
Development of models for large molecules and electrolytes in solution for process engineering

Jonathan Walter¹, Stephan Deublein¹, Jadran Vrabec², and Hans Hasse¹

¹ Lehrstuhl für Thermodynamik, Technische Universität Kaiserslautern,
Erwin-Schrödinger-Str. 44, 67663 Kaiserslautern, Germany
jonathan.walter@mv.uni-kl.de

² Thermodynamik und Energietechnik, Universität Paderborn, Warburger Straße
100, 33098 Paderborn, Germany

1 Introduction

Two of the most challenging tasks in molecular dynamics simulation are the simulation of long-range interactions like in electrolyte solutions and the internal degrees of freedom like in hydrogels. Both tasks lead to time consuming simulations with big systems. Therefore, massively parallel high performance computers are needed for both tasks. The first step of the present work was to test and validate different force fields for electrolyte solutions and hydrogels.

2 Simulation of electrolyte solutions

The characterization of electrolyte systems is computationally very expensive. The ionic influence, noticeable even at long distances away from the charge, requires large simulation systems and the use of special, time consuming algorithms that allow for a truncation of the ionic interactions at length scales accessible in molecular simulation. Examples of such algorithms are the classical Ewald-Summation [Ewa21] and its derivatives like Particle-Mesh-Ewald-Summation [DYP93] or Particle-Particle Particle-Mesh method [EHL80].

In the early stages of research on electrolyte systems, the effort was mainly directed to the development of ion models, which were capable of reproducing static structural properties of the ionic solutions [RS90, FT64, DC02]. Recently, however, such models have been proven to be too inaccurate for the prediction of basic thermodynamic properties of the electrolyte solution [HHvdV06]. Since the models were parametrized solely at short distances, the long distance effects of the ions are underestimated. These effects can be seen in particular in the density and the activity of the salt mixture.

Our recent research effort has evaluated numerous single charge ion models regarding their ability to predict the density of ionic solutions. Currently, it

is focused on the development of molecular ion models that are capable to reproduce and predict thermodynamic properties of ionic systems at various temperatures and ion concentrations.

2.1 Methods

The first investigated system consists of sodium and chloride ions as electrolytes and explicit water as solvent. The ions were modelled as Lennard-Jones spheres with a central charge. Water models were taken from literature. We determine the density of the ionic solution in isobaric-isothermal (NPT) Monte-Carlo simulations with 1000 particles at ambient temperature and pressure. The long-range charge-charge interactions were calculated using Ewald summation with a cutoff radius of half the box length L and the Ewald parameter κ of $5.6/L$. The simulation program employed was *ms2*, which is developed by our group.

2.2 Results

The results for the density of electrolyte systems are highly dependent on the uncertainties of density of the pure solvent itself. To diminish these influences and for a better comparison between different solvent models we show all results in reduced form $\tilde{\rho}$, normalizing the density of the electrolyte system ρ_e by the density of pure solvent ρ_s .

$$\tilde{\rho} = \frac{\rho_e}{\rho_s} \quad (1)$$

Influence of water model

At first, the influence of the molecular model for the solvent on the density of the ionic system was investigated. This study is limited to the three most established water models, namely SPC [BPvGH81], SPC/E [BGS87], and TIP4P [JCM⁺83], and is performed at ambient temperature of 25 °C, covering a wide range of salt concentrations in solution. The sodium chloride ions were described by the force field of Balbuena et al. [BJR96], which is widely in use. Their parameters, shown in Table 1, were kept constant for all simulations.

The calculations of the electrolyte solutions at various ion concentrations show that their density in reduced form is independent of the solvent model, cf. Figure 1. It was confirmed that this behavior is not only valid for the ion model of Balbuena et al., but for other models of sodium chloride and for other ions as well (not shown here).

The independence of $\tilde{\rho}$ from the solvent model facilitates the evaluation of

literature models for ions as well as the development of own ion models significantly. In future studies, only one solvent description has to be considered for the characterization of an electrolyte system.

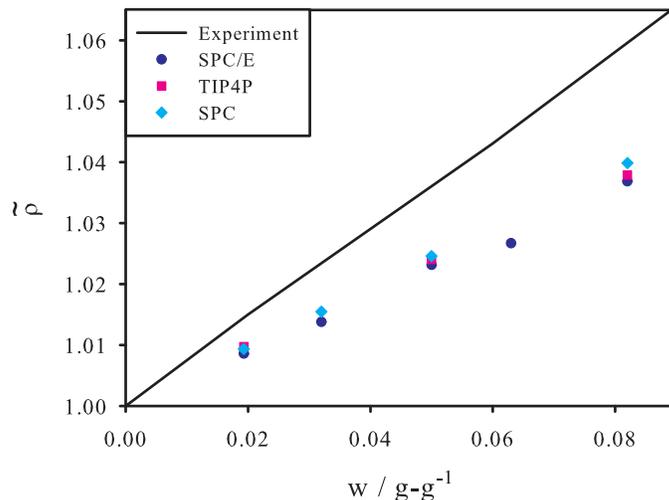


Fig. 1. Plot of the reduced density $\tilde{\rho}$ of an aqueous sodium chloride solution as a function of the salt concentration, given in weight fractions w . Different symbols indicate different solvent models.

Model evaluation and development

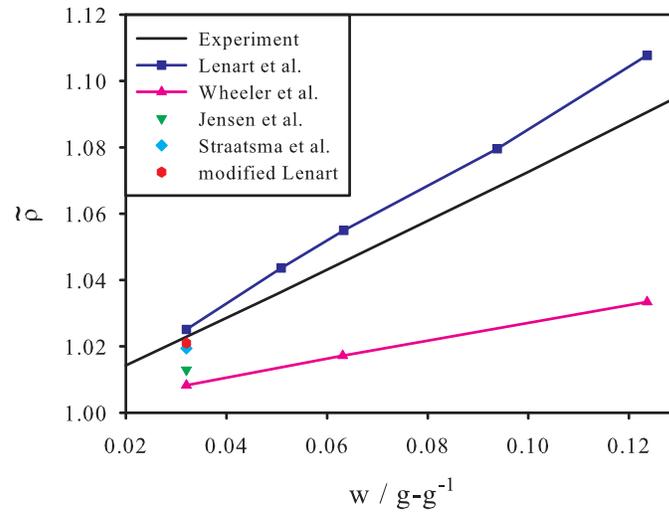
In a subsequent study, different ion models were investigated regarding their ability to predict densities of electrolyte solutions over a wide range of ion concentrations. A total of four different models, listed in Table 1, were analyzed. The ions were completely dissolved in SPC/E-water.

All ion models in the study capture the characteristic linear increase of density with increasing sodium chloride concentration in solution, as it is clearly visible in Figure 1 and 2. However, the simulation results deviate from experimental values considerably for the normalized density. A possible reason for this aberration are the problems in describing the solvent “water” accurately. The errors of its model influence the parametrization of the ion, which causes the deviation visible in our analysis.

First results indicate that it is possible to improve the results by fitting the ion force fields to the density data, also shown in Figure 2. This is currently explored in ongoing work.

Table 1. Different ion models for sodium chloride from literature

Model	Ion	σ [Å]	ϵ/k_B [K]	q
Balbuena et al. [BJR96]	Na ⁺	2.69	61.87	+ 1
	Cl ⁻	3.79	68.07	- 1
Lenart et al. [LJP07]	Na ⁺	2.443	14.329	+ 1
	Cl ⁻	3.487	117.76	- 1
Wheeler et al. [WN04]	Na ⁺	2.35	55.30	+ 1
	Cl ⁻	4.42	54.2	- 1
Straatsma et al. [SB88]	Na ⁺	2.85	24.12	+ 1
	Cl ⁻	3.75	64.69	- 1
Jensen et al. [JJ06]	Na ⁺	4.07	0.06	+ 1
	Cl ⁻	4.02	85.383	- 1

**Fig. 2.** Plot of the normalized density $\tilde{\rho}$ of an aqueous sodium chloride solution as a function of the salt concentration, given in mass fractions w . Different symbols indicate different ion models.

2.3 Conclusions

Current models of simple single charged ions are not yet capable of reproducing basic thermodynamic properties quantitatively. Further research effort on the model development is needed to gain accurate predictions for thermodynamic properties of electrolyte solutions. Our approach of a quantitative characterization of electrolyte systems with normalized densities facilitates and accelerates this process. The amount of single simulations necessary for

the model development is decreased significantly without loss of accuracy.

2.4 Computational demands

All simulations presented in Section 2.2 were carried out with the MPI based molecular simulation program *ms2* developed in our group. Typical simulation runs employ 8 CPUs running for 96 hours. For model optimization, a large number of independent simulations are necessary and can be performed in parallel. For the prediction of other thermodynamic data like activity coefficients, up to 32 CPUs running for 96 hours or more depending on the system are required.

3 Simulation of hydrogels

Hydrogels have been a research topic of growing interest in recent years. Some of the applications for hydrogels are absorbers, drug delivery [PBLI00], microvalves, microactuators [vdLOB04] or immobilised catalysts. There is substantial research in the field of hydrogels, however, these promising materials are not yet fully understood.

In this work, the behavior of the Poly(*n*-isopropylacrylamide) (PNiPAM) single chain is examined by molecular dynamics simulation on the atomistic level. PNiPAM is used here as it is one of the better known hydrogels and shows a significant temperature dependence with respect to swelling. Early experimental investigations on PNiPAM polymers in aqueous solutions [HG68] were done in 1968. E.g. the lower critical solution temperature (LCST) of PNiPAM in water of about 305 K was found.

With molecular dynamics it is possible to predict the behavior of hydrogels. In the literature the hydrogels are simulated at two different levels of detail, coarse-grain models and atomistic models. With the coarse-grain models the influence of solvent [LDBD99] or ions in the solvent on the hydrogel [MKH06, LH03] was investigated. The results of these simulations are different states of conformation for the hydrogel and the transition between them. Atomistic models need more computer resources but the full detail of the simulated hydrogel can be analysed. The advantage of atomistic models is that the dynamic properties like diffusion coefficient the complete structure of the hydrogel like hydration shell or hydrogen bonds can be obtained. For polymers, atomistic simulations with e.g. PAA [ND98], Polyvinylalcohol (PVA) [NS01, MPvG97], PNiPAM [LLAF04, TTN96] can be found in literature. In these investigations mainly the properties of water like first hydration shell, diffusion coefficient, orientation or hydrogen bonds were evaluated.

These investigations were mostly done with small systems of up to 1000 solute molecules. Therefore, it was not possible to simulate polymers and hydrogels of realistic size. There also seem to be no validations of different force fields

for hydrogels in the literature. The second problem is that in many cases the comparison with experiments is difficult or not attempted at all. The approach of this work is to find a suitable force field for PNiPAM and to compare the simulation results to experimental data. For this approach different force fields from the literature were tested with single PNiPAM chains in water at different temperatures.

3.1 Methods and molecular models

The simulations for the PNiPAM single chains were all performed with version 4.0.3 of the GROMACS simulation package [vdSLH⁺05, HKvdSL08]. The advantage of GROMACS is the optimized code for single processors and also massively parallel simulation. Three force fields for the polymer PNiPAM Gromos-87 [vGB87], Gromos-96 53a6 (G53a6) [vGBE⁺96] and OPLS-AA [JTR88, JMTR96] and two models for water SPC/E [BGS87] and TIP4P [JCM⁺83] for water were used in this work. Gromos96 and G53a6 are united-atom force fields, OPLS-AA is an all-atom force field. The parameters of the PNiPAM force fields are listed in Table 2.

For all force fields a mixing rule with the geometrical mean for both σ and ϵ

Table 2. Forcefield parameters for PNiPAM

Atom	Gromos-87			G53a6			opls-aa		
	σ / nm	ϵ / J	charge	σ / nm	ϵ / J	charge	σ / nm	ϵ / J	charge
CH2	0.3965	0.5856	0.00	0.4070	0.4105	0.00	0.3500	0.2761	-0.12
CH	0.6211	0.0544	0.00	0.5019	0.0949	0.00	0.3500	0.2761	-0.06
C	0.3361	0.4058	0.38	0.3581	0.2774	0.45	0.3750	0.4393	0.50
O	0.2626	1.7245	-0.38	0.2760	1.2791	-0.45	0.2960	0.8786	-0.50
N	0.2976	0.8767	-0.28	0.3136	0.6398	-0.31	0.3250	0.7113	-0.50
H	0.0000	0.0000	0.28	0.0000	0.0000	0.31	0.0000	0.0000	0.30
CH	0.6211	0.0544	0.00	0.5019	0.0949	0.00	0.3500	0.2761	-0.14
CH3	0.3786	0.7533	0.00	0.3748	0.8672	0.00	0.3500	0.2761	-0.18
H in CH _x	-	-	-	-	-	-	0.0000	0.0000	0.06

was used.

$$\sigma_{ij} = \sqrt{\sigma_i \cdot \sigma_j} \quad (2)$$

$$\epsilon_{ij} = \sqrt{\epsilon_i \cdot \epsilon_j} \quad (3)$$

To test the suitability of the force fields two issues were tackled here. The force field should be able to show the temperature dependence on the conformation and both the collapse and the stretching of single PNiPAM chain. Simulations with all six combinations of the polymer/water force fields were performed at the temperatures 280 and 360 K. These temperatures are well

below and well above the LCST. At the lower temperature, the single chain should be in a stretched conformation, at the higher temperature it should be in a collapsed conformation. The simulations were started both from stretched and from collapsed initial conformations.

For equilibration, the single chain in water was simulated in the NPT ensemble over 100 000 timesteps. The Berendsen barostat [BPvG⁺84] and the velocity-rescale thermostat [BDP07] were used. The pressure was 1 bar and the timestep length 1 fs for all simulations. After equilibration, 1 to $3 \cdot 10^7$ production time steps were performed. The initial configurations for different degrees of collapse were taken from different temporal stages of the simulation at 360 K.

To analyze the results, the radius of gyration was calculated in all simulations. The radius of gyration was defined as

$$R_g = \left(\frac{\sum_i ||r_i||^2 m_i}{\sum_i m_i} \right)^{1/2} \quad (4)$$

and characterizes the degree of stretching of polymer chains.

3.2 Results

Figures 3 and 4 show the simulation results for PNiPAM with the different force fields at 280 and 360 K, being below and above the LCST. In Figure 3 the simulation results at 280 K are presented. At this temperature the single chain in equilibrium should be in a stretched conformation. Only two force field combinations, i.e. OPLS-AA with SPC/E and G53a6 with TIP4P, are able to produce the stretched configuration at 280 K.

Figure 4 shows the results for the same type of simulations at 360 K. At this temperature, the single chain should be in a collapsed configuration. All force field combinations produce the collapsed conformation for this temperature. The only noticeable difference in these simulations is that in the simulation with the force fields G53a6 and TIP4P the conformation transition occurs later in the simulation. 360 K is near the LCST that this force field shows for PNiPAM (results are not shown here). That is the reason for the late conformation transition in the simulation. The lowest line for 280 K shows that once completely collapsed the chain will not unfold again in reasonable time. This comparison of the different force fields shows two results: The two force field combinations that are able to yield both the stretched and the collapsed configuration of the single chain are OPLS-AA with SPC/E and G53a6 with TIP4P. Furthermore, the force field combinations that predict qualitatively correct conformation changes are not suggested by the authors. Note that the OPLS-AA force field was developed for TIP4P water and G53a6 for SPC/E water.

Secondly, it was shown that the force fields are able to show conformation transitions in both directions. For this test, only the force fields OPLS-AA

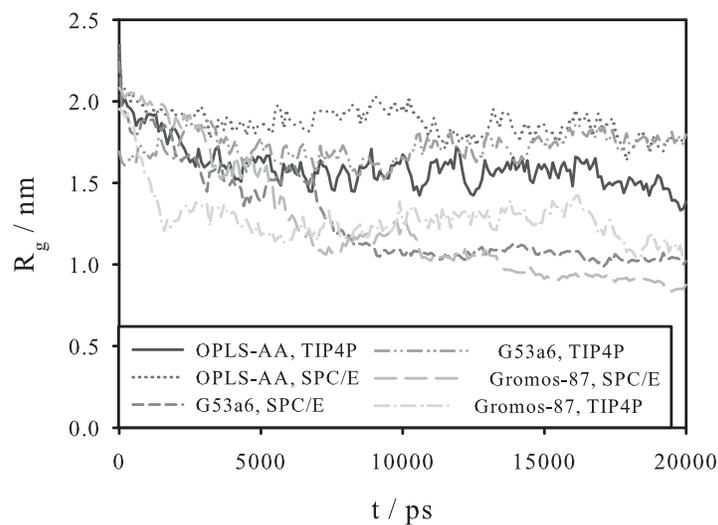


Fig. 3. Radius of gyration for different force field combinations at 280 K over simulation time. The simulations were performed with a chain of 30 monomers of PNiPAM and 14 482 water molecules.

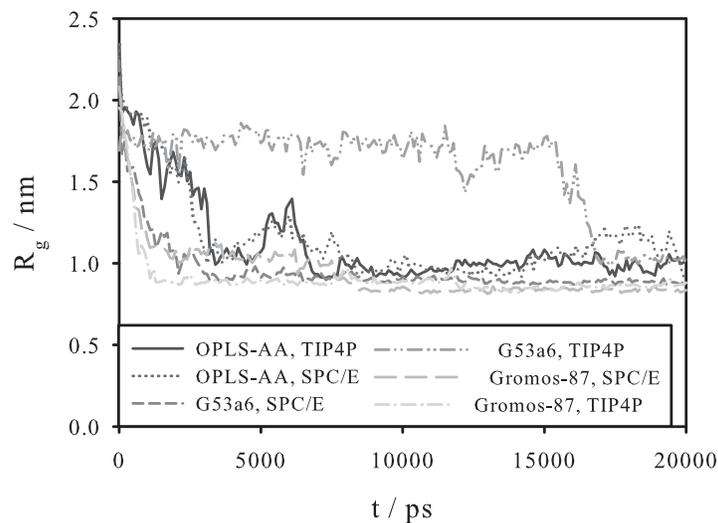


Fig. 4. Radius of gyration for different force field combinations at 360 K over simulation time. The simulations were performed with a chain of 30 monomers of PNiPAM and 14 482 water molecules.

with SPC/E and G53a6 with TIP4P were used. The results of these simulations can be seen in Figures 5 and 6. Figure 5 shows simulation results of single PNIPAM chain with OPLS-AA and SPC/E water. The two lines at the top and at the bottom are the simulations starting in the stretched configuration. In the center are simulations starting with configurations in between the stretched and the collapsed single chain. These simulations were performed at 280 K in order to test the conformation transition from the collapsed to the stretched single chain. The result is that this conformation transition can be simulated but is slower than the conformation transition in the other direction.

The same simulations for G53a6 with TIP4P water can be seen in Figure 6.

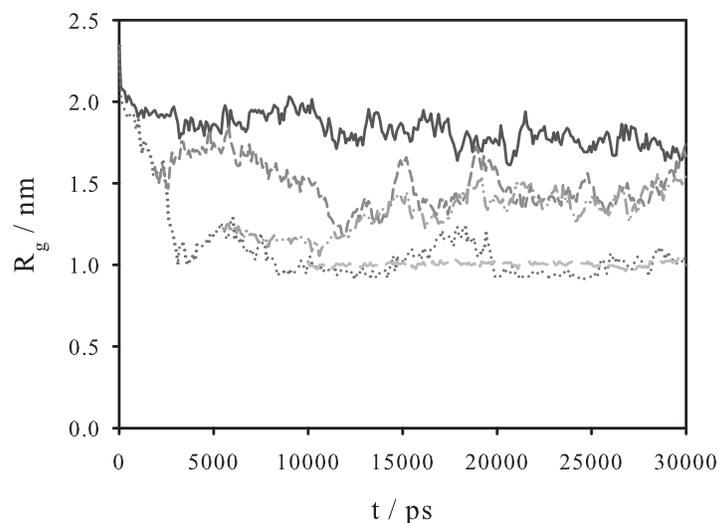


Fig. 5. Radius of gyration at 360 (dotted line) and 280 K (all other lines) over simulation time with different initial configurations for OPLS-AA with SPC/E water. The simulations were performed with a chain of 30 monomers of PNIPAM and 14 482 water molecules.

For this force field combination, the transition of the conformation is fast in both directions.

The comparison of the two force field combinations OPLS-AA with SPC/E and G53a6 with TIP4P shows that both force fields are able to predict the conformation transition in both directions. And for both force field combinations the radius of gyration in equilibrium for 280 K is about 1.8 nm and for 360 K about 0.8 nm.

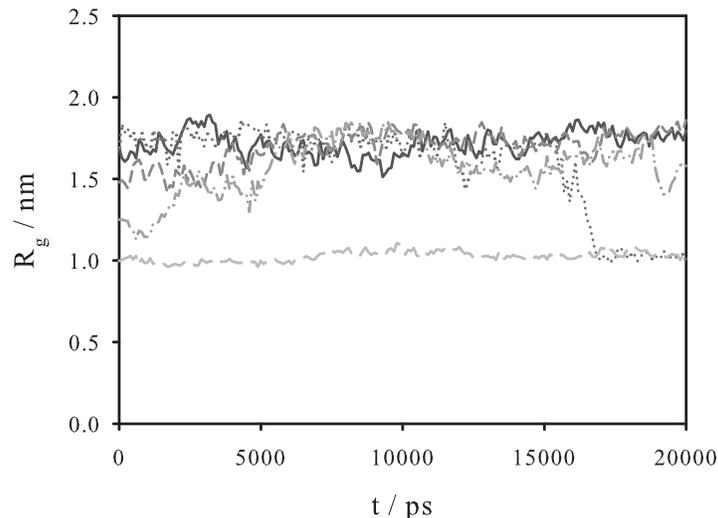


Fig. 6. Radius of gyration at 360 (dotted line) and 280 K (all other lines) over simulation time with different initial configurations for G53a6 with TIP4P water. The simulations were performed with a chain of 30 monomers of PNiPAM and 14 482 water molecules.

3.3 Conclusion

The present results show two things about the usability of protein force fields from the literature for PNiPAM simulations. The first is that force fields that were fitted to thermophysical data like OPLS-AA show better results than force fields that were only fitted to structural data. The second is that it is possible to simulate PNiPAM in water with these force fields and the results also show a qualitatively correct temperature dependence of the radius of gyration for these polymer chains.

3.4 Computational demands

All presented simulations in Section 3.2 were carried out with the MPI based molecular simulation program GROMACS. The parallelization of the molecular dynamics part of GROMACS is based on the eighth shell domain decomposition method [HKvdSL08]. With GROMACS, typical simulation runs to determine the radius of gyration in equilibrium employ 64–128 CPUs running for 1–3 days. For these simulations very large systems must be considered comprising typically about 58 800 interaction sites. Table 7 demonstrates the good scaling of the program on the HP XC4000 cluster at the Rechenzentrum of the Universität Karlsruhe (TH). For these simulations a maximum memory

of 284 MB and a maximum virtual memory of 739 MB was used.

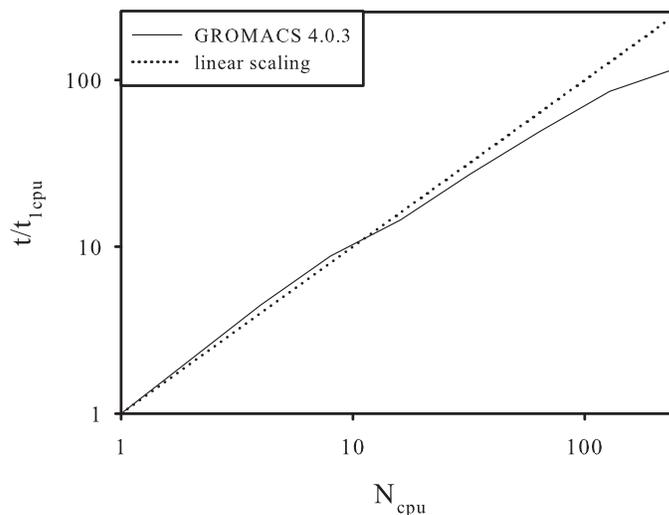


Fig. 7. Scaling of the massively parallel program GROMACS 4.0.3 on HP XC4000, simulation time reduced with the simulation time on one processor over number of processors. Simulated was a PNIPAM chain with 30 monomers in 14 482 water molecules.

References

- [BDP07] G. Bussi, D. Donadio, and M. Parrinello. Canonical sampling through velocity rescaling. *Journal of Chemical Physics*, 126:014101, 2007.
- [BGS87] H. J. C. Berendsen, J. R. Grigera, and T. P. Straatsma. The missing term in effective pair potentials. *Journal Of Physical Chemistry*, 91:6269–6271, 1987.
- [BJR96] P. B. Balbuena, K. P. Johnston, and P. J. Rossky. Molecular dynamics simulation of electrolyte solutions in ambient and supercritical water. 1. ion solvation. *Journal of Physical Chemistry*, 100:2706–2715, 1996.
- [BPvG⁺84] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola, and J. R. Haak. Molecular dynamics with coupling to an external bath. *Journal of Chemical Physics*, 81:3684–3690, 1984.

- [BPvGH81] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans. *Intermolecular Forces*. D. Reidel Publishing Company, 1981.
- [DC02] L. X. Dang and T. M. Chang. Molecular mechanism of ion binding to the liquid/vapor interface of water. *Journal of Physical Chemistry B*, 106:235–238, 2002.
- [DYP93] T. Darden, D. York, and L. Pedersen. Particle mesh ewald - an $n \cdot \log(n)$ method for ewald sums in large systems. *Journal of Chemical Physics*, 98:10089–10092, 1993.
- [EHL80] J. W. Eastwood, R. W. Hockney, and D. N. Lawrence. P3m3dp - the 3-dimensional periodic particle-particle-particle-mesh program. *Computer Physics Communications*, 19:215–261, 1980.
- [Ewa21] P. P. Ewald. The calculation of optical and electrostatic grid potential. *Annalen der Physik*, 64:253–287, 1921.
- [FT64] F. G. Fumi and M. P. Tosi. Ionic sizes + born repulsive parameters in nacl-type alkali halides .i. huggins-mayer + pauling forms. *Journal of Physics and Chemistry of Solids*, 25:31–44, 1964.
- [HG68] M. Heskins and J. E. Guillet. Solution properties of poly(*n*-isopropylacrylamide). *Journal of Macromolecular Science, Part A*, 8:1441–1455, 1968.
- [HHvdV06] B. Hess, C. Holm, and N. van der Vegt. Osmotic coefficients of atomistic nacl (aq) force fields. *Journal of Chemical Physics*, 124:164509, 2006.
- [HKvdSL08] B. Hess, C. Kutzner, D. van der Spoel, and E. Lindahl. Gromacs 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. *Journal of Chemical Theory and Computation*, 4:435–447, 2008.
- [JCM⁺83] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein. Comparison of simple potential functions for simulating liquid water. *Journal of Chemical Physics*, 79:926–935, 1983.
- [JJ06] K. P. Jensen and W. L. Jorgensen. Halide, ammonium, and alkali metal ion parameters for modeling aqueous solutions. *Journal of Chemical Theory and Computation*, 2:1499–1509, 2006.
- [JMTR96] W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives. Development and testing of the opls all-atom force field on conformational energetics and properties of organic liquids. *Journal of American Chemical Society*, 118:11225–11236, 1996.
- [JTR88] W. L. Jorgensen and J. Tirado-Rives. The opls potential functions for proteins, energy minimizations for crystals of cyclic peptides and crambin. *Journal of the American Chemical Society*, 110:16571666, 1988.
- [LDBD99] A. V. Lyulin, B. Dünweg, O. V. Borisov, and A. A. Darinskii. Computer simulation studies of a single polyelectrolyte chain in poor solvent. *Macromolecules*, 32:3264–3278, 1999.

- [LH03] H. J. Limbach and C. Holm. Single-chain properties of poly-electrolytes in poor solvent. *Journal of Physical Chemistry B*, 107:8041–8055, 2003.
- [LJP07] P. J. Lenart, A. Jusufi, and A. Z. Panagiotopoulos. Effective potentials for 1 : 1 electrolyte solutions incorporating dielectric saturation and repulsive hydration. *Journal of Chemical Physics*, 126:044509, 2007.
- [LLAF04] G. Longhi, F. Lebon, S. Abbate, and S. L. Fornili. Molecular dynamics simulation of a model oligomer for poly(*n*-isopropylamide) in water. *Chemical Physics Letters*, 386:123–127, 2004.
- [MKH06] B. A. Mann, K. Kremer, and C. Holm. The swelling behavior of charged hydrogels. *Macromolecular Symposium*, 237:90–107, 2006.
- [MPvG97] F. Müller-Plathe and W. F. van Gunsteren. Solvation of poly(vinylalcohol) in water, ethanol and an equimolar water-ethanol mixture: structure and dynamics studied by molecular dynamics simulation. *Polymer*, 38/9:2259–2268, 1997.
- [ND98] P. A. Netz and T. Dorfmueller. Computer simulation studies on the polymer-induced modification of water properties in polyacrylamide hydrogels. *Journal of Physical Chemistry B*, 102:4875–4886, 1998.
- [NS01] B. Nick and U. W. Suter. Solubility of water in polymers - atomistic simulations. *Computational and Theoretical Polymer Science*, 11:49–55, 2001.
- [PBLI00] N. A. Peppas, P. Bures, W. Leobandung, and H. Ichikawa. Hydrogels in pharmaceutical formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, 50:27–46, 2000.
- [RS90] B. G. Rao and U. C. Singh. A free-energy perturbation study of solvation in methanol and dimethyl-sulfoxide. *Journal of the American Chemical Society*, 112:3803–3811, 1990.
- [SB88] T. P. Straatsma and H. J. C. Berendsen. Free-energy of ionic hydration - analysis of a thermodynamic integration technique to evaluate free-energy differences by molecular-dynamics simulations. *Journal of Chemical Physics*, 89:5876–5886, 1988.
- [TTN96] Y. Tamai, H. Tanaka, and K. Nakanishi. Molecular dynamics study of water in hydrogels. *Molecular Simulation*, 16:359–374, 1996.
- [vdLOB04] H. van der Linden, W. Olthuis, and P. Bergveld. An efficient method for the fabrication of temperature-sensitive hydrogel microactuators. *Lab on a Chip - Miniaturisation for Chemistry and Biology*, 4:619–624, 2004.
- [vdSLH⁺05] D. van der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, and H. J. C. Berendsen. Gromacs: Fast, flexible, and free. *Journal of Computational Chemistry*, 26:1701–1718, 2005.

- [vGB87] W. F. van Gunsteren and H. J. C. Berendsen. *Gromos-87 manual*. Biomos BV Nijenborgh 4, 9747 AG Groningen, The Netherlands, 1987.
- [vGBE⁺96] W. F. van Gunsteren, S. R. Billeter, A. A. Eising, P. H. Hünenberger, P. Krüger, A. E. Mark, W. R. P. Scott, and I. G. Tironi. *Biomolecular Simulation: The Gromos 96 Manual and User Guide*. vdf Hochschulverlag AG an der ETH Zürich, Zürich, Switzerland, 1996.
- [WN04] D. R. Wheeler and J. Newman. Molecular dynamics simulations of multicomponent diffusion. 1. equilibrium method. *Journal of Physical Chemistry B*, 108:18353–18361, 2004.