Scrutinizing the hydration shell of proteins from SAXS and MD simulations: Effects of water models and force fields

Johanna-B. Linse[1] and Jochen S. Hub[1]

[1]Theoretical Physics and Center for Biophysics, Saarland University, Saarbrücken 66123, Germany

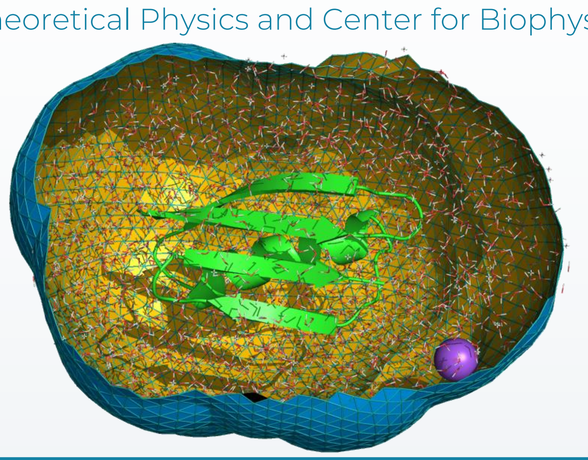


Fig. 1 Water inside the envelope (blue surface) contribute to calculated SAS curves.

Introduction

- Proteins in solution are surrounded by a hydration shell
- A hydration shell consists of several hydration layers (HL)
- HL are formed by the water molecules near the protein surface
- HL influences the structure and activity of a protein
- SAXS or SANS provide information on the hydration shell
- SAXS/SANS curves were computed for several proteins:
  - Xylanase, Lysozyme, GB3 domain, and RNaseA
  - Protein force fields
  - Water models.
- Using MD simulations & explicit-solvent SAXS/SANS calculations to investigate how variations of the hydration shell manifest in variations of R_g & I_0

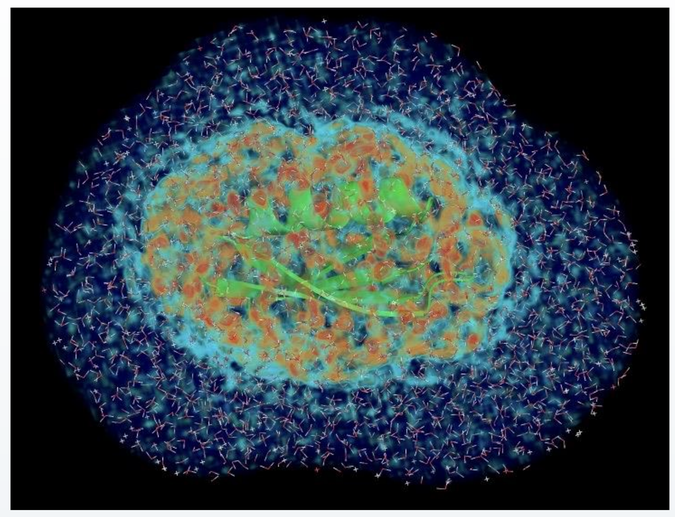


Fig. 2 The first (orange) and second (light blue) hydration layer that form the hydration shell around the protein.

SAS experiments

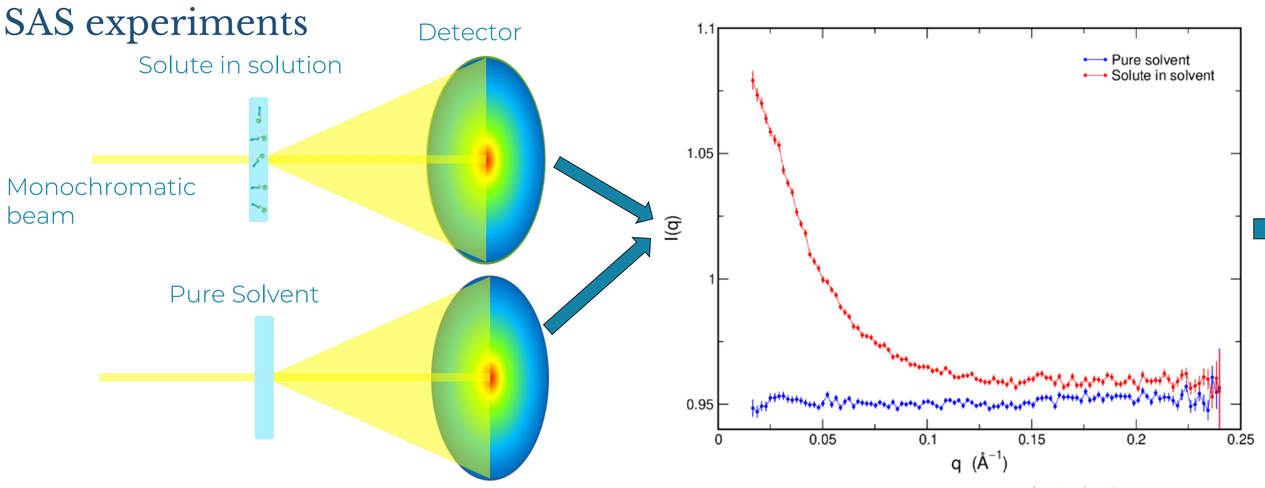


Fig. 3 Schematic representation of the experimental setup of a SAS measurement (left) and the post-processing of the scattering data (right).
To get scattering from pure-solute: subtract pure solvent scattering from solute in solution scattering.
Experimental data in the two plots are taken from Ref.7.

Calculate SAS curves from MD simulation

1. Run Free MD

- Free MD simulations, one for each replica with the protein-RNA complex in solution.
- To get the scattering from the pure-solute, one free MD simulation with pure solvent is conducted.

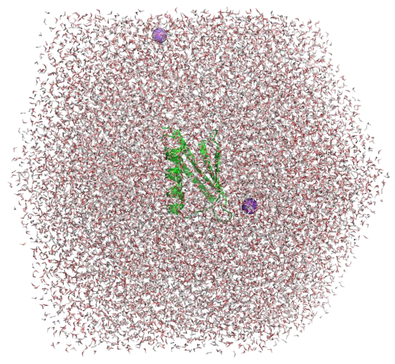
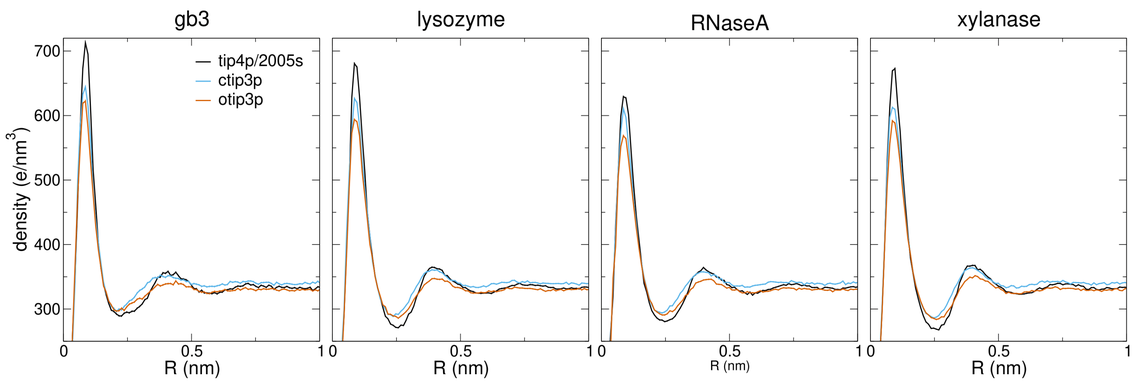


Fig. 4 Simulation box with protein in solvent.

2. Calculating SAXS/SANS curves from MD

- Built an envelope around the solute, which includes all solvent atoms of the hydration shell (Fig. 1).
- All atoms inside the envelope are taken into account during the SAXS/SANS calculations.
- No free parameter in the SAS calculations
- Scattering curves are calculated from the MD trajectories with an in house Gromacs version [1, 2].



Results

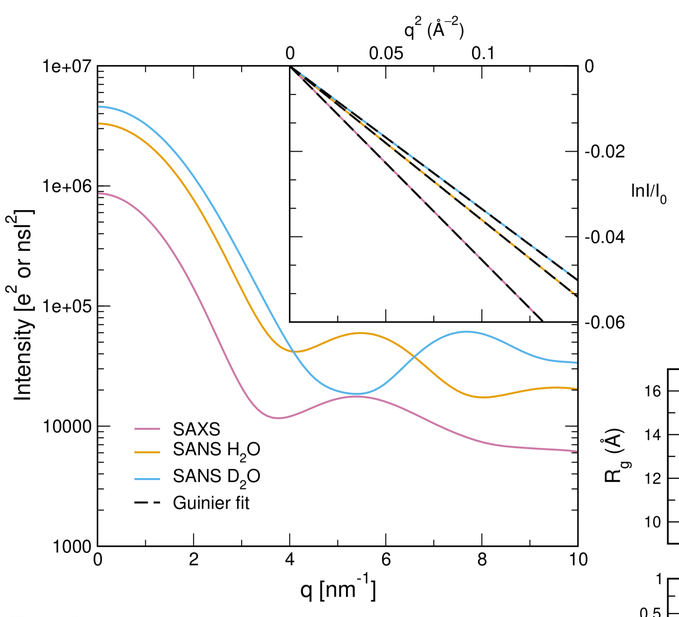


Fig. 5 Calculated SAXS and SANS curves from MD simulations. Guinier plot together with linear fits $\frac{\ln(I)}{I_0} \approx -\frac{q^2 R_g^2}{3}$ (dashes black line) that gives R_g.

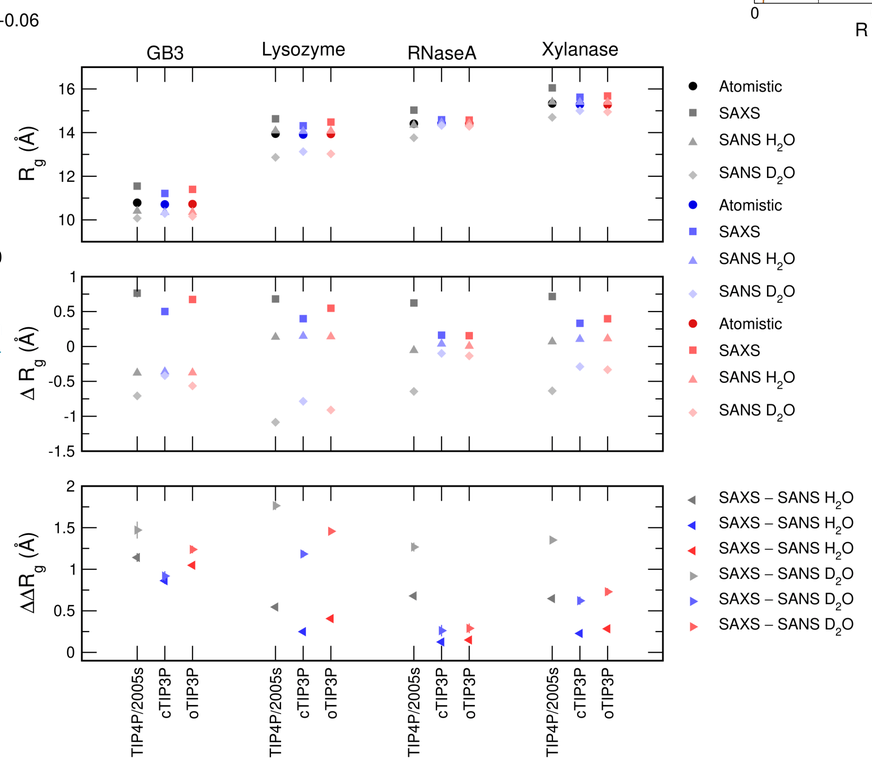
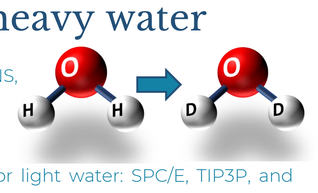


Fig. 7 R_g, ΔR_g and $\Delta\Delta R_g$ for the four different proteins and the three different water model/force field combinations (amber99sbws & TIP4P/2005s [3], charmm36 & cTIP3P [5], and charmm36 & oTIP3P [4]).

Three- and four-site models for heavy water

Motivation

- Heavy water is frequently used in biophysical experiments (SANS, NMR, ...)
- Modeling such experiments requires force fields for heavy water



Results

- Developed on the basis of three- and four-site water models for light water: SPC/E, TIP3P, and TIP4P/2005
- H2O models were modified as little as possible, only to the extend needed to reproduce experimental properties of D2O.
- Specific characteristics of the H2O models were maintained.

		SPC/E-HW	TIP4P/2005-HW	TIP3P-HW	Expt.
Density	kg/m^3	1106.169(5)	1103.998(5)	1092.168(6)	1104.4[a]
$-E_{pot}^{MD}$	kJ/mol	48.486(2)	48.660(2)	41.215(2)	
E_{pol}	kJ/mol	5.74264	4.51086		
$-E_{\mathrm{pot}}$	kJ/mol	42.774(2)	44.149(2)	41.215(2)	-
ΔH_{vap}	kJ/mol	45.223(2)	46.629(2)	43.694(2)	45.138[b]
Diffusion coefficient	10^{-5} cm^2/s	1.691(2)	1.613(2)	4.246(4)	1.87-1.9[c]
Compressibility	10^{-6} bar^{-1}	44.2(1)	47.0(2)	57.7(3)	46.5[d]
< #H-bonds >		3.65617	3.68684	3.403227	3.76±0.1[e]

Tab. 1 Experimental and calculated parameters of liquid heavy water at 298.15 K and 1 bar.

[a] CRC handbook of chemistry and physics : a ready-reference book of chemical and physical data.2003-2004, 84th ed. (CRC, Boca Raton, Fla. : London, 2003)
[b] A. Crabtree and M. Siman-Tov, "Thermophysical properties of saturated light and heavy waterfor advanced neutron source applications," (1993)
[c] D. J. Wilbur, T. DeFries, and J. Jonas, "Self-diffusion in compressed liquid heavy water," J.Chem. Phys.65, 1783–1786 (1976)
L. G. Longsworth, "The mutual diffusion of light and heavy water," J. Phys. Chem.64, 1914–1917 (1960)
R. Mills, "Self-diffusion in normal and heavy water in the range 1-45.deg." J. Phys. Chem.77,685–688 (1973)
J. S. Murday and R. M. Cotts, "Self-diffusion in liquids: H2O, D2O, and na," J. Chem. Phys.53,4724–4725 (1970)
[d] F. J. Millero and F. K. Lepple, "Isothermal compressibility of deuterium oxide at various temperatures," J. Chem. Phys.54, 946–949 (1971)
[e] A. K. Soper and C. J. Benmore, "Quantum differences between heavy and light water," Phys. Rev. Lett. 101, 065502 (2008)

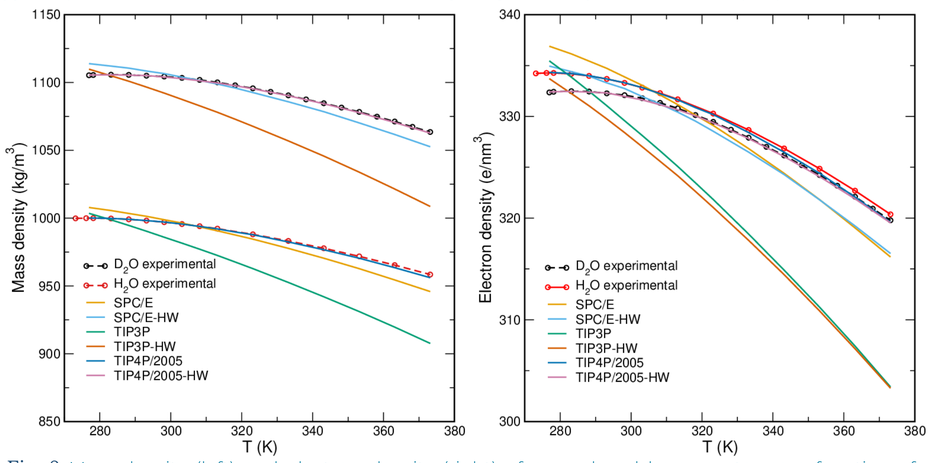


Fig. 8 Mass density (left) and electron density (right) of normal and heavy water as a function of temperature at 1 bar.

Reference

J.-B. Linse and J. S. Hub, Three- and Four-Site Models for Heavy Water: SPC/E-HW, TIP3P-HW, and TIP4P/2005-HW, J. Chem. Phys. 154, 194501 (2021) https://doi.org/10.1063/5.0050841

Conclusion

- Different proteins exhibit different hydration layer contrasts
- The water model significantly influences the hydration layer
- Our calculation provides a novel route for comparing hydration layers between simulation and experiments, for validating water models, and, thereby, for scrutinizing the hydration layer of proteins.

References

[1] Chen, P. and Hub, J.S., Biophys. J., 107, 435-447 (2014), http://waxsis.uni-goettingen.de/

[2] M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess, and E. Lindahl, SoftwareX1-2, 19 – 25 (2015)

[3] R. B. Best, W. Zheng, and J. Mittal, J. Chem. Theory Comput.10, 5113–5124 (2014)

[4] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. 79, 926–935 (1983)

[5] A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. T. K. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher, B. Roux, M. Schlenkrich, J. C. Smith, R. Stote, J. Straub, M. Watanabe, J. Wiórkiewicz-Kuczera, D. Yin, and M. Karplus,, J. Phys. Chem. B 102, 3586–3616 (1998).

[6] J. Huang, S. Rauscher, G. Nawrocki, R. Ting, M. Feig, B. de Groot, H. Grubmüller, andA. MacKerell, Nat. Methods14, 71–73 (2017)

[7] Jakub Macošek, Bernd Simon, Johanna-Barbara Linse, Pravin Kumar Ankush Jagtap, Sophie L Winter, Jaelle Foot, Karine Lapouge, Kathryn Perez, Mandy Rettel, Miloš T Ivanović, Pawel Masiewicz, Brice Murciano, Mikhail M Savitski, Inga Loedige, Jochen S Hub, Frank Gabel, Janosch Hennig, *Nucleic Acids Research*, Volume 49, Issue 15, (2021), Pages 8866–8885, https://doi.org/10.1093/nar/gkab635