Doctoral Thesis

Computational nanofluidics for the study of biomolecular flows

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Computational Nanofluidics for the Study of Biomolecular Flows

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presented by
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Abstract

Nanotechnology and biology are two areas of scientific research where recent progress has disclosed a variety of new perspectives. The advances in both fields prepared the grounds for interdisciplinary studies and recent findings promise novel applications that could lead to a technological revolution in medicine. In particular the advent of carbon nanotubes (CNTs) gave rise to speculations on future applications. CNTs are tubular carbon molecules which can be imagined to function as nanometer size pipes and pores. In this respect, they could mimic transmembrane pores and channels and they could be used to manipulate the transport across the membranes of cells and cellular organelles. Specifically, CNT based nanopores are envisioned to transport biomolecules across cellular membranes for biomedical purposes. In this thesis we assess the viability of transmembrane RNA transport through CNT nanopores.

Life on earth has evolved in an environment that is characterized by the presence of water. Consequently, biological systems such as cells and their cytoplasm consist, to a large percentage, of water. The interaction of transmembrane pores with water will be highly influential to their transport properties. To assess the viability of transmembrane pores based on CNTs, it is therefore mandatory to understand their interaction with aqueous solutions.

Throughout the first part of this thesis we study the water carbon interaction in detail. In an initial study we assess the interaction between water and benzene and between water and naphthalene using a quantum mechanical approach. We compare and evaluate different correction schemes for density functionals and we recommend a correction scheme to be used in future studies.

Due to the limitations of quantum mechanical methods to small systems we then focus on molecular dynamics simulations. After an introduction to molecular dynamics we present a methodological advancement to steered molecular dynamics. In molecular dynamics simulations the interactions between particles are modeled using empirical interaction potentials. This reduces the computational cost significantly and allows to simulate systems with several ten-thousand atoms. Due to the empirical nature of the interaction potentials, the model assumptions and simplifications need to be validated carefully to ensure their legitimacy.
It is a common simplification in molecular dynamics to neglect the polarizability of matter. Graphite and CNTs are however susceptible to polarization effects due to their metallic character. Furthermore, water molecules carry a strong dipole moment. We therefore developed a polarizable force field for the water graphite interaction and we quantified the contribution of polarizability. It is found that polarizability must only be included if the structure of water or isolated molecules close to the graphitic surface are considered.

Transmembrane channels that control the transport of water across the membrane are usually narrow and accommodate only a single file of water molecules. Narrow CNTs can be imagined to replace these pores for water transport in a biological environment. We report that this application benefits from the curvature induced static dipole moment of CNTs. The dipole moment brings forth a structural arrangement of the water molecules inside narrow CNTs, which in turn inhibits the transport of protons across the pore. Contrary, the effect of the static dipole moment is negligible in large CNTs which allows for bulk water structures inside.

We conclude the thesis with a large scale molecular dynamics study on specific realizations of CNTs as transmembrane pores. We study CNTs inside different membranes and we find that the structure of lipid bilayers strongly influences the electrostatic potential map. Depending on the hydrophilicity of the pore rims, lipid molecules may mask the pore with zones of high electrostatic potential. The characteristics of electrophoretically driven RNA transport in those pores is assessed in a series of simulations. We find that the transport velocity depends exponentially on the transmembrane electrostatic potential difference. Furthermore, the transport velocity is strongly influenced by the structure of the RNA which may cause trapping. In conclusion, our simulations predict the possible use of CNTs as transmembrane pores for RNA transport.
Riassunto

La nanotecnologia e la biologia sono due campi di ricerca scientifica in cui ultimamente il progresso ha creato numerose opportunità. Gli avanzamenti in entrambi i settori hanno preparato le basi per studi interdisciplinari, e scoperte recenti promettono nuove applicazioni che potrebbero rivoluzionare la medicina. In particolare l’avvento dei nanotubi di carbonio (NTC) promette numerose applicazioni future. Gli NTC sono molecole cilindriche tubiformi di carbonio dalle proprietà interessanti. Grazie alla loro struttura tubiforme, gli NTC sono particolarmente adatti per essere usati come condotti o pori su scala nanometrica. Come tali permetterebbero il trasporto di singole biomolecole attraverso delle membrane cellulari a scopo biomedicinale e biotecnico. Questa tesi presenta alcune investigazioni relative alle possibilità di effettuare un trasporto di RNA attraverso un nanoporo dovuto all’inserimento di un NTC in una membrana.

La vita terrestre si è sviluppata in un ambiente caratterizzato dalla presenza dell’acqua. Di conseguenza, sistemi biologici come cellule e il loro citoplasma contengono una grande percentuale di acqua. L’interazione di pori attraverso le membrane e il loro ambito acquoso ha una influenza cruciale sulle loro proprietà di trasporto e la loro funzionalità. Risulta quindi fondamentale analizzare in dettaglio l’interazione tra gli NTC ed il loro ambiente, prima di sviluppare congegni basati sugli NTC.

Nella prima parte di questa tesi rivalutiamo in dettaglio l’interazione tra acqua e carbonio. In uno studio iniziale consideriamo le interazioni tra acqua e benzene e tra acqua e naftalene. Paragoniamo i potenziali di interazione ottenuti dalla teoria dei funzionali di densità da un lato, e dei calcoli basati su metodi di meccanica quantistica più precisi ma molto più costosi dall’altro. Durante questi paragoni valutiamo sistematicamente degli schemi di correzione per i funzionali di densità, tra i quali emergono degli schemi appropriati per studi futuri.

Il costo computazionale dei calcoli di meccanica quantistica limita la grandezza dei sistemi che possono essere considerati. Per studi di realizzazioni specifiche di pori basati su NTC è dunque necessario ricorrere ad un metodo diverso: la dinamica molecolare in cui le interazioni sono basate su potenziali empirici e semplificati. Questa semplificazione delle interazioni tra atomi riduce il costo computazionale
e permette il calcolo di sistemi tre ordini di grandezza maggiore. Dato che i potenziali nella dinamica molecolare sono empirici, è necessaria un attenta convalida e una legittimazione delle semplificazioni che si sono fatte.

Una semplificazione che viene spesso incontrata nella dinamica molecolare consiste nell’ignorare effetti di polarizzazione. Dovuto al fatto che la grafite e gli NTC possiedono delle caratteristiche metalliche, gli effetti di polarizzazione potrebbero essere importanti, soprattutto in ambienti acquosi. Abbiamo sviluppato un campo di forza polarizzabile per la grafite, il quale ci ha permesso di valutare il contributo della polarizzabilità sull’interazione tra grafite e acqua. Abbiamo scoperto che dobbiamo considerare la polarizzabilità in un modo esplicito solamente se ci interessano degli effetti vicino alla superficie o se ci interessa la struttura dell’acqua vicino a della grafite.

I canali attraverso delle membrane che controllano il trasporto d’acqua sono di solito angusti e offrono spazio per una sola fila di molecole d’acqua. L’utilizzo di NTC stretti potrebbe permettere di restituire tali canali per il trasporto d’acqua in un ambito biologico. Con una analisi dettagliata di dinamica molecolare, abbiamo dimostrato che il momento di dipolo statico degli NTC conviene a una tale applicazione. Questo momento di dipolo, orientato in direzione radiale e dovuto alla superficie curvata degli NTC, cambia la struttura dell’acqua all’interno degli NTC e risulta in una riduzione di conduzione dei protoni. Al contrario, in NTC di raggio ampio (5 nm), l’acqua contenuta nel NTC esibisce proprietà d’acqua liquida e l’effetto del dipolo statico può essere ignorato.

Basato su questi studi di convalida, presentiamo finalmente uno studio di dinamica molecolare su vasta scala. Facciamo delle simulazioni di una realizzazione specifica di un nanoporo basato sugli NTC attraverso delle membrane. Studiamo i potenziali elettrostatici intorno a questi tubi e troviamo che la struttura della membrana ha un’influenza notevole sul potenziale elettrostatico nelle vicinanze. A seconda dell’idrofobicità dei bordi del nanotubo, i lipidi della membrana possono mascherare il poro con zone di alto potenziale elettrostatico. Successivamente, in una serie di simulazioni, abbiamo studiato il trasporto elettroforetico di RNA in NTC attraverso delle membrane. In questo studio troviamo che la velocità di trasporto dipende esponenzialmente dalla differenza di potenziale tra i due lati della membrana. Per di più, la velocità di trasporto dipende fortemente dalla struttura del RNA, la quale può provocare un’ostruzione del poro. In conclusione, le nostre simulazioni suggeriscono la fattibilità dell’uso di NTC come pori attraverso membrane biologiche.
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List of Symbols

Latin Letters

\( a_0 \) Bohr radius
\( c \) this is a small c
\( f_{d,n} \) damping function of order \( n \)
\( f \) force
\( \hbar \) Planck’s constant divided by \( 2\pi \)
\( i \) imaginary unit
\( m \) mass, multiplicity
\( n \) order, counter
\( n_{\nu,\alpha} \) number of valence electrons of atom \( \alpha \)
\( p \) momentum
\( \bar{p}_\alpha \) average polarizability of molecule \( \alpha \)
\( p_{\alpha} \) isotropic polarizability of atom \( \alpha \)
\( q \) charge
\( r \) distance
\( r_0 \) reference distance
\( r_m \) reference distance
\( r_g \) radius of gyration
\( r \) position
\( r_{ij} \) vector connecting position \( i \) and \( j \)
\( r_{ij} \) distance between \( i \) and \( j \)
\( t \) time
\( z \) orthogonal distance from plane

\( C_{n,\alpha\beta} \) dispersion coefficient of order \( n \) for species \( \alpha \) and \( \beta \)
\( E \) electric field
\( E \) energy
\( \hat{E} \) energy operator
$E_0$ ground state energy
$E_{DFT}$ energy from density functional theory
$E_{Disp}$ dispersion energy
$\mathcal{E}_{\uparrow\downarrow}$ non-classical electron-electron interaction energy functional
$E_{tot}$ total energy
$\mathcal{E}_{XC}$ exchange correlation energy
$\mathcal{F}$ universal density functional
$H$ Hamiltonian
$\hat{H}$ Hamiltonian operator
$I_\alpha$ Ionization energy of molecule $\alpha$
$J$ coulombic electron-electron interaction energy functional
$K$ kinetic energy
$K_h$ harmonic force constant
$K_M$ Morse force constant
$K_m$ dihedral force constant of multiplicity $m$
$K_\Theta$ force constant for angular potential
$N$ number of particles
$N_\alpha$ Slater-Kirkwood effective number of electrons
$N_C$ number of constraints
$N_f$ number of degrees of freedom
$P$ pressure
$P_{id}$ ideal pressure
$P_{vir}$ virial pressure
$T$ temperature
$T$ kinetic energy functional
$T_S$ kinetic energy of non-interaction Kohn-Sham orbitals
$U$ potential energy
$V$ potential energy function, volume
$V_{retrain}$ restraint potential energy function
$V_{XC}$ exchange correlation potential
$Z_0$ reference distance from plane
$Z_A$ ionic charges

**Greek Letters**

$\alpha$ isotropic polarizability, identifier
$\beta$ identifier, parameter for Morse potential, Ewald damping factor
\( \epsilon_0 \)  permittivity of vacuum
\( \epsilon_C \)  exchange operator
\( \epsilon_{IJ} \)  Lennard-Jones well depth parameter for species \( I \) and \( J \)
\( \epsilon_X \)  correlation operator
\( \epsilon_{XC} \)  exchange correlation operator
\( \mu \)  dipole moment
\( \lambda \)  Lagrange multiplier
\( \phi \)  Kohn-Sham orbital
\( \rho \)  electron density, density, number density
\( \sigma_{IJ} \)  Lennard-Jones separation parameter for species \( I \) and \( J \)
\( \chi \)  spin orbital
\( \omega \)  plasma frequency

\( \Delta \beta \)  deviation from the design turning angle
\( \Delta E_{\text{corr}} \)  energy correction
\( \Phi_{ijkl} \)  dihedral angle between particles \( i,j,k \) and \( l \)
\( \Phi_{0,m} \)  dihedral reference angle of multiplicity \( m \)
\( \Psi \)  wavefunction
\( \Theta \)  contact angle
\( \Theta_{ijk} \)  angle between particles \( i,j \) and \( k \)
\( \Theta_0 \)  reference angle
Chapter 1

Introduction

Nanotechnological progress in the latest decades disclosed new perspectives in research, practical applications and technologies. One of the most promising fields in this respect is nanotechnology. Nanotechnology is characterized by the ability to manipulate length scales of the order of nanometers and time scales of the order of nanoseconds. Many novel concepts, applications, materials and technologies have recently been suggested to operate on these length and time scales. While there are already many applications of nanotechnology, there are still many more to come and we would like to contribute.

In this thesis we will address a very promising compound – carbon nanotubes (CNTs) – and a possible application. CNTs are carbon molecules with a tubular shape and unique properties. Due to their shape and their properties it has been suggested that they may work as nanometer size syringes or nanopores. In this thesis we address the application of CNTs as nanometer size pores and the physics of CNTs in an aqueous environment. In series of studies we present new methods and concepts and use them to gather knowledge that is necessary for the design of CNT based devices. The results reported bridge a wide range both in theory and practice, as both, modeling aspects and physics of carbon nanotubes are studied.

Most of the contributions in the field of nanotechnology are obtained from experimental research. Experiments may however be costly, the results may be interpreted in different ways and most important, questions may remain unanswered. Scientific simulation may provide an alternate approach that could help to circumvent the problems encountered by experimentalists. Although scientific computation and simulation face many problems by themselves, they may help to resolve some of the problems encountered by experimentalists. Simulation and experiment should, however, always be understood as complementing approaches each providing aspects to the understanding which otherwise could not be obtained. In this thesis we focus on the simulation of nanometer size systems and in particular on CNTs, their interaction with water and their behavior when embedded in
membranes.

The goal of this thesis is to assess the viability of transmembrane RNA transport through CNT nanopores. We performed several studies on conceptual problems to reach this goal. The methods applied range from high level quantum mechanics calculations to large scale molecular dynamics simulations. The systems which are studied are as different as the methods used. Nevertheless, the thesis is devoted to a single goal: the understanding of CNT based transmembrane pores. Here we provide a short introduction to the contents of this thesis in order to facilitate an overview. The thesis is structured as follows:

Chapter 2: Membranes, Pores and Carbon Nanotubes

The motivation of this thesis is found where biology, medicine and nanotechnology meet. Recent years have seen an incredible progress in all these fields. While biology and medicine have always been closely related, a direct link to nanotechnology is not obvious. New materials like fullerenes and CNTs have however opened a field of possible applications to nanotechnology which are targeting biological systems, i.e. cells and membranes. Transport processes across membranes are playing a crucial role in the biology of a cell and are usually controlled by transmembrane pores. The importance of these transport processes is emphasized by the fact that many diseases are caused by malfunctioning transmembrane pores. CNTs may be fabricated in a size similar to transmembrane pores. Thus, CNTs were suggested to be used as artificial pores and nanometer size syringes. This would allow to modify and control the transport across cellular membranes. In this chapter we introduce the reader to the structure of biological membranes and membrane channels. Further, background information on CNTs is presented and an overview on CNT based applications is provided. The chapter concludes with the motivation of this thesis: the use of CNT transmembrane pores for the transport of biomolecules.

Chapter 3: Molecular Interaction Potentials within Density Functional Theory

Quantum mechanics (QM) provide a fundamental description of any system. In theory, QM calculations do not depend on parameters and it would be desirable to use the most sophisticated approach to QM for any calculation. Due to the excessive cost of the most rigorous QM methods, however, very often simplified approaches are chosen, e.g. density functional theory (DFT). In DFT the Schrödinger
equation is solved in terms of the electron density instead of the wave function. The result obtained with DFT is in theory correct if the true density functional is used. But the true density functional is not known and it has to be approximated. Depending on the realization of the density functional several simplifications are introduced which cause a loss of accuracy. One of the main reasons for the loss of accuracy is the dispersion energy contribution, a weak interaction arising due to the correlation of spontaneously induced dipole moments. The dispersion energy contribution is usually missing in current density functionals. The asymptotic behavior of the dispersion energy at large distances is however known and parameters can be estimated. Thus, it should be possible to compensate on an ad-hoc basis for the missing dispersion energy contribution in DFT. Several methods to correct DFT results from current density functionals are compared to each other. This comparison is performed on water-benzene and water-naphthalene clusters. Based on the results a correction scheme is recommended to be used if water-carbon systems are to be simulated. The chapter is concluded with the presentation of a framework which allows to bound a range for the interaction energy of a single water molecule on graphite.

Chapter 4: Molecular Dynamics Simulation – An Introduction

Studying nanoscale systems solely based on first principles becomes prohibitively expensive very quickly. With increasing system size the need for simplified models increases. The method of choice to study systems on the scale of several nanometers is Molecular Dynamics (MD) simulation, which allows for the study of molecular ensembles of up to millions of atoms. MD simulations rely on a simplified description of the force between the individual atoms, a so-called force field. During the course of a simulation, the Newtonian equations of motions are integrated to obtain the particle trajectories. The force field defines the forces acting in a system which are in turn used to compute the particle trajectories. Thus, it is crucial for the results obtained with an MD simulation how accurately the force field describes the molecular interactions. Despite of its conceptual simplicity, MD simulations are subject to several computational issues which have to be addressed. The efficient computation of the nonbonded interactions, the boundary conditions to the molecular system and the sampling of rare events are only a few of the problems which have been active areas of research in recent years. This chapter introduces concepts of MD which will be necessary for the understanding of the following chapters.
Chapter 5: Generalized Steering for Molecular Dynamics

Rare events and slow processes are difficult to study in MD. Time scales in MD are in the order of nanoseconds and only recently simulations are overcoming the micro second limit. Any process which takes longer than several nanoseconds or only occurs every several nanoseconds is therefore hardly accessible by pure MD simulation. For processes, however, where an energy barrier is the cause for the slow evolution or the rareness of the process, steered molecular dynamics (SMD) provides a solution to this problem. SMD has become a very popular tool to study various problems which would not be accessible by standard MD simulation. In this chapter the concept of SMD is extended to collective variables. Whereas SMD in its original form was only working on atomic coordinates, this extension allows to work on complex trajectories and along complicated reaction coordinates. The concept is illustrated by applying it to several collective variables: a radius of gyration, an angle, atomic distances and a center of mass distance.

Chapter 6: Polarizability Effects in the Water-Carbon Interaction

CNTs and fullerenes have been envisioned to be key compounds in the development of novel tools and devices on the nanoscale. Many applications have been suggested for biomedical and biological purposes. With respect to those applications it has to be considered that life on earth has evolved in water and terrestrial biological systems are composed of up to 99% water. Therefore, the aforementioned applications will be required to function in aqueous environments and the water-carbon interaction is of preeminent importance. Even more so as the surface to volume ratio is highly increased at the nanoscale. Here, we study the effect of polarizability on the water-graphite interaction. Introducing polarizability in our force field allows us to recover an optimal geometry for water on graphite consistent with QM predictions. In the presented model, the interaction parameters are estimated by reproducing the experimental values of the contact angle of water droplets on graphite. With these interaction parameters we obtain an improved interaction energy for the single molecule interaction energy of water on graphite. Thus, the inclusion of polarizability significantly influences a single molecule on graphite. In contrast, bulk water properties close to graphite are hardly changed. Summarizing, the inclusion of polarizability may allow us to improve description of water on graphite with regards to reference data from simulation and experiment.
Chapter 7: Dipole

CNTs are closely related to graphite and thus the modeling approach to both of them is similar. From quantum mechanical considerations it is however known that CNTs should exhibit a static dipole moment in radial direction. This static dipole moment is induced by the curvature of the CNTs. The presence of this dipole moment could significantly influence the operability of CNT based devices on the nanoscale, e.g. CNT based nanopores or nanometer size syringes. In this chapter we present a study on the structure and dynamics of water inside narrow, short CNTs. Modeling the dipole or neglecting it leads to significant differences in the water structure and the transport properties. For large CNTs with 2.5 nm radius we study the effect on a droplet inside the tubes. We quantify the effect of the static dipole moment by considering the droplets contact angle with the tube wall and the orientation of water molecules close to the tube wall. The effects due to the static dipole moment of CNTs are found to be insignificant. In summary, the static dipole moment across the tube shell influences the water structure in the vicinity of CNTs only when the water molecules are isolated to a large extent and not subject to nearby bulk conditions.

Chapter 8: Membrane

The structure of CNTs suggest that they may function as nanometer size syringes or pores in biological membranes. In particular, CNTs could be imagined to replace biological pores to transport biomolecules across cell membranes. In this chapter we present the results of a large scale MD study on CNTs acting as transmembrane pores. In particular we assess the viability of such an application of CNTs. In a conceptual study we consider both, a lipid bilayer as a realistic model for a biological membrane and dodecane layer as a membrane mimic. The amphiphilic nature of the phospholipids and their head groups are found to play an important role in the overall behavior of the system. The electrostatic potential maps of pores in a membrane mimic and in a lipid bilayer differ significantly. A rearrangement of the lipid head groups in the vicinity of the pore openings changes the local electrostatic potential. The RNA transport across a transmembrane CNT is found to depend exponentially on the transmembrane potential difference and a strong hydrophobic interaction between the RNA bases and the CNT determines the RNA structure inside the CNT during the transport process. RNA transport across a lipid bilayer is found not to differ significantly from the transport across a membrane mimic. A realization of transmembrane nanopores based on CNTs

seems therefore realistic.

**Chapter 9: Conclusions**

The main findings of this thesis are summarized and conclusions are drawn.

**Chapter 10: Outlook**

An outlook on future research is given.
The goal of this thesis is to assess the viability of CNT based transmembrane nanopores for the transport of RNA. In this chapter we will provide background information on membranes, transmembrane pores and CNTs. This information is provided to facilitate the understanding of the following chapters. Furthermore, we will also emphasize the motivation for these studies.

2.1 Membranes

Biological membranes enclose cells and organelles and separate the contents of a cell or an organelle from their surroundings. The spatial separation of the cell interior from the outside world is vital. Only the close integration of the cytoplasm, the different organelles and eventually the nucleus or the genetic material allows cells to survive. The organelles, which are themselves encompassed by a membrane, account for important functions within the cell. Many important biochemical processes take place inside organelles or on their surface, i.e. their membrane. But not only do membranes separate: they control also the transport processes between their interior and their surroundings, i.e. they control what is taken up into a cell and what is expelled. These transport processes sustain differences in ionic concentration, pH and electrostatic potential which are crucial for the a cell to function.

Biological membranes are mixtures of proteins, cholesterol and lipids. The lipids are responsible for the structure of the membrane and the membrane proteins and the cholesterol are embedded in the lipids. The lipids are amphiphilic, i.e. they have long hydrophobic tails and a polar hydrophilic head, see figure 2.1. Typical lipids in membranes are phospholipids: two long hydrophobic alkane chains of variable length and a choline group are attached to a glycerol backbone. The choline group has a zwitterionic character with a positively charged ammonium and a negatively charged phosphate group. The alkane tails are attached to the glycerol backbone by ester groups, see figure 2.1. The lipids form a lipid bi-
Figure 2.1: The figure shows a visualization of a phospholipid (left) and its chemical structure (right). A phospholipid consists of a polar head (indicated with a gray/dotted circle) and long hydrophobic lipid tails. In the visualization only hetero atoms are shown for clarity (carbon – grey, nitrogen – blue, phosphorus – yellow and oxygen – red). The phosphate and the ammonium group are part of the choline group which is attached to the glycerol backbone of the lipid. Together with the ester groups they form the lipid head. The ester groups bind the hydrocarbon tails of variable length to the glycerol backbone.
layer, i.e. the lipids are ordered in two layers. The hydrophilic heads are exposed to the outside and the hydrophobic tails are oriented towards and interacting with each other between the two planes formed by the lipid heads [109], see figure 2.2. In this way, the hydrophilic heads are interacting with the aqueous solutions on either side of the membrane and the lipid tails avoid solvation.

Pure lipid bilayers undergo several phase transitions. With increasing temperature the lipid bilayer undergoes a transition from a crystalline subgel phase via the flat gel phase to a fluid phase [179]. The only phase which is relevant for biological systems is the fluid phase [335]. The phase transition for pure phospholipids from the gel phase to the liquid phase, however, only occurs around 50°, which is well beyond physiological temperatures. What seems a contradiction at first may be resolved by the presence of different compounds in biological membranes. Cholesterol and phospholipids with unsaturated lipid tails disrupt the close packing of the lipid tails and lower the temperature for a phase transition [7, 335]. Cholesterol has however another important function in a lipid bilayer, too. Cholesterol immobilizes the first few lipid tails in its vicinity and reduces the flexibility of the lipid bilayer. Consequently, the permeability of the membrane to water-soluble molecules is decreased.

Apart from lipids and cholesterol membranes contain various proteins. Membrane proteins are categorized in two groups: integral and peripheral membrane proteins. The former are also called transmembrane proteins and span across the
whole membrane. They are usually amphipatic, with hydrophobic and hydrophilic zones interacting with the corresponding zones of the lipid bilayer. For transmembrane proteins it is important that the hydrophobic domain matches the hydrophobic domain of the lipid bilayer [163, 232, 282]. Mismatches result in perturbations of the bilayer which decay only slowly [232] and may interfere with membrane stability. Peripheral membrane proteins do not span across the lipid bilayer [335]. They are either attached to other membrane proteins or anchored to the cytoplasmic surface of the membrane.

2.2 Transmembrane transport and pores

The function of membranes is not limited to the separation of the cytoplasm from the outside world. A biological membrane also controls the take up and the release of ions and molecules. The transport across a membrane occurs in different ways and is one of most fascinating fields of current research. We can distinguish between active and passive transport across an intact biological membrane. Active transport is referred to, if the process is actively driven by an additional energetic contribution. Passive transport in contrast is solely driven by diffusive mechanisms and the electrochemical potential gradient [318]. Passive transport may be subdivided in three classes: simple diffusion across the cell membrane and diffusion facilitated by channels or carrier proteins [255]. In the following we will focus on passive transport facilitated by transmembrane channels [111]. For more information about the other transport processes the reader is referred to textbooks [255].

2.2.1 Transmembrane channels

The malfunction of transport in transmembrane channels can lead to a variety of diseases which underlines their importance. Diseases caused by channel disfunctions are generally referred to as channelopathies. Channelopathies are encountered in many different forms [14, 58, 88, 137, 272]: renal disorders (e.g. Bartter syndrome, Liddle syndrome, Dent’s disease, kidney stones), endocrine disorders (e.g. hypoglycemia), bone diseases (e.g. osteopetrosis), neurological diseases (e.g. epilepsy, ataxia, complete color-blindness, deafness, Usher syndrome), cardiac arrhythmias and muscular disorders (e.g. periodic paralysis, myotonia). For more information on these and further diseases, the reader is referred to the cited reviews and the references therein. Most channelopathies severely affect the quality
of life of the diseased. Current medical research tries to develop new treatments that allow to cure or to disburden the affected people. This task will be significantly facilitated by the understanding of transmembrane channels and the according transport processes.

Transmembrane channels or transmembrane pores are usually complex proteins that show quite a heterogeneous interior. This heterogeneity, both in terms of geometry and in terms of the characteristics of the pore walls, is largely responsible for their biological functions [118], e.g. it determines the selectivity of the pore with regards to the molecules or the ions it transports. The shape of the pore is determined by the underlying protein and so are the characteristics of the pore, e.g. whether the walls are rather hydrophilic or hydrophobic. Knowing the protein structure of a transmembrane channel is therefore the first step towards the understanding of the mechanisms of selective transmembrane transport.

We will now present four transmembrane pores and explain how they function and what determines their selectivity. The four transmembrane channels which will be reviewed are potassium channels, gramicidin A, aquaporine and α-Hemolysin.

**Gramicidin A**

Gramicidin A is one of the best characterized transmembrane channels [73]. It permits the passage of protons and alkali cations but it gets blocked by calcium ions [73, 129, 318]. Gramicidin consists of 15 amino acids, which are all hydrophobic, as it is expected for such a small transmembrane protein [73, 318]. It has been used widely in experimental [10, 173] and computational studies [263, 303, 337], mainly due to its small size, which makes it a prototypical model for other pores.

Experimentally, two structural types of the gramicidin A channel have been identified. Both structures are dimers and are illustrated in figure 2.3. The first structure corresponds to two helices stacked on top of each other [12, 167] and the second structure is a double helix with the two proteins nested into each other [13, 48]. The average pore radius for the double helical structure is about 0.2 Å wider than in the stacked structure (1.6 vs. 1.4 Å) [73]. It is not clear which of these two structures is more important for ion conduction. In a recent molecular dynamics study, however, de Groot et al. [73] found that the stability of the structure depends on the chemical environment and significantly influences the water permeation rate.

Recently, Liu et al. [199] studied the transport of sodium cations across a gramicidin channel. In a steered molecular dynamics study they found that during the translocation, the sodium ion is stabilized by backbone carbonyl oxygens and wa-
Aquaporin

At least ten different mammalian aquaporins have been identified in water-permeable tissues [39]. The aquaporins may be classified in two different groups: orthodox aquaporins which are water selective and aquaglyceroporins which allow water, glycerol and some other solutes to permeate [39]. The transport process through aquaporins is a passive process which is driven by the osmotic pressure gradient across the membrane [221, 305]. There are however cellular mechanisms to control the transport through aquaporins. Törnroth-Horsefield et al. [305] showed that a change in the cytoplasmic pH triggers a conformational change of the protein which occludes the pore.

Orthodox aquaporins are highly water selective and inhibit the permeation of other solutes or even protons [345]. Although gramicidin and aquaporin both contain single file water structures, their permeability for proton transport differs strongly. While proton transport occurs rapidly through the former, it is inhibited
Figure 2.4: Illustration of the aquaporin complex in a lipid bilayer and the water transport in the pore. A reorientation of the boomerang-shaped blue water molecules within the pore is clearly visible and prevents the proton transport across the pore. The image was created by Tajkhorshid and Schulten [115].

for the latter [253, 293]. Several recent computational studies were targeted to explain this effect. de Groot and Grubmüller [72] and Tajkhorshid et al. [293] showed that a reorientation of the single water chain in orthodox aquaporins is essential for the inhibition of proton transfer. This reorientation is triggered by a relatively small zone in the constriction region of the pore where a single water molecule is forced to act as a hydrogen bond donor to both its neighbors in the single water hydrogen bonded chain in the pore [293, 352]. The pore and the water reorientation are illustrated in figure 2.4.

Further studies emphasize the importance of the protein structure on the conductance [156]. E.g. Wang et al. [330] could show that the capability of aquaglyceroporins to transport glycerol relies on a very basic tuning of the pore size. The barriers that need to be overcome during a passage through the pore were assessed by Jensen et al. [155] who presented steered molecular dynamics studies of sugar transport through a aquaglyceroporin. But still, aquaporins remain an attractive subject to research as the complex machinery is not yet completely understood.
Figure 2.5: Illustration of the potassium channel in a lipid bilayer (left), figure taken from Bernèche and Roux [29]. The potassium channel has a selectivity filter which closely matches the size of the potassium ions (middle). The filter is lined with carbonyl groups (right). The ion transport may be gated by constriction of the pore opening (middle). The middle figure is from Shrivastava and Bahar [277] and the figure on the right from Noskov et al. [235].

Potassium Channels

Biological membranes usually show a high permeability for potassium ions. Especially the nervous system relies strongly on the ability of potassium channels to transport potassium ions rapidly [255].

Potassium channels are highly selective towards potassium and show a very small permeability for other ions [84]. The pore has a complex geometry with varying diameter and a total length of 4.5 nm. A tunnel of 1.8 nm connects the inside of the cell to a cavity of approximately 1 nm in diameter, located in the middle of the protein. The cavity is followed by a narrow region of 1.2 nm which connects the cavity to the exterior of the cell and acts as the selectivity filter [28, 84]. The structure of the channel is illustrated in figure 2.5.

The selectivity arises due to a structurally close fit between the potassium ion and the carbonyl groups lining the rigid and narrow pore [84, 127, 235, 350, 351], see figure 2.5. While many different potassium channels are known, the residue sequence in the narrowest region of the pore is highly preserved [235]. Mutations in this sequence result in the loss of selectivity [84].
2.2. TRANSMEMBRANE TRANSPORT AND PORES

Figure 2.6: Illustration of the heptameric α-hemolysin channel in a lipid bilayer. The protein has a heptameric structure and a mushroom-like shape. Its stem is embedded in the membrane and the cap is located on the outside. The images is taken from Aksimentiev and Schulten [6].

The potassium channels of the nervous system are voltage gated. In a recent study, Long et al. [200] showed that the gating is induced by a conformational change of relatively large independent domains which are loosely attached to the channel. Upon a change of the transmembrane potential, these domains perform a large scale movement, to accommodate charged residues in an energetically more favorable position. The mechanical work induced on the connection of these domains with the pore leads to a constriction of the pore and closes it [200], see figure 2.5.

α-Hemolysin

α-Hemolysin is a rather large water filled transmembrane pore with an inner diameter of approximately 1.5 nm. It binds in its monomeric form to the cell membrane where it self-assembles and leads to an uncontrolled dissipation of molecules and ions across the membrane [17, 110]. The rapid loss of vital molecules as ATP and the discharge of ions across the membrane leads to a breakdown of membrane potential. These effects are usually combined with an osmotic swelling that can cause rupture of the membrane (lysis). In summary, α-Hemolysin is a strong cytotoxin which permeates mammalian cell membranes [17, 30, 31, 117, 218].

α-Hemolysin is a heptameric protein with a mushroom-like shape [6, 285], see figure 2.6. Its stem protrudes through the membrane and the cap sits on top of the membrane. Inside the cap there is a large vestibule with a large opening at the top
Figure 2.7: Cut through the $\alpha$-hemolysin channel in a lipid bilayer. A large vestibule is located in the cap of the mushroom like protein. The channel which goes through the stem has a minimal diameter of approximately 1.5 nm. The narrowest zone is located at the transition from the stem to the cap, where it connects to the vestibule. The image is taken from Aksimentiev and Schulten [6].

of the cap. The channel which goes through the stem has its narrowest zone at the transition from the stem to the cap, where it connects to the vestibule [6]. The $\alpha$-hemolysin channel is illustrated in figure 2.7.

$\alpha$-Hemolysin is stable over a wide range of pH and temperature [223] and it binds spontaneously to various lipid bilayers [176]. $\alpha$-Hemolysin has been genetically engineered to allow the conductance to be switched on and off [19, 265] and can therefore be used for the controlled delivery of small molecules.

A remarkable property of $\alpha$-Hemolysin is, that it allows for the transport of linear macromolecules. With a transmembrane potential difference, single stranded RNA and DNA can be driven through the pore [3, 166, 222]. Because of this property it has been suggested to use it as a nanopore sensor capable of sequencing RNA or DNA [126, 191]. In the prospect of these applications, Aksimentiev and Schulten [6] assessed $\alpha$-Hemolysin and the electrostatic potential maps in its vicinity. Very recently Mathé et al. [214] studied DNA transport in $\alpha$-Hemolysin and reported that the constriction of RNA inside the pore significantly influences the translocation. In particular, they found a directional bias on the DNA transport, both in experimental and theoretical results.
2.3 Carbon nanotubes

Carbon nanotubes (CNTs) are tube like molecules or molecular compounds which consist only of graphitic carbon. Since their discovery by Iijima [144] CNTs have attracted constantly increasing interest [18] and researchers from diverse fields concentrated their efforts on CNTs.

Due to unique mechanical, chemical and electronic properties novel applications were suggested for CNTs. In this section we will provide an introduction to the chemical structure of CNTs and we will review their physical properties. This is followed by a non-conclusive listing of possible applications for CNTs. The tubular shape of CNTs suggests they may be used as pipes on the nanometer scale and in particular as nanopores or nanosyringes. In this thesis we want to assess the viability of CNT based nanopores. Therefore we conclude the chapter with a review of recent studies on artificial nanopores and related applications.

2.4 Structure

Single-walled CNTs (SWCNTs) have the structure of a seamlessly rolled up graphitic sheet. A SWCNT is uniquely defined by the chiral vector that specifies the roll-up direction

\[ C(n, m) = na_1 + ma_2, \quad \text{where} \quad (n, m) \in \mathbb{N}, n \geq m, \]

where \( a_1 \) and \( a_2 \) are the basis vectors as defined in figure 2.8. Due to the form of their edges, SWCNTs with \( m = n \) are called armchair tubes and SWCNTs with \( m = 0 \) are called zig-zag tubes. All other tubes are called chiral. The circumference of the CNT is given by the length of the chiral vector and accordingly we get for the tube radius

\[ r = \frac{|C(n, m)|}{2\pi} = \frac{a\sqrt{m^2 + mn + n^2}}{2\pi} \]

where the lattice constant in the graphite sheet is \( a = 1.42\sqrt{3} \, \text{Å} \).

Multi-walled CNTs (MWCNTs) either consist of several concentric SWCNTs or a graphite sheet rolled up around itself, similar to a rolled up newspaper. While typical diameters of SWCNTs are in the order of 1 nm MWCNTs can have inner diameter of up to 1 \( \mu \)m. Both SWCNTs and MWCNTs have been found with lengths up to the order of 1 cm [353].
Figure 2.8: The structure of single-walled CNTs as defined by the chiral vector. A zig-zag (6,0), a chiral (5,3) and an armchair (4,4) CNT are shown in the top. The chiral vectors of those CNTs are indicated on the honeycomb lattice of a graphite sheet below.
2.5. PROPERTIES

CNTs are produced in four main approaches: the arc discharge, the laser ablation, the chemical vapor deposition and the high-pressure carbon monoxide method. These synthesis methods will not be presented here. For detailed information on these methods we refer to a recent article of Kang et al. [164], reviews of Dai [67], Nikolaev [234] and Baughman [18] and to the books of Saito [270] and Harris [123].

2.5 Properties

The interest in CNTs has to be attributed to their unique physical properties. CNTs are very strong with a tensile strength up to 60 GPa [18, 343] and relatively low density for a solid ($\sim 1400 \text{ kg m}^{-3}$). With Young’s moduli of the order of 1 TPa [18, 271] CNT are one of the strongest materials known so far.

Single walled CNTs are excellent electrical conductors [295, 296] but depending on the chiral vector, they can act as semiconductors. CNTs are also very good thermal conductors along their axis and isolating otherwise [54, 237, 340].

Another fascinating attribute to CNTs is their simple yet complex structure. The weak interaction between concentrical CNTs in MWCNTs makes them perfect linear or rotational bearings [64] and recently a nanoscale motor was presented with a CNT as an axle [94]. The tubular shape suggests similar applications as for macroscopic tubes, e.g. as tubes and syringes to transport materials on the nanoscale, see below.

Due to the interest in biomedical applications the physiological action and especially the toxicity of CNTs is of major concern. CNTs have been found to pose a big risk if inhaled and are found to be much more toxic than carbon black [185]. Various cells exposed to hydrophobic CNTs showed cell cycle arrest or apoptosis [41, 63, 79, 87, 157, 210, 228]. In contrast, functionalized hydrophilic CNTs that were intravenously administered were found to leave the body quickly in the urine [280] and Dumortier et al. [87] find that functionalized hydrophilic CNTs do not act cytotoxic. Functionalized CNTs may therefore be the key to biomedical applications of CNTs [87].

2.6 Applications

Applications for CNTs have been suggested in abundance. Due to the unique properties of CNTs, novel applications were proposed and known applications could
be realized at new length scales. In the following a selection of prominent applications is presented. The overview does not strive for completeness and is kept minimal. For further information on specific applications the reader is referred to the cited publications.

**Mechanical applications**

The unprecedented strength of CNTs makes them ideal components for composites [32, 68] and fibers [18, 316]. An application which has already been commercialized is the use of CNTs as tips for atomic force microscopes. The small and controlled dimensions of CNTs and their mechanical strength facilitate their use as tips for atomic force microscopes and make them superior to other tips [55, 120, 192, 323].

Another idea which is indirectly linked to the structure of CNTs is their use for hydrogen storage. The large surface area of CNT structures, relatively low density and their chemical similarity to carbon black could make them suitable for this purpose [101, 102, 135, 188, 346, 347].

**Electronic applications**

CNTs can be considered as a 1-dimensional conductor or semiconductor. These unique electronic characteristics of CNTs have been exploited in a series of novel electronic devices:

- The first intramolecular logic gate [76]
- Single electron transistors [254]
- Logic circuits [16, 76]
- Field-effect transistors [18, 296]

CNTs were also suggested to act as quantum wires themselves [295] or to act as mold to produce nanometer size wires of controlled dimensions [168]. Arrays of CNTs may be used as supercapacitors and the conductivity of CNTs suggests their use as highly efficient electrodes [18].

**Sensors**

Functionalized CNTs may act as nanometer size sensors to detect proteins [56] and single stranded DNA [136, 193, 197, 349]. The CNTs act as a support for
functionalizations that bind only to specific target molecules. This allows to probe systems for the occurrence of specific molecules, e.g. proteins or DNA of a given sequence. Many other applications of functionalized CNTs may be imagined and Lin et al. [197] presented a review on different functionalizations of CNTs and possible sensor applications.

In a slight modification on concepts presented before, Wong et al. [336] reported on the use of functionalized CNTs for a chemical force microscope. A chemical force microscope is used for chemically sensitive imaging. Functionalizations which interact strongly with specific chemical groups are covalently linked to an atomic force microscope tip. The force recorded by the atomic force microscope then depends on the chemical properties of the surface.

Upon exposure to nitrogen dioxide or ammonia the electrical resistance of CNTs changes dramatically [175]. This effect may be used to detect these gases even at very dilute concentrations. For more information and references on CNT-based gas sensors the reader is referred to the review of Terrones [298].

The flow of polar liquids (e.g. water) over CNT bundles induces a voltage [104], which depends logarithmically on the flow velocity. This effect can be exploited to construct a highly sensitive CNT-based flow sensor. Furthermore, the deflection of single walled CNTs changes their electrical resistance. This effect has already been used in highly sensitive pressure sensors [288] and it could also be used for flow sensors.

Pores and Tubes

On this last class of applications we will elaborate in greater detail as it is the motivation for the studies presented in the following chapters. Many biological processes involve the transport of biomolecules across cell membranes [85, 279]. Their tubular shape suggests that CNTs may function as nanometer size syringes or pipes. Furthermore, the dimensions in which CNTs could be fabricated are similar to pores in biological membranes. Thus, CNTs could be used as artificial pores across cell membranes or to stabilize pores formed by electroporation. In this sense, CNTs could offer the key to a world of nanometer size pores, valves and tubes, which allow to manipulate cells in very specific ways. These applications could make CNTs the key to emerging fields as as single-molecule and single-cell medicine and nanotechnology based medical applications. And not surprisingly, CNTs have been suggested to be used to for DNA gene delivery [238].

Recently, the insertion of nanometer size tubes into membranes was assessed by means of coarse grained molecular dynamics simulations [202, 203, 287] and
influence of those tubes on the structure of the membrane was quantified [232, 286]. The nanotubes in these studies are a generic model for several kinds of membrane spanning proteins [232] and the results may carry over to CNTs. CNTs however, have a similar but simpler structure than most proteins and may be easier to manipulate in a controlled fashion due to their stability.

To approach the application of CNTs as nanometer size pores or syringes several recent studies assessed the interaction of small CNTs with water [140, 324, 352, 354] and ion transport in CNT based pores [161, 250]. Furthermore, first studies addressed RNA and DNA transport in CNTs and CNT based membranes [103, 341] and the interaction between these molecules [205]. There are even first experimental studies which report on the insertion of single-stranded DNA into CNTs [236].

In the following chapters we will consider CNTs for the delivery of RNA across a biological membrane, see figure 2.9. Understanding such a transport process should allow for insights on a conceptual level that allow to understand biological pores and it should provide a first step to nanometer size devices that allow to deliver single molecules in a controlled fashion. For a reliable study, we must however first assess our models, which will be done in the following.

Figure 2.9: Illustration of a CNT (yellow) in lipid bilayer (turquoise and red) acting as a nanopore for RNA transport. A single stranded piece of RNA is shown inside the CNT. The system is solvated in an aqueous solution.
Chapter 3

Molecular Interaction Potentials within Density Functional Theory

For the study of CNT based transmembrane nanopores it is crucial to know how they interact with their environment. As CNTs are novel compounds there is no established information on the interaction with their surroundings and existing model potentials which are used in molecular dynamics simulation are hardly validated. Quantum mechanics provides a fundamental description of any molecular system and does not depend on empirical parameters. Quantum mechanical calculations should therefore allow to compute interaction potentials and to validate existing interaction potentials. This validation has to be performed before any further studies can be addressed.

In this chapter we study the interactions between water molecules, aromatic compounds and graphite. We show how this can be accomplished within a density functional theory framework. The chapter starts with a short introduction to quantum mechanics which is followed by a more detailed introduction to density functional theory. This introduction highlights that current density functionals do not reproduce the dispersion interaction in weakly bound systems correctly. Then we present an approach to correct for the missing dispersion interaction contribution. Different variations of this approach are then tested on the water benzene cluster and the water naphthalene cluster. This is followed by first considerations on how the approach could be extended to semiconducting surfaces and graphite in particular. The chapter is concluded with an outlook on future directions of research and an overview on recent studies.

3.1 Quantum mechanics

In the framework of quantum mechanics (QM), physical systems are mathematically represented by a wavefunction Ψ. The differential equation which describes
the system evolution in space and time was developed in 1925 by Schrödinger:

\[ i\hbar \frac{\partial}{\partial t} \Psi = \hat{E}\Psi = \hat{H}\Psi = -\frac{\hbar^2}{2m} \nabla^2 \Psi + V(r, t)\Psi, \]  

(3.1)

where \( i \) is the imaginary unit, \( \hbar \) is Planck’s constant divided by \( 2\pi \). The time is represented by \( t \) and the energy operator by \( \hat{E} \). The Hamiltonian operator \( \hat{H} \) is the sum of the potential energy operator \( V(r, t) \) and the kinetic energy operator, wherein \( m \) is the mass of the particle. The Schrödinger equation (3.1), though mostly used in its time-independent form, is the basis for the computational approach to the following problems:

- determining structural properties: conformation and configuration of molecular systems, geometry optimizations
- finding energies under given conditions: heat of formation, conformational stability, chemical reactivity and spectral properties.

Analytic solutions of the Schrödinger equation are only known for special cases, where the potential energy contribution to the Hamilton operator is particularly simple. This is for example the case if there is no potential energy contribution (free particle) or in the case of a single electron in the field of a nucleus (hydrogen atom).

There are several ways to solve the Schrödinger equation numerically. The so-called ab initio methods for example, do not depend on fitted parameters and allow to calculate the properties of interest fully deterministically. However, they may still rely on model approximations as the Born-Oppenheimer approximation [40] or the choice of underlying basis sets [292] to model the wavefunction. For a detailed introduction into different methods and the according approximations the reader is referred to quantum chemistry text books, e.g. [292].

Semi-empirical methods rely on fitted parameters or pragmatic computational approximations. The main advantage in using semi-empirical methods is the reduced computational cost, which enables the simulation of systems one to two orders of magnitude larger in size. Therefore, phenomena can be studied on different scales and some of the size restrictions of ab initio methods can be overcome.

Typical examples for high-order ab initio calculations are the second-order Møller-Plesset [227] (MP2) approach and the even more rigorous self consistent coupled cluster approach (SC-CC). Both methods reproduce the interaction energy of weakly bound molecular systems reasonably well. The results obtained
3.2 Introduction to Density Functional Theory

with SC-CC are generally superior to those obtained with MP2, although the accuracy of the results obtained with the latter is usually sufficient. The systems that can be studied with these methods are limited in size due to the high computational cost. Practically, SC-CC computations are limited to system sizes of 10-20 atoms, whereas MP2 calculations have been reported for systems up to approximately 125 atoms [93].

In density functional theory (DFT) quantum mechanical problems are solved in terms of the electron density instead of the wavefunction. DFT is in theory correct, but the true density functional is not known. The use of approximate density functionals makes DFT a semi-empirical approach that provides an intermediate accuracy at significantly lower computational cost than the methods discussed before. It is therefore possible to study quantum mechanical properties and processes on a much larger scale than other ab initio methods. In particular, DFT allows to study relatively large systems with up to several hundred atoms. Such systems are ideal to study long range interactions between distant molecules, one of the most important applications of QM methods. Determining the exact interaction between two molecules is of preeminent interest for the calibration of simplified interaction potentials. Such interaction potentials are usually used in other computational methods, e.g. in molecular dynamics simulation.

In the following section a short introduction to DFT is provided. For a detailed introduction to DFT the reader is referred to standard textbooks [172, 240]. This introduction is followed by a study on how weakly bound systems can be treated within DFT.

3.2 Introduction to density functional theory

Density Functional Theory (DFT) introduces a significant simplification to the quantum mechanical problem as posed by the Schrödinger equation, while still allowing to retrieve information from first principles. In DFT, the calculations of atomistic and molecular properties are based on the electron density only. This is in contrast to other quantum mechanical methods which use the complicated $N$-electron wave function with its dependence on $3N$ spatial plus $N$ spin variables instead. Due to its simplicity in theory and its predictive power in practice DFT has become a very successful method. A short introduction is given in the following, which presents the key concepts and the history of DFT. This introduction is, however, by no means complete, see [172, 240] for further information.
CHAPTER 3. MOLECULAR INTERACTION POTENTIALS WITHIN DENSITY FUNCTIONAL THEORY

3.2.1 Historical overview

Already in the mid twenties of the 19th century, the early years of quantum mechanics, Thomas and Fermi [96, 302] tried to base quantum chemical calculations solely on the electron density. In particular, they derived an expression for the kinetic energy of a uniform electron gas and for the energy of an atom. These expressions represent the first genuine density functionals, the role of which will be discussed later. The conceptual novelty of this work was in the mere fact that the energy is given completely in terms of the electron density, which laid the cornerstone to DFT. In 1930 the Thomas-Fermi-Dirac-Model was presented which extended the Thomas-Fermi-Model to include an exchange contribution. Further attempts in the development of DFT followed (e.g. by Slater who presented a local approximation of the exchange energy [281]), but DFT did not gain significant importance until the early sixties.

The breakthrough came only in 1964 with two theorems by Hohenberg and Kohn [133] which provide the theoretical foundation of DFT as it is known today. In the first theorem Hohenberg and Kohn [133] proved, that the ground state electron density $\rho(r)$ is determined uniquely by a given external potential. In turn, the ground state energy of a system is determined (within a constant) by the electron density. The second theorem introduces the variational principle, which states that there is a density functional which delivers the lowest ground state energy of the system if and only if the input density is the true ground state density $\rho_0$. While the first theorem states that for any given external potential there exists a unique solution, the second theorem provides the framework on how to determine it. To obtain the true ground state electron density, it is thus sufficient to minimize the energy obtained when applying the correct density functional to the electron density in question.

The precondition to make these two theorems practicably applicable is however, that the correct density functional must be known. Unfortunately, this is not the case and efforts to develop improved approximations to the correct density functional continue.

3.2.2 The density functional

In the previous section it was highlighted that DFT is theoretically correct, provided the density functional is known. However, the true density functional is not known and only approximations of different accuracy exist. These approximations have been proved to be extremely valuable in various fields. Certain problems,
however, could not be addressed with DFT, mainly due to the approximate nature of the functionals. As we will be focusing on such problems later in this chapter, a more detailed introduction to the structure of density functionals is given here. It will be shown how the unknown universal density functional can be approached. The avenue sketched here was suggested just one year after the Hohenberg-Kohn theorems by Kohn and Sham [322].

The Hohenberg-Kohn theorems state that the ground state energy of an atomic or molecular system with \( N \) electrons subject to an external potential \( V_{Ne} \) is given by

\[
E_0 = \min_{\rho \to N} \left\{ \mathcal{F}[\rho(r)] + \int \rho(r)V_{Ne}dr \right\},
\]

where \( \mathcal{F} \) is the universal density functional. Equation 3.2 states that the correct electron density minimizes the energy determined by the functional. This minimal energy is the correct ground state energy of the system.

Conceptually, the functional can be split into different contributions: the electron kinetic energy \( T \), the coulombic electron-electron interaction \( J \) and the non-classical electron-electron interaction \( E_{ncl} \). In more formal terms

\[
\mathcal{F}[\rho(r)] = T[\rho(r)] + J[\rho(r)] + E_{ncl}[\rho(r)].
\]

Of these different terms only the exact form of the coulombic electron-electron interaction functional is known

\[
J[\rho(r)] = \frac{1}{2} \int \int \rho(r_1)\rho(r_2)\frac{d\mathbf{r}_1d\mathbf{r}_2}{r_{12}}.
\]

For the electron kinetic energy and the non-classical interaction terms, the exact expressions in terms of electron density are not known. It is however known that the electron kinetic energy can be expressed in terms of a summation over the Laplace operator acting on the different spin orbitals \( \chi_i \)

\[
T = -\frac{1}{2} \sum_i^N \langle \chi_i | \nabla^2 | \chi_i \rangle.
\]

The spin orbitals are however not accessible in DFT. Instead of using the spin orbitals, Kohn and Sham [322] suggested to only compute as much as possible of the true kinetic energy exactly and to treat the remainder in an approximate manner. Hence, the so-called Kohn-Sham-orbitals \( \phi_i \) are used to obtain the exact
kinetic energy of the non-interacting reference system with the same density as the interacting system

$$T_S = -\frac{1}{2} \sum_i^N \langle \phi_i | \nabla^2 | \phi_i \rangle.$$  (3.6)

This effectively reduces the problem to a single electron system, which can be solved more easily. The non-interacting kinetic energy $T_S$ is however not equal to the true kinetic energy of the interacting system. This inequality holds even if the systems share the same density

$$T_S \neq T.$$  (3.7)

This difference has to be accounted for in a different way. Usually, this remainder from the Kohn-Sham approximation to the kinetic energy is treated in a composite expression with the non-classical contributions to the interaction energy. The functional term which deals with these expressions is called the exchange correlation functional, which results in the exchange correlation energy

$$\mathcal{E}_{XC} = (T [\rho(r)] - T_S [\rho(r)]) + \mathcal{E}_{ncl} [\rho(r)].$$  (3.8)

Therefore, the problem which has to be solved in order to determine the energy of a system, now simplifies to the eigenvalue problem

$$\left( -\frac{1}{2} \nabla^2 + \int \frac{\rho(r_2)}{r_{12}} dr_2 + V_{XC}(r_1) - \sum_A^M \frac{Z_A}{r_{1A}} \right) \phi_i = \left( -\frac{1}{2} \nabla^2 + V_{eff}(r_1) \right) \phi_i = \epsilon_i \phi_i.$$  (3.9)

where $V_{XC}$ is the potential due to the exchange correlation energy $\mathcal{E}_{XC}$, $M$ is the number of nuclei and $Z_A$ are the charges of the nuclei.

### 3.2.3 The exchange correlation functional

While the Kohn-Sham approach as sketched before is generally applicable and correct, a distinction between two cases should be made: the hypothetical situation with the exact exchange correlation functional at hand and the current situation where only an approximation to the exchange correlation functional is available.
Since the Kohn-Sham approach does not contain any approximation whatsoever, the results obtained with the exact exchange correlation functional should correspond to the correct solution of the Schrödinger equation. But, the exact form of the exchange correlation functional is not known and if it was, then its functional form would most probably be of a very complex kind and of non-local dependence on density. Various attempts have been made to approximate the exchange correlation functional which have lead to a variety of density functionals. The differences between different density functionals are only due the approximation of the exchange correlation functional. The quality of a DFT calculation therefore only depends on the quality of the approximation to exchange correlation functional and the resulting exchange correlation energy. Unfortunately, there is no systematic strategy on how to obtain and to improve an exchange correlation functional.

However, there are a few physical constraints which a density functional has to fulfill to be reasonable. These rules can be used as guidelines when developing exchange correlation functionals. Amongst these rules are the sum rules for the exchange-correlation holes (An exchange-correlation hole describes the renormalized depletion of electron density in space when instead of an independent electron, two interacting electrons are considered.). The closer an exchange-correlation hole emerging from an exchange correlation functional is to the true hole, the better the approximation. Further criteria include the cusp condition of the exchange-correlation hole at zero distance between the two electrons and certain scaling conditions and asymptotic properties of the corresponding exchange-correlation potentials. For more detail, the reader is referred to the relevant literature, e.g. Perdew and Burke or Adamo et al. [1, 243]. The quality of a density functional does not necessarily increase with the number of physical constraints met. Therefore, density functionals have to be carefully tested and their performance has to be assessed.

In the following a brief review on exchange correlation functionals, their properties and the underlying concepts will be provided.

The local density approximation

In the local density approximation (LDA) the exchange correlation energy is computed by assuming that the exchange correlation energy of a point in space with a given electron density to be equal to the exchange change correlation energy of homogeneous electron gas at the same density. Integrating over space leads to

\[ \mathcal{E}_{XC} = \int \epsilon_{XC} [\rho(\mathbf{r})] \rho(\mathbf{r}) d\mathbf{r} = \int \epsilon_{X} [\rho(\mathbf{r})] \rho(\mathbf{r}) d\mathbf{r} + \int \epsilon_{C} [\rho(\mathbf{r})] \rho(\mathbf{r}) d\mathbf{r}. \]  (3.10)
Where the exchange part $\epsilon_X$ is based on the theoretical result of Bloch and Dirac [33, 80]:

$$\epsilon_X = -\frac{3}{4} \sqrt{3\rho(r)/\pi}, \quad (3.11)$$

This exchange is often called Slater exchange due to the similarity to Slater’s approximation of the Hartree-Fock exchange. For the correlation part $\epsilon_C [\rho(r)]$ no explicit expression is known. However, various analytical forms have been fitted to numerical energy calculations of homogeneous electron gas (the most famous calculations were probably presented by Ceperley and Alder [51] which were based on a Monte Carlo approach). Important representations of the correlation part based on the LDA have been presented, for example by Vosko et al. [321], Perdew and Wang [244].

The generalized gradient approximation

The moderate accuracy delivered by the LDA is insufficient for most calculations of chemical interest. A straight-forward approach to improve the exchange correlation functionals beyond the LDA is the inclusion of the local gradient of the charge density in the functional. In other words, the LDA is interpreted as the first term of a Taylor series expansion of the true functional. By including the next lower term, a better approximation for the exchange correlation functional should be obtained. This leads to the so-called gradient expansion approximation, which often and surprisingly performs worse than the LDA.

The reason for the poor performance of the gradient expansion approximation is that the exchange correlation hole, corresponding to a functional in the gradient expansion approximation, has lost many of its physical properties, which made it meaningful before within LDA. These properties can be reinforced again. I.e. all non-negative parts of the gradient expansion approximation exchange correlation hole can be set to zero. Furthermore, the exchange and the correlation holes are truncated such that they contain one and zero electron charges, respectively. Functionals constructed in this way obey the generalized gradient approximation (GGA).

Usually, the exchange correlation functional is split into two parts, the exchange and the correlation contribution, for which many different approximation have been suggested. The exchange contribution is often written as the LDA exchange energy plus a correction term, which in turn can be either a semi-empirical expression [20] or a rational functional of the reduced density gradient [243]. For
the correlation part, different approximation also exist. They are either obtained through fitting procedures [241] or are derived from expressions for conceptual systems [187]. In general, all correlation energy functionals could be combined with any of the exchange functionals, however, the number of used combinations is limited.

**Performance of the functionals**

Due to recent advances in the development of density functionals, DFT has become a well established tool to understand and predict electronic structure properties of atoms, molecules and solids [158], reaction paths [37] and catalytic reaction mechanisms [34]. LDA results are comparable or even better than the result obtained within the Hartree-Fock approximation. Furthermore, LDA has been successfully applied to derive molecular properties as equilibrium structures and harmonic frequencies. But when it comes to the description of bonds the performance of LDA remains relatively poor. LDA systematically overestimates atomization energies which results in strong.

GGA functionals have been shown to improve LDA results significantly and in particular to remedy the poor description of bonds. Even hydrogen bonds can be described with good accuracy [278].

However, all current density functionals fail in the description of long-range dispersion interactions, generally denoted as van der Waals interactions [181, 246]. In particular, the current density functionals fail to describe the leading $r^{-6}$ dispersion interaction term correctly [247], which originates from correlated instantaneous dipole fluctuations and can be derived using perturbation theory [216]. Nevertheless, there are calculations where density functionals provide good estimates for the interaction energy of weakly bound systems [220]. These results, which are mostly obtained within the local density approximation, are mainly due to favorable error cancellation [269, 339].

**The quest for the dispersion energy**

The failure of current density functionals to represent the dispersion interaction term correctly can be attributed to the fact that the functionals are based on local electron density its gradient and the local kinetic energy density [245]. Therefore, these functionals fail by construction to reproduce the van der Waals interaction as they contribute to the interaction energy even at distances where electron overlap is negligible,
Currently large efforts are undertaken to develop new density functionals that allow for the correct treatment of the van der Waals interaction. The groups of Lundqvist and Langreth \[11, 139, 138, 269\] have presented various symmetry dependent density functionals to treat the long-range dispersion interaction and applied it to graphite \[269\]. Their work is based on a double local density approximation and compares in this respect to the approach of Rapcewicz and Ashcroft \[260\]. The applicability of the double local density approximation is however limited to systems with non-overlapping densities. Misquitta \textit{et al.} \[225\] used frequency dependent density susceptibilities provided by time-dependent DFT to determine the dispersion energy of monomers at all finite distances. Furthermore, Kohn \textit{et al.} \[174\] presented a scheme that is valid at all distances, but is also computationally very demanding.

In the following, however, a different route will be chosen. We will not try to find a complicated density functional which would treat the dispersion interaction correctly. Instead we try to account for it by introducing a damped correction term \[338, 339\]. This idea has been applied to Hartree-Fock calculations \[83, 294\] and more recently to a density functional-based, self-consistent tight binding method \[89\]. The correction terms and the accompanying damping functions for DFT presented in the literature differ and their performance with regard to each other will be compared in the following sections. This is done in order to determine, whether an optimal representation of long-range forces along with current density functionals would allow for accurate simulations of large molecular systems of biological importance.

### 3.3 Dispersion corrected density functionals

In this section a survey on different dispersion correction schemes for density functionals is given. These models are then applied to two test systems in sections 3.4 and 3.5 and compared with the results of the uncorrected functionals. The test systems are a water benzene cluster in three different geometrical configurations and a water naphthalene cluster in eight configurations.

#### 3.3.1 Correction schemes

As highlighted in the previous section, current density functionals do not account for the dispersion interaction. In order to correct for this deficiency, a term \(E_{\text{Disp}}\) is added to the DFT interaction energy to obtain the total potential energy \(E_{\text{tot}}\) of
interacting molecules [83]

\[ E_{\text{tot}} = E_{\text{DFT}} + E_{\text{Disp}}, \]  

(3.12)

where \( E_{\text{DFT}} \) is the DFT interaction energy computed with an approximated exchange correlation functional. The representation of the dispersion energy contribution varies in the literature [339, 338, 89], but in general it is written as a two-body interaction of the following form:

\[ E_{\text{Disp}} = - \sum_n \sum_{\alpha>\beta} f_{d,n}(r_{\alpha\beta}) \frac{C_{n,\alpha\beta}}{r_{\alpha\beta}^n}. \]  

(3.13)

Here, \( \alpha \) and \( \beta \) are the centers of a pair of interacting particles, \( r_{\alpha\beta} \) is the distance between them, \( C_{n,\alpha\beta} \) and \( f_{d,n} \) are the interaction coefficient and the related damping function of order \( n \). The need for a damping function arises from the fact that the dispersion energy expansion is only an asymptotic expansion, and it becomes physically unrealistic at small distances \( r \) [2]. In particular, it diverges at short range and has to be damped in order to remain physically meaningful. In other words, a damping function has to allow for the full correction at long range, for no correction at short range and for a smooth transition where the overlap becomes important.

At long range, i.e. where overlap is negligible, current density functionals do not account for the dispersion contribution. At intermediate range, i.e. in the transition from negligible overlap to overlap, some density functionals result in energies which seem to account partially for dispersion. Since some of the short-range dispersion effects are already contained in the DFT functional, the damping function has to take this into account. The damping function is therefore clearly dependent on the exchange correlation functional and the dispersion contribution is only a correction term. Equation (3.12) is a partitioning of the total interaction energy into a DFT and a dispersion contribution. In this case the DFT contribution should be the total interaction energy excluding the dispersion interaction energy. A clear partitioning is however not possible at the moment, as the extent to which dispersion is included in current density functionals is not known.

In this section we focus on physically motivated dispersion corrections subject to different damping functions. The joint performance will indicate whether the interplay of dispersion correction, damping function and density functional successfully corrects for dispersion while avoiding a double accounting of it.
CHAPTER 3. MOLECULAR INTERACTION POTENTIALS WITHIN DENSITY FUNCTIONAL THEORY

Molecular correction

Wu et al. [339] proposed the introduction of a correction term of the form (3.13) for each pair of molecules. The dispersion coefficients $C_{6,\alpha\beta}$ are then determined according to [216]

$$C_{6,\alpha\beta} = \frac{3}{2} \bar{p}_\alpha \bar{p}_\beta \frac{I_\alpha I_\beta}{I_\alpha + I_\beta},$$  \hspace{1cm} (3.14)

where $\bar{p}_\alpha$ denotes the average molecular polarizability of molecule $\alpha$ and $I_\alpha$ its ionization energy.

Additionally, the introduction of a higher-order correction term is discussed in [339] and the following empirical relationship

$$\frac{C_8}{C_6} = 45.9a_0^2$$  \hspace{1cm} (3.15)

is proposed [339] to estimate the coefficient $C_8$ for systems involving benzene. Here, $a_0$ is the Bohr radius. The damping function is suggested [83]

$$f_{d,n}(r) = \left[ 1 - \exp \left( -\frac{2.1}{n} - \frac{0.109}{n^2} r^2 \right) \right]^n.$$  \hspace{1cm} (3.16)

where $n$ is an order parameter and takes the values 6 and 8 for the dipole-dipole and the dipole-quadrupole interaction respectively.

Atomic correction

As an alternative to the molecular-based correction scheme, one can introduce a correction term of the form (3.13) for each atom pair. The corresponding atomic dispersion coefficients $C_{n,\alpha\beta}$ are calculated based on atomic polarizabilities $p_\alpha$ listed by Miller [224], who calculated them to reconstruct the total molecular polarizability of a wide range of compounds. For atoms of type $\alpha$ the dispersion coefficient $C_{6,\alpha\alpha}$ is then given as [121]

$$C_{6,\alpha\alpha} = 0.75 \sqrt{N_\alpha p_\alpha^3}.$$  \hspace{1cm} (3.17)

Halgren [121] proposes the following relationship to determine $N_\alpha$, the Slater-Kirkwood effective number of electrons,

$$N_\alpha = 1.17 + 0.33 n_{\nu,\alpha},$$  \hspace{1cm} (3.18)
3.3. DISPERSION CORRECTED DENSITY FUNCTIONALS

where \( n_{\nu,\alpha} \) is the number of valence electrons of atom \( \alpha \) and \( N_{\alpha} \) for hydrogen is set to 0.8. For diatomic coefficients \( C_{6,\alpha\beta} \), Halgren [121] recommends the Slater-Kirkwood combination rule

\[
C_{6,\alpha\beta} = \frac{2C_{6,\alpha\alpha}C_{6,\beta\beta}p_\alpha p_\beta}{p_\alpha^2 C_{6,\beta\beta} + p_\beta^2 C_{6,\alpha\alpha}}.
\]  

(3.19)

Elstner et al. [89] used equations (3.17-3.19) to compute their dispersion coefficients. Alternatively, Wu and Yang [338] proposed to use a modified Slater-Kirkwood combination rule instead:

\[
C_{6,\alpha\beta} = \frac{2 \left( C_{6,\alpha\alpha}^2 C_{6,\beta\beta}^2 N_{\alpha} N_{\beta} \right)^{\frac{1}{3}}}{\left( N_{\beta}^2 C_{6,\alpha\alpha} \right)^{\frac{1}{3}} + \left( N_{\alpha}^2 C_{6,\beta\beta} \right)^{\frac{1}{3}}}.
\]  

(3.20)

This rule is motivated by the fact that \( N_{\alpha} \) can be treated as a parameter, as it is less dependent on the molecular environment of the atom than the polarizability [338]. Furthermore, Wu and Yang [338] used atomic dispersion coefficients fitted to given molecular coefficients and propose the following two damping functions:

\[
f_d(r) = \left( 1 - \exp \left( -3.54 \left( \frac{r}{r_m} \right)^7 \right) \right)^2
\]  

(3.21)

and

\[
f_d(r) = \frac{1}{1 + \exp \left( -23 \left( \frac{r}{r_m} - 1 \right) \right)}
\]  

(3.22)

where \( r_m \) is the sum of the atomic van der Waals radii obtained from Bondi [38]. These two damping functions perform well with the functionals PW91 [242] and B3LYP [21]. Wu and Yang [338] recommend (3.21) as it decreases more slowly than (3.22) and produces better results for their test systems. They explain this with possible deficiencies of the exchange and correlation functionals to account for dispersion even at overlap and conclude that there may also be a need for the dispersion correction at these distances.

Elstner et al. [89] propose a damping function that performs well with the PBE [243] density functional in a self-consistent-charge, density-functional tight-binding method

\[
f_d(r) = \left[ 1 - \exp \left( -3.0 \left( \frac{r}{r_0} \right)^7 \right) \right]^4,
\]  

(3.23)
where \( r_0 = 3.8 \) Å for first row elements. Note that as the damping function (3.23) was developed for an extended tight-binding method, it might not be fully suited to a pure DFT approach.

### 3.4 Dispersion corrected density functionals applied to the water benzene cluster

Several ways to correct DFT results for dispersion effects where presented in the previous section. Now, we evaluate the performance of these correction schemes, i.e. the molecular and three different atomic corrections, for different density functionals. The atomic corrections comprise three schemes, the combination of equations (3.17, 3.18, 3.20), with either damping function (3.21) or damping function (3.22) and the combination of equations (3.17-3.19) with damping function (3.23).

Besides the functionals B3LYP [21, 187], PW91 [242], PBE [243] and B3VWN5 [21, 321], that have been recommended to be used with dispersion-corrected DFT [89, 338, 339], we tested the performance of the BLYP [20, 187] and HCTH/120 [35] functional subject to these correction schemes.

Comparison of the correction schemes is performed on a water molecule interacting with a benzene molecule. The small size of the water benzene cluster allows more rigorous computational approaches and detailed MP2 studies are available [93, 99, 291]. Furthermore, the interaction of water with aromatic systems is of great interest for the understanding of fundamental phenomena in biological systems [143]. Interaction energy profiles are compared for three cluster configurations characterized by the relative orientation of the water dipole to the plane of the benzene molecule (see figure 3.1):

**Down** The water dipole points towards the center of mass of the benzene molecule, and is orthogonal to the plane spanned by the carbon atoms. The hydrogen atoms of the water molecule are aligned parallel to the line joining two opposing carbon atoms in the aromatic ring.

**Parallel** The plane of the water molecule and of the benzene molecule are parallel. The dipole of the water molecule is aligned parallel to the line joining two opposing carbon atoms in the aromatic ring. The oxygen atom is centered on top of the aromatic ring.

**Up** This is the same geometry as the geometry *Down* but with the water dipole pointing away from the benzene molecule.
In these three configurations different types of interaction are dominant. In the geometries Down and Up the electrostatic interaction is important, resulting in attraction and repulsion respectively. In the case of the geometry Parallel the interaction energy profile is purely repulsive at the MP2 level of theory. The absolute value of the interaction energy as well as the slope of its profile are small at distances greater than 3.5 Å. Only small errors in the prediction of the interaction energy will alter the shape of the profile in this range. Hence, it is a very sensitive indicator for the quality of a representation of the interaction energy.

To quantify the performance of the correction schemes, two different approaches for calculating the deviation from the reference data are considered. In the first and most standard approach, a piecewise constant integration of the absolute deviation along the interaction energy profile is averaged over the range of interest and over the three configurations. In the second approach, we focus on the configurations which are more important in a finite temperature molecular dynamics run. To quantify this effect we do not only compare the interaction energy profiles as described above but weight the difference with Boltzmann factors $e^{-\beta V(r)}$ based on the reference potential $V(r)$ at the corresponding distance. We take here $\beta = \frac{1}{k_B T}$ with the temperature $T = 300$ K and we refer to this as the Boltzmann weighted average. Unless it is explicitly referred to the Boltzmann weighted average, the average error was calculated following the former method. In the following only reference to selected error measures will be made, the complete set is however available in Appendix A.

DFT calculations were performed with CPMD [60], a plane wave DFT code. The cutoff for the plane wave basis was set to 90 Rydberg in combination with Trouiller-Martins pseudopotentials [307]. To calculate the non-local part of the pseudopotentials the Kleinmann-Bylander scheme [169] was applied. A computational cell of $25 \times 25 \times 30 a_0$ was used to calculate the DFT-based interaction energies.
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Figure 3.2: Interaction energy profiles for the water benzene interaction from uncorrected DFT. The first graph shows the results for geometry Up, the second for Parallel and the third for Down. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.

The reference interaction energy profile is obtained by counterpoise-corrected MP2 calculations. The calculations were performed with the program Gaussian 98 [100] using 6-311G(2d,2p) basis sets [150].

3.4.1 Uncorrected density functionals

We begin by discussing the performance of the uncorrected density functionals on our test system. Graphs showing the interaction energies for all geometries and functionals investigated can be found in figure 3.2. None of the functionals considered reproduces the reference data throughout all three interaction energy profiles. Nevertheless, for the geometries Parallel and Up the PW91 functional provides an excellent estimate with a maximal deviation of no more than 0.66 kJ mol$^{-1}$ and an average error of 0.33 kJ mol$^{-1}$. However, the agreement is much poorer for the geometry Down where the deviation amounts up to 3.78 kJ mol$^{-1}$ with an average error of 1.57 kJ mol$^{-1}$. Nevertheless, the performance is still the best of all density functionals and only the PBE functional gives comparable results.

The results for the B3LYP, BLYP and B3VWN5 functionals show the largest deviations. It has already been argued in [339] that functionals such as PW91 reproduce the correct interaction energy only by coincidence. Thus they yield reasonable results for rare gas dimers, but the attraction they show comes from the exchange energy contribution, which should be repulsive, and not from the
3.4. DISPERSION CORRECTED DENSITY FUNCTIONALS APPLIED TO THE WATER BENZENE CLUSTER

Figure 3.3: Interaction energy profiles for the water benzene interaction from DFT corrected with a molecular correction term. The first graph shows the results for geometry Up, the second for Parallel and the third for Down. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.

correlation energy contribution. Conversely, the rare gas interaction as described by the BLYP and B3VWN5 is repulsive throughout the whole interaction energy profile and so is Becke’s hybrid exchange [339]. It would be wrong to assume that the interaction energy obtained with these functionals is dispersion free, as its contribution could be small or even have the wrong sign. However, the character of the deviation which is of comparable size in all three geometries is promising with regard to the approach of using an additive, distance dependent correction at intermediate and long range.

3.4.2 Molecular correction

For the water benzene interaction, we calculate the molecular $C_6$ dispersion coefficient to be $12027\,\text{kJ mol}^{-1}\,\text{Å}^6$, using equation (3.14). The average polarizabilities are $10.4\,\text{Å}^3$ [348] for benzene and $1.5\,\text{Å}^3$ [300] for water. The ionization energies are $9.24\,\text{eV}$ [97] and $12.62\,\text{eV}$ [304] respectively. The interaction energy profiles obtained from DFT corrected on a molecular basis are shown in figure 3.3.

Excellent agreement between the reference data and the corrected HCTH functional is obtained for the geometry Down, with a mean deviation of $0.4\,\text{kJ mol}^{-1}$ and a maximum deviation of $2.51\,\text{kJ mol}^{-1}$. In this geometry, a comparable performance is found only for functional B3LYP (with a mean error of $1.13\,\text{kJ mol}^{-1}$) which is mainly due to underestimated interaction in the range between $3.75\,\text{Å}$ and
5 Å. For the other functionals significant deviations are reported. While PBE and PW91 show good agreement at distances larger than 4 Å, the description breaks down at short ranges where overlap starts to become important.

In the other configurations, the functionals based on the LYP and VWN5 correlation functional perform best, showing good agreement with the reference data. In particular for the geometry $Up$, the corrected B3VWN5 functional outperforms the other functionals, resulting in a mean deviation from the reference data of 0.34 kJ mol$^{-1}$. While never giving the smallest error for a specific geometry, the corrected B3LYP functional results in the best overall estimate for the interaction energy. The other functionals that show partially or throughout good performance in geometry $Up$ overestimate the interaction, resulting in weak binding in geometries $Parallel$ and $Down$.

The introduction of a dispersion correction of order 8 resulted in larger deviations for all tested functionals. In the range between 3 Å and 4 Å, the dispersion correction is too strong, which results in large deviations from the reference data.

Summarizing, none of the six density functionals corrected on a molecular basis reproduces all reference interaction energy profiles. The B3LYP functional results in the lowest mean deviation throughout all geometries (1.09 kJ mol$^{-1}$), whereas the BLYP and the B3VWN5 functional perform comparably with mean deviations of 1.23 and 1.29 kJ mol$^{-1}$ respectively. The breakdown of the molecular correction can be assigned to anisotropies that are not accounted for by a single molecular correction, as they become important at distances which roughly correspond to the size of the molecules in question. In particular the fact that the performance is strongly geometry-dependent underlines this conclusion.

However, if Boltzmann-corrected errors are compared, the molecularly corrected HCTH functional results in the lowest error for all the combinations of correction schemes and functionals considered in this chapter. This is mainly due to the excellent agreement in the geometry $Down$, which is strongly weighted by the Boltzmann factors due to the low interaction energy. Whether this conclusion is valid for other systems remains to be seen, especially as the results for the geometries $Up$ and $Parallel$ indicate a fortuitous agreement for the geometry $Down$.

### 3.4.3 Atomic correction

The dispersion coefficients for the atomic correction based on atomic polarizabilities from [224] are listed in table 3.1. They compare well to the coefficients listed in Wu and Yang [338] and Elstner et al. [89]. For diatomic coefficients obtained with mixing rule (3.20) the resulting values are approximately 7% smaller than
3.4. DISPERSION CORRECTED DENSITY FUNCTIONALS APPLIED TO THE WATER BENZENE CLUSTER

Table 3.1: Dispersion coefficients $C_{6,\alpha\alpha}$ in kJ mol$^{-1}$Å$^{6}$ based on atomic polarizabilities from Miller [224] listed along with dispersion coefficients from Wu and Yang [338] and Elstner et al. [89].

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydrogen</th>
<th>Carbon</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>this work</td>
<td>163</td>
<td>1881</td>
<td>684</td>
</tr>
<tr>
<td>Wu and Yang [338]</td>
<td>163</td>
<td>1577</td>
<td>669</td>
</tr>
<tr>
<td>Elstner et al. [89]</td>
<td>155.34</td>
<td>1791</td>
<td>–</td>
</tr>
</tbody>
</table>

the ones obtained with the original Slater-Kirkwood combination rule (3.19). The interaction energy profiles from DFT corrected on an atomic basis are shown in figure 3.4.

If mixing rule (3.19) is used along with damping function (3.23), the PBE functional is found to perform best. However, the performance in different geometries varies, showing significant deviations especially in geometry Parallel where the corrected PBE functional results in a potential well instead of being repulsive throughout. But also in geometry Up the potential energy profile appears to be distorted. Dispersive interaction energy contributions are overestimated and if compared with results from pure DFT with the PW91 functional, the mean error for all geometries is slightly larger (0.87 kJ mol$^{-1}$ vs. 0.74 kJ mol$^{-1}$). In contrast, if Boltzmann-weighted errors are compared, the corrected PBE functional performs significantly better than the uncorrected PW91 functional. If only geometries Parallel and Up are considered the B3LYP functional has the best performance. However, it deviates significantly in geometry Down, where it fails to reproduce the depth of the potential well.

If mixing rule (3.20) is used along with damping function (3.22), the overall performance of the B3LYP functional is found to be best. It reproduces the interaction energy profiles well, with a maximal deviation of 2 kJ mol$^{-1}$ and a mean deviation throughout all geometries of 0.52 kJ mol$^{-1}$. This result is especially reassuring when considering the treatment of the exchange energy within the B3LYP functional, which does not lead to erroneous attraction [339] for noble gases. Therefore this suggests a successful partitioning of the total interaction energy along the lines of equation (3.12).

Wu and Yang state [338] that equation (3.21) is better suited for damping than equation (3.22) as the former decreases more slowly. If their recommendation is followed and damping function (3.21) is used, the results for the functionals
Figure 3.4: Interaction energy profiles for the water benzene interaction from DFT corrected with an atomic correction term. Different correction schemes are sorted by columns, different geometries are sorted by rows. The first column shows the results for mixing rule (3.19) and damping function (3.23). The second column shows the results for mixing rule (3.20) and damping function (3.21) and the third column shows the results for mixing rule (3.20) and damping function (3.22). The first row shows the results for geometry Up, the second for Parallel and the third for Down. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
3.4. DISPERSION CORRECTED DENSITY FUNCTIONALS APPLIED TO THE WATER BENZENE CLUSTER

HCTH, B3LYP, PW91 and PBE deviate further from the reference data than with damping function (3.22). Especially at short range, where the damping according to (3.22) leads to a small dispersion contribution, the dispersion interaction seems to be overestimated if (3.21) is used. This correction scheme results in the lowest mean deviation for the BLYP density functional of 0.93 kJ mol$^{-1}$, which is also smallest if compared to the other functionals within this setup. The deviation reported for the BLYP functional is mainly due to a minor distortion of the interaction energy profile for geometry Down.

The results reported in this section do not change if the deviation from the reference data is weighted with Boltzmann factors.

3.4.4 Conclusions

In the case of the water benzene interaction the uncorrected PW91 density functional shows a good performance for the geometries Up and Parallel. However, the large deviations for the geometry Down indicate that error cancellation has a large effect on its performance. Like the other uncorrected functionals it fails to reproduce the van der Waals interaction in this geometry.

The interaction energy profiles are much improved if corrected for dispersion energy, even if the correction is only molecule based. The Boltzmann-weighted average error indicates best performance for the molecularly corrected HCTH functional. This is also the case if it is compared to atomic correction schemes. Significant variations in the accuracy throughout the different configurations indicate however the coincidental nature of this result.

If corrected for dispersion interaction in an atomic correction scheme, the PBE functional and the B3LYP functional generally show much improved results. The approach of Elstner et al. [89] is successful in correcting the PBE functional which result in relatively small errors.

The B3LYP density functional results in the most consistent description of the interaction energy profiles, if corrected according to [338] with a modified Slater-Kirkwood mixing rule (3.20) and an appropriate damping function (3.22). Its behavior is superior to any of the other schemes listed in this work and its use is recommended for further work on the study of water interacting with aromatics.

Though never outperforming the other functionals, the BLYP density functional results in consistent profiles. In particular if corrected with the modified Slater-Kirkwood mixing rule (3.20) and the first damping function (3.21) suggested by Wu and Yang [338]. This result is of major interest due to the widespread use of the BLYP functional, especially in plane wave codes and in Car-Parrinello [50]
Table 3.2: Recommended correction schemes for selected density functionals. The PW91 density functional is recommended to be used in its uncorrected form. The error refers to the mean deviation over all three configurations of the test system.

<table>
<thead>
<tr>
<th>density functional</th>
<th>damping function</th>
<th>mixing rule</th>
<th>error [kJ mol(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PW91</td>
<td>–</td>
<td>–</td>
<td>0.74</td>
</tr>
<tr>
<td>BLYP</td>
<td>eqn. (3.21)</td>
<td>eqn. (3.20)</td>
<td>0.93</td>
</tr>
<tr>
<td>B3LYP</td>
<td>eqn. (3.22)</td>
<td>eqn. (3.20)</td>
<td>0.52</td>
</tr>
<tr>
<td>PBE</td>
<td>eqn. (3.23)</td>
<td>eqn. (3.19)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

simulations of liquid water. A short compilation of suggested correction schemes for selected functionals may be found in table 3.2.

The results in this section indicate that the correction of DFT with a damped dispersion contribution might be far from generally applicable. A set of corrections and damping functions has to be tailored to the problem. The difference in comparison with Wu and Yang [338] concerning the damping function to be used along with the B3LYP density functional indicates that a detailed validation of the approach is needed for every new class of systems.

3.5 Dispersion corrected density functionals applied to the water naphthalene cluster

In this section we evaluate the performance of the molecular and three atomic correction schemes on the water naphthalene cluster. The density functionals considered in this section are B3LYP [21, 187], PW91 [242], PBE [243] BLYP [20, 187] and HCTH/120 [35].

For each scheme we compute interaction energy profiles for the water naphthalene cluster in eight different conformations. Two locations of the water molecule are considered: one with the oxygen atom centered on top of an aromatic ring and one with the oxygen atom centered on top of the carbon bond separating the two aromatic rings. In both locations two orientations of the water molecule are considered: the plane spanned by the water molecule is either orthogonal or in line with the main axis of the naphthalene molecule. All geometries were evaluated, once with the water dipole pointing perpendicularly towards the naphthalene plane and
3.5. DISPERSION CORRECTED DENSITY FUNCTIONALS APPLIED TO THE WATER NAPHTHALENE CLUSTER

once with the inverse orientation. An illustration of these different conformations may be found in the Appendix B.1.

We do not consider geometries with the water dipole parallel to the aromatic plane as they do not provide additional information [356]. Where not stated otherwise, all distances refer to the distance of the water oxygen to the naphthalene plane.

The performance of the correction schemes is quantified in two ways. On one hand a piecewise constant integration of the absolute deviation from the reference energy profile is performed to obtain the average error. On the other, during integration the absolute deviation is weighted with Boltzmann factors $e^{-\beta V(r)}$ based on the reference potential $V(r)$ at the respective distance. We take $\beta = \frac{1}{k_B T}$ and set the temperature $T = 300$ K. $k_B$ is the Boltzmann constant.

DFT calculations are performed using CPMD [60], a plane wave DFT code. The computational cell was set to $25 \times 25 \times 50 a_0$ for the calculations of DFT-based interaction energies. A cutoff of 90 Rydberg was applied for the plane wave basis and Trouiller-Martins pseudopotentials [307] were used. The non-local part of the pseudopotentials are calculated according to the Kleinmann-Bylander scheme [169].

The reference interaction energy profile is obtained by counterpoise-corrected MP2 calculations. The calculations were performed using Gaussian 98 [100] with 6-311G(2d,2p) basis sets.

The full set of interaction energy profiles discussed below and the according error measurements are listed in detail in Appendix B. In the following only a few key figures are presented to highlight the most prominent findings. For more detail, see Appendix B.

3.5.1 Uncorrected density functionals

The density functionals PW91, PBE and HCTH show reasonable agreement with the reference data for the geometries in which the dipole is pointing away from the naphthalene plane. However, for the opposite orientation of the water molecule, all functionals fail to reproduce the strength of the interaction reliably. The PW91 density functional results in the lowest mean deviation ($1.41 \text{kJ mol}^{-1}$) and the lowest Boltzmann weighted error of all uncorrected density functionals. Still, this functional underestimates the binding strength significantly for the geometries of low interaction energy, i.e. the geometries where the water dipole is pointing towards the naphthalene plane, (see Figure 3.5). These results are fully consistent
CHAPTER 3. MOLECULAR INTERACTION POTENTIALS WITHIN DENSITY FUNCTIONAL THEORY

Figure 3.5: The interaction energy profile for the water molecule centered on top of the bond separating the two aromatic rings of naphthalene with the dipole pointing perpendicularly towards (left) and away from (right) the naphthalene plane. The water plane is orthogonal to the main axis of the naphthalene. Some of the uncorrected density functionals show good agreement for the latter case whereas the attraction is clearly underestimated in the former. Solid line: reference data, dashed lines with symbols: DFT results, circles: BLYP, stars: B3LYP, squares: HCTH, crosses: PBE, diamonds: PW91.

with the results reported for the water benzene cluster in the previous section and in Zimmerli et al. [356].

3.5.2 Molecular correction

The molecular correction does not account for anisotropies in the dispersion contribution due to the geometry of the molecule. It is therefore expected to break down at some critical molecular size.

For the water naphthalene interaction, we calculate a molecular dispersion coefficient of 17736 kJ mol\(^{-1}\) Å\(^6\) using equation (3.14). The average polarizabilities are 1.5 Å\(^3\) [300] for water and 16.5 Å\(^3\) [128] for naphthalene. The ionization energies are 12.62 eV [304] and 8.15 eV [274], respectively.

This scheme applied to the HCTH functional leads to excellent results in the water benzene case: the lowest Boltzmann weighted error for all schemes is obtained. In the case of the water naphthalene cluster there are however significant deviations in interaction energy profiles especially for the geometries in which the water molecule is on top of the carbon carbon bond separating the two aromatic rings with the water dipole pointing away from the bond. The usually purely re-
The interaction energy profile for the water molecule centered on top of the carbon carbon bond separating the two aromatic rings of naphthalene with the dipole pointing away from the naphthalene plane. The plane spanned by the water molecule is orthogonal to the main axis of the naphthalene. The molecularly corrected HCTH functional (dashed line with squares) shows strong attraction with a deep minimum at approximately 3 Å, whereas the reference potential is purely repulsive (solid line).

In general, the dispersion contribution is too large for geometries in which the water molecule is centered on top of the bond which is connecting the two aromatic rings. This effect can be attributed to the functional form of the correction, which positions the two centers of interaction at the centers of mass of the molecules. While geometries centered on top of the bond and on top of an aromatic ring result in very similar interaction energies on a MP2 level of theory, there are large discrepancies between the molecularly corrected DFT interaction energies. Both of these effects can be attributed to the breakdown of the molecular correction scheme that ignores the geometry of the molecules and their orientation with regard to each other.
CHAPTER 3. MOLECULAR INTERACTION POTENTIALS WITHIN DENSITY FUNCTIONAL THEORY

Figure 3.7: The interaction energy profile for the water molecule centered on top of the bond joining the two aromatic rings of the naphthalene molecule with the dipole pointing towards the naphthalene plane. The plane spanned by the water molecule is parallel to the main axis of the naphthalene molecule. The solid line is the MP2-reference data, the dashed lines represent the corrected PBE functional, crosses indicate a correction according to [89], circles according to [338] using damping function (3.22).

3.5.3 Atomic correction

In the previous section and in Zimmerli et al. [356], for the water benzene system, it is recommended to use a corrected B3LYP density functional according to Wu and Yang [338] along with a modified Slater-Kirkwood mixing rule (3.20) and damping function (3.22). For the water naphthalene cluster the agreement of the reference data and the corrected B3LYP functional is also good, with an average error of 1.25 kJ mol\(^{-1}\). The Boltzmann weighted errors also indicate good agreement in the geometries with low interaction energy.

However, on the water naphthalene cluster, the correction scheme presented by Elstner et al. [89] using equations (3.19) and (3.23) applied to the PBE density functional give the most consistent results with respect to the reference data. The average error is 1.04 kJ mol\(^{-1}\) and the Boltzmann weighted error is also one of the lowest in this study, see Appendix B. Comparable results are also obtained if the PBE functional is corrected according to Wu and Yang [338] using equations (3.20) and (3.22). While in the first case the dispersion contribution seems to be underaccounted for, there seems to be a tendency for overaccounting it in the latter case (Figure 3.7).

If the BLYP functional should be corrected for dispersion, the results of the current study indicate that the approach of Wu and Yang [338] using equations (3.20)
Figure 3.8: The interaction energy profile for the water molecule centered on top of an aromatic ring of naphthalene with the dipole pointing towards the naphthalene plane. The plane spanned by the water molecule is parallel to the main axis of the naphthalene. The reference data (MP2) is represented by the solid line, the dashed line with circles represents the data obtained with the BLYP functional corrected according to [338] using damping function (3.21). The interaction energy is overestimated in the range of 3.5 Å to 5.5 Å, the absolute deviation however never exceeds 3 kJ mol⁻¹.

and (3.21) should be used. However, we also confirm that in this framework, the interaction energy is overestimated. This results in an attraction which is roughly 3 kJ mol⁻¹ too weak in the range of 3.5 Å to 5.5 Å when the water dipole points towards the surface (see figure 3.8).

Except for functional BLYP the correction according to Wu and Yang [338] using equations (3.20) and (3.22) gives better results than the ones damped with function (3.21).

3.5.4 Conclusions

The results presented in this section indicate that accurate accounting of the dispersion interaction is crucial for the description of the interaction of water with aromatics. Current density functionals can give reasonable results for specific geometries. In particular the PW91 density functional results in a good approximation for geometries where the water dipole is pointing away from the naphthalene surface. However, as the quality of these results is geometry dependent, its predictive power is limited.

For the water naphthalene interaction, the molecular correction scheme pre-
sent in Wu et al. [339] breaks down gradually, though still delivering good results in terms of average errors. Correction schemes based on atomic dispersion contributions are shown to be successful in predicting the interaction energy for the water naphthalene cluster in a consistent way. In particular the correction scheme suggested by Elstner et al. [89] performs well in combination with the PBE functional. Furthermore, the scheme by Wu and Yang [338] performs well in combination with the B3LYP functional. For the calculation of the water aromatic interaction we therefore recommend to use either of the latter correction schemes.

In general, the results reported in the previous section and in Zimmerli et al. [356] are found to hold not only for the interaction of water with benzene but also for higher aromatics.

3.6 Extending dispersion corrected density functionals to semiconductor surfaces

Here we present the first steps towards a method that allows to find bounds for the interaction energy between a small molecule and a flat semiconductor surface using density functional calculations with correction terms for the dispersion energy. An upper and a lower bound to the interaction energy are obtained, treating the solid surface as an isolator and as Jellium, respectively. To illustrate the presented approach, the interaction energy between water and graphite is calculated and it is found to be in between 2.9 kJ/mol and 25 kJ/mol.

The water graphite interaction has been widely discussed in recent literature [93, 332]. It can be considered as a prototypical system to study the interaction of fullerenes and CNTs and water. However, the estimates for the interaction energy exhibit large variations ranging from -5.07 kJ/mol [331] to -24.3 kJ/mol [93] resulting in a large uncertainty. To the author’s knowledge no direct measurements of the interaction energy between water and graphite have been performed. Recently, Werder et al. [332] presented a review of interaction potentials for the water graphite interaction. In the same article the influence of the interaction energy on the contact angle of water on graphite could be determined. But, as there are contradictory measurements of water graphite contact angles, the actual interaction could not definitely be determined.
3.6. EXTENDING DISPERSION CORRECTED DENSITY FUNCTIONALS TO SEMICONDUCTOR SURFACES

3.6.1 The dispersion correction

The approaches presented in the previous sections will now be extended. While we concentrated on the interaction between atoms or small molecules before, we will deal here with a semi-infinite flat semiconductor surface and a small molecule. We will show how to find a narrow band of possible interaction energies between the surface and the molecule. To achieve this, two models will be presented on how the bulk semiconductor phase can be modeled. First, it is modeled as a bulk phase of non-interacting particles. Second, it is modeled as a perfect conductor (Jellium).

The dispersion correction for a slab of non interacting particles

Again, we consider a dispersion correction term as presented in equation (3.12). The functional form of the dispersion correction will conceptually remain the same as presented in equation (3.13). Now, it is considered that the semi-infinite flat semiconductor phase should be modeled as a bulk solid of non-interacting particles. Under these presumptions the relationship presented by Mavroyannis [216] can be used to obtain an approximation for a dispersion coefficient of order six, cf. equation (3.14). This relationship was derived for the van der Waals interaction of two neutral molecules indicated by the indices 1 and 2, where $\alpha$ are the corresponding polarizabilities and $I$ the ionization energies.

As already discussed in section 3.3.1 a dispersion correction has always to be paired with an appropriate damping function, as the $r^{-6}$ behavior of the correction only holds in the asymptotic limit. Again, we suggest to use the damping function presented by Douketis et al. [83], as presented in equation (3.16).

Further we can assume that the individual carbon atoms represent a reasonable breakdown of the semi-infinite graphite slab. Based on this assumption the problem of determining the dispersion correction reduces to the problem of finding appropriate polarizabilities and ionization energies. Note that this directly implies that the individual carbon atoms are not interacting. We can now estimate the polarizabilities and ionization energies conservatively such that the resulting $C_6$ coefficient represents a lower bound of possible $C_6$ coefficients. In this way we ensure that the dispersion correction represents the upper limit of the dispersion contribution. This is due to the fact that the dispersion interaction is an induction effect. Assuming non-interacting particles the induction effects are minimal, and thus the according interaction energy represents an upper limit.
The dispersion correction for a semi-infinite perfect conductor

In section 3.3.1 only the interaction between atoms or small molecules was considered. However, in the idealized case of a small molecule interacting with a half-space there exists a similar ansatz. Using specific geometric information on the system the following expression can be derived to describe the dispersion interaction [344]

$$\Delta E_{corr} = \frac{C_3}{(z - Z_0)^3} g_3(z - Z_0) = \frac{C_3}{z^3} \hat{g}_3(z),$$

(3.24)

where $z$ indicates the distance of the molecule orthogonal to the surface, and $Z_0$ is the reference plane relevant to the interaction. $g_3$ is a damping function and $C_3$ is the dispersion coefficient of order three.

In this case, the half-space is assumed to be an ideal conductor with perfect electronic behavior, i.e. Jellium. The van der Waals interaction for such systems depend on $r^{-3}$ with the coefficient [42]

$$C_3 = \frac{1}{8}\alpha_1 I_1.$$  

(3.25)

Equation 3.25 depends only on properties of the molecule. The slab which is considered to be an ideal electron gas with positive background charge does not enter the expression. The fact that the interaction is based on the Jellium assumption implies a perfect polarizability of the interacting half-space. This maximizes any induction effect, i.e. any effect which could lead to a van der Waals type of interaction. This allows to estimate a lower bound for the interaction energy of any molecule with a half-space.

Also within this ansatz the damping function remains indispensable. To the knowledge of the author, there are no damping functions which would be applicable to $r^{-3}$ dispersion corrections. However, it can be shown that in the asymptotic limit ($z \to \infty$) an order three correction with dispersion coefficient $C_3$ is related to an order six correction with dispersion coefficient $C_6$ [145]

$$C_3 = \frac{\pi \rho C_6}{6},$$  

(3.26)

where $\rho$ is the number density of the relevant centers for an order six correction. This relationship provides therefore a basis to relate any $C_3$ coefficient to an $C_6$ coefficient of particles at density $\rho$. Through this $C_3$ to $C_6$ mapping the problem of a missing damping function can be circumvented. Thus in order to estimate the lower bound to the interaction energy only the polarizability and the ionization energy of the molecule in question have to be estimated.
3.6. EXTENDING DISPERSION CORRECTED DENSITY FUNCTIONALS TO SEMICONDUCTOR SURFACES

Table 3.3: Polarizability of graphite orthogonal to the graphene planes $\alpha_{zz} \left(\text{Å}^3\right)$, calculated for different cases.

<table>
<thead>
<tr>
<th>Number of Sheets</th>
<th>Atoms in Cell</th>
<th>$\alpha_{zz}$ per Atom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>3.18</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>3.16</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>3.37</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>3.86</td>
</tr>
<tr>
<td>2 (bulk)</td>
<td>64</td>
<td>5.48</td>
</tr>
</tbody>
</table>

3.6.2 The bounds of the water graphite interaction

To calculate the interaction energy of graphite with water using a $C_6$ coefficient as defined by equation (3.14) we need to specify the polarizability and the ionization energies for either species first.

The polarizability of water 1.60 Å$^3$ is obtained from Putrino et al. [256] and was validated for the functional in use. The polarizabilities obtained for the current functional (HCTH-120) are lower than the ones reported by Putrino et al. [256] and resulted in an average value of 1.37 Å$^3$. This value still agrees well to the experimental value of 1.50 Å$^3$ [300]. For consistency the value obtained for the HCTH-120 functional entered the calculation of the interaction energy between water and benzene. The ionization energy of water is 12.62 eV [304].

The polarizability for graphite was determined for a single sheet, a double sheet and bulk graphite according to the method reported in Putrino et al. [256]. The calculations were performed in orthorhombic cells in all three cases, using a supercell setup in the case of only a single or a double layer. For a single sheet of graphite a convergence study in terms of the total energy was performed, considering periodic cells of different sizes. The resulting polarizabilities orthogonal to the graphene planes are listed in Table 3.3. The polarizability of graphite enters equation (3.14) to estimate the upper bound of the interaction energy. In order to ensure that the absolute value of the dispersion energy contribution interaction energy would be minimal, the minimum value for the polarizability of graphite of 3.18 Å$^3$/atom was considered in further calculations.

We calculated a band gap of 2.9 eV for a triclinic unitcell of graphite containing 8 carbon atoms with four k-points and Lanczos diagonalization and four additional states. The ionization energy has to be at least as big as the band gap. Thus, this is a good estimate for the calculation of the minimal absolute interaction energy.
CHAPTER 3. MOLECULAR INTERACTION POTENTIALS WITHIN DENSITY FUNCTIONAL THEORY

ionization energies of polyaromatics are constantly decreasing with increasing system size benzene 9.24 eV [97], triphenylene 8.0 eV [66], coronene 7.21 eV [275]. This trend in the experimental ionization energies of polyaromatics and the actual magnitude of the band gap suggest that the band gap should be a reasonable estimate for the ionization energy of graphite.

Based on aforementioned approximations we estimate a minimal $C_6$ coefficient to be 218.2 kJ/Å$^6$ for the graphite water interaction. Using the ionization energy for water of 12.62 eV [304], combined with a polarizability of 1.60 Å$^3$ [256] the $C_3$ coefficient for the graphite water interaction is estimated to be at maximum 243.5 kJ/Å$^3$, assuming Jellium like properties for graphite. This corresponds to a $C_6$ coefficient of approximately 5500 kJ/Å$^3$ (using equations (3.26)).

The DFT based interaction energy profile was calculated with the HCTH-120 functional in a fully periodic super cell setup. The dimension orthogonal to the graphite sheet was increased until the interaction between neighboring cells was negligible. The graphite was modeled using a single layer of 32 carbon atoms and the water molecule was always centered on top of an aromatic ring with its dipole pointing orthogonally into the graphite surface. Using the interaction energy profile from DFT, the damping function (3.16) and the the two $C_6$ coefficients, the minimal and the maximal interaction energy profile for water interacting with graphite are determined. In Figure 3.9 both interaction energy profiles are shown, and the area in between them indicates the possible range for the interaction of a water molecule with a graphite surface. In Figure 3.9 we shown also the interaction energies as predicted by the GROMOS force field [312] and by the 12-6 interaction potential by Werder et al. [332].

3.6.3 Conclusions

The range of possible interaction energies is disappointingly large and hardly narrows the criteria for a reasonable choice of an interaction energy profile. The agreement between traditional interaction potentials and the newly determined bounds from DFT are reasonable for a first approximation and the two results do not contradict each other. The two empirical potentials considered lie within the range predicted by the ab-initio calculations.

However, considering the bound for the strongest interaction which results in an estimate of approximately -25 kJ/mol suggests that the interaction energy estimate of -24.3 kJ/mol by Feller and Jordan [93] should be considered with care. The present strongest interaction energy estimates is based on the Jellium assumption. However, graphite is far from being ideal, which is obvious when considering its
Figure 3.9: Upper and lower bounds (solid line) to the interaction energy compared with two force field expressions GROMOS (dotted) [312] and Werder et al. [332] (dashed). The upper bound is obtained through the assumption of a non-interacting plane of molecules, whereas the lower bound is obtained through the assumption of an ideal metal (Jellium).
two dimensional structure. As will be highlighted below, the actual interaction energy is considered to be much lower and the interaction energy presented by Feller and Jordan is considered to be subject to significant basis set superposition error effects [249].

Currently, the interaction energy ranges obtained through the approach presented in this previous section are promising, but they do not improve traditional estimates. However, the approach presented is only a rough engineering approximation which can be further improved. In particular, the ideality assumption in the Jellium model can be corrected by assuming a real conductor and correcting for non-idealities. Mavroyannis [215] reported that $C_3$ should be scaled by a prefactor depending on the plasma frequency $\omega_p$ of the according material leading to a corrected $C_3'$:

$$C_3' = C_3 \frac{\hbar \omega_p}{\sqrt{2} I_1} + \frac{\hbar \omega_p}{\sqrt{2}}, \quad (3.27)$$

where $\hbar$ is Planck’s constant and $I_1$ is again the ionization energy. In this section, effects due to non-ideality were neglected, as the plasmon frequency is a quantity which is hard to determine. However, Jensen et al. [154] reported a plasmon frequency for graphite of approximately 60 meV at room temperature. Combined with the water ionization energy, this results in $C_3'$ being 20 – 25% lower than of the according $C_3$ coefficient. Further improvements of the dispersion energy estimates could lead to a significantly narrower range of possible interaction energies and make a source of quantitative information in the development of interaction potentials.

### 3.7 Outlook

The presented methods have been published in [355] and [356]. A similar study was presented in the following by Grimme [116]. In this work the dispersion corrected BLYP and PBE density functionals were applied to a wide range of different complexes and the results presented here were confirmed. Also Grimme [116] finds a significantly improved performance of dispersion corrected DFT if compared to pure DFT. However, his results do also confirm the concerns raised here. In particular, dispersion corrected DFT does not always lead to an improvement of the results. And when an improvement is obtained it is highly dependent on the system. While the results of pure DFT tend to reflect a binding energy which is
too low, the results of dispersion corrected DFT tend to deviate in either direc-
tion and the quality of the results is hard to judge, especially when no reference
data is available. Nevertheless, dispersion corrected DFT provides an improved
description of weakly bound systems and can be used to predict system properties
[195].

The development of different methods has also continued. Groups of Lundqvist
and Langreth have followed and extended the approach present in earlier work [52,
170, 171] providing now density functional for a wide range of different systems.
A new and very promising approach has been presented by Lilienfeld et al. [319,
320]. Lilienfeld et al. add an atom centered nonlocal term to the exchange-
correlation potential. This non-local term is calibrated using density functional
perturbation theory. Within this framework Lilienfeld et al. are able to com-
pute correct equilibrium geometries and dissociation energies for a wide range
of weakly bound complexes.

Despite many recent advances open questions remain and basic concepts have
to be understood. In this context I would like to cite Becke and Johnson [22]
in a very recent publication. After deriving analytically a simple expression to
compute the dipole dipole interaction energy (referred to as “Eq. (17)”), they
state: “Initial tests of Eq. (17) [...] gave interesting results. Despite the simplicity
of the underlying model, Eq. (17) reproduces known $C_6$ values with remarkable
accuracy if divided by a factor of 4. [...] That Eq. (17) does work well with a
modified prefactor is, in our opinion, fascinating.” This citation characterizes well
the current state of research in this field. Many good approximations for exchange
correlation functionals or other forms of corrections have been found which make
DFT a valuable tool today. However, the analytic derivation of improved models
is extremely complicated and a successful route is not always obvious.

I believe the dispersion interaction within DFT will remain an active field of
research. Considering the current efforts many advances should follow in near
future. It is a fascinating field as the solution to the current problems is not obvious.
A breakthrough will however make DFT even more successful than it has been to
date.
Chapter 4

Molecular Dynamics Simulations – An Introduction

Molecular Dynamics (MD) is the main computational tool used in this thesis. In this chapter we outline the key aspects of the method as they pertain to the simulations in this thesis. This introduction to MD does not strive for completeness and for further information the reader is referred to a number of text books [9, 259]. After a historical overview, Newton’s equations of motions are presented as they form the foundation of MD. This is followed by an extensive introduction to the basics of force fields. Finally, some important computational issues in MD simulations are briefly reviewed.

4.1 Introduction

4.1.1 Motivation

The goal of this thesis is to understand whether carbon nanotubes can be used as nanopores to transport RNA across a membrane. In this respect we need to characterize prototypical nanofluidic systems and we have to explore specific nanoscale phenomena. Due to their size, such systems are not accessible to quantum mechanical calculations as we sketched them in the previous chapter. The computational cost of quantum mechanical simulations limits them to systems containing only a few hundred atoms and time scales in the order of a few picoseconds. When simulating systems of several thousand atoms and time scales of several nanoseconds, their behavior is usually modeled using MD simulations. The concept of MD simulations involves the computation of the trajectories of particles that model the atoms of the system, as they result from simplified interaction force fields.
4.1.2 Historical overview

MD has been extensively used to model the structural and dynamical properties of complex fluids and solids. The first MD simulations date back to the mid-1950s and were presented by Fermi et al. [95]. Shortly after, the phase diagram of a hard sphere system was investigated in the seminal work of Alder and Wainwright [8]. Only a few years later, Aneesur Rahman at the Argonne National Laboratory published his famous work on correlations in the motion of atoms in liquid argon [257]. In 1967 Loup Verlet calculated the phase diagram of argon using the Lennard-Jones potential [189] and computed correlation functions to test theories of the liquid state [313, 314]. A couple of years later, phase transitions in the same system were investigated by Hansen and Verlet [122]. In 1971 Rahman and Stillinger reported the first simulations of liquid water [258]. Since then, MD simulations have provided a key computational element in physical chemistry, material science, and nanofluidics for the study of pure bulk liquids [9], solutions, polymer melts [301], and multiphase and thermal transport [49, 162, 213, 328].

4.2 Molecular dynamics

In MD simulations a system of \( N \) particles is propagated in space and time according to Newton’s equations of motion

\[
\frac{d\mathbf{r}_i(t)}{dt} = \frac{\mathbf{p}_i(t)}{m_i} \quad \text{and} \quad \frac{d\mathbf{p}_i(t)}{dt} = \mathbf{f}_i(t), \quad i = 1, \ldots, N. \tag{4.1}
\]

The system is specified in terms of cartesian coordinates \( \mathbf{r} = (r_1, r_2, \ldots, r_N) \) and particle momenta \( \mathbf{p} = (p_1, p_2, \ldots, p_N) \). Where \( \mathbf{f}_i \) is the force and \( m_i \) is the mass of the particle \( i \). The force is obtained as the gradient of a potential \( U \)

\[
\mathbf{f}_i(t) = -\nabla U(r). \tag{4.2}
\]

The potential energy \( U \) with the kinetic energy of the system

\[
K(\mathbf{p}) = \sum_i \frac{p_i^2}{2m_i}, \tag{4.3}
\]

leads to the Hamiltonian

\[
H(\mathbf{r}, \mathbf{p}) = K(\mathbf{p}) + U(\mathbf{r}). \tag{4.4}
\]
The core of any MD program is the numerical integration of the equations of motion (4.1). The equations of motions are discretized in time and a small time step $\delta t$ is chosen. A commonly used integration scheme is the leap-frog integration scheme which is second order accurate and stable. Within this scheme, the velocities and the positions are not synchronous. Instead, while all positions are defined at time $t$, the velocities are only defined with an offset of $\delta t/2$. Thus positions and velocities are staggered in time with regards to each other. The integration usually starts with the calculation of the forces on all atoms at a given time $t$. The forces are then used to update the velocity of time $t - \delta t/2$ and to obtain the new velocities at time $t + \delta t/2$. These velocities are then used to update the particle positions and to obtain the particle position in $t + \delta t$. Both, positions and velocities are kept constant throughout one timestep.

From the equations of motion we see that all results depend directly on the forces acting in a system and thus on the potential energy. The potential energy of the system therefore plays a crucial role in every MD simulation. It is usually specified in a so-called force field, which is an approximation of the true interatomic forces arising from the interaction of electrons and nuclei. The qualitative and quantitative results of MD simulations are intimately related to the ability of the force field to represent the underlying system. Due to this crucial role we will discuss force fields in more detail in section 4.4. First, however, we will explain how macroscopic system properties may be derived from MD simulations.

4.3 System properties

MD simulations are often used to study macroscopic properties. The link between the atomistic or molecular representation of a system and macroscopic properties is established by statistical mechanics, which provides the theoretical and mathematical foundation for this task.

Properties like temperature and pressure may be computed as statistical averages based on particle momenta and atomic positions. From statistical mechanics [9] the system temperature is defined as

$$T(t) = \frac{2K(p)}{N_f k_B},$$

(4.5)

where $N_f = 3N - N_C$ denotes the number of degrees of freedom in the system, $N$ the number of atoms and $N_C$ the number of constraints. The system pressure
in a computational cell of volume $V$ is defined as

$$P(t) = \frac{2K(p)}{3V} + \frac{W}{3V} = P_{id} + P_{vir}, \quad (4.6)$$

where the ideal pressure $P_{id}$ is corresponding to a system of non interacting particles and the virial pressure

$$P_{vir} = \frac{W}{3V} = -\frac{\sum_i \sum_{j>i} r_{ij} f_{ij}}{3V} \quad (4.7)$$

arises due to particle interaction of force $f_{ij}$ between pairs of particles $i$ and $j$ at distance $r_{ij}$, which form the virial $W$.

### 4.4 Force fields for molecular dynamics simulations

A force field describes the potential energy which is needed in a MD simulation. Several “generic” force fields have been developed. There are general purpose force fields capable of describing a wide range of molecules such as the Universal Force Field [261]. Other force fields have been derived for specific types of molecules or chemical systems: graphitic and diamond forms of carbon [43], covalent systems [299], various models for liquid water [24, 159, 208, 297], zeolites [47], biomolecules such as AMBER [59], GROMOS [312] or CHARMM for proteins [44] and also for organic molecules [217].

Force fields are generally empirical in the sense that a specific mathematical form is chosen and parameters are adjusted to reproduce experimental data such as bond lengths, energies, vibrational frequencies and density [105, 208]. In addition, generic force fields are usually developed to be suitable for a wide range of molecules. One should be aware of this attribute when considering these generic force fields for the study of a specific system. In this case it is not uncommon to conduct QM calculations for a small system in order to calibrate MD potentials for the system under consideration.

Most force fields have a similar structure that will be described in the following. The description is not complete and particularities of specific force fields have been omitted. This rather theoretical introduction will be completed by a detailed description of force field contributions to water-carbon-nanotube systems.
4.4 FORCE FIELDS FOR MOLECULAR DYNAMICS SIMULATIONS

4.4.1 The structure of force fields

The potential energy function or the force field provides a description of the relative energy and forces of an ensemble. This description includes energy for distortions and vibrations of the molecules, and interaction energies between the molecules. Classical force fields are usually built up as composite potentials, i.e., as sums over many terms rather than simple potential energy expressions. Mostly, pair potentials \( V(r_{ij}) \) are used, but multi-body contributions such as \( V(r_{ij}, r_{ik}) \), and \( V(r_{ij}, r_{ik}, r_{il}) \) may also enter the expression, thus

\[
U = \sum_{i,j} V(r_{ij}) + \sum_{i,j,k} V(r_{ij}, r_{ik}) + \sum_{i,j,k,l} V(r_{ij}, r_{ik}, r_{il}),
\]

(4.8)

where \( r_{ij} \) is the distance between \( i \)-th and \( j \)-th atoms. The explicit form of \( V \) may vary and will be discussed later. This simple approach of a composite potential is generally applicable, though for reasons of computational efficiency the terms involving more than two interacting particles are only used for well specified groups of atoms, i.e. angle and dihedral potentials.

The contribution to the interaction potential can be distinguished in: intramolecular and intermolecular contributions. While the former describe interactions which arise in bonded systems, the latter are usually pair terms between distant atoms.

In the following an overview on the most common potential energy contributions will be given. These contributions are present in almost all force fields.

4.4.2 Intramolecular terms

Various intramolecular potentials are used to describe the dynamics of chemical bonds and their interactions. The potential

\[
V(r_{ij}) = \frac{1}{2} K_h (r_{ij} - r_0)^2
\]

(4.9)

emerges from a consideration of simple harmonic oscillators [95], where \( r_{ij} \) and \( r_0 \) denote the bond length and the equilibrium bond distance, respectively. The force constant of the bond is given by \( K_h \). Alternatively, the Morse potential [229]

\[
V(r_{ij}) = K_M (e^{-\beta(r_{ij} - r_0)} - 1)^2
\]

(4.10)

can be used, which allows for bond breaking. Here \( K_M \) and \( \beta \) are the parameters of the potential.
At coordination centers, i.e. atoms where several bonds come together, bond angle terms are applied. Functional forms include harmonic bending

\[ V(\theta_{ijk}) = \frac{1}{2} K_\theta (\theta_{ijk} - \theta_0)^2 \]  

(4.11)

or the harmonic cosine bending

\[ V(\theta_{ijk}) = \frac{1}{2} K_\theta (\cos \theta_{ijk} - \cos \theta_0)^2, \]  

(4.12)

where \( \theta_{ijk} \) is the angle formed by the bonds between the \( i \)-th, the \( j \)-th, and the \( k \)-th atom. \( \theta_0 \) is the equilibrium angle.

The third widely used contribution are dihedral angle potentials, which are employed for systems involving chains of bonded atoms. The dihedral angle potentials ensure a consistent ordering over several centers and are usually of the functional form of a Fourier series expansion with frequencies \( m \) where the sum can contain up to 12 terms. [211, 267]

\[ V(\phi_{ijkl}) = \frac{1}{2} \sum_{m=0}^{n} K_m \cos (m\phi_{ijkl} + \phi_{m,0}). \]  

(4.13)

The dihedral angle between particles \( i, j, k \) and \( l \) is given by \( \Theta_{ijkl} \). The potentials may be shifted by \( \phi_{m,0} \).

The functional form of intramolecular interaction potentials is usually a presumption. It is chosen such, that it allows for a convenient determination of the according parameters. A framework for an efficient evaluation of intramolecular interactions in quantum mechanics is provided by linear response. The aforementioned potentials have been constructed such, that the according potential parameters can be obtained either by equilibrium quantum mechanical calculations or by linear response.

Usually, the parameters for the intramolecular terms are determined from quantum chemistry calculations on small molecules and model molecules that represent pieces of larger molecules. As an example, Walther et al. [327] report on how the dihedral potential of a CNT is fitted to quantum chemistry calculations of tetracene (C_{18}H_{12}) using density functional theory [100]. Further examples are available in the AMBER force field specification [59].

### 4.4.3 Intermolecular terms

When choosing a potential function to calculate the interatomic forces, the following criteria are of major importance:
• **Accuracy**: the simulation should reproduce the properties of interest as closely as possible.

• **Transferability**: the force field expressions should be applicable to situations for which the force field was not explicitly fitted.

• **Efficiency**: force evaluations are generally the most time-consuming part of a simulation and they should be as efficient as possible.

The proper balance between these criteria depends to a large extent on the system to be investigated.

Usually, MD simulations consider intermolecular potential energy contributions from van der Waals terms and electrostatics. Both the van der Waals and the electrostatic potentials will be introduced below.

### The van der Waals interaction

The van der Waals contribution to the potential energy is usually modeled using a Lennard-Jones 12-6 potential [189]

\[
V(r_{ij}) = 4\epsilon \left[ \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^{6} \right]
\]

where \( \epsilon \) is the depth of the potential well, and \( \sigma \) is related to the equilibrium distance between the atoms. The parameters are usually obtained through fitting to experimental data and/or theoretical considerations. For multi-atomic fluids \( \epsilon \) and \( \sigma \) may not be available for any combination of atom species. In these cases, the Lorentz-Berthelot mixing rules [9] allow to estimate the interaction parameter for an unknown pair of atom species from the interaction parameters of the individual atom species

\[
\epsilon_{IJ} = \sqrt{\epsilon_I \epsilon_J}, \quad \sigma_{IJ} = \frac{1}{2} (\sigma_I + \sigma_J).
\]

Here \( I \) and \( J \) denote the \( I \)-th and \( J \)-th atomic species. However, recent work [283] has shown this approach to be inadequate for accurate liquid simulations, as quantities like the mass density of a liquid are sensitive to the choice of parameters.

Variants to the Lennard-Jones 12-6 potential are used for special geometries. For example for surfaces an averaged Lennard-Jones 10-4 potential may be obtained.
by integration of the Lennard-Jones 12-6 potential \[107\]

\[
V(z) = 4\epsilon\sigma^2 \left[ \left( \frac{\sigma}{z} \right)^{10} - \left( \frac{\sigma}{z} \right)^{4} \right]
\]  

(4.16)

where \( z \) is the wall normal distance.

The Lennard-Jones potentials are usually truncated beyond a certain cutoff radius. This can be justified by the fast decay of the Lennard-Jones potential. Typical cutoff values are \( 1.5\sigma \) for purely repulsive interactions, and \( 2.5\sigma \) up to \( 10\sigma \) for homogeneous and inhomogeneous systems, respectively.

**The electrostatic potential**

Long-range electrostatic interactions in MD are described by the Coulomb potential

\[
V(r_{ij}) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}},
\]

(4.17)

where \( q_i \) and \( q_j \) refer to the electric charges of the \( i \)-th and \( j \)-th atoms, and \( \epsilon_0 \) is the permittivity of vacuum. Usually, fractional charges are used for atoms of polar molecules and integral charges for mono-atomic ions.

### 4.4.4 Water and carbon nanotubes

In this section the interplay of the different force field contributions is illustrated. We will do this by reviewing the water CNT interaction. From the modeling perspective the water CNT interaction is a relatively simple interaction, yet it covers most aspects which are of importance to current force fields.

Three interactions contribute to the model of interaction potentials in water carbon systems. A description of the water, the graphite and their interaction. These contributions have to be balanced and accurate.

**Water models**

Water models have been of preeminent interest since the inception of MD simulations. The reason for this interest is due to the importance of water because of its omnipresence. Many different water models have been presented throughout the years [26, 24, 70, 159, 160, 258, 297] and are well established. Today’s most popular models in MD simulations are rather simple three site models, which model
each atom within the water molecule as a point in space with a certain mass and charge [24, 26, 160] and carry a single Lennard-Jones site on the oxygen. The configuration is kept fixed by rigid bonds and constrained angles. More sophisticated models have been developed in order to improve the quantitative results in predicting physical properties. Additional charge sites have been included [160], polarizability has been considered [69] and bonds and angles have been considered to be flexible [297]. However, the three site model remains the most important water model in MD, its extensions being rather limited. In this thesis, the TIP3P [160], the SPC/E [24] and the RPOL [70] water models will be used.

**Carbon nanotubes and graphite**

Several potentials have been developed recently for graphite and CNTs. This was mainly motivated by the properties of novel carbon structures as fullerenes and CNTs. The model used throughout this thesis is based on a Morse bond, a harmonic cosine potential for the bending angle and a two-fold torsion potential [327]. There are different models used in the literature which mostly model the bonds and angles with harmonic potentials and use a slightly different torsion potential [140]. Often, carbon structures such as graphite and CNTs are however not simulated in full detail. The structure is kept rigid and the intramolecular degrees of freedom are removed. This is computationally advantageous as it usually allows for an increased simulation time step and therefore a reduced computational cost since the intramolecular interaction terms do not have to be computed.

**The water carbon nanotube interaction**

Traditionally, the interaction between graphitic systems, which include CNTs, and water are modeled using a single Lennard-Jones contribution between every carbon and oxygen atom. Variants include interaction potentials which include Lennard-Jones interaction terms on the water hydrogen atoms. The parameters for these interaction potentials are either obtained from other interaction potentials using Lorentz-Berthelot mixing rules (4.15), deduced from atomic polarizabilities or fitted to reproduce macroscopic properties. For example, Werder et al. [332] presented interaction parameters which would reproduce the experimental contact angle of water on graphite and earlier Markovic et al. [212] fitted their interaction potentials to scattering experiments of water on graphite. Werder et al. [332] also presented a detailed review of water graphite interaction potentials previously used in MD simulations.
Coulombic interactions are usually omitted for graphite or CNT water interaction as the single species model of graphite or CNTs do not presume charges on the carbon atoms. The electrostatic interaction may however be more complicated than it seems at first sight and many questions had to be answered in the modeling process. When considering intermolecular interactions, intramolecular electronic effects may play an important role. The special electronic structure of graphite and CNTs gives rise to a quadrupole moment on their surface. The effect of this quadrupole moment on the water CNT interaction was assessed but not found to be important [327]. Furthermore, when considering CNTs, a static dipole moment is induced by the bending of the graphite sheet [86]. This effect was found to be important for small CNTs and will be reported in more detail in chapter 7. However, both effects can be neglected when considering graphitic systems or CNTs with diameters greater than 5 nm.

Another important contribution to the interaction energy of CNTs and water is polarization. Moulin et al. [230] presented studies where they considered dynamic polarization of CNTs subject to the electric field generated by water. While Moulin et al. did not find important effects, we found significant differences in both, the single water optimal geometry on graphite and the water structure close to the surface which could be of technical importance, see chapter 6.

The added complexity in this problem is that water close to graphitic systems is strongly affected by very short ranged interactions. This leads to the finding that water in confined geometries behaves drastically different than in bulk systems [140, 354]. When using MD simulations to reliably understand and analyze such systems, it is important to develop suitable models and interaction potentials which hold in such environments.

### 4.4.5 Force fields for membrane simulations

In chapter 8 we will consider the simulation of a specific realization of CNT based nanopores in a lipid bilayer. Most current force fields provide extensions and specific models for membrane simulations. For example, Smolodyrev and Berkowitz [284] presented a united atom extension to the AMBER 96 [59] force field. Another recent force field for phospholipids was presented by Chandrasekhar [53] as an extension to the GROMOS [312] force field.

Extensions to membranes for force fields have been designed to reproduce various properties of real membranes and provide good approximations for their description. Different force fields for membranes usually result in similar physical properties. Thus, the decision on what force field to use is mainly determined by
the requirement that the force field should integrate with the description of the remaining system. We are here interested in RNA transport in the vicinity of lipid bilayers. We use the AMBER 96 [59] force field to model RNA, as it is known to provide a good description of RNA and DNA. In order to model the membrane we use an extension to the AMBER force field as proposed by Smondyrev and Berkowitz [284]

4.5 Computational issues in molecular dynamics

4.5.1 Time step

The integration time step in MD simulations is usually determined by the requirement for energy conservation in the microcanonical ensemble. Most current force fields are designed such that they allow for time steps in the order of 2 fs.

Increasing the time step is usually limited by bond vibrational frequencies, which depend on the mass of the atoms involved in the bond. By far the lightest atom in biological systems is hydrogen, which has a mass of about a tenth of the mass of hetero atoms. Thus bonds involving hydrogen result in relatively high frequencies, and are therefore the limiting factor in the integration of the equations of motion. To resolve this bottleneck, these bonds are constrained at a constant bond length, which allows to increase the time step significantly (2 fs instead of 0.2 fs). The increase in the time step overcompensates for the computational cost of ensuring the constraints.

4.5.2 Constraints

Instead of using explicit potentials to model intramolecular potential energy contributions, intramolecular distances can be constrained to target values. Constraints in MD were introduced by Ryckaert et al. [268] in alkane simulations. Constrains are imposed using iterative procedures such as SHAKE [98, 180, 310], SETTLE [226], or direct methods [342]. Currently, SHAKE is widely used and we sketch the method below.

Consider the constraint equations

\[ |r_{k,a} - r_{k,b}|^2 - r_{k,0}^2 = K_k = 0 \] (4.18)
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with

\[ \mathbf{r}_i = \tilde{\mathbf{r}}_i + \sum_{k=1}^{N} \lambda_k \frac{\partial K_k}{\partial \mathbf{r}_i} \]  

(4.19)

where \( \tilde{\mathbf{r}}_i \) is the unconstrained position of the \( i \)-th particle and \( r_{k,0} \) is the constraint distance of the \( k \)-th constraint. SHAKE solves the non-linear coupled constraint equations using a Jacobi iteration over the Lagrange multipliers \( \lambda_k \) with

\[ \lambda_k = -\left. \frac{K_k}{\left( \frac{\partial K_k}{\partial \lambda_k} \right)} \right|_{\lambda=0} \]  

(4.20)

updating the particle positions according to equation 4.19 and resetting all \( \lambda_k = 0 \) at each iteration.

Constraints, have become very important, as most currently used water models consider constrained bond lengths and angles, e.g. [24, 160]. The reason for the popularity of constrained water models has been indicated before: bonds involving hydrogen atoms show high bond vibrational frequencies, much higher than bonds connecting two hetero atoms. This high frequency motion requires a small integration time step in order to be reasonably resolved. Removing these intramolecular degrees of freedom by constraining these bonds alleviates the problem, as time steps can be chosen 5 to 10 times larger. Furthermore, the high-frequency oscillation of the O-H bonds in water formally falls into a regime where quantum mechanical effects become important. Thus, using constraints this modeling problem is circumvented, too.

4.5.3 Restraints

It is difficult to set up a system for an MD simulation such that all positions and velocities correspond to an ensemble realization. Instead, approximations to such realizations are used to start MD simulations and the systems are equilibrated to the desired state. For biomolecules often crystallographic structure information is used and it is desirable to preserve that structure during the equilibration process. The system should not be fixed completely but it should be allowed to relax high stresses within the biomolecule. This is usually achieved by restraining the atoms or a selection of the atoms of the molecule in question during equilibration.
When the atoms of a molecule are restrained, their coordinates $r_i$ are coupled to the reference coordinates $r_{i,0}$ using a harmonic potential

$$V_{\text{restrain}} = \frac{k}{2} (r_i - r_{i,0})^2. \quad (4.21)$$

The coupling constant $k$ is a parameter which determines by how much the molecule should be allowed to deform.

### 4.5.4 Ensembles

The state of a thermodynamic system is characterized by a given set of state variables or properties. These properties include pressure, temperature, composition, density, surface tension and free energy.

In statistical mechanics we distinguish between macroscopic and microscopic states. A microscopic state is a specific realization of the system where all velocities and positions of the particles in the system are known, i.e. a point in phase space. In contrast, a macroscopic state corresponds to a thermodynamic state, which is defined by average, macroscopic quantities like density, pressure and temperature. All microscopic states which are a realization of a specific macroscopic state belong to it and form an ensemble.

MD simulations are usually performed under well specified thermodynamic conditions and thus specific ensembles are sampled. Although any set of thermodynamic variables which specifies a state could be used to determine the ensemble, only a few specific combinations are of practical relevance in MD simulation. The most popular ensembles:

- **Microcanonical ensemble (NVE):** the thermodynamic state of a system is defined by its composition $N$ (the number of particles and their type), its volume $V$ and the total energy $E$.

- **Canonical ensemble (NVT):** the thermodynamic state of a system is defined by its composition $N$, its volume $V$ and temperature $T$.

- **Isothermic-Isothermal ensemble (NPT):** the thermodynamic state of a system is defined by its composition $N$, its pressure $P$ and temperature $T$.

### 4.5.5 Evaluation of long range forces

MD simulations are usually very time consuming. The computationally most expensive part in a standard MD run is the evaluation of the long range nonbonded
forces. Nominally, the nonbonded interactions should be evaluated between every pair of atoms (in the case of pairwise interactions). The evaluation of the nonbonded interaction term therefore increases quadratically with the number of atoms, as the number of possible pairs in a system with \( N \) atoms is equal to \((N^2 - N)/2\). This scaling becomes prohibitively expensive when large systems are considered and fast algorithms have been developed to circumvent this problem.

**Cutoff schemes**

A simple way to overcome the \( \mathcal{O}(N^2) \) scaling of the force evaluation, is to introduce a cutoff \( r_c \). It is assumed that force contributions beyond the cutoff distance, are negligible and can be omitted. This allows to reduce the computational cost to \( \mathcal{O}(N) \).

To achieve the aforementioned reduction in computational cost, however, the atoms have to be handled efficiently and information on their relative position has to be stored. Different algorithms have been presented to tackle this task. Amongst the most popular approaches are Verlet lists [313] and cell lists [9], which have been implemented in various ways.

The reduction in computational expense due to cutoff schemes, however, comes at the price of a loss of accuracy. One of the most severe implications of this is the loss of energy conservation within an MD simulation. The problem with energy conservation depends on the energy contribution at the cutoff distance. This contribution usually decreases with increasing cutoffs and at an infinite cutoff the non-truncated result is recovered. In this limit, however, the speed-up of a cutoff schemes is lost.

The Coulomb potential is usually the potential which vanishes the slowest. Due to its \( r^{-1} \) dependence, truncation effects are particularly important. To overcome this problem, the use of shifting and switching functions have been suggested. A particular approach uses a smooth tapering of the potential energy function [289, 327, 332]

\[
V(r_{ij}) \approx \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}} S(r_{ij})
\]  

where \( S(r) \) is a smoothing function, e.g.,

\[
S(r_{ij}) = \begin{cases} 
(1 - (r_{ij}/r_c)^2)^2 & r_{ij} < r_c \\
0 & r_{ij} \geq r_c 
\end{cases}
\]  

(4.23)
The results obtained however from MD simulations using a truncation scheme may be significantly different from the full treatment of the electrostatic interactions, in particular, for systems with inhomogeneous charge distributions and for ionic solutions [315]. Significant discrepancies were also found at the liquid vapor interface [231]. The results obtained however with the correct treatment of the electrostatics may be less accurate [198, 208], if a force field was calibrated for a truncation scheme.

**Advanced schemes**

As highlighted in the previous paragraph, the use of cutoff schemes for electrostatic interactions may introduce significant errors. An alternative approach to evaluate electrostatic interactions has been known since the early 1920’s as the Ewald summation [91]. This approach is however limited to periodic systems. The standard implementation of the traditional Ewald summation scales as $O\left(N^2\right)$. At the expense of extensive memory consumption it can however be implemented in $O\left(N^{\frac{3}{2}}\right)$.

In the Ewald summation technique the electrostatic interaction is split up into a short-range and a long-range contribution. At every point charge of the system a Gaussian charge distribution of opposite charge is added. This counter charge damps the charge-charge interaction such that it decays very rapidly. To compensate for the Gaussian charge distributions, we now add the same charge distributions to the system, but with the same sign as the point charges. Their interaction is now evaluated separately. The Gaussian charge distributions are transformed into Fourier space where the Poisson equation is solved and then they are transformed back. Due to the Gaussian form of the charge distributions, this procedure can be formulated analytically and performed directly in a single step, see appendix C for more information.

Based on the concept of the Ewald summation technique other methods have been suggested, increasing its efficiency in both memory consumption and scaling. Recent advances to the original Ewald summation technique [91, 251] include the the particle-mesh Ewald method [71], the smooth particle mesh Ewald method [90], or the particle-particle-particle-mesh technique [131, 132, 207, 326]. The concept in these methods is to use a grid to solve for the potential field or a part of it. On the grid fast Fourier transforms are used to solve for the governing, usually Poisson-type, equation linking the charge distribution with the potential and the electric field. This reduces the order of these methods to $O\left(N \log N\right)$. 
The potential and the electric field can then be interpolated from the grid with high accuracy back on the particles. For a detailed description of the smooth particle mesh Ewald method see appendix C.

The Cell Multipole Method [77, 114, 273] provides an alternative to the Ewald summation based schemes for non-periodic systems. A special realization, the Reduced Cell Multipole Method [78], was developed for periodic systems. The multipole methods rely on the replacement of the far field interactions of a number of particles, a cluster, by the multipole expansion of the charge distribution of this cluster and scales nominally as $O(N \log N)$. The algorithm achieves an $O(N)$ scaling [114], by allowing groups of particles to interact with each other by translating the multipole expansion into a local Taylor expansion. Up to now, this approach did not gain significant practical importance in MD simulations due to the extensive computational cost of the translation and the cluster cluster interaction, which scales $O(P^4)$ where $P$ is the number of terms retained in the truncated multipole expansion.

### 4.5.6 Boundary conditions for molecular dynamics

In a typical MD simulation there are usually about 100 particles per nm$^3$. Even for a relatively small system of $10 \times 10 \times 10$ nm$^3$ this leads to a number of particles in the order of 100,000. A simulation on 100,000 particles is, however, still a very large MD simulation for today's standards. Thus normal MD simulations are carried out in very small volumes. Due to the small system sizes the systems are very susceptible to undesirable boundary effects. Their presence would require an extension of the simulation domain and make simulations prohibitively expensive. It is therefore mandatory to avoid boundary effects as much as possible.

When using solid walls to bound a computational domain a strong structuring in the liquid near the wall is introduced. This structuring persists for approximately 1 nm in liquid water [332]. This effect may be minimized using wall potentials which simulate a continued liquid past the wall. Werder et al. [334] showed that with such potentials density fluctuations could be reduced for liquid argon close to the boundary of a computational domain.

Alternatively, the system may be placed in vacuum [9] or a periodic system may be assumed. Using periodic boundary conditions, the original computational box is surrounded with identical images of itself. Usually, if periodic boundary conditions are applied a cubic or rectangular parallelepiped computational domain is used, but theoretically all space filling shapes (e.g., truncated octahedron) are possible [9]. Periodic boundary conditions on small systems may however introduce
artifacts if the system is not inherently periodic [142].

Petraglio et al. [252] presented an alternative method for nonperiodic boundary conditions. The method considers a finite sphere embedded in a reaction field described by image charges. Initial studies provide optimized parameters for two standard solvents, water and acetonitrile. The dynamic properties are found to be comparable to the ones obtained with periodic boundary conditions [252].

Another approach are stochastic boundary conditions. They allow a reduction of the explicitly simulated domain by partitioning the system into two zones with different functionality: a reaction and a reservoir zone. The reaction zone is the one to be studied while the reservoir zone contains the portion which is of minor interest to the study. The reservoir zone is excluded from MD calculations and is replaced by random forces whose mean corresponds to the temperature and pressure in the system. The reaction zone is further subdivided into a reaction zone and a buffer zone. The stochastic forces are only applied to atoms in the buffer zone. In [27] stochastic boundary conditions are derived and in [45] the application to a water model is described.

4.5.7 Metadynamics

Metadynamics [183, 184] is a powerful method to explore a free energy surface defined in terms of a moderate number of selected collective variables. The method relies on history dependent potential consisting of Gaussian contributions in the space of collective variables. The Gaussian potential contributions make a return to formerly explored points in the space of the collective variables less favorable and therefore promote the exploration of other domains. The method which was originally presented by Laio and Parrinello [183, 184], proved to be extremely valuable to identify the free energy surface and to find transition states and mechanisms. It is currently one of the most powerful methods to quantitatively assess rare events.

4.5.8 Nonequilibrium molecular dynamics

For the study of non-equilibrium processes or dynamic problems, such as flows in capillaries and confined geometries, non-equilibrium MD (NEMD) was found to be a very efficient tool. It is based on the introduction of a flux in thermodynamic properties of the system [9, 57]. NEMD has been used on a variety of problems, e.g. for the study of rheological issues [201], to evaluate the shear viscosity of simple fluids [266] and to compute transport coefficient [65]. Tuckerman et al. [308]
presented a modified NEMD approach to ensure energy conservation. For detailed background about the underlying statistical mechanics of nonequilibrium systems, the reader is referred to [82].

Another form of NEMD is steered molecular dynamics (SMD), applied by Grubmüller et al. [119] to determine the rupture force of proteins. It has also been proven to be extremely valuable also in many other fields in subsequent studies [146]. The principle of SMD is to superimpose a time-dependent force on selected atoms or molecules such that the molecules or the system are driven along certain degrees of freedom in order to investigate rare events. The concept of SMD will be presented in more detailed in chapter 5 where an extension to SMD is presented.
Chapter 5

Generalized Steering for Molecular Dynamics

MD simulations are one of the most popular approaches to study biophysical systems. Biological processes often evolve over times scales that are not accessible to MD simulations. This is the case for example when large energy barriers are present. A popular method to overcome this problem is steered molecular dynamics (SMD) where a system is forced along a prescribed trajectory of certain variables. This allows us to study rare events which could otherwise not be observed with standard MD.

This chapter presents an extension of SMD to trajectories of functions of variables, so-called collective variables. A generalized steering on collective variables is demonstrated in the folding of a nona-alanine peptide and the expulsion of RNA from a CNT. The results indicate that the present approach enables the exploration of configurations that may not be easily accessible by SMD otherwise.

5.1 Introduction

SMD [119] is a method to overcome energy barriers by forcing the system in question along a suitable trajectory. The method was first introduced to study the dissociation of biotin from avidin and streptavidin [119, 147]. Since then, SMD has been extensively utilized to study various problems ranging from the identification of ligand binding pathways [149] to elastic properties of peptides and unfolding of the muscle protein titin [146, 206]. In addition it has been shown by Park and Schulten [239] how SMD can be used to extract potentials of mean force using Jarzynski’s identity [152, 153].

In SMD a system is usually evolved along the trajectories of individual atoms. In a recent work, however, Laio and Parrinello [183] demonstrated that a system may be more effectively described through suitably chosen collective variables, which are functions of atomic properties and positions. In this chapter, we will make use of collective variables to extend the applicability of SMD. In particular, we show
how SMD can be generalized to steer a system along a trajectory given in terms of collective variables.

First, the concepts of SMD and collective variables are presented, followed by the description of the generalization. Second, two example applications are presented. In the first example, the folding of a peptide is compared for a steering imposed on its radius of gyration and for a steering imposed on the angle defined by its end groups and a central backbone atom. The second example reports on the expulsion of a short single stranded RNA fragment from a CNT where the center of mass distance is used as the collective variable.

5.2 The method

We give a brief description of the two underlying components of our method namely:

- SMD and
- collective variables.

Then, a generalized steering on collective variables is presented.

5.2.1 Steered Molecular Dynamics

System configurations which are energetically unfavorable are difficult to study in MD as the system hardly visits such configurations. SMD resolves this problem by steering the system from an initial configuration towards a target value for one or several atom coordinates. This is done in a way that the system is either passing through the energetically unfavorable configuration or the system is reaching it at the end of the simulation.

In SMD a time dependent restraint potential $V_s$ enters the Lagrangian. This potential is also called the steering potential and couples an atomic position to a restraint point $\mathbf{r}_0$. $V_s$ is often modeled by a harmonic potential as

$$V_s = \frac{k(t)}{2} (\mathbf{r} - \mathbf{r}_0(t))^2$$

(5.1)

where $k$ is the coupling constant. We identify two commonly used approaches to steer a system. First, the coordinates of the restraint point are fixed to $\tilde{\mathbf{r}}_0$ and the strength of the harmonic coupling is linearly increased in time [119, 147],

$$k = k(t) = \alpha t \quad \text{and} \quad \mathbf{r}_0(t) = \tilde{\mathbf{r}}_0.$$  

(5.2)
Alternatively \cite{148, 290}, the restraint point is evolved along a certain trajectory to its final position while the strength of the coupling remains fixed to $\tilde{k}$,

$$ r_0 = r_0(t) \quad \text{and} \quad k(t) = \tilde{k}. \quad (5.3) $$

The latter approach can be applied to relatively complicated trajectories of a large number of atoms, e.g. to the angular movement of two protein domains \cite{148}.

**5.2.2 Collective variables**

Collective variables are computed as a function of one or several individual particle coordinates

$$ \sigma = \sigma (r_i). \quad (5.4) $$

Collective variables may be used to describe a complex rearrangement in terms of a single quantity. Recent examples include the number of contact sites, the number of five-membered rings in ice crystals \cite{81} and a local electric field \cite{183}. Other possible collective variables could include the distance between two centers of mass or the angle between three centers of mass or the radius of gyration.

**5.2.3 Generalized steering on collective variables**

We propose to generalize the concept of SMD to steer a system along a set of collective variables. In particular, we suggest to couple collective variables to a steering potential instead of coupling individual coordinates

$$ V_s = \frac{k(t)}{2} (\sigma - \sigma_0(t))^2. \quad (5.5) $$

Given a potential acting on a collective variable, the force $f_i$ on particle $i$ is then given by

$$ f_i = -\frac{\partial V_s (\sigma)}{\partial \sigma} \frac{\partial \sigma (r_i)}{\partial r_i}. \quad (5.6) $$

The collective variables can now be steered, using either of the two variants of SMD presented above.

A trajectory may be defined in terms of several collective variables. In this case the steering potential may be applied to each collective variable individually,
which allows for individual coupling constants to the different collective variables. Alternatively, the steering potential may be applied on a norm of the vector defined by the differences of the current realizations of the collective variables and their reference values.

Steering indirectly through collective variables can be more appropriate and more convenient than the classical steering on single atomic coordinates as we will show in specific examples.

5.3 Applications

We will now demonstrate the conceptual advantage of generalized steering in MD. The proposed generalization is first applied to two studies of the folding of the nona-alanine peptide. This is followed by a study on the expulsion of RNA from a CNT.

In all simulations we used the AMBER 96 force field [59] and TIP3P water [160]. A timestep of 1 fs was used and the bonds involving hydrogen atoms were constrained. For the last application, the non-bonded interactions of the CNT carbon atoms are described using the parameters of \( sp^2 \) carbons in the AMBER 96 forcefield (\( \sigma_{CC} = 0.34 \) nm and \( \epsilon_{CC} = 0.36 \) kJ mol\(^{-1} \)). The bond, angle and torsion potentials for the CNT are taken from Walther et al. [327]. The constraints are enforced using the SHAKE [268] algorithm and the simulations were carried out using the MD package FASTTUBE [332].

5.3.1 Folding of nona-alanine

We implement the generalized steering to the folding of nona-alanine. It is steered along trajectories of collective variables that cannot be easily described in terms of distances between single atoms. The nona-alanine peptide is acetylated at the N-terminus and protected with N-methylamine on the C-terminus. Its initial conformation is \( \alpha \)-helical. It is solvated in 2544 water molecules in a periodic box of initially \( 4.3 \times 4.3 \times 4.3 \) nm. Throughout all simulations we use an NPT system subject to a Berendsen thermostat with a coupling constant of 0.1 ps and a Berendsen barostat [25] with a coupling constant of 0.5 ps.

As collective variables we first consider the radius of gyration of nona-alanine

\[
r_g = \sqrt{\frac{\sum_{i=1}^{N} m_i (r_i - r_0)^2}{\sum_{i=1}^{N} m_i}}
\]
where $\mathbf{r}_0$ denotes the center of mass and $\mathbf{r}_i$ and $m_i$ are the coordinates and masses respectively of the $N$ atoms in nona-alanine. In a second simulation two intramolecular distances, namely between the $\alpha$-carbon of the central amino acid and the methyl group carbon atoms of the end groups, and their angle are steered in a concerted fashion. Considering the limited time of simulation, the strong coupling and the sharp changes in the collective variables, the observed structures are not expected to represent optimal or equilibrium configurations.

**Case A: Steering on the radius of gyration:** The solvated peptide was initially equilibrated for 50 ps. After this equilibration, the radius of gyration amounted to 0.5417 nm. Subsequently, the system was steered through the radius of gyration for 250 ps with a coupling constant of 50’000 kJ nm$^{-2}$ mol$^{-1}$. Then the steering was turned off for another 100 ps of free dynamics, totaling a simulation of 400 ps. The steering schedule is illustrated in figure 5.1a. The steering is well reflected in the trajectory of the radius of gyration, which closely follows the reference value. This was ensured by choosing a relatively strong coupling.

Various conformations were visited during the steering and some of them are depicted in figure 5.1a. Significant differences in the conformations could be identified, as helical and hairpin-like structures were observed at small radii of gyration. At intermediate radii of gyration there is a preference for partially folded structures, i.e. structures where only one part of the peptide is stretched and the other part is packed in a hairpin-like or helical structure. In figure 5.1b we show the resulting evolution of the two intramolecular distances defined above. The correlation of either of these two trajectories with the trajectory of the radius of gyration is very limited and both show large fluctuations.

**Case B: Steering on two intramolecular distances and their angle:** After an initial equilibration of 50 ps the two distances described before are linearly stretched from their current values, of 0.955 nm and 0.999 nm respectively, to a target value of 1.25 nm. This stretching was performed using a steering with a coupling constant of 50’000 kJ nm$^{-2}$ mol$^{-1}$ over the course of 50 ps. The two intramolecular distances were then restrained to 1.25 nm with the same coupling potential for the following 260 ps.

Immediately after the two intramolecular distances had reached their stretched state, the steering on their angle is initiated starting from $90.25^\circ$. The angle was coupled to a target angle with a force constant of 10’000 kJ rad$^{-2}$ mol$^{-1}$. The schedule for the steering of the angle is depicted in figure 5.2. After 360 ps of
Figure 5.1: a) Radius of gyration of nona-alanine along a generalized SMD run. The green line indicates the actual radius of gyration while the blue line indicates the target value. The structures are snapshots of the peptide configuration at the corner points of the trajectory taken in intervals of 50 ps. b) The two intramolecular distances from the methyl carbon atoms of the end groups and the $\alpha$-carbon of the central amino acid during the same simulation of case A (red and green) and during the simulation of case B (black and blue).
5.3. APPLICATIONS

Figure 5.2: Angle between the carbon atoms of the end groups and the $\alpha$-carbon of the central amino acid of nona-alanine during a generalized SMD run. The carbon atoms contributing to the angle are indicated in yellow. The snapshots show the structure of the nona-alanine peptide and were taken at 100, 180, 280 and 360 ps.

In this example we use as a collective variable the distance between the centers of mass of a CNT and a piece of RNA. We use a hydroxyl terminated single stranded fragment of RNA consisting of six adenosine nucleotides. The RNA is placed in a single walled (14,14) CNT of 2.35 nm length (1.87 nm carbon-to-carbon diameter corresponding to a pore size of approximately 1.5 nm). The whole system is solvated with 6508 water molecules and 5 sodium ions in a computational box of
originally $5.9 \times 5.9 \times 5.9$ nm.

We present this application to show that in the generalization of SMD to arbitrary collective variables the first step is to use the center of mass instead of individual atoms. There have been previous steering simulations based on the center of mass [61, 155]. The aspect, however, that this is the first step towards a generalization of SMD has not yet been elucidated.

The system temperature is controlled using a Berendsen thermostat with a coupling time of 0.5 ps throughout the whole simulation. During the first 20 ps of the simulation, the system was relaxed at constant volume followed by 80 ps of coupling to ambient pressure using a Berendsen barostat. This resulted in a simulation box size of $59.06 \times 59.06 \times 59.06$ nm. Then the system was further equilibrated at constant volume during 100 ps, totaling 200 ps of equilibration, before the steering began.

After the equilibration, the distance between the centers of mass of the RNA and the CNT was 0.714 nm. To steer the RNA out of the CNT the reference distance was slowly increased from 0.714 nm to the final value of 2.8 nm reached after 1000 ps. The strength of the coupling constant was set to 50'000 kJ nm$^{-2}$ mol$^{-1}$. After the 1000 ps of steering the CNT and the RNA were constrained at a center of mass distance of 2.8 nm for another 300 ps.

The trajectory in terms of distance between the centers of mass is shown in figure 5.3. The RNA which is initially placed in A-form inside the nanotube quickly maximizes the hydrophobic interaction between the base groups of the nucleotides and the tube wall. Together with the geometric confinement, this leads to a strong distortion of the RNA inside the tube which is consistent with results reported in other works [103, 341]. When the steering is started, the configuration is further distorted and the RNA bulks up at the tube entrance. This is attributed to a more favorable interaction of the nucleotides with the CNT than with water, favoring that RNA remains inside the tube. The RNA leaves the CNT by slowly creeping around the tube edge, after reaching a relatively compact state at the tube entrance. This movement is consistent with the hydrophobic attachment of the RNA bases to the CNT reported by Yeh and Hummer [341]. It allows for a sustained contact between RNA bases and the CNT while increasing the distance between the centers of mass. A relatively large part of RNA detaches from the CNT at approximately 700 ps, after 500 ps of steering. This corresponds to a center of mass distance of approximately 2 nm. During this detachment a single nucleotide maintains close contact to the CNT and only peels off in the subsequent 200 ps. The structure is significantly perturbed due to the confinement in the CNT and when the RNA detaches completely from the nanotube it assumes a coiled up structure. Some of
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Figure 5.3: a) Center of mass distance between a six nucleotide fragment of RNA (AAAAAA) and a CNT during a steered molecular dynamics run. Configurations during the simulations are represented by nine snapshots taken every 125 ps between 200 ps and 1200 ps. b) Running average of the steering force acting on the center of mass distance during the steering. Note the minimum around 700 to 800 ps when the RNA detaches from the CNT.
the base pairs are stacked, but the overall structure is disordered and remains so throughout the limited simulation time of approximately 0.5 ns where the RNA is detached from the CNT.

A running average on the force acting on the center of mass distance was computed with an averaging window of 50 ps and samples taken every 0.001 ps, see figure 5.3b. As soon as the steering is started the force acting on the center of mass distance is quickly rising to a value of approximately 50 pN. The maximal force of approximately 100 pN at 700 ps coincides with the detachment of a relatively large part of the RNA from the tube. After this peak force, the force is decreasing gradually towards 0. The first 200 ps to 300 ps after the peak force are again subject to a force in the order of 50 pN which is attributed to the subsequent detachment of individual nucleotides after the expulsion of the relatively large part of RNA from the tube.

We note that steering on the center of mass allows for a reorientation of the two molecules with regard to each other. The simulation may explore a different and possibly more appropriate configuration space than the one that would have been achieved by pulling on a single or several atoms of the RNA in a prescribed direction [119].

### 5.4 Conclusions and discussion

We have extended the method of SMD by applying it to collective variables. The concept of the present generalized SMD has been demonstrated in two case studies involving the folding of a nona-alanine peptide and the expulsion of RNA from a CNT. In these case studies the collective variables were the radius of gyration and two intramolecular distances and their angle in the case of a nona-alanine peptide and the distance between the centers of mass in the case of the RNA expulsion from a CNT. These examples demonstrate that the generalization of SMD to collective variables can provide additional insight in the exploration of the configuration space. Steering along trajectories of collective variables enables the exploration of configuration changes that are hard to visit by steering along the trajectories of single atomic coordinates.
Chapter 6

Polarizability Effects in the Water-Carbon Interaction

An appropriate description of the interaction potentials is crucial in MD. In that respect the use of a rigorous quantum mechanical description is desirable. However, this is not possible due to the computational expense and simplified model potentials have to be used. In this chapter we examine the current water-carbon interaction potentials for MD and we assess the effects of polarizability. In particular, we determine whether it is important to consider polarizability to model the interaction between water and aromatic carbon. This allows us to validate current interaction potentials for studies presented later in this thesis.

It is shown, that the inclusion of polarizability allows to recover the optimal orientation of a single water molecule on graphite as suggested by Feller and Jordan, [93]. Within the same context the interaction energy of a single water molecule on graphite is closer to the predictions of quantum mechanical simulations. The Lennard-Jones interaction parameters are obtained through a fit to the macroscopic contact angle of water on graphite. On the other hand bulk properties are hardly influenced by polarizability.

Recent quantum mechanical results by Lin et al. [195], however, show that the single water orientation of Feller and Jordan [93] is only an approximation and the true orientation is significantly different. Thus the model presented here will have to be reconsidered, before being used in further studies.

6.1 Motivation and introduction

The water graphite interaction has been studied extensively in recent literature [195, 249, 332]. The interest in this particular interaction is motivated to a large extent by novel carbon nano-structures such as CNTs and fullerenes. These structures have been envisioned to provide the key to sensor and actuator applications at
the nanoscale [178, 196]. Since the surface-to-volume ratio is significantly higher for devices at the nanoscale, these devices are strongly influenced by their surroundings. It is therefore mandatory to understand and to quantify the interactions in molecular systems that are relevant for the design of such devices.

Traditionally, the interaction potential between water and graphite has been obtained by fitting experimental data [212, 332] or quantum mechanical systems [249]. The water graphite interaction is usually modeled using a single Lennard-Jones interaction between the carbon atoms and the oxygen atoms of water. Variations include the consideration of the graphite quadrupole moment [212, 327], local polarization [212] and additional Lennard-Jones type interactions [44, 249]. These interaction potentials, however, fail to reproduce the optimal configuration of a single water molecule on graphite as suggested by Feller and Jordan [93] except for an interaction potential that was explicitly fitted to do so [249]. More recent and qualitatively superior quantum mechanical data presented by Lin et al. [195], however, suggests a different optimal configuration. This configuration can be reproduced with standard force fields.

In this article we will present a physically motivated model for the water graphite interaction based on polarizability. It is shown that this interaction model reproduces the optimal orientation of the ab-initio calculations of Feller and Jordan [93] and it improves the estimated single water-graphite interaction energy. The parameters which are used for the Lennard-Jones interaction energy have been obtained by fitting the experimental contact angle of a water droplet on graphite. We will show that the influence on the bulk water structure close to polarizable graphitic surfaces is negligible and we conclude with a discussion of the results presented herein.

### 6.2 Methods and model

We use the revised polarizable water model (RPOL) of Dang et al. [69], where polarizability effects are included using a linear response approach and isotropic polarizabilities $\alpha_i$

$$\mu_i = \alpha_i E_i (q, \mu).$$  \hspace{1cm} (6.1)

Here, the dipole moment $\mu_i$ induced on site $i$ is proportional to the electric field $E_i$ at site $i$. The electric field itself depends on all charges $q$ and dipole moments $\mu$ in the system.
6.3. A SINGLE WATER MOLECULE ON A SINGLE GRAPHITIC SHEET

In all simulations, the graphite was kept fixed and the bond lengths were set to 1.418 Å. The carbon atoms have been assigned an isotropic polarizability of 1.4 Å$^3$ [212]. Induced dipole terms are always masked within graphite nearest neighbors, second nearest neighbors and third nearest neighbors.

The interaction between graphite and water consists of a single Lennard-Jones interaction between carbon and oxygen only and the electrostatic interaction between induced dipole moments and charges. The parameters for this Lennard-Jones interaction are $\sigma_{CO} = 0.319$ nm and $\epsilon_{CO} = 0.41$ kJ mol$^{-1}$. They are obtained through a fit to the experimental contact angle of water on graphite. The fitting procedure is described in detail below.

The induced dipole moments are calculated iteratively until self-consistency to a precision of $10^{-6}$ Debye [306]. The electrostatic interactions including the dipolar interactions are evaluated using a Smooth Particle Mesh Ewald (SPME) approach [306]. For the interpolation in the SPME routine we use sixth order B-splines and $\beta$, the parameter determining the decay of the direct electrostatic interaction, was set to 3.0 nm$^{-1}$.

We use the SPC/E water model of Berendsen et al. [24] for reference simulations of non-polarizable systems. In these simulations the interaction between graphite and water is modeled by a single Lennard-Jones potential between the oxygen and carbon atoms [332].

6.3  A single water molecule on a single graphitic sheet

The model for the water graphite interaction is assessed in terms of the minimum energy conformation of a single water molecule on graphite. For this purpose we consider a system with a single layer of graphite and a single water molecule. The graphitic layer extends over 11.789 × 11.9112 nm in a periodic box with height 15 nm. The water molecule is randomly placed with the oxygen atom 0.35 nm above the graphitic layer. We use a simulated annealing approach to determine the minimum energy configuration. This is done over a period of 50 ps and the velocities are scaled with a constant factor of 0.999 at every time-step. Two distinct minima in terms of potential energy were found which will be described in detail below.
6.3.1 The lowest energy conformation

In the lowest energy orientation, all water atoms are aligned collinearly on the line connecting two opposing carbon atoms of an aromatic ring. We call these two atoms \( C_1 \) and \( C_2 \), see Figure 6.1. The oxygen atom is almost centered on top of the aromatic ring at a height of 2.947 Å slightly displaced towards \( C_1 \). The distance between \( C_1 \) and the oxygen atom is 3.401 Å and 3.430 Å between \( C_2 \) and the oxygen atom, respectively. The hydrogen-oxygen bond which points in the direction of \( C_2 \) is aligned parallel to the graphite sheet. The other one is pointing towards \( C_1 \) and the alignment of the hydrogen, oxygen and \( C_1 \) are close to collinear, see Figure 6.1.

The total interaction energy in this orientation amounts to -11.455 kJ mol\(^{-1}\) of which -5.475 kJ mol\(^{-1}\) is contributed by the Lennard-Jones interaction energy. This orientation has an intriguing similarity with the orientations obtained from ab-initio simulations [93] but it is in contradiction to more recent and more rigorous quantum mechanical calculations [195].

6.3.2 The local minimum energy configuration

The second local minimum energy configuration is illustrated in Figure 6.2. In this configuration the oxygen atom is centered at a height of 3.007 Å above of an aromatic ring and the water dipole is pointing orthogonally away from the graphite. The water atoms are aligned collinearly on the line connecting the two midpoints of two opposing carbon-carbon bonds within an aromatic ring. The total inter-
action energy amounts to -10.054 kJ mol\(^{-1}\), of which -5.906 kJ mol\(^{-1}\) are contributed by the Lennard-Jones interaction energy.

### 6.4 The contact angle of a polarizable water droplet on graphite

In a recent study, Werder et al. [332] reported a linear relationship between the contact angle of a water droplet on graphite and the interaction energy of a single water molecule with graphite. This relationship was used to calibrate the Lennard-Jones interaction parameters. This relationship depends on the functional form of the interaction potential in use [151, 249]. Therefore the fitting procedure [332] is repeated.

We followed the procedure of Werder et al. [332] in this work: a droplet of 2500 RPOL [70] water molecules is equilibrated on a 11.789 × 11.9112 nm stacked double layer of graphite with an interlayer distance of 3.4 Å. The computational cell is 10 nm in the dimension orthogonal to the graphite surface and we used a 64 × 64 × 64 grid for the SPME routines. The system was initially equilibrated for 100 ps with a Berendsen thermostat with a coupling constant of 0.1 ps. It was then further relaxed during 200 ps. After equilibration, samples were taken every 0.2 ps during 400 ps and the contact angle was evaluated according to [332].

In Figure 6.3 the measured contact angles are plotted with respect to the energy parameter of the Lennard-Jones interaction \(\epsilon_{CO}\). The uncertainty of the measurements was assessed using four-fold cross-validation and was estimated to be two degrees. A linear fit predicts the following dependence of the contact angle \(\Theta\) on the energy parameter of the Lennard-Jones interaction potential \(\epsilon_{CO}\) near

---

**Figure 6.2:** Side (left) and top (right) view of the locally optimal geometry for a single water molecule on graphite. The oxygen atom is centered on top of an aromatic ring.
CHAPTER 6. POLARIZABILITY EFFECTS IN THE WATER-CARBON INTERACTION

Figure 6.3: Contact angle of polarizable RPOL water on a polarizable stacked double layer of graphite as a function of the carbon oxygen Lennard-Jones interaction energy. A linear fit predicts the experimental contact angle of 86° for $\epsilon_{CO} \approx 0.41$ kJ mol$^{-1}$.

Therefore, for $\epsilon_{CO}$ of 0.41 kJ mol$^{-1}$ the experimental contact angle of 86° should be recovered.

### 6.5 Water structure at the polarizable surface

The inclusion of polarizability changes the properties of a single water molecule on a graphite surface significantly. The extent to which this effect carries over to bulk water in the vicinity of a polarizable graphite surface is not clear. To elucidate this issue, we consider the canonical system of water in between two graphitic sheets and assess the water structure in their vicinity.

The system consists of two graphite sheets, 5.34 nm apart, with 1024 water molecules in between. This system is contained in a computational box of $2.456 \times 2.5524 \times 12.0$ nm and the graphite sheets are periodic in the first two dimensions. The electrostatic interactions are evaluated using SPME with a $32 \times 32 \times 64$ grid. All other parameters are taken as described earlier.
The system is equilibrated using a Berendsen thermostat during 100 ps with a coupling time of 0.1 ps. The system is then further relaxed during 100 ps. After relaxation the system is simulated in the NVE ensemble and samples are taken every 0.2 ps during 800 ps.

The density profile for oxygen when polarizability is considered is virtually indistinguishable from its non-polarizable counterpart. This is not the case with the hydrogen density profiles. The density maxima are slightly more pronounced for the polarizable model, see figure 6.4. Furthermore, the hydrogen density profile for the polarizable force field shows a small additional peak close to the surface. These differences, albeit minute, suggest a reorientation of the water molecules close to the surface such that the hydrogen atoms of the water molecules tend to point more towards the surface.

We now validate the hypothesis of a water reorientation close to the wall. For this purpose we consider the distribution of the cosine of the angle $\Phi$ formed between
the surface normal and the water dipole. Additionally, we consider the cosine of the angle $\Psi$ formed between the surface normal and the line joining the hydrogen atoms of a water molecule. The probability density distributions are measured for slabs of width 0.3 Å. Distributions are shown in Figure 6.5 for slabs centered at 2.65 Å, 2.95 Å, 3.25 Å and 3.55 Å from the surface. A noticeable reorientation is limited to a zone of less than 1 Å, i.e. to the slabs at 2.65 Å, 2.95 Å, 3.25 Å. For the slab at 3.55 Å the effects are negligible. We confirm that the water dipoles have a preferential alignment parallel to the surface at short distances from the wall if polarization effects are neglected for the graphite [327]. When polarizability is considered the density distribution of $\cos(\Phi)$ is shifted towards values close to -1, i.e. the dipole moment is more likely to point into the surface. For $\Psi$ we notice a shift towards a cosine of approximately 0.8 ($35^\circ$) in the layer closest to the graphitic surface. Further away from the surface, the effect is weak if not negligible. Summarizing, we find a reorientation in the slab closest to the surface that corresponds to a shift towards the optimal orientation of a single water molecule on graphite.

At distances farther than 3.25 Å away from the graphite surface, the water orientations predicted by either model are almost indistinguishable. The water orientation at these distances agrees well with the orientations reported by Lee et al. [186] and Wallqvist [325]. The influence of surface polarizability is therefore locally very limited and negligible at practical distances from the graphite surface.

To quantify the influence of surface polarizability we choose an unphysical scenario. Reference simulations of polarizable water close to a non-polarizable graphite wall showed orientational profiles which were indistinguishable from the results neglecting polarizability. Therefore, the changes in the orientation have to be fully attributed to the polarizability of graphite and not to the use of a polarizable water model.

### 6.6 Discussion

The inclusion of polarizability changes the water graphite interaction potentials. Fitted Lennard-Jones interaction parameters are used that to reproduce the experimental contact angle of water on graphite. The quantum mechanical predictions of Feller and Jordan [93] on the optimal orientation of a single water molecule on a graphite sheet are recovered. Although this configuration is in contradiction with recent more rigorous results by Lin et al. [195] it is of significant interest, as it is consistent with the optimal geometry of a single water molecule interacting
Figure 6.5: Distributions of the cosine of $\Phi$ (left) and $\Psi$ (right). $\Phi$ is the angle between the water dipole and the surface normal, $\Psi$ is the angle between the line connecting the two hydrogen atoms of a water molecule and the surface normal. Distributions are plotted for a polarizable force field (dotted) and a non-polarizable force field (solid). Graphs are presented for bins at 2.65 Å (top), 2.95 Å, 3.25 Å and 3.55 Å (bottom) from the surface with a bin width of 0.3 Å.
with benzene [93, 195] The interaction energy of \(-11.455 \text{ kJ mol}^{-1}\) is closer to the quantum mechanically predicted one of \(-12.14 \text{ kJ mol}^{-1}\) [195] than in most previous interaction potentials [332]. The difference with regards to the quantum mechanically predicted interaction energy of \(24.3 \text{ kJ mol}^{-1}\) of Feller and Jordan [93] has to be considered with care. It has been reported by Karapetian and Jordan [165] that the interaction energy in this study is most likely overestimated due to a large uncertainty in the basis set superposition error.

The influence on the bulk water phase close to graphite are limited. A significant effect is only reported for the layer of water molecules closest to the graphite surface. The computational cost of a self-consistent treatment of polarizability is large compared to the cost of non-polarizable simulations. We therefore recommend to consider the use of a polarizable graphite model only for studies where the surface-to-volume ratio is substantial, i.e. systems that consider single or double layers of water molecules in the vicinity of graphite. If polarizability is to be considered, we recommend, however, to revise the present model to reproduce the correct orientation of a single water molecule on graphite [195]. Such a model should be used in studies where the actual water orientation at the surface is important. In this respect a simplified approach might suffice in doing so [212]. We recommend the modeling approach of Werder et al. [332] for systems where the focus is on the bulk water phase.
Single-walled carbon nanotubes (SWCNTs) are essentially rolled up graphite sheets. This results in similarities in terms of structure and physical properties. There are however also significant differences between graphite and CNTs. Recently, Dumitrića et al. [86] reported on the presence of a significant static dipole moment across carbon nano shells. In particular, strong dipole moments have been found in CNTs. The dipole moments arise due to the strain imposed from the bending of the graphene sheet into the tubular shape of a CNT. Dumitrića et al. [86] found that they are inversely proportional to the tube radius

\[ \mu = \frac{0.82 \text{ Debye} \, \angstrom}{R}. \]  

(7.1)

Here, the dipole moment \( \mu \) is given in Debye and the radius in \( \angstrom \). Thus, the strength of the dipole moments increases for smaller CNTs and possible effects are expected to be more pronounced for small tubes. In contrast to dynamically induced dipole moments (see chapter 6 and [212]) or the quadrupole moment of graphite [327] a permanent dipole moment has so far not been considered and may have a significant influence on the system. This has to be validated before specific applications of CNTs can be studied in detail.

In this chapter, we study the influence of the static dipole across a nanotube shell on the surrounding fluids. Here we consider water. The effect being dependent on the size of the CNT, two different setups are considered. First, we study the system proposed by Hummer et al. [140]. A narrow CNT serves as a model for a nanometer size pore. Second, we extend the work of Werder et al. [331, 332] by studying the effect of a static dipole on the contact angle of water droplets inside CNTs.
CHAPTER 7. THE CURVATURE INDUCED STATIC DIPOLE MOMENT OF CARBON NANOTUBES: INFLUENCE ON TRANSPORT, WETTING AND WATER STRUCTURE

7.1 The effect of the static dipole moment on water inside small carbon nanotubes

Understanding the interaction of water with small CNTs is essential for the rational design of nanopores for water transport and has been the subject of intense research efforts [23, 108, 140, 327, 331, 341]. The simple structure of CNTs allows to reduce the complexity of the system which favors new insights on a conceptual level [140]. Despite the hydrophobic nature of CNTs [327], Hummer et al. first demonstrated that a short CNT could fill with a single line of water molecules and could therefore act as a possible model system for biological channels [140]. Subsequent studies quantified the influence of different system properties, e.g. the influence of the pore diameter, the tube helicity [329], its length and the water carbon interaction [324]. More recent studies have focused on the filling and the ordering of water molecules inside the CNT. Mann and Halls [209] reported on proton transport through a CNT and Dellago et al. [75] showed that defects within the quasi one-dimensional hydrogen bonded chain of water molecules could significantly alter the rate of proton transport through a CNT. Zhu and Schulten [352] quantified this effect using a statistical analysis and considered the influence of charged atoms in the tube wall. They reported on a charge distribution which was equivalent to having dipole moments parallel to the tube axis.

In this section we model the CNT curvature-induced dipole moment following the work of Dumitrića et al. [86]. We report on the results of MD simulations of narrow finite-length SWCNTs immersed in water. We show that this dipole moment generates a non-uniform electric field which changes the energy landscape in the CNT and alters the water conduction process. The simulations show an increased filling and a geometrical rearrangement of the single-file water chain inside the tube in contrast to similar studies [140, 352]. Subject to the dipole moment water molecules change their orientation and a water molecule within the chain acts as a hydrogen bond donor to both its neighbors, i.e. an $L$-defect is created [75], see figure 7.1. The $L$-defect may interfere with the ability of CNTs to transport protons, similar as in aquaporins [293], because fast proton transfer according to the Grotthuss mechanism becomes impossible [75]. The analysis of the water energetics and structural characteristics inside and in the vicinity of the CNT helps to identify the role of the dipole moment. Furthermore, their understanding allows to suggest possible mechanisms for controlled water and proton transport at the nanoscale.
7.1. THE EFFECT OF THE STATIC DIPOLE MOMENT ON WATER INSIDE SMALL CARBON NANOTUBES

Figure 7.1: (a) In a quasi-onedimensional hydrogen bonded chain of water molecules each water molecule acts as a hydrogen bond donor to one of its neighbors and as an acceptor to the other. (b) The central water molecule acts as a hydrogen bond donor to both of its neighbors forming an L-defect. The hydrogen bonds are indicated with dotted lines. The water molecules are represented by a set of three circles. Black and white circles represent oxygen and hydrogen atoms.

7.1.1 The model

MD simulations a short CNT are performed. It is in armchair configuration with a chiral vector of (6,6) corresponding to a tube of diameter 0.81 nm. The tube is 1.34 nm long. This corresponds to the CNT originally studied in Ref. [140]. The present model employs the SPC/E [24] water model and describes the nonpolar interaction between water and carbon using a Lennard-Jones potential between the carbon and oxygen atoms. Interaction parameters proposed by Werder et al. [332] are used: $\epsilon_{CO} = 0.392 \text{ kJ mol}^{-1}$ and $\sigma_{CO} = 0.319 \text{ nm}$. These parameters were found to reproduce the experimental contact angle of water on a graphite surface of 86°. The Lennard-Jones interactions are truncated at a cutoff distance of 1 nm. The electrostatic interactions are calculated using the Smooth Particle Mesh Ewald (SPME) method [90]. The parameter determining the decay of the real part of the interaction potential for the SPME method is set to $3.0 \text{ nm}^{-1}$. The charges are interpolated using fourth order B-splines to a mesh with $80 \times 48 \times 16$ grid points. Given the size of the computational box of $13.614 \times 9.498 \times 3.166 \text{ nm}$, this results in a maximal grid spacing of less than 0.2 nm.

The curvature induced static dipole moment per carbon atom is calculated according to the relationship proposed by Dumitriča et al. [86], see equation 7.1. For a CNT with a diameter of 0.8 nm the dipole moment is 0.2 Debye per carbon atom. We model the static dipole moment across the CNT surface by placing two particles with charges of 0.5 e and -0.5 e displaced by $4.16 \times 10^{-3} \text{ nm}$ radially in-
CHAPTER 7. THE CURVATURE INDUCED STATIC DIPOLE MOMENT OF CARBON NANOTUBES: INFLUENCE ON TRANSPORT, WETTING AND WATER STRUCTURE

Figure 7.2: The setup used to model the curvature induced static dipole moment. Two charges of equal size \( q_d \) but opposite in sign are placed at equal radial distance \( l \) from a carbon atom in the tube wall of a CNT (dashed line) with radius \( R \).

side and outside the CNT from each carbon atom. A sketch of the setup is given in figure 7.2. This approach allows for the treatment of all electrostatic interactions within the standard SPME method. The relative error between the interaction energy of a point dipole interacting with a charge at distances larger than 0.2 nm and the current model is smaller than 0.05 %. This is less than the uncertainty of the underlying model [86].

7.1.2 Simulation setup

The CNT is placed in the center of the computational box and 2464 water molecules are placed in a slab configuration around the CNT with the free surfaces parallel to the tube axis, see figure 7.3. Atmospheric conditions are ensured throughout the simulations by the free surfaces of the water slab. This approach avoids possible artifacts introduced by a barostat through the calculation of pressure and the large empty volume in the interior of the CNT. The orientation and the position of the tube are kept fixed in the center of the computational box throughout the simulation. The center of mass of water is constrained in order to prevent the water slab from expelling the essentially hydrophobic CNT after long simulation times. The system is equilibrated for 0.2 ns at a temperature of 300 K using a Berendsen thermostat with a coupling constant of 0.1 ps. After equilibration, the thermostat is turned off and the simulations are run in the microcanonical ensemble for approximately 12 ns with samples collected every 0.2 ps.
Two setups are considered to assess the effect of the static dipole moment:

- **Case P**: A 1.35 nm SWCNT immersed in a slab of water without modeling of the dipole moment.

- **Case D**: A 1.35 nm SWCNT with a static dipole moment modeled as described in the previous section. All other parameters of the set-up are the
same as those of case P. Furthermore, we consider simulations of CNTs with lengths of 1.5 and 2.7 nm to study the influence of the length on the filling of the CNT.

7.1.3 Transport and filling

Set-up $P$ is validated by monitoring water conduction in a SWCNT immersed in water and comparing it to the original work of Hummer et al. [140]. Figure 7.4a shows the evolution of the number of water molecules inside the CNT during the course of the simulation. The water occupancy of the CNT fluctuates with sharp transitions between two distinct states: empty and filled. This is consistent with results reported by Hummer et al. [140]. However, in [140] the CNT was filled 11 % of the time while we observe a filled state during 25 % of the 12 ns simulation. This increase is attributed to the energy of the water-carbon Lennard-Jones interaction potential [332] used in the present study. It is 45 % stronger than the one used in [140]. The filling of the CNT is found to be very sensitive to the interaction potential. An increase of 10 % for the present carbon-oxygen Lennard-Jones interaction energy results in a permanent filling with occupancy graphs similar to those shown in figure 7.4b. This result is consistent with results reported by Hummer et al. [140] and Waghe et al. [324].

During the course of the simulation 66 water molecules were found to enter the CNT from one side and leave on the other. The transport of water molecules through the tube amounts to approximately 22 molecules per nanosecond while the tube is filled. This number is within the range of transport rates reported by Hummer et al. [140], who observed an average of 17 molecules per nanosecond and variations between 9 and 30 molecules per nanosecond. In summary, water molecule flow rates and occupancy of the CNT are in quantitative agreement with the results reported in [140] and [324] and there is similar qualitative behavior regarding the emptying and filling of the nanotube.

In case $D$ the water molecules fill the CNT immediately and the CNT remains filled for the entire simulation, see figure 7.4b. Only very short intervals of lower occupancy are observed, see figure 7.4b. The rate of transport of water molecules through the CNT amounts to 10 molecules per nanosecond. This rate of transport is lower than in case $P$. We attribute the strong preference for the filled state in this case to an increased interaction of the water molecules with the electric field generated by the dipole moment distributed across the short nanotube. This is illustrated in figure 7.5. The field is strongest toward the tube entrances with the leading components in axial direction, pointing into the tube. The axial compo-
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![Graphs showing the time history of water molecules inside a CNT](image)

Figure 7.4: (a) and (b) show the time history of the number of water molecules inside a 1.35 nm CNT as a function of simulation time. In (a) the CNT is modeled without and in (b) with a static dipole moment. (c) shows the number of water molecules in a 2.7 nm CNT with a dipole moment. The top part shows the occupancy in the whole CNT, whereas the lower part shows the occupancy in the central 50% of the same tube. The coinciding emptying events in both plots shows that the breaking of the water chain occurs in the center of the tube and not at the ends.

...ments vanish towards the center of the tube and the electric field becomes radially oriented.
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Figure 7.5: The electric field due to the static dipole moment across the nanotube wall. It is strongest 0.004 nm outside the tube entrances and points into the CNT along the axis of the CNT. The axial components towards the middle of the tube and the field becomes radially oriented. The positions of the carbon atoms are indicated by black circles, the field direction and magnitude by arrows and the field force by red isolines.

7.1.4 The water structure inside the carbon nanotube

The radial density profiles for oxygen and hydrogen atoms inside the CNT, exhibit small differences between case P and D, see figure 7.6. The hydrogen density is slightly shifted towards the center of the tube and the oxygen density is slightly shifted towards the tube wall.

The dipole moment, however, significantly affects the orientation of the water molecules inside the CNT and the orientation of the water dipole moment relative to the tube axis, see figure 7.7. In case P a unidirectional hydrogen bonded chain is formed. It is similar to the one reported in [140, 309] with a high probability of the orientation of the water dipole moment to form angles of 30° and 150° with the tube axis. The oxygen-carbon interaction acts so as to confine the water oxygens to a cylinder with radius of 0.1 nm, see figure 7.6. The orientation of the water dipole is determined by the hydrogen bonding in the water chain inside the nanotube, see figure 7.8a.

In case D the presence of the electric field triggers an orientational change within the chain of water molecules. The peaks of the original probability distribution (figure 7.7) are shifted to 25° and 155°. Additionally, there is a peak at around 90° which we attribute to the presence of an L-defect [75]. This is confirmed
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Figure 7.6: Radial number density distributions [nm$^{-3}$] within the tube are shown for oxygen (solid lines) and hydrogen atoms (dashed lines) for a CNT without (squares) and with (circles) a static dipole moment. The radial number density distribution of oxygen atoms shows a maximum around 0.09 nm, whereas the distribution for hydrogen has a clear maximum at the tube center with a shoulder towards larger radii.

by observations of water molecules inside the CNT forming an $L$-defect, see figure 7.8b. This defect has significant influence on the proton transport rates in quasi one-dimensional water chains [75, 352].

The angle of the water dipole moment changes across such an $L$-defect from approximately $30^\circ$ on one side to about $90^\circ$ at the defect and approximately $150^\circ$ on its other side, see figures 7.7 and 7.8b. The shift in the probability distribution between case $P$ and case $D$ is mainly due to a reorientation of the water molecules near the entrance of the nanotube while the peak at $90^\circ$ is due to the presence of the $L$-defect at the center of the tube.

The formation of an $L$-defect is energetically unfavorable when considered on its own. The difference in the interaction energy between three water molecules in a single hydrogen bonded chain and three water molecules forming an $L$-defect is found to be on average 8 kJ mol$^{-1}$. However, favorable overall energetics are obtained when the interactions of the CNT dipole moment with the water molecules near the entrance of the CNT are also considered. Even a single water molecule in the electric field at the entrance of the tube experiences a reduction in potential...
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Figure 7.7: Probability density distribution of the angle between the water dipole moment and the tube axis. The asymmetric shape in the case without a dipole moment (solid line) is due to the limited sample size. For an angle of $0^\circ$ ($180^\circ$) the water dipole is parallel (antiparallel) to the tube axis, for an angle $90^\circ$ it is perpendicular to the tube axis. An additional peak at around $90^\circ$ is observed for the CNT with a static dipole moment (dashed line). It is attributed to the presence of an L-defect.

Figure 7.8: Typical water organization inside a CNT without (a) and a CNT with a static dipole moment (b). In (a) the water molecules form an uniformly oriented hydrogen bond chain. In (b) the directionality is opposite towards either end and in the middle a water molecule donates two hydrogen bonds and accepts none, i.e. it forms an L-defect.
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energy of about 16 kJ mol\(^{-1}\), if its dipole is pointing away from the tube.

At the entrance the CNT dipole moment reaches its maximum strength \(3.5 \text{ V nm}^{-1}\) and it affects strongly the nearby water molecules orienting them along the axis of the CNT while pointing to the opposite direction of the electric field. The interaction of the reoriented water molecules with the electric field is the main contributor to the change in interaction energy leading to the strong preference of the filled state (figure 7.4b) and the presence of the \(L\)-defect at the middle of the nanotube.

The findings presented here are consistent with the results from a recent study by Vaitheeswaran et al. [309]. In their work it was shown that for a constant external electric field of \(1 \text{ V nm}^{-1}\) a filled CNT is energetically more favorable than an empty one. Subject to such a field the water dipoles are collectively oriented against the direction of the electric field. The electric field induced by the nanotube dipole results in a re-orientation of the water molecules, similar to the effect of an external electric field, albeit in opposite directions at each entrance. Hence, two chains of water dipoles with opposite orientations are favorable in either half of the nanotube. In the center of the tube the electric field is weakest with its leading components in the radial direction. This favors the alignment of a water molecule with its dipole normal to the tube axis. With a water molecule in this orientation in the middle of the tube, two hydrogen bonded chains with opposite orientation can be accommodated in either half of the nanotube. Hence, the resulting \(L\)-defect in the center of the nanotube accommodates the energetically favorable water orientations at each end of the tube.

The axial number density profiles of the oxygen and hydrogen atoms shown in figure 7.9 indicate increased structuring of the water molecules inside the tube for case \(D\) as compared to case \(P\). This is attributed to a change in sign of the gradient of the electric field at the tube entrances, see figure 7.5. Outside this region, water molecules with their dipole moment pointing away from the tube are pulled towards the tube. Inside the tube, water molecules with their dipole moment pointing out of the tube are pushed towards the end. This results in an effective compression of the water molecules at the entrance region of the tube resulting in the aforementioned structuring. This structuring is more pronounced for shorter nanotube lengths. The 1.35 nm tube accommodates an even number of six water molecules inside the tube, see figure 7.9a. Thus, on average there are two water molecules around the tube center that are equally likely to participate in an \(L\)-defect with the location of the \(L\)-defect switching dynamically between the two. This is demonstrated by the axial number density profile for the oxygen atoms, which does not show a density peak at the the tube center, see figure 7.9a.
Figure 7.9: (a) Oxygen (solid lines) and hydrogen (dashed lines) number densities are shown inside a CNT along the tube axis for a CNT of 1.35 nm length. The CNT is modeled without a dipole moment (squares) and with a dipole moment (circles), respectively. The oxygen density profile shows six peaks in the presence of a dipole compared to five in its absence. For the tube with a dipole, the hydrogen density peaks are staggered with regard to the oxygen density peaks. The lack of a peak in hydrogen density at the center of the tube indicates the presence of an L-defect. The number densities in (b) and (c) are for a CNT with a dipole moment of 1.5 nm and 2.7 nm length, respectively. The results for the 1.5 nm tube are similar to the results obtained for the 1.35 nm tube. For the 2.7 nm tube, distinct maxima in the oxygen density are present towards the tube ends and become less pronounced towards the center of the tube. Towards the center of the tube the local density maxima for hydrogen disappear.

The hydrogen density profile lacks a peak between the two off-center oxygen density peaks. A slightly longer tube (1.5 nm) with the same dipole moment fits an additional molecule, containing a total of seven water molecules, see figure 7.9b. This results in a density peak for oxygen atoms in the center of the tube while symmetrically around it two hydrogen density peaks indicate the position of the
For short nanotubes the axial components of the electric field directly determine the water structure throughout the tube. This is reflected by an augmented structure within the oxygen density, that is found to persist throughout the 1.35 nm CNT. The oxygen density structure in the 1.5 nm CNTs is not significantly different although a relative reduction of structuring is observed. However, for nanotubes longer than 2 nm the axial components of the electric field affect the water structure only near the entrance of the nanotube. Thus the peaks in the oxygen density profile for the 2.7 nm long CNT persists near the tube ends while in the center of the tube the density peaks become less expressed, see figure 7.9b and figure 7.9c.

The 2.7 nm CNT exhibits full occupancy for most of the time, but we also observe intervals where about half of the water molecules leave the tube, see figure 7.4c. The partial emptying is primarily affecting the occupancy in the middle of the tube as observed by comparing the occupancy of the whole tube with the occupancy of the central 50%, see figure 7.4c. This reduction in occupancy for the long nanotube, is consistent with the weaker axial component of the electric field at the center of the nanotube.
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7.2 Dipole effect on contact angles of droplets in large carbon nanotubes

The applications which have been suggested for CNTs is not limited to small CNTs and their use as nanometer size pores. In fact, most applications were suggested considering larger CNTs. For example, to transport biologically relevant molecules the tube diameter has to be at least in the order of 1.5 nm [341]. Such CNTs could be used as a nanometer size syringe [134]. It is therefore mandatory to study the influence of the static dipole moment across carbon nano shells also for large CNTs.

Here, we present an extension of the previously presented MD simulations of water in CNTs considering the curvature induced static dipole moment. Water inside relatively large single-walled and multi-walled CNTs is considered. A small influence on the contact angle of water droplets inside CNTs is reported. In the course of the same simulations, we also find significant dependence of the water carbon contact angle on truncation of long range electrostatics.

7.2.1 The model

The water molecules are modeled using the SPC/E model [24] in all but two validation simulations which employ a flexible model (SPC/F) [297]. The CNTs are modeled rigidly by fixing the positions of the carbon atoms. Alternatively and for validation purposes, the CNTs are modeled using a Morse potential for the bonds, a harmonic angle potential and a twofold torsion potential [327].

The nonbonded interactions between carbon and water are modeled using a Lennard-Jones type interaction potential between carbon and oxygen with $\epsilon_{CO} = 0.392 \text{ kJ mol}^{-1}$ and $\sigma_{CO} = 0.319 \text{ nm}$ [332]. The Lennard-Jones interactions are truncated at a cutoff distance of 1 nm. The Coulomb interaction is calculated using the smooth particle mesh Ewald (SPME) method [90]. To consider truncation induced artifacts, the Coulomb interaction is also considered in a smoothly truncated cutoff scheme as described in [190] with a cutoff of 1 nm. For validation purposes we also reproduced simulations as presented in [331] with the interaction potential presented by Bojan and Steele [36], with $\epsilon_{CO} = 0.3135 \text{ kJ mol}^{-1}$ and $\sigma_{CO} = 0.319 \text{ nm}$ and considering a flexible water model.

The dipole moment of the carbon atoms is modeled in the same way as in the previous section, we displace two charges of 0.5 e but opposite sign radially from the carbon atom, (see section 7.1.1). We also estimate the cumulative effect of the dipole moment in multi-walled carbon nanotubes (MWCNTs). This is done by
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![Graph](image)

Figure 7.10: Comparison of the interaction energy for the dipole-dipole interaction (dashed line) to the magnitude of the Lennard-Jones interaction (solid line) [332], for a CNT with 5 nm in diameter. This has been computed one water molecule and one carbon atom. Additionally the interaction with a fivefold dipole across the tube wall is shown (dotted line).

Considering single and double walled CNTs with a two-, five- and tenfold of the predicted dipole moments. In these cases, the charges are modified to be 1 e, 2.5 e and 5 e respectively and the radial displacement is kept constant.

The interaction energies for a single water molecule and a carbon atom due to the Lennard-Jones interaction and the interaction energy between the water dipole and the dipole moment of a single carbon atom are comparable in strength, see figure 7.10. This comparison is based on a CNT with a diameter of 5 nm and we used the Lennard-Jones parameters of Werder et al. [332]. Furthermore, the dipole across the CNT wall and the water dipole of the SPC/E water model are assumed to be aligned. Different alignments cause the dipole-dipole interaction energy to decrease rapidly due to its angle dependence.

7.2.2 Simulation setup

The simulation setup is motivated by Werder et al. [331]. A SWCNT in zigzag conformation with a diameter of 5 nm, i.e. a (64,0) CNT, is filled with a droplet of water. For the droplet 2112 water molecules are initially placed on a 12 layer cubic lattice of cylindrical shape. This results in an initially flat, 2.37 nm thick cylindrical drop, wherein the orientation of the water molecules is random. The simulation cell spans $10 \times 10 \times 14.0382$ nm, and the CNTs extend periodically through the simulation cell along the third dimension.
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The box size is reduced to 10.2096 nm in the direction of the tubes when double walled CNTs are considered. The tubes are set up concentrically in the middle of the box. The interior tube is kept as a (64,0) CNT, whereas the exterior tube is modeled as a (72,0) CNT, see figure 7.11.

Figure 7.11: The initial conditions used for the simulations of MWCNTs consist out of a double walled CNT (64,0)/(72,0) filled with a drop of water, where the water molecules are initially placed on a cubic lattice with 12 layers. Only a part of the CNT is shown for visualization purposes.

In *ab-initio* simulations, it has been found that the presence of the second CNT does not significantly influence the static dipole moment across the CNT shell. The dipole moment is reduced by less than 5% with regard to its original strength. The effect due to a static dipole moment in MWCNTs can therefore be modeled based on an additive representation of the relationship (7.1) presented earlier in this chapter.

The SPME parameter determining the decay of the real part of the interaction potential is set to 3.0 nm\(^{-1}\) and the interpolation is performed with fourth order B-splines. The grid spanning the computational box consists of 64 grid points in each dimension, resulting in a maximal grid spacing of 0.22 nm.

During the first 4 ps of the simulation the system is coupled to a Berendsen thermostat at a temperature of 300 K. Then the system is further equilibrated dur-
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ing 196 ps. In the second part of the equilibration the thermostat is switched off. Statistics are then collected during 200 ps in the microcanonical ensemble with samples taken every 0.04 ps.

7.2.3 Diagnostics

The contact angle is evaluated as described in Werder et al. [332], based on an approach presented by Nijmeijer et al. [233]. A density profile is obtained from the simulation trajectories for the drop inside the CNT through a cylindrical binning using constant volume bins. This is followed by a two step procedure to extract the contact angle from this profile. First, the location of the equimolar dividing surface is determined for each vertical set of bins of the drop by fitting a sigmoid through each slab [74]. Second, a circular best fit through these points is extrapolated to the graphite surface where the contact angle is measured. For this fit, the points lying within 0.75 nm of the tube wall are excluded in order to avoid the influence of layering close to the tube wall on the contact angle measurements. Furthermore, points that belong to fitted density profiles which predict bulk densities lower than 500 or higher than 1200 kg m\(^{-3}\) are excluded. The procedure is illustrated in figure 7.12.

7.2.4 The contact angle of a water droplet in single walled carbon nanotubes

The present simulations of water droplets inside SWCNTs — an overview of which is shown in table 7.1 — are validated against a similar case presented by Werder et al. [331]. They used a flexible water model and their calculation was based on a water carbon Lennard-Jones potential from Bojan and Steele [36]. In contrast, we intend to use the rigid SPC/E water model and a Lennard-Jones interaction potential which was fitted to reproduce the contact angle of water on a graphite surface [332]. In order to quantify the influence of each of these differences a series of simulations is performed which is summarized in table 7.1.

Results of the validation run using a flexible tube, the flexible water model and the interaction potentials from Bojan and Steele [36] compare very well to the ones published in [331] with a deviation of less than 5° ([331]: 107.6°, our result: 112°). In two further simulations with the same Lennard-Jones potential [36] we confirm that the change from a flexible SPC water model (SPC/F) [297, 331] to the rigid water model (SPC/E) [24] and the change from a flexible to a rigid tube do not influence later findings. The results show a change of less than 3° in the
Figure 7.12: Isodensity profiles of a drop inside a CNT with contact angle $\Theta$. The distance from the tube axis is denoted by $r$ and $z$ indicates the vertical distance from the drop center of mass. The contact angle is measured at the tube walls (dashed lines). A layer of 0.75 nm is excluded from the fitting (dotted line). Points in the equimolar dividing surface are determined (circles) and used to fit a circular drop outline (solid line).
contact angle, which corresponds to the uncertainties in the simulation results. The accuracy estimation presented here and later on are based on a comparison of the contact angle on either side of the water droplet.

A significant decrease of approximately 10° in the contact angle is observed when changing the parameters of the Lennard-Jones potential for the water carbon interaction to the ones proposed by Werder et al. [332]. This shows that the major differences in the contact angle in the simulations which are presented here and the ones presented in [331] arise due to the change in the Lennard-Jones potential.

We study the influence of the static dipole across the CNT wall in the framework of SPME. Upon transition from truncated electrostatic interactions to SPME the contact angle is lowered by about 3°. Note that this is still for a CNT without a static dipole moment across its shell. The contact angle remains virtually unaltered when introducing a static dipole moment. This finding holds even if the static dipole moment is increased to a 10 times of its predicted value. The increased dipole is considered to have an upper bound for the effect due to the cumulative dipole of multiple carbon shells as in MWCNTs and to estimate the susceptibility to model uncertainties. The interaction energy between the tube wall and the water, and the forces acting on the water molecules in the interior change significantly when considering such a strong dipole. Based on [332] we would expect a significant change in the contact angle. This is, however, not the case.

The aforementioned results are checked for convergence of the SPME method in terms of the number of grid points. Upon doubling the number of grid points the total energy of the system changes by less than $10^{-4} \%$ and remains virtually constant thereafter, i.e. it changes only by less than $10^{-5} \%$ upon doubling the number of grid points again. Doubling the size of the computational cell in the directions orthogonal to the tube axis ensured that periodic images of the drop would not alter the results. The number of grid points in these directions is also doubled and the change in the total interaction energy is found to be less than $10^{-4} \%$.

In the framework of smoothly truncated electrostatics the introduction of a static dipole moment leads to a lowering of the contact angle. At a tenfold value of the predicted dipole, wetting behavior of the water droplet within the CNT is observed (contact angle: 63°). Note that at a tenfold dipole moment we did not observe any effect in the SPME simulations. This behavior is considered an artifact due to the truncation.

The structure of the water inside the CNT is analyzed using radial density distributions within the tube. They are shown in figure 7.13. The structuring of the water becomes more pronounced upon increasing the Lennard-Jones interaction
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Table 7.1: Influence of the dipole moment per carbon atom $\mu_C$ across the CNT shell on the contact angle of a water droplet inside a CNT. The Lennard-Jones parameters are taken from Bojan and Steele [36] and Werder et al. [332]. The tube is modeled flexible, using a bond, angle and torsion potential or rigid by freezing the carbon atoms.

energy and the layering of water molecules close to the tube wall is much more pronounced. The first peak and the first well become more pronounced upon increasing the interaction strength. The introduction of a dipole moment across the tube shell however reduces the structuring of the radial density distribution, see figure 7.13.

7.2.5 The contact angle of water droplets in multi-walled carbon nanotubes

We compare water droplets confined in MWCNTs to the SWCNTs simulations in the previous section. We first consider double-walled CNTs. Again, we assess the effect due to a static dipole moment and quantify its influence on the contact angle of a water droplet within the CNTs. Radial density distributions and a orientation of the water molecules close to the tube wall are reported. The detailed simulation setup and the modeling of the dipole moment is as before. We simulated the systems with SPME, the tubes are kept rigid and the SPC/E water model is used. The simulation results are summarized in table 7.2.

Introducing a second tube wall in the absence of any static dipole moment lowers the contact angle significantly ($\approx 9^\circ$). This is consistent with results for water droplets on graphite [332]. Introducing a static dipole moment does not change the
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Figure 7.13: Radial density profile within the central 1.2 nm of a drop inside a CNT, orthogonal to the tube axis. Increasing the Lennard-Jones interaction strength (left) from [36] (dashed line) to [332] (solid line) results in a more pronounced layering. Electrostatics and the Lennard-Jones interactions are truncated in the left graph. Effect due to the introduction of a static dipole moment are shown, too (right). Structuring becomes less significant for the predicted dipole moment (dashed line) and even less for a tenfold (dotted line) if compared to the case without a dipole moment (solid line). These results are obtained with an SPME treatment of the electrostatics.

contact angle much, see table 7.2. We conclude that the effect of the static dipole moment is negligible. Especially if we compare it to the effect of the Lennard-Jones contribution of the second wall.

The introduction of dipole energy terms does not promote further layering and the radial density distribution within the tube remains virtually unaltered, see figure 7.2.5.

The orientation of the water molecules within the drop inside the CNT, is such that the water dipole is aligned mostly tangentially to the tube wall. This allows for an optimal interaction between the different water molecules, but not with a dipole in radial direction across the tube wall. The orientation is not significantly changed by the presence of a moderate dipole. The loss in interaction energy due to the perturbation in the water orientation is indeed not compensated by the gain in the interaction energy due to the interaction with the dipole moment of the tube wall, see figure 7.2.5. A reorientation is found only when the dipole moment reaches values which exceed the magnitude of the water dipole moment. Then the contact angle changes. In particular, when going to dipole moments of a hundredfold of the theoretically predicted value, the water wets the CNT and exhibits a contact angle close to $0^\circ$. Under these conditions also the orientation of
the water molecules changes. However, the orientational change is limited to the first layer and does not extend into the bulk liquid, see figure 7.2.5.

This may explain the differences noted in the previous section between the truncation results and the SPME results for a tenfold dipole. The smooth truncation of the potential increases the resulting force. Therefore, the effect due to the static dipole moment across the tube shell is enhanced and the behavior of the system is altered.

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Table 7.2: Influence of the dipole moment per carbon atom $\mu_C$ across the inner/outer nanotube shell on the contact angle of a water droplet inside a double walled CNT. The Lennard-Jones parameters are taken from Werder et al.[332]. The tube is modeled rigidly.
7.2. DIPOLE EFFECT ON CONTACT ANGLES OF DROPLETS IN LARGE CARBON NANOTUBES

Figure 7.14: Radial density profile within the central 1.2 nm of a drop inside a double walled CNT, orthogonal to the tube axis. Results for a tube without dipole (solid line), with the predicted dipole (dashed line) and a tenfold of the predicted dipole (dotted line) are shown. The differences between the different setups are very small.

Figure 7.15: Probability densities to find a water molecule with a specific orientation are plotted. The orientation is quantified in terms of the angle between the water dipole moment and the tube radius. Distributions are shown at distances of 0.285 nm (solid) and 0.89 nm (dashed) from the tube wall (left) and at 0.434 nm (right). The signs indicate no dipole (+), a tenfold dipole (○) and a hundredfold dipole (∗). Distributions of water orientations close to the CNT wall (left) show a tangential alignment of the water dipole moment with the tube wall. This preference decays rapidly and is not present anymore at distances of approximately 0.9 nm. A hundredfold dipole moment only results in a reorientation in the closest layer to the wall, a tenfold dipole moment has negligible effect.
7.3 Conclusions

We studied the effect of the curvature induced static dipole moment on water conduction in narrow SWCNTs and on water droplets in relatively large SWCNTs and their multi-walled counterparts.

In narrow CNTs the dipole moment induces an inhomogeneity in the characteristics of the CNT and gives rise to an axial electric field that is strongest at the tube entrances and smaller towards the middle of the tube. This field has a significant influence on both the filling behavior and the orientation of water molecule chains inside the CNT. The presence of the dipole moment results in an $L$-defect in the quasi one-dimensional water chain inside the tube. This effect could have major implications in the use of CNTs as nanoscale pores or channels [75, 352]. For example, controlled proton conduction could be achieved by suitably manipulating an external electric field superimposed on the electric field of the CNT curvature induced dipole.

Minor effects are observed for large CNTs. The influence of a static dipole moment across the nanotube shell on the contact angle remains negligible for tubes of 5 nm in diameter or larger. Since even an tenfold dipole moment does not lead to a significant change in the contact angle, a curvature induced dipole moment will not be important for multi-walled CNTs either. A change in the Lennard-Jones interaction between the tube wall and the water inside the tube is however found to be of major importance. We expect that a change in the chemical composition of the tube wall will therefore influence the contact angle much stronger than the static dipole moment across the CNT wall. Adsorbates and chemical endgroups such as hydroxyl-, aldehyde- and carbonategroups have dipole moments similar to the one of water molecules and which may protrude from the CNT. The presence of such groups may disrupt the hydrogen bond network of water and should be much more important with respect to the resulting wetting behavior of water inside CNTs. These expectations have been confirmed in a subsequent study of Kotsalis et al. [177].

We conclude that the radial dipole moment of CNTs is only important at small radii, where the dipole moment is particularly strong and where the stabilizing 3-dimensional hydrogen bond network of water is missing. The curvature induced dipole moment may therefore be neglected for CNTs that allow for bulk-like water structures inside. In CNTs, which restrict the water to pseudo 1-dimensional structures the dipole moment must be considered if quantitative results are aimed for. If CNTs are however used as handy structures for qualitative and conceptual studies on the effects of constriction, the dipole moment may be neglected, too.
Chapter 8

RNA Transport through Transmembrane Carbon Nanotubes

In this chapter we assess the viability of electrophoretic transport of RNA through carbon nanotubes embedded in membranes using molecular dynamics simulations. Doped and naked carbon nanotubes are inserted into a dodecanne membrane and a dimyristoylphosphatidylcholine lipid bilayer and we assess the electrostatic potential maps in the presence and in the absence of a transmembrane potential difference. The interaction of the lipid head groups with the single-walled-nanotube rims characterizes the structure of the electrostatic potential across the pore. The electrophoretic transport of RNA is affected by its hydrophobic interaction with membrane head groups and the nanotube and the results indicate an exponential voltage dependence of the speed of translocation.

8.1 Introduction

Many biological processes involve the transport of biomolecules across cell membranes [85, 279] and understanding transmembrane transport processes will be the key to emerging fields such as single molecule medicine and nanotechnology based medical applications. Studying relevant biological systems is usually hindered by their complexity. Transmembrane transport is controlled by membrane proteins which form transmembrane channels and transporters [214], but it may also be externally initiated, e.g. by viruses. Due to the complexity of this field conceptual approaches are needed.

In a series of recent studies Aksimentiev et al. [6, 112, 113, 124, 125] reported on the electrophoretically driven transport of DNA in nanometer size silica pore. These works report on various aspects of the translocation, e.g. the microscopic kinetics, deformations, stretching and the electric response of DNA in the pore. The insights from these studies of DNA transport in the confinement of an artificial sil-
CHAPTER 8. RNA TRANSPORT THROUGH TRANSMEMBRANE CARBON NANOTUBES

RNA transport through silica nanopores carry over to studies of DNA transport in $\alpha$-hemolysin [6, 214], a process of major biological importance. Thus, apart from providing a first step towards possible applications like DNA sequencing [182] the studies on silica nanopores contribute to the understanding of the transport of DNA and RNA in biological pores and may eventually allow for comparison with experimental results of electrophoretically driven RNA transport in $\alpha$-hemolysin [4].

CNTs [144] and their unique physical properties have motivated studies on many novel applications [204, 264]. Their structure suggests that nanotubes may function as nanometer size syringes or pores in biological membranes and they could stabilize pores formed by electroporation. CNTs have been suggested to be used for DNA gene delivery [238] and first studies on the toxicity of CNTs show promising results, as intravenously administered CNTs were found to leave the body quickly [280]. Recent experiments also report on the insertion of single-stranded DNA into single-walled CNTs [236].

But not only the possible application of CNT based pores is of major interest. It has been shown that membranes and pore structure are important factors in transmembrane transport [73]. CNT based pores have a well defined structure and may be considered the canonical model for a nanometer size pore. Due to this prototypical nature of CNT based pores conclusions on biological pores may be drawn and promote the understanding of biological processes.

Recently, the insertion of nanometer size tubes into membranes was assessed by means of coarse grained MD simulations [202, 203, 287] and their influence on the structure of the membrane was quantified [232, 286]. The nanotubes in these studies are a generic model for several kinds of membrane spanning proteins [232] and the results may carry over to CNTs. CNTs however have a similar but simpler structure than most proteins and may be easier to manipulate in a controlled fashion due to their stability. In this sense, CNTs could offer the key to a world of nanometer size pores, valves and tubes, which allow to manipulate cells in very specific ways.

To approach the application of CNTs as nanometer size pores or syringes several recent studies assessed the interaction of small CNTs with water [140, 324, 352, 354] and ion transport in CNT based pores [161, 250]. Furthermore, first studies addressed RNA and DNA transport in CNTs and CNT based membranes [103, 341] and the interaction between these molecules [205]. But CNTs can also be imagined to function as a pore and to transport RNA or DNA across cellular membranes mimicking biological processes. Understanding such a transport process should allow for insights on a conceptual level that allow to understand biological pores and it should provide a first step to nanometer size devices that
allow to deliver single molecules in a controlled fashion.

In this chapter we will study how CNTs can act as nanometer size pores across cell membranes and we will determine the characteristics of transport processes in such pores. In the following the methodology used in this study will be explained in detail along with the setup of the simulations. Then we will report on the electrostatic potential maps of CNTs in dodecane membranes and dimyristoylphosphatidylcholine (DMPC) lipid bilayers. This is followed by a characterization of RNA translocation in a CNT across a dodecane membrane and first results on RNA translocation in a CNT across a DMPC lipid bilayer.

8.2 Methods

8.2.1 Molecular Dynamics

We use Molecular Dynamics (MD) simulations to study the systems which will be presented in the following. The simulations were performed using the MD package FASTTUBE [332] and the results were visualized with VMD [141]. All membrane simulations were carried out at constant area and temperature. The electrostatic interactions were computed with the Smooth Particle Mesh Ewald method [90]. A $32 \times 32 \times 48$ grid was used and validation studies using a $48 \times 48 \times 64$ grid did not show differences in the quantities such as the electrostatic potential maps and the motion of RNA in the pores. The van der Waals interactions and the real space contribution to the Coulomb interaction were calculated using a cutoff of 1 nm. All systems were kept at a temperature of 323 K by applying a Berendsen thermostat with a characteristic time of 0.1 ps [25]. The systems were equilibrated to atmospheric conditions using a Berendsen barostat with a characteristic time of 0.1 ps [25].

All simulations employ the AMBER 96 force field [59] with the extension of Smondyrev and Berkowitz [284] for phospholipids. A time step of 2 fs was used and all bonds involving hydrogen were kept rigid throughout the simulations. Dodecane was modeled in an united atom approach analogously to the lipid tails in Smondyrev and Berkowitz [284]. Water was modeled using the TIP3P water model [160].

The carbon nanotubes were modeled using the Lennard-Jones parameters for aromatic sp$^2$-carbon of the AMBER 96 force field [59]. The bond, angle and dihedral interaction potentials for the CNT were modeled as in Walther et al. [327]. Hydroxyl and hydrogen termini of the CNTs are modeled according to corresponding groups in tyrosine in the AMBER 96 force field [59]. The charges of the hy-
droxyl and hydrogen termini were locally balanced on the carbon atoms where the terminal groups are attached to the CNT (0.1587 e for the hydroxyl groups and -0.1656 for the hydrogen termini).

The membranes

The dodecane membrane was set up in a 6.1 nm × 6.1 nm × 10 nm computational box. A slab of 192 dodecane molecules in random orientation with a height of 2.5 nm was placed in between two slabs of 3610 water molecules, each approximately 3.1 nm high. After energy minimization, this system was equilibrated subject to a Berendsen barostat and a Berendsen thermostat for 180 ps [25] with characteristic times of 0.1 ps each. The Berendsen barostat only acted in the direction orthogonal to the membrane. After equilibration, the system was relaxed at constant temperature for another 20 ps. The final extend of the computational domain was 6.1 nm × 6.1 nm × 8.214 nm.

Coordinates for the dimyristoylphosphatidylcholine (DMPC) lipid bilayer were obtained from the Tieleman group. These coordinates are the result of a 1 ns simulation of 128 DMPC molecules solvated in 3655 water water molecules.

The carbon nanotubes

The nanotubes in this study are based on a (14,14) “armchair” type CNT with a length of 2.35 nm that has a 1.87 nm carbon-to-carbon diameter, which corresponds to a pore size of approximately 1.5 nm [341]. Two variations of this base-type CNT were considered: The naked CNT (with the unfilled valences at the ends) and a tube where alternating hydroxyl and hydrogen termini were added to the edge (H/OH CNT).

The CNT diameter was chosen to be comparable to the constriction region of the α-hemolysin channel [285, 341, 6] and the CNT length was chosen such that the hydrophobic mismatch with the DMPC membrane would be minimal. Recent studies showed that a hydrophobic mismatch can have a strong influence on the membrane structure in its vicinity [163, 232]. Due to the limited size of the computational domain the membrane could not compensate for the effects of a hydrophobic mismatch, which leads to a destabilization of the lipid bilayer structure.

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1 We used the PDB file dmpc_npat.pdb from http://moose.bio.ucalgary.ca/index.php?page=Downloads

2 In test simulations with longer CNTs we found a significant thickening of the membrane around the CNTs which lead to subsequent membrane rupture further away from the CNTs
8.2. METHODS

The RNA

In the simulations where RNA transport was considered we used single stranded RNA consisting of 20 adenosine nucleotides. The RNA is hydroxylated at both ends and the charge of the whole system is balanced by adding potassium counter ions randomly to the solvent.

8.2.2 Setup and equilibration

Inserting the CNT in a membrane

The setting up of CNTs embedded in membranes is a non-trivial task [92] that is hindered by the by the irregular shape and motion of the membrane lipids. In this study we propose a novel technique in order to insert CNTs into pre-equilibrated membranes. Initially the solvent around the membrane was removed. In the case of the DMPC bilayer 7 lipid molecules were removed from either side of the lipid bilayer, corresponding to the area occupied by a (14,14) CNT. In order to insert the CNT into the imperfect cavity in the DPMC bilayer or into the unaltered dodecane membrane we chose a scaling approach: The carbon nanotube was contracted to a single line of carbon atoms and we set the Lennard-Jones lengthscales $\sigma$ of all interactions between the CNT and its surrounding set to zero. This structure was then centered into the cavity of the DMPC bilayer or inserted into the dodecane membrane. Subsequently the CNT was slowly grown back to its prescribed form. First the lengthscale parameters of the Lennard-Jones interactions were linearly scaled to their original value during an initial 2 ps. In the following 28 ps the radius of the CNT was grown back to its original size. During this process the positions of the CNT atoms were adjusted so that they correspond to a linear scaling of the CNT radius. Furthermore, the motion of the membrane atoms was restricted to the two in-plane dimensions only and the velocity components of the membrane atoms in the two in-plane dimensions were capped at a maximal value of 0.3 nm ps$^{-1}$. The system was equilibrated for 1 ns and subsequently samples were taken every 1 ps during the course of 1 ns.

We note that the present approach differs from the insertion technique presented in Faraldo-Gomez et al. [92] in that it does not require triangulation and it relies only on quantities which are computed routinely in MD simulations.
Solvation

After the insertion of CNT into the membrane the system is solvated by two slabs of an approximately 1 molar potassium chloride solution that were placed on either side of the membrane. We added and 8127 water molecules to the dodecane membrane and 8211 water molecules to the DMPC bilayer. In both cases the water contained 150 potassium and 150 chlorine ions.

For the DMPC bilayer, during the first 40 ps of solvation all phosphorous atoms are kept fixed and the water is relaxed to wet the membrane. This is followed by 4 ps of dynamics where the phosphorous atoms is restricted to move only within the plane of the membrane. After further relaxation and a total simulation time of 60 ps the system is relaxed using a Berendsen barostat during 200 ps. This is followed by a further relaxation at constant volume for 40 ps.

To solvate the dodecane membrane, the dodecane molecules were kept fixed during the first 40 ps of simulation and the water was relaxed to wet the membrane. In the following the velocity of the dodecane molecules was capped at 0.3 nm ps$^{-1}$ for 4 ps. After a total simulation time of 80 ps the system was coupled to a Berendsen barostat for 120 ps. Then the system was further equilibrated at constant volume for another 100 ps to obtain a total of 300 ps for solvation, relaxation and equilibration.

Insertion of RNA into CNTs

The RNA is initially placed in the solvent so that the first phosphorous atom from the 3′-terminus is situated 0.8 nm outside the CNT on the tube axis. For the first 46 ps the whole RNA was restrained. After this initial relaxation, only the first phosphorous atom from the 3′-terminus was restrained at its initial position, while the rest of the RNA was allowed to move freely. Both, the RNA and the membrane were solvated simultaneously.

After solvation and relaxation a steering was applied to pull the RNA into the CNT [149]. A harmonic guiding potential with a force constant of 30’000 kJ nm$^{-2}$ mol$^{-1}$ was applied to the first phosphorous atom from the 3′-terminus. The RNA was threaded into the CNT by moving the reference point of the steering potential along the CNT axis during 280 ps. After the steering the phosphorous atom was restrained at the opening of the CNT to allow for relaxation of structural strain imposed during the steering. Figure 8.1 illustrates the system after the insertion of the RNA into the CNT.
8.3. THE ELECTROSTATIC POTENTIAL

The electrostatic potential characterizes to a large extent the transport in transmembrane pores [5]. In this study we consider naked and H/OH carbon nanotubes in the presence and in the absence of an imposed electrostatic potential difference across the membrane. First we study a dodecane membrane, i.e. a membrane mimetic, followed by studies of a lipid bilayer.

The molecules in the dodecane membrane are randomly oriented while the lipid molecules all have a similar orientation with regards to the bilayer. The head groups, are organized in two planes on either side of the membrane interior and significantly alter the electrostatic potential in the vicinity of the membrane and also within a transmembrane pore, as will be shown later.

The electrostatic potential is assessed following the approach of Aksimentiev et al. [6]. Based on the atomic positions from the trajectory of the system we evaluate the electrostatic potential using the SPME [90] routine of our molecular dynamics package [332]. The instantaneous electrostatic potential is then radially averaged, providing an axisymmetric electrostatic potential map. The mean elec-
CHAPTER 8. RNA TRANSPORT THROUGH TRANSMEMBRANE CARBON NANOTUBES

Figure 8.2: Electrostatic potential map for a CNT in a dodecane membrane. The left half of the figure shows the corresponding radially averaged density profile, with the dodecane molecules (blue) and the CNT (red). There is no potential difference acting across the membrane.

trostatic potential map was obtained by averaging these instantaneous potential maps over at least 1ns of an MD trajectory.

8.3.1 Electrostatics of a CNT in a membrane

CNT in a dodecane membrane

We present the electrostatic potential map of a H/OH-CNT in an approximately 2.5 nm thick dodecane membrane, see figure 8.2. The electrostatic potential map for a naked CNT exhibited a similar structure.

The location of the membrane and the CNT is represented by radially averaged density profiles of the constituent atoms. The electrostatic potential map exhibits distinct zones of high and low potential while the location of the membrane and the tube is well reflected in the electrostatic potential map. Between the bulk of the ionic solution and the interior of the dodecane membrane there is a potential difference of 0.65 V. This potential difference is in close agreement to the potential difference which is found between bulk water and the interior of a lipid bilayer [284]. The CNT interior forms a channel of low electrostatic potential across the membrane.
8.3. THE ELECTROSTATIC POTENTIAL

CNT in DMPC bilayer

The electrostatic potential maps presented here are averages over 1 ns with samples taken every 1 ps after 5 ns of equilibration. The electrostatic potential maps for a H/OH-CNT and for a naked CNT in a DMPC lipid bilayer are shown in figure 8.3. For the H/OH-CNT we find a channel of low electrostatic potential connecting both sides of the membrane. At either end of the transmembrane CNT zones of high electrostatic potential are protruding into the channel and constrict it to about 1 nm in diameter as opposed to 1.5 nm within the tube. For the naked CNT the effects at either end of the CNT become more pronounced and we observe zones of high electrostatic potential which extend across the whole channel forming barriers of high electrostatic potential, see figure 8.3.

Both electrostatic potential maps are significantly different from the electrostatic potential map reported for a CNT in a dodecane membrane. The differences are attributed to the fact, that the lipid bilayer is thicker than the dodecane membrane and the lipid heads extend further into the solution than the CNTs. The lipid molecules arrange in an hourglass shape that is widening above the area of constriction. The lipid head groups are fanning out over the tube rims and are partially covering the pore openings. This effect is well illustrated by the radially averaged density profiles shown in figure 8.3.

The differences between the naked and the H/OH-CNT is attributed to the solvation of the ester groups of the lipids. In the case of the H/OH-CNT the ester groups are stabilized by the hydrogen and especially the hydroxyl groups at the tube rim (figure 8.4). We observe hydrogen bonds between the carbonyl oxygen of the ester group and the hydroxyl groups. In the case of the naked CNT this interaction is missing. As a consequence the lipids slide along the CNT towards the water phase such that the ester groups come into contact with the water at the tube rim, see figure 8.4. This allows for solvation of the carbonyl groups and is energetically more favorable. The lipid head groups are therefore extending farther over the tube rim than in the H/OH case which allows the ammonium groups to leap farther into the area of the tube opening (figure 8.3 and figure 8.4).

The instantaneous electrostatic potential map shows significant variations. These variations are quantified by the standard deviation of the electrostatic potential (figure 8.5). We note that the standard deviation is particularly large in the zone occupied by the lipid head groups. The charge separation of the choline group promotes significant local changes of the electrostatic potential. In the area of the tube opening we find fluctuations in the electrostatic potential. These oscillations have a frequency in the order of 5 ns$^{-1}$ and they are more pronounced for the
Figure 8.3: The electrostatic potential map of a CNT acting as a nanopore in a DMPC lipid bilayer. The figures show on the left side the radially averaged density profiles of the CNT-carbon atoms (red) and the DMPC-nitrogen atoms (blue) and on the right side the electrostatic potential map. There is no electrostatic potential difference acting across the membrane. The figures show a H/OH CNT (left) and a naked CNT (right) inside the membrane. We note zones of high electrostatic potential which protrude into the pore area for both cases, but in the case of a naked CNT (right) these zones actually form a barrier across the whole aperture.
8.3. THE ELECTROSTATIC POTENTIAL

Figure 8.4: Sample lipids at the rims of a naked CNT (left) and a H/OH-CNT. The lipids at the naked CNT leap farther into solution and into the tube area. For the H/OH-CNT the lipids are fixed with the ester groups at the tube rim. The hydroxyl groups form hydrogen bonds with the lipids.

naked CNT than for the H/OH-CNT. We attribute this effect to reorientation of the lipid head groups whose motion is strongly correlated, see figure 8.6. This finding is consistent with the finding that the lipid head groups are protruding farther over the tube rim for the naked CNT than for the H/OH-CNT, see figure 8.4. Considering the standard deviation (figure 8.5) of the electrostatic potential map and the oscillations in the area of the tube opening, we expect that the mean electrostatic potential maps may differ significantly from instantaneous realizations.

8.3.2 Application of a transmembrane voltage difference

CNT in a dodecane membrane

We assess the electrostatic potential map of the same H/OH-CNT in a dodecane membrane as before, but this time subject to an electrostatic potential difference of 0.95 V [62, 5, 6]. The system was equilibrated for 1 ns and subsequently samples were taken every 1 ps during the course of 1 ns. The electrostatic potential map is shown in figure 8.7. On either side of the membrane the electrostatic potential is almost constant while it changes sharply within the transmembrane nanopore so that the location of the nanopore can be easily identified.
Figure 8.5: Standard deviation (right half of the graphs) of the electrostatic potential maps (left half of the graphs) for a H/OH (left) and a naked CNT (right) in a DMPC lipid bilayer. The standard deviation is largest in the area of the lipid heads and lowest in the center of the lipid bilayer. The standard deviation is comparable in size with the electrostatic potential.

Figure 8.6: The electrostatic potential in the tube opening correlates with the orientation of the head groups. The figures show the radially averaged density distribution of the ammonium group (blue) of the DMPC molecules around the CNT (red) on the left side and the corresponding electrostatic potential map on the right side. As the density is shifted from the center of the tube towards the tube rims the strength of the electrostatic potential in the tube center diminishes and the electrostatic potential protruding into the tube area retracts.
Figures 8.7: Electrostatic potential map for a CNT in a dodecane membrane. The left half of the figure shows the corresponding radially averaged density profile, with the dodecane molecules (blue) and the CNT (red). A potential difference of 0.955 V is acting across the dodecane membrane.

The electrostatic potential maps reported for the CNT in the dodecane membrane mimic strongly resemble the electrostatic potential maps for solid state nanopores presented by Heng et al. [125]. The structure of the map is qualitatively the same, although the dimensions and the shape of the pore are different.

**CNT in a DMPC membrane**

The electrostatic potential maps for both, naked and H/OH CNTs at an electrostatic potential difference of 1.05 V are shown in figure 8.8. For the H/OH-CNT we observe a constant electrostatic potential on both sides of the membrane. At the opening of the carbon nanotube on the side of high electrostatic potential we find a barrier in electrostatic potential. This barrier is just outside the CNT, see figure 8.8. On the side of low electrostatic potential a similar barrier is absent for the H/OH CNT and the pore opening is reflected in a bay of low electrostatic potential extending into the pore. This bay in low electrostatic potential indicates the absence of lipid head groups in the area of that tube opening, which is also confirmed by the radially averaged density profiles, see figure 8.8. This may facilitate the access of molecules to the pore and their eventual transport.

For the naked CNT we also observe a barrier in high electrostatic potential on
CHAPTER 8. RNA TRANSPORT THROUGH TRANSMEMBRANE CARBON NANOTUBES

Figure 8.8: Electrostatic potential map for a H/OH (left) and a naked (right) carbon nanotube in a DPMC bilayer. The system is subject to an electrostatic potential difference of 1.05 V. The map looks qualitatively the same for potential differences between 0.2 and 1.5 V. The left half of the figures shows contour lines of the radially averaged density profiles of DMPC nitrogen (blue) and the CNT carbon atoms (red).

The characteristics of these electrostatic potential maps persist at other potential differences. From potential differences of 0.2 V up to potential differences of 1.5 V the electrostatic potential maps showed the same characteristics, i.e. the barriers in high electrostatic potential and the bay of low electrostatic potential in the case of the H/OH-CNT.

The asymmetry of the electrostatic potential map of the H/OH-CNT, i.e. the electrostatic barrier on one side and the bay on the other, is attributed to a reorientation of the membrane subject to the electrostatic potential difference in the vicinity of the tube entrance. The ammonium groups of the lipids carry a positive net charge of approximately 1 e \[284\]. Due to the electrostatic potential difference applied to the system, the ammonium groups of the lipids on the side of high electrostatic potential are pushed into the area of the tube opening (compare figure 8.9). On the side of high electrostatic potential, a peak of ammonium density is shifted by about 0.7 nm from the tube rim towards the tube center for the H/OH-CNT. For the naked CNT we observe a similar effect with an ammonium density peak just outside the tube opening that is pushed about 0.7 nm into the tube onto the tube.
Figure 8.9: Schematic on how the head groups of the lipids close to the carbon nanotube re-orient depending on the direction of the electric field. On the side where the electric field points away from the membrane, the ammonium group of the phospholipid (black) is pushed towards the membrane and thus also over the carbon nanotube rim (arc). On the other side, the head groups of the lipids are stretched and ammonium group is pulled away from the the membrane. The phosphate group is indicated by a white sphere.

wall, and figures 8.8 and 8.3 Consequently we observe a zone of high electrostatic potential arises for the H/OH CNT which was not present in the situation without a potential difference. For the naked CNT the barrier in electrostatic potential on the side of high electrostatic potential is pronounced and is shifted into the the tube. On the other side of the membrane with low potential, the ammonium groups are subject to electrostatic forces which pull them away from the membrane, compare figure 8.9. For the ammonium groups close to the tube entrance this keeps them in a more upright position. For the H/OH-CNT the lipid head groups are hardly leaping into the tube area even in the absence of an electrostatic potential difference, see figure 8.4. As a consequence, the electrostatic potential difference has hardly any effect on their density distribution on the side of low electrostatic potential, see figure 8.8 and 8.3. For the naked CNT in the absence of an electrostatic potential difference, the lipid head groups are leaping into the area of the tube opening, see figure 8.3. As the electrostatic potential difference is applied, the ammonium den-
sity retracts by about 0.5 nm away from the tube axis. The barrier in electrostatic barrier reported in the absence of an electrostatic potential difference across the membrane is weaker but still persists in the presence of a potential difference.

We note that these electrostatic potential maps are significantly different from the ones obtained for a CNT in a dodecane membrane (figure 8.7) and solid state nanopores [124]. In particular, we observe barriers in electrostatic potential and different maps for H/OH and naked CNTs. These differences are attributed to the lipid head groups which reorient subject to an imposed electrostatic potential difference.

8.4 RNA translocation in transmembrane CNTs

We present a series of molecular dynamics studies of RNA transport through a CNT in a dodecane membrane and a DMPC bilayer.

8.4.1 RNA across a dodecane membrane

We report on the transport of a single-stranded piece of RNA consisting of 20 adenosine nucleotides through a H/OH-CNT and a naked CNT in a dodecane membrane.

In a series of molecular dynamics simulations with the H/OH-CNT we varied the transmembrane potential differences from 1.43 V to 2.10 V in steps of 0.096 V. Additional simulations with the H/OH-CNT were carried out at 0.96 V, at 1.20 V and at 2.15 V. Simulations with a naked CNT across the membrane were carried out at 1.51 V to 2.01 V in steps of 0.1 V. At potential differences of 2.4 V and larger we observed membrane rupture, thus simulations under such conditions were not possible.

Inside the tube the RNA bases maximize contact with the CNT and are attached flat onto the tube walls (figure 8.10). This is attributed to a strong hydrophobic interaction between the RNA bases and the CNT [341, 103]. We observed pairs of stacked nucleotide bases, too, where one base is attached to the tube wall and covered by the other. The RNA backbone is exposed toward the tube center (figure 8.10). This allows for the phosphate and sugar groups of the backbone to be solvated by the water inside the CNT. Upon entry into the CNT the RNA bases are folded backwards with regards to the direction of translocation [214] and during the translocation, the nucleotide bases are sliding along the tube walls (figure 8.10). The bases remain in this orientation until they reach the other end of the CNT.
For potential differences of 1.20 V and more the RNA was driven through the CNT in relatively short time spans of the order of 10 ns. The time needed for translocation through the pore depends on the potential difference. We measured the average speed of translocation based on the time needed from the exit of nucleotide 3 from the tube until the exit of nucleotide 16. This definition of translocation time avoids end-effects due to the first nucleotides being expelled from the tube or due to reduced hydrophobic interactions towards the end of the simulation, when the RNA is not extended across the whole CNT anymore. For potential differences between 1.20 and 2.15 V we observe a correlation with the speed of translocation. A least squares fit of an exponential [341] to the data results in the following relationship

$$v = 0.087 \frac{N_{uc}}{ns} \exp (2.57\Delta V) ,$$

(8.1)

of translocation speed $v$ in nucleotides per nano second from the potential difference $\Delta V$.

The instantaneous speeds of translocation exhibit large fluctuations (figure 8.12) that are attributed to the trapping of RNA, which is in turn caused by conforma-
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Figure 8.11: Translocation speed in nucleotides per nano second plotted versus the potential difference across the membrane. Both, translocations in a H/OH-CNT (+) and a naked CNT (o) are plotted. An exponential is fitted to the data.

Translocational changes of RNA. The trapping events are easily identified by tracking the position of the phosphate groups of the RNA. In figure 8.12 several trapping events can be identified for a potential difference of 1.43 V, with the longest one lasting for approximately 1.2 ns. The trajectories of the phosphate groups in figure 8.12 exhibit step-like characteristics. These steps are associated to individual bases entering the CNT. The bases of the RNA outside the CNT are stacked. When a base enters the CNT, the hydrophobic contact to its neighboring base has to be broken and the interfacial area is hydrated. Simultaneously water is expelled from in between the base and the CNT wall and the base attaches to the tube wall. Along this process the RNA bases are folding backwards with regards to the direction of transport. During this event an energy barrier has to be overcome, which leads to the short trapping in time and to the step-like behavior. Step-like trajectories are only observed for potential differences below 1.55 V. Beyond this threshold we still observe trapping of the RNA, but events where individual nucleotides are leaving a stacked geometry and enter the tube could not be identified by a step-like trajectory anymore. The strong driving forces at large potential differences mask the sequential breaking of the stacking.
Figure 8.12: The trajectories of the RNA phosphate groups within the CNT. The two ends of the CNT are indicated by dashed lines. A bold dashed line indicates a step-like motion between 2 ns and 3.5 ns. Afterwards, the RNA gets trapped for a relatively long time span from approximately 4 ns until 5.2 ns.
At 1.2 V the RNA translocation is slow and varies strongly in time. We observe periods of trapping with intermittent periods of fast translocation. The periods of trapping extend over time spans of the order of nano seconds and the longest trapping event we observed lasted for 4.3 ns. Between periods of trapping we observe a rapid translocation with speeds of the order of 4 nucleotides per nano second.

At electrostatic potential differences of 0.955 V the RNA gets trapped after 1 ns, in which the first two nucleotides are expelled from the tube. In the following 8 ns of simulation no noticeable motion was observed. The RNA inside the CNT shows only minimal spacial fluctuations in the order 0.2 nm along the tube axis. The RNA tail on the entry side of the membrane shows dynamic behavior similar to free RNA in solution. After 7 ns of simulation one of the terminal attaches onto the membrane and remains attached to the membrane throughout the rest of the simulation.

After the translocation the bases do not spontaneously leave the CNT. Only eventually they are pushed away by the RNA following from within the CNT. One of the first nucleotides, however, usually reattaches quickly to the outside of the tube or the dodecane membrane. In the following, the RNA which leaves the tube buckles and forms a loop, which eventually turns into a coiled up structure. The RNA which has a limited flexibility behaves similar to a sheet of paper that is pushed together on a table.

The expelled RNA remains coiled up at the tube exit, during the limited simulation times of 5 to 10 ns. In none of the simulations the RNA completely left the CNT. One or two of the terminal bases always remained hydrophobically attached to the CNT, [5]. This happened even if the bases which left the tube first did not remain attached or did not reattach to the tube or the membrane.

8.4.2 RNA across a DMPC bilayer

We report on the transport of a single-stranded piece of RNA consisting of 20 adenosine nucleotides through a H/OH-CNT in a DMPC bilayer. During the simulation, the system was subject to a potential difference of 1.6V.

The RNA structure within the CNT in the DMPC lipid bilayer does not significantly differ from the RNA transport within a CNT in a dodecane membrane. Again, the RNA bases are folded backwards with regards to the direction of transport and strongly attached to the tube wall. The backbone is exposed towards the center of the tube.

The speed of translocation is found to be 1.5 nucleotides/ns. This speed is lower
8.4. RNA TRANSLOCATION IN TRANSMEMBRANE CNTS

Figure 8.13: Snapshot of lipid head groups interacting with RNA (grey) in a transmembrane H/OH-CNT (black/red/white). The lipids are indicated with a colored stick model and and the phosphorous (gold) and nitrogen (blue) atoms within 7 Å of the RNA are indicated with spheres. Both figures show the same snapshot at an angle of 90°.

than the speeds observed for a CNT in a dodecane membrane at the same voltage difference. It is however of the same order of magnitude. The slower speed is consistent with expectations. The lipid head groups of the DMPC membrane extend over the CNT and interact with the RNA, see figure 8.13. This slows the RNA motion down. Furthermore, the motion of the RNA is also sterically hindered, as the lipid heads partially obstruct the pore opening, similar to the effect described by de Groot et al. [73] and comparable to entropic barriers [194]. Consequently, we observe a deceleration of the translocation. The translocation of RNA across the pore takes approximately 12 ns. We visualize this process with a series of snapshots along the trajectory in figure 8.14.

The translocation is very similar to the translocation across a dodecane membrane except for the behavior of the RNA after it is expelled from the CNT. Contrary to the simulations of translocation through a dodecane membrane the RNA does not reattach to CNT on the CNT, as the lipid molecules shield the outside of the CNT. Instead, the RNA leaves the exit area and protrudes into solution. After about 10 ns the foremost nucleotides get into contact with the lipid bilayer. The RNA is however not adsorbed on the lipid bilayer surface but readily diffuses back into solution.
Figure 8.14: The figure shows 8 snapshots along an MD trajectory of the translocation of RNA through a H/OH-CNT in a DMPC lipid bilayer. The snapshots are taken every 1.4 ns from 1.4 ns until 11.2 ns.

8.5 Conclusions

We studied CNTs embedded in membranes acting as transmembrane nanopores. The CNTs are chosen such that they match the hydrophobic domain in the middle of the membrane. We found that the electrostatic potential map of such a pore depends significantly on the membrane in its vicinity and a membrane mimetic like dodecane may not capture these effects. If an electrostatic potential difference is applied across the membrane causes the lipid heads of the lipid bilayer leap into the pore opening. The rearrangement of the lipid heads results in an electrostatic potential barrier across the pore. This effect could be of physiological importance and it may help to explain zones of protein based transmembrane pores, that are situated outside the membrane and extend into solution.

The transport of RNA across a carbon nanotube transmembrane pore compare well with results reported on synthetic silica nanopores [125] and the effects of constriction are similar to results on α-hemolysin [124]. While transport velocities in transmembrane CNTs seem to exceed those of in α-hemolysin, they seem to be slower than in synthetic silica pores [125]. Although the electrostatic potential map for a CNT in a dodecane membrane is significantly different from a CNT in a lipid bilayer, the transport process of RNA across the system is comparable. A no-
notherable difference was only found in the speed of translocation, as the lipid head
groups of the DMPC bilayer create an entropic barrier, which slows the transloca-
tion down. The conceptual nature of the dodecane membrane, however, makes it
the ideal system to study transmembrane transport.

Even at strong transmembrane potential differences the RNA is never completely
released from the CNT. A few of the terminal nucleotide bases always remain
hydrophobically attached to the CNT. Chemical modifications to the CNT interior
and the tube rims which weaken the hydrophobic interaction of RNA bases and
the CNT could be considered to promote the detachment of the RNA from the
CNT. Possible applications may however benefit from the fact that RNA does not
detach from the RNA. The sustained attachment may allow to retract the RNA
after exposing it to the cell interior.
Chapter 9

Conclusions

This thesis addressed physical problems and modeling issues that are important for the understanding and for the development of CNT transmembrane pores. The studies presented in this thesis cover methodological grounds from quantum mechanics to large scale MD simulation. In chapter 3 we assessed the interaction between water and aromatic carbon compounds in detail and we evaluated correction schemes for density functionals. For the simulation of rare events a method for generalized steering in molecular simulations is described in chapter 5. Then we assessed the influence of polarizability on the interaction of graphitic carbon and water in chapter 6.

Furthermore we considered curvature effects on the interaction between CNTs and water in chapter 7. Finally, we presented a detailed study on a specific realization of a CNT based transmembrane pore in chapter 8. The main findings and contributions of this thesis are summarized below.

Dispersion corrections for density functionals

We studied the interaction of water with small aromatic molecules and graphite. Interaction energies of current density functionals were corrected for the dispersion energy contribution and compared to high level quantum mechanical data. This comparison allows one to identify promising correction schemes for current density functionals. In particular the correction scheme suggested by Elstner et al. [89] performs well in combination with the PBE functional. Also the scheme by Wu and Yang [338] performs well in combination with the B3LYP functional.

The corrected density functionals usually result in lower error measures than uncorrected functionals. While this might be interpreted as a reassuring result, there are however major problems:
1. **The improvements by the correction schemes are not systematic:** Even for two systems as similar as the water-benzene and the water-naphthalene cluster the optimal correction scheme is not the same. Also the orientation of the test molecules affects the relative performance of the correction schemes.

2. **Loss of systematics of the error:** When using uncorrected density functionals we know that we are missing an attractive contribution to the total interaction energy. Thus we have a systematic error, but we are aware of it. Using corrected density functionals we do not know whether we over or underestimate the interaction energy, e.g. we most probably make an error, but we do not know of what sign.

These two problems indicate that dispersion corrected density functionals have to be used with great care. Nevertheless, dispersion corrected density functionals have been used in several recent studies and allow for the evaluation of molecular interactions at a relatively low computational cost. In a comparative study over a wide range of systems Grimme [116] also obtains results that confirm the concerns raised here.

**Generalized steering for molecular simulations**

We generalized the concept of steered molecular dynamics by applying a steering potential to collective variables instead of particle coordinates. We illustrated the generalization in two case studies involving the folding of a nona-alanine peptide and the expulsion of RNA from a CNT. In these case studies the systems are steered along trajectories defined in terms of the radius of gyration, two intramolecular distances and their angle or the distance between two centers of mass.

The realization of similar trajectories solely based on individual atomic coordinates would have been difficult to achieve. Thus, steering along trajectories of collective variables enables the exploration of changes that are hard to visit by steering along the trajectories of single atomic coordinates.

The presented method is particularly useful for MD studies where the system behavior along a specific but complex reaction coordinate is of interest. Although the generalized steering could be used to reconstruct potentials of mean force from the work exerted in a steered molecular dynamics run [239], there are other methods which are more suitable, e.g. metadynamics [183, 184].
Polarizability of graphite

We presented a force field for the water graphite interaction that includes polarization effects. In that study, the water is described by the RPOL water model [70] and polarization is modeled using isotropic polarizabilities on all particles. The graphite polarizabilities are estimated from theoretical considerations and we fitted the Lennard-Jones interaction parameters between water and carbon to reproduce the experimental contact angle of water on graphite.

The optimal orientation of a single water molecule on graphite is significantly influenced by polarizability. In particular, we reproduce an orientation similar to the one reported by Feller and Jordan [93] and the interaction energy for a single water molecule on a graphite sheet is in close agreement with recent quantum mechanical calculations by Lin et al. [195]. The orientation reported by Feller and Jordan [93] is however not in agreement with recent and more accurate quantum mechanical calculations [195].

While a single water molecule close to a graphitic surface is strongly influenced, the changes in a bulk water phase close to the surface are limited. Significant effects are only reported for the layer of water molecules closest to the graphite surface.

The computational cost of a self-consistent treatment of polarizability is large compared to the cost of non-polarizable simulations. We therefore recommend the consideration of a polarizable graphite model only for studies where the surface-to-volume ratio is substantial, i.e. systems that consider single or double layers of water molecules in the vicinity of graphite, or for studies where the actual water orientation at the surface is important. For systems, however, where the focus is on the bulk water phase, we recommend the modeling approach of Werder et al. [332].

Curvature effects in CNTs

We studied the effect of the curvature induced static dipole moment of CNTs on water structure and conduction in small CNTs and on water droplets in relatively large single- and multi-walled CNTs.

In small CNTs the dipole moment gives rise to an axial electric field that is strongest at the tube entrances and smaller towards the middle of the tube. This field has a significant influence on both the filling behavior and the orientation of water molecule chains inside the CNT: It results in an $L$-defect in the quasi one-dimensional water chain inside the tube. An $L$-defect blocks proton transfer
along a quasi one-dimensional water chain and could therefore abet the use of CNTs as nanoscale pores or channels [75, 352]. Furthermore, controlled proton conduction could be achieved by suitably superimposing an external electric field to the electric field of the CNT curvature induced dipole.

In large CNTs (5 nm in diameter or more) the curvature induced dipole moment is negligible. Neither the contact angles of water droplets nor the microscopic water structure close to the tube walls change significantly. We also note that the dipole moment is not important for MWCNTs of this size, because not even a tenfold dipole moment changes the observables.

We conclude that the radial dipole moment of CNTs is only important at small radii. There the dipole moment is particularly strong and the stabilizing 3-dimensional hydrogen bond network of water is missing.

Changes in the carbon water Lennard-Jones interaction allow to account for changes in the chemical composition of the tube wall. In contrast to the curvature induced dipole moment, such changes have a direct influence on the contact angle. The presence of adsorbates and chemical endgroups such as hydroxyl-, aldehyd- and carbonate-groups protruding from the CNT wall are therefore much more important with respect to the resulting wetting behavior of water inside CNTs. This is not only the case due to changes in the Lennard-Jones interaction but also due to the fact that many of these functional groups have dipole moments similar those of water. Thus, they are able to disrupt the hydrogen bond network of water. These expectations have been confirmed in a subsequent study of Kotsalis et al. [177].

From a theoretical point of view the contact angles of water droplets in CNTs may be considered to be understood to a large extent. As in any theoretical work, also here it would be desirable to find an experimental validation for these theoretical findings. In several studies, Gogotsi et al. [106, 219, 262] presented experimental contact angles of aqueous liquids in CNTs. The contact angles reported by Gogotsi et al. are different to the ones reported here. These differences can however not be rated unless we know the chemical composition of the droplets inside the CNT and the characteristics of the tube wall – this is currently not the case. The development of experiments on contact angles in pristine or at least well characterized systems will be one of the challenges of the near future.

**RNA transport in transmembrane CNTs**

This thesis concludes with a MD study on RNA transport in transmembrane CNTs. The electrostatic potential map of such CNT nanopores depends on the characteristics of the tube rims and on the membrane in its vicinity. An electrostatic potential
difference across the membrane results in a rearrangement of the lipid heads close to the pore, which tend to leap into the pore opening. The rearrangement of the lipid heads results in an electrostatic potential barrier across the pore. This effect could be of physiological importance and it may help to explain the bulky rims of protein based transmembrane pores which extend beyond the membrane into solution.

The transport of RNA across a CNT transmembrane pore is consistent with translocation studies reported on synthetic silica nanopores [125] and the effects of constriction are similar to results on α-hemolysin [124]. The translocation is slower through a CNT embedded in a dodecane membrane than in a DMPC lipid bilayer as the lipid head groups of the DMPC bilayer slow the translocation down. In general, transport velocities in transmembrane CNTs seem to exceed those of in α-hemolysin and they seem to be slower than in synthetic silica pores [125].

After the translocation, 2 to 5 of the terminal nucleotide bases always remain hydrophobically attached to the CNT. Even at strong transmembrane potential differences the RNA is never completely released from the CNT. Chemical modifications to the CNT interior and the tube rims which weaken the hydrophobic interaction of RNA bases and the CNT could be considered to promote the detachment of the RNA from the CNT. Possible applications may however benefit from the fact that RNA does not detach from the CNT. The sustained attachment may allow to retract the RNA after exposing it to the cell interior.
Due to the interdisciplinary nature of this thesis we present an individual outlook to the different subtopics of the thesis and we will conclude with an outlook on CNT based nanopores.

**Dispersion corrections for density functionals**

We showed that dispersion corrections are an appropriate engineering solution to resolve problems of current density functionals. Comparison and application studies like [116] show that dispersion corrections may indeed improve the results obtained from density functional theory. The concerns raised in this thesis regarding the systematics of the error are however confirmed. Nevertheless, if the correction schemes are carefully validated, the dispersion corrected density functionals allow for more accurate quantum chemical simulations at the moderate cost of density functional theory. We expect therefore further studies employing this approach in the near future.

In the long run, we expect the method as it is presented here to become redundant because of improved density functionals. Various research groups work on the improvement of exchange correlation functionals and several advances were communicated in recent years, see references [52, 170, 171] and [319, 320]. These approaches allow for the treatment of weakly bound systems in a self-consistent manner, e.g. on the same level of theory and do not hinge on the blemish of being an ad-hoc approach.

**Generalized steering for molecular simulations**

Future studies will prove the presented method to be useful for MD studies where the system behavior along a specific but complex reaction coordinate is of interest. We expect future steering studies to be formulated the longer the more in terms of collective variables. A possible application of the algorithm is found in the
structural dynamics of the \textit{Lac} repressor-DNA complex. The \textit{Lac} repressor-DNA complex shows a large scale angular motion which could well be described using collective variables, e.g. the angle between three centers of mass. Steering along this angle may allow to gain insight on the functionality of the \textit{Lac} repressor-DNA complex.

\textbf{Polarizability of graphite}

The description of a single water molecule on graphite is not yet resolved. For future research we recommend a reassessment of two simplified interaction models presented by Marković \textit{et al}. [212]. In a detailed study Marković \textit{et al}. recommend a model that does not consider polarizability but includes additional Lennard-Jones interactions parameters between the water hydrogen atoms and the carbon atoms. This model is known to reproduce a optimal orientation for a single water molecule on graphite similar to the one reported in by Lin \textit{et al}. [195, 249]. In the same study, Marković \textit{et al}. also consider a model, which includes a local first-order approximation to polarizability and additional Lennard-Jones interactions between water hydrogen and and carbon. Marković \textit{et al}. do not actually recommend the use of that latter model, as they find the scattering of water molecules similarly well reproduced by the former, simpler interaction potential. However, both potentials may lead the way to an optimal water graphite interaction potential. Such a potential would be able to reproduce at least four quantities of interest: the optimal orientation of a single water molecule on a graphitic sheet, the according interaction energy, the contact angle of water on graphite and the scattering of water on graphite.

Even if the studies suggested above result in new interaction potentials, we do not expect them to change any bulk water properties in the vicinity of graphite. Any changes beyond the first layer of water molecules would be a surprise.

We expect the graphite water interaction to remain an active area of research. The conceptual simplicity of the system and actual complexity of the physics make it a beautiful problem, which will continue to fascinate scientists.

\textbf{Curvature effects in CNTs}

The influence of the curvature induced dipole on water in CNTs was discussed in detail in this thesis. The influence on water outside CNTs is however still an open question. We observed negligible influence on bulk water inside CNTs and therefore we do not expect any influence outside either. If there is however con-
fined water outside the tube, we expect an influence similar to the effect observed in small tubes. This may be the case between different CNTs in arrays of stacked CNTs.

Further open questions include the influence on the interaction with molecules different from water. This has to be quantified in further studies and the molecules of interest would have to be defined in the respective project.

The CNTs studied in this section are very small. The controlled manipulation of CNTs at these scales is difficult and accordingly experimental validation will be difficult. With recent progress in manufacturing and handling CNTs it may become possible in the near future.

**RNA transport in transmembrane CNTs**

In this thesis we showed that it should be possible to use transmembrane CNTs to transport RNA across a lipid bilayer. This result is reassuring for future research on the use of CNTs as pores in general. The transport of RNA is only one of several interesting transport problems across cell membranes. Also, ions and glycerol are transported in membrane channels. Thus CNTs could be imagined to act as ion channels or channels for other molecules. The key to such applications is however the selectivity of the pore.

Future research will have to consider variations of the transmembrane CNTs. Variations in diameter should be considered as well as variations in length. The variations in diameter would be targeted at the selectivity and specificity of the pore. The variations in length should be targeted at facilitating the transport. Extended hydrophilic zones on both ends of the CNT could act as funnels which screen the lipids from the pore entrance. Similar functionality is found in transmembrane proteins which usually extend well beyond the membrane.

The chemical structure is of preeminent importance for the selectivity of a CNT based transmembrane pore. The chemical structure of the pore interior will directly decide on its selectivity and the efficiency of the transport process.

Current simulations are subject to large driving forces in order to allow for the simulations to complete within the observable time spans of MD. Simulations should be extended beyond these computational limits. This can only be achieved with new algorithms which allow for the coupling of different simulation methods on different scales, both in time and space [15, 276, 317, 334]. These algorithms should allow to consider effects which are currently neglected, to mention a few:

- The delivery of RNA to the pore opening which is governed by diffusion and convection
• The insertion of the RNA into the pore

• Long strands of RNA may buckle, twist and coil up

The complexity of these questions and the universal character of the problems mentioned above make them attractive fields for research. The abundance of possible benefits from artificial nanopores in fields like nanotechnology, biotechnology and medicine even increase the attractiveness. I hope that the findings and techniques presented in this thesis will become part of the foundation to future research in this direction.
Appendix A

Error Measures for Energy Profiles for Benzene Water Cluster

In this appendix the errors relative to second order Møller-Plesset perturbation theory are summarized for different dispersion corrections schemes. In particular, the errors for pure DFT, a molecular correction scheme and three different atomistic correction schemes are reported. For detailed information about the underlying models and calculations the reader is referred to chapter 3.

A.1 Uncorrected density functional theory

The errors relative to second order Møller-Plesset perturbation theory are summarized in table A.1 for pure DFT.

A.2 Molecular correction

In table A.2 the errors relative to second order Møller-Plesset perturbation theory are summarized for DFT corrected using a molecular correction scheme as proposed by Wu et al. [339]. The underlying Equations for the dispersion coefficient can be found in (3.14) and the according damping function is given in (3.16).

A.3 Atomistic correction schemes

Three different atomistic schemes are considered for the dispersion correction. In the following, the errors relative to second order Møller-Plesset perturbation theory are summarized.

First we consider the scheme as proposed by Elstner et al. [89]. The underlying Equations for the combination of dispersion coefficients can be found in (3.19) and
### Table A.1: Summarized deviations of uncorrected DFT calculations relative to second order MP2 calculations

<table>
<thead>
<tr>
<th>Functional</th>
<th>mean deviation [kJ/mol]</th>
<th>((k_B T)) weighted deviation [kJ/mol]</th>
<th>((3k_B T)) weighted deviation [kJ/mol]</th>
<th>maximum deviation [kJ/mol]</th>
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<tbody>
<tr>
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<td>4.86</td>
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<td>PBE</td>
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<td>2.71</td>
<td>4.99</td>
</tr>
<tr>
<td>PW91</td>
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<td>22.89</td>
<td>1.81</td>
<td>3.78</td>
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</table>

### Table A.2: Summarized deviations of DFT calculations corrected according to Wu et al. [339] using dispersion coefficients (3.14) and damping function (3.16)

<table>
<thead>
<tr>
<th>Functional</th>
<th>mean deviation [kJ/mol]</th>
<th>((k_B T)) weighted deviation [kJ/mol]</th>
<th>((3k_B T)) weighted deviation [kJ/mol]</th>
<th>maximum deviation [kJ/mol]</th>
</tr>
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<td>PW91</td>
<td>2.59</td>
<td>19.22</td>
<td>2.78</td>
<td>10.47</td>
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</table>
### Table A.3: Summarized deviations of DFT calculations corrected according to Wu and Yang [338] using mixing rule (3.19) and damping function (3.23).

<table>
<thead>
<tr>
<th>Functional</th>
<th>mean deviation [kJ/mol]</th>
<th>((k_B T)) weighted deviation [kJ/mol]</th>
<th>((3k_B T)) weighted deviation [kJ/mol]</th>
<th>maximum deviation [kJ/mol]</th>
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<td>5.11</td>
<td>1.39</td>
<td>3.58</td>
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</table>

Wu and Yang proposed a different correction scheme [338]. The underlying Equations for the combination of dispersion coefficients can be found in (3.20) and the according damping function is given in (3.21) The summarized errors may be found in table A.4.

Alternatively, Wu and Yang suggest the use of the damping function (3.22). With this, the following errors are obtained The summarized errors may be found in table A.5.

### Table A.4: Summarized deviations of DFT calculations corrected according to Wu and Yang [338] using mixing rule (3.20) and damping function (3.21).

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<th>((3k_B T)) weighted deviation [kJ/mol]</th>
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<td>1.66</td>
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<tr>
<td>HCTH</td>
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<td>21.97</td>
<td>2.55</td>
<td>9.13</td>
</tr>
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<td>PW91</td>
<td>2.84</td>
<td>38.77</td>
<td>4.14</td>
<td>16.91</td>
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</table>
Table A.5: Summarized deviations of DFT calculations corrected according to Wu and Yang [338] using mixing rule (3.20) and damping function (3.22).

<table>
<thead>
<tr>
<th>Functional</th>
<th>mean deviation [kJ/mol]</th>
<th>$(k_B T)$ weighted deviation [kJ/mol]</th>
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<td>PW91</td>
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<td>7.57</td>
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</table>

Appendix B

Interaction Energy Profiles for Naphthalene Water Cluster

In this appendix the errors relative to second order Møller-Plesset perturbation theory are summarized for different dispersion corrections schemes. In particular, the errors for pure DFT, a molecular correction scheme and three different atomistic correction schemes are reported for the water naphthalene cluster. For detailed information about the underlying models and calculations the reader is referred to chapter 3.

B.1 Conformers

A set of eight different geometrical conformations was considered throughout the calculations (Fig. B.1), and for each scheme the interaction energy profiles were computed for the water naphthalene cluster in all eight different conformations. Two locations of the water molecule are considered, one with the oxygen atom
Figure B.1: The different conformations of the water naphthalene cluster are illustrated. In the top row, the water dipole moment is pointing towards the aromatic plane, whereas it is pointing away in the bottom row. In the first two columns, the water molecule is centered on the central bond of the naphthalene molecule, whereas it is centered on top of an aromatic ring for the latter two columns. The alignment of the plane spanned by the water molecule with regard to the main axis of the naphthalene molecule is alternating from column to column. The plane spanned by the water molecule is orthogonal with regard to the main axis of the naphthalene molecule in one column and alternatively it is parallel to the aforementioned axis in the next column.

centered on top of an aromatic ring and one with the oxygen atom centered on top of the carbon bond separating the two aromatic rings. In both of these locations two orientations of the water molecule are considered, the plane spanned by the water molecule is either orthogonal or in line with the main axis of the naphthalene molecule. All geometries, were evaluated, once with the water dipole pointing perpendicularly towards the naphthalene plane and once with the inverse orientation. The different conformers are shown in Fig. B.1.

B.2 Uncorrected density functional theory

The errors relative to second order Møller-Plesset perturbation theory are summarized in Table B.1 for pure DFT. The according interaction energy profiles may be found in Figs. B.2 and B.3. The results have been discussed in Section 3.5.
APPENDIX B. INTERACTION ENERGY PROFILES FOR NAPHTHALENE WATER CLUSTER

Figure B.2: Interaction energy profiles for the water naphthalene interaction from uncorrected DFT. The graphs in the first column correspond to configurations where the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second column it is parallel. In the first row the water molecule is centered on the central bond and in the second row it is centered on top of one of the aromatic rings, the dipole moment points orthogonally towards the naphthalene. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Figure B.3: Interaction energy profiles for the water naphthalene interaction from uncorrected DFT. The graphs in the first column correspond to configurations where the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second column it is parallel. In the first row the water molecule is centered on the central bond and in the second row it is centered on top of one of the aromatic rings, the dipole moment points orthogonally away from the naphtalene. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Table B.1: Summarized deviations of uncorrected DFT calculations relative to second order MP2 calculations.

<table>
<thead>
<tr>
<th>Functional</th>
<th>Mean deviation [kJ/mol]</th>
<th>$(k_B T)$ weighted deviation [kJ/mol]</th>
<th>$(3k_B T)$ weighted deviation [kJ/mol]</th>
<th>Maximum deviation [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP</td>
<td>2.71</td>
<td>68.30</td>
<td>4.69</td>
<td>16.06</td>
</tr>
<tr>
<td>BLYP</td>
<td>3.16</td>
<td>90.76</td>
<td>6.10</td>
<td>22.56</td>
</tr>
<tr>
<td>HCTH</td>
<td>1.90</td>
<td>54.10</td>
<td>3.48</td>
<td>17.77</td>
</tr>
<tr>
<td>PBE</td>
<td>1.70</td>
<td>45.06</td>
<td>3.00</td>
<td>10.07</td>
</tr>
<tr>
<td>PW91</td>
<td>1.41</td>
<td>36.88</td>
<td>2.38</td>
<td>8.52</td>
</tr>
</tbody>
</table>

Table B.2: Summarized deviations of DFT calculations corrected according to Wu et al. [339] using dispersion coefficients (3.14) and damping function (3.16).

<table>
<thead>
<tr>
<th>Functional</th>
<th>Mean deviation [kJ/mol]</th>
<th>$(k_B T)$ weighted deviation [kJ/mol]</th>
<th>$(3k_B T)$ weighted deviation [kJ/mol]</th>
<th>Maximum deviation [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP</td>
<td>1.62</td>
<td>15.28</td>
<td>1.54</td>
<td>8.43</td>
</tr>
<tr>
<td>BLYP</td>
<td>1.43</td>
<td>36.53</td>
<td>2.51</td>
<td>6.44</td>
</tr>
<tr>
<td>HCTH</td>
<td>1.44</td>
<td>5.43</td>
<td>0.96</td>
<td>9.74</td>
</tr>
<tr>
<td>PBE</td>
<td>1.58</td>
<td>11.73</td>
<td>1.42</td>
<td>11.68</td>
</tr>
<tr>
<td>PW91</td>
<td>1.77</td>
<td>17.81</td>
<td>1.78</td>
<td>12.96</td>
</tr>
</tbody>
</table>

B.3 Molecular correction

In Table B.2 the errors relative to second order Møller-Plesset perturbation theory are summarized for DFT corrected using a molecular correction scheme as proposed by Wu et al. [339]. The underlying Equations for the dispersion coefficient can be found in (3.14) and the according damping function is given in (3.16).

The according interaction energy profiles may be found in Figs. B.4 and B.5. The results have been discussed in Section 3.5.
Figure B.4: Interaction energy profiles for the water naphthalene interaction from dispersion corrected DFT using the molecular correction scheme. The graphs in the first column correspond to configurations where the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second column it is parallel. In the first row the water molecule is centered on the central bond and in the second row it is centered on top of one of the aromatic rings, the dipole moment points orthogonally towards the naphthalene. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Figure B.5: Interaction energy profiles for the water naphthalene interaction from dispersion corrected DFT using the molecular correction scheme. The graphs in the first column correspond to configurations where the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second column it is parallel. In the first row the water molecule is centered on the central bond and in the second row it is centered on top of one of the aromatic rings, the dipole moment points orthogonally away from the naphthalene. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
### B.4 Atomistic correction

Three different atomistic schemes are considered for the dispersion correction. In the following, the errors relative to second order Møller-Plesset perturbation theory are summarized.

First we consider the scheme as proposed by Elstner et al. [89]. The underlying Equations for the combination of dispersion coefficients can be found in (3.19) and the according damping function is given in (3.23) The summarized errors may be found in Table B.3.

Wu and Yang proposed a different correction scheme [338]. The underlying Equations for the combination of dispersion coefficients can be found in (3.20) and the according damping function is given in (3.21) The summarized errors may be found in Table B.4.

Alternatively, Wu and Yang suggest the use of the damping function (3.22).
Table B.5: Summarized deviations of DFT calculations corrected according to Wu and Yang [338] using mixing rule (3.20) and damping function (3.22).

<table>
<thead>
<tr>
<th>Functional</th>
<th>mean deviation [kJ/mol]</th>
<th>($k_B T$) weighted deviation [kJ/mol]</th>
<th>(3 $k_B T$) weighted deviation [kJ/mol]</th>
<th>maximum deviation [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP</td>
<td>1.25</td>
<td>9.55</td>
<td>1.07</td>
<td>5.84</td>
</tr>
<tr>
<td>BLYP</td>
<td>1.49</td>
<td>31.95</td>
<td>2.41</td>
<td>12.34</td>
</tr>
<tr>
<td>HCTH</td>
<td>1.21</td>
<td>9.93</td>
<td>1.11</td>
<td>7.55</td>
</tr>
<tr>
<td>PBE</td>
<td>1.09</td>
<td>14.36</td>
<td>1.09</td>
<td>3.30</td>
</tr>
<tr>
<td>PW91</td>
<td>1.38</td>
<td>22.28</td>
<td>1.71</td>
<td>4.55</td>
</tr>
</tbody>
</table>

With this, the following errors are obtained. The summarized errors may be found in Table B.5.

The according interaction energy profiles may be found in Figs. B.6, B.7, B.8, and B.9. The results have been discussed in Section 3.5.
Figure B.6: Interaction energy profiles for the water naphthalene interaction from DFT corrected with an atomic correction term. Different correction schemes are sorted by columns, different geometries are sorted by rows. The first column shows the results for mixing rule (3.19) and damping function (3.23). The second column shows the results for mixing rule (3.20) and damping function (3.21) and the third column shows the results for mixing rule (3.20) and damping function (3.22). For the graphs in the first row the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second row it is parallel. In both rows, the water molecule is centered on the central bond and the water dipole moment points orthogonally towards aromatic plane. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Figure B.7: Interaction energy profiles for the water naphthalene interaction from DFT corrected with an atomic correction term. Different correction schemes are sorted by columns, different geometries are sorted by rows. The first column shows the results for mixing rule (3.19) and damping function (3.23). The second column shows the results for mixing rule (3.20) and damping function (3.21) and the third column shows the results for mixing rule (3.20) and damping function (3.22). For the graphs in the first row the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second row it is parallel. In both rows, the water molecule is centered on an aromatic ring of naphthalene and the water dipole moment points orthogonally towards aromatic plane. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Figure B.8: Interaction energy profiles for the water naphthalene interaction from DFT corrected with an atomic correction term. Different correction schemes are sorted by columns, different geometries are sorted by rows. The first column shows the results for mixing rule (3.19) and damping function (3.23). The second column shows the results for mixing rule (3.20) and damping function (3.21) and the third column shows the results for mixing rule (3.20) and damping function (3.22). For the graphs in the first row the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second row it is parallel. In both rows, the water molecule is centered on the central bond and the water dipole moment points orthogonally away from the aromatic plane. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Figure B.9: Interaction energy profiles for the water naphthalene interaction from DFT corrected with an atomic correction term. Different correction schemes are sorted by columns, different geometries are sorted by rows. The first column shows the results for mixing rule (3.19) and damping function (3.23). The second column shows the results for mixing rule (3.20) and damping function (3.21) and the third column shows the results for mixing rule (3.20) and damping function (3.22). For the graphs in the first row the water plane is orthogonal to the leading axis of the naphthalene molecule, in the second row it is parallel. In both rows, the water molecule is centered on an aromatic ring of naphthalene and the water dipole moment points orthogonally away from the aromatic plane. Black line: reference data, green with squares: B3VWN, blue with diamonds: BLYP, red with circles: B3LYP, cyan with triangles: HCTH, brown with pluses: PBE, orange with stars: PW91.
Appendix C

The electrostatic interactions between dipoles and charges

In this appendix the electrostatic interaction between charges and dipoles and their computation will be described in detail. In particular, it will be focused on the computation of the interaction energy, the force and the electric field. After the continuum representation of the interactions, the Ewald representation will be considered and the efficient computation based on the smooth particle mesh Ewald scheme will be explained. These algorithms have been implemented in FASTTUBE and the presented summary is based on the seminal work of Toukmaji et al. [306]. This appendix is therefore rather intended to be a documentation of the code implemented in FASTTUBE. For the theoretical background the reader is referred to standard literature for the Ewald summation [9] or to the appropriate journal publications of Essman et al. [90] and Toukmaji et al. [306].

C.1 Continuum electrostatics

The charge-charge interaction

The continuum representation of the charge-charge interaction and the according force are given by:

\[ U = \frac{1}{4\pi \epsilon_0} \frac{q_i q_j}{r} \]  \hspace{1cm} (C.1)

\[ F = \frac{1}{4\pi \epsilon_0} \frac{q_i q_j}{r^3} \vec{r} \]  \hspace{1cm} (C.2)

Where \( q \) is the charge on particles \( i \) and \( j \) at distance \( r \) and the permittivity of vacuum is represented by \( \epsilon_0 \). The electric field generated by a charge \( q_j \) is given
by

$$E = \frac{1}{4\pi\varepsilon_0} \frac{q_j}{r^3} r.$$  \hspace{1cm} (C.3)

The force acting on a charge in an electrical field is therefore given by

$$F = qE.$$  \hspace{1cm} (C.4)

**The charge-dipole interaction**

The charge-dipole interaction and the according force are given by

$$U = \frac{1}{4\pi\varepsilon_0} \left( \frac{\mu_j \cdot r}{r^3} \right) q_i.$$  \hspace{1cm} (C.5)

$$F = \frac{1}{4\pi\varepsilon_0} \left( \frac{3.0 (r \cdot \mu_j) r q_i}{r^5} - \frac{\mu_j q_i}{r^3} \right).$$  \hspace{1cm} (C.6)

where $\mu_j$ is the dipole moment on particle $j$. Thus, the electric field generated by a dipole $\mu_j$ is

$$E = \frac{1}{4\pi\varepsilon_0} \left( \frac{3.0 (r \cdot \mu_j) r}{r^5} - \frac{\mu_j}{r^3} \right).$$  \hspace{1cm} (C.7)

**The dipole-dipole interaction**

The dipole-dipole interaction and the according force are

$$U = \frac{1}{4\pi\varepsilon_0} \left( -\frac{3(\mu_1 \cdot r)(\mu_j \cdot r)}{r^5} + \frac{\mu_1 \cdot \mu_j}{r^3} \right).$$  \hspace{1cm} (C.8)

$$F = \frac{1}{4\pi\varepsilon_0} \left( -\frac{15(\mu_1 \cdot r)(\mu_j \cdot r) r}{r^7} + \frac{3(\mu_1 \cdot r)\mu_j}{r^5} + \frac{3(\mu_j \cdot r)\mu_i}{r^5} + \frac{\mu_1 \cdot \mu_i r}{r^5} \right).$$  \hspace{1cm} (C.9)

Thus for a dipole $\mu$ in an electric field

$$U = -\mu \cdot E$$  \hspace{1cm} (C.10)

and accordingly

$$F = \nabla (\mu \cdot E).$$  \hspace{1cm} (C.11)
C.2 Ewald summation techniques

In periodic domains Ewald summation techniques allow to compute electrostatic interactions efficiently. The concept of the Ewald summation relies on a splitting of the interaction energy into three contributions

\[ U = U_{\text{dir}} + U_{\text{rec}} + U_{\text{self}}. \]  

(C.12)

The direct interaction \( U_{\text{dir}} \) is laid out such that it converges within a cutoff distance \( r_c \). Further contributions are the reciprocal energy \( U_{\text{rec}} \) and the self energy term \( U_{\text{self}} \). Where \( U_{\text{self}} \) is relatively simple and \( U_{\text{rec}} \) may be evaluated as a lattice sum. In the following we will highlight the different terms in more detail and it is focused on the computational and implementational aspects. For a detailed derivation of the Ewald summation, the reader is referred to standard textbooks, which treat this topic extensively, e.g. [9].

C.2.1 Direct interaction

The direct interaction is a two body interaction between all particles. Effectively, it is a damped electrostatic interaction. Due to the damping the contribution is negligible after a certain cutoff distance \( r_c \), which allows for an efficient computation in cell list or Verlet list [313] approaches. It is convenient to write the damped direct interactions by defining the series

\[ B_0 (r) = \frac{\text{erfc} (\beta r)}{r} \] 

(C.13)

\[ B_k (r) = \frac{1}{r^2} \left[ (2k - 1) B_{k-1} (r) + \frac{(2\beta^2)}{\beta \sqrt{\pi}} \exp (-\beta^2 r^2) \right], \quad k > 0, \] 

(C.14)

subject to the following relationship

\[ \frac{dB_k (r)}{dr} = -r B_{(k+1)} (r). \]  

(C.15)

Here \( \beta \) is a parameter that determines the damping of the direct electrostatic interaction. The charge-charge interaction can then be defined as

\[ U_{\text{dir}} = \frac{1}{4\pi \epsilon_0} B_0 (r) q_i q_j \] 

(C.16)
and the resulting force is

$$F_{dir} = \frac{1}{4\pi\varepsilon_0} r B_1 (r) q_i q_j.$$  \hfill (C.17)

Similarly, we obtain for the charge-dipole interaction the direct interaction energy and the force:

$$U_{dir} = \frac{1}{4\pi\varepsilon_0} B_1 (r) (\mu_j \cdot r) q_i$$  \hfill (C.18)

$$F_{dir} = \frac{1}{4\pi\varepsilon_0} \left[ B_2 (r) r (\mu_j \cdot r) q_i - B_1 (r) \mu_j q_i \right]$$  \hfill (C.19)

Finally, the screened dipole-dipole interaction is

$$U_{dir} = \frac{1}{4\pi\varepsilon_0} \left[ B_1 (r) (\mu_j \cdot \mu_i) - B_2 (r) (\mu_j \cdot r) (\mu_i \cdot r) \right]$$  \hfill (C.20)

$$F_{dir} = \frac{1}{4\pi\varepsilon_0} \left[ -r B_3 (r) (\mu_j \cdot r) (\mu_i \cdot r) + B_2 (r) \left\{ \mu_j (\mu_i \cdot r) + \mu_i (\mu_j \cdot r) + r (\mu_j \cdot \mu_i) \right\} \right].$$  \hfill (C.21)

These terms can all be evaluated in a straightforward manner and are common to all Ewald type techniques.

### C.2.2 Self interaction

The self energy does not vary in the different summation techniques and can be written as a sum over all particles $i$ in the system

$$U_{self} = -\frac{\beta}{\sqrt{\pi}} \sum_i^N \left( q_i^2 + \frac{2\beta^2}{3} |\mu_i|^2 \right),$$  \hfill (C.22)

where $\beta$ is a screening parameter used to achieve fast convergence of the direct interaction. This self energy results in a self electric field given by:

$$E_{self} (r_i) = \frac{4\beta^3}{3\sqrt{\pi}} \mu_i.$$  \hfill (C.23)

Note that there is no self force.
C.2.3 Reciprocal interaction

The reciprocal part of the interaction energy can be calculated in different ways. The conceptually most simple way is the standard Ewald summation technique. Here, the interaction which has not been considered in the direct interaction is accounted for. To do this a summation over all periodic images of the system in question is performed which is achieved using a Fourier transform. More advanced techniques include the Particle Mesh Ewald (PME) and the Smooth Particle Mesh Ewald method, where the charges are interpolated to a grid and the poisson equation is solved using fast Fourier transforms. First the standard Ewald Summation technique will be sketched and then the SPME method will be presented.

**Standard Ewald Summation**

The reciprocal energy can be written as

\[
U_{rec} = \frac{1}{2\pi V} \sum_{m \neq 0} \frac{\exp \left( -\pi^2 m^2 \beta^2 \right)}{m^2} \times \sum_{i=1}^{N} \sum_{j=1}^{N} (q_i + \mu_i \cdot \nabla_i) (q_j + \mu_j \cdot \nabla_j) \exp \left( 2\pi i m \cdot (r_j - r_i) \right)
\]  

(C.24)

where \( m \) are the reciprocal lattice vectors. This multiple sum can be rewritten and simplified to

\[
U_{rec} = \frac{1}{2\pi V} \sum_{m \neq 0} \frac{\exp \left( -\pi^2 m^2 \beta^2 \right)}{m^2} S(m) S(-m)
\]  

(C.25)

using the structure factors defined as

\[
S(m) = \sum_{j=1}^{N} (q_j + \mu_j \cdot \nabla_j) \exp \left( 2\pi i m \cdot r_j \right)
\]

(C.26)

\[
= \sum_{j=1}^{N} (q_j + 2\pi i \mu_j \cdot m) \exp \left( 2\pi i m \cdot r_j \right)
\]
The corresponding reciprocal force is then given by

\[ F_{\text{rec}} = \frac{2i}{V} \sum_{m \neq 0} \frac{m \exp \left( -\pi^2 m^2 / \beta^2 \right)}{m^2} \times \exp \left( -2\pi i m \cdot r_i \right) S(m) \]  

(C.27)

and the electric field is

\[ E_{\text{rec}} = \frac{2i}{V} \sum_{m \neq 0} \frac{m \exp \left( -\pi^2 m^2 / \beta^2 \right)}{m^2} \times (q_i - 2\pi i \mathbf{p}_i \cdot m) \exp \left( -2\pi i m \cdot r_i \right) S(m). \]  

(C.28)

In the standard Ewald summation these sums are evaluated directly. Implemented in the traditional way, this summation scales quadratically with the number of particles and is therefore prohibitively expensive. It has, however, been shown that it can be implemented in order \( N^{3/2} \) steps at the cost of excessive memory consumption [248].

The computational cost of the traditional implementation and the excessive memory consumption of the more efficient implementation are a significant disadvantage. This disadvantage can be overcome if the charge and dipole contributions are interpolated to a grid and Fast Fourier Transforms (FFTs) are used to compute the aforementioned sums more efficiently. This approach is implemented in FASTTUBE and will be outlined in the next section.

**Smooth Particle Mesh Ewald**

In the Smooth Particle Mesh Ewald approach (SPME) the electrostatic structure factors are approximated by replacing the exponentials by appropriate interpolation of their values onto nearby grid points [306, 90]. The sketch of the approach presented here relies strongly on the description presented by Toukmaji et al. [306]. For details beyond this summary the reader is therefore referred to the aforementioned publication.

We are considering a grid of \( K_1, K_2 \) and \( K_3 \) grid points with scaled fractional coordinates

\[ u_i = \frac{K_i}{L_i} r_i, \]  

(C.29)
where \( L_i \) is the extent of the domain in dimension \( i \). First it is important to note that

\[
\exp(2\pi i \mathbf{m} \cdot \mathbf{r}) = \exp\left(2\pi i \frac{m_1 u_1}{K_1}\right) \exp\left(2\pi i \frac{m_2 u_2}{K_2}\right) \times \exp\left(2\pi i \frac{m_3 u_3}{K_3}\right). \tag{C.30}
\]

Now these exponentials can be approximated using simple Euler exponential splines, thus:

\[
\exp\left(2\pi i \frac{m_i u_i}{K_i}\right) \approx b_i \left(\frac{m_i}{K_i}\right) \sum_{k=-\infty}^{\infty} M_p (u_i - k) \exp\left(2\pi i \frac{m_i k}{K_i}\right) \tag{C.31}
\]

where \( M_p \) are splines of order \( p \) and the spline of order 1 is defined as

\[
M_1(u) = \begin{cases} 
1 & \text{if } 0 \leq u \leq 1 \\
0 & \text{otherwise}
\end{cases} \tag{C.32}
\]

and splines of arbitrary order may be computed recursively

\[
M_{p+1}(u) = \int_{-\infty}^{\infty} M_p(u - s) M_1(s) ds = M_p \times M_1(u). \tag{C.33}
\]

The coefficients are defined as follows

\[
b_i \left(\frac{m_i}{K_i}\right) = \frac{\exp\left(2\pi i \frac{(p-1)m_i}{K_i}\right)}{\sum_{k=0}^{p-2} M_p (k + 1) \exp\left(2\pi i m_i \frac{k}{K_i}\right)}. \tag{C.34}
\]

If the charge density is now interpolated to the grid points \((k_1, k_2, k_3)\) this results in the following sum which is locally restricted, due to the finite support of the splines and therefore scales linearly with the number of particles.

\[
Q^R (k_1, k_2, k_3) = \sum_{i=1}^{N} (q_i + \mu_i \cdot \nabla_i) \times [M_p (u_{1i} - k_1) M_p (u_{2i} - k_2) M_p (u_{3i} - k_3)]. \tag{C.35}
\]
APPENDIX C. THE ELECTROSTATIC INTERACTIONS BETWEEN DIPOLES AND CHARGES

It can now be shown that the structure factor can then be approximated as

$$\tilde{S}(m) = b_1 \left( \frac{m_1}{K_1} \right) b_2 \left( \frac{m_2}{K_2} \right) b_3 \left( \frac{m_3}{K_3} \right) Q^F (m_1, m_2, m_3)$$

for $-\frac{1}{2} \leq \frac{m_\alpha}{K_\alpha} < \frac{1}{2}, \alpha = 1, 2, 3$

for $-\frac{1}{2} \leq \frac{m_\alpha}{K_\alpha} < \frac{1}{2}, \alpha = 1, 2, 3$

$$0, \text{ otherwise}$$

(C.36)

Here $Q^F$ is the discrete Fourier transform of the interpolated charges density

$$Q^F (m_1, m_2, m_3) = \sum_{k_1=0}^{K_1-1} \sum_{k_2=0}^{K_2-1} \sum_{k_3=0}^{K_3-1} Q^R (k_1, k_2, k_3)$$

$$\times \exp \left[ 2\pi i \cdot \left( \frac{m_1 k_1}{K_1} + \frac{m_2 k_2}{K_2} + \frac{m_3 k_3}{K_3} \right) \right].$$

(C.37)

With these redefined structure factors it is now possible to compute the approximate reciprocal energy as

$$\tilde{U}_{\text{rec}} = \frac{1}{2\pi V} \sum_{m \neq 0} \exp \left( -\frac{\pi^2 m^2 \beta^2}{m^2} \right) \tilde{S}(m) \tilde{S}(-m).$$

(C.38)

The coefficients $b_i$ and the prefactor which is multiplied with the structure factors, both, do not depend on the charge distribution and may therefore be precomputed in the influence function $G^F$

$$G^F (m_1, m_2, m_3) = \frac{1}{\pi V} \exp \left( -\frac{\pi^2 m^2 / \beta^2}{m^2} \right)$$

$$\left| b_1 \left( \frac{m_1}{K_1} \right) \right|^2 \cdot \left| b_2 \left( \frac{m_2}{K_2} \right) \right|^2 \cdot \left| b_3 \left( \frac{m_3}{K_3} \right) \right|^2$$

for $-\frac{1}{2} \leq \frac{m_\alpha}{K_\alpha} < \frac{1}{2}, m^2 \neq 0$

$$= 0, \text{ otherwise.}$$

(C.39)

Thus the reciprocal energy can be written as

$$\tilde{U}_{\text{rec}} = \frac{1}{2} \sum_{m \neq 0} G^F (m) \cdot Q^F (m) \cdot Q^F (-m)$$

$$= \frac{1}{2} \sum_{m_1=0}^{K_1-1} \sum_{m_2=0}^{K_2-1} \sum_{m_3=0}^{K_3-1} Q^R (m) \left( G^R \ast Q^R \right) (m)$$

(C.40)

(C.41)
which corresponds to a convolution in real space. The corresponding approximate potential can then be written as:

\[
\tilde{\Phi}_{\text{rec}}(r_i) = \frac{1}{2} \sum_{m_1=0}^{K_1-1} \sum_{m_2=0}^{K_2-1} \sum_{m_3=0}^{K_3-1} M_p(u_{1i} - m_1) M_p(u_{2i} - m_2) \\
\times M_p(u_{3i} - m_3) \left( G_R \star Q^R \right)(m)
\]  \hfill (C.42)

To compute the approximate reciprocal energy, first the charge distribution \(Q^R\) is interpolated onto a grid of \(K_1, K_2\) and \(K_3\) grid points. This charge distribution is then transformed into Fourier space using fast Fourier transforms in order to obtain \(Q^F\). \(Q^F\) is then multiplied pointwise with the precomputed \(G^F\). The product is then transformed back into real space to obtain the convolution \((G^R \star Q^R)\). To obtain the reciprocal energy this is then multiplied pointwise at every grid point with the charge distribution and summed up.

Obtaining the electric field and the forces is slightly more complicated as the derivatives with regards to the particle positions \(r_i\) have to be taken. For the electric field this results in

\[
E_{\text{rec}}(r_i) = - \left( \frac{\partial \tilde{\Phi}_{\text{rec}}}{\partial u_{1i}} \nabla u_{1i} + \frac{\partial \tilde{\Phi}_{\text{rec}}}{\partial u_{2i}} \nabla u_{2i} + \frac{\partial \tilde{\Phi}_{\text{rec}}}{\partial u_{3i}} \nabla u_{3i} \right)
\]  \hfill (C.43)

with

\[
\frac{\partial \tilde{\Phi}_{\text{rec}}}{\partial u_{\alpha i}} \nabla u_{\alpha i} = \sum_m \frac{\partial}{\partial u_{\alpha i}} \left[ M_p(u_{1i} - m_1) M_p(u_{2i} - m_2) \\
\times M_p(u_{3i} - m_3) \right] \left( G^R \star Q^R \right)(m).
\]  \hfill (C.44)

For the force, we obtain accordingly

\[
F_{\text{rec}}(r_i) = - \left( \frac{\partial \tilde{U}_{\text{rec}}}{\partial u_{1i}} \nabla u_{1i} + \frac{\partial \tilde{U}_{\text{rec}}}{\partial u_{2i}} \nabla u_{2i} + \frac{\partial \tilde{U}_{\text{rec}}}{\partial u_{3i}} \nabla u_{3i} \right)
\]  \hfill (C.45)

with

\[
\frac{\partial \tilde{U}_{\text{rec}}}{\partial u_{\alpha i}} \nabla u_{\alpha i} = \sum_m \frac{\partial Q^R}{\partial u_{\alpha i}}(m) \left( G^R \star Q^R \right)(m).
\]  \hfill (C.46)
Here, the evaluation of the partial derivative is slightly more tricky, as

$$\frac{\partial Q^R}{\partial u_{1i}}(m_1, m_2, m_3) =$$

$$= q_i \frac{\partial M_p}{\partial u_{1i}} (u_{1i} - m_1) M_p (u_{2i} - m_2) M_p (u_{3i} - m_3)$$

$$+ (\mu_i \cdot \nabla u_{1i}) \frac{\partial^2 M_p}{\partial u_{1i}^2} (u_{1i} - m_1) M_p (u_{2i} - m_2) M_p (u_{3i} - m_3)$$

$$+ (\mu_i \cdot \nabla u_{2i}) \frac{\partial M_p}{\partial u_{1i}} (u_{1i} - m_1) \frac{\partial M_p}{\partial u_{2i}} (u_{2i} - m_2) M_p (u_{3i} - m_3)$$

$$+ (\mu_i \cdot \nabla u_{2i}) \frac{\partial M_p}{\partial u_{1i}} (u_{1i} - m_1) M_p (u_{2i} - m_2) \frac{\partial M_p}{\partial u_{3i}} (u_{3i} - m_3) \quad (C.47)$$

As the interpolation scales linearly, however, the step which scales least favorably are the Fourier transformations. Since we are operating on a grid we can use Fast Fourier Transformations that scale $O(N \log N)$. This scaling is a significant improvement with regards to the scaling of the traditional Ewald summation.
Appendix D

Molecular dynamics with FASTTUBE

FASTTUBE is a molecular dynamics package that was developed at ETH Zurich. It was initially written to simulate CNTs and mono-atomic Lennard-Jones fluids. Later, it was parallelized and extended to include flexible and rigid water models and a generalized framework for the treatment of non-bonded pair interactions was added [333]. During this thesis the code was extended to include any kind of bonded interactions describing bonds, angles and torsion potentials. Support for the AMBER 96 force field [59] was ensured and additional software to generate topologies for RNA, DNA and peptides was added. Amongst many features, a parallel implementation of smooth particle mesh ewald [90], the support for polarizable force fields, metadynamics [183] and generalized steered molecular dynamics were added, too. The extensions and some basic functionality is documented here. For a detailed and complete documentation of FASTTUBE the thesis of Thomas Werder [333] should be considered, too.

D.1 Units

FASTTUBE operates with a consistent set of units. These units apply throughout the whole program as well as in the input output routines. A summary can be found in table D.1.

D.2 Flowchart

The essential parts of the time stepping algorithm of FASTTUBE are depicted in figure D.1. The components of the flowchart are explained below.

1. Initialization. In this step, FASTTUBE reads data files containing the positions and velocities of all particles in the system, the connectivity (i.e. topology), the control instructions and the force field information.
Measure & Unit & Conversion Factors \\
--- & --- & --- \\
Length & nm & $10^{-9}$ m \\
Time & ps & $10^{-12}$ s \\
Mass & amu & $1.6606 \times 10^{-27}$ kg \\
Temperature & K & \\
Charge & e & $1.602 \times 10^{-19}$ C \\
Energy & kJ mol$^{-1}$ & 0.2390 kcal mol$^{-1}$ \\
Force & kJ mol$^{-1}$ nm$^{-1}$ & \\
Pressure & kJ mol$^{-1}$ nm$^{-3}$ & 16.606 bar \\
Velocity & nm ps$^{-1}$ & $10^{-3}$ m s$^{-1}$ \\
Density & amu nm$^{-3}$ & 1.6606 kg m$^{-3}$ \\
Electrical fields & kJ mol$^{-1}$ e nm & 0.0104 V nm$^{-1}$ \\

*Table D.1: The units of the MD package FASTTUBE.*

2. **Boundary.** Periodic boundary conditions are applied in all directions. Ghost layers are created and, in parallel runs, exchanged between processors [333].

3. **Polarizability.** If a polarizable force field is considered, the electric field at the particle positions is computed. From this, the individual dipole moments are computed and an updated electric field is computed. This loop is repeated until convergence.

4. **Force computation.** All particles are ranked in cell lists. The forces are computed as the gradient of the interaction potential.

5. **Velocity update.** The new velocities are obtained from the leap-frog scheme.

6. **Position update.** New unconstrained positions are computed from the leap-frog scheme.

7. **SHAKE.** The SHAKE algorithm is used to resolve the constraints and the positions are corrected to satisfy the constraints.

8. **External Bath.** A Berendsen thermostat and a Berendsen barostat are applied to equilibrate the system specific temperature $T$ and pressure $P$. The thermostat scales the velocities of the individual particles of the center of mass velocities of molecules. The barostat scales the positions of the individual particles and the size of the computational domain.
D.3. POLARIZABILITY

Figure D.1: Flowchart of the MD package FASTTUBE.

9. **File Output.** At predefined frequencies the new positions, velocities, forces and energies are written to trajectory files for later analysis.

**D.3 Polarizability**

Support for polarizable force fields is available in FASTTUBE. The implementation closely follows Toukmaji *et al.* [306] and may be used with SPME or truncation. Starting from an initial guess, the electric field and the dipole moments in the system are computed until self-consistency. Convergence is checked on the root
mean square change of the dipole moments

\[ \text{rms}^2 = \frac{1}{N} \sum_{i=1}^{N} |\mu_i(m, t) - \mu_i(m-1, t)|^2 < \text{(tolerance)}^2, \]  

where \( \mu_i(m, t) \) indicates the dipole moment of particle \( i \) in the \( m \)-th iteration at time \( t \). The tolerance for energy conservation is set to 0.00021 e nm, which corresponds to \( 10^{-3} \) Debye [306]. First and second order predictor schemes are available [306] in order to reduce the number of iterations needed to reach self-consistency.

To simulate dipole dynamics we implemented a Car Parrinello extended Lagrangian approach [306]. Due to parameter dependent results, the implementation was not committed to the main branch of FASTTUBE. The code is, however, available in a separate repository.

D.4 Force computation

In chapter 4 it is indicated, that the interactions in MD simulations may be divided into intra- and intermolecular interactions. FASTTUBE implements a wide range of interactions, a summary of which is given below.

D.4.1 Intramolecular interactions

Bonds

There are four bond models implemented in FASTTUBE: a dummy bond, a constrained bond, the Morse bond and the harmonic bond potential. The dummy bond considers a pair of particles to be bonded, but does not compute any interaction. In a constrained bond the distance between two particles will be kept constant throughout the course of a simulation, this is ensured using the SHAKE algorithm, see chapter 4 and section D.6. The Morse bond potential was presented in equation 4.10 and the harmonic stretching potential was considered in equation 4.9.

Angles

There are four angle models implemented in FASTTUBE: a dummy angle potential, a constrained angle potential, a harmonic angle potential and a harmonic
angle potential. While in the dummy angle potential a triplet of particles is con-
considered to form an angle, there is no interaction computed. A constrained angle is
kept constant throughout the course of a simulation by a modified SHAKE algo-
algorithm, see section D.6. The harmonic cosine and the harmonic angle potentials are
implemented as in equations 4.11 and 4.12.

Dihedrals

Four different torsion potentials are implemented in FASTTUBE: a twofold torsion
potential, a n-fold torsion potential a dummy torsion potential and a correction po-
tential for 1-4 interactions. While the dummy torsion considers four particles to
form a dihedral, there is no interaction computed. The 2-fold torsion is retained
in the code for backward compatibility, but as it is only a specific realization of
the general n-fold torsion it will not be discussed here. The n-fold torsion potential
corresponds to a single term in the sum reported in equation 4.13, the code
currently supports multitudes (n) up to 4. The correction potential for 1-4 interac-
tions is a work around for conflicts between different force fields. Usually, force
fields consider a contribution from the nonbonded interactions for the 1-4 interac-
tion of dihedrals. If different force fields are mixed, some of the 1-4 interactions
have to be corrected. The correction potential therefore allows for the inclusion
of fractional contributions of the Lennard-Jones and Coulomb interaction on 1-4
pairs.

D.4.2 Intermolecular interactions

Intermolecular interactions in MD are usually pair based interactions. FASTTUBE
provides a general framework to treat nonbonded pair based interactions. Cur-
rently implemented intermolecular interactions include variants to the standard
Lennard-Jones interaction with

\[ V_{LJ} = 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^n - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right], \]  

(D.2)

where the parameter \( n \) may be 7, 10, 11, 12 or 18. \( \epsilon_{ij} \) and \( \sigma_{ij} \) are parameters
which have to be set by the user. Other interaction potentials include the Coulomb
interaction (see equation 4.17 and appendix C) and the Buckingham potential [46],
which has the following functional form

\[ V_B = a_{ij} \exp \left( -b_{ij}r_{ij} \right) - \frac{c_{ij}}{r_{ij}^6}, \]  

(D.3)
where $a_{ij}$, $b_{ij}$ and $c_{ij}$ are parameters which have to be set by the user.

Nonbonded interactions are computed in a cell list approach [9] and are truncated after a cutoff radius that is set by the user. The coulomb interaction between charges and charges, charges and dipoles and dipoles and dipoles may also be computed in a smooth particle mesh Ewald based approach, where the pair based interaction is modified and long range contributions are corrected for by a mesh based approach, see appendix C.

### D.4.3 Long range electrostatics

Long range electrostatics in FASTTUBE may be truncated or may be treated with Ewald summation or Smooth Particle Mesh Ewald (SPME) [90]. For a detailed description of the Ewald summation technique and the SPME, please refer to appendix C.

### D.5 Time integration

The discretized equations of motion 4.1 are integrated using the leap frog algorithm [130]

\[ v_i^{n+1/2} = v_i^{n-1/2} + \delta t f_i^n / m_i, \]  
\[ r_i^{n+1} = r_i^n + \delta t v_i^{n+1/2}. \]  

The positions $r_i$ and $v_i$ are computed shifted by half a time step $\delta t$. The forces $f_i$ at time $n\delta t$ are used to update the velocities at time $(n - 1/2)\delta t$ and to obtain the velocities at time $(n + 1/2)\delta t$. With these velocities the positions at time $n\delta t$ are updated to obtain the positions at time $(n + 1)\delta t$. From the positions at time $(n + 1)\delta t$ new forces may now be computed. The local integration error is of $O(\delta t^3)$ in both, positions and velocities. The leap frog algorithm is an accurate and simple integration scheme [311].

### D.6 SHAKE

A description of the standard shake algorithm is provided in chapter 4. Additionally to the standard SHAKE algorithm FASTTUBE provides a similar algorithm to treat constrained angles. Angles are usually constrained using a pseudo bond
between the two particles that are not bonded. In FASTTUBE, a different approach is chosen and the angles are directly constrained. The constraint equations 4.18 are reformulated to

$$\cos \Theta_k^2 - \cos \Theta_{k,0}^2 = K_k = 0, \quad (D.6)$$

where $\Theta_k$ is the realization of the angle in constraint $k$ with target value $\Theta_0$. Apart from the reformulated constraint equation, the algorithm is identical to the one sketched in chapter 4. Shaking a water molecules in terms of two bonds and an angle instead of two bonds and a pseudo bond reduces the iterations needed until convergence of SHAKE by a factor of five. There are several alternate approaches to SHAKE which are however not implemented in FASTTUBE.

D.7 External baths

Both temperature and pressure usually do not correspond to target values after an MD simulation setup. The system has to be equilibrated to reach those target values. FASTTUBE provides the possibility to couple both, pressure and temperature to an external bath, according to an algorithm presented by Berendsen et al. [25].

D.7.1 Thermostat

Particles or molecules may be coupled to a Berendsen thermostat [25]. Given the system temperature $T$ and the reference temperature $T_0$, the Berendsen thermostat scales the velocities of the thermostated particles according to

$$v_{t+1/2, i} = v_{t+1/2, i} \left(1 + \frac{\delta t}{\tau_T} \left(\frac{T_0}{T} - 1\right)\right)^{\frac{1}{2}}, \quad (D.7)$$

where the strength of the coupling is determined by $\tau_T$, the characteristic time of coupling. For $\tau_T = \delta t$ the instantaneous temperature corresponds always to the reference temperature. A weaker coupling is obtained with $\tau_T > \delta t$. This results in the system temperature equilibrating to the target temperature, where the actual value of $\tau_T$ determines the speed of this process.

Barostat

The pressure is controlled by coupling the system to an external reservoir [25]. In a first order approximation, the pressure is inversely proportional to the volume.
Scaling the volume of the computational domain allows to control the pressure $P$. In FASTTUBE the volume is scaled with the factor

$$s = 1 + \Delta t \frac{\xi}{\tau} (P - P_0),$$  \hspace{1cm} (D.8)

where the ratio of compressibility $\xi$ and coupling time $\tau$ acts as a coupling parameter between the pressure $P$ and its reference value $P_0$.

The computational box may be scaled isotropically in all dimensions with a scaling factor

$$s' = s^\frac{1}{3}.$$  \hspace{1cm} (D.9)

Alternatively, anisotropic scaling may be considered. There are different ways of anisotropic scaling:

- Use the trace of the pressure tensor to scale all dimensions independently.
- Couple two dimensions of the pressure tensor and scale them independently from the third.
- Apply the whole scaling only in one or two dimensions of the computational box.

When the computational domain is rescaled all particle positions in that dimension are rescaled, too.

### D.8 Initialization and energy minimization

#### D.8.1 Velocity capping

Initial conditions for molecular dynamics simulations may be subject to large stresses and unfavorable configurations. This is usually the case when the van der Waals radii of two particles overlap. The resulting forces from frustrated initial conditions may exceed what can be handled with the integrator, presuming a usual time step. FASTTUBE implements a velocity capping approach to relax such configurations. If the absolute velocity exceeds a capping value, the velocity components are rescaled to the capping value. Alternatively, the three velocity components may also be capped individually.
D.8.2 Simulated annealing and quenching

In simulated annealing the temperature of a system is constantly reduced, until a minimum energy configuration is reached. Reducing the temperature corresponds to reducing the kinetic energy and therefore the velocity of the particles in the system. In FASTTUBE it is possible to rescale the velocities at every timestep with a constant factor, that is smaller than unity.

This approach can be used as a simulated annealing procedure to a minimum energy conformation. Usually, scaling factors close to unity are used for this purpose. Alternatively, this approach can be used to quench the system, i.e. to remove energy very quickly. When system is quenched, the scaling factor is usually chosen smaller than in simulated annealing.

D.9 External electrical fields

An external electrical field $E$ is imposed on the system by applying an additional force $f_{i}^{el}$ to all charged particles $i$ with charge $q_i$

$$f_{i}^{el} = q_{i}E.$$  (D.10)

FASTTUBE does not consider an energy contribution for the particles which are moving in the external electrical field. Simulations subject to an external electrical field are therefore not energy conserving and have to be thermostated.

D.10 Advanced methods

D.10.1 Collective variables

Collective variables are computed as a function of one or several individual particle coordinates

$$\sigma = \text{sigma}(x_{i})$$  (D.11)

Reaction pathways are usually defined in terms of collective variables, i.e. reaction coordinates. A framework to handle collective variables is implemented in FASTTUBE and a collection of collective variables is available, including for example the center of mass distance between two molecules, the radius of gyration, dihedral angles and more.
D.10.2 Metadynamics

**FastTube** comes with an implementation of Metadynamics [183]. A history dependent potential in the space of one or several collective variables promotes the sampling of configuration space in terms of the collective variables. At the realizations of collective variables from previous times \( t' \) Gaussian potential contributions are added to the potential energy landscape \( V_0 \) of the system

\[
V_{\text{effective}} = V_0 + \sum_{t' \leq t} W e^{-\frac{|\sigma(t) - \sigma(t')|^2}{2\delta_s}},
\]

where the height of the Gaussians is \( W \) and their width is determined by \( \delta_s \). The parameters for a metadynamics run are the height, the width of the Gaussians and the frequency at which the Gaussians are added. The Gaussian potentials make visited points in configuration space energetically less favorable and therefore hinder the system to return.

At the end of a metadynamics run, the potential energy landscape may be reconstructed from the Gaussians. The accuracy depends on the parameters of metadynamics. For a reasonable sampling, the width of the Gaussians should be approximately a third of the potential wells that should be reconstructed. The height of the Gaussians determines the resolution of the energy landscape and has to be determined together with the frequency of sampling, which is mainly determined by the diffusivity in the sampling space [183, 184].

D.10.3 Generalized steered molecular dynamics

**FastTube** implements a generalized version of steered molecular dynamics. A time dependent steering potential is applied to collective variables in order to steer a system along a given reaction coordinate. The method is described in detail in chapter 5.

D.10.4 Generalized restraints

Generalized restraints act on collective variables. A harmonic restraint potential acts on a collective variable and couples it harmonically to a restraint value \( \sigma_0 \)

\[
V_{\text{restraint}} = \frac{k}{2} |\sigma - \sigma_0|^2
\]

(D.13)
where $k$ is a coupling constant. Restraint potentials may be one-sided only and only act if the value of the collective variable $\sigma$ is larger (or smaller) than a threshold value $\sigma_0$. One-sided restraints may be used in metadynamics in order to restrict the sampling to a zone of interest.

D.11 Biomolecule builder

Biomolecule builder is an auxiliary program that allows to construct topologies for biomolecules as DNA, RNA and peptides. The program constructs the biomolecules from their respective building blocks, the nucleotides for RNA and DNA and amino acids for peptides. The building blocks are geometrically rearranged in space and reconnected. RNA and DNA are constructed in a helical configuration and peptides are stretched along the backbone. Different termini are available for the peptides. The configurations have to be minimized in configurational energy before they are used for an MD simulation.
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