Biological Systems: Revolutionizing Health and Biomaterials

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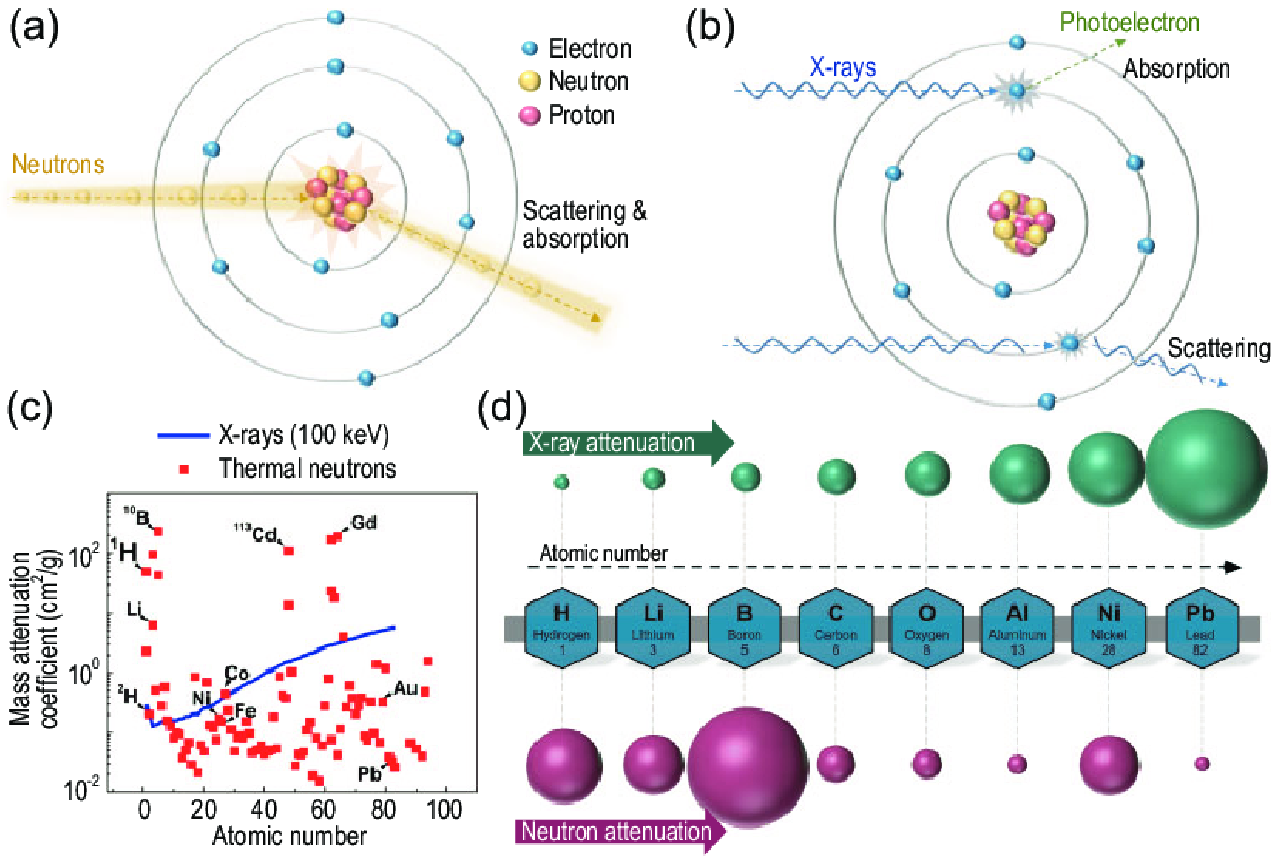
Second target Station Grand Challenges Workshop – Washington DC, August 24-27th.

Neutrons to Study Biological Systems

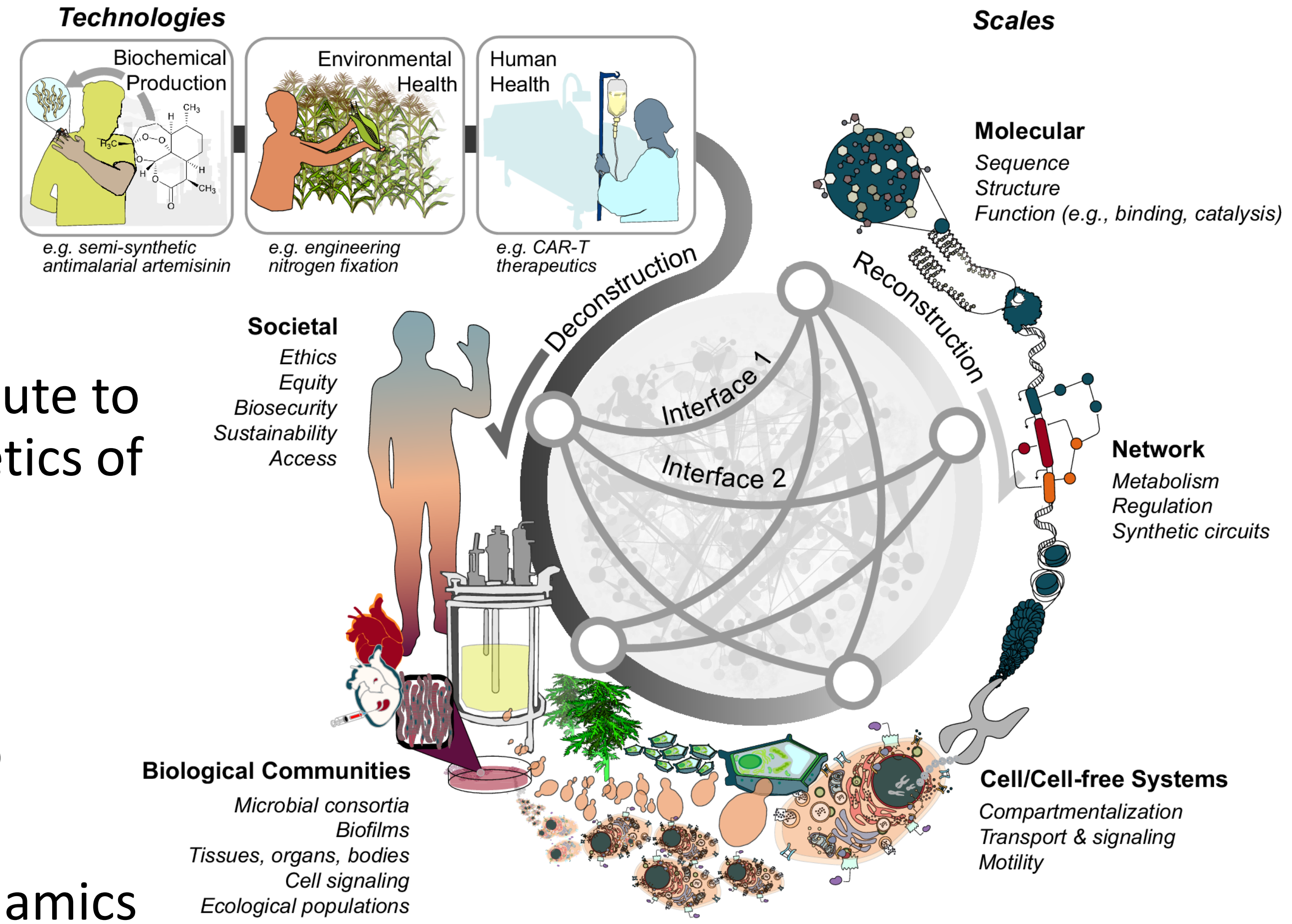
- Only technique capable of locating every proton within macromolecules.
- Hydrogen make up about half the atoms in proteins, proteins make up assemblies, assemblies make up cells etc.
- Hydrogen atoms are key players in mediating interactions and are fundamental to the energy landscape and therefore mechanism
- The energy scales are matched to the motions of atoms and molecules enabling the study of dynamics



Gao et al., National Science Review 10(11), 2023

Engineering the Principles of Life (Synthetic Biology)

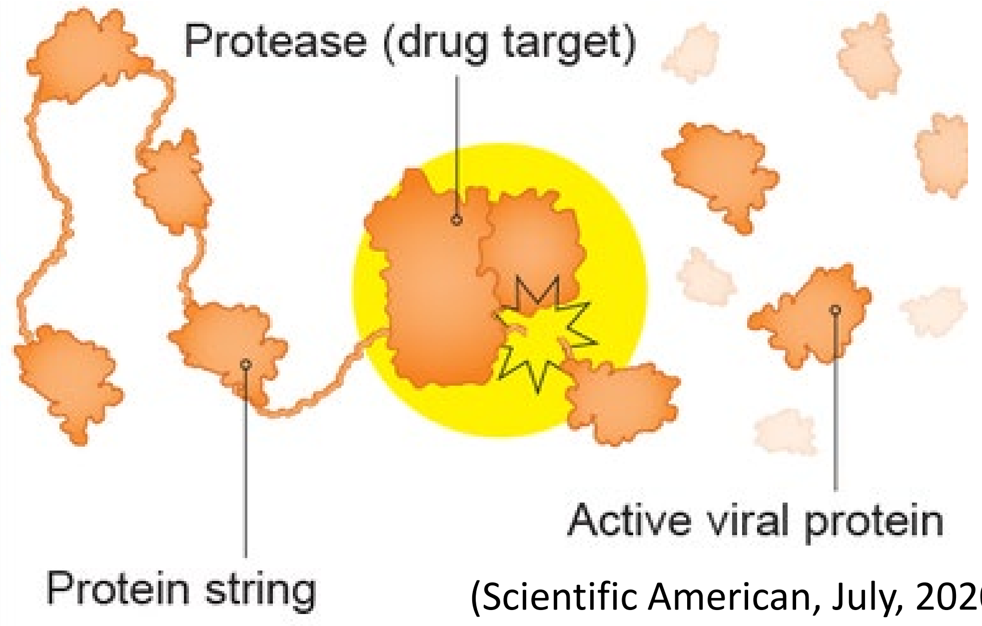
- How do hydrogen bonds contribute to the specificity, stability, and kinetics of enzymatic reactions?
- How do protons move through complex protein systems?
- How does structured water help stabilize biology?
- What is the distribution and dynamics of hydrogen in cells?
- How do lipids modulate protein function?



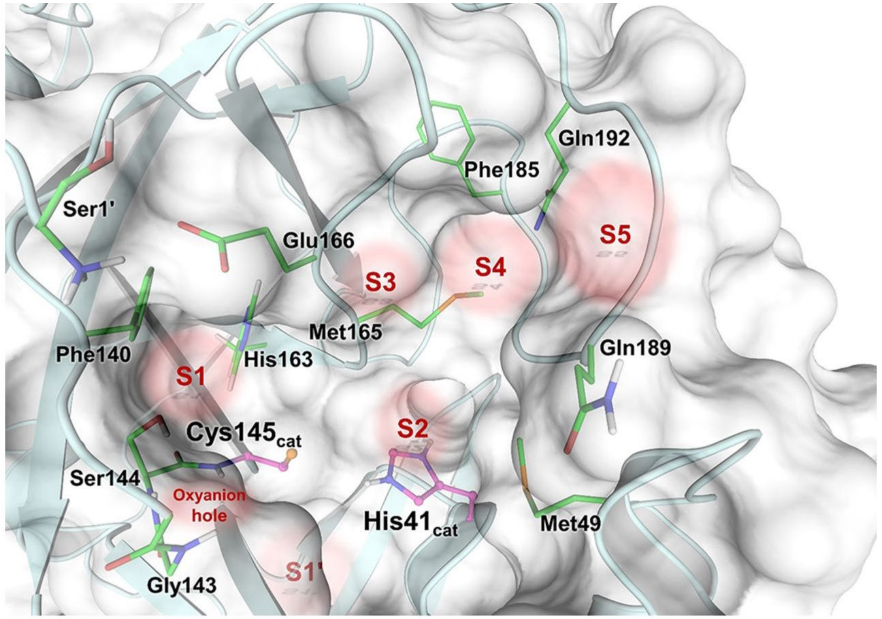
Karim et al., Nature Communications volume 15, 5425 (2024)

Biosecurity and Biopreparedness

- Developing lipid nanoparticle delivery systems.
- Structure and function of hydrogen rich threats such as toxins and pathogenic viruses
- Optimizing hydrogen bonding and hydration properties of vaccines and antibodies
- Understanding how pathogens survive and how to defeat them
- Studying mechanisms at physiological temperatures



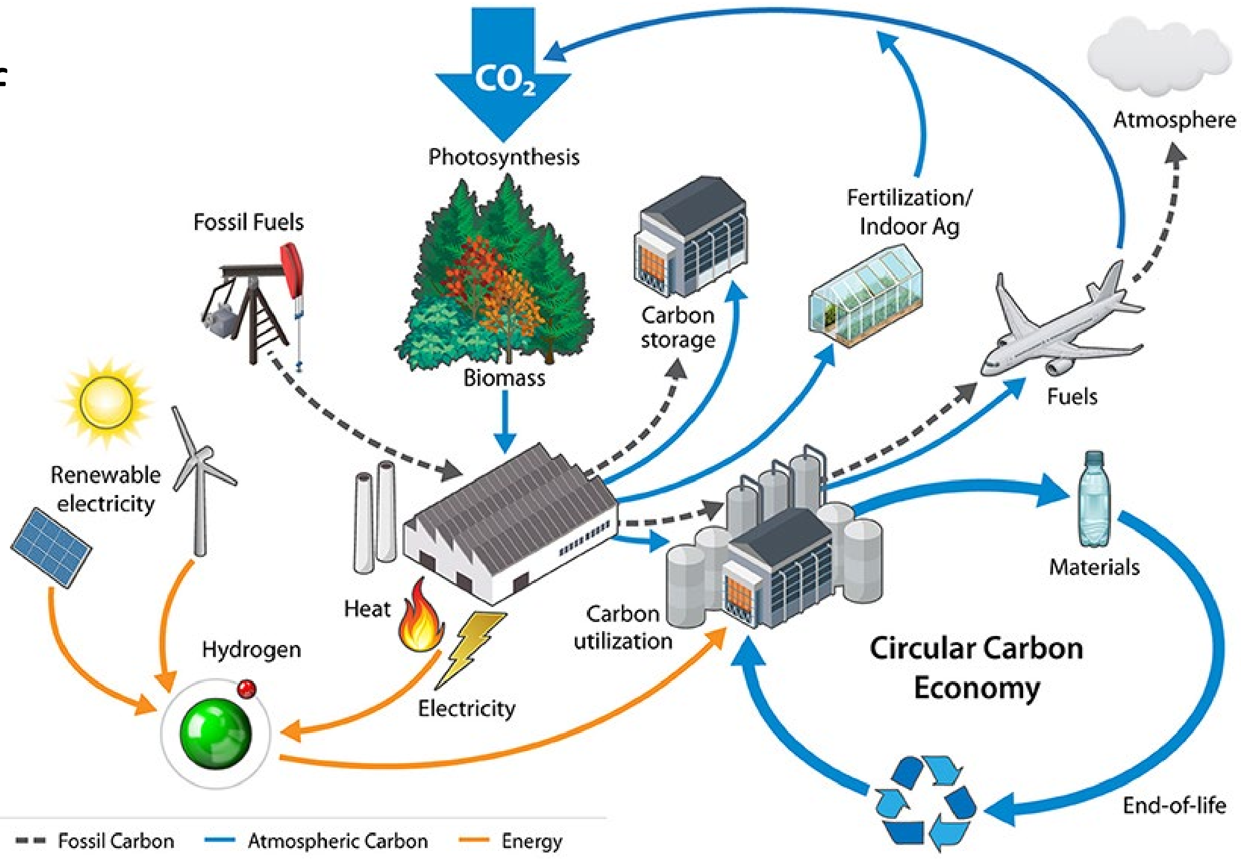
(Scientific American, July, 2020)



Catalytic site of SARS–CoV-2 main protease - Kneller at al., JBC 295 (60), 2020

Bioenergy and the Circular Bioeconomy

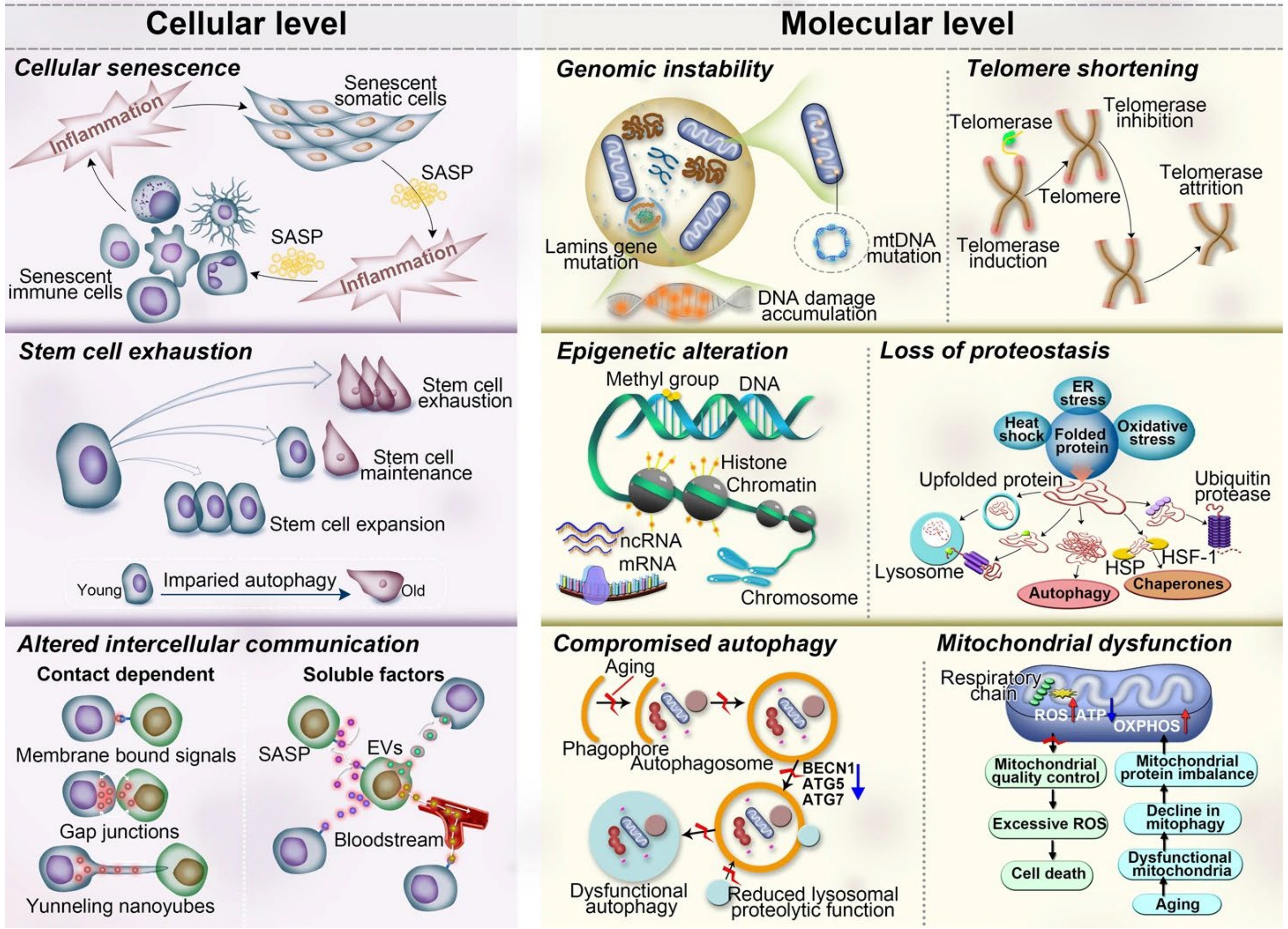
- How do hydrogen bonds influence enzyme stability and efficiency - design of more robust biocatalysts for renewable energy applications
- Understanding hydrogen positions and pathways in metalloenzymes and synthetic catalysts to advance carbon-neutral energy solutions.
- Whole-cell and organelle imaging can visualize hydrogen-rich biomolecules, advancing systems biology models for microbial communities used in bioenergy production and waste bioremediation.



Tan and Lamers, Front. Sustain., 11 July 2021

Understanding the Molecular Basis of Health, Aging, and Well-Being

- Neutron techniques leverage isotopic substitution enabling precise studies of metabolic pathways, signaling networks, and stress responses
- Scattering techniques can investigate hydrogen and hydration dynamics in amyloid fibrils or prion proteins, important for age related diseases.
- Enable the accurate characterization protein ligand interactions, providing critical data to optimize drug binding, efficacy, and selectivity



Ageing example adapted from Guo et al., Signal Transduction and Targeted Therapy, 7, 391 (2022)

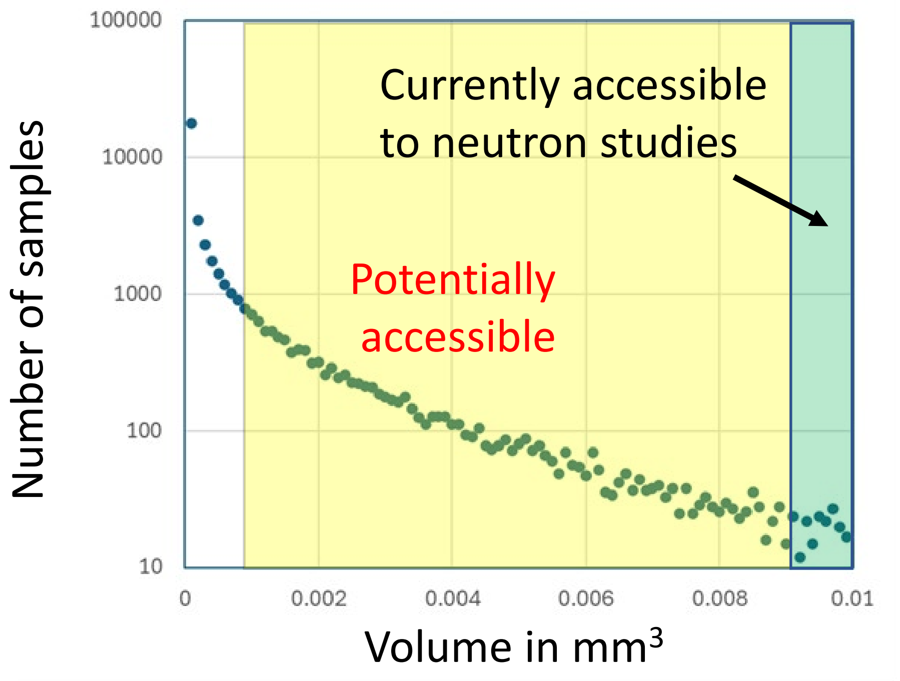
Enhancing Accessibility for the Expanding Scientific Community

- Experiment that takes days or weeks become hours or even minutes.
- More researchers will have access.
- The analysis of smaller or lower-concentration biological samples becomes possible.
- Higher brightness enables the use of advanced techniques such as neutron spin echo, neutron reflectometry, and small-angle neutron scattering (SANS) with unprecedented resolution and speed.
- Brightness improvements make it feasible to study biological systems under more native-like conditions, such as whole cells or organelles bridging the the gap between in vitro and in vivo studies.
- high-resolution time-resolved studies of fast biological processes, such as enzyme-substrate interactions, proton transfer, or allosteric signaling become possible
- Faster experiments and reduced sample size requirements lower the barriers for smaller research groups, early-career scientists, and underrepresented institutions

Case for diffraction

- Structural biology has led to multiple Nobel Prizes. Each experiment provides profound detail of biological mechanism.
- Neutrons provide the detailed information to understand enzymatic processes that no other technique can.
- There are about 15 new neutron bases structural models per year with 30% coming from the SNS.
- A 50x increase in brightness could allow the technique to be used with challenging samples, and/or increase the investigations carried out by at least an order of magnitude.
- This provides information on hydrogen and protonation state that starts to extend the ability of AI modelling approaches.

A dedicated workshop will be releasing a report on this area



Data taken from a high-throughput synchrotron beamline on ~50K of the typical crystal samples seen (Snell *et al*. in preparation) – note the vertical log scale.

With an increase in brightness of 50x the potential samples that could be studied with neutrons balloons to many of those available to the community.

Case for other biological instrumentation

- **Small and Wide-Angle Neutron Scattering** - High-brightness cold neutrons allows for excellent energy and spatial resolution maximizing Time-of-Flight studies. This will improve the way data is processed and recombined, enable larger structures and assemblies to be measured regularly, and will allow for novel data treatments dealing with inelastically scattered neutrons.
- **Inelastic Scattering** - The nature of the source is ideal for improving the temporal resolution and data acquisition rates for all inelastic scattering experiments. This will enable measurment of picosecond scale molecular vibrations to near-nanosecond scale diffusional motions of solvents and metabolites, to the many-nanosecond scale domain motion of proteins, nucleic acid chains, and lipid membranes. This provides expansive temporal resolution.

An exciting future

- **Neutron imaging** – There are potentially revolutionary improvements over pinhole-camera designs of current neutron imaging and the spatial resolution of neutron images has progressed over time. With high intensity cold neutrons, the goal of a neutron microscope for biological and other materials is on the horizon. This would enable systems level studies integrating other neutron and adjacent imaging techniques
- **Neutron polarization -** Polarization ratios using common 3He spin flippers are strongly wavelength dependent, Improvements in both flux, and polarization ratios due to the nature of the new source will enable completely new data analysis method and make new classes of experiments possible.

Summary

- **An integrated systems wide approach** to studying biological samples at time and length scales that span mechanisms will be required to address grand challenges. This will take time and resources with prioritization of capability.
- Ancillary support will be needed in sample preparation (biodeuteration) and outreach and training.
- The combination of a strong biodeuteration program with higher flux, higher resolution neutron spectroscopy will tell us more about the way lipids, proteins, nucleic acids, metabolites and solvents move at the molecular time and length scale.
- The increased knowledge in this area can leverage machine learning and AI modeling approaches.
- The STS provides a pathway for the SNS and the nation to make a unique impact to biological knowledge over unprecedented length and time scales.