The European Spallation Source

FASEM 24

2024-03-15

Esko Oksanen Instrument Scientist,

Macromolecular Crystallography

The European Spallation Source And some neutron crystallography

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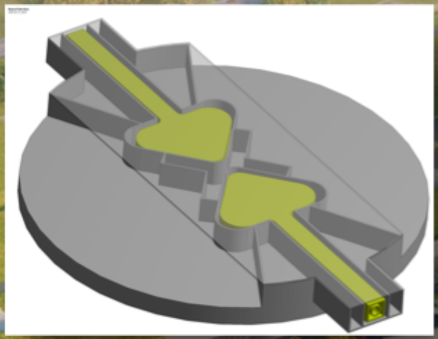
Macromolecular Crystallography

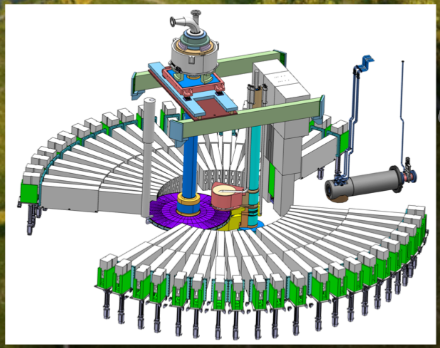
ESS High Level Design

EUROPEAN SPALLATION SOURCE

Flat moderator delivering smaller and brighter neutron beams

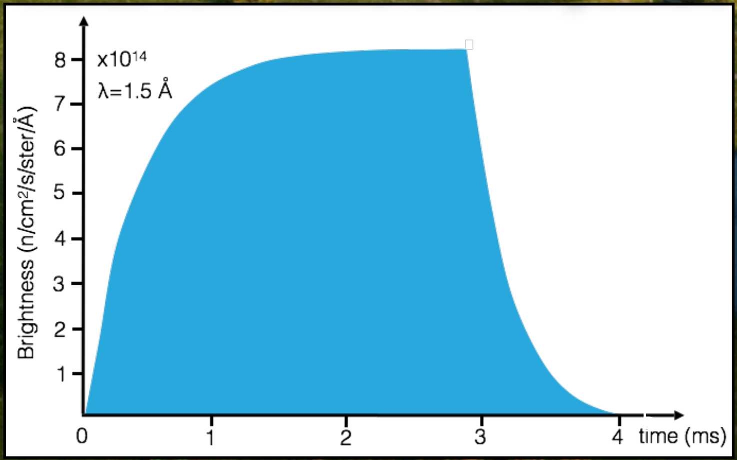


High Power Accelerator means more neutrons



An Innovative Target Station that can host >30 instruments

High brightness and tuneable resolution makes new measurements possible



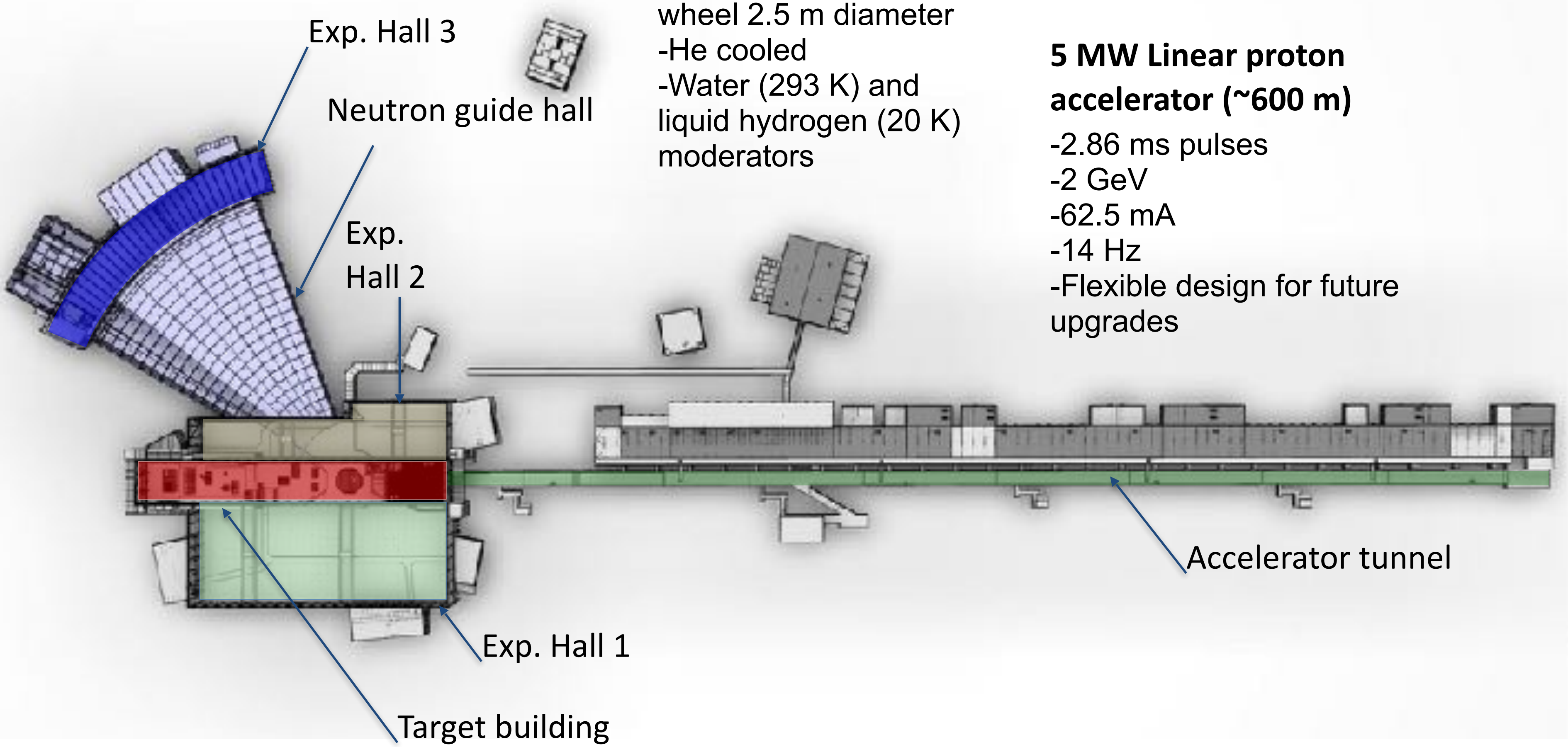
The world's brightest neutron source

Target station

- -Rotating tungsten wheel 2.5 m diameter
- -He cooled
- -Water (293 K) and liquid hydrogen (20 K) moderators

5 MW Linear proton accelerator (~600 m)

- -2.86 ms pulses
- -2 GeV
- -62.5 mA
- -14 Hz
- -Flexible design for future upgrades



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Target station

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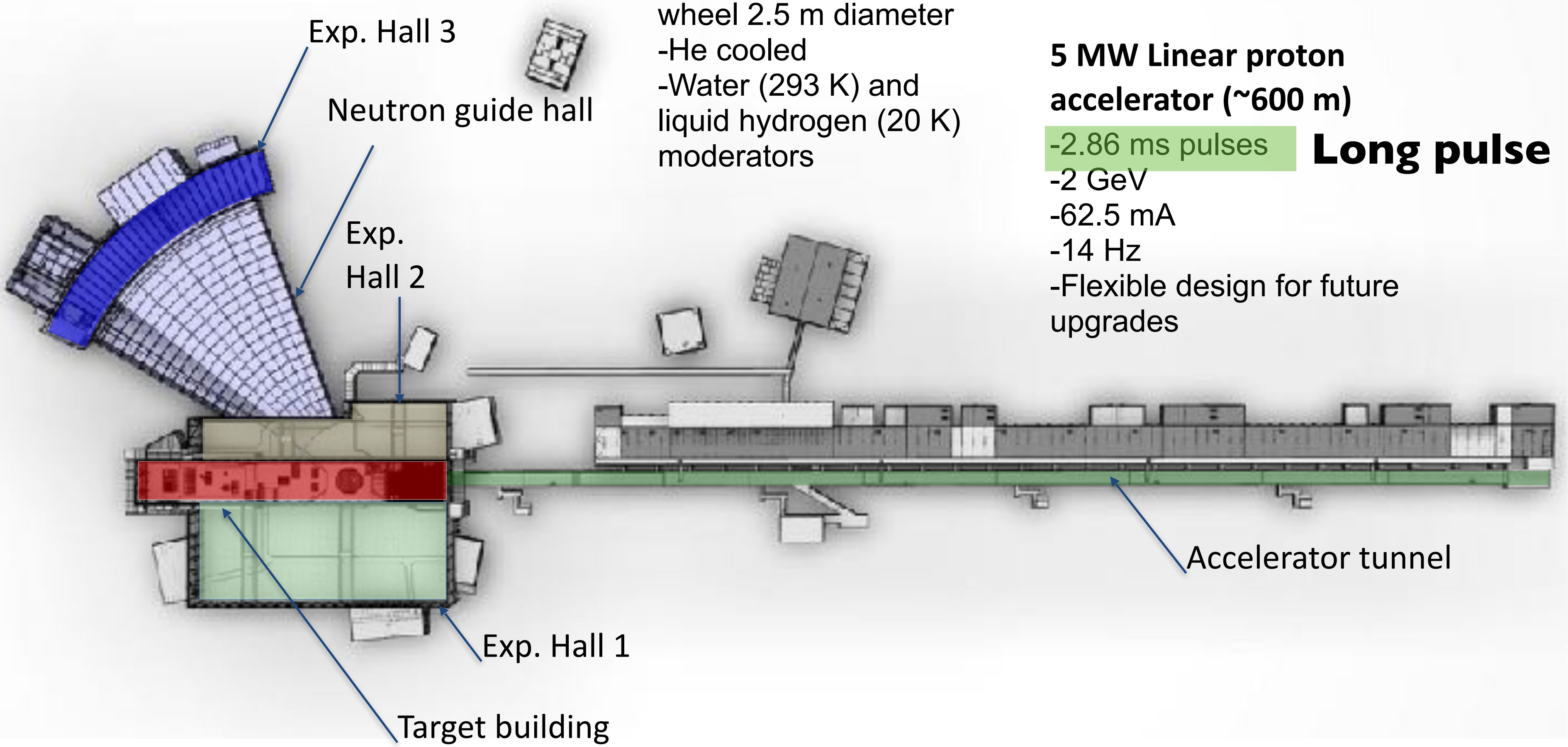
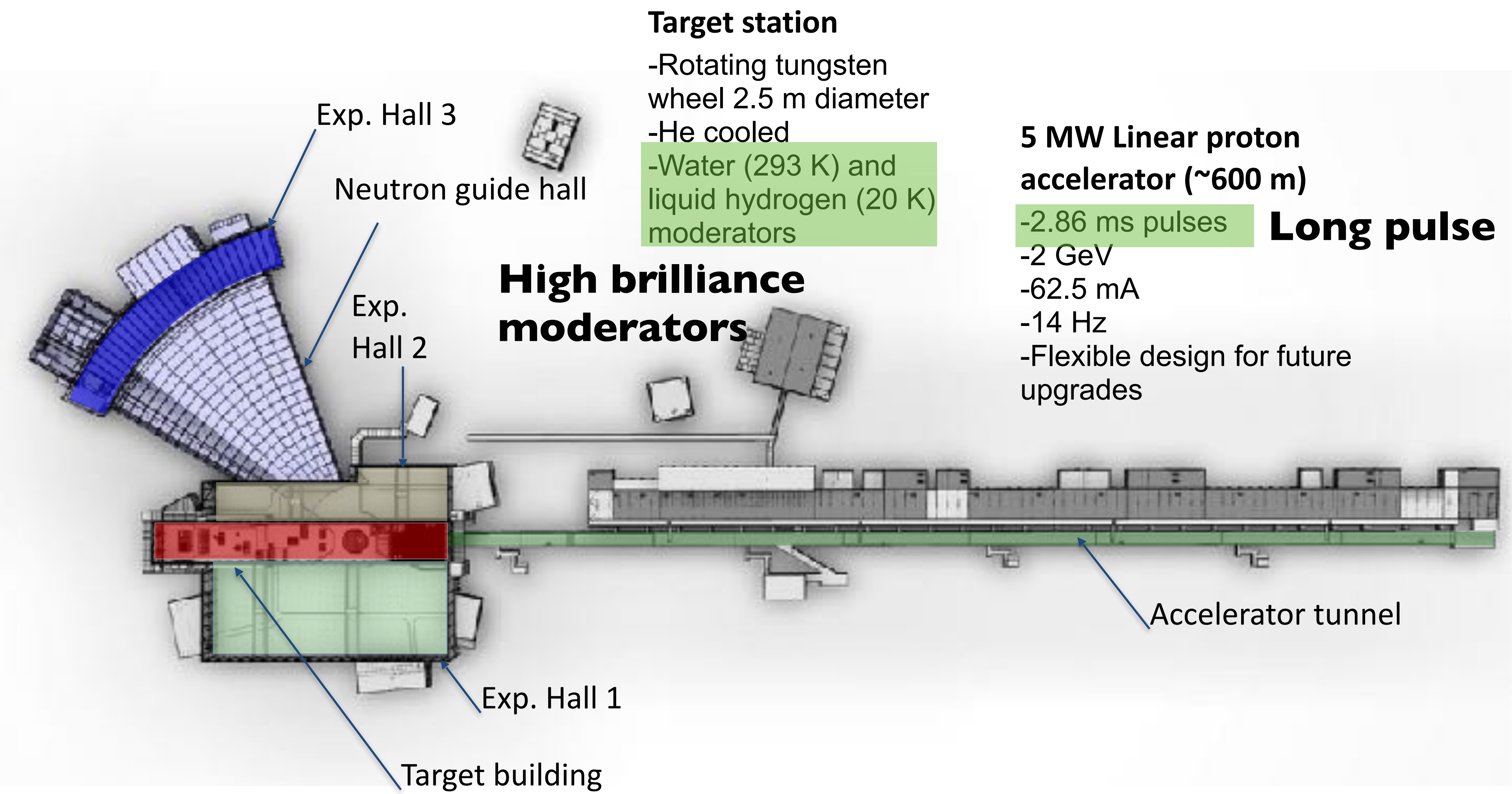
-2.86 ms pulses **Long pulse**
-2 GeV
-62.5 mA
-14 Hz
-Flexible design for future upgrades



The world's brightest neutron source



The world's brightest neutron source

Target station

-Rotating tungsten wheel 2.5 m diameter
-He cooled
-Water (293 K) and liquid hydrogen (20 K) moderators

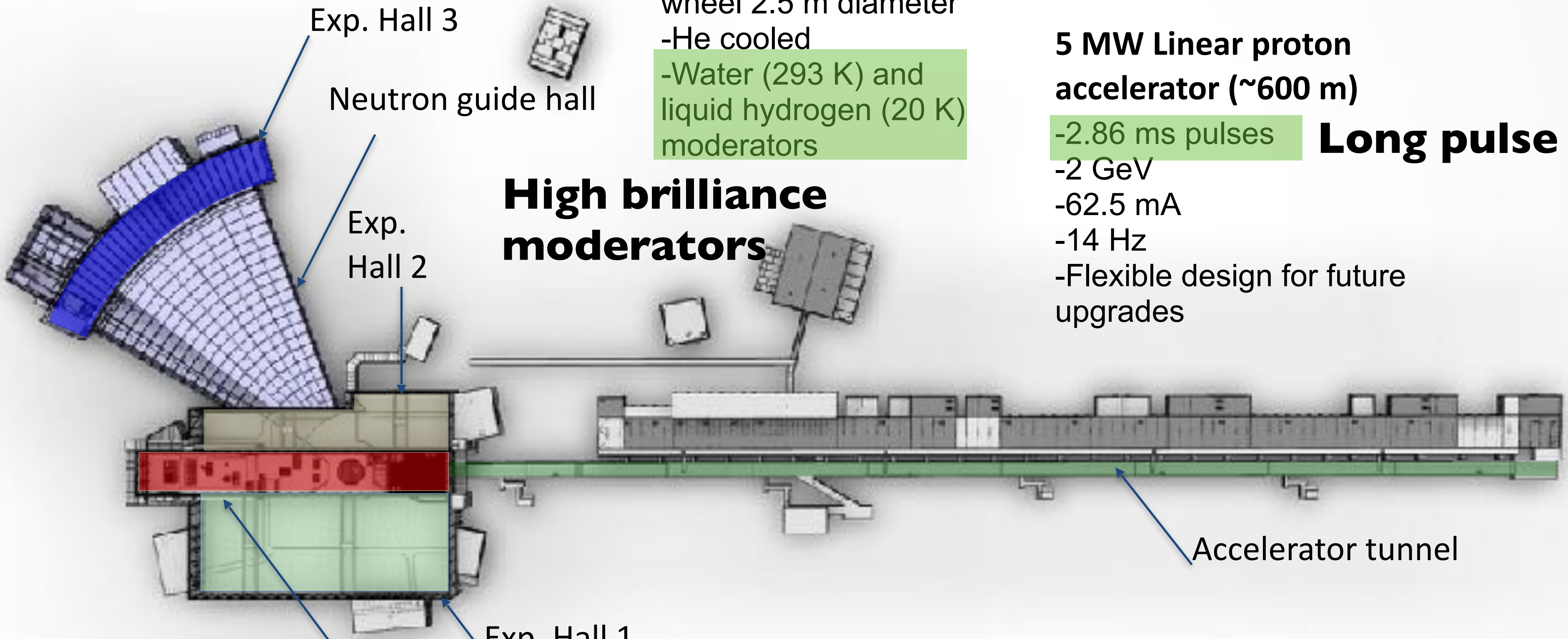
High brilliance moderators

Life science can make good use of the long pulse!

5 MW Linear proton accelerator (~600 m)

-2.86 ms pulses
-2 GeV
-62.5 mA
-14 Hz
-Flexible design for future upgrades

Long pulse



A European Project

Host countries

Sweden, Denmark

Construction
47.5%

Operations
15%

Budget for construction €1.84 billion
Estimated annual budget €140 million

Non host member countries

Czech Republic, Estonia, France, Germany, Hungary, Italy, Norway, Poland, Spain, Switzerland, United Kingdom.

Construction
52.5%
(of which 70% is in-kind deliverables)

Operations
85%

A European Project

EUROPEAN SPALLATION SOURCE

How will it be built?

Aarhus University
Atomki - Institute for Nuclear Research
Bergen University
CEA Saclay, Paris
Centre for Energy Research, Budapest
Centre for Nuclear Research, Poland, (NCBJ)
CNR, Rome
CNRS Orsay, Paris
Cockcroft Institute, Daresbury
Elettra – Sincrotrone Trieste
ESS Bilbao
Forschungszentrum Jülich
Helmholtz-Zentrum Geesthacht
Huddersfield University
IFJ PAN, Krakow
INFN, Catania
INFN, Legnaro
INFN, Milan
Institute for Energy Research (IFE)
Rutherford-Appleton

Laboratory, Oxford (ISIS)
Copenhagen University
Laboratoire Léon Brillouin (CEA/CNRS/LLB)
Lund University
Nuclear Physics Institute of the ASCR
Oslo University
Paul Scherrer Institute (PSI)
Polish Electronic Group (PEG)
Roskilde University
Tallinn Technical University
Technical University of Denmark
Technical University Munich
Science and Technology Facilities Council
UKAEA Culham
University of Tartu
Uppsala University
WIGNER Research Centre for Physics
Wroclaw University of Technology
Warsaw University of Technology
Zurich University of Applied Sciences (ZHAW

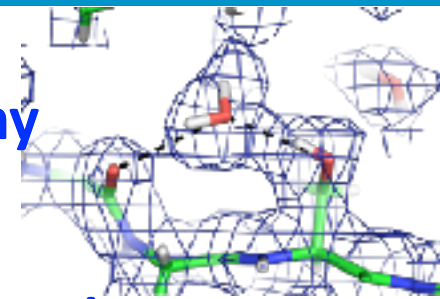
ESS Timeline

- 2003 Concept design of ESS presented
- 2009 Decision to site ESS in Lund
- 2012 ESS design update phase complete
- 2014 Start of construction
- 2019 Start of initial operations phase
- 2024 Today
- 2025 First neutrons
- 2026 First science
- 2027 Construction phase completed

Why neutrons for biological structures?

- We can see light atoms → hydrogen positions

Crystallography



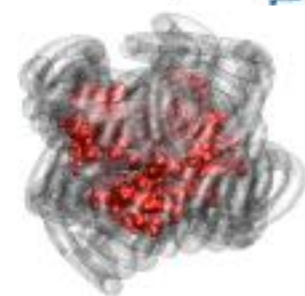
- We can use isotope labelling to create contrast → protein-protein complexes, membranes

Small angle scattering

Reflectometry

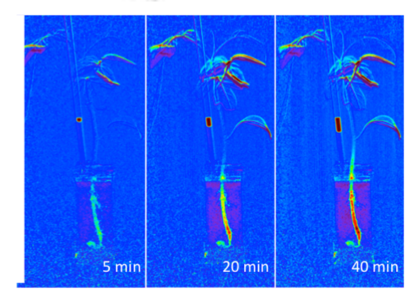
- We can observe dynamics with neutron energy changes → relating dynamics to function

Inelastic scattering

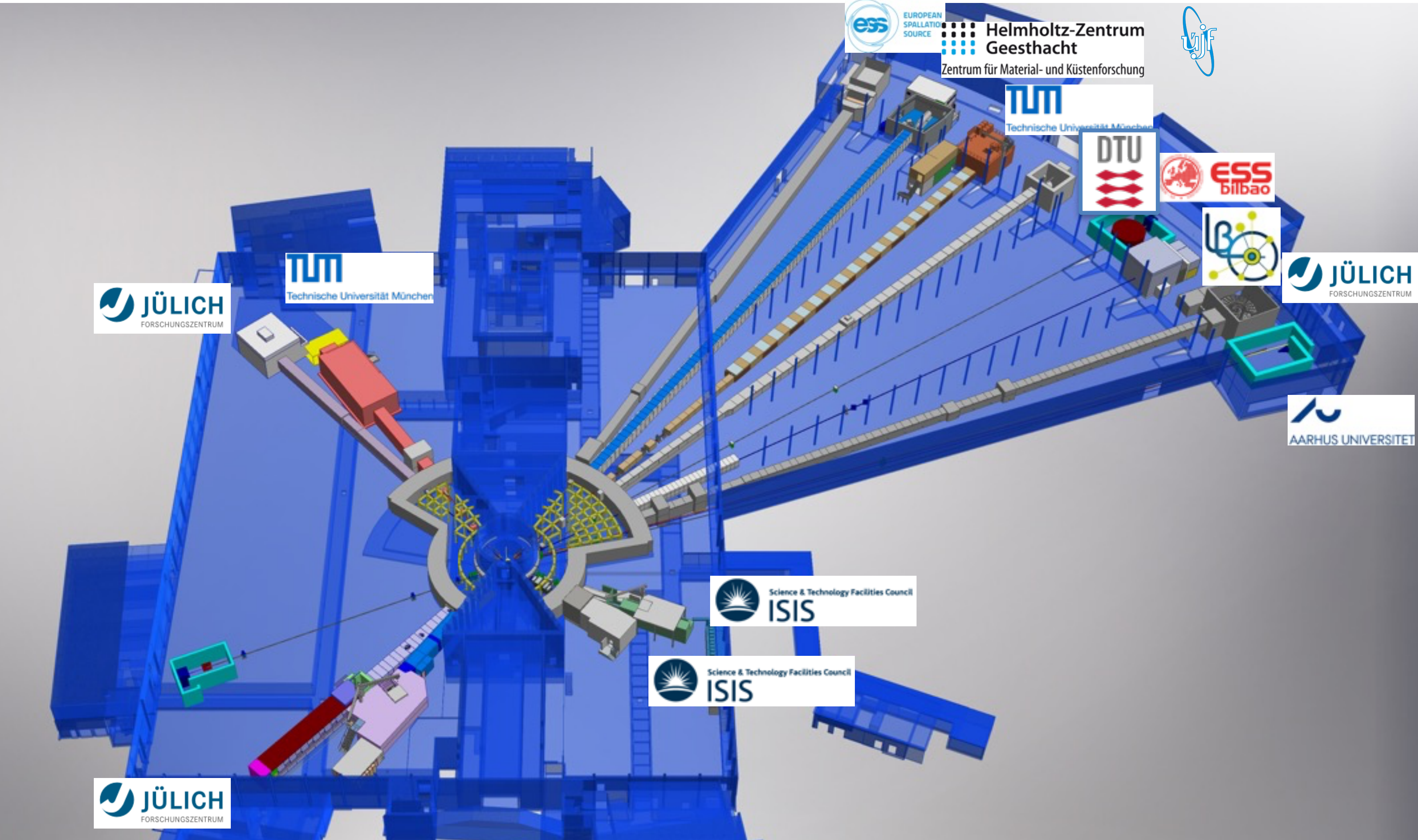


- We can see through large objects → water transport

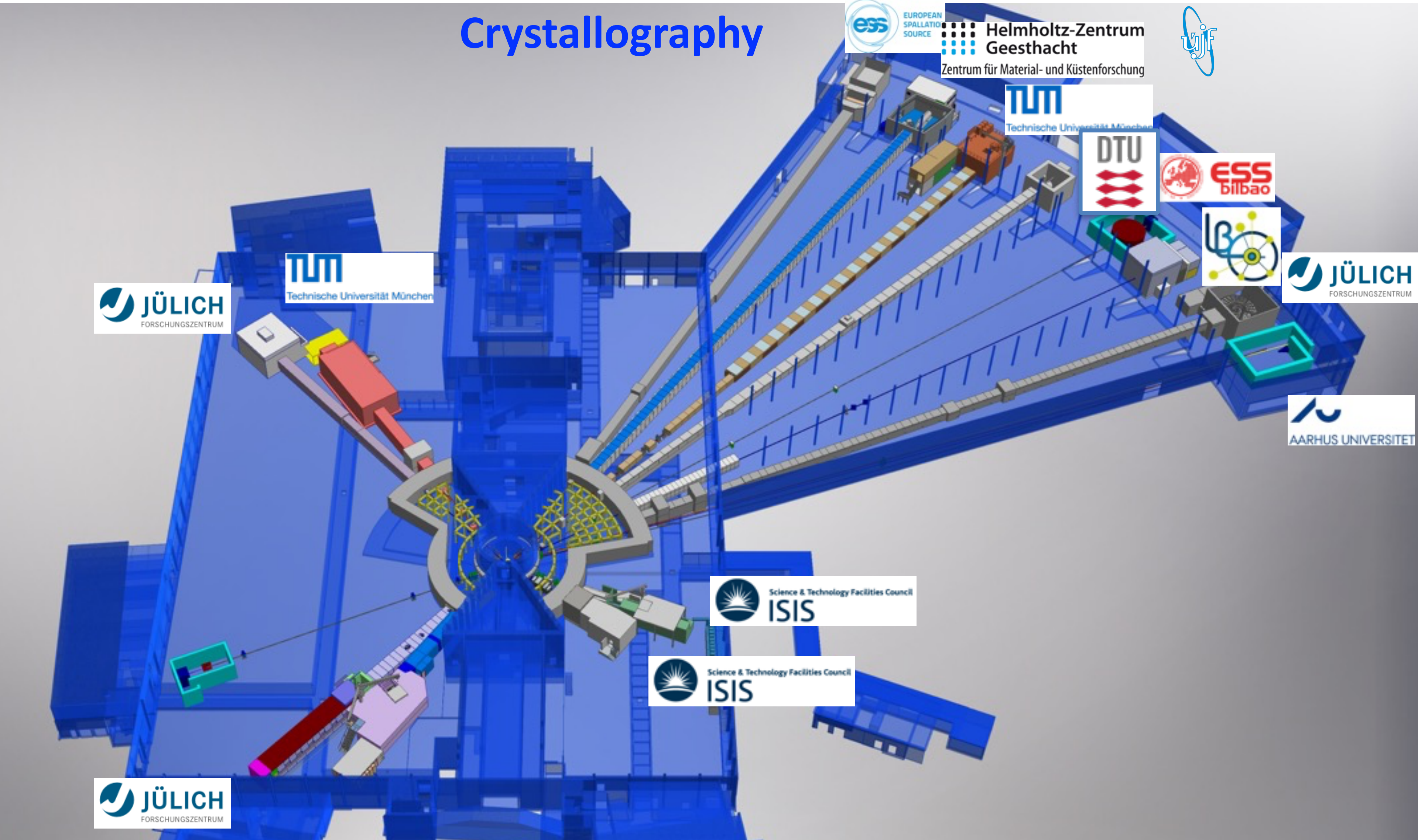
Imaging



ESS Instrument suite



ESS Instrument suite



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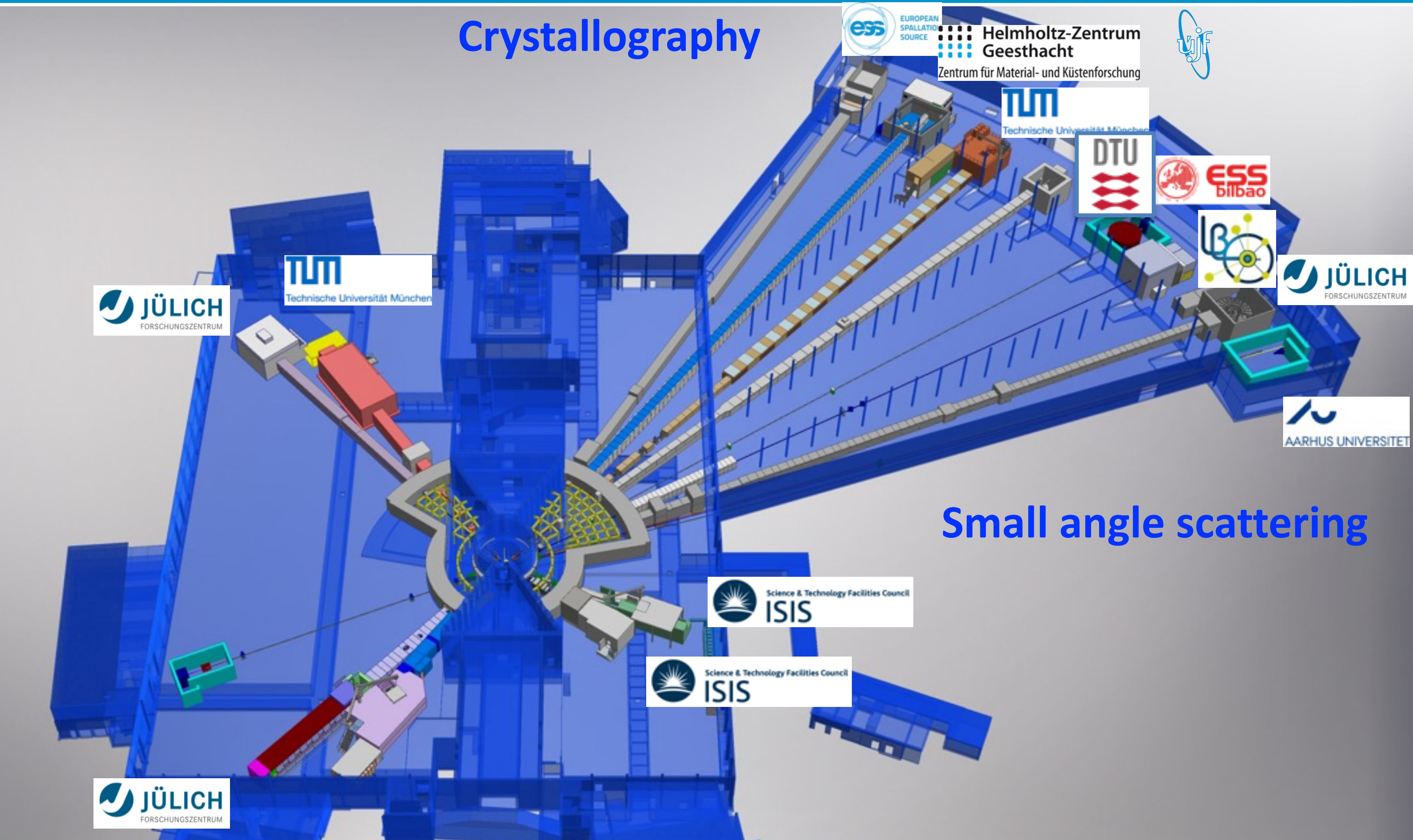

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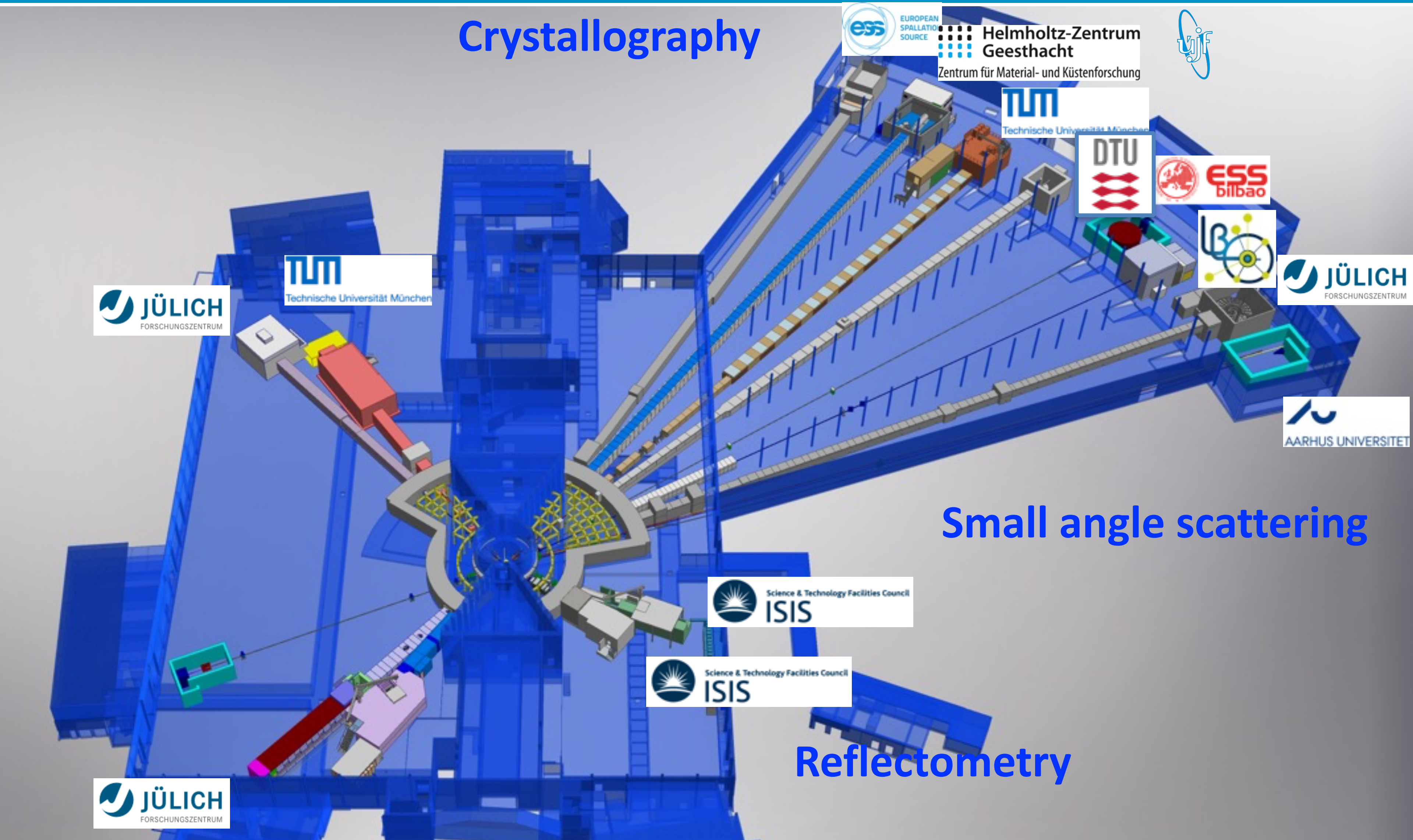

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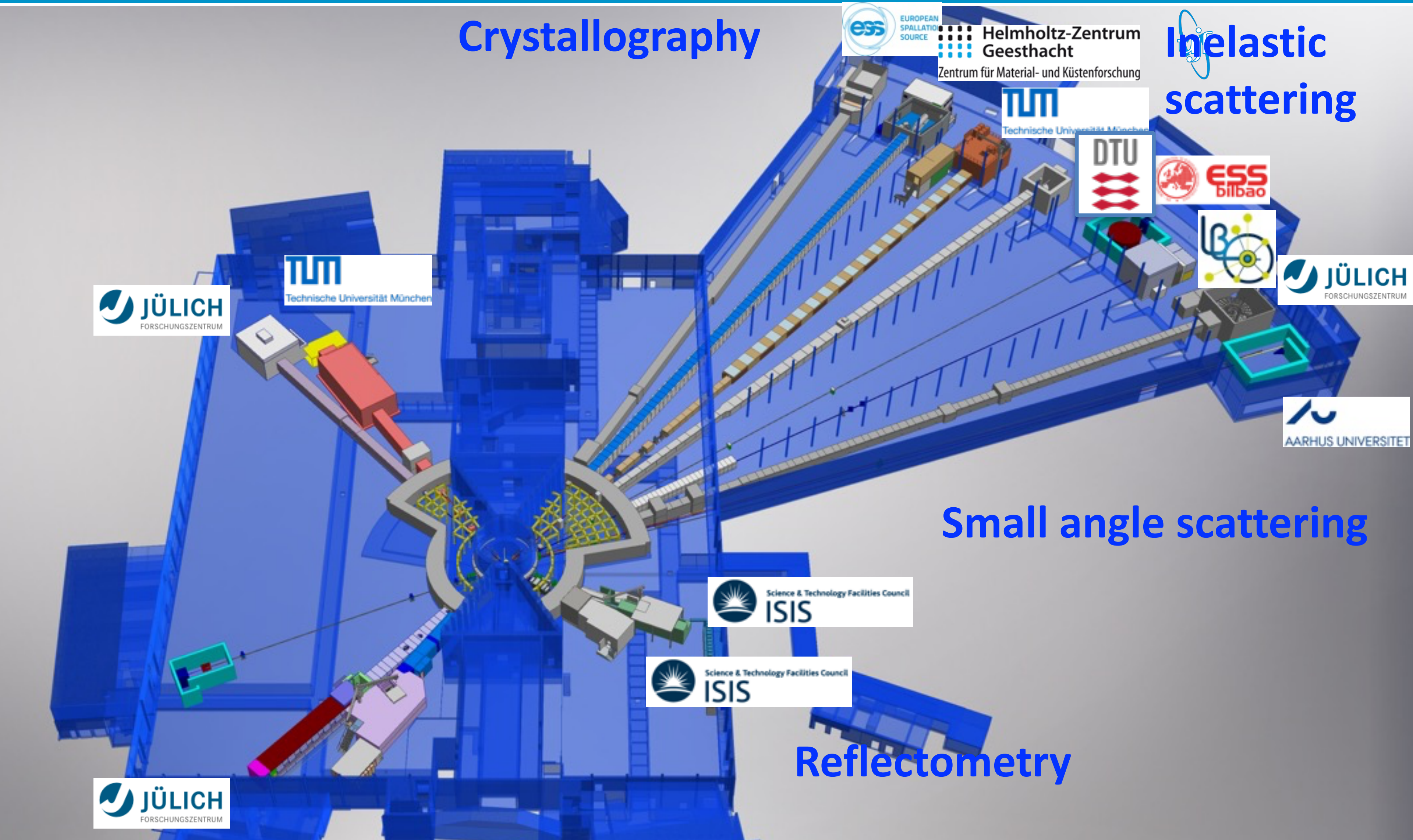

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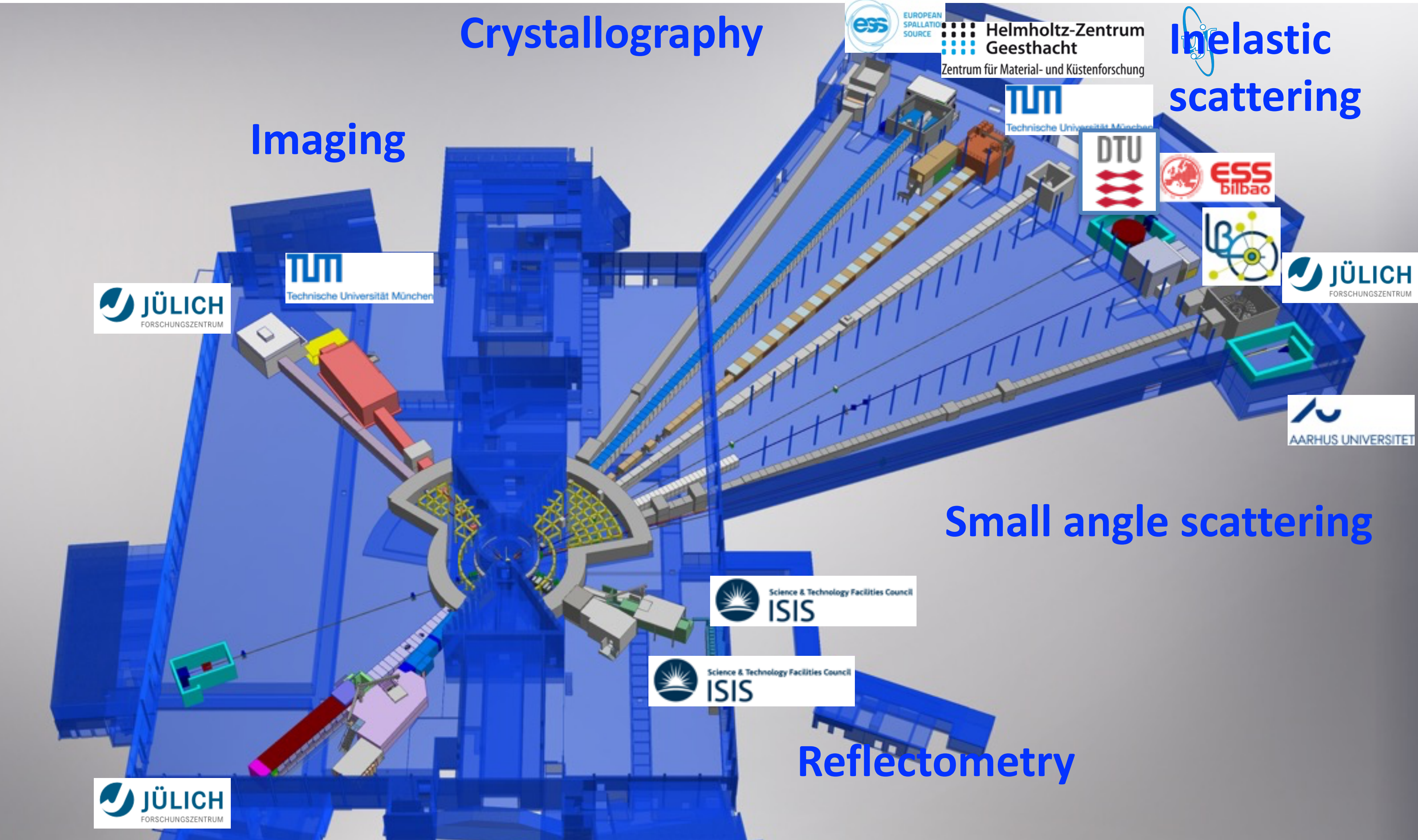
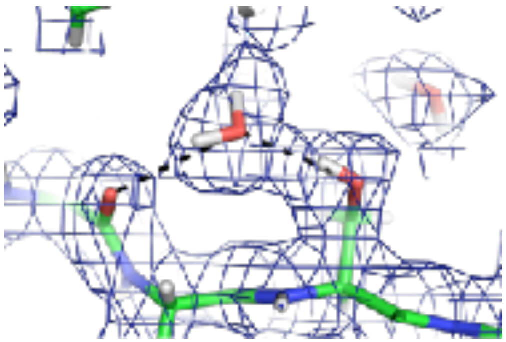
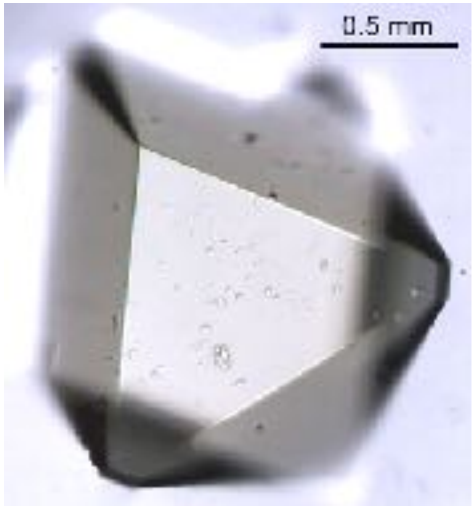


Neutron Macromolecular Crystallography





Oksanen, E *et al. J. R. Soc. Interface* 2009, ***6*** *Suppl 5*, S599-610.

☺Hydrogens are visible

☺No radiation damage

☹Large crystals needed

☹Data collection takes weeks

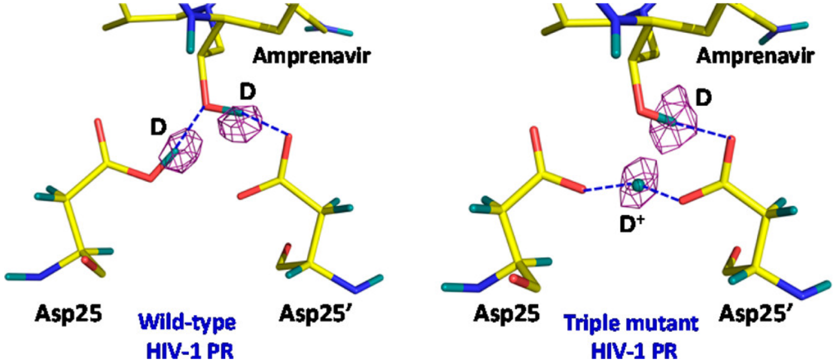
☹Few instruments available

Where are hydrogens important?

Enzyme mechanisms

Protein-ligand interactions

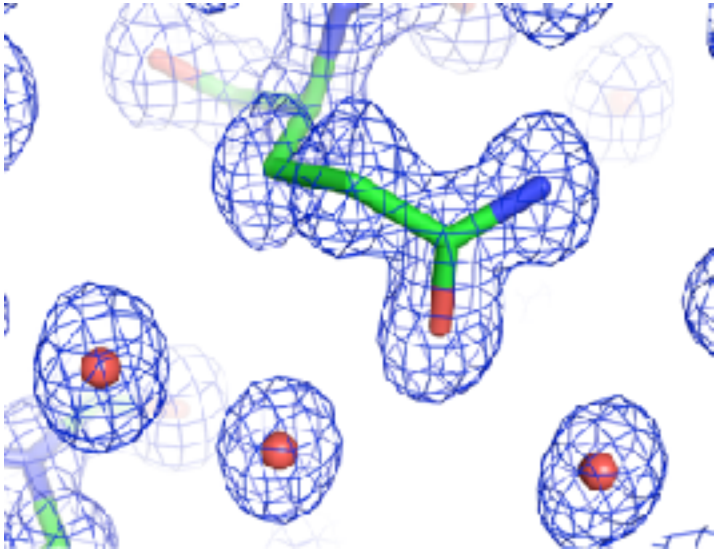
Proton transport across membranes



Gerlits et al., (2017) J. Med. Chem. **60**, p.2018

Limits of X-ray crystallography

- X-rays scatter from electrons
- Even at atomic resolution only part of hydrogens visible
- Aldose reductase (0.66 Å) 54% of hydrogens visible
- The more polar the less visible



X-ray (1.1 Å)

Why is hydrogen interesting?

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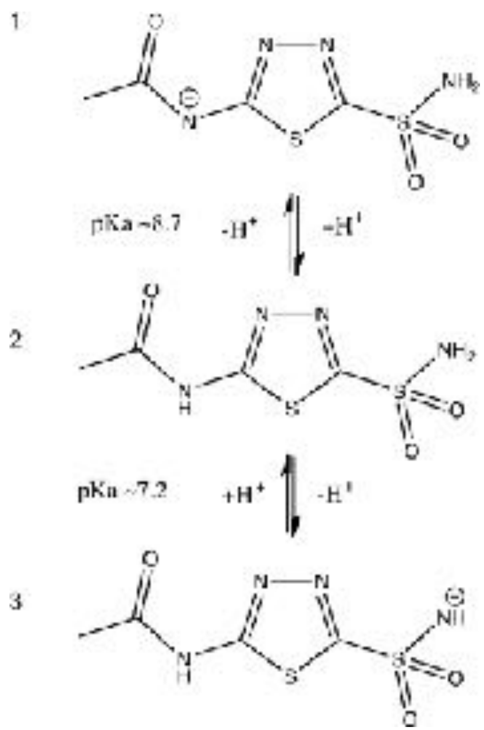
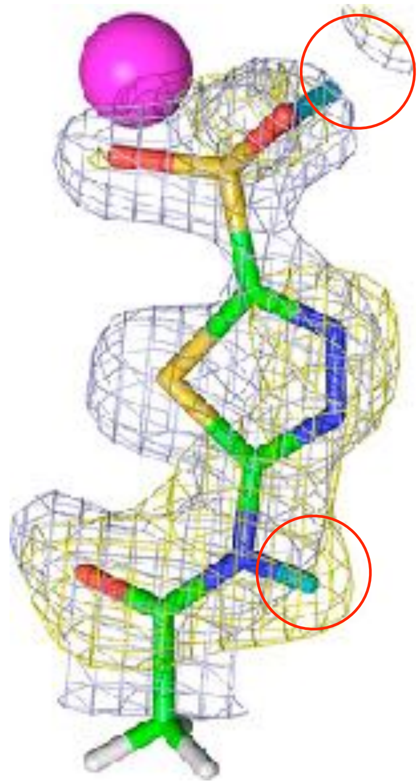
Ligand binding and protonation states
Acetazolamide in Human Carbonic Anhydrase II

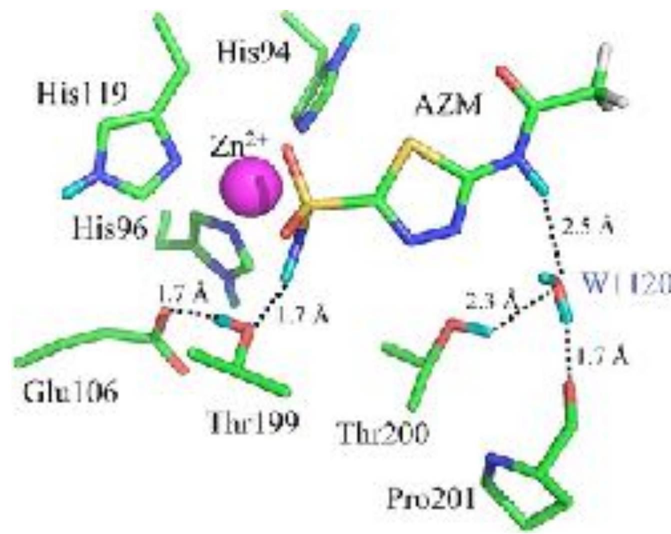
Three possible protonation states at physiological pH



Protonation state clearly determined by neutrons



Provides full picture of ligand binding

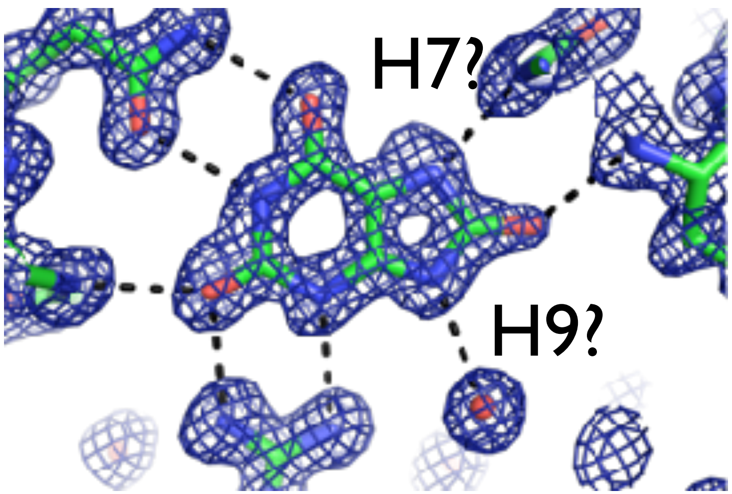


Fisher SZ *et al.* JACS (2012);**134**:14726-14729

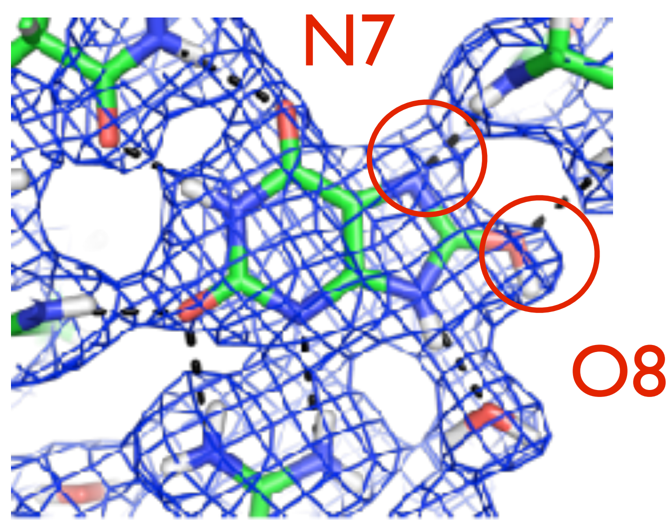
Why is hydrogen interesting?

Enzyme mechanism

Urate oxidase



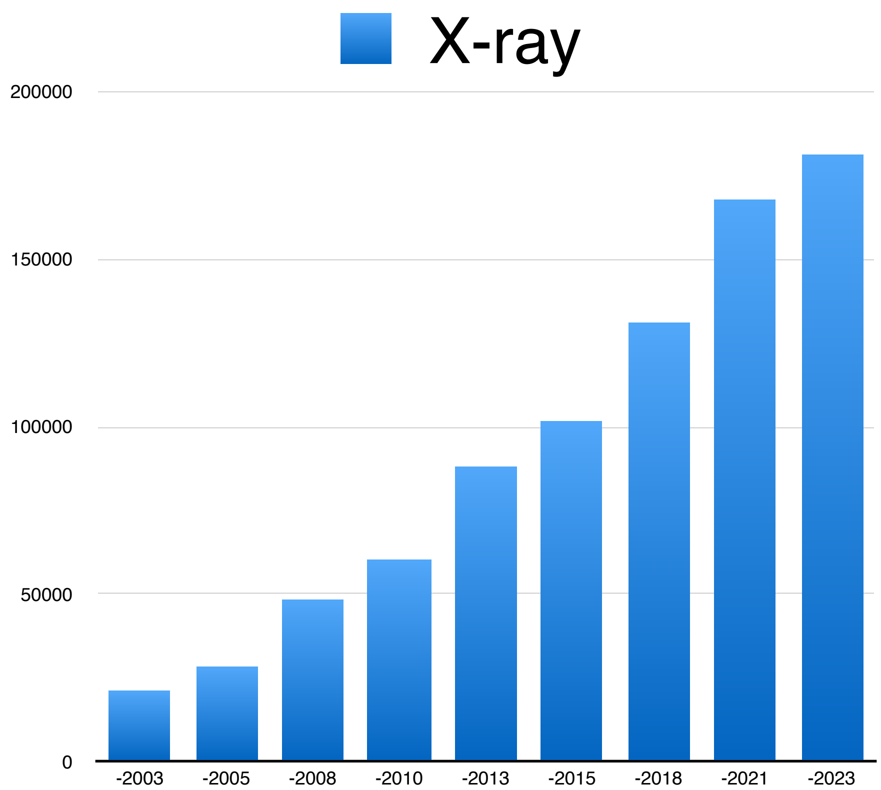
Mono- or dianion?

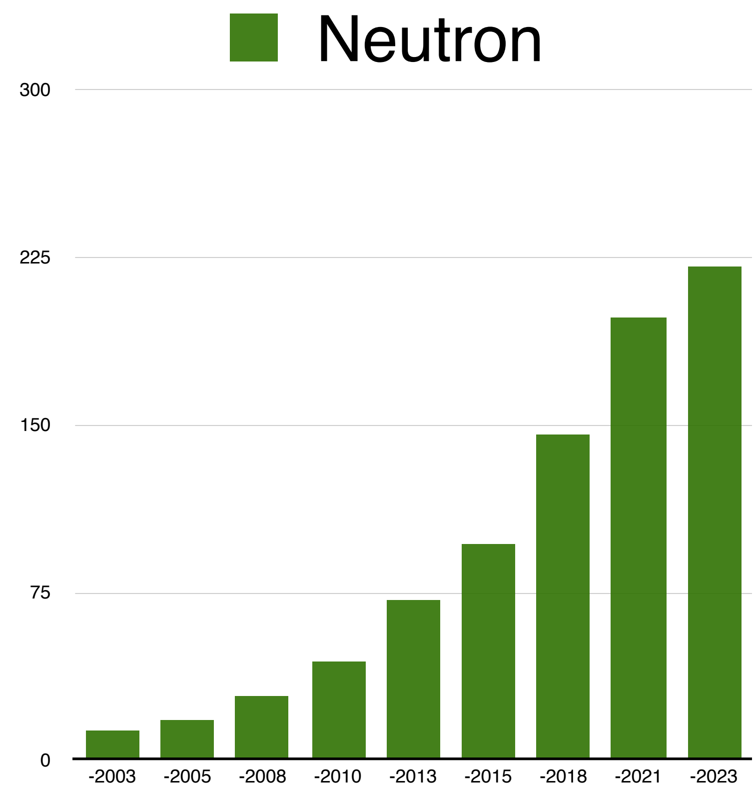


Unexpected enol form
(8-hydroxyxanthine)

Oksanen, E.; Blakeley, M. P.; El-Hajji, M.; Ryde, U.; Budayova-Spano, M. *PLoS ONE* (2014), ***9***, e86651

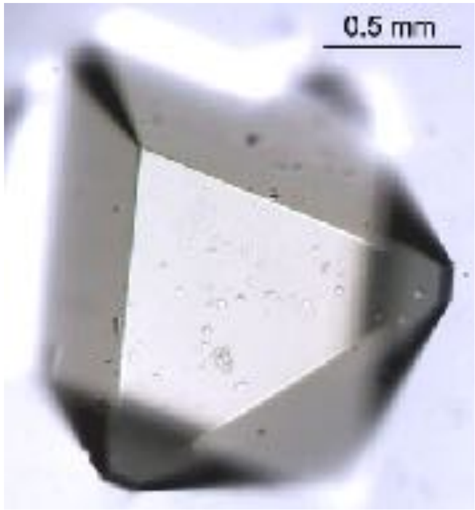
Neutron crystallography is still difficult





Challenges for neutron crystallography

- **Weak neutron sources**
  - Bigger crystals → more diffracting volume
  - Use Laue geometry → make all neutrons count
- **Incoherent scattering**
  - Exchange ^1H to ^2H (deuterium)
  - Produce perdeuterated protein



Oksanen, E *et al. J. R. Soc. Interface* **2009**, *6 Suppl 5*, S599-610.

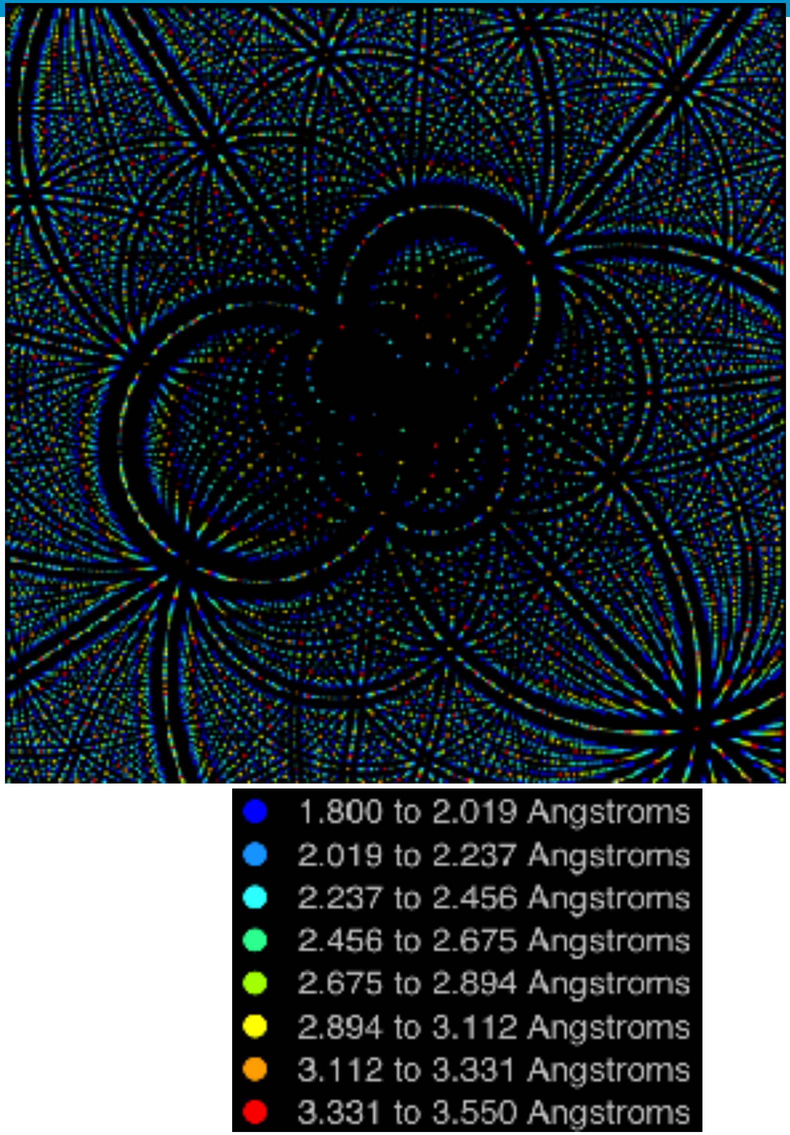
What can we do about incoherent scattering?

EUROPEAN SPALLATION SOURCE

- Replace all hydrogen by deuterium
- Exchange of mother liquor by D_2O & deuterated reagents ← Indispensable!
- Perdeuteration of protein = expression in D_2O & deuterated carbon source ← Very helpful

Laue Crystallography -using more wavelengths

- Uses more of the available flux than monochromatic methods
- Signal at one λ- background at all
- Data processing is more complicated → harmonic & spatial overlap
- Very sensitive to crystal mosaicity



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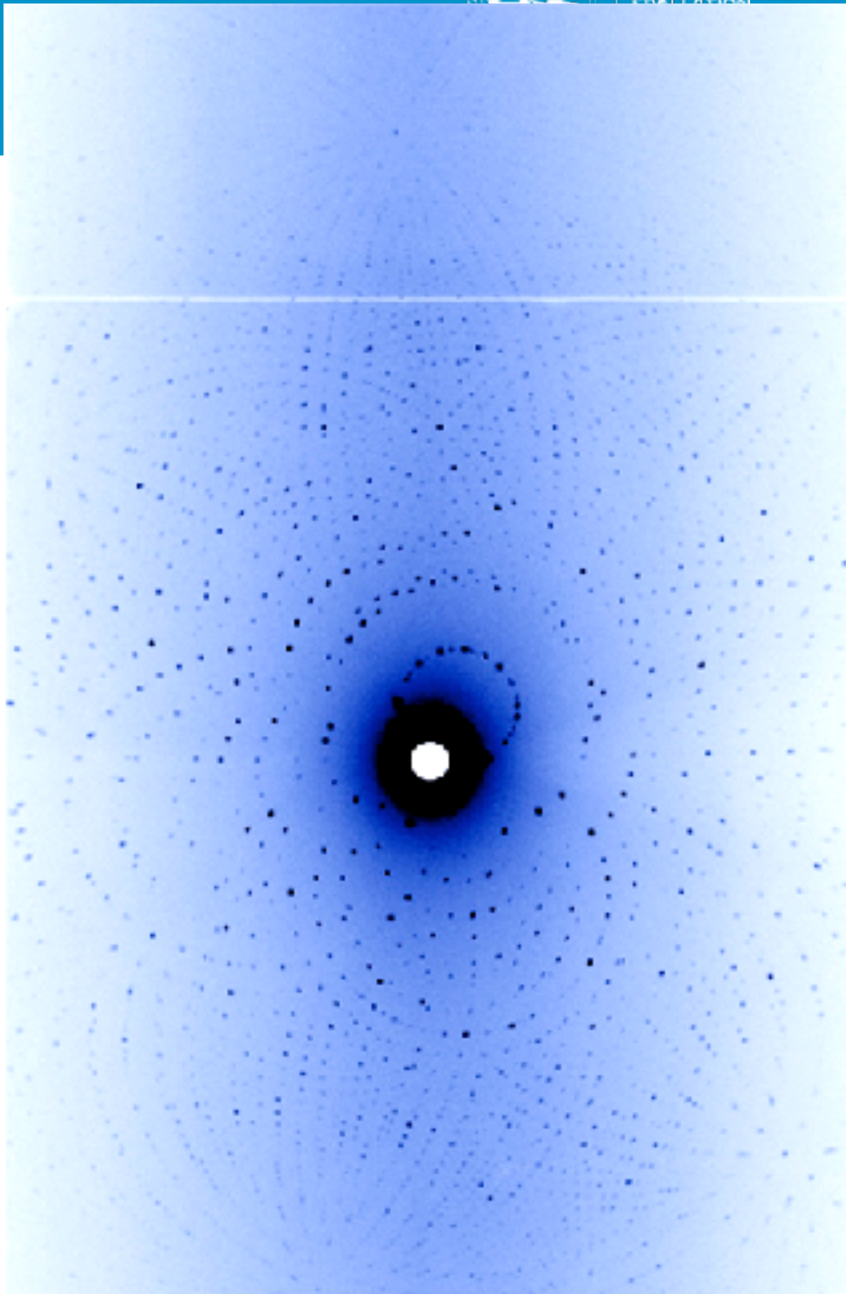
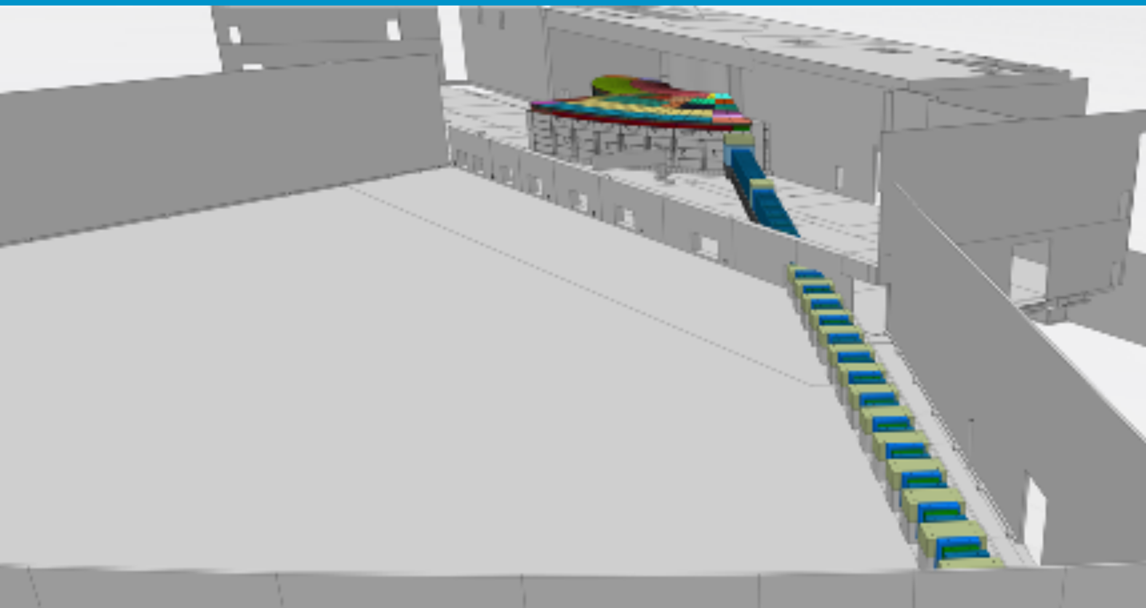


NMX – Macromolecular diffractometer at ESS



Where are hydrogens important?

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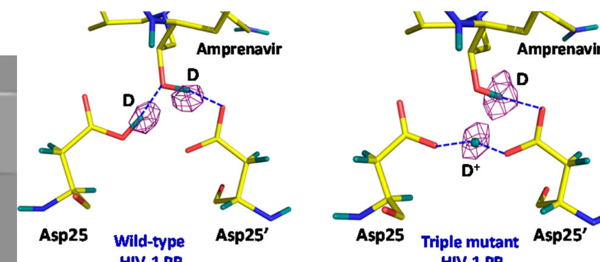
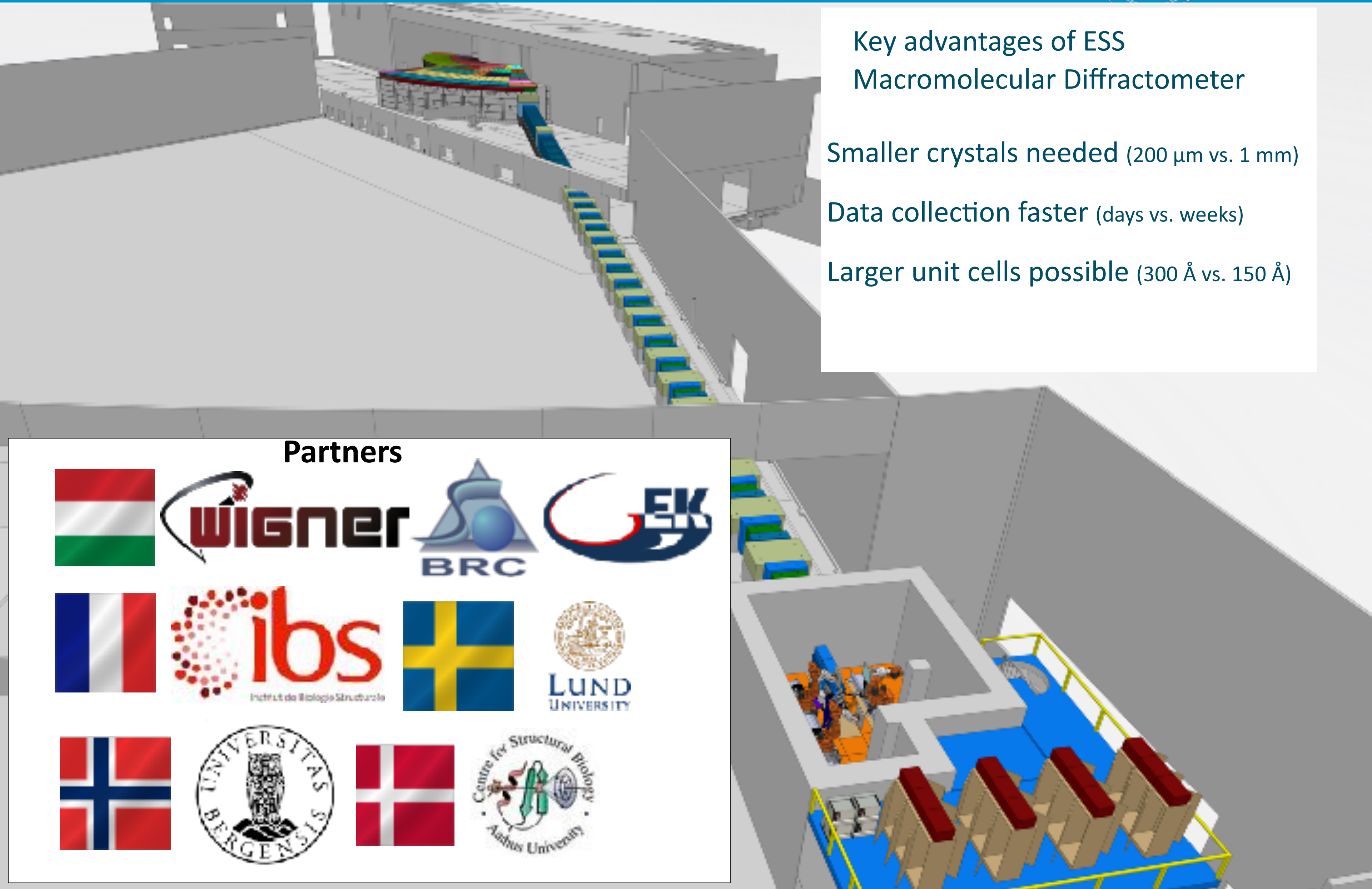
Proton transport across membranes



Partners

NMX – Macromolecular diffractometer at ESS



Key advantages of ESS Macromolecular Diffractometer

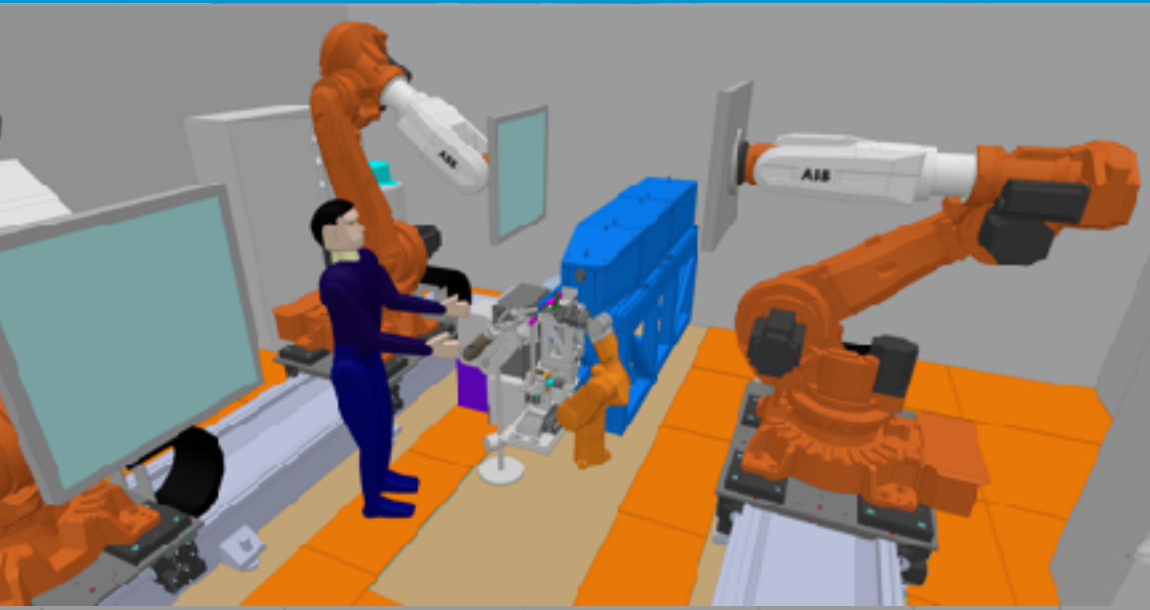
Smaller crystals needed (200 µm vs. 1 mm)

Data collection faster (days vs. weeks)

Larger unit cells possible (300 Å vs. 150 Å)

Partners

NMX – Macromolecular diffractometer at ESS



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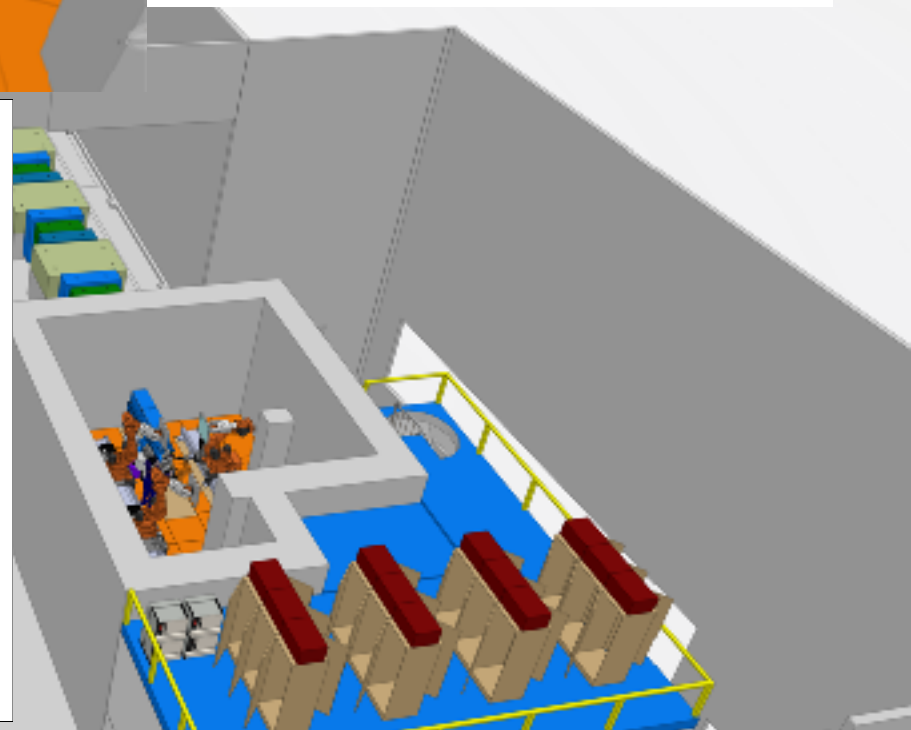
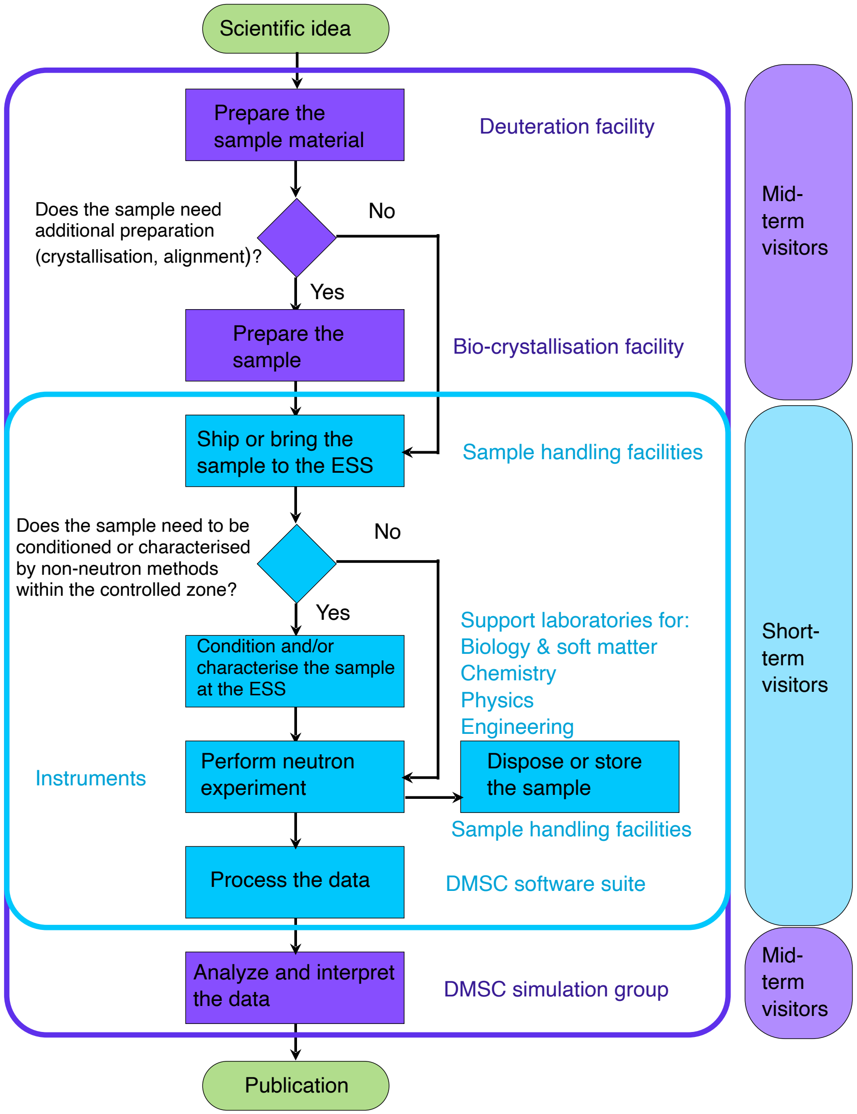


Supporting facilities



DEMAX platform together with Lund University

Questions?

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