



HAL
open science

Uncovering the Dynamics of Confined Water Using Neutron Scattering: Perspectives

Heloisa Bordallo, Gérald Kneller

► **To cite this version:**

Heloisa Bordallo, Gérald Kneller. Uncovering the Dynamics of Confined Water Using Neutron Scattering: Perspectives. *Frontiers in Physics*, 2022, 10, 10.3389/fphy.2022.951028 . hal-03927973

HAL Id: hal-03927973

<https://hal.science/hal-03927973>

Submitted on 11 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Uncovering the Dynamics of Confined Water Using Neutron Scattering: Perspectives

Heloisa N. Bordallo^{1*} and Gerald R. Kneller²

¹Niels Bohr Institute, University of Copenhagen, Copenhagen, Denmark, ²Centre de Biophysique Moléculaire CNRS and University of Orléans, Orléans, France

The main characteristic of liquid water is the formation of dynamic hydrogen bond networks that occur over a broad range of time scales from tens of femtoseconds to picoseconds and are responsible for water's unique properties. However, in many important processes water does not exist in its bulk form, but in confined nanometer scale environments. The investigation of this confined water dynamics is challenging since the intermediate strength of the hydrogen bonds makes it possible to alter the structure and dynamics of this constrained water. Even if no single experimental technique can give a full picture of such intricate dynamics, it is well established that quasielastic neutron scattering (QENS) is a powerful tool to study the modification of hydrogen bonds in confinement in various materials. This is possible because *neutrons tell us where the atoms are and what they are doing*, can detect hydrogen, are penetrative and non-destructive. Furthermore, QENS is the only spectroscopic technique that provides information on the dynamics and atomic-motion amplitudes over a predetermined length scale. However scientific value of these data is hardly exploited and never to its full potential. This perspective highlights how new developments on instrumentation and data analysis will lead to appreciable progress in our understanding of the dynamics of complex systems, ranging from biological organisms to cloud formation.

Keywords: water, complex systems, neutron scattering, dynamics, modelling

INTRODUCTION

Everything that happens in a complex system can be fully rationalized by a description at the level of matter in motion—atoms and molecules moving, exerting forces, interacting, and exchanging energy with each other [1, 2]. From a simplistic point of view, we can argue that structure-enabled interactions derive from the arrangement of the component molecules, while information on how these interactions change in space and time relates to function. In real organisms the function is enabled by multiscale atomic motions. This is indeed characteristic of many systems where water dynamics is a key component of function [2, 3]. An excellent experimental tool for describing such complex water interactions on multiple length and time scales is quasielastic neutron scattering (QENS). Here, QENS is an ideal tool due to the neutron's natural scattering sensitivity [4–6] and scattering length density contrast between H and D [7]. QENS further allows to study motions in the time region of 10^{-9} to 10^{-13} s, while monitoring such motions in space from 0.1 to 10 nm [8, 9]. This is vital since in complex systems competing short- and long-range interactions result in frustration, and this complex coupling between different variables leads to a non-

OPEN ACCESS

Edited by:

Helge Pfeiffer,
KU Leuven, Belgium

Reviewed by:

Yuri Gerelli,
Marche Polytechnic University, Italy

*Correspondence:

Heloisa N. Bordallo
bordallo@nbi.ku.dk

Specialty section:

This article was submitted to
Biophysics,
a section of the journal
Frontiers in Physics

Received: 23 May 2022

Accepted: 09 June 2022

Published: 04 July 2022

Citation:

Bordallo HN and Kneller GR (2022)
Uncovering the Dynamics of Confined
Water Using Neutron Scattering:
Perspectives.
Front. Phys. 10:951028.
doi: 10.3389/fphy.2022.951028

Markovian, scale-invariant multiple scale relaxation process [10]. In QENS experiments these variables are the positions of the H-atoms in time. Additionally, the neutron's natural scattering contrast between hydrogen (H) and deuterium (H₂, D), both in magnitude and phase, provides for an extraordinary method for highlighting (or hiding) H-containing components in complex systems [5], making neutron scattering especially successful for studies of structural characteristics [11] and dynamics of confined water [3, 4, 6–8, 12–14]. Furthermore, QENS is the only spectroscopic technique that provides information on the dynamics and atomic-motion amplitudes over a predetermined length scale [15–17].

QENS unique ability to access information on the geometry of the motion and its utmost importance for complex soft systems where long-range order is mostly absent will become even more distinct with the increased neutron flux coupled with the development of new instrumentation available on cutting-edge neutron sources [18–20]. New neutron spectrometers will allow simultaneous access to broad regions of time and space and, consequently a better description of complex water interactions. Analysis, interpretation, and modeling of QENS data is however complex, and this is a significant barrier to generating scientific innovation from the experiments performed. While QENS spectra contain the desired information to understand the dynamics in complex soft systems where long-range order is mostly absent [21], our current methods of analysis fail to completely capture the full dynamic nature arising from the multiscale atomic motions [22]. This hinders a more generalized understanding of the mechanisms behind their organizing nature. On one hand, the complex molecular mechanism describing the water dynamics probed by QENS is poorly captured in molecular dynamics (MD) models. The challenge here is the lack of accuracy of the interatomic potentials, hampering real predictive modelling of atomic-scale dynamics in time [23]. While on the other, the complexity of such process makes the analysis, interpretation, and modeling of QENS data difficult [3, 6, 16]. Usually in QENS analysis, empirical models for special atomic motion types are used to extract diffusion coefficients and mean-square displacements [24, 25]. This approach works well when dealing with simple processes. In complex systems, such as water dynamics in a constrained local environment, however, one is faced with an incompletely described problem, needing probabilistic methods to choose between likely models. An alternative, and very promising, approach is to compute the QENS spectrum theoretical parameters to identify physical models to analyze QENS data [14, 15, 26], and thus provide the needed experimental verification by using an energy landscape-based method [12, 27]. In this new framework the QENS spectrum is described by its form, and the parameters related to the structure of the energy landscape; a concept in which the (free) energy of the system is represented by a convex envelope with many local minima and a distribution of barrier heights localized in a restricted domain of phase space.

In this Perspective article, we briefly describe why and how the MIRACLES time-of-flight backscattering spectrometer [19, 28] being built at the European Spallation Source in Lund [18] will

increase our understanding of water dynamics in complex systems. We will also discuss on how the vast scientific value of these data can be better exploited by using a new methodology in which the QENS spectrum theoretical parameters are computed and used to identify physical models to analyze QENS data [15, 16, 26]. In this short Perspective, we do not attempt to lengthily review the field of QENS (and neutrons in general), we refer the interested reader to a very stimulating book where a general introduction into the production and properties of neutrons is followed by a series of papers describing the neutron scattering techniques used to study biological and biologically relevant systems [29].

WATER DYNAMICS IN BIOSYSTEMS AND THE MIRACLES BACKSCATTERING INSTRUMENT AT THE EUROPEAN SPALLATION SOURCE

As mentioned in the Introduction, QENS is unique in its ability to provide temporal and spatial information on molecular motions in the same measurement. Detailed microscopic characterization of diffusive motions in systems with nm length scale confinement have been carried out successfully for some time [5]. Furthermore, the ability to access information on the geometry of the motion is of utmost importance in systems where long-range order is mostly absent, such as in soft matter, including polymers, biomaterials, and macromolecules in living systems. The new generation spallation source and reactor backscattering spectrometers have already opened new doors in recent years for high-resolution neutron spectroscopy. For instance, in life sciences it is now possible to unravel the complex dynamics of such water-dependent complex morphologies using neutron spectroscopy [30]. Nevertheless, structural information from QENS experiments on complex systems depends on the observation-time $(\Delta t)_H$, which is defined by the spectrometer setting and its resolution function [31]. As a consequence, data from experiments carried out on a single time scale defined by $(\Delta t)_H$, i.e. implying a single Fourier-time window, are usually incomplete. This implies that even if current QENS methods allow for a range of observation time covering four orders of magnitude (10^{-9} – 10^{-13} s), a combination of several different spectrometers is normally required to obtain a full understanding of the relevant dynamics [17, 32, 33]. However, the extraordinary flexibility of the time-of-flight backscattering spectrometer MIRACLES [19, 28] being built at ESS will bring a paradigm shift to QENS studies. The variable energy resolution of MIRACLES will allow to better focus on either the water dynamics (well covered at 10 μ eV energy resolution) [17] or on proteins/membranes interactions (well covered at 2 μ eV energy resolution) [34]. Additionally, the high flux offered by MIRACLES will provide for data of high statistical accuracy to be collected faster, thus avoiding biological degradation. Finally, the wider scattering vector (directly related to the geometry of the motion) at higher-energy resolutions together with the large energy transfer range will make it

possible to fully explore restricted diffusion and fitting the free-like water contribution. The technical origin of these striking capabilities rests on the instrument design that optimizes the use of the long source pulse provided by the ESS. It is thus foreseen that MIRACLES will engender unprecedented opportunities for neutron scattering in areas of science not yet fully explored by QENS, such as life sciences, biomaterials, and climate change [29, 35, 36]. This will make MIRACLES to not only do what can be done today much faster, but more importantly, provide for appreciable progress in our understanding of the dynamics of complex systems, ranging from polymers to biological organisms. Questions might remain in how one can disentangle the convoluted dynamics of the hydrogen atoms in living organisms even if we can separate their dynamics by varying the observation time. Certainly, such studies are facilitated with neutron scattering supported by deuteration [7]. This is however a very challenging subject, which has triggered a fascinating study by Okuda et al [37] to which we refer the reader. It is therefore expected that new neutron instrumentation will generate further developments in this area as well. Lastly, the time and space domain covered by Molecular Dynamics (MD) simulations is ideally matched to that offered by MIRACLES. This property facilitates a symbiotic relationship between QENS and MD, in which MD can be used to understand QENS, and conversely QENS can be used to improve and confirm the potentials used in MD. This area of research has grown considerably in the last years, and will continue to do so [38, 39].

Case 1: Short Time Dynamics of Water in Living Systems

Molecular crowding and complexity in and around cells can in principle produce marked slowing of diffusion as well as anomalous and complex diffusive behaviors, such as strongly size-dependent diffusion [40, 41]. Indeed, it is widely assumed that the time scale of diffusion dynamics governs many important biological processes. Thus, information about mobile and immobile fractions of labeled molecules and their diffusion properties are essential for processes such as nuclear organization and signaling in cell division, differentiation, and migration. In pharmaceutical research, it would permit the improvement of drug delivery systems relying on the slow release or on the control of docking [42–44]. Complex dynamics of protein solutions as a function of the ionic strength and protein surface charge patterns is usually studied using light scattering [45]. However, light scattering can only access the global collective diffusion of proteins in solution and cannot detect the internal motions of the proteins or the self-dynamics. Incoherent neutron scattering, on the other hand can provide unique and unambiguous access to the self-diffusion coefficient, but the investigations of the diffusion dynamics of living systems using neutron spectrometers has been severely hindered until recently because of the limited flux provided by the instruments. However, the advent of such research has just begun due to the development of the third-generation neutron backscattering instruments [4, 30, 46–48], but continued growth will depend on the highest-flux and flexibility provided

by the backscattering spectrometer MIRACLES. Additionally, neutron scattering offers the unique capability of performing experiments in various extreme environments, such as humidity [49], pressure [50], electrical stimuli [51], pump probe [52].

Case 2: Dynamics of Biomolecules in Non-aqueous Environments

Biomolecules embedded in non-aqueous environments may exhibit novel exploitable properties, such as altered functionality and increased stability. For example, enzymatic selectivity—including substrate-, stereo-, regio- and chemoselectivity—can be markedly affected and sometimes even inverted by the solvent [53]. On the other hand, sugars and more generally polyols show an outstanding ability in preserving structure and functionality of biomolecules, which has been largely exploited in food, pharmaceutical and biotechnology sciences to optimize protein lyophilization and long-term storage of pharmaceuticals [54]. Fast protein dynamics has been shown to play a key role in determining and tuning these modified functional and stability properties [55]. Currently this type of study is restricted to an approach called elastic window scan [34], while the analysis of the quasielastic signal is very often neglected because of the poor statistics achievable in these cases [56]. The high flux available on MIRACLES, together with its variable energy resolution, will provide efficient simultaneous measurements of both elastic and quasielastic responses in this important time window, thus offering vital information on the coupling between protein and solvent dynamics, on a timescale often left unexplored, yet crucial for the delicate balance between biological functionality and stability.

Case 3: Climate Change and Ice Nucleation

Clouds affect climate, but changes in the climate, in turn, affect the clouds. This relationship implies that clouds modulate Earth's radiation and water balances. Retention of water may increase the freezing probability of water and can in turn serve as seeds for secondary nucleation of ice crystals that potentially grow into cirrus clouds, which can modify the radiative balance and change the climate. Dust, usually a primary catalyst, plays a large role in what takes place in clouds as it supports ice formation [57]. An improvement of our understanding of ice nucleation in clouds is therefore crucial to understanding the effects of global warming. In addition, pollen, bacteria, and spores of fungi can also induce ice nucleation [58]. Since microorganisms, which inhabit plant surfaces, are able to initiate the ice formation, this process can result in frost injury to frost-sensitive plants, which does, of course, have a rather negative effect on agricultural crop yields. Knowledge of water structure and water adsorption behavior on these catalyzing particles is therefore essential for any investigation of this process of ice nucleation. A determination of the dynamics and the structure of condensed water on the surface of chemical and biological ice nucleators would form the basis for sub-sequent parameterization of cloud physics models. However, until now, this type of information is scarce [59, 60]. In the future, the time scale covered by MIRACLES will allow observing relaxation processes related to the coupling of the

water hydrogen-bond to the dust-surface groups [31], while Raman scattering can be used to map the vibrational spectroscopic features arising from the hydration shells and the catalyst [61]. Thus a combination of *in-situ* Raman spectroscopy and imaging with systematic neutron studies performed on MIRACLES, can provide answers to the following questions: How important is the catalyst concentration for ice nucleator? Is aggregation of dust particles important? Can we distinguish relevant changes in the hydration shell before freezing?

EXPECTED IMPACT OF NEW MODELLING APPROACHES TO PROPERLY DESCRIBE WATER-MEDIATED INTERACTIONS OBSERVED BY QUASIELASTIC NEUTRON SCATTERING

Implementation of quantum interpretation of QENS describing the emergent properties of complex systems are urgently needed for a better description of the physical and chemical processes involved in complex systems. Development of “minimalistic” models to explain multiscale relaxation and anomalous diffusion, accounting for the non-Markovian properties of the dynamical heterogeneity of the water molecules constrained in a hydration environment is a promising idea [12, 15, 16, 26]. The concept is to capture the form of QENS spectra with very few parameters and to relate these parameters to the form of the multi-minima “energy landscape” which is explored by the scattering atoms [12]. Here the dynamics of a complex system is described by transitions between different states instead of using the traditional method of trying to fit a QENS spectrum by models for specific atomic motions. The main point of this proposed approach is that it accounts with very few, physically interpretable parameters for the multiscale dynamics in complex systems. The key word here is the “self-similarity” of the observed QENS spectra, i.e., their form invariance under a change of the time/frequency scale. Further development of this new physical interpretation of QENS experiments requires, in a first step, replacing the traditional least squares fitting method for these minimal multiscale models that consider the self-similarity, the most important physical property of the relaxation and diffusion processes in complex systems. The second step is to explore the full information contained on the experimental elastic incoherent structure factor (EISF). The insight resulting from Ref. [15] that the EISF probes effectively the size of the wave function of the hydrogen atoms and not the amplitude of their motions provides a radically new interpretation of elastic neutron scattering, which is central for a quantum mechanical understanding of energy landscapes. It gives also a new physical interpretation for the complex quantum version of the classical van Hove correlation functions, where we consider simply classical trajectories to explain the diffusion process. This methodology will enable to capture the dynamic nature of complex systems and understanding the dynamics of

hydration (interfacial) water. It is our view that a proper description of water-mediated interactions will impact many areas of research, ranging from the understanding of cloud formation [50] and long-term stability of protein therapeutics [62, 63] to improved food processing [64] and conservation of museum artifacts [65].

OUTLOOK

Chemical and physical properties are governed by quantum mechanics and to view these complex interactions, we are constructing a multi-billion large-neutron source in Lund [18]. ESS will provide unprecedented access to quantitative structural and functional information from the atomic scale to the relevant mesoscales where real-world functionality often emerges in materials and complex biological systems. Neutron spectroscopy allows for direct measurements of space- and time-dependent information, which in principle can be compared directly with theoretical calculations. More specifically, QENS data gives insight in particularly crowded environments in the nanometer-nanosecond window, and biological applications are particularly important in this context [4, 5, 16, 40, 41]. To exploit QENS’ full potential and allowing for instance to link QENS studies of protein dynamics with spectroscopic or kinetic experiments on biologically relevant time scales, such as dielectric and fluorescence correlation spectroscopy [66], harvesting information contained in QENS spectra needs a radical change in paradigm [12, 15, 16, 26]. We consider that theoretical and molecular dynamics modelling, and consequently development of new models that provide direct insight into physical properties of bio-materials and -molecules, must be rigorously developed and implemented in the analysis of the experimental data.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

HB is grateful for the valuable discussions with the late R. E. Lechner, D. N. Argyriou, M. Hagen, W. P. Gates, L. P. Aldridge, M.-C. Bellissent-Funel, F. J. Villacorta, M. H. Petersen and all the collaborators in the MIRACLES proposal to the European Spallation Source.

REFERENCES

- Cairns AB, Cliffe MJ, Paddison JAM, Daisenberger D, Tucker MG, Coudert F-X, et al. Encoding Complexity Within Supramolecular Analogues of Frustrated Magnets. *Nat Chem* (2016) 8:442–7. doi:10.1038/nchem.2462
- Persson E, Halle B. Cell Water Dynamics on Multiple Time Scales. *Proc Natl Acad Sci U S A* (2008) 105:6266–71. doi:10.1073/pnas.0709585105
- Bordallo HN, Aldridge LP, Churchman GJ, Gates WP, Telling MTF, Kiefer K, et al. Quasi-Elastic Neutron Scattering Studies on Clay Interlayer Space Highlighting the Effect of the Cation in Confined Water Dynamics. *J Phys Chem C* (2008) 112:19982–91. doi:10.1021/jp803274j
- Martins ML, Dinitzen AB, Mamontov E, Rudić S, Pereira JEM, Hartmann-Petersen R, et al. Water Dynamics in MCF-7 Breast Cancer Cells: A Neutron Scattering Descriptive Study. *Sci Rep* (2019) 9:8704. doi:10.1038/s41598-019-45056-8
- Ashkar R, Bilheux HZ, Bordallo H, Briber R, Callaway DJE, Cheng X, et al. Neutron Scattering in the Biological Sciences: Progress and Prospects. *Acta Cryst Sect D Struct Biol* (2018) 74:1129–68. doi:10.1107/s2059798318017503
- Rasmussen MK, Pereira JEM, Berg MC, Iles GN, de Souza NR, Jalarvo NH, et al. Dynamics of Encapsulated Hepatitis B Surface Antigen. *Eur Phys J Spec Top* (2019) 227:2393–9. doi:10.1140/epjst/e2019-700103-x
- Inoue R, Oda T, Nakagawa H, Tominaga T, Saio T, Kawakita Y, et al. Dynamics of Proteins with Different Molecular Structures Under Solution Condition. *Sci Rep* (2020) 10:21678. doi:10.1038/s41598-020-78311-4
- Nanda H, García Sakai V, Khodadadi S, Tyagi MS, Schwalbach EJ, Curtis JE. Relaxation Dynamics of Saturated and Unsaturated Oriented Lipid Bilayers. *Soft Matter* (2018) 14:6119–27. doi:10.1039/c7sm01720k
- Bordallo HN, Aldridge LP, Fouquet P, Pardo LC, Unruh T, Wuttke J, et al. Hindered Water Motions in Hardened Cement Pastes Investigated Over Broad Time and Length Scales. *ACS Appl Mater Inter* (2009) 1:2154–62. doi:10.1021/am900332n
- Wolf YI, Katsnelson MI, Koonin EV. Physical Foundations of Biological Complexity. *Proc Natl Acad Sci U S A* (2018) 115:E8678. doi:10.1073/pnas.1807890115
- Schiebel J, Gaspari R, Wulsdorf T, Ngo K, Sohn C, Schrader TE, et al. Intriguing Role of Water in Protein-Ligand Binding Studied by Neutron Crystallography on Trypsin Complexes. *Nat Commun* (2018) 9:3559. doi:10.1038/s41467-018-05769-2
- Kneller GR. Franck-Condon Picture of Incoherent Neutron Scattering. *Proc Natl Acad Sci U.S.A* (2018) 115:9450–5. doi:10.1073/pnas.1718720115
- Calandrini V, Hamon V, Hinsin K, Calligari P, Bellissent-Funel M-C, Kneller GR. Relaxation Dynamics of Lysozyme in Solution Under Pressure: Combining Molecular Dynamics Simulations and Quasielastic Neutron Scattering. *Chem Phys* (2008) 345:289–97. doi:10.1016/j.chemphys.2007.07.018
- Larsen SR, Michels L, dos Santos ÉC, Berg MC, Gates WP, Aldridge LP, et al. Physicochemical Characterisation of Fluorohectorite: Water Dynamics and Nanocarrier Properties. *Microporous Mesoporous Mater* (2020) 306:110512. doi:10.1016/j.micromeso.2020.110512
- Saouessi M, Peters J, Kneller GR. Frequency Domain Modeling of Quasielastic Neutron Scattering from Hydrated Protein Powders: Application to Free and Inhibited Human Acetylcholinesterase. *J Chem Phys* (2019) 151:125103. doi:10.1063/1.5121703
- Saouessi M, Peters J, Kneller GR. Asymptotic Analysis of Quasielastic Neutron Scattering Data from Human Acetylcholinesterase Reveals Subtle Dynamical Changes upon Ligand Binding. *J Chem Phys* (2019) 150:161104. doi:10.1063/1.5094625
- Berg MC, Benetti AR, Telling MTF, Seydel T, Yu D, Daemen LL, et al. Nanoscale Mobility of Aqueous Polyacrylic Acid in Dental Restorative Cements. *ACS Appl Mater Inter* (2018) 10:9904–15. doi:10.1021/acsami.7b15735
- Andersen KH, Argyriou DN, Jackson AJ, Houston J, Henry PF, Deen PP, et al. The Instrument Suite of the European Spallation Source. *Nucl. Instrum. Nucl. Instr Methods Phys Res Section A Acc Spectrometers Detectors Associated Equip* (2020) 957:163402. doi:10.1016/j.nima.2020.163402
- Villacorta FJ, Rodríguez DM, Bertelsen M, Bordallo HN. Optimization of the Guide Design of MIRACLES, the Neutron Time-Of-Flight Backscattering Spectrometer at the European Spallation Source. *QuBS* (2022) 6:3. doi:10.3390/qubs6010003
- Mamontov E, Boone C, Frost MJ, Herwig KW, Huegle T, Lin JYY, et al. A Concept of a Broadband Inverted Geometry Spectrometer for the Second Target Station at the Spallation Neutron Source. *Rev Scientific Instr* (2022) 93:045101. doi:10.1063/5.0086451
- Castellanos MM, McAuley A, Curtis JE. Investigating Structure and Dynamics of Proteins in Amorphous Phases Using Neutron Scattering. *Comput Struct Biotechnol J* (2017) 15:117–30. doi:10.1016/j.csbj.2016.12.004
- Farmer TO, Markvardsen AJ, Rod TH, Bordallo HN, Swenson J. Dynamical Accuracy of Water Models on Supercooling. *J Phys Chem Lett* (2020) 11:7469–75. doi:10.1021/acs.jpcllett.0c20158
- Chan H, Narayanan B, Cherukara MJ, Sen FG, Sasikumar K, Gray SK, et al. Machine Learning Classical Interatomic Potentials for Molecular Dynamics from First-Principles Training Data. *J Phys Chem C* (2019) 123:6941–57. doi:10.1021/acs.jpcc.8b09917
- Aldridge LP, Larsen SR, Bordallo HN. Octave Program for Fitting Quasi-Elastic Neutron Scattering Data. *Physica B* (2019) 561:75–8. doi:10.1016/j.physb.2018.12.027
- van Hove L. Correlations in Space and Time and Born Approximation Scattering in Systems of Interacting Particles. *Phys Rev* (1954) 95:249–62. doi:10.1103/physrev.95.249
- Petersen MH, Vernet N, Gates WP, Villacorta FJ, Ohira-Kawamura S, Kawakita Y, et al. Assessing Diffusion Relaxation of Interlayer Water in Clay Minerals Using a Minimalist Three-Parameter Model. *J Phys Chem C* (2021) 125:15085–93. doi:10.1021/acs.jpcc.1c04322
- Frauenfelder H, Young RD, Fenimore PW. The Role of Momentum Transfer During Incoherent Neutron Scattering Is Explained by the Energy Landscape Model. *Proc Natl Acad Sci U.S.A* (2017) 114:5130–5. doi:10.1073/pnas.1612267114
- Tsapatsaris N, Lechner RE, Markó M, Bordallo HN. Conceptual Design of the Time-Of-Flight Backscattering Spectrometer, MIRACLES, at the European Spallation Source. *Rev Scientific Instr* (2016) 87:085118. doi:10.1063/1.4961569
- Fitter J, Gutberlet T, Katsaras J. *Neutron Scattering in Biology: Techniques and Applications*. Berlin, Heidelberg: Springer-Verlag Berlin Heidelberg (2006).
- Martins ML, Bordallo HN, Mamontov E. Water Dynamics in Cancer Cells: Lessons from Quasielastic Neutron Scattering. *Medicina* (2022) 58:654. doi:10.3390/medicina58050654
- Lechner RE. Observation-Time Dependent Structural Information from Quasielastic Neutron Scattering. *Phys B Condensed Matter* (2001) 301(1–2): 83–93. doi:10.1016/S0921-4526(01)00516-6
- Foglia F, Berrod Q, Clancy AJ, Smith K, Gebel G, Sakai VG, et al. Disentangling Water, Ion and Polymer Dynamics in an Anion Exchange Membrane. *Nat Mater* (2022) 21:555–63. doi:10.1038/s41563-022-01197-2
- Lima RJS, Okhrimenko DV, Rudić S, Telling MTF, Sakai VG, Hwang D, et al. Ammonia Storage in Hydrogen Bond-Rich Microporous Polymers. *ACS Appl Mater Inter* (2020) 12(52):58161–9. doi:10.1021/acsami.0c18855
- Yamada T, Takahashi N, Tominaga T, Takata S-i, Seto H. Dynamical Behavior of Hydration Water Molecules Between Phospholipid Membranes. *J Phys Chem B* (2017) 121(35):8322–9. doi:10.1021/acs.jpcc.7b01276
- Benetti AR, Jacobsen J, Lehnhoff B, Momsen NCR, Okhrimenko DV, Telling MTF, et al. How Mobile Are Protons in the Structure of Dental Glass Ionomer Cements? *Sci Rep* (2015) 5:8972. doi:10.1038/srep08972
- King MD, Rennie AR, Thompson KC, Fisher FN, Dong CC, Thomas RK, et al. Oxidation of Oleic Acid at the Air-Water Interface and its Potential Effects on Cloud Critical Supersaturations. *Phys Chem Chem Phys* (2009) 11(35): 7699–707. doi:10.1039/b906517b
- Okuda A, Inoue R, Morishima K, Saio T, Yunoki Y, Yagi-Utsumi M, et al. Deuteration Aiming for Neutron Scattering. *Biophys Physicobiol* (2021) 18: 16–27. doi:10.2142/biophysico.bppb-v18.003
- Smith JC, Tan P, Petridis L, Hong L. Dynamic Neutron Scattering by Biological Systems. *Annu Rev Biophys* (2018) 47:335–54. doi:10.1146/annurev-biophys-070317-033358
- Arbe A, Alvarez F, Colmenero J. Insight into the Structure and Dynamics of Polymers by Neutron Scattering Combined with Atomistic Molecular Dynamics Simulations. *Polymers* (2020) 12(12):3067. doi:10.3390/polym12123067

40. Ellis RJ. Macromolecular Crowding: An Important but Neglected Aspect of the Intracellular Environment. *Curr Opin Struct Biol* (2001) 11(1):114–9. doi:10.1016/s0959-440x(00)00172-x
41. Kumar M, Mommer MS, Sourjik V. Mobility of Cytoplasmic, Membrane, and DNA-Binding Proteins in *Escherichia coli*. *Biophys J* (2010) 98(4):552–9. doi:10.1016/j.bpj.2009.11.002
42. Martins ML, Eckert J, Jacobsen H, Dos Santos EC, Ignazzi R, de Araujo DR, et al. Probing the Dynamics of Complexed Local Anesthetics via Neutron Scattering Spectroscopy and DFT Calculations. *Int J Pharmaceutics* (2017) 524(1-2):397–406. doi:10.1016/j.ijpharm.2017.03.051
43. Macha IJ, Ben-Nissan B, Vilchevskaya EN, Morozova AS, Abali BE, Müller WH, et al. Drug Delivery from Polymer-Based Nanopharmaceuticals-An Experimental Study Complemented by Simulations of Selected Diffusion Processes. *Front Bioeng Biotechnol* (2019) 7:37. doi:10.3389/fbioe.2019.00037
44. Pereira JEM, Eckert J, Rudic S, Yu D, Mole R, Tsapatsaris N, et al. Hydrogen Bond Dynamics and Conformational Flexibility in Antipsychotics. *Phys Chem Chem Phys* (2019) 21(28):15463–70. doi:10.1039/c9cp02456e
45. Soraruf D, Roosen-Runge F, Grimaldo M, Zanini F, Schweins R, Seydel T, et al. Protein Cluster Formation in Aqueous Solution in the Presence of Multivalent Metal Ions - A Light Scattering Study. *Soft Matter* (2014) 10(6):894–902. doi:10.1039/c3sm52447g
46. Grimaldo M, Roosen-Runge F, Zhang F, Seydel T, Schreiber F. Diffusion and Dynamics of γ -Globulin in Crowded Aqueous Solutions. *J Phys Chem B* (2014) 118(25):7203–9. doi:10.1021/jp504135z
47. Liberton M, Page LE, O'Dell WB, O'Neill H, Mamontov E, Urban VS, et al. Organization and Flexibility of Cyanobacterial Thylakoid Membranes Examined by Neutron Scattering. *J Biol Chem* (2013) 288(5):3632–40. doi:10.1074/jbc.M112.416933
48. Marques MPM, Batista de Carvalho ALM, Mamede AP, Dopplapudi A, García Sakai V, Batista de Carvalho LAE. Role of Intracellular Water in the Normal-to-Cancer Transition in Human Cells-Insights from Quasi-Elastic Neutron Scattering. *Struct Dyn* (2020) 7(5):054701. doi:10.1063/4.0000021
49. Gates WP, Bordallo HN, Aldridge LP, Seydel T, Jacobsen H, Marry V, et al. Neutron Time-Of-Flight Quantification of Water Desorption Isotherms of Montmorillonite. *J Phys Chem C Nanomater Inter* (2012) 116(9):5558–70. doi:10.1021/jp2072815
50. Foglia F, Hazael R, Meersman F, Wilding MC, Sakai VG, Rogers S, et al. *In Vivo* Water Dynamics in *Shewanella Oneidensis* Bacteria at High Pressure. *Sci Rep* (2019) 9(1):8716. doi:10.1038/s41598-019-44704-3
51. Ignazzi R, Gates WP, Diallo SO, Yu D, Juranyi F, Natali F, et al. Electric Field Induced Polarization Effects Measured by *In Situ* Neutron Spectroscopy. *J Phys Chem C* (2017) 121(42):23582–91. doi:10.1021/acs.jpcc.7b08769
52. Golub M, Guillon V, Gotthard G, Zeller D, Martinez N, Seydel T, et al. Dynamics of a Family of Cyan Fluorescent Proteins Probed by Incoherent Neutron Scattering. *J R Soc Interf* (2019) 16(152):20180848. doi:10.1098/rsif.2018.0848
53. Klibanov AM. Improving Enzymes by Using Them in Organic Solvents. *Nature* (2001) 409(6817):241–6. doi:10.1038/35051719
54. Cicerone MT, Pikal MJ, Qian KK. Stabilization of Proteins in Solid Form. *Adv Drug Deliv Rev* (2015) 93:14–24. doi:10.1016/j.addr.2015.05.006
55. Olsson C, Zangana R, Swenson J. Stabilization of Proteins Embedded in Sugars and Water as Studied by Dielectric Spectroscopy. *Phys Chem Chem Phys* (2020) 22(37):21197–207. doi:10.1039/d0cp03281f
56. Sakai VG, Khodadadi S, Cicerone MT, Curtis JE, Sokolov AP, Roh JH. Solvent Effects on Protein Fast Dynamics: Implications for Biopreservation. *Soft Matter* (2013) 9:5336. doi:10.1039/c3sm50492a
57. Häusler T, Gebhardt P, Iglesias D, Rameshan C, Marchesan S, Eder D, et al. Ice Nucleation Activity of Graphene and Graphene Oxides. *J Phys Chem C* (2018) 122(15):8182–90. doi:10.1021/acs.jpcc.7b10675
58. O'Sullivan D, Murray BJ, Ross JF, Whale TF, Price HC, Atkinson JD, et al. The Relevance of Nanoscale Biological Fragments for Ice Nucleation in Clouds. *Sci Rep* (2015) 285:8082. doi:10.1038/srep08082
59. Weiss F, Kubel F, Gálvez Ó, Hoelzel M, Parker SF, Baloh P, et al. Metastable Nitric Acid Trihydrate in Ice Clouds. *Angew Chem Int Ed* (2016) 55(10):3276–80. doi:10.1002/anie.201510841
60. Maeda N. Brief Overview of Ice Nucleation. *Molecules* (2021) 26(2):392. doi:10.3390/molecules26020392
61. Mael LE, Busse H, Grassian VH. Measurements of Immersion Freezing and Heterogeneous Chemistry of Atmospherically Relevant Single Particles with Micro-Raman Spectroscopy. *Anal Chem* (2019) 91(17):11138–45. doi:10.1021/acs.analchem.9b01819
62. Kumru OS, Joshi SB, Smith DE, Middaugh CR, Prusik T, Volkin DB. Vaccine Instability in the Cold Chain: Mechanisms, Analysis and Formulation Strategies. *Biologicals* (2014) 42(5):237–59. doi:10.1016/j.biologicals.2014.05.007
63. Feng S, Peters GHJ, Ohtake S, Schöneich C, Shalaev E. Water Distribution and Clustering on the Lyophilized IgG1 Surface: Insight from Molecular Dynamics Simulations. *Mol Pharmaceutics* (2020) 17(3):900–8. doi:10.1021/acs.molpharmaceut.9b01150
64. Jangam SV. An Overview of Recent Developments and Some R&D Challenges Related to Drying of Foods. *Drying Technol* (2011) 29(12):1343–57. doi:10.1080/07373937.2011.594378
65. Enevold R, Flintoft P, Tjellden AKE, Kristiansen SM. Vacuum Freeze-Drying of Sediment Cores: An Optimised Method for Preserving Archaeostratigraphic Archives. *Antiquity* (2019) 93:370. doi:10.15184/aqy.2019.98
66. Wissner RF, Steinauer A, Knox SL, Thompson AD, Schepartz A. Fluorescence Correlation Spectroscopy Reveals Efficient Cytosolic Delivery of Protein Cargo by Cell-Permeant Miniature Proteins. *ACS Cent Sci* (2018) 4(10):1379–93. doi:10.1021/acscentsci.8b00446

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Bordallo and Kneller. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.