Self-assembly via anisotropic interactions

Modeling association kinetics of patchy particle systems and self-assembly induced by critical Casimir forces

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1 Introduction

1.1 Self-assembly

Self-assembly is a key concept in soft condensed matter science. It is the non-dissipative spontaneous formation of structural order due to reversible interactions between individual components \[1, 2\]. A multitude of examples can be found in nature and include micelle or vesicle formation, folding of proteins, signaling networks via protein-protein binding, virus assembly, fibrilization of amyloidogenic peptides and compaction of DNA into chromosomes, see Fig. 1.1 for cartoon impressions of some of these processes. These examples show that the size and nature of the components and the interactions are diverse. Amphiphilic molecules assemble into micelles and vesicles, whereas entire proteins called capsomeres form the virus capsid protecting the genetic material, and the list could go further with length-scales reaching for the stars.

![Cartoon Impressions of Self-assembly Processes](image)

Figure 1.1: Examples of self-assembly in cartoon form where particles interact via the attractive purple patches. Left is an example of particle polymerization which could be used to depict fibrilization of amyloidogenic peptides [3]. Middle is part of a Kagome lattice built out of tri-block patchy particles of which the successful self-assembly has been reported [4]. Right is an image of particles clustering in micellar or tubular structures which Kraft et al. and Granick have shown to be realizable with patchy colloids [4–6].

Components typically do not change character before and after integration into the self-assembled structure. However, this is not always true as building blocks can also have changing internal structure. For example, amyloidogenic proteins...
folded into their native 3D structures do not form fibrils. It is the (partially) unfolded state of these proteins with the hydrophobic patches exposed that fibrilize into long chains. However, what is distinctive of self-assembly is that the individual components are not irreversible glued to each other such as a carbon atom in graphite. A bond is considered reversible if the energy of the bond is on the order of the thermal energy, $k_B T$, where $k_B$ is the Boltzmann constant and $T$ the temperature, as a single bond then still has considerable probability to break simply by thermal agitation, \emph{i.e.} the ceaseless random motion of molecules that is associated with heat. In the self-assembly examples mentioned above weak reversible interactions are crucial for shape and function. Proteins are allowed to diffuse through the lipids of cell membranes. Wrongly folded proteins or mistakes made in virus assembly can be fixed. Compacted DNA can be unwound when its necessary to read the genetic code.

We can find many more examples in a wide variety of scientific fields where systems ‘spontaneously’ organize into ordered patterns: in Belousov-Zhabotinsky reactions oscillating patterns emerge, in Rayleigh-Bénard convection regular structures of convections cells develop, in bacterial colonies cells grow in fractal shapes and in the desert sand dunes form undulations. However, in these examples continuous input of energy or reactants is necessary and these systems when forming these structures and patterns are therefore never in equilibrium. If the energy input to these systems is cut off, the formed structure would decay over time. We reserve the term self-organization to these type of non-equilibrium processes, and self-assembly specifically when no energy is dissipated and the system remains essentially in equilibrium. Of course, self-assembling systems can still be out of equilibrium. For example, it is the relaxation from a dilute solution stable at a high temperature towards the self-assembled ground-state structure when the temperature is lowered which is the process of self-assembly.

Although historically the term self-assembly was used in the study of virus capsids, when it was recognized that viruses self-assemble into mono-disperse finite-sized structures out of only a small set of subunits \cite{7-9}, today the principles of self-assembly hold great potential to be used for making building blocks for functional materials in nanotechnology, and thus the term has permeated into not only biology, physics and chemistry, but also materials science.

\subsection{Colloidal patchy particles}

This thesis discusses the self-assembly of colloidal particles. The term colloidal spans the group of particles with dimensions between 1 nm and 1 \(\mu\)m. Therefore, we can in principle view globular proteins and micrometer cells also as colloidal particles, or shorter, as colloids. Colloids have various applications and can be found in everyday materials such as in milk or mayonnaise as microscopic fat particles or in paint as tiny bits of pigment.

Another way to specify a particle as colloidal, is when in solution it is randomly buffeted around and its trajectory can be appropriately described by Brownian
motion, the erratic motion of particles due to constant collisions with solvent molecules. Due to Brownian motion, colloids are in principle able to explore configurations of the system autonomously. This is in stark contrast, of course, with larger particles such as sand grains which sediment and do not show Brownian motion. For these particles to form structural order input of energy is required. Additionally, colloids are large enough to be observed under a microscope. As such, well-defined mono-disperse colloidal systems have played a big role in the advancement of physics of soft condensed matter and nowadays serve as model systems to study phase transitions, e.g. nucleation, freezing, etc.

Colloids can also play the role of “atoms” and “molecules” in hierarchical structures for tomorrows materials. Much is known about how atoms form molecules, namely through retrosynthetic analysis where almost every large complex molecule can be constructed out of smaller cheaper molecules [10, 11]. Additionally even to some extent how molecules assemble into supramolecular structures, such as crown ethers, cryptands, catenanes and rotaxanes [12]. However, design principles for the assembly of objects on the (sub)micrometer scale with targeted functional properties remain largely unclear, due to the hierarchical assembly of a large number of constituents it requires. However, even though the blueprint of self-assembly for microscopic particles is not known, buildings blocks are numerous. Aside to naturally occurring colloids, recent advances in colloidal synthesis make it possible to create almost mono-disperse (sub)micrometer particles in various shapes and sizes: spheres, cubes, rods, plates, ellipsoids, tetrahedron, stars or snowman [13, 14]. Moreover, it has also become possible to selectively change part of the surface of colloids, creating anisotropy not through changing the shape, but by changing the physiochemical properties along the surface of particles [4, 15, 16]. Over the years, ‘patchy particles’ have become the umbrella term for these type of particles. Returning to the natural colloids, such as proteins, virus capsids or even cells, we see that they are also not isotropic. Capsomeres are globular proteins with attractive hydrophobic patches exposed on the surface. Amphiphilic molecules are anisotropic in shape due to a hydrophilic head and a hydrophobic tail. As such, anisotropic interactions is what drives self-assembly into finite size or open structures. The reason for this is twofold.

Firstly, adding anisotropy to microscopic particles helps in the design of building blocks for complex structures. Endowing particles anisotropy can result in discrete directed bonds, i.e. valency, between particles where the connection to molecular bond formation through electronic orbitals is quickly established. As seen in Fig. 1.1 colloids with two opposing binding sites or valences should form one-dimensional colloidal polymers, three valencies in one plane and each pair separated by 120 degrees will form a two-dimensional beehive and a tetrahedral valency quickly reminds us of carbon and in principle can assemble in the three dimensional colloidal diamond structure which is a holy grail for photonic crystals with a band-gap in the visible region. However, it turns out that the virtuality of the drawing board is far removed from the reality of the lab. Although certain successes have been reported [4, 5, 16-19], it remains problematic to actually de-
sign and observe targeted supracolloidal structures and discoveries are still mostly fortuitous. One such example is the Kagome crystal whose experimental successful formation was reported in 2011 [4] and a theoretical explanation of the stability of the crystal was given in 2013 [20]. Predictions from computer simulations and theory are, therefore, beneficial in the design of supracolloidal structures.

Secondly, anisotropic interactions are imperative for particles to cluster into finite size structures pre-empting bulk phase separation. Although maybe trite, it is important to realize that isotropic particles can not form finite size clusters before a liquid or solid phase kicks in. This stems from the fact that for finite size clusters to be stable, a strong interaction is necessary between colloids. For example, to induce dimer formation for colloids that interact with a range on the order of a tenth of the diameter, the bond strength should be on the order of ten times the thermal energy. However, at these bond energies, particles that solely bind via isotropic interactions have already long before condensed into a bulk phase. Therefore, it is critical for self-assembly that bulk phase separation is suppressed by lowering the temperature of condensation by means of lowering the bonding volume possible for interaction, i.e. creating valencies. Of course, when particles interact both anisotropically and isotropically, it is possible that finite sized structures form out of a condensed phase [3, 21].

Successful self-assembly of microscopic particles often relies on simple interactions such as hard sphere interactions, Van der Waals forces, depletion interactions, electrostatic, magnetic, sticky DNA, hydrophobic forces or critical Casimir forces [4, 5, 16, 18, 19, 22–26]. Kraft et al. have shown that by creating snowman shaped particles with one smooth and one rough lobe with differing depletion force strengths causes finite size micelle formation [5]. Moreover, by adding a second rough lob tubular structures are formed [6]. Janus particles, where half of the surface is repulsive or inert and the other half is attractive due to hydrophobic forces, dispersed in water arrange into micellar and tubular structures [17]. By adding another valency, a tri-block particle has shown to arrange into the Kagome lattice [4]. Additionally, Evers et al. have used the combination of anisotropically shaped micrometer particles, polymer repulsion and hydrophobic attractive forces to make virus like shells [19]. Finally, developments in partial surface functionalization with DNA, have opened up routes for very precise control due to the precise specificity of DNA base-pairs [16, 25].

### 1.3 Critical Casimir forces and patchy particles

Recently it has been shown that particles suspended in a critical binary liquid also experience a force [27–31]. This effective force was first recognized by Fisher and de Gennes in 1978 and is nowadays coined the critical Casimir force, reminiscent of the quantum Casimir force which occurs between parallel conducting plates in vacuum which confine zero-point fluctuations of the electromagnetic field when they are brought close to each other [32]. According to Fisher and de Gennes a thermodynamic analogue exists where an effective force between two surfaces
arises due to the confinement of solvent fluctuations (in density or in composition) between the two boundaries. When the correlation length (the effective size of the fluctuations) becomes of the order of the separation between these boundaries, the critical Casimir force becomes significant. The critical Casimir force lends its name due to the fact that this will be the case near the critical point of a binary liquid, at which the correlation length of the fluctuations diverges. Only recently was this force experimentally realized with colloids due to the advent of single particle manipulations with optical tweezers and advanced microscopy tools. Direct measurement using a single colloidal sphere and a planar surface immersed in a binary liquid mixture of water and 2,6-lutidine, observed that while approaching the critical temperature, the interaction increased both in range and in depth [28]. Additionally, Hertlein et al. showed that if the two opposing surfaces, from the sphere and the wall, preferentially adsorb different components of the solvent, a repulsive effective force arises. Interestingly, it has been demonstrated that the critical Casimir forces can also induce bulk phase transitions of colloids, even when the solvent mixture is prepared off critical [33–37]. By using refractive and density matched particles, 3D reconstructed confocal microscopy images show that isotropic sub-micrometer particles condense reversibly from a gas state first into a liquid state and subsequently into a FCC crystal upon approaching the critical point. Combined with a computational study it is demonstrated that this force can be modeled with a combination of an electrostatic repulsion and an attraction which is temperature dependent due to the fact that the range and the strength are dependent on the correlation length [34].

As mentioned above, if both surfaces preferentially adsorb the same component of the binary liquid, an attraction arises. In contrast, the surfaces repel when they have opposing chemical preferences. Therefore, critical Casimir forces highly depend on the boundary conditions imposed by the surface of the submerged particles. It opens up the possibility to use Casimir forces combined with patchy particles where the physicochemical properties, and thus the boundary conditions, can change along the surface due to the patches of the particle. The critical Casimir force is universal and does not require further functionalization of the surface similar to sticky DNA colloids, but is dependent on the nature of the surface of the particles. Moreover, Casimir forces take maximum advantage of the solvent fluctuations, and as such are temperature dependent and reversible. Thus critical Casimir forces can also be employed to induce self-assembly of patchy particles by tuning the temperature, mimicking molecular bonding at the colloidal scale, see Fig. 1.2.

It is interesting to note that there is considerable theoretical debate on the origin of the critical Casimir forces and the applicability of effective potentials to describe such interactions [38–41]. On the one hand there is the original work of Fisher and de Gennes which is analogous to the quantum version of the Casimir force, where the fluctuations in composition cause the interactions between surfaces. Several theoretical studies have shown how the universal scaling function behaves under different conditions, and these have been measured experimentally [42–47]. On the other hand, an attraction also arises by preferential adsorption
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Figure 1.2: Cartoon of the effects of submersing isotropic colloidal particles (left) or patchy particles (right) in a critical binary liquid of water and lutidine. The $x$-axis is the volume percentage of lutidine and the $y$-axis is the temperature. The thick grey line indicates where the mixture transitions from a completely mixed phase (below the line) to a demixed phase (above the line). In the blue and orange regions colloids start to attract as fluctuations arise whose correlation length increases with temperature and diverges at the critical point. Critical Casimir forces due to these fluctuations have been shown to induce phase transitions from gaseous to liquid to FCC crystal states upon raising the temperature from $T_{gas}$ to $T_{liq}$ to $T_{cryst}$ also when the binary liquid of water and lutidine is prepared off-critical \cite{34, 36}. Left of the critical point lutidine is the minority component. On this side, particles with hydrophobic surfaces (orange) attract most strongly due to wetting of lutidine on the surface. Hydrophilic particles (blue) attract most strongly on the right side of the phase diagram. By incorporating both preferential wetting properties in one particle, i.e. making patchy particles, an even richer phase diagram is possible as shown on the right cartoon picture where use is made of the preferential wetting that should induce anisotropic bonding.

and the free energy gain in mixing adsorption profiles of two surfaces, which are necessarily also dependent on the correlation length. Especially when the mixture is prepared off-critical, the main driving force of the Casimir interaction is elusive and very much open to debate. The similarity between these two explanations, both depending on the solvent correlation length, makes it very difficult to study experimentally which explanation is closer to the truth. In this thesis we adopt a heuristic approach, which entails that we are interested in the effective result of the Casimir force and the applicability to self-assembly of anisotropic colloids. As such we do not give an answer to this open question. However, this discussion on the origin of the critical Casimir force being explained by either wetting effects or confined critical fluctuations does not detract from the fact that solvent mediated forces are highly promising for assembly of patchy particles.
1.4 Molecular simulation and simple models

Although the position of colloids can be observed over time under a microscope, the link between structure formation and the interactions between particles is not trivially understood. Molecular simulation often gives additional, explanatory or predicting information to experimental studies as it has access to detail still inaccessible to modern experimental techniques [48].

In molecular simulation we need to input all the interactions between all particles and integrate the equations of motion or use Monte Carlo to sample configuration space. At the most fundamental level, all matter and interactions should be described using quantum mechanics. However, for systems with particles large in size and number it becomes close to impossible to solve the multi-body time-dependent Schrödinger equation. Therefore, we make use of effective potentials, obtained through coarse graining, where most of the degrees of freedom of the system are effectively integrated out. Effective potentials keep the most essential ingredients of the interactions underlying the phenomena under study. Although it seems a limitation of computer simulations, distilling out the essential physics from a problem and incorporating it into a model that explains the trends quantitatively (or even qualitatively), leads to more understanding than simply using all positions and momenta of each atom as input into a black box and solving the Schrödinger equation. In this respect, globular proteins and synthetic colloids are closely related. By coarse graining proteins by leaving out most of the atomic details, they start to resemble colloidal particles synthesized in the lab. Of course, viewing proteins as rigid colloidal frameworks only works well for globular proteins whose internal structure does not change by for example unfolding of the native protein structure. When considering virus assembly, capsomer proteins that make up the virus typically remain globular. In chapter 4 and 5 we use this property of capsomers and model the proteins as inert spheres with attractive patches on the surface.

Figure 1.3: Picture of models used for simulation of colloidal suspensions. On the left isotropic particles interact through a square well potential where they repel when the hard cores (blue and orange) overlap and only attract if the purple regions overlap. In the case of the Kern-Frenkel potential for patchy particles in the middle, the bonding volume is reduced by an angular modulation which decreases the purple regions. A more realistic model can also be used where the patches continuously fade as the particles misalign gradually. A different way of incorporating directionality is by depositing one or multiple smaller particles on the bigger centre sphere. All constituents then interact through isotropic potentials.
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For colloidal systems, the solvent is typically left out of the calculation as the effective interaction between colloids is usually not dependent on the state of the solvent. Note however, that this assumption is still under debate for the critical Casimir force. A famous example where colloidal particles have successfully been modeled is the DLVO theory that describes the isotropic effective interaction in colloidal suspensions as a combination of an isotropic electrostatic repulsion and an isotropic van der Waals attraction [49]. Moreover, the depletion potential and the critical Casimir force has also been similarly modeled with a simple pair-potential [34, 35]. In theory and computer simulation, the simple square well potential is also extensively used, relying on the fact that thermodynamic properties of the system are usually not dependent on the microscopic details of the potential as dictated by the generalized law of correspondent states (GLCS) [50, 51]. Since these models are fundamentally isotropic in nature and the 'usual' potentials act on the centre of mass of the two particles, a modification is necessary to describe the interaction between anisotropic particles.

There are (at least) two different ways of making effective interactions directional. Firstly, an isotropic effective potential, $U_{iso}(r)$, such as the square well or Lennard-Jones potential, can be multiplied with a factor, $f(r, \Omega)$, which is dependent on the relative orientation of particles.

$$U(r, \Omega) = U_{iso}(r) f(r, \Omega)$$  \hspace{1cm} (1.1)

Typically, $f(r, \Omega)$ is a switching function which depends on the surface overlap of two opposing patches. Systematic studies have been performed with the Kern-Frenkel model, which extends the square well potential to patchy particles by excluding discrete parts of the bonding volume where the degree of exclusion is given by a patch width [52–60], see Fig. 1.3. When patchy interactions depend continuously on the surface overlap of patchy particles, continuous switching functions are employed (e.g. Gaussian) [61–64]. The advantage of these type of potentials is that the range and patch width can be varied independently. A disadvantage is that a particle pair can only form one bond assuming that patches are not allowed to overlap. A second way of adding directionality is by using a more molecular viewpoint where a particle is built out of two or more constituents where the constituents can in principle vary in size. All constituents interact through an isotropic potential which can depend on what type of pair of constituents, $\alpha\beta$, is considered:

$$U(r, \Omega) = \sum_{\alpha,\beta} U_{\alpha\beta}(r, \Omega)$$  \hspace{1cm} (1.2)

This is especially useful when the particle is anisotropic in shape [5, 6, 65]. However, spherical particles with patches on the surface can also be represented by one or more small particles deposited on the surface of a larger center particle [66, 67]. A disadvantage of this type of model is that the effective patch width is coupled to the range with which the small particle interacts as shown in Fig. 1.3 however no angles need to be calculated which simplifies the calculation significantly especially when using Brownian dynamics. Deciding which type of model gives the most natural potential highly depends on the patchy particle of interest.
1.5 Kinetics of self-assembly

Numerous theoretical and numerical work have studied the thermodynamic phase behavior of patchy particles, predicting not only interesting building blocks for novel functional materials, but also demonstrating new physical properties \[55, 66, 68, 69\]. These studies assume a more thermodynamic viewpoint of self-assembly, in which the system will always reach the global minimum of the free energy on going from a collection of disordered particles to the final structure. All potential energy interactions between particles, \(U\), determine the weight of configurations whereas the number of configurations at this energy determines the entropy, \(S\). The sum is the free energy, \(F = U - TS\). Despite the fact that the free energy is indispensable information to understand the principles of self-assembly, in experiments of synthetic colloids the global free energy minimum, \(i.e\). the thermodynamic stable state, is not always found. Due to the fact that prior to complete assembly a system can reach meta-stable states from which escape can be rare, it becomes very difficult to reach the target state \[70–74\]. From this we can appreciate the fact that

\[
\begin{align*}
G & \xleftarrow{k_{AG}} A \\
A & \xrightarrow[k_{AC}]{} C \\
A & \xleftarrow[k_{CA}]{} G \\
C & \xrightarrow[k_{GC}]{} G \\
G & \xrightarrow{k_{GA}} A
\end{align*}
\]

Figure 1.4: A cartoon image depicting how particles can assemble properly into the ordered structure, \(C\), or into the random aggregate, \(A\), out of the disordered state, \(G\) with the rate constants, \(k_{\alpha\beta}\), that gives the timescale of each process. In order for \(C\) to assemble in an appropriate length of time, \(k_{GC}\) needs to be bigger than \(k_{GA}\) as \(k_{AC}\) and \(k_{AG}\) is usually very low for kinetically trapped states. Naturally, more intermediate states are possible in between each transition. In this thesis we study simple association and dissociation processes that should give insight into the complete assembly problem.

Biological systems have found a way to circumvent this problem. When considering for example virus assembly, it is remarkable that a collection of protein subunits
self assemble into impressive mono-disperse superstructures as seen in Hepatitis, Ebola or the Tobacco virus. To understand such assembly we should ask what are the barriers and rate constants between stable states? Which transient intermediates are important and lead to proper structure formation and which intermediates are dead ends? How do additional isotropic or anisotropic interactions between particles change the assembly pathway and the rate of formation? What effect do rotational dynamics have in exploring configuration space?

Clearly, knowing the kinetics of the system is just as important as it explains on which time-scale a system relaxes to the ground-state and determines how long we have to wait in the lab for thermodynamic equilibrium to set in. Moreover, the prediction of time-scales of associating proteins via specific binding sites is also important in understanding the temporal response of bio-chemical networks [73]. Fundamental to growth and nucleation of supracolloidal structures are association and dissociation processes and the rate constants between possible bound states, see Fig. 1.4.

Modeling association and dissociation of particles has a long tradition in physics and chemistry [67, 76–86]. We can start by considering a simple assembly process, the binding of one particle to a binding site. The binding of a diffusive particle $A$ to another particle $R$ in a volume $V$ is denoted by the reaction $A + R \rightleftharpoons AR$. The reaction rate equations are:

$$\frac{d[AR]}{dt} = +k_+ [A][R] - k_- [AR], \quad \frac{d[A]}{dt} = -k_+ [A][R] + k_- [AR]$$  \hspace{1cm} (1.3)

where $[X]$ denotes the concentration of component $X$ and $k_+$ and $k_-$ are the association and dissociation rate constants, respectively. Alternatively we can describe this as a two state problem, denoting the bound state $AR$ as $B$ and the unbound state $A + R$ by $U$. The rate equation then becomes:

$$\frac{dp_B}{dt} = -k_{BU} p_B + k_{UB} p_U, \quad \frac{dp_U}{dt} = +k_{BU} p_B - k_{UB} p_U$$  \hspace{1cm} (1.4)

where $p_B$ and $p_U$ denote the population (or probability) of finding the system in the bound state $B$ or unbound state $U$, respectively. The two equations are related by noting that $p_B/p_U = [AR]/[A]$, $[A] = [R]$ and $k_+ [R] = k_{UB}$ and $k_- = k_{BU}$. It is now easy to see, that we can generalize Eq. (1.4) to any number of states and write down a master equation which is a generic gain-loss equation for the probabilities for each stable state $I$, $p_I$, where the rate constant between state $I$ and $J$ is given by $k_{IJ}$:

$$\frac{p_I(t)}{dt} = \sum_J k_{JI} p_J(t) - k_{IJ} p_I(t)$$  \hspace{1cm} (1.5)

by choosing an appropriate rate constant matrix, $K$, we can rewrite Eq. (1.5) as:

$$\dot{p}(t) = Kp(t)$$  \hspace{1cm} (1.6)
where \( \mathbf{p}(t) \) is the vector of components \( p_I(t) \) and \( \dot{\mathbf{p}}(t) \) is its time derivative. The formal solution of Eq. 1.6 with given initial \( \mathbf{p}(0) \) is as follows:

\[
\mathbf{p}(t) = e^{Kt} \mathbf{p}(0)
\]  

(1.7)

Although this expression is convenient, without knowledge of \( K \), it does not help to find \( \mathbf{p}(t) \) explicitly [87]. Obtaining all the rate matrix elements is thus the crux of the problem. Note that if \( K \) is known, also the stationary solution, \( \mathbf{p}^{eq}(t) \), in the long-time limit, \( t \to \infty \), can be found which leads to the detailed balance equation:

\[
k_{IJ}p^{eq}_I = k_{JI}p^{eq}_J
\]  

(1.8)

Although analytical techniques exist to calculate the (dis)association rate constant [78, 81], this is usually only possible for isotropic particles. When intermediates formed during the assembly process are non-spherical, analytical solutions become difficult to find. Instead of trying to solve the problem analytically, Brownian dynamics simulations have therefore been extensively used to study association kinetics of anisotropic particles, typically in the context of proteins or other biomolecules. Northrup et al. in Ref. [83] developed a method to calculate the association rate constant between two proteins based on Brownian dynamics in conjunction with simple models, where trajectories are initiated from random configurations where particles are separated by a distance \( \sigma \) and a trajectory is terminated when the particles collide in the correct orientation or are separated enough that recollision is negligible. By monitoring many of these trajectories, the probability that particles starting at a distance \( \sigma \) associate rather than diffuse away and escape into the bulk can be calculated which is related to the effective association rate constant.

Although anisotropy can be taken into account in these techniques [67], when multiple pathways via strongly bound intermediates become important, these methods based on the free diffusive behavior of particles become highly inefficient, especially when dissociation and rebinding are important processes to consider. For this purpose, recently developed path sampling techniques are used which are able to alleviate problems of long lived stable intermediates [88, 89].

### 1.6 Outline of the thesis

In this thesis different questions in self-assembly are studied considering not necessarily the thermodynamic behavior of patchy particles, but how by changing the underlying potential, multivalency or dynamics, structure formation is influenced. The first part of the thesis (chapter 3) deals with extraction of a pair-potential from experimental microscopy data on colloidal systems consisting of anisotropic particles. And in the second part (chapter 4, 5, 6) we study the association and dissociation of patchy particles with one or multiple binding sites and discuss how it affects the overall (un)binding rate constants and assembly mechanism. Moreover, we also study how changing the dynamics, to be specific the rotational
motion of particles, influences the self-assembly pathway of three-patch particles forming a tetrahedron.

Chapter 2 briefly reviews computational techniques, such as Monte Carlo and Brownian Dynamics, used to sample the configurational space of colloidal particles. Moreover, the calculation of radial distribution functions, virial coefficients, translational and rotational diffusion constants will be discussed. Furthermore, this thesis extensively makes use of path sampling methods developed to simulate so-called rare events necessary to study the kinetics of self-assembly. Several technical details on path sampling methods are explained. Chapter 3 reports on modeling of experiments on colloidal self-assembly induced via the critical Casimir force with a simple temperature dependent pair-interaction between particles. We present a framework for optimizing a potential based on a simple model via experimental microscopy images. The optimized potential from experimental data predicts correctly the onset of aggregation for these particles and gives a possible explanation for the collapse of network structures formed via a non-equilibrium experimental protocol very near the critical point by extrapolating the model to temperatures very close to the critical point. The remainder of the thesis is concerned with the dynamics and kinetics of (dis)association of patchy particles. In chapter 4 we investigate how changing the dynamics of particles, in contrast to their interaction can also influence the kinetics of self-assembly of multivalent patchy particles. We show that when rotational diffusion is lowered, experimentally possible by changing the environment of particles via molecular crowders or external fields, the tendency to form trapped structures is decreased as rotational motion induces the exploration of intermediate frustrated structures. We present a simple master equation model to further exemplify this observation. In chapter 5 we show that multivalency of patchy particles does not change the thermodynamics of polyhedron structure formation, but affects the kinetics. Multivalency affects both the frequency of visiting trapped states and the residence time within frustrated states during association. Chapter 6 presents a study of the association kinetics of dimer formation of patchy particles where one particle is decorated with additional binding sites other than the target binding site. We discuss how these decoy binding sites affect the kinetics by rebinding and how adding an isotropic interaction further affects the rebinding probability. Moreover, we show how the isotropic interaction between particles forming a multicomponent structure can also lead to cooperativity in binding, qualitatively changing the association kinetics.

It is evident from the underlying motivations of these chapters that when discussing the (dis)association or self-assembly of anisotropic particles a multitude of diverse questions arises, from how to extract effective anisotropic potentials from experimental data to how rotational dynamics and multivalency influences kinetics. Since, as soon as the interactions between particles become anisotropic, the number of degrees of freedom to study increases, such as the number of patches per particle, the arrangement of these patches, the width or size of the patches, surface mobility of the patches, the nature of interaction per patch and possibly even the shape of the patches. Together with the possibility of changing the shape of the particle itself, the possibilities are close to infinite, all of which nowadays is
not just a theoretical abstraction anymore but in principle can be achieved experimentally. Of course, in this thesis only a small subset of questions are selected and even the system sizes are limited to a minimum in most chapters, however the topics discussed can transcend these limitations and the findings apply more generally. The method of extracting potentials described in chapter 3 also extends to other patchy particles that can be modeled by a rigid framework similar to molecules and does not necessarily depend on the use of critical Casimir forces. Chapter 4 demonstrates how not only the interaction between particles matter for successful assembly, but also which pathway over the free energy landscape is taken and how this can be influenced by rotational diffusion. Furthermore, the prediction of time-scales for particles with additional binding sites in chapter 6 can be used to study bio-chemical networks via multi-scale simulation techniques. Finally, the use of path sampling techniques and technical details discussed in chapters 4 to 6 are applicable to other patchy particle systems, also much larger in size. To summarize, this thesis reflects the different faces of self-assembly of patchy particles and provides generic insight in the relevant association processes, which can be used in future research.