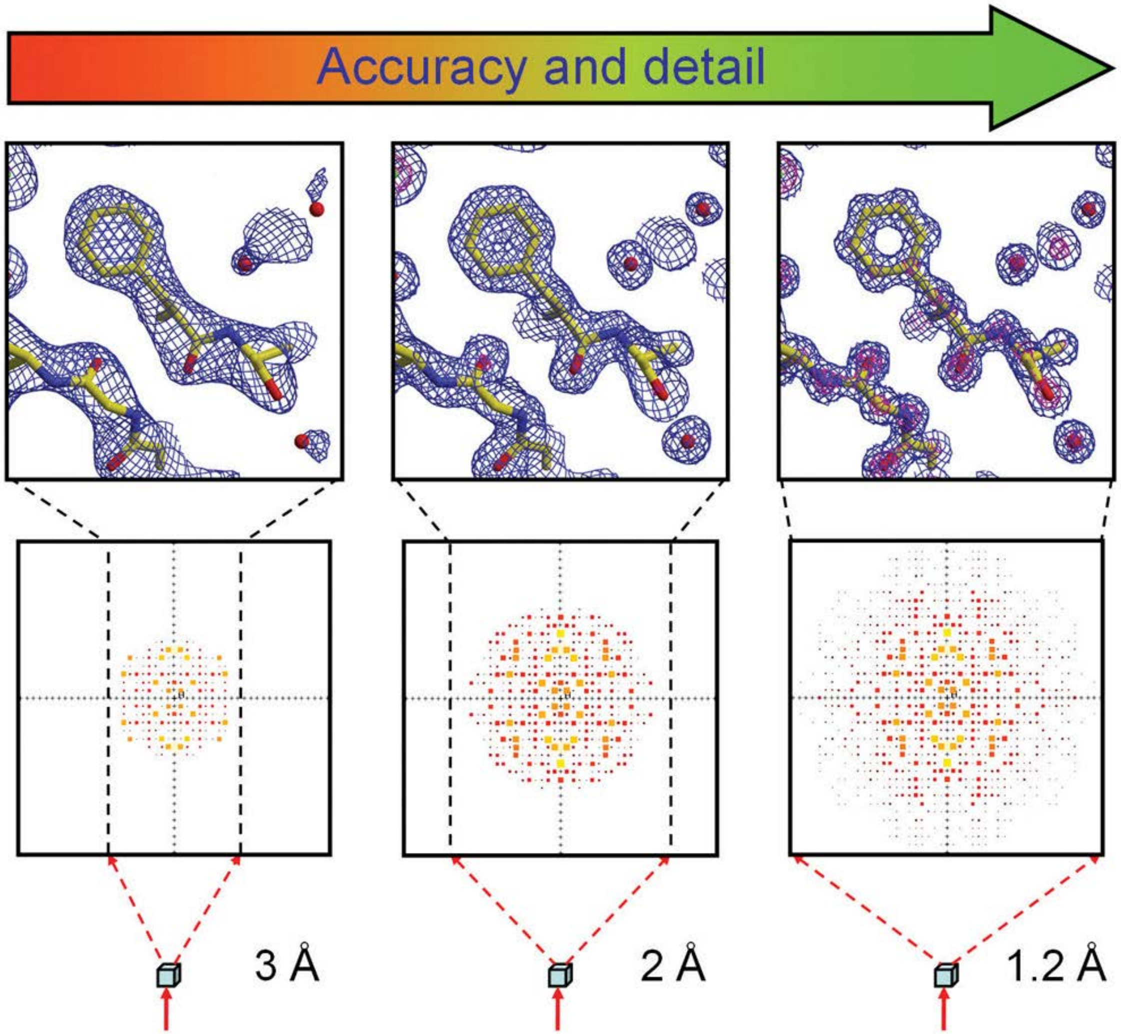
Phasing methods:

- Molecular replacement
- Anomalous diffraction
- Isomorphous replacement
- *Ab initio* phasing

Picture from Ruppweb (http://www.ruppweb.org/Xray/Phasing/Phasingt.html)

MAX IV

Macromolecular crystallography –Resolution

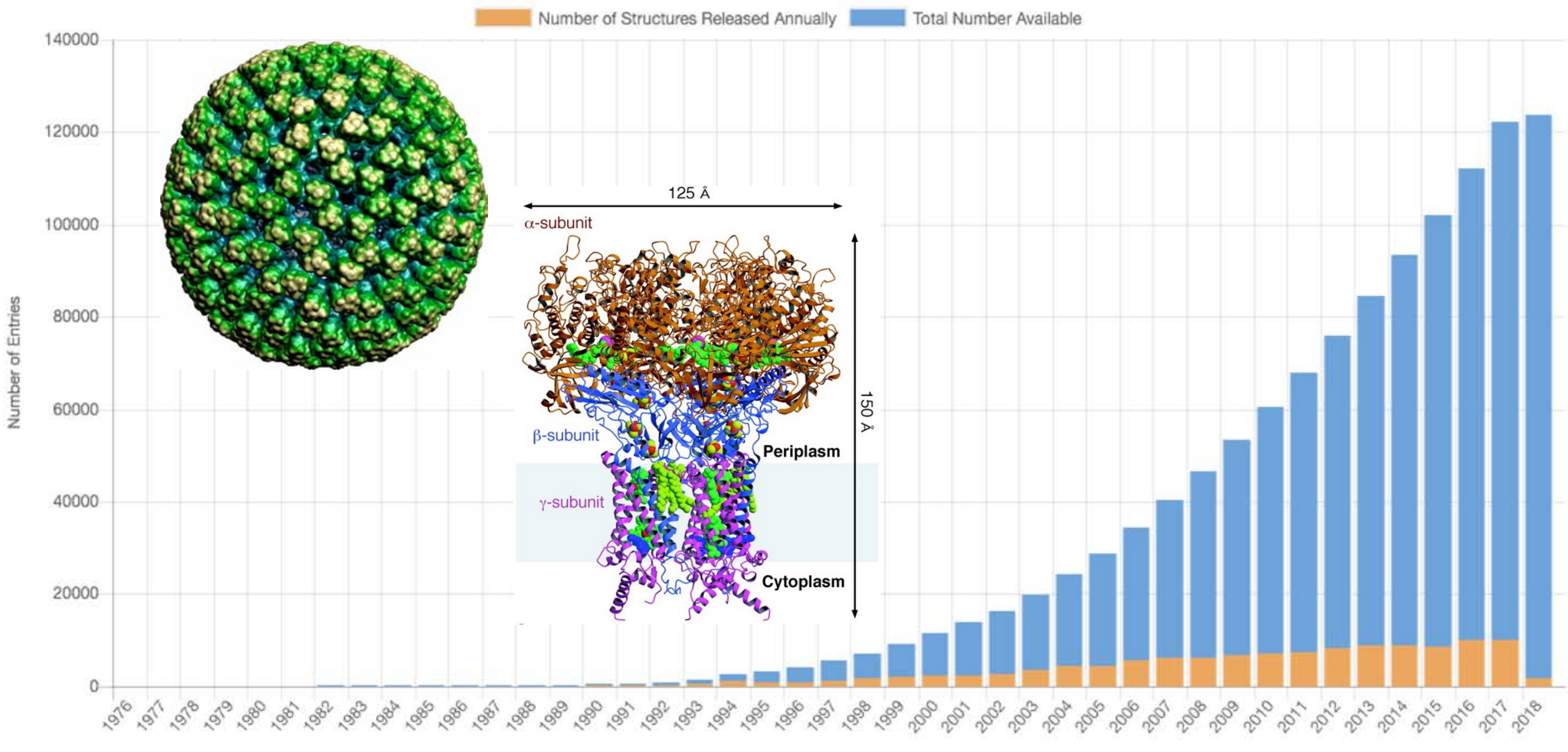


Bragg law

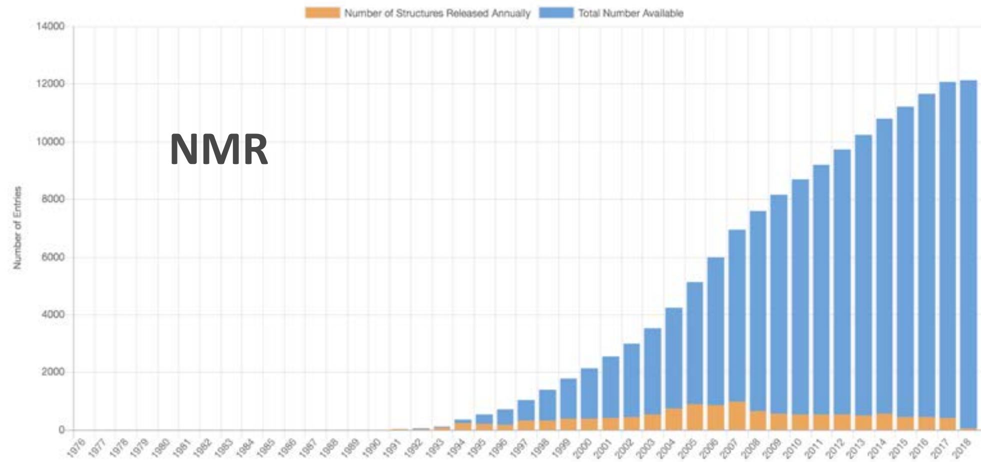
$$d = n\lambda / 2\sin\Theta$$

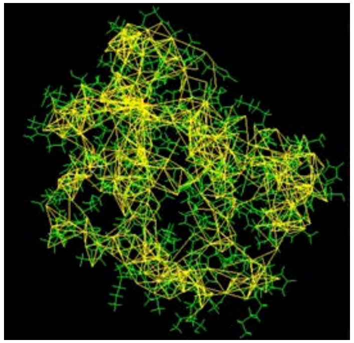
Picture from Ruppweb (http://www.ruppweb.org/Xray/Phasing/Phasingt.html)

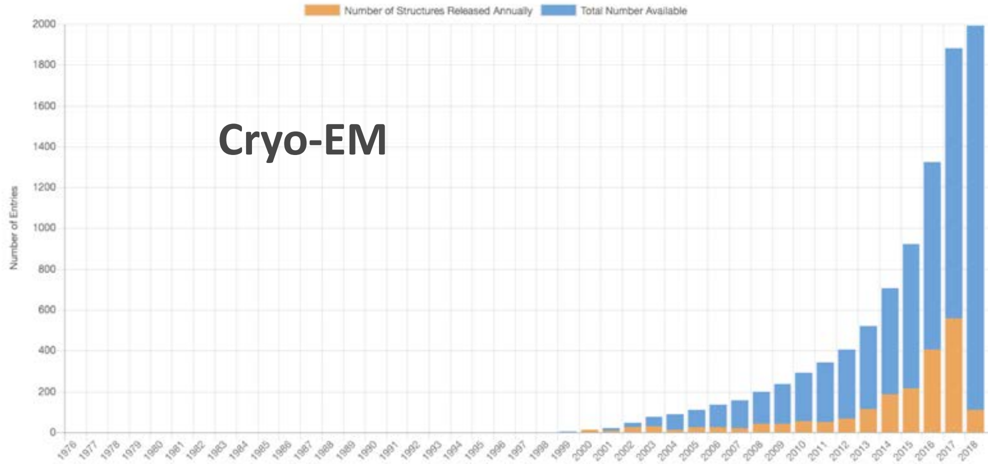
Macromolecular crystallography – Potential

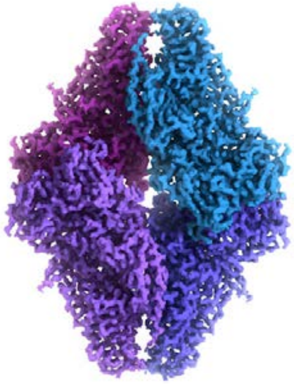


Macromolecular crystallography –Potential

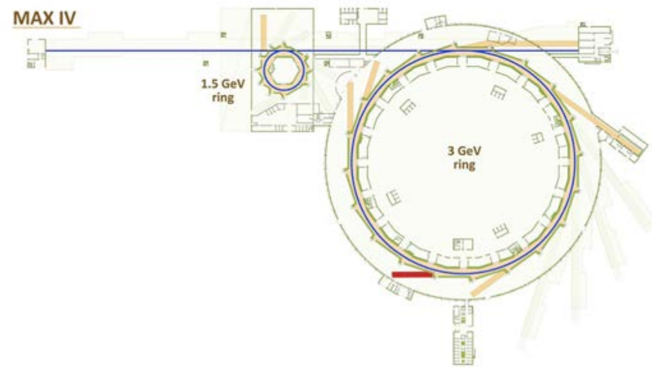








Macromolecular crystallography



MedMAX II

MedMAX I

NanoMAX
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coSAXS

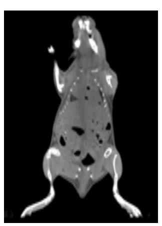
BioMAX MicroMAX

FemtoMAX
Balder

10^{-6} m

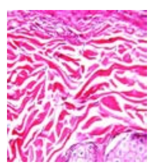
10^{-9} m

10^{-10} m

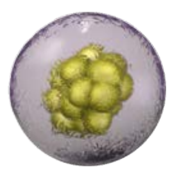


Animals

Organs



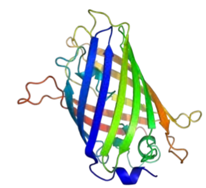
Tissues



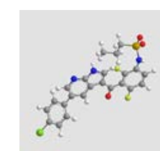
Cells

Micro-
structures

Molecular
complexes



Biomolecules



Atoms

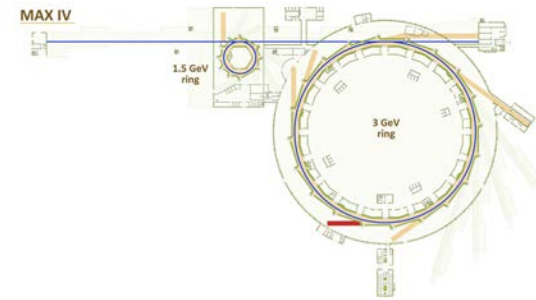
Disease
models

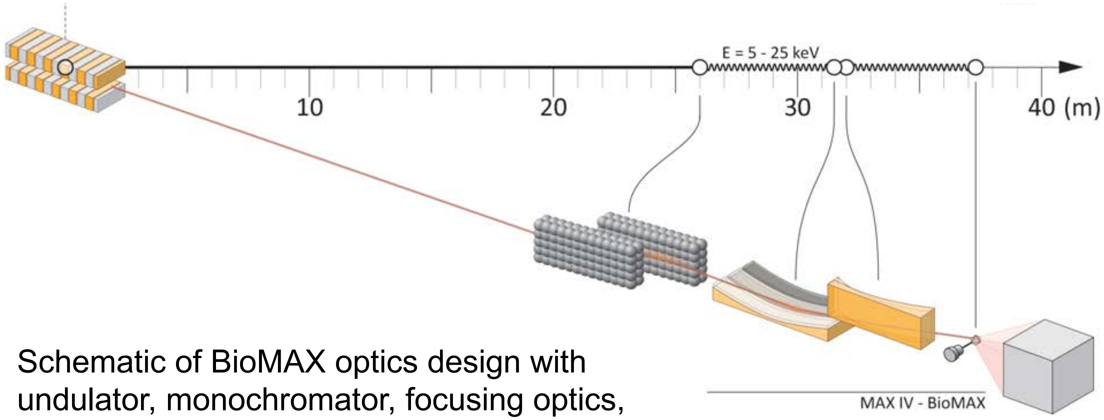
Histopathology

Cell Biology

Molecular Medicine/Chemical Biology

BioMAX Overview





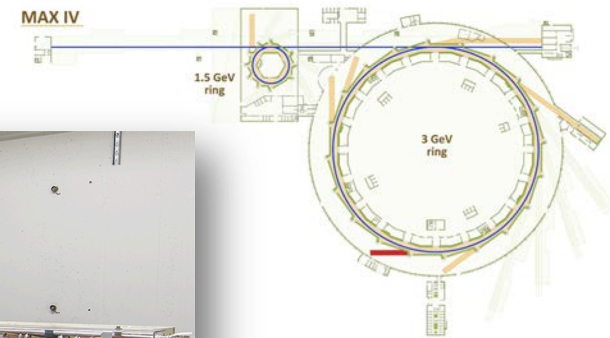
Schematic of BioMAX optics design with undulator, monochromator, focusing optics, sample and detector.

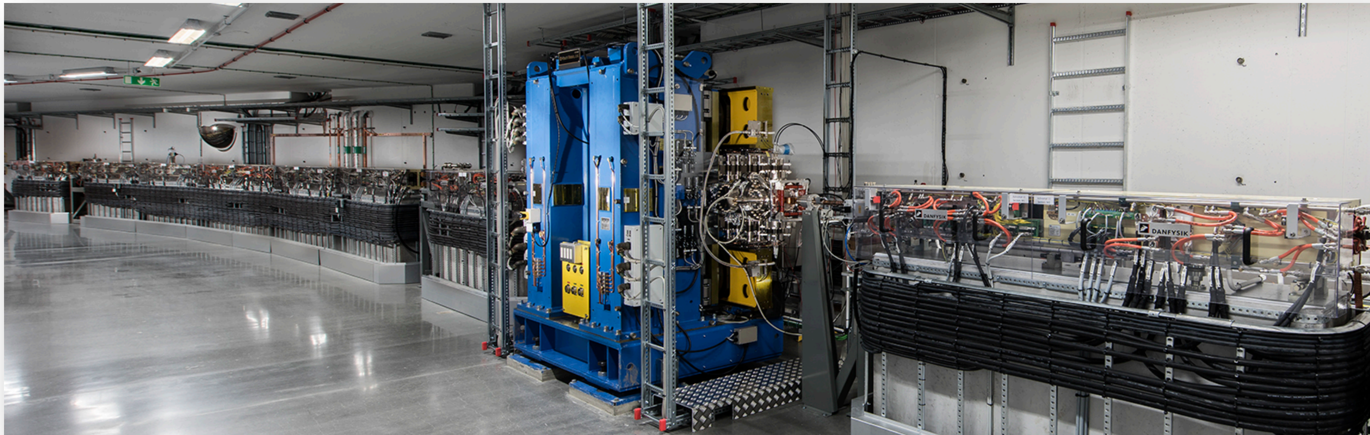
Beamline characteristics:

- ***Support all relevant techniques for MX***
- Beam characteristics:
  - Small focus (**20 x 5 µm²** hxv FWHM)
  - Low divergence (**0.1 x 0.1 mrad²**)
  - High flux (**2x 10^{13} phot/s x 0.1% bw**)
- MD3 Microdiffractometer
- Large energy range (5-25 keV)
- Short data collection times (2-30 ms /frame)
- High throughput environment

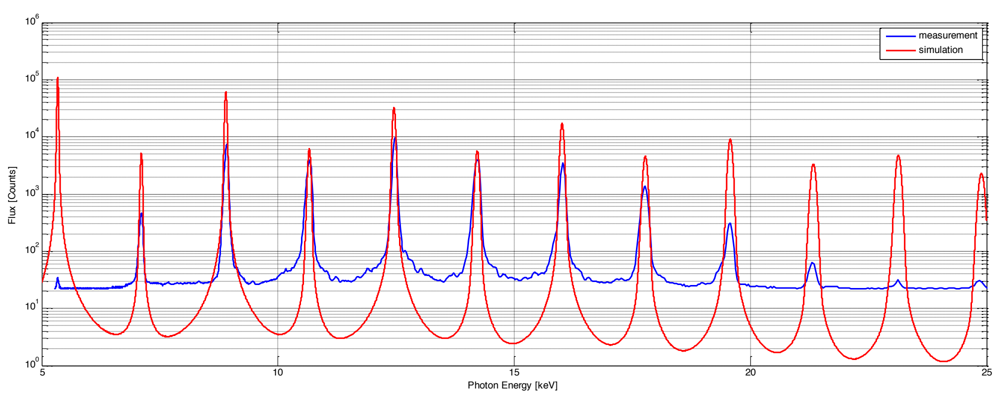
2017-2019: 71 proposals, 506 users, 5860 samples, 9495 datasets

BioMAX Undulator

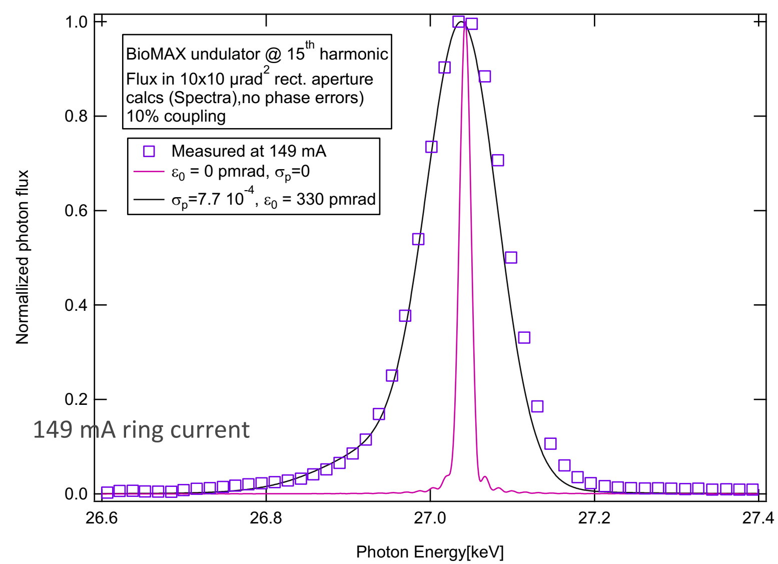




In-vacuum undulator



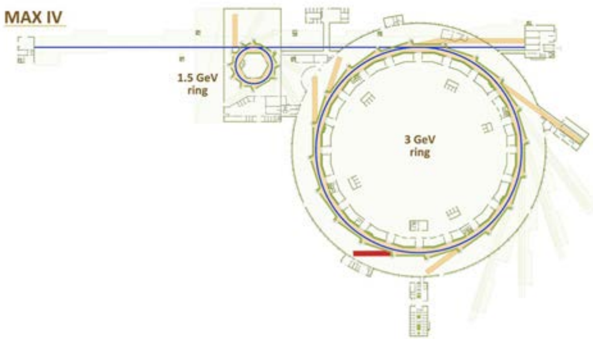
3 mA ring current, courtesy of H. Tarawneh



149 mA ring current

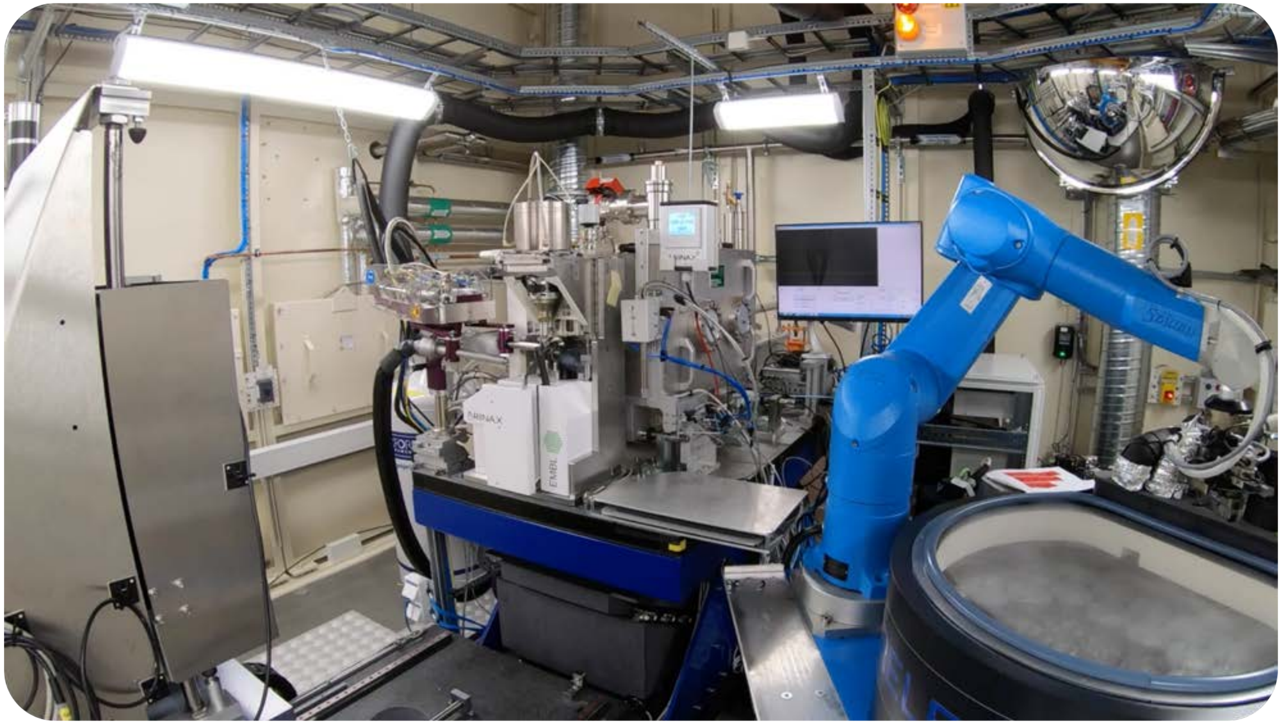
Data by T. Ursby and D.Olsson

BioMAX experimental station



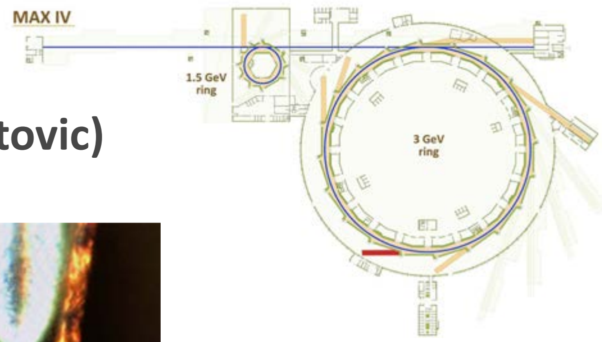
Experimental environment

- MD3 micro-diffractometer
- Eiger 16M hybrid pixel detector
- ISARA sample changer
- Operations center
- Sample preparation lab
- BioLab



BioMAX experimental station

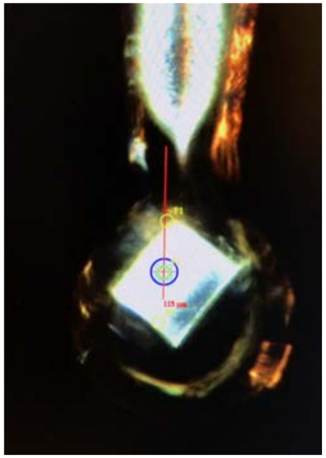
BioMAX Commissioning



Complete data collection within 4 sec., Cubic Insulin (R. Lizatovic)

Exp. Conditions:

- Exposure time: 10 msec
- Omega increment: 0.2 deg
- Omega range: 80 deg
- Images 400
- Total time dc.: 4 sec



20 deg/sec frame rotation

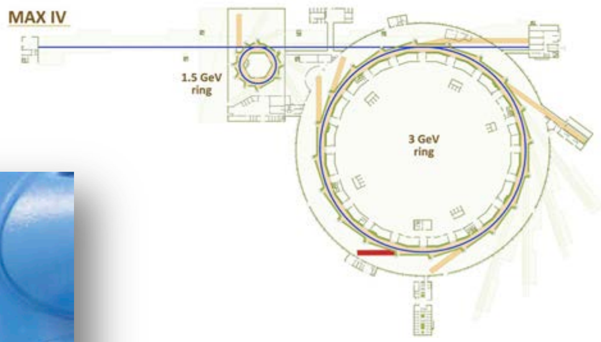
SUBSET OF INTENSITY DATA WITH SIGNAL/NOISE >= -3.0 AS FUNCTION OF RESOLUTION

RESOLUTION LIMIT	NUMBER OF REFLECTIONS OBSERVED	UNIQUE	POSSIBLE	COMPLETENESS OF DATA	R-FACTOR observed	R-FACTOR expected	COMPARED	I/SIGMA	R-meas	CC(1/2)	Anomal Corr	SigAno	Nano
4.00	6270	1300	1310	99.2%	2.9%	3.0%	6256	45.08	3.2%	99.9*	29*	1.060	566
2.83	11197	2365	2366	100.0%	3.1%	3.3%	11191	38.25	3.5%	99.9*	7	0.878	1102
2.32	14470	3037	3039	99.9%	4.7%	4.6%	14465	26.92	5.3%	99.8*	8	0.961	1443
2.01	17158	3613	3617	99.9%	6.8%	6.4%	17146	19.05	7.7%	99.5*	8	0.916	1717
1.79	18415	4058	4061	99.9%	12.4%	11.7%	18402	10.67	14.1%	98.5*	8	0.895	1942
1.64	20452	4485	4489	99.9%	24.2%	23.0%	20438	5.83	27.4%	95.3*	9	0.910	2152
1.52	22549	4937	4945	99.8%	52.3%	50.5%	22527	2.80	59.4%	81.2*	12*	0.910	2374
1.42	23919	5220	5224	99.9%	123.2%	131.0%	23901	1.05	139.6%	49.3*	5	0.738	2525
1.34	25184	5663	5673	99.8%	366.2%	432.1%	25130	0.20	416.7%	7.5	1	0.573	2709
total	159614	34678	34724	99.9%	5.8%	5.9%	159456	11.23	6.6%	99.9*	8	0.835	16530

NUMBER OF REFLECTIONS IN SELECTED SUBSET OF IMAGES	160866
NUMBER OF REJECTED MISFITS	1252
NUMBER OF SYSTEMATIC ABSENT REFLECTIONS	0
NUMBER OF ACCEPTED OBSERVATIONS	159614
NUMBER OF UNIQUE ACCEPTED REFLECTIONS	34678

Final table from CORRECT.LP

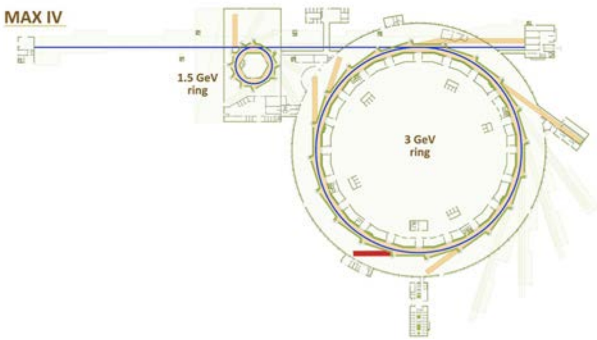
Hclab – Room temperature



HClab facility operational

First Si chip operation at BioMAX, (B. Vestergaard, UC)

X-ray detector



Eiger 16M hybrid pixel detector:

- Sensitive area: 311.2 × 327.8 mm^2
- 4150 × 4371 = 18’139’650 pixels
- Pixel size 75 x75 μm^2
- Scan speed:
  - 133 Hz (16M)
  - 750 (4M)

Challenges

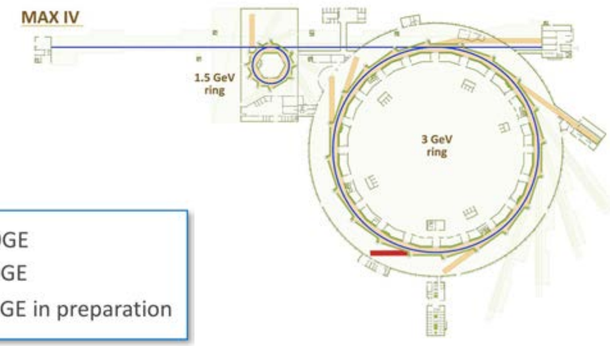
- HDF5/Nexus file format
- Data streaming for real time analysis
- Large data volumes
  - Av. dataset size 10-20 Gb (15 sec)
- Data storage & processing for users

Eiger 16M hybrid pixel detector

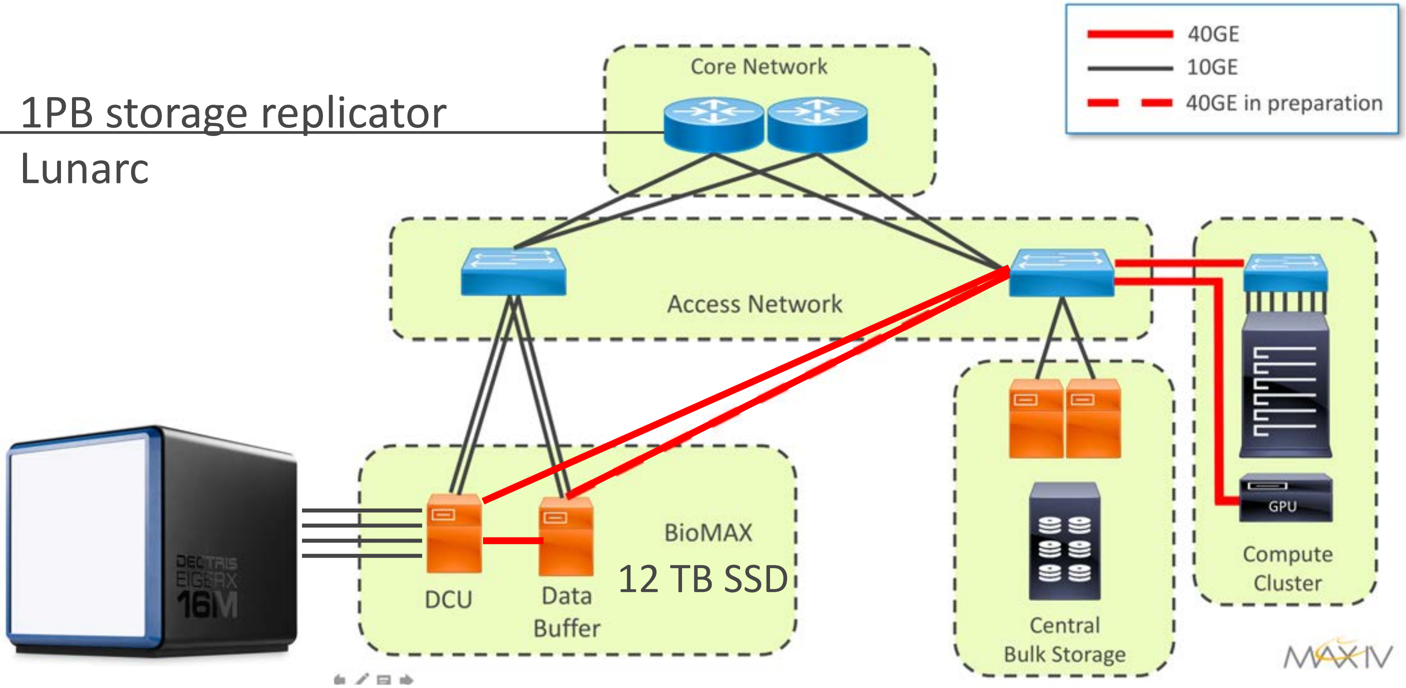
MAX IV

IT environment

Eiger 16M IT-environment



1PB storage replicator
Lunarc



Courtesy of Artur Barczyk

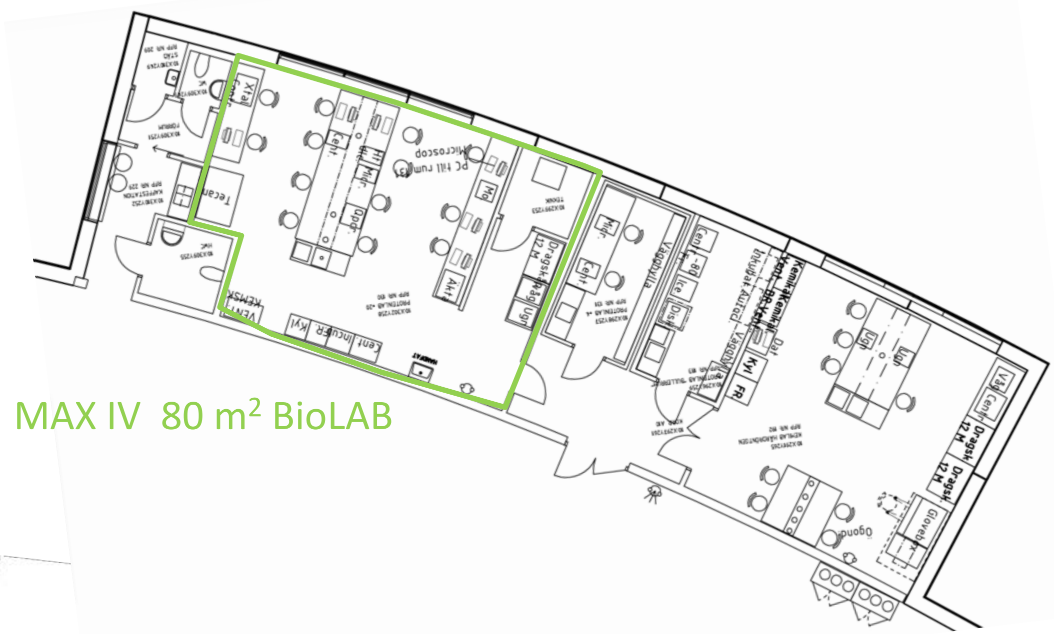
250 TB installed

544 CPU cores
+576 cores 2017

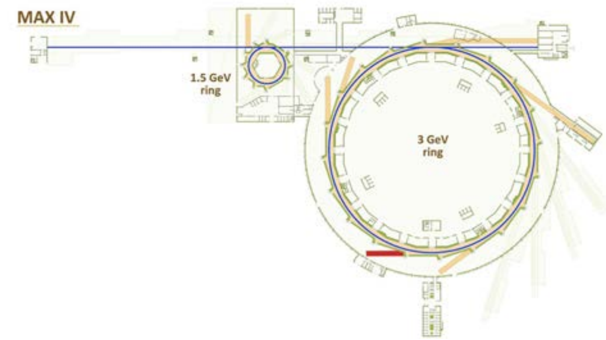
KITS

- Optimized data storage of all BioMAX data
- Automated data processing within minutes
- Alternative data retrieval via Globus (www.globus.org)

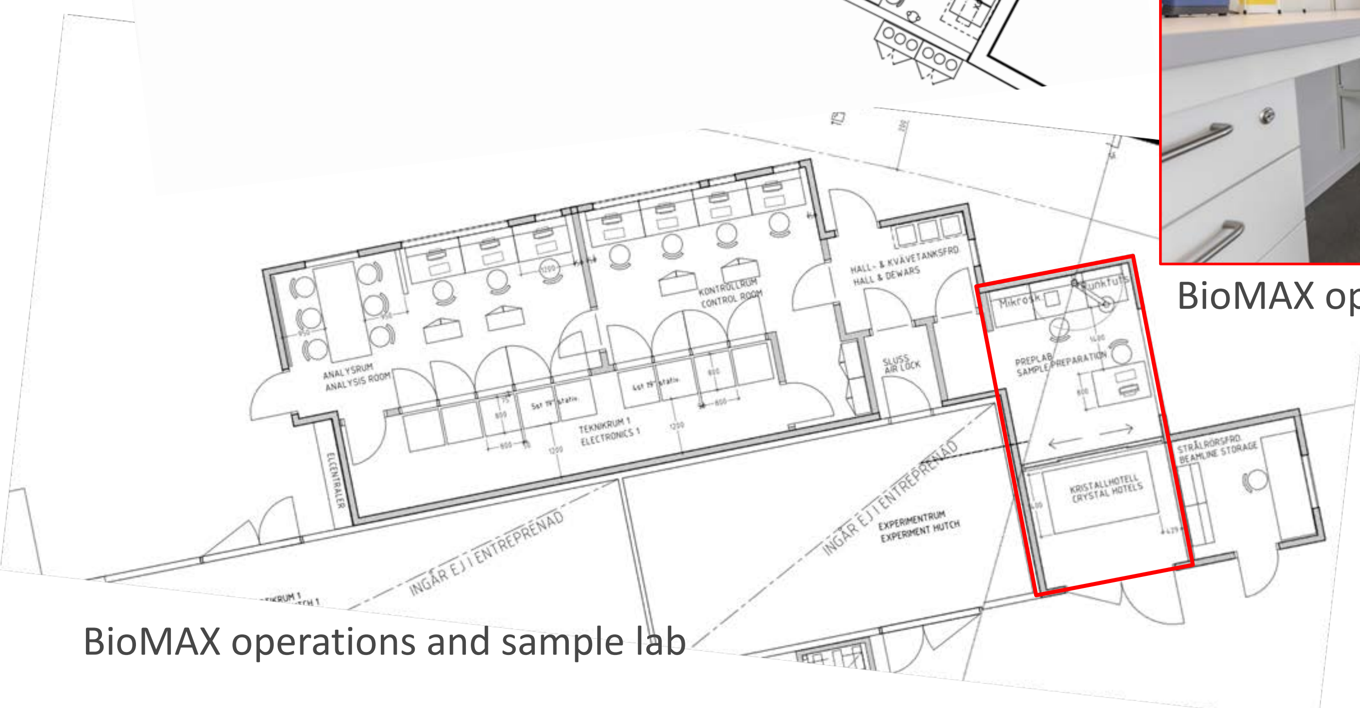
Lab facilities



MAX IV 80 m[2] BioLAB

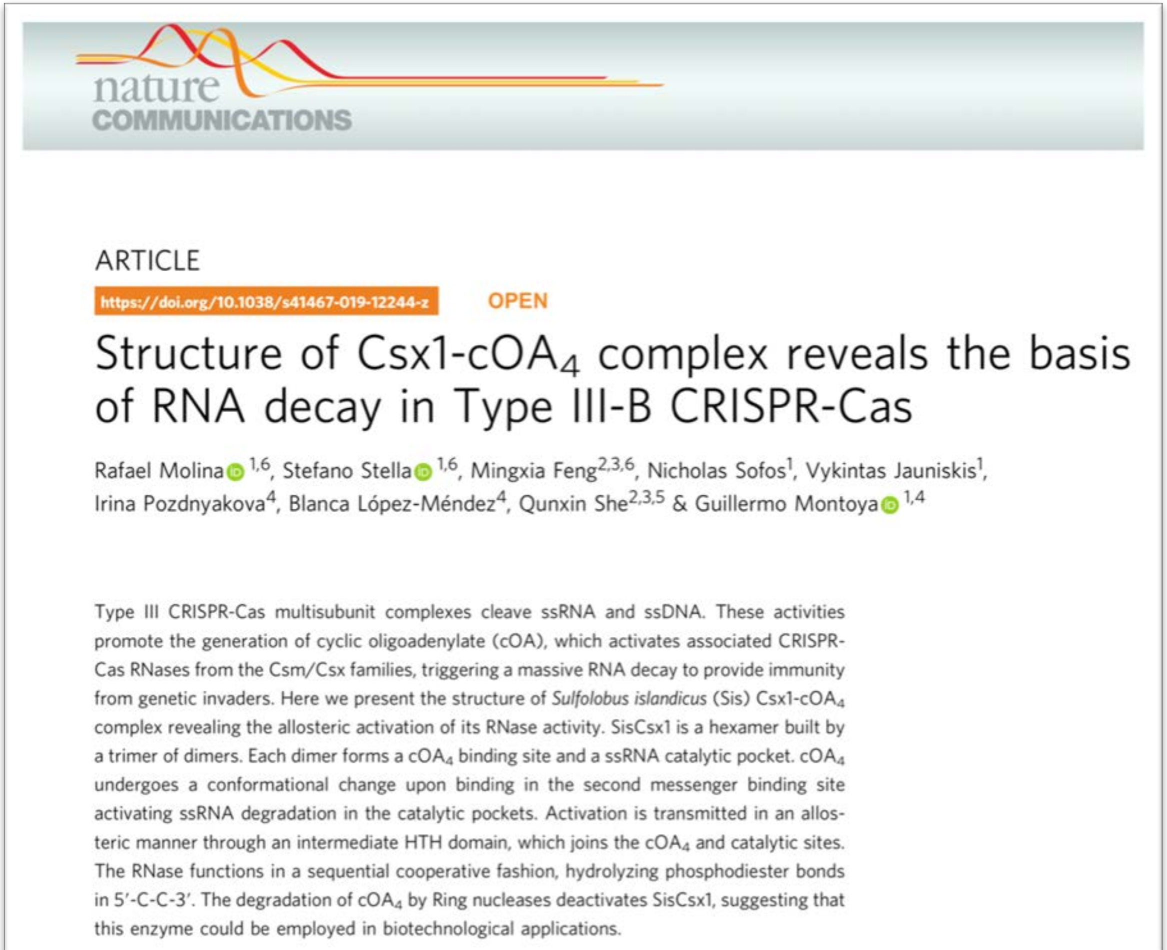


BioMAX operations and sample lab



BioMAX operations and sample lab

BioMAX Research



nature COMMUNICATIONS

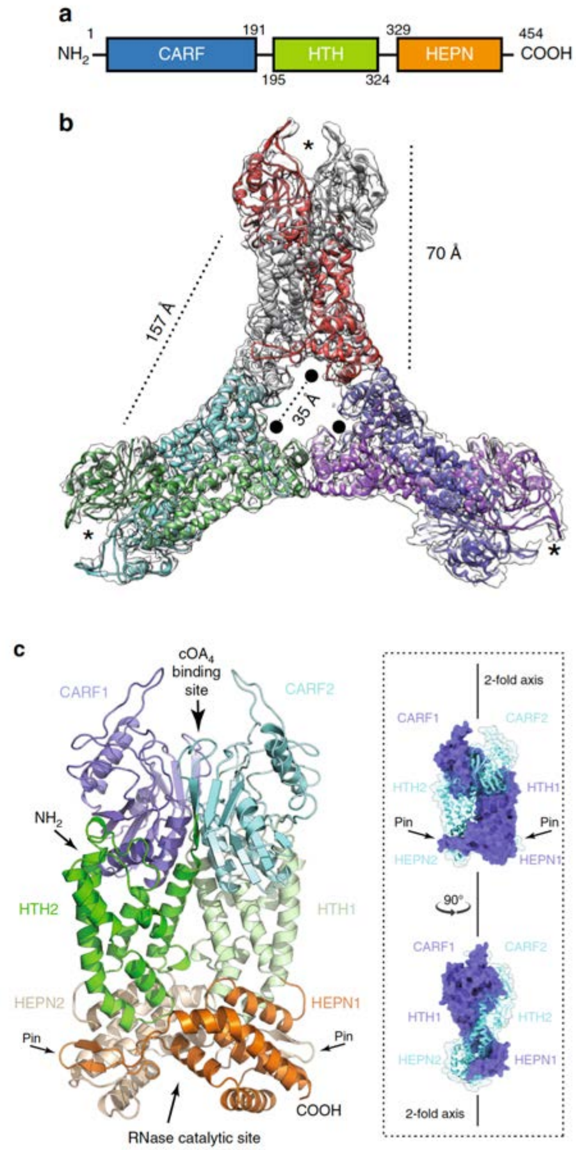
ARTICLE

https://doi.org/10.1038/s41467-019-12244-z OPEN

Structure of Csx1-cOA$_4$ complex reveals the basis of RNA decay in Type III-B CRISPR-Cas

Rafael Molina[1,6], Stefano Stella[1,6], Mingxia Feng[2,3,6], Nicholas Sofos[1], Vykintas Jauniskis[1], Irina Pozdnyakova[4], Blanca López-Méndez[4], Qunxin She[2,3,5] & Guillermo Montoya[1,4]

Type III CRISPR-Cas multisubunit complexes cleave ssRNA and ssDNA. These activities promote the generation of cyclic oligoadenylate (cOA), which activates associated CRISPR-Cas RNases from the Csm/Csx families, triggering a massive RNA decay to provide immunity from genetic invaders. Here we present the structure of *Sulfolobus islandicus* (Sis) Csx1-cOA$_4$ complex revealing the allosteric activation of its RNase activity. SisCsx1 is a hexamer built by a trimer of dimers. Each dimer forms a cOA$_4$ binding site and a ssRNA catalytic pocket. cOA$_4$ undergoes a conformational change upon binding in the second messenger binding site activating ssRNA degradation in the catalytic pockets. Activation is transmitted in an allosteric manner through an intermediate HTH domain, which joins the cOA$_4$ and catalytic sites. The RNase functions in a sequential cooperative fashion, hydrolyzing phosphodiester bonds in 5′-C-C-3′. The degradation of cOA$_4$ by Ring nucleases deactivates SisCsx1, suggesting that this enzyme could be employed in biotechnological applications.



BioMAX Research

SCIENCE ADVANCES | RESEARCH ARTICLE

CHEMISTRY

Multiplicity conversion based on intramolecular triplet-to-singlet energy transfer

A. Cravcenco[1], M. Hertzog[1], C. Ye[1], M. N. Iqbal[2], U. Mueller[3], L. Eriksson[2], K. Börjesson[1]*

The ability to convert between molecular spin states is of utmost importance in materials chemistry. Förster-type energy transfer is based on dipole-dipole interactions and can therefore theoretically be used to convert between molecular spin states. Here, a molecular dyad that is capable of transferring energy from an excited triplet state to an excited singlet state is presented. The rate of conversion between these states was shown to be 36 times faster than the rate of emission from the isolated triplet state. This dyad provides the first solid proof that Förster-type triplet-to-singlet energy transfer is possible, revealing a method to increase the rate of light extraction from excited triplet states.

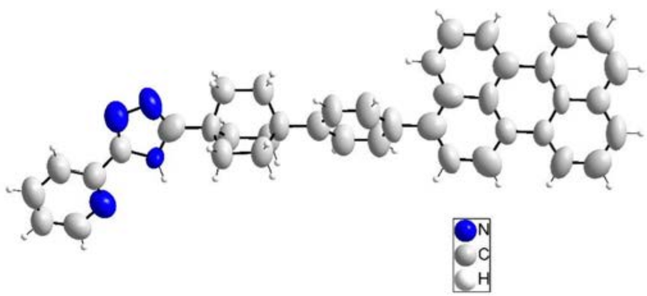


Fig. S7. Structure of the ligand (19), as solved by x-ray diffraction.

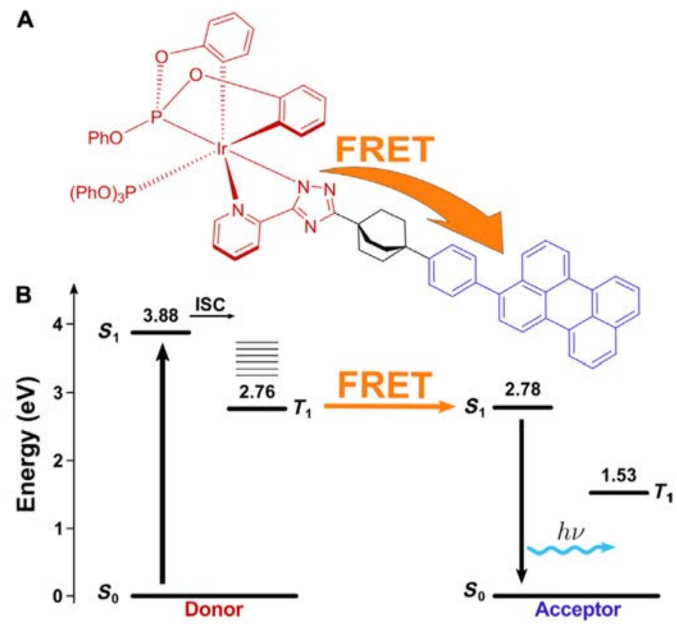


Fig. 1. Structure and energy levels of the dyad. (**A**) The DBA molecule used in this study. (**B**) Jabłoński diagram showing triplet-to-singlet energy transfer via dipole-dipole interactions, i.e., the Förster-type resonance energy transfer (FRET) mechanism.

Scientific results

BioMAX Research

Journal of
Medicinal
Chemistry

Article

Cite This: *J. Med. Chem.* 2018, 61, 5279–5291

pubs.acs.org/jmc

Enhancing Action of Positive Allosteric Modulators through the Design of Dimeric Compounds

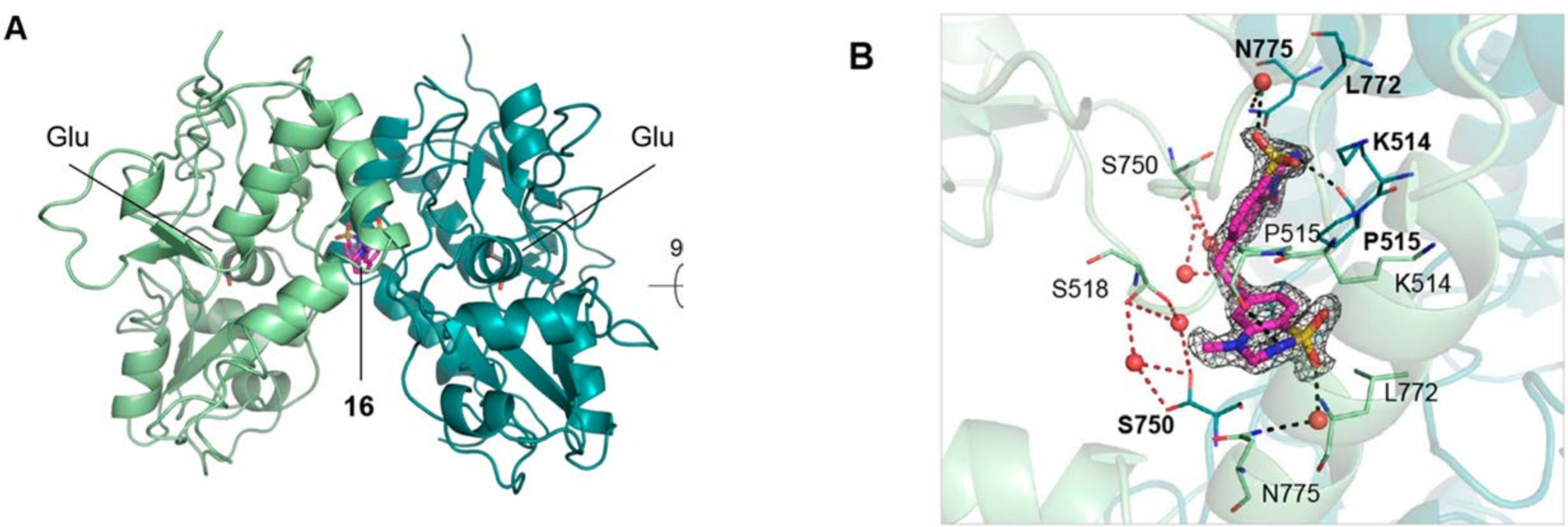
Thomas Drapier,[†] Pierre Geubelle,[†,‡] Charlotte Bouckaert,[§] Lise Nielsen,[∥] Saara Laulumaa,[∥] Eric Goffin,[†] Sébastien Dilly,[†] Pierre Francotte,[†] Julien Hanson,[*,†,‡] Lionel Pochet,[*,§] Jette Sandholm Kastrup,[*,∥] and Bernard Pirotte[*,†]

[†]Laboratory of Medicinal Chemistry, Center for Interdisciplinary Research on Medicines (CIRM), ULiège, Quartier Hôpital, Avenue Hippocrate, 15, B36, B-4000 Liège, Belgium

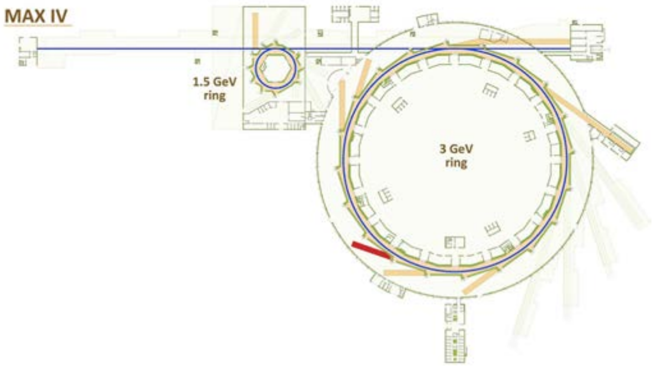
[‡]Laboratory of Molecular Pharmacology, GIGA-Molecular Biology of Diseases, ULiège, B34, Quartier Hôpital, Avenue de l'hôpital, 11, B-4000 Liège, Belgium

[§]NAmur MEdicine & Drug Innovation Center (NAMEDIC), NARILIS, UNamur, rue de Bruxelles 61, B-5000 Namur, Belgium

[∥]Biostructural Research, Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

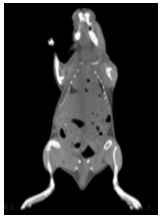


Life science at different length scales



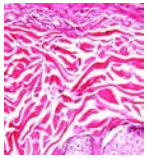
MedMAX II | MedMAX I | NanoMAX SoftiMAX | coSAXS | BioMAX | MicroMAX | FemtoMAX Balder

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



Animals

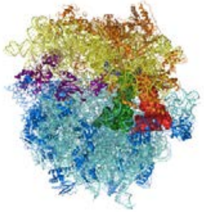
Organs



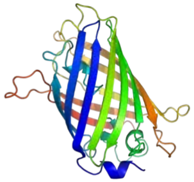
Tissues

Cells

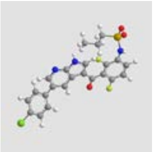
Micro-structures



Molecular complexes



Biomolecules



Atoms

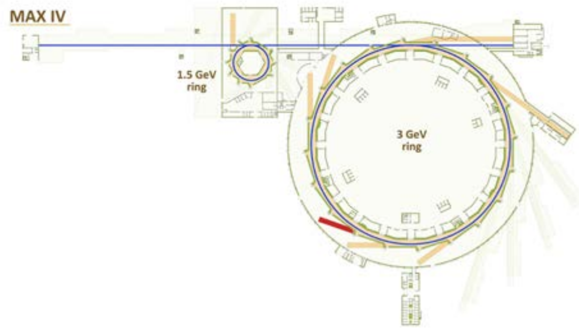
Disease models

Histopathology

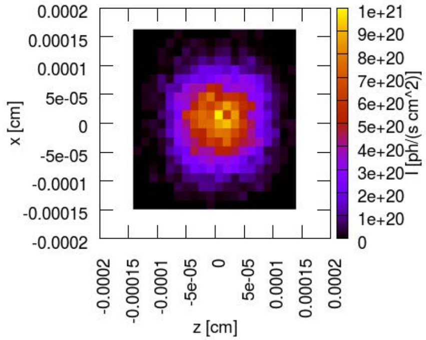
Cell Biology

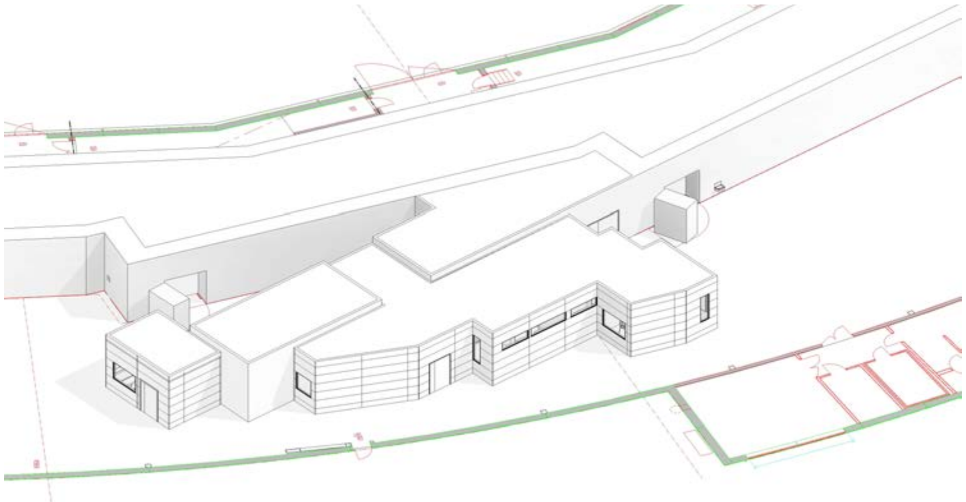
Molecular Medicine/Chemical Biology

MicroMAX



Thomas Ursby: email: thomas.ursby@maxiv.lu.se





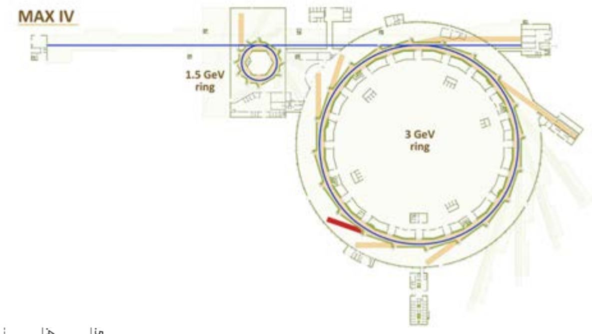
Plans for the second MX beamline

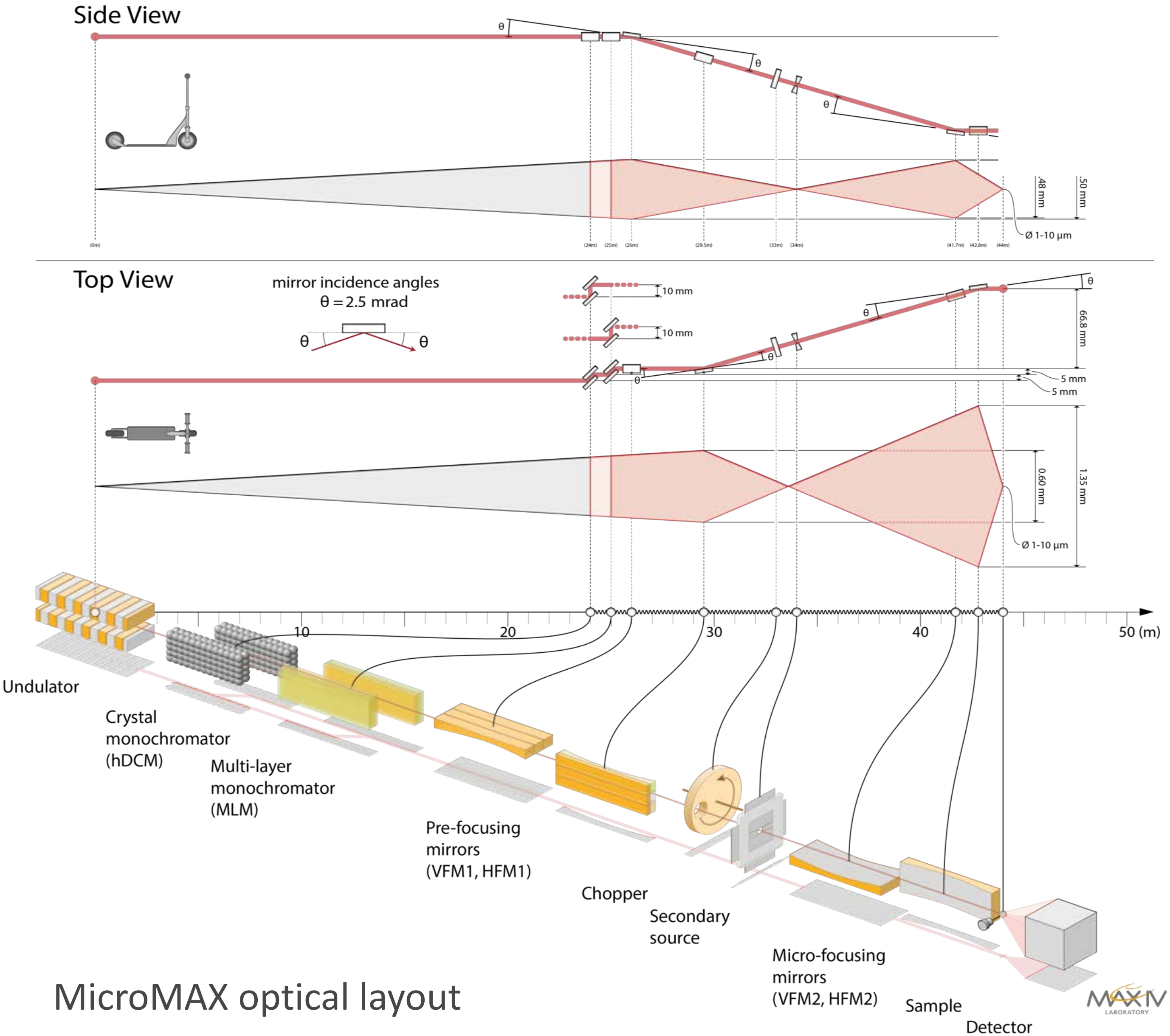
- Microfocus beamline
- **1 x 0.7** μm^2 beam at sample
- Photon flux $\mathbf{10^{13}}$ **-** $\mathbf{10^{15}}$phot/sec
- Traditional setup (goniometry, sample environment)
- Exploratory setup (serial crystallography, fixed target single shot)
- Optimal source for most demanding projects (large complexes, membrane proteins)

Status: funded by Novo Nordisk Foundation

MAX IV

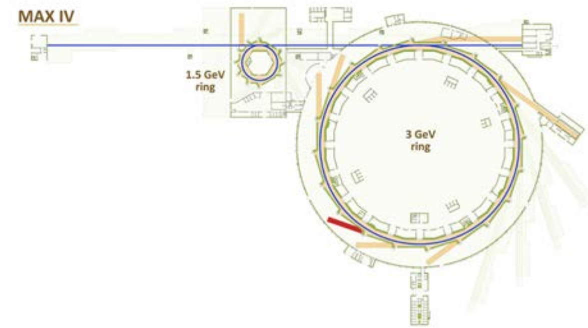
MicroMAX

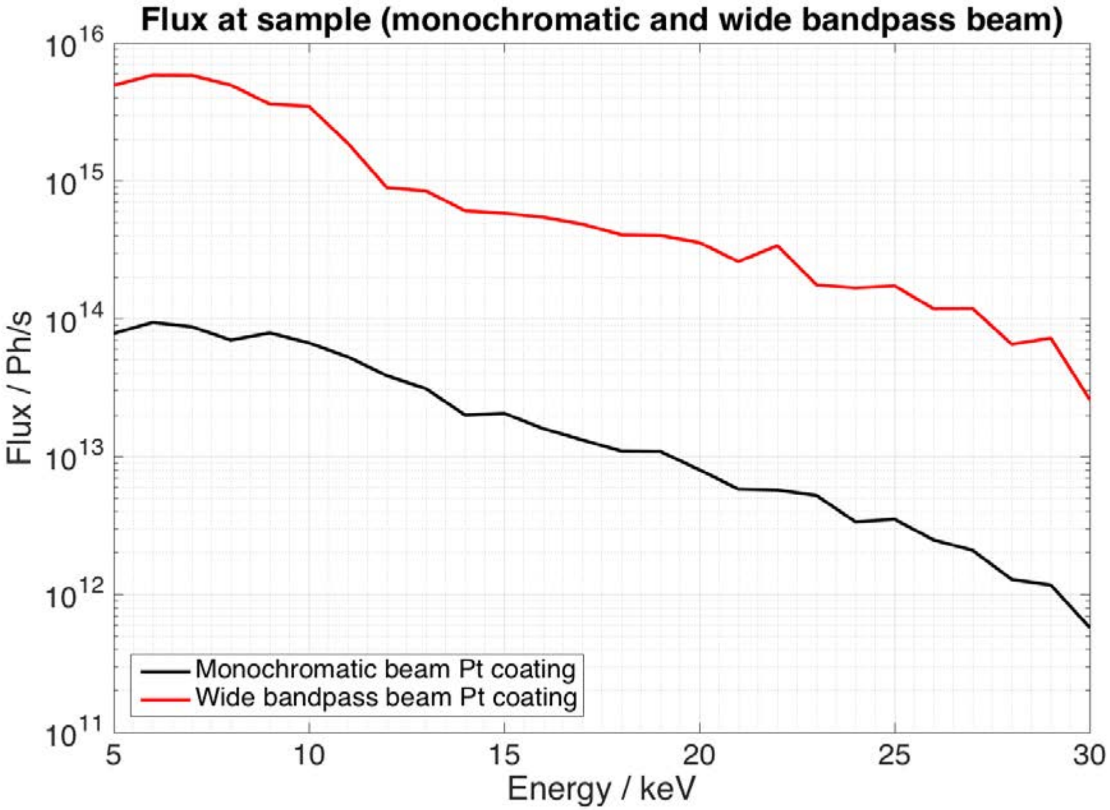


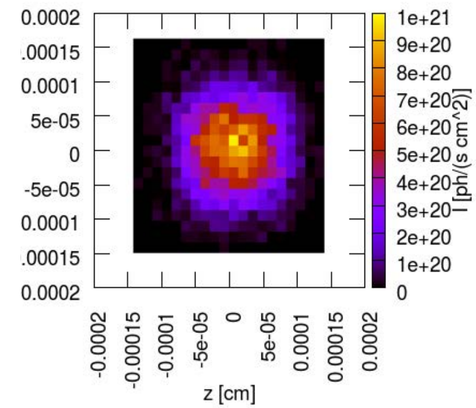


MicroMAX optical layout

MicroMAX

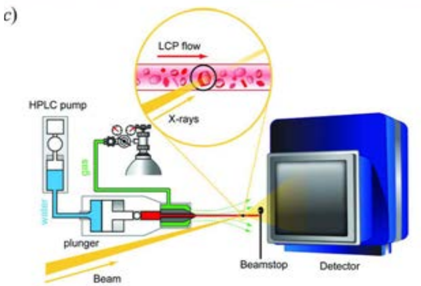


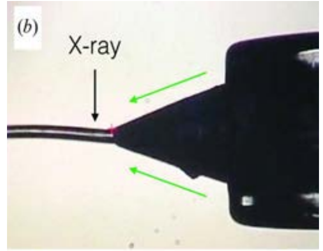


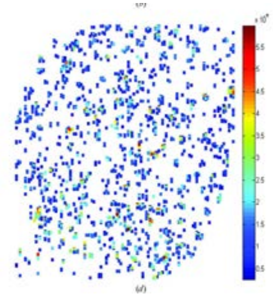


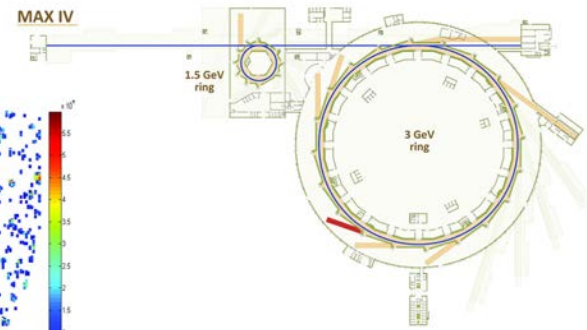
Status: Preparation of funding application

MicroMAX

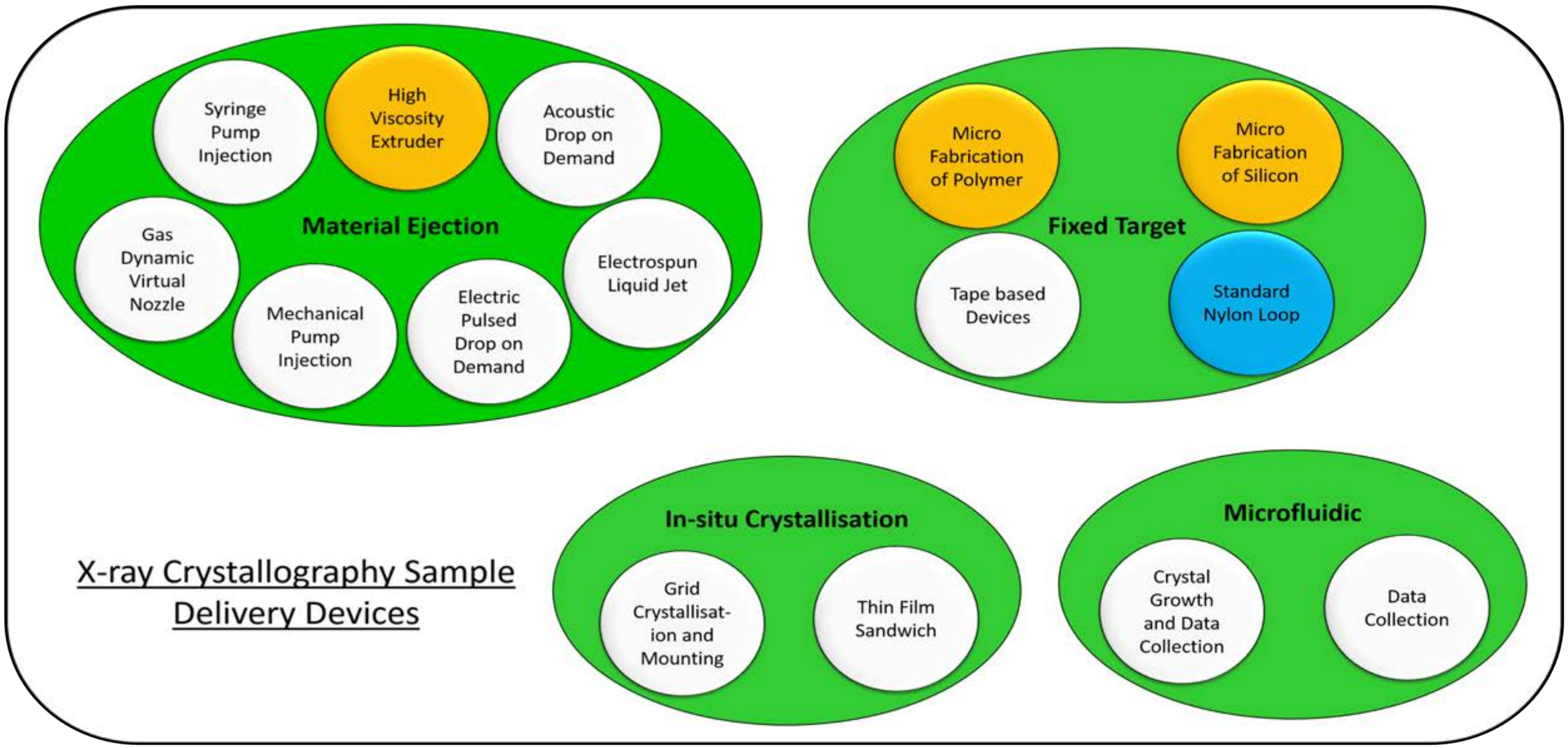








IUCrJ **Nogy et al., Gati *et al.***

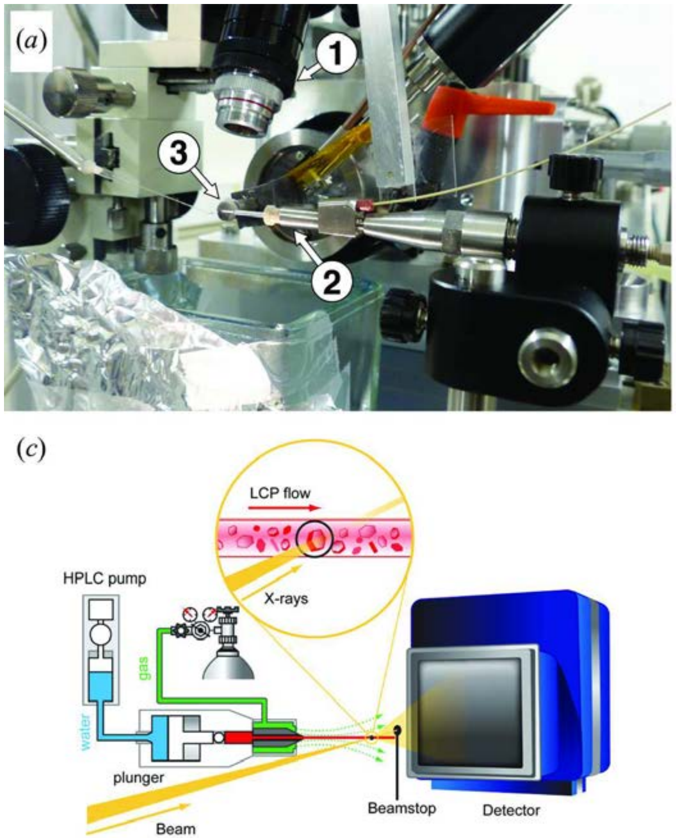


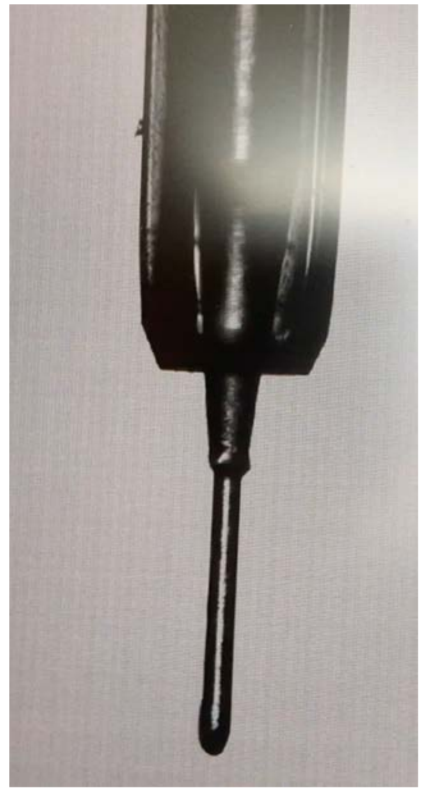
Novel sample delivery for micro-crystallography

HVE-Injector project

Collaboration with MPI-Heidelberg

The experimental setup at the ID13 microfocus beamline. (a) (1) Microscope focused on the jet. (2) LCP injector with (3) nozzle close to the beamstop. (b) A view of the LCP nozzle as seen through the ...





HVE extruder design for BioMAX by courtesy of Bruce Doak, MPI-Heidelberg

- Integration into BioMAX
- Future user facility for BioMAX users

IUCrJ

Nogly *et al.*

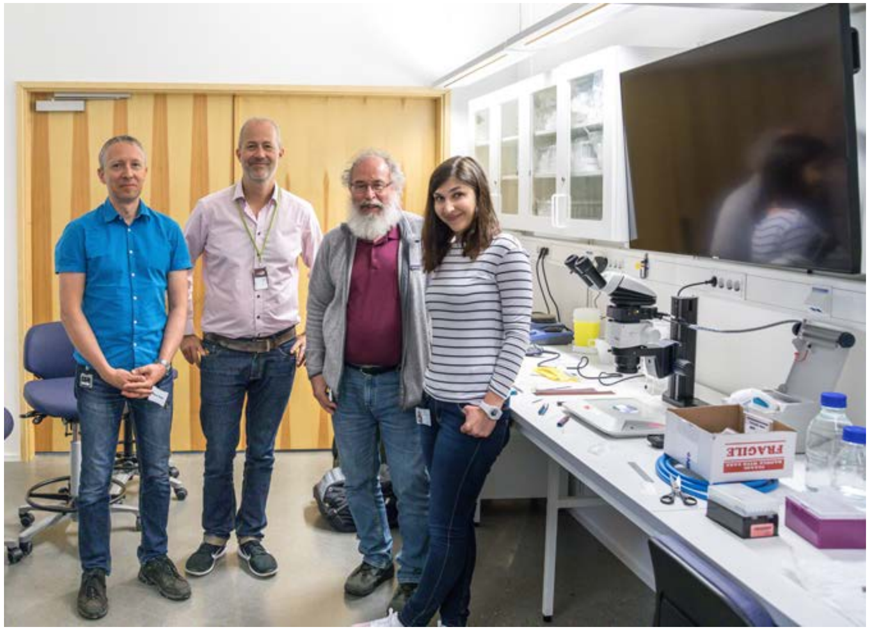
Volume 2 | **Part 2** | March 2015 | Pages 168–176 | 10.1107/S2052252514026487

MAX IV

1. HVE-Injector experiment

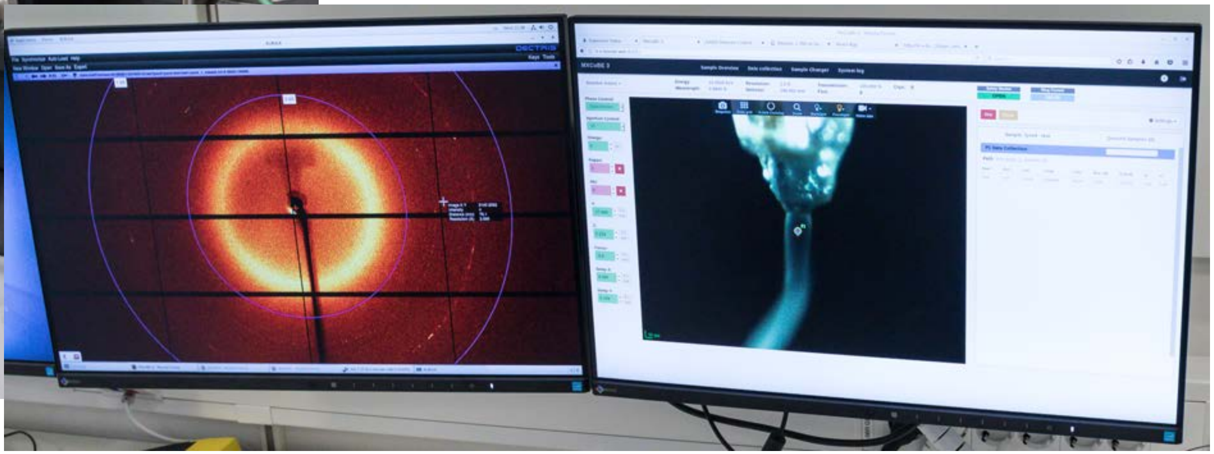
A. Shilova, Jie Nan & Uwe Mueller
Robert Shoeman & Marco Kloos

May 2018



HVE experimental team (MPI-Heidelberg, MAX IV)

Extruder mounted at MD3



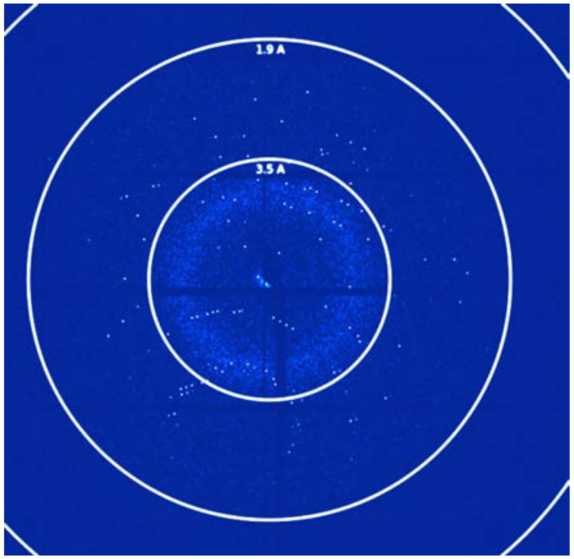
Data and extrusion viewer during experiment

MAX IV

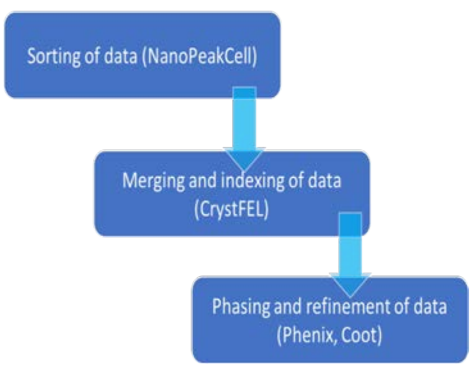
1. HVE-Injector experiment

A. Shilova

HEW Lysozyme



Diffraction image



Parameters	Lysozyme 10 µm
Wavelength, Å	0.98
Beam size, μm^2	20*5
Beam flux, photons/sec	$1*10^{13}$
Space group	$P\ 4_3 2_1 2$
Unit cell, Å	a=b=79.2, c=38.36, α=β=γ=90°
Exposure per crystal, ms	2.8
No. collected frames	122000
Average hit rate (NanoPeakCell), %	22.3
No. of indexed patterns (CrystFEL)	19511
Indexing rate (CrystFEL), %	73
No. of total/unique reflections	15774/8668
Resolution range, Å	56-1.9
Completeness, %	100
SNR (I/σ(I)) overall	6.4
B factor from Wilson Plot. $Å^2$	41
Rsplit, %	8.53 (50)
CC*	0.99 (0.90)
Rwork/Rfree, %	18/20

MAX IV

2. HVE experiment

4.-7. June 2018

A. Shilova, J. Nan & U. Mueller
Bränden & Neutze group

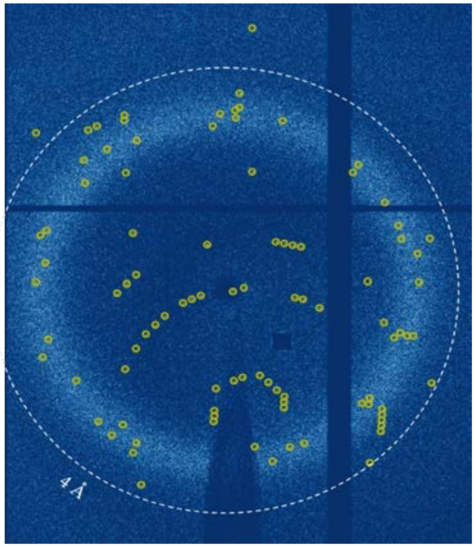
Bränden, Neutze team at BioMAX

MPI HVE injector

ASU – LCP injector

- 3 proteins injected
- 10 TB+ of data
- Data processing on-going

A. Shilova



Cytochrome c oxidase

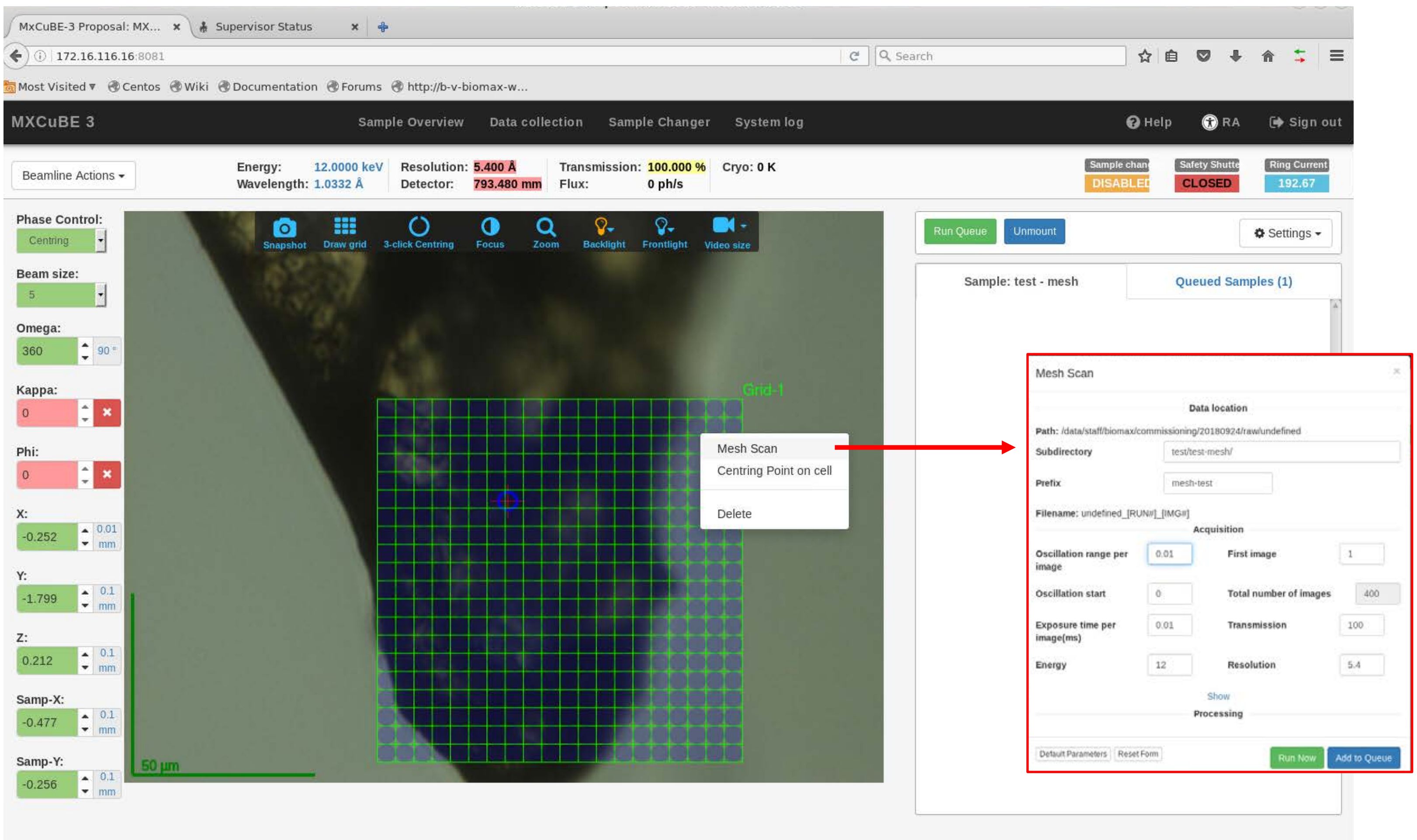
Parameters	BCO
Wavelength, Å	0.98
Beam size,μm^2	20*5
Beam flux, photons/sec	$1*10^{13}$
Space group	C2
Unit cell, Å	a=145.17 b=100.15, c=96.64,α=γ=90º, β=126.64
Exposure per crystal, ms	2.8
No. collected frames	253766
Average hit rate (NanoPeakCell), %	3.5
No. of indexed patterns (CrystFEL)	6513
Indexing rate (CrystFEL), %	68
No. of total/unique reflections	27514/18454
Resolution range, Å	75.94-3.5
Completeness, %	100
SNR (I/σ(I)) overall	2.7
B factor from Wilson Plot. $Å^2$	68
Rsplit, %	34.02 (50)
CC*	0.90 (0.88)
Rwork/Rfree, %	32/36

Experiment was performed with user groups from Gothenburg University (Richard Neutze group and Gisela Branden)

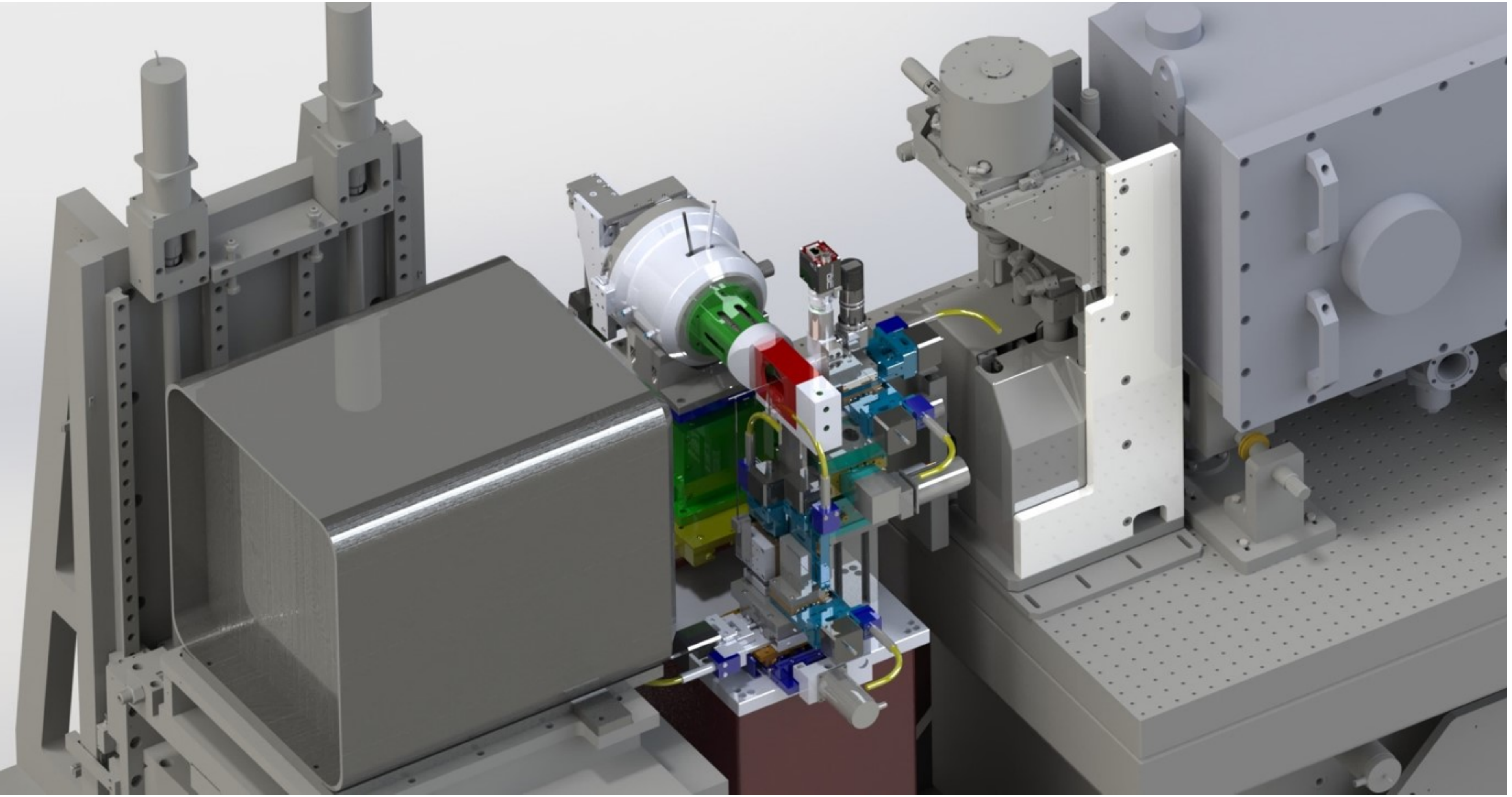
MAX IV

Raster-scan using MXCuBE3

J. Nan & M. Eguiraun
D. De Sanctis, M. Oskarson



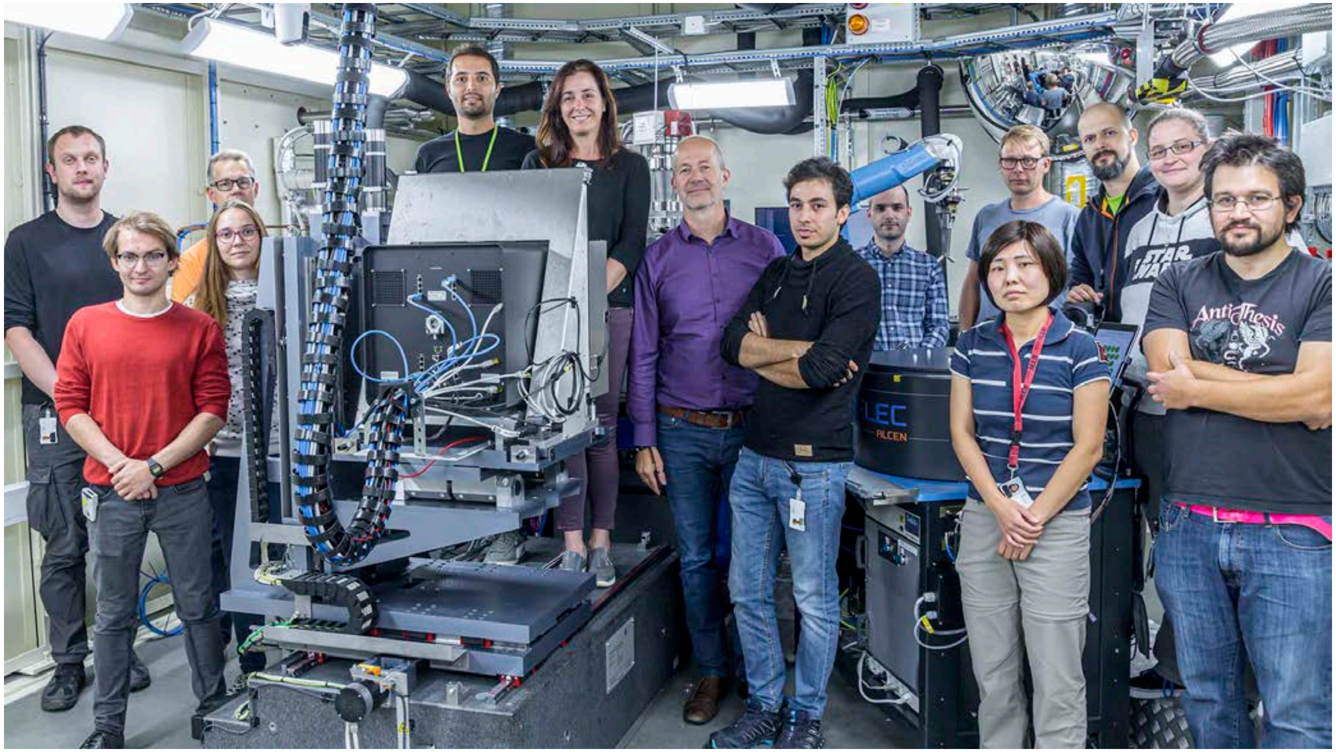
Fixed target scanning station: Roadrunner 3



Project in collaboration with
Alke Meents CFEL/DESY

Acknowledgement

The MX group



From left to right:

- Oskar Aurelius
- Vladimir Talibov
- Laila Benz
- Thomas Ursby
- Gustavo Lima
- Ana Gonzalez
- Uwe Mueller
- Vahid Haghighat
- Mikel Eguiraun (KITS)
- Jie Nan
- Johan Unge
- Mirko Milas
- Monika Bjelcic
- Elmir Jagudin

- All BioMAX users

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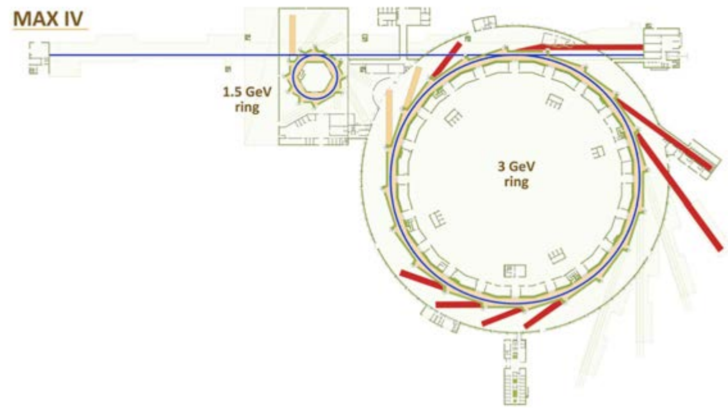
Swedish University of Agricultural Sciences
Umeå University
University of Gothenburg
Uppsala University

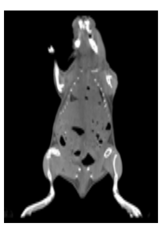
MAX IV

Life science at different length scales



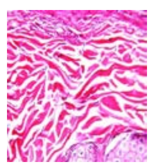
MedMAX II | MedMAX I | NanoMAX SoftiMAX | coSAXS | BioMAX | MicroMAX | FemtoMAX Balder

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

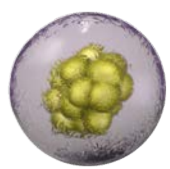


Animals

Organs

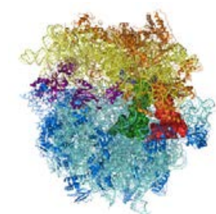


Tissues

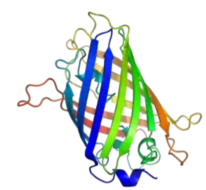


Cells

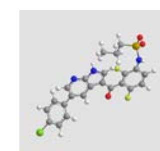
Micro-structures



Molecular complexes



Biomolecules



Atoms

Disease models

Histopathology

Cell Biology

Molecular Medicine/Chemical Biology