League of Advanced European Neutron Sources

LENST is a consortium of European neutron sources with the aim of strengthening European science by developing a coherent strategy to meet current and future demands of the scientific communities.

Membership:

• Institute Laue Langevin ILL (Chair: H. Schober)
• European Spallation Source ESS
• Forschungszentrum Jülich FZJ
• Heinz Maier-Leibnitz Zentrum MLZ
• Paul Scherrer Institute PSI
• ISIS Neutron and Muon Source
• Budapest Neutron Centre BNC
• Institute for Energy Technology IFE
• Laboratoire Léon-Brillouin LLB

https://www.lens-initiative.org
Science Using Neutrons

Solving the grand challenges facing our societies often requires the development of new high-performance materials. Research on materials will provide the basis for the technologies of the future that are needed to achieve a sustainable high standard of living all over the globe.

Tailor-made materials and material systems are required for the advancement of all key technologies, from information technology and renewable energy concepts, to safer and more environmentally friendly transport systems, to life-saving medical applications. Probing materials with neutrons stands as one of the pillars of the analytical techniques in this chain of discovery.

LENS will help develop these technologies by optimising the use of resources for neutron investigations through strategic coordination among the neutron facilities.

Neutrons have exciting abilities which allow scientists to understand the world around us at the atomic and molecular level, in a non-destructive manner. This makes neutron science one of the most useful analytical techniques used across numerous science and technology disciplines. Due to the characteristics of neutrons – making them suited to investigate magnetic properties, light elements or big samples – they can address scientific questions arising from many grand societal challenges and make great socio-economic impacts.

Ensuring healthy lives and promoting wellbeing is a key current and future grand challenge for society. These challenges are wide-ranging, from the transmissible diseases such as Malaria or Zika which affect life expectancy, to age-related diseases like Alzheimer’s or Parkinson’s which reduce quality of life. Understanding the complex biological processes that regulate our bodies is critical to understanding these threats, as well as learning how to minimise the damage they cause. Researchers must take advantage of all the tools at their disposal, particularly those that offer insight at the molecular scale.

Neutrons are a particularly valuable analytical tool as they are able to target very specific information, often with atomic resolution, in various sample environments. In the field of human health research – which relies heavily on the study of biological materials – neutrons’ non-destructive manner is particularly advantageous, empowering neutron science to enable a wide range of discoveries that have a real-world impact on improving health.

https://www.lens-initiative.org
LENS WG3: Synergies in Technological Development and Operation

- Deuteration technologies
- Sample environments
- Technologies for polarized neutrons
- Moderator systems
- Neutron delivery systems
- Detectors
- Future sources
- Standardisation

⇒ Collaboration between technical groups
⇒ Participation in /support for science driven PAs

Pilot Action: Coherent action towards solving a specific scientific/societal challenge using neutrons:

PA1: Electronic Spectroscopy of Quantum Material at Extremes of Magnetic Fields
PA2: New Materials from Extreme Synthesis Routes
PA3: Global Health Challenges
PA4: Energy Storage Systems
WG3 Pilot Action 3: “Global Health Threats”

Goal: *To develop experimental and analytical strategies to support neutron science investigating the molecular mechanisms of disease processes and solutions to global health challenges, e.g. aging-related diseases and resistant/new pathogens*

- Diabetes II (100M), Alzheimers (44M), Parkinsons(10M)
- Cardiovascular disease
- Cancer
- Antibiotic resistance and emerging pathogens

- Detection and diagnostics
- Drug development & delivery
- Treatment and prevention

**Novel therapeutics e.g. antimicrobials**

**New materials for drug delivery, formulation**

*To develop better diagnostics, therapeutics and prevention strategies, need to investigate these in a physiologically relevant environment*
Cells are full of different membrane compartments, each with a unique function:

**Aging related health challenges:**
- Amyloid-lipid coaggregation: in neurodegenerative diseases
- Lipid oxidation: aging, programmed cell death, cancer
- Lipid metabolism: in diabetes type II, cardiovascular disease

**Pathogens**
- Interaction with different cells
- Binding to membrane protein receptors
- Entry through cell membranes
- Release and replication inside host cells

**Therapeutics**
- Membrane protein drug targets
- Novel antimicrobials to combat antibiotic resistance
- Antimicrobial peptides, antifungal/parasitic agents, synthetic analogues

**Drug delivery**
- Development of new delivery materials
- Interaction with membranes
- Intracellular delivery of drugs - crossing the cell membrane
- Release of drugs from lipid vesicles at/inside the target cell

*Most of these disease processes and their treatment involve cell membranes and lipids*
Neutrons are an excellent probe for complex biological systems such as cell membranes and can probe their structure and dynamics under physiological conditions

- in situ and functional studies of multicomponent systems using deuterium labeling
- Unique and complementary information to other experimental probes and computational tools.

Neutron reflection: 1D membrane structure and composition, protein, drug, pathogen binding etc.

SANS: solution structure of proteins, receptor and antibody complexes, lipid nanodiscs/micelles, liposomes

Grazing incidence SANS: lateral membrane structures at the nm-length scales

Membrane diffraction: 1D structures of internal lipid membrane organisation

Neutron spectroscopy: protein, lipid and water dynamics

Neutron Protein Crystallography: H-atom bonding, enzyme mechanisms and structure-based drug discovery
So why doesn’t everyone use neutrons for biomedical studies?

The main challenge is to increase the impact and medical relevance of neutron studies by improving the range of samples that can be studied and how they are manipulated:

1) DEUTERIUM LABELING AND PRODUCTION OF BIOLOGICALLY AND MEDICALLY RELEVANT SAMPLES:
   • Deuteration of lipids, proteins, drugs and materials for drug delivery/diagnostic materials for neutron contrast
   • Recreation of realistic models of relevant biological environments: specific cell membrane compositions, membrane sample reconstitution, membrane protein reconstitution
   • Membrane protein deuteration and crystallization are challenging

2) AUTOMATION AND INCREASING SCIENTIFIC OUTPUT:
   • Automation of sample handling and changing - challenging for liquid samples and in-situ experiments
   • New and future instruments enable smaller samples/fast measurements: need to increase automation to make use of this.
   • Automation important for biological safety and remote experiments, which could become more important now.

3) Large samples required for some neutron experiments
   • Explore new ways to use polarized neutrons for detecting low signals
   • Focusing optics, new sources, faster/more efficient detectors
So why doesn’t everyone use neutrons for biomedical studies?

The main challenge is to increase the impact and medical relevance of neutron studies by improving the range of samples that can be studied and how they are manipulated:

Long-term sustainable development is required to continuously address new scientific challenges, and this should clearly be done in close collaboration with the research communities.

Responding to sudden changes such as the Covid-19 pandemic also requires that sufficient in-house competence exists at neutron sources to tackle quick development.

Automation and remote experiments are not always possible but much more could be done.

3) Large samples required for some neutron experiments
   • Explore new ways to use polarized neutrons for detecting low signals
   • Focusing optics, new sources, faster/more efficient detectors
Possible Technical Implementation in LENS WG3

### Preliminary project: 2020-2021

<table>
<thead>
<tr>
<th>Deuteration Technologies</th>
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<tbody>
<tr>
<td>• Survey of current methods</td>
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<tr>
<td>• User consultation: survey/workshop</td>
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<tr>
<td>• Deuteration of key mitochondrial lipids</td>
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<td>• Existing user collaborations/ projects</td>
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<table>
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<tr>
<th>Sample Environment</th>
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<tbody>
<tr>
<td>• Survey of current limitations</td>
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<tr>
<td>• Workshops to identify solutions and to define requirements</td>
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<tr>
<td>• Survey of commercial technologies</td>
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<tr>
<th>Polarized Neutrons</th>
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<tbody>
<tr>
<td>• Polarised QENS/NSE/GINSES tests</td>
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### Long term projects/development:

<table>
<thead>
<tr>
<th>Deuterntion Technologies</th>
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<tr>
<td>• Deuteration to recreation of relevant cellular environments with neutron contrast</td>
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<tr>
<td>• Development of deuteration, purification and sample reconstitution methods</td>
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<tr>
<th>Sample Environment</th>
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<tr>
<td>Topic 1 - Automatic sample injection/delivery</td>
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<td>Topic 2 – Automated sample changing</td>
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<tr>
<td>Topic 3 – Controlled humidity chamber(s)</td>
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<td>Topic 4 – Lower sample background</td>
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<tr>
<td>• Detailed comparison of existing technologies</td>
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<tr>
<td>• Identification of commercial suppliers</td>
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<td>• Prototype design and construction</td>
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### Synergies with other PAs in:

- Moderator Systems
- Neutron Delivery Systems
- Detectors
- MD Simulation/Software (WG4)

+++ Scientific Research collaborations!!!
Webinar series on “Global Health Threats”

Engage with research communities and discuss challenges and developments
Disseminate current capabilities and LENS activities
Develop connections to other RIs and promote neutrons
Position for future funding opportunities: Horizon Europe

Webinar topics August 2020 onwards:
• Cancer
• Amyloid aggregation and Alzheimers/Parkinsons disease
• Cardiovascular disease
• Diabetes type II
• Antibiotic resistance
• Drug development and delivery systems

https://www.lens-initiative.org/2020/06/02/lens-webinars/
Thank you!

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+ everyone else from WG3 who participated in LENS PA3 discussions