WE WILL LIVE ON THIS PLANET AT LEAST FOR THE NEXT 10 000 YEARS.

This statement leads to the motivation of my talk and will give rise to a GNEUS project

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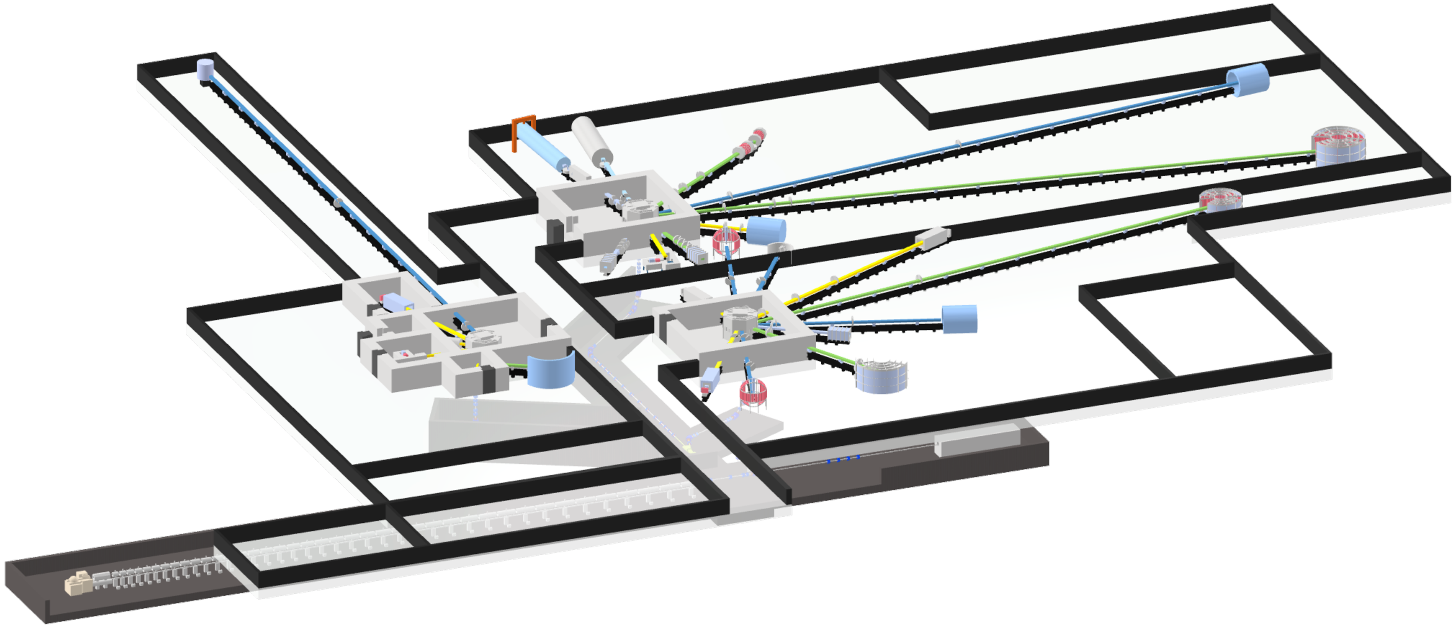
HIGH BRILLIANCE SOURCE
JÜLICH Forschungszentrum

WE HAVE TIME.

- There is no need to panic.
- We will have time to investigate the machinery of live (and other interesting phenomena) in great depths.

WE WILL BUILD A DEDICATED INSTRUMENT FOR MACROMOLECULAR CRYSTALLOGRAPHY ON A HICANS NEUTRON SOURCE.

- Because this is the most cost efficient way to produce neutrons without adding too much entropy caused by the daughter nuclei of fission or the radioactivity of spallation.

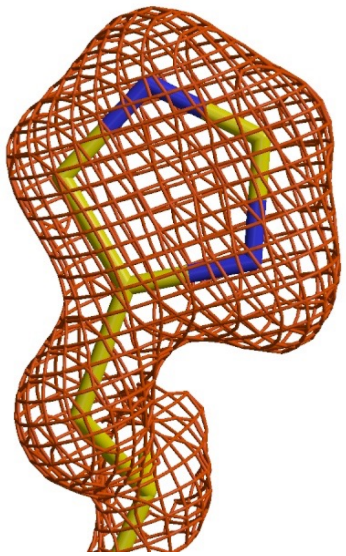


SCIENCE CASE AND CONCEPTS OF A MACROMOLECULAR DIFFRACTOMETER FOR THE HIGH BRILLIANCE NEUTRON SOURCE (HBS)

Tobias E. Schrader, JCNS

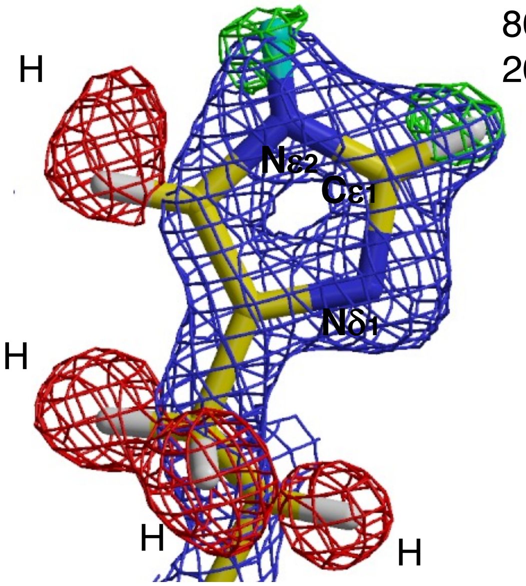
X-ray data versus neutron data on the same protein:

X-ray d_{min}= 1.5Å:



2Fo-Fc map; +1.5σ

neutrons d_{min}= 1.5Å:



2Fo-Fc map; +1.5σ

Fo-Fc omit-map; -3.0σ

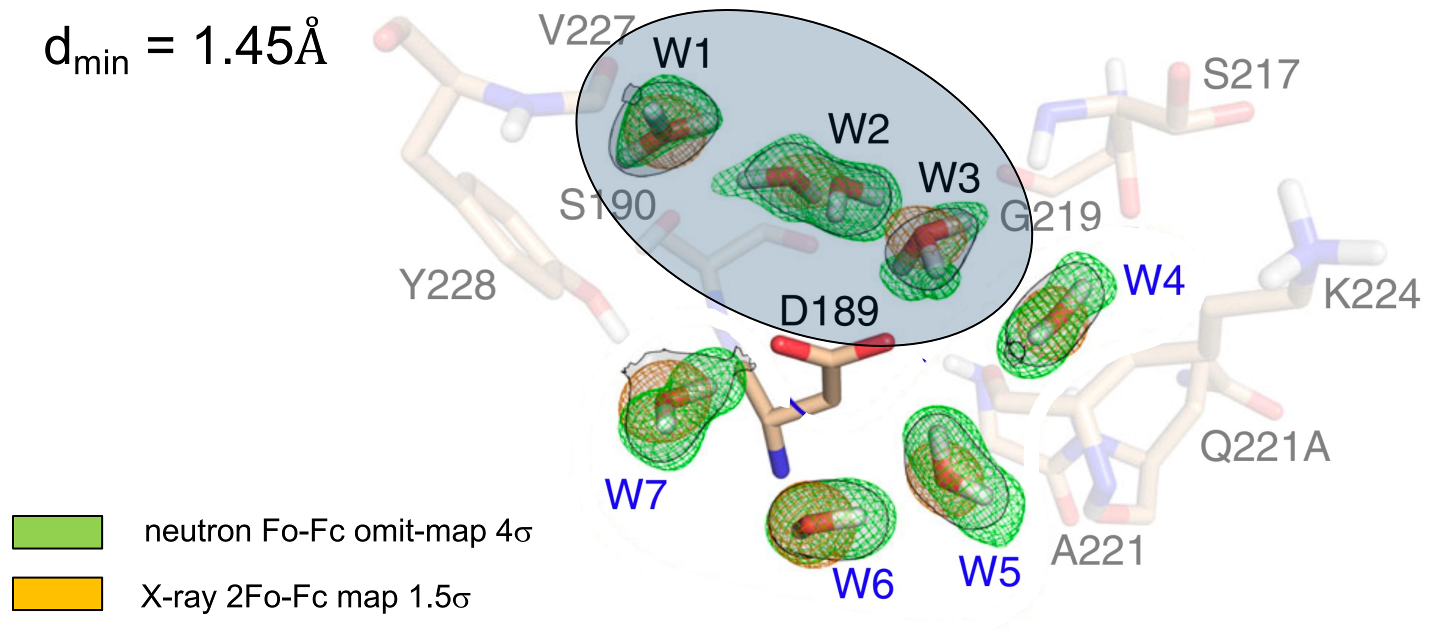
Fo-Fc omit-map; +3.0σ

Niimura N, Chatake T, Ostermann A, Kurihara K, Tanaka T. (2003) Z. Kristallogr. 218:96

Slides: Courtesy of Andreas Ostermann

Water structure in binding pocket of the unliganded form of trypsin:

d_{min} = 1.45Å



➡ the ligand-free binding pocket is occupied by water molecules characterized by a paucity of H-bonds and high mobility

Group of Prof. G. Klebe (Univ. Marburg)

Schiebel J. et al., Nat. Commun. (2018), 9:3559

Slides: Courtesy of Andreas Ostermann

Water structure in binding pocket of the unliganded form of trypsin:

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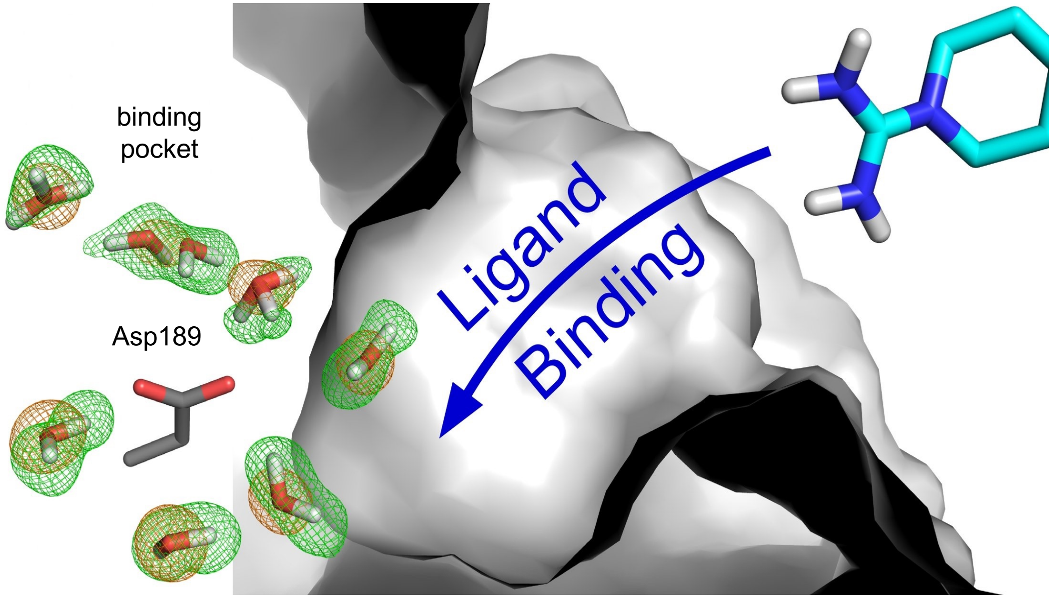


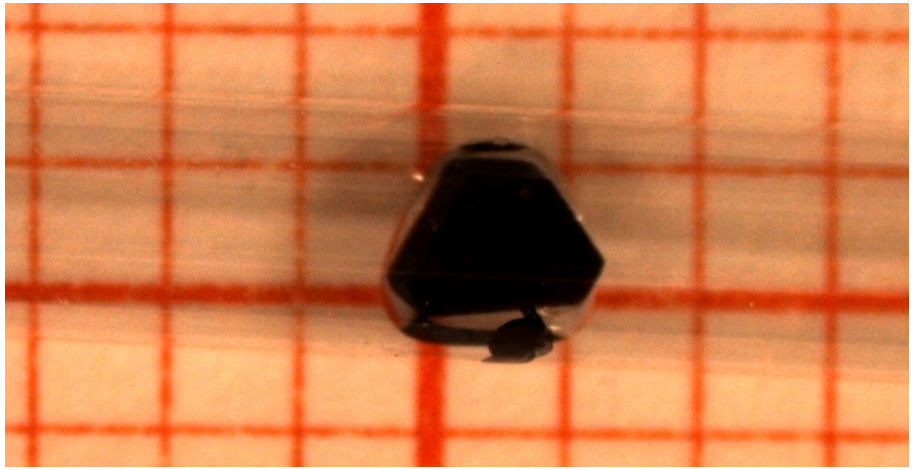
➡ It is likely that this phenomenon can be a key factor in fuelling ligand binding via water displacement

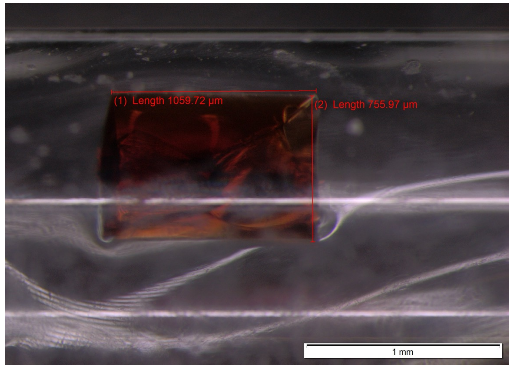
Group of Prof. G. Klebe (Univ. Marburg)

Schiebel J. et al., Nat. Commun. (2018), 9:3559

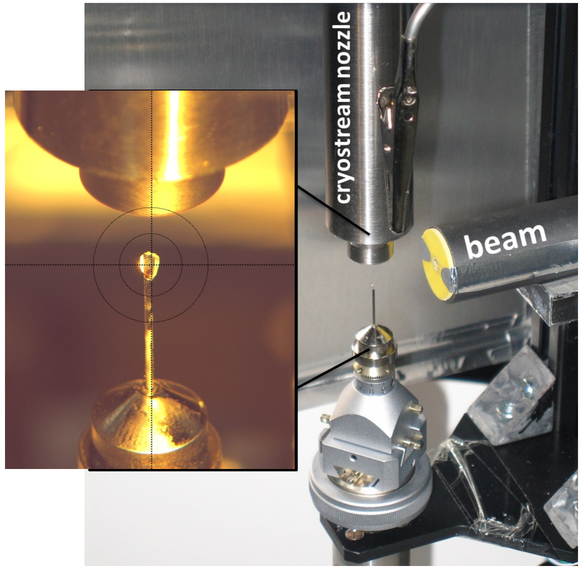
Slides: Courtesy of Andreas Ostermann

PROTEIN CRYSTAL NECESSARY FOR THIS METHOD





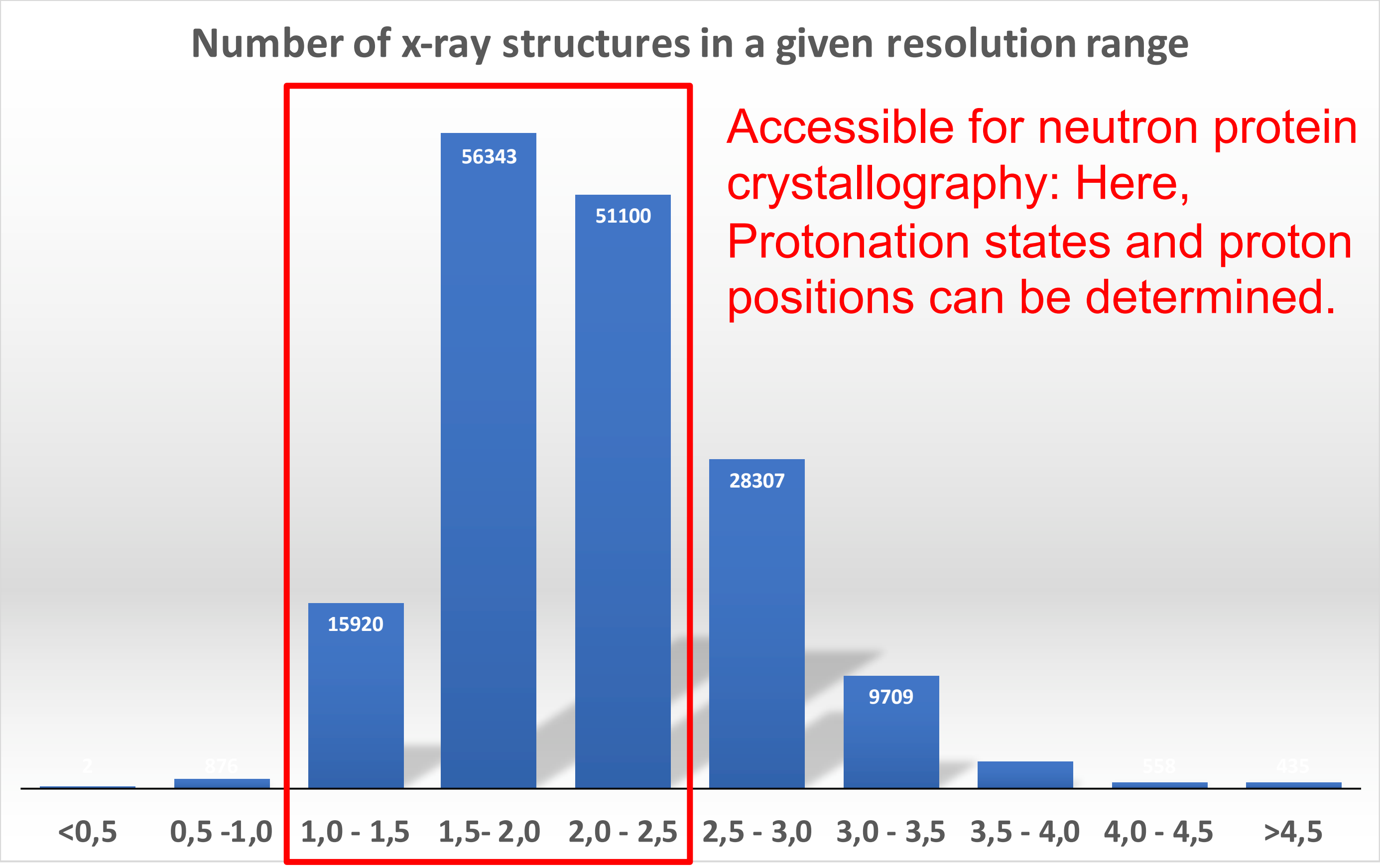
Room temperature



Cryostream at 100 K

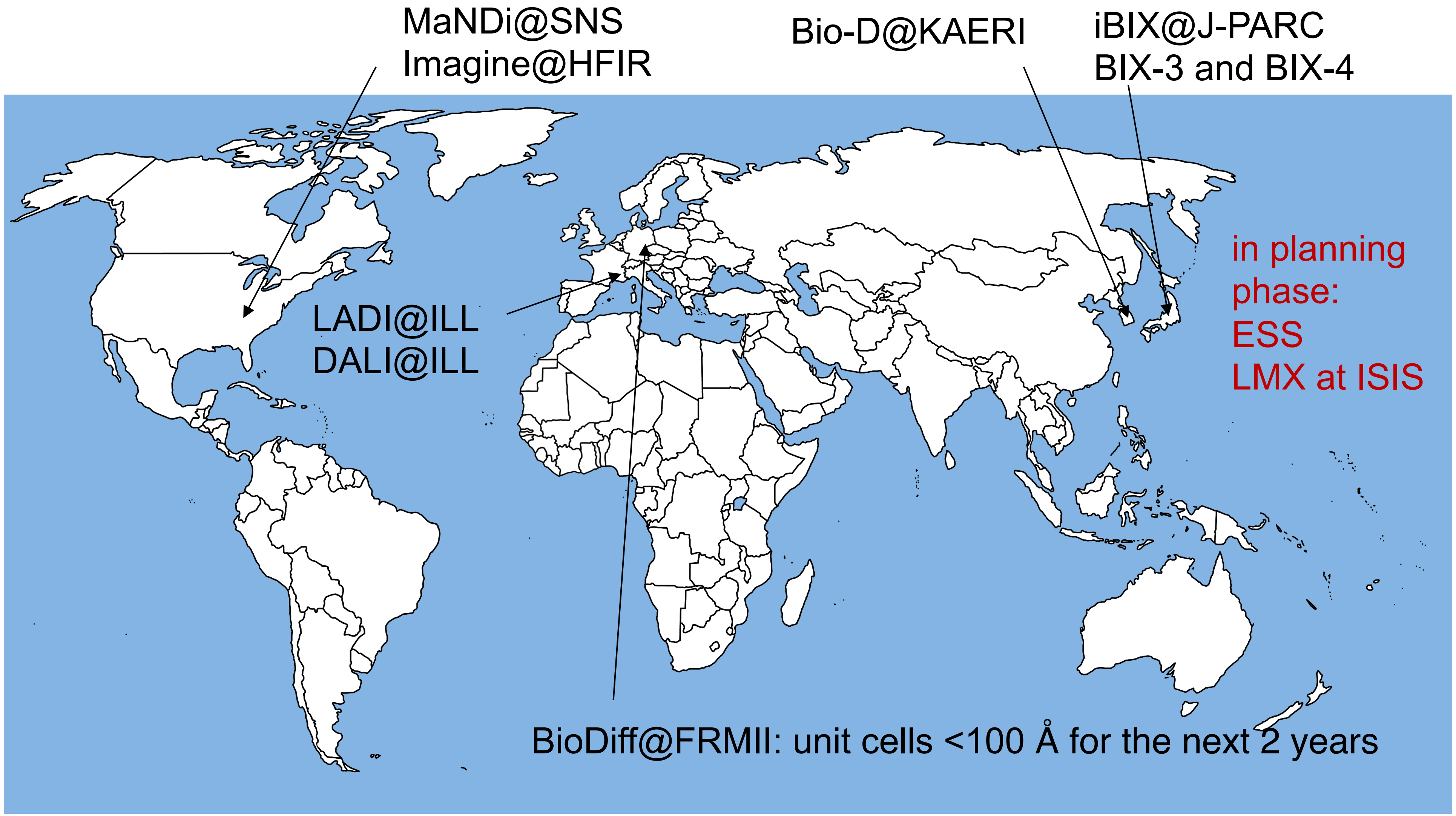
Typical:
1 mm^3
Minimal:
0.1 mm^3

WHAT IS THE ACCESSIBLE MARKET PLACE?



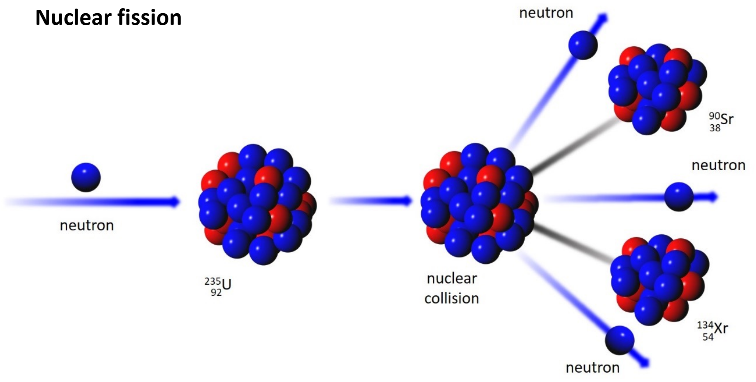
- But many proteins are not enzymes, so the protonation states are not so relevant...

World map of neutron diffractometers optimized for protein crystals



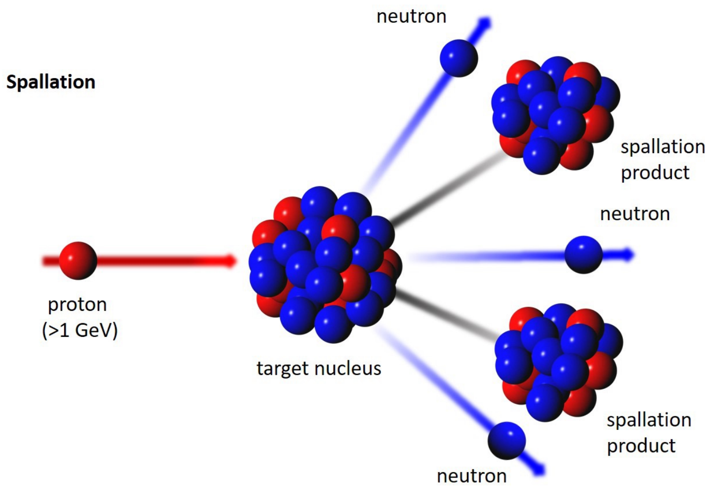
How to get neutrons

Nuclear fission



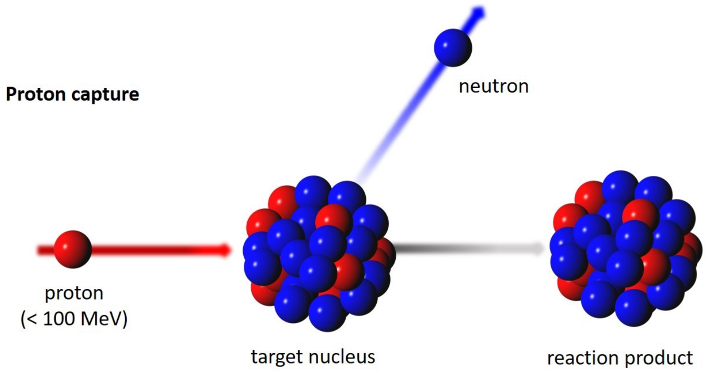
Reactor based neutron source
(ILL, FRM II, NIST, JINR, ANSTO a.m.m.)

Spallation



Spallation based neutron source
(ESS, ISIS, SINQ, SNS, CSNS, J-PARC, KEK)

Nuclear processes



Accelerator based neutron source
(LENS, RANS, HUNS, NUANS, IREN a.o.)

HBS project: A HiCANS facility

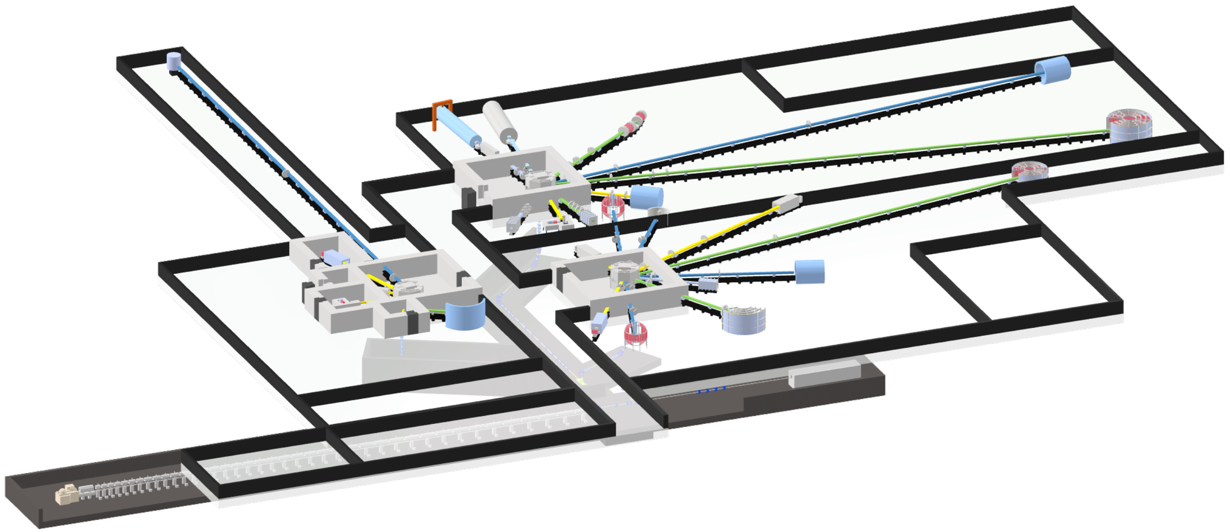
Project rationale

High current linear accelerator
- 100 mA, 70 MeV pulsed proton beam
- Variable frequency

Several target stations
- Optimize pulse structure (length, rep. rate)
- Optimize thermal spectrum

Every beam port serves only 1 Instrument
- Optimize cold source spectrum
- Optimize geometry
- Integrate neutron optics with beam port

Small shielding
- Neutron guide around cold source
- Chopper at <2 m from target



www.fz-juelich.de/jcns/jcns-2/EN/Forschung/High-Brilliance-Neutron-Source/_node.html

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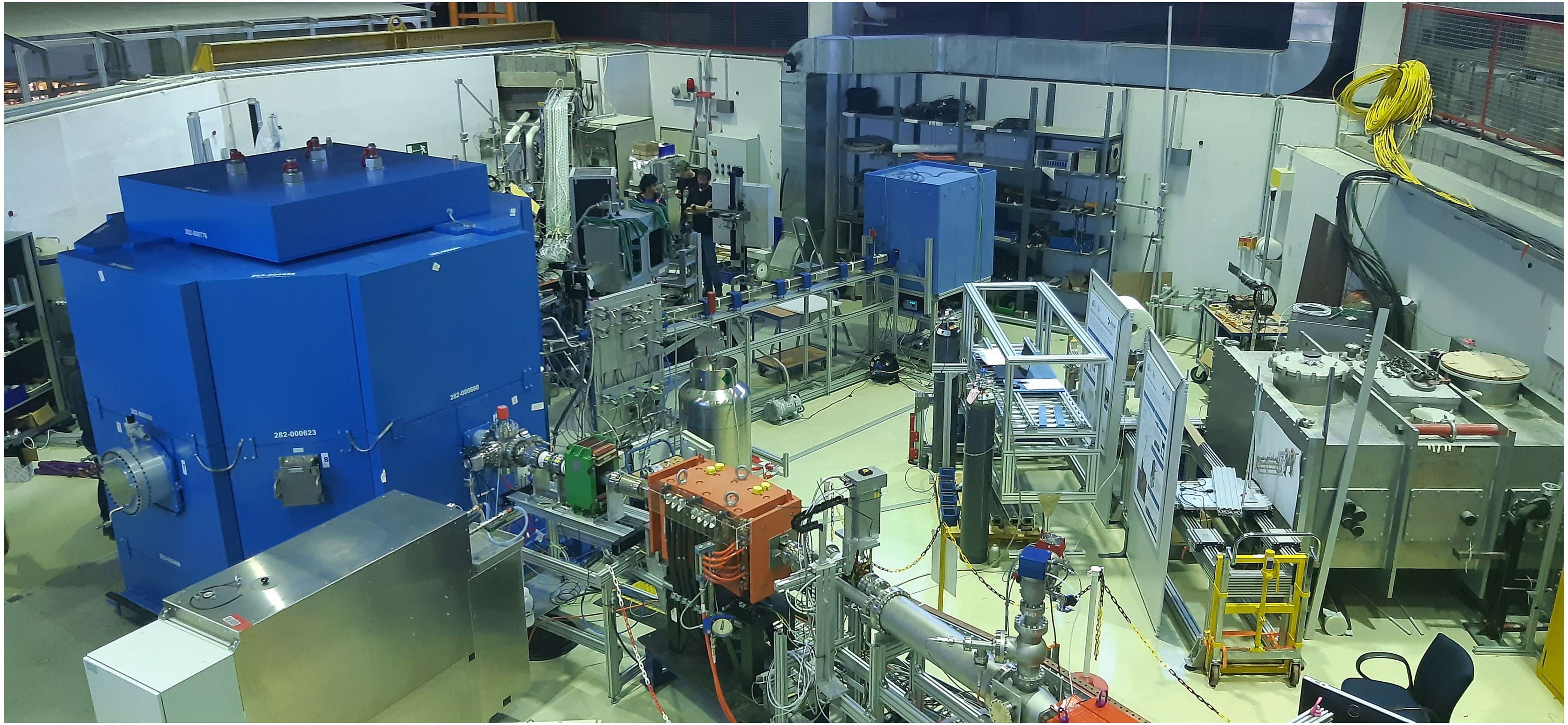
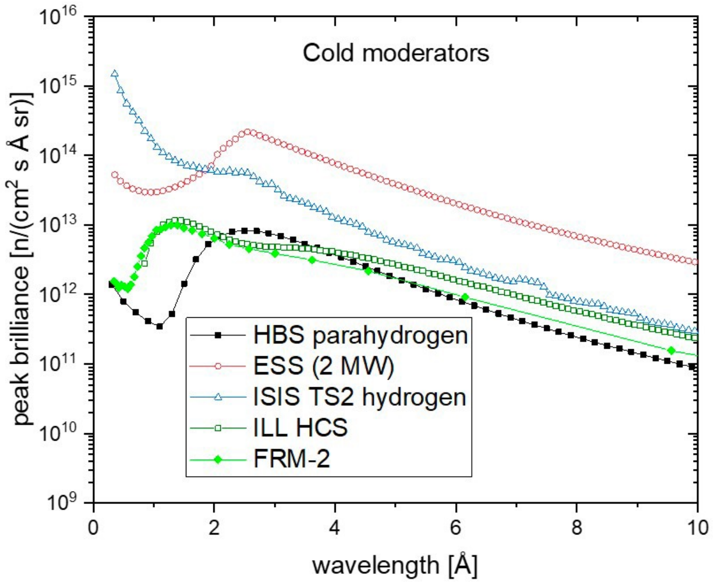
HBS Target-Moderator-Reflector Unit

Experimental Platform at Big Karl @ COSY



Thermal versus cold Moderator of HBS



Simulated brilliance as a function of wavelength of the 24 Hz HBS target station for the cold moderator (right) in comparison with simulated brilliance values of neutron facilities that exist or are under construction

Source: Techical Design Report of HBS, unpublished

MAIN INSTRUMENT PARAMETERS

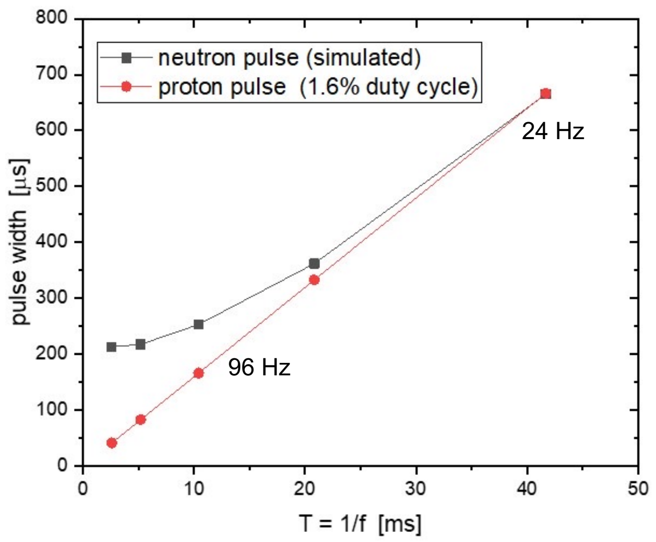
Band width: $\Delta\lambda = \frac{3956\ m\text{Å}/s}{L f}$

- Resolution:

$$\frac{\Delta d}{d} = \sqrt{\left(\frac{\Delta t}{T_{OF}}\right)^2 + \left(\frac{\Delta L}{L}\right)^2 + (\cot\theta_B \cdot \Delta\theta_B)^2}$$

$$= \sqrt{\left(\frac{\tau}{L\lambda/_{3956\ m\text{Å}/s}}\right)^2 + \left(\frac{\Delta L}{L}\right)^2 + (\cot\theta_B \cdot \Delta\theta_B)^2}$$

dominating for short wavelengths | negligible for long instruments | dominating in forward scattering



Improved resolution by pulse shaping requires instrument length: $L = D_{min} + \frac{D_{min}}{\alpha\ N_{WFM}}$

f: source frequency
α: duty cycle
τ: pulse length
L: instrument length
D_{min}: min. chopper distance
λ: wavelength
θ_B: Bragg angle
N_{WFM}: number of frames in wavelength frame multiplication

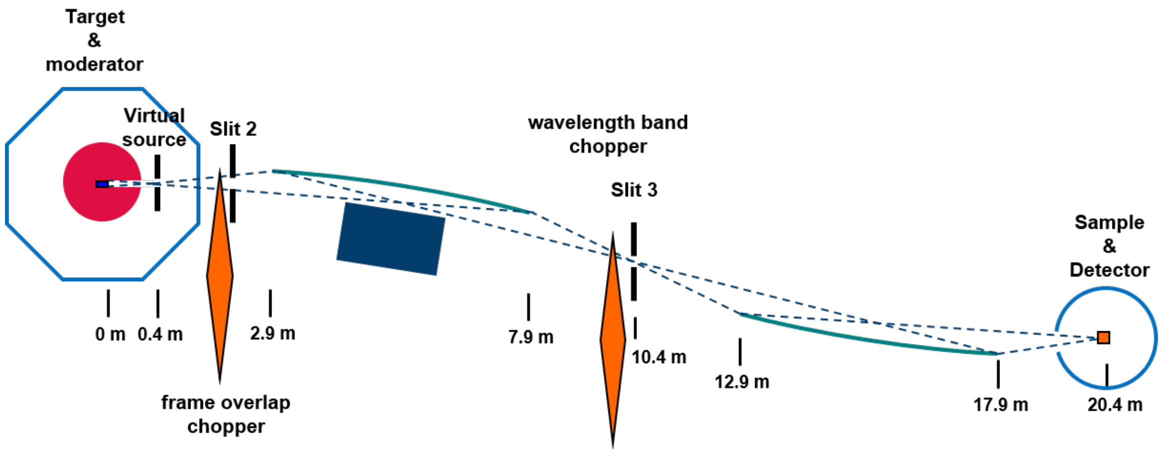
A 20 m instrument at the 96 Hz target station or a 80 m instrument at the 24 Hz target station?

Instrument Name	Source	Flux	neutron pulse	instrument length	rep rate	div FWHM	total deltad/d at given scattering angle		
		n/s/cm^2	µs	m	Hz	° degree	5°	45°	85°
MANDI	SNS	4,50E+07	17,4	30	60	0,8	15,96%	1,40%	0,17%
EWALD	SNS		43,3	60	15	0,38	7,58%	0,68%	0,15%
iBIX	J-PARC	7,00E+07	500	40	25	0,2	4,69%	2,50%	2,47%
NMX	ESS		2860	156	14	0,1	4,14%	3,63%	3,63%
NMD	HBS 96Hz 20 m		254	20,4	96	0,7	14,18%	2,75%	2,47%
NMD	HBS 24Hz 80m		666,7	80	24	0,7	14,06%	2,05%	1,65%

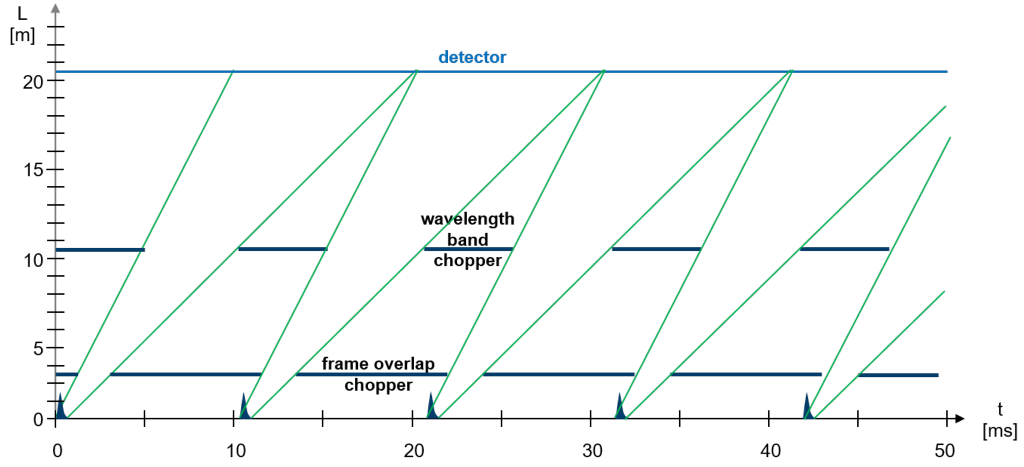
Design considerations:
1. Flux
2. Flux
3. Resolution in reciprocal space
4. Round or Flat top uniform beam profile

MACROMOLECULAR DIFFRACTOMETER (BIODIFF)

Design



λ_{min} [Å]	λ_{max} [Å]	Δλ [Å]	Δt/t [%]	duty cycle [%]	res. time [μs]		BT	$Div_{hor,fwhm}$ [deg]	$Div_{vert,fwhm}$ [deg]	Ω [sr]	Φ_{avrg} [n/(cm²s)]
2.00	4.00	2.00	3.0%	1.60%	170		0.55	0.70	0.70	1.493E-04	9.5E+07
f [Hz]	T_{period} [ms]	N_{suppr}	L [m]	τ_{proton} [μs]	$\tau_{neutron}$ [μs]	ToF_{min} [ms]	ToF_{avrg} [ms]	ToF_{max} [ms]	τ/ToF_{min}	τ/ToF_{avrg}	τ/ToF_{max}
96	10.4	1	**20.4**	167	252	10.3	15.5	20.6	2.44%	1.63%	1.22%



- Applications
  - Single crystals of proteins and other biological molecules (Laue diffraction)
- Concept and Requirements
  - TOF diffractometer using whole pulse
  - Medium resolution Δλ/λ < 3%
  - High flux in 1 x 1 mm²
  - Low background
  - Variable divergence and 'clean' distribution
- Choices
  - Cold moderator
  - Medium frequency (96 Hz, 167 μs)
  - 20.4 m total length
  - SELENE optics
  - Large detector coverage (3° - 170° ?)
- Characteristics
  - Bandwidth: 2 Å, standard: 2 – 4 Å
  - d-range : 1.0 – 76 Å
  - Resolution: 1.3% - 3.0%
  - Estimated flux at sample: 10^8 n/(cm²s)
- Staff
  - Design: Tobias Schrader
  - Simulations: Zhanwen Ma

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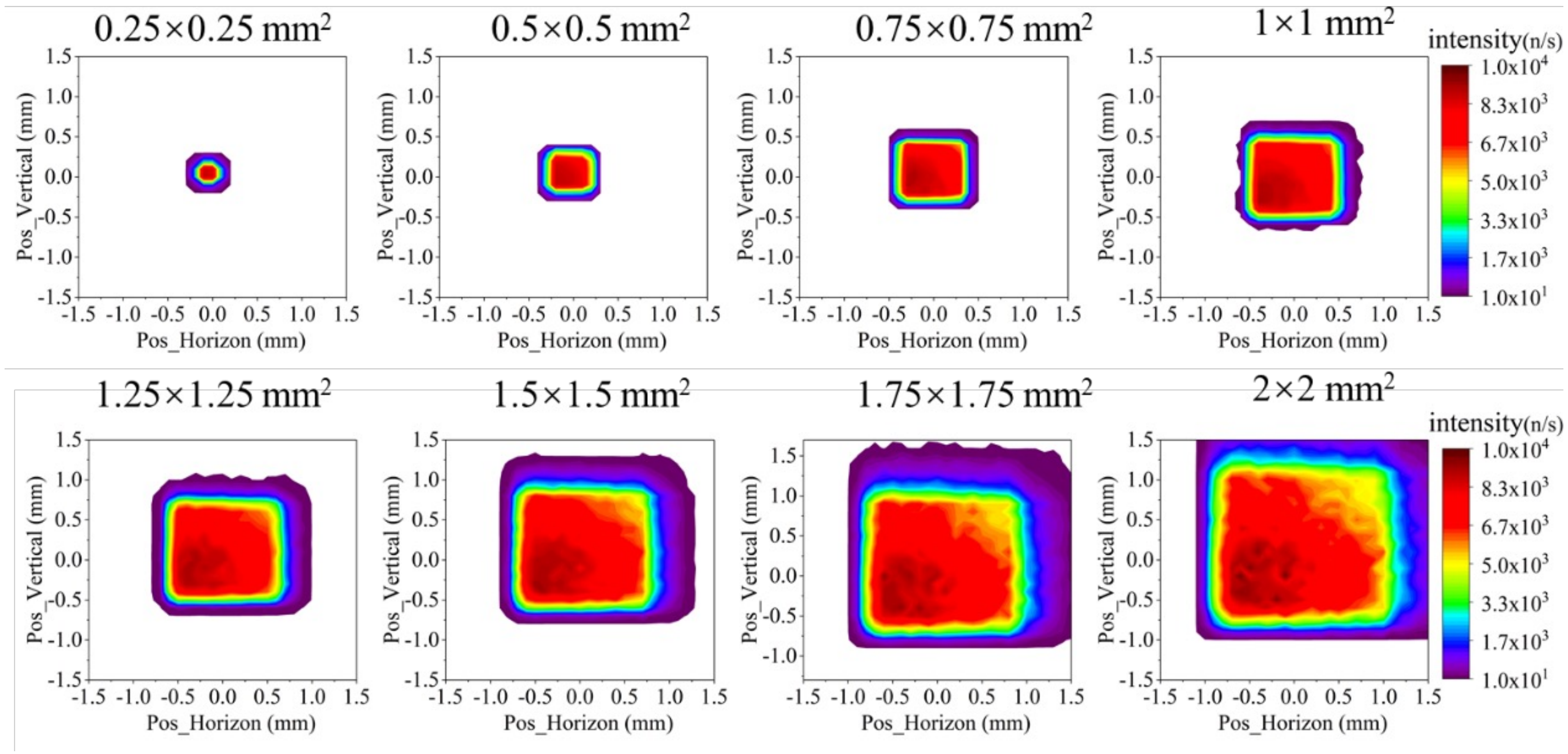
BeamProfile at Sample position of the 20 m instrument

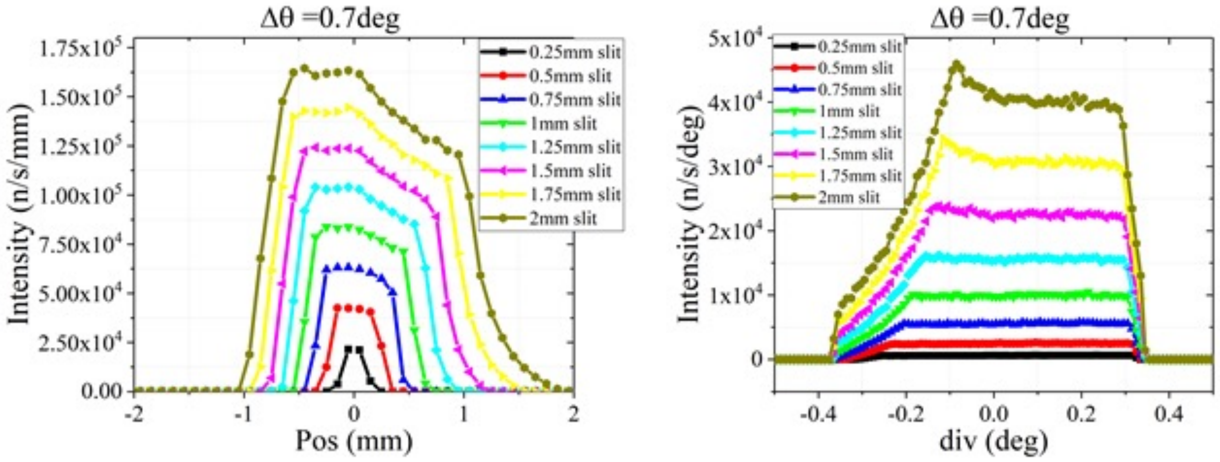


Neutron spatial distribution at the sample position at different virtual source sizes. $\Delta\theta$ is set at 0.7 deg and

2 Å < λ < 4 Å. The intensity is given in (n/s).

Source: Zhanwen Ma et al., unpublished

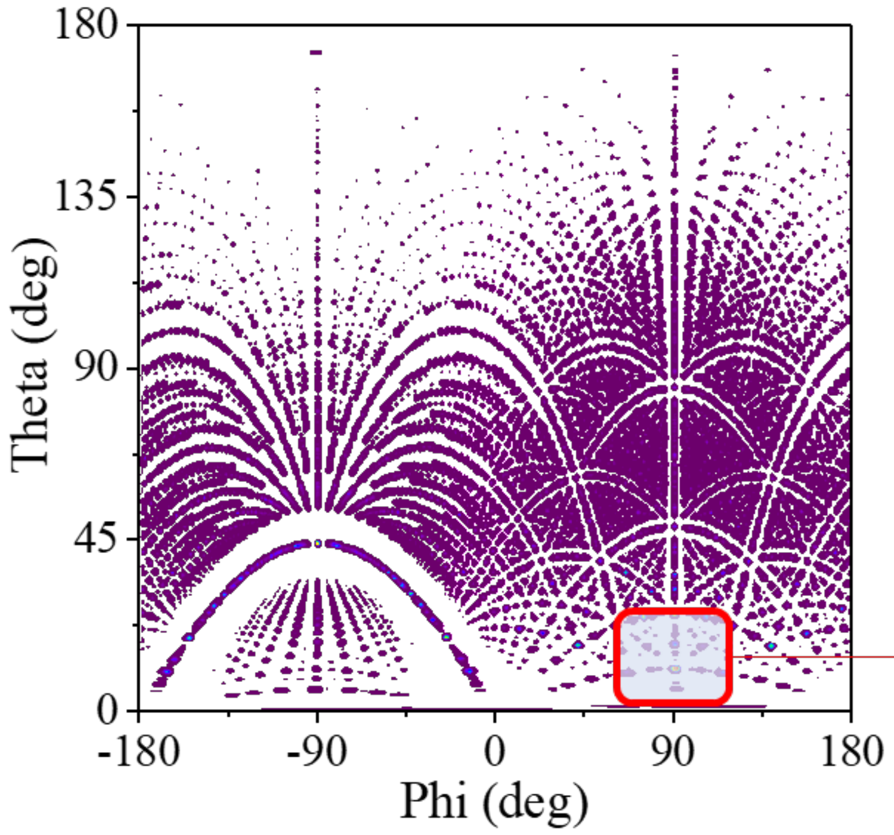
BeamProfile at Sample position of the 20 m instrument

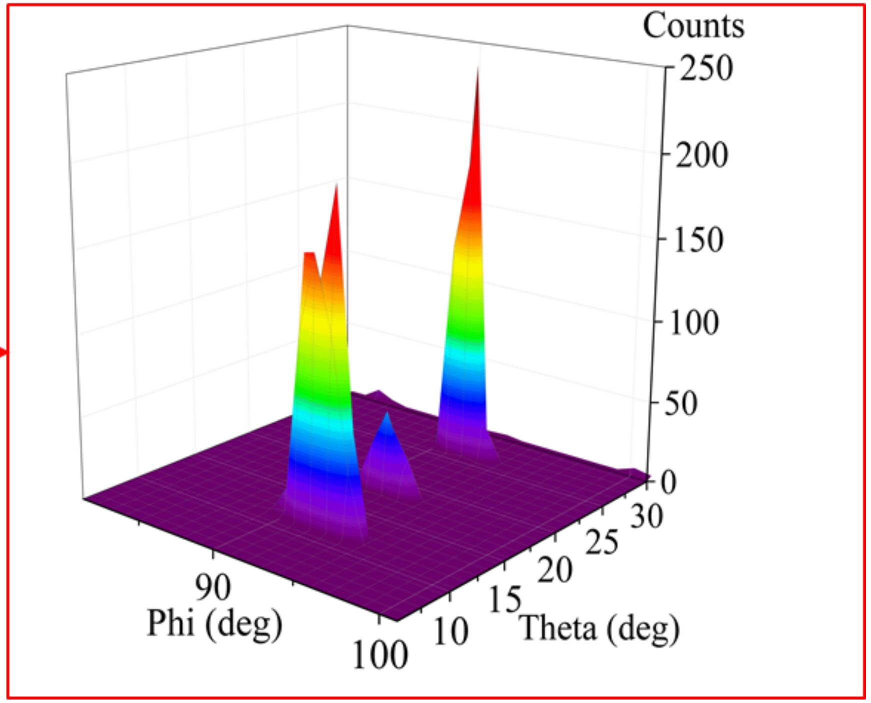


Integrated neutron spatial distribution (left) and divergence distribution (right) at the sample plane at different source sizes.

Source: Zhanwen Ma et al., unpublished

The 20 m instrument Diffraction from a virtual Myoglogin crystal



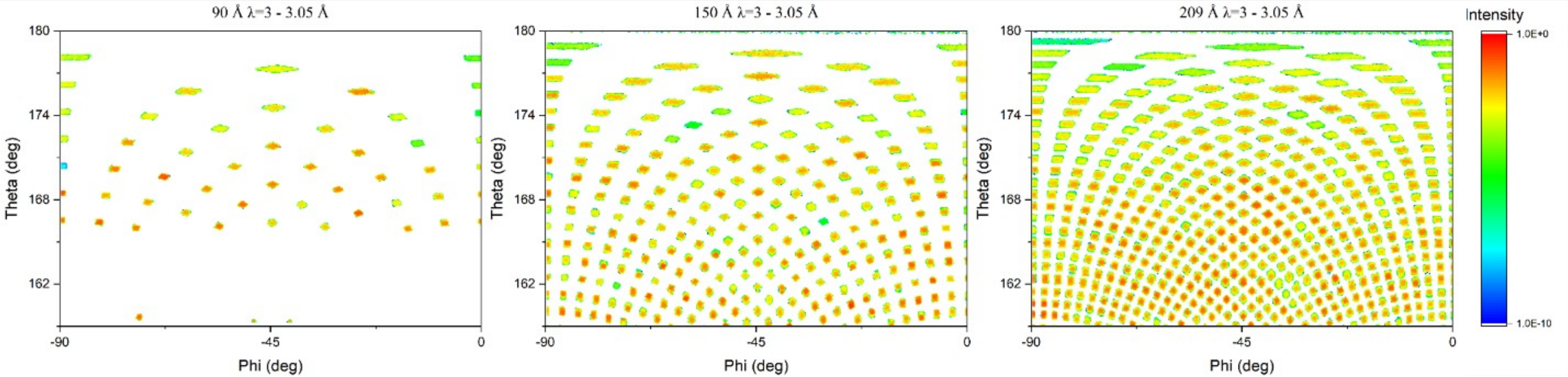


Simulated diffraction of a myoglobin sample from MMD at HBS onto a 4 π spherical detector with the 0.7 deg divergence and 2 – 4 Å wavelength range.

Source: Zhanwen Ma et al., unpublished

WHAT IS THE LIMIT IN UNIT CELL SIZE?

Using real structure factors calculated from protein models deposited in the protein database



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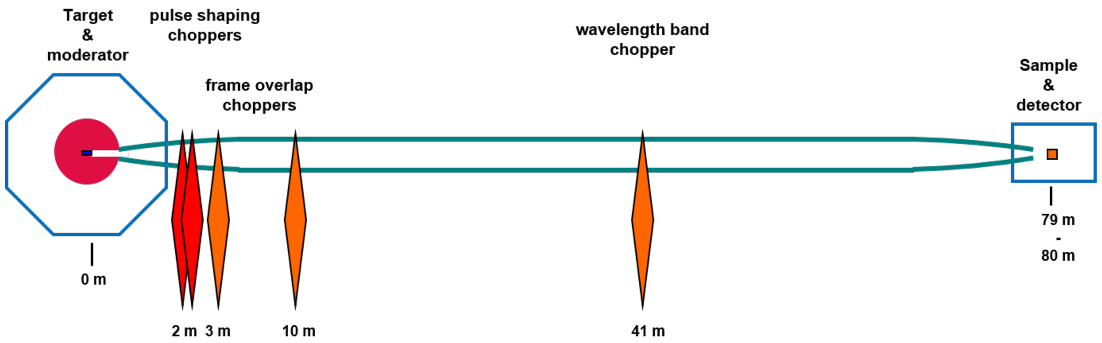
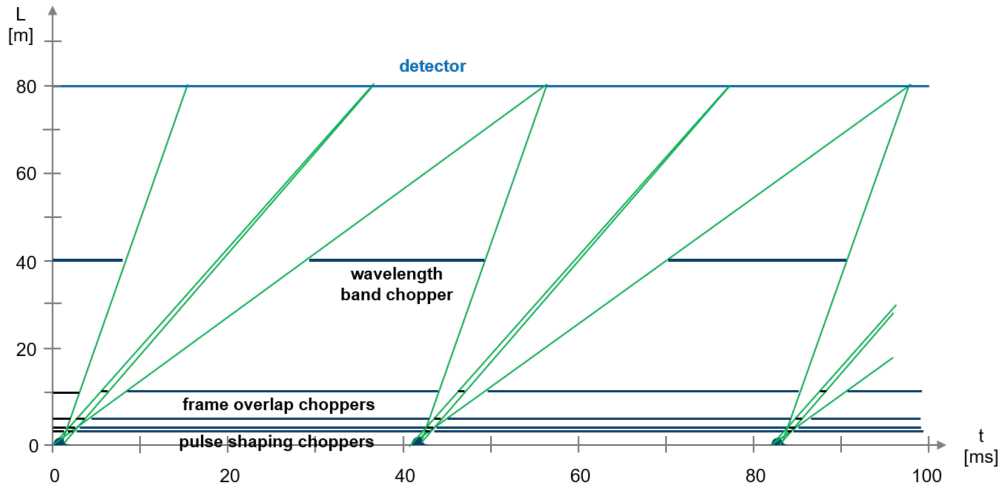
The 80 m Single Crystal Diffractometer

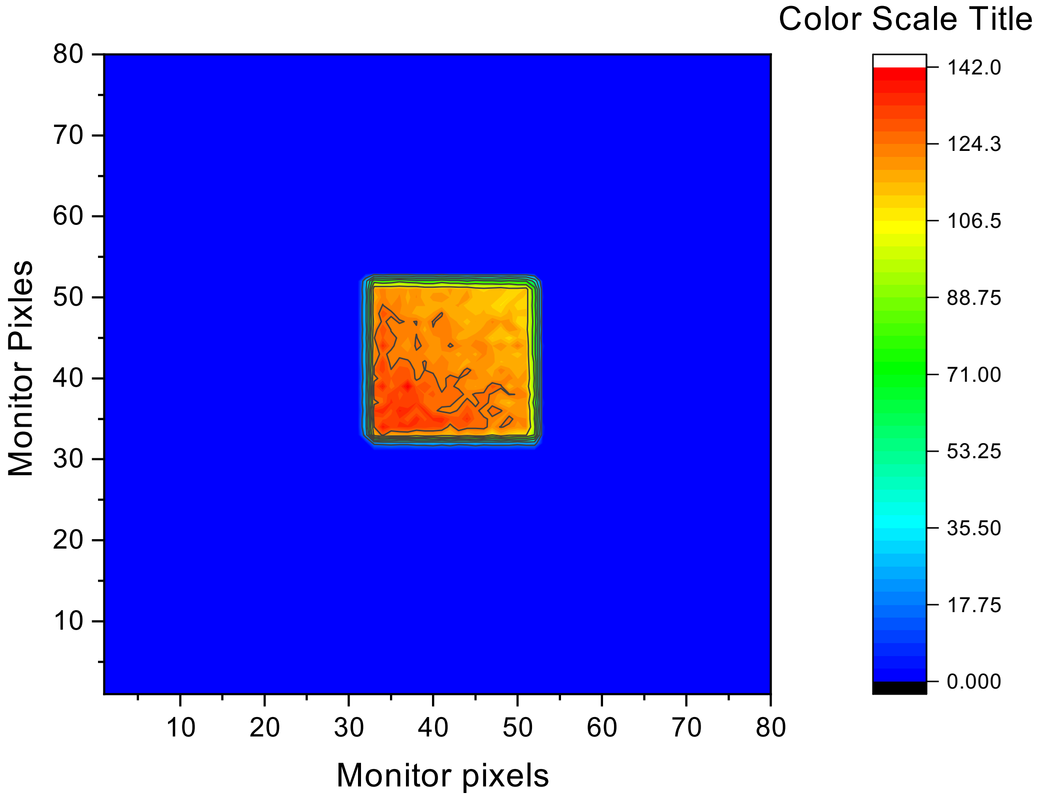




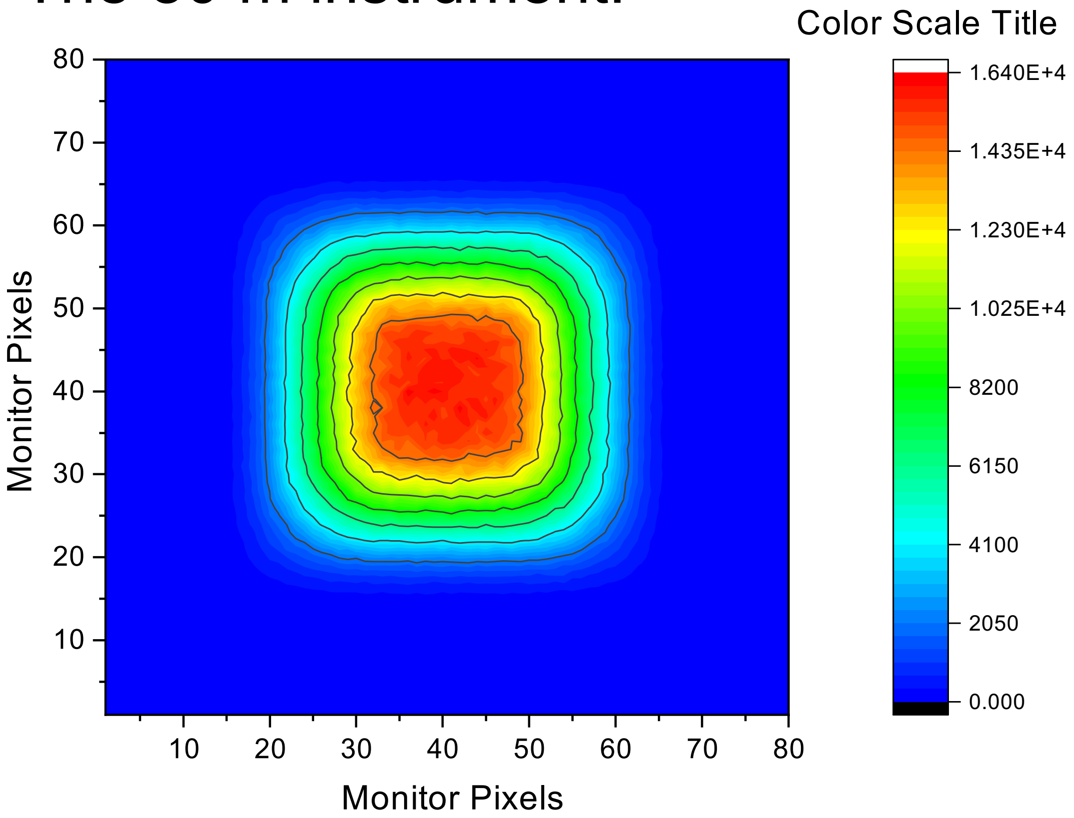
- **Applications**
  - All kinds of powder samples
- **Concept and Requirements**
  - TOF diffractometer using pulse shaping and wavelength frame multiplication
  - Variable up to very high resolution
- **Choices**
  - Thermal moderator
  - Low frequency (24 Hz, 667 μs)
  - 80 m length (source to detector)
  - Detector range: 7° - 175°
- **Characteristics**
  - Bandwidth: 1.65 Å, standard: 0.75 – 2.4 Å
  - d-range : 0.32 – 16.7 Å
  - High-Resolution option (100 μs pulse)
    - 0.17 – 0.59% (θ>90°), 0.04% for 175°
    - Estimated flux at sample: $1 \cdot 10^6$ n/(cm²s)
  - High-Intensity option (667μs pulse)
    - 0.47 – 1.4% (θ>90°)
    - Estimated flux at sample: $5 \cdot 10^8$ n/(cm²s)

Comparison between the two instruments:

The 20 m instrument:



The 80 m instrument:



The 80 m instrument offers twice the flux of the 20 m instrument in a wavelength band of 2-4 Å.

Disadvantage of the 80 m instrument: A lot of neutrons have to be absorbed near the sample position.

Conclusions

- The planned HBS at the Forschungszentrum Jülich can offer an instrument which is interesting to the protein crystallography community.
- The 80 m instrument has twice the flux and a 1.5 times better resolution in reciprocal space.
- The user community has to be involved in instrument design and instrument usage.

HBS Team

+ Andreas Ostermann (TUM),
Zhanwen Ma, Zamaan Raza

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Z. Ma
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- Core group: design, verification, instrumentation

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IKP-4:
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M. Rimmler
R. Similon

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INM-5:
B. Neumaier

- Radio isotopes

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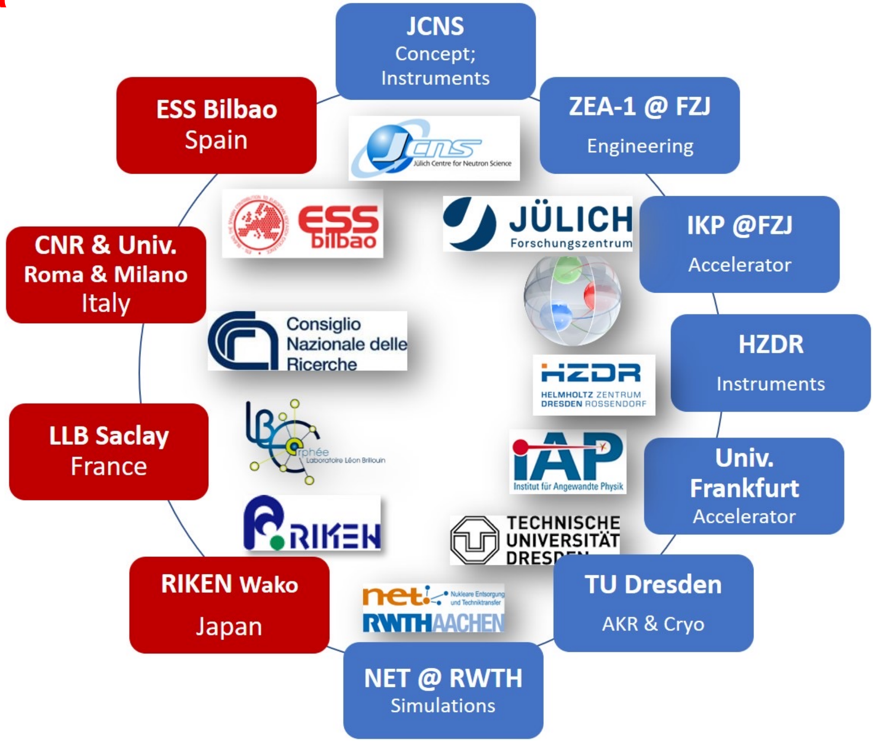
O. Meusel

- Accelerator

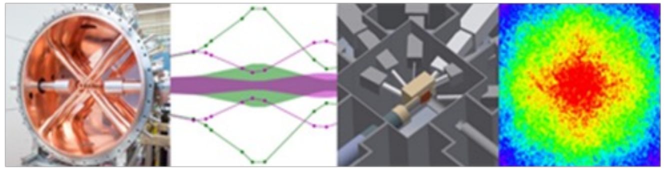
GSI / HIM
GSI Helmholtzzentrum für Schwerionenforschung GmbH

W. Barth

- Accelerator



HBS Innovationpool Project



Federal Ministry of Education and Research

FB Matter: MML, MT

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