Understanding nanoparticle aggregation

By

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ABSTRACT

Nanoparticles form the fundamental building blocks for many exciting applications in various scientific disciplines. However, the problem of the large-scale synthesis of nanoparticles remains challenging. It is necessary to understand the nanoparticle aggregation for the rational design of reactors for high-throughput synthesis of nanoparticles with well-controlled properties. Often, nanoparticle aggregation is modeled using stochastic methods based on scaling arguments and assumptions about the nanoparticle interaction potential. Therefore, a more rigorous approach is desired for understanding nanoparticle aggregation. In this dissertation, a novel framework integrating experiments and multi-scale simulations for studying nanoparticle aggregation is presented.

Atomic force microscopy (AFM) was employed to measure the force between polystyrene (PS) micro- and nanoparticles. Specifically, AFM was used to directly measure the force (in air) between a 300 nm PS nanoparticle and a PS film, which was compared with the force measured between a 2 µm PS particle and a PS film. A novel approach based on layer-by-layer assembly to functionalize an AFM probe was developed and applied to the measurement of the force between nanoparticles. The nanoparticle force was deduced from the variation of force between a silica colloidal probe (5-30 µm) functionalized with a monolayer of 300 nm PS particles and a PS film as a function of the diameter of the silica particle. It was shown that continuum models are inadequate to explain the measured forces, which underlines the need for a more rigorous multiscale modeling methodology to understand nanoparticle interaction potential.

In principle, nanoparticle interaction potentials can be derived from electronic structure calculations for a molecule using a multiscale modeling approach. To this end, a systematic method of coarse-graining based on force matching was implemented and applied to coarse-grain three common solvent molecules (carbon tetrachloride, benzene and water) to their center of mass. The coarse-grained potentials derived from first principles based effective fragment potential (EFP) were able to reproduce the structural properties that were in reasonable agreement with those obtained using EFP molecular dynamics while achieving a computational speed-up of four orders of magnitude.
The nanoparticle interaction potential determines the morphology of corresponding aggregates. On the other hand, the aggregation kinetics are governed by the diffusivity of the aggregates. Therefore, it is essential to relate the aggregate morphology to its mobility in order to study aggregation kinetics. The diffusion of nanoparticle aggregates in the limit of infinite dilution was studied as a function of their mass ($N$) and fractal dimension ($d_f$) using molecular dynamics simulations in the presence of explicit solvent molecules. The diffusion coefficient ($D_o$) for aggregates was found to scale as $D_o \propto N^{-d_f}$. The ratio of the hydrodynamic radius to the radius of gyration was found to be independent of mass for aggregates of a given fractal dimension, thus enabling an estimate of the diffusion coefficient for a fractal aggregate based on its radius of gyration.

The research presented in this work provides a robust framework integrating experiments and multiscale simulations for studying nanoparticle aggregation.
CHAPTER 1: INTRODUCTION

Introduction

At nanometer length scales, materials exhibit unique properties that are significantly different from their bulk properties due to effects resulting from high surface area to volume ratios and quantum confinement [1, 2]. Owing to their unique properties, nanoparticles have a wide range of exciting applications as basic building blocks in catalysts, magnetic devices, polymer composites, sensors, paints, pharmaceuticals, coatings and adhesives [3-7].

Together with their numerous applications, there are many challenges associated with nanoparticles; and perhaps one of the most important challenges for chemical engineers to address is the problem of large-scale synthesis of nanoparticles with precisely controlled properties, such as purity, size distribution and crystalline structure. Unfortunately, today’s commercial reactors for the synthesis of nanoparticles are designed empirically and important product properties such as polydispersity are typically controlled by varying the process conditions [8]. In colloidal (liquid phase) or aerosol (gas phase) reactors for the synthesis of nanoparticles [9], turbulent mixing brings the chemical precursors together, which then react to form nuclei that grow by surface addition and aggregation thus forming nanoparticles [8]. Therefore, computational tools that can model aggregation and predict the properties of the final product are necessary for the rational design of reactors for high-throughput synthesis of nanoparticles.

The development of computational methodologies for modeling nanoparticle aggregation is a very challenging problem because the phenomena governing aggregation take place at length scales ranging from sub-nanometer dimensions to the macroscopic dimensions of the reactor (cm or m). At length scales less than 1 nm nucleation resulting from high concentration of chemical precursors takes place and nuclei grow rapidly into nanoparticles (10-50 nm) [10, 11]. Modeling the contributions due to the surface chemistry of the nanoparticles is important because it plays an important role in aggregation kinetics by governing specific interactions such as hydrogen bonding between nanoparticles. At 1-100 nm length scales Brownian motion leads to nanoparticle aggregation resulting in ‘local aggregates’ of typical size 0.1-10 μm [12]. Such ‘local aggregates’ form because at typical Reynolds numbers in a reactor and at length scales below 10 μm, the shear rates and the precursor...
concentrations are locally uniform [13, 14]. At larger length scales (0.01-1 mm), the shear in the system will lead to aggregation and breakage of ‘local aggregates’ and at the length scale of the reactor dimensions, the turbulence in the reactor governs the aggregation. To study this multi-scale problem, an interdisciplinary approach that brings together chemists, chemical engineers, mechanical engineers and physicists is needed as shown in Figure 1.1. Continuous feedback at each interface is necessary to iteratively improve the multi-scale modeling methodologies.

Nanoparticle surface forces
< 1 nm
Quantum Chemistry

Brownian aggregation
1 – 100 nm
Molecular Simulations

Shear-induced restructuring
0.1 – 10 μm
Brownian Dynamics

Shear-induced aggregation
0.01 – 10 mm
Direct Numerical Simulations

Turbulent reacting flow
0.01 – 1 m
Large Eddy Simulations

AFM Experiments
Force between Nanoparticles

Light Scattering Experiments
Aggregate Size and Fractal Dimension

Figure 1.1: Organization of the inter-disciplinary research framework for modeling nanoparticle aggregation at vastly varying multiple length-scales. The experimental contributions are shown at the bottom.

The research described in this dissertation concerns Brownian aggregation (without shear) of nanoparticles taking place at length scales between 0.1 nm and 0.1 μm as highlighted by the gray box in Figure 1.1. Specifically, the objective is to develop a systematic coarse-graining methodology capable of using the quantum chemical data from the molecules comprising the nanoparticle to derive the effective interaction potential between a pair nanoparticles. Insights obtained from the direct measurement of the forces between nanoparticles using Atomic Force Microscopy (AFM) will be used to refine the coarse-graining methodology and to better understand the mechanisms governing nanoparticle aggregation. While the interaction potential between nanoparticles governs the morphology of nanoparticle aggregates, their diffusive behavior governs the aggregation kinetics. To this end, molecular simulations will be employed to study the diffusion of nanoparticle aggregates as a function of their mass and morphology. Such a multi-scale approach that integrates modeling and experimentation is necessary to elucidate the underlying principles behind nanoparticle aggregation. This represents both the uniqueness and the challenge of the work described in this thesis.
References

CHAPTER 2: RESEARCH OBJECTIVES

Introduction

The overall goal of this research is to advance our understanding of nanoparticle aggregation in systems without shear at 0.1-100 nm length-scales by combining molecular simulations and atomic force microscopy (AFM) experiments. The framework followed in this research to pursue this objective is shown in Figure 2.1. Monodisperse polystyrene (PS) micro- (2 µm) and nanoparticles (300 nm) have been chosen as the model system because they are widely used to study colloidal aggregation [1-3] and they can be easily functionalized to produce a desired set of surface chemistry properties.

Understanding Nanoparticle Aggregation

Systematic Coarse-graining
Quantum Chemical Data

Polystyrene
Nanoparticle

Atomic Force Microscopy
Direct Measurement of Colloidal Forces

Nanoparticle Interaction Potential

Diffusion of Nanoparticle Aggregates

Figure 2.1: Research Plan
A two-pronged approach involving molecular modeling and AFM experiments is used to gain insight into the nanoparticle interaction potential and mechanism of nanoparticle aggregation. Specifically, a systematic coarse-graining methodology is developed for deriving an effective nanoparticle interaction potential from quantum chemistry. A novel approach, involving layer-by-layer assembly, is developed for the measurement of the force between PS nanoparticles (300 nm) using AFM and the results are interpreted in conjunction with the forces measured between PS microparticles (2 μm). The insights from the experiments are valuable in refining the coarse-graining methodology and enhance our understanding of cluster morphology and aggregation mechanisms. The diffusion of nanoparticle aggregates, which depends upon their size and morphology, plays an important role in the aggregation kinetics and the final cluster size distribution in a system of aggregating nanoparticles. To this end, molecular dynamics simulations have been used to systematically study the dependence of the diffusion of nanoparticle aggregates on their morphology and size. The overall research objective has been broken down into the following specific goals.

**Specific Goal 1: Forces between PS Micro- and Nanoparticles Using AFM**

PS nanoparticles are commercially manufactured using an emulsion polymerization method [4-6]. The surface of these nanoparticles is not atomically smooth and the charged terminal groups of PS chains, carboxyl and/or sulfate, on the nanoparticle surface can lead to interactions between nanoparticles that are markedly different from idealized models [7, 8]. Therefore, in order to validate the nanoparticle interaction potential derived from quantum chemistry, it is necessary to utilize the insights obtained from the experimental measurement of the forces between PS nanoparticles.

Atomic force microscopy (AFM) [9] provides an experimental method to measure forces between microscopic objects of sub-micron sizes. AFM has the unique ability to measure the force exerted on an AFM probe (an optical lever) by a substrate as a function of the separation between them, i.e. a force curve. It is sensitive enough to measure the forces of the order of 10⁻⁹ N, which are typical of forces between colloidal particles [7, 8, 10-13]. Therefore, the force curves between colloidal particles can be measured by functionalizing the substrate and the AFM probe with PS colloidal particles as shown in Figure 2.2.
Based on continuum models, the force between a pair of spherical particles is expected to be half the force between a particle and a flat surface assuming the interaction is dominated by van der Waals forces [14]. If such relationships are observed in real systems then the force between a pair of nanoparticles can be deduced from the force between a nanoparticle and a film. Therefore, AFM was used to measure the force between a PS microparticle (2 µm) and a PS film and a pair of PS microparticles and verify the continuum theory. These measurements shed light on the effect of surface roughness and surface chemistry on the measured forces.
While a micron-sized particle can be attached to an AFM probe using an adhesive and micromanipulators under an optical microscope, this approach does not work for nanoparticles. An experimental protocol was developed to functionalize an AFM probe with a PS nanoparticle to enable the measurement of a nanoparticle force using AFM. To this end a layer-by-layer assembly procedure was used to functionalize large silica microparticle attached to an AFM probe with a monolayer of PS nanoparticles. By studying the variation of the force as a function of the number of nanoparticles at the apex of the core silica microparticle, the force between a pair of nanoparticles can be deciphered as illustrated in the schematic in Figure 2.3. These experiments will provide new insights into the nature and strength of nanoparticle interactions and their implication on aggregation kinetics.

Specific Goal 2: Systematic Goarse-Graining for Multiscale Modeling

At the molecular length-scale, quantum chemical (ab-initio) calculations provide very accurate quantitative information about a system consisting of a few molecules but such computations are very expensive and cannot be used to simulate the nanoparticles which contain millions of molecules. Therefore, there is a need to develop a systematic methodology for coarse-graining the quantum chemical data to make the simulations of systems containing larger number of molecules computationally feasible.
The purpose of coarse-graining is to reduce the number of degrees of freedom in an ‘atomistic’ system by representing a group of atoms as a single site called a coarse-grained (CG) site. The effective pair potential between these CG sites is determined such that it is representative of the average interaction potential of these groups of atoms in the corresponding atomistic system, thus preserving the relevant physics of the system. Such a reduction in the degrees of freedom makes the molecular simulation of the CG system much faster compared to the atomistic system facilitating the study of large systems.

To this end, an algorithm for force matching method [15] of systematic coarse-graining is developed, implemented and tested. In collaboration with Prof. Mark Gordon at Iowa State University, force matching was employed to systematically coarse-grain three common solvent molecules, carbon tetrachloride, water and benzene, each to their center of mass. The data required for force matching was generated by Prof. Gordon’s group using atomistic molecular dynamics with the Effective Fragment Potential (EFP) [16], which is a first-principles-based method for describing intermolecular interactions. The coarse-grained potentials were tested for their ability to reproduce the structural properties of the underlying atomistic molecular dynamics.

Following this approach, an effective PS nanoparticle pair potential can be obtained systematically as shown in Figure 2.4.

Figure 2.4: Coarse-graining scheme to obtain the effective PS nanoparticle pair potential
Specific Goal 3: Diffusion of Fractal Aggregates

While specific nanoparticles form aggregates of defined morphologies depending on their interaction potential, it is essential to understand the diffusion of aggregates over the entire spectrum of their morphologies. It is well known that nanoparticles form self-similar fractal aggregates whose morphology is characterized by their fractal dimension [17]. Strongly attractive nanoparticles aggregate in the diffusion-limited regime and form open aggregates [18]. On the other hand, weakly attractive nanoparticles aggregate in the reaction-limited regime and form compact aggregates [19].

![Figure 2.5: Two dimensional projections of fractal aggregates containing 256 nanoparticles. (a) df = 1.8, (b) df = 2.5](image)

The diffusion of nanoparticle aggregates in the limit of infinite dilution was studied as a function of their mass ($N$) and fractal dimension ($d_f$) using molecular dynamics simulations in the presence of explicit solvent molecules. The calculated diffusion coefficients were corrected for the effects of long range hydrodynamic interactions that are unavoidable in simulations of finite system size with periodic boundary conditions. The ratio of hydrodynamic radius to the radius of gyration ($\beta$) of fractal aggregates is the most common metric reported in the literature for characterizing the dynamic properties of fractal aggregates. However, there is considerable inconsistency in the value of $\beta$, which were obtained from experiments [3, 18-21], theoretical models [22-30] or particle based simulations [31-36]. The approach described in this work addresses this ambiguity in the values of $\beta$. 
Conclusion

The successful completion of the above-mentioned specific goals will result in a unified framework that effectively integrates multiscale computational tools and experiments and provide an enhanced understanding of nanoparticle aggregation. Such a framework is necessary to perform macroscopic simulations (e.g. CFD) with high degrees of accuracy, thus facilitating the rational design of efficient commercial reactors and other process equipment for high throughput synthesis of nanoparticles with controlled properties.

References

CHAPTER 3: LITERATURE REVIEW

Atomic Force Microscopy

Introduction

Since the invention of the atomic force microscope (AFM) by Binnig, Quate and Gerber [1], it has been employed in the investigation of a wide variety of research problems [2-4], such as atomic resolution imaging [5-9], spatial chemical composition of the surfaces [10-14], biological applications [15-19], nanolithography [20, 21], phase imaging [22-24], microscopic friction [25], colloidal interactions [26-34], etc. AFM is also known as scanning probe microscope (SPM) and the scanning force microscope (SFM). Unlike other microscopy techniques, AFM is capable of measuring the height of features together with the two-dimensional spatial resolution of the substrate. Other high resolution microscopy techniques are suitable only for certain types of samples or require samples to be modified, e.g., scanning electron microscopy (SEM) and scanning tunneling microscopy (STM) require the substrate to be conductive, whereas for AFM substrates do not need to be modified, in other words, a large variety of substrates can be studied using AFM. These unique capabilities along with its high resolution render AFM amenable to applications in the areas mentioned above.

AFM Assembly and Imaging

![Image of a Si$_3$N$_4$ cantilever taken from www.veecoprobes.com; typically an AFM cantilever is 100-200 μm long and the tip height is about 3-5 μm. The radius at the apex of pyramidal tip is about 50 nm](veecoprobes.com)

Figure 3.1: Image of a Si$_3$N$_4$ cantilever taken from www.veecoprobes.com; typically an AFM cantilever is 100-200 μm long and the tip height is about 3-5 μm. The radius at the apex of pyramidal tip is about 50 nm
The AFM images a surface by scanning it with a sharp probe in the XY plane while simultaneously recording the vertical deflection at a given point in the XY plane, Z(X,Y). Naturally, the AFM probe is an important component of the AFM assembly. The AFM probe consists of a cantilever with a small pyramidal tip as shown in Figure 3.1 and is generally made of silicon nitride (Si₃N₄) or silicon (Si).

![Figure 3.2: Schematic of AFM operation](image)

The AFM probe is mounted on the piezoelectric-scanner as shown in Figure 3.2. The movement of the piezoelectric scanner in X, Y and Z directions is controlled precisely by applying an appropriate voltage across the piezoelectric-crystal, which responds with expansion or contraction. As the probe scans the peaks and valleys on the substrate it experiences vertical deflection, which is measured using an optical lever system. A laser is shone on the back of AFM cantilever from where it gets reflected onto the photodetector. The vertical deflection of the cantilever corresponds to the difference of the voltages recorded in the top and bottom halves of the detector due to the position of the laser spot.

Usually for imaging, AFM is operated such that an electronic feedback system adjusts and records the voltage applied across the piezoelectric crystal in order to keep a characteristic property of the laser spot fixed while scanning the features on the substrate, depending on the mode of operation.
In the contact mode when the tip is in physical contact with the substrate, the AFM operates in constant vertical deflection mode, i.e. the laser spot is kept fixed on the detector by feedback control during the scan. On the other hand, soft samples are imaged using the tapping mode. In the tapping mode, the AFM probe is made to oscillate vertically, leading to intermittent contact of the tip with substrate, thus reducing the contact time between the tip and the sample compared to contact mode. Consequently, in tapping mode the possibility of damaging a soft sample is minimal compared to contact mode, which albeit is faster of the two. In tapping mode, AFM is operated such that the RMS amplitude of the probe oscillations is kept constant by a feedback loop while scanning the substrate. AFM can also be used in application-specific modes such as non-contact mode, friction mode, force modulation mode, etc.

**Force Curves**

![Figure 3.3: Schematic showing the stages of a force curve cycle obtained using AFM](image)

A force curve refers to the sequence of vertical force measurements between tip and the substrate as function of the separation between them at given X and Y coordinates. In this mode the electronic
feedback loop is turned off. A force curve consists of two parts, the approach to the substrate and the retraction from the substrate as shown in Figure 3.3. The information whether the nature of interaction between the tip and sample is van der Waals or electrostatic is obtained from the approach curve and the information about the adhesive characteristics of tip and substrate contact is given by the retraction curve. Characterization of such molecular level forces using AFM is also referred to as chemical force microscopy (CFM).

As the tip is made to approach the substrate from large separation \((Z = \infty, \text{Stage A})\) the tip experiences no force from substrate in the beginning, therefore, the laser spot stays at its place, but in the close proximity the substrate exerts force on the tip (Stage B), say van der Waals type, deflecting the tip toward the substrate. The deflection is recorded through the photodetector and when multiplied by the spring constant of the cantilever yields the force. The deflection increases as the separation between the tip and substrate decreases until the force gradient exceeds the spring constant of the cantilever at which point tip “snaps in” to the surface (Stage C) of substrate. Further attempts to move the tip closer to the substrate results in repulsive force on the tip from the substrate (Stage D) because they are in contact and this region is known as the constant compliance region. This completes the approach force curve.

However, the retraction curve does not necessarily follow the approach curve. On the retraction of the probe away from surface, the tip does not break off from the surface at the snap-in point of the approach curve. This is because of the adhesive force between the tip and substrate when they are in contact. If the force curve is measured in air, then the condensation of water present at the contact between the tip and the substrate resulting in capillary forces also contribute to the adhesive forces between the tip and substrate. As the probe is moved further away, the pull-off force overcomes the adhesive force (Stage E) and the probe breaks off the substrate and the probe is retracted until it reaches the separation where the approach curve started, thus completing the retraction force curve.

**Calibration**

The X, Y and Z motion of the piezoelectric scanner is calibrated by imaging a calibration standard with features of known dimensions. This is necessary to obtain the accurate topography of the substrate. Usually this calibration can be carried out to 1% accuracy.
As the feedback loop is switched off during the force curve mode, the photodetector is used to measure the vertical deflection of the AFM cantilever. Therefore, for the accurate measurement of the deflection it is essential to calibrate the sensitivity (nm/V) of the photodetector in order to convert the photodetector voltage into distance. Sensitivity of the detector is given by the slope of the approach force curve in the constant compliance region. While determining the sensitivity, the force curve should be obtained against a hard surface, such as a silicon wafer, which is suitable for this purpose. To convert the deflection data into force, the deflection needs to be multiplied by the spring constant of the cantilever according to Hooke’s law, $F = kx$, where $k$ is the spring constant and $x$ is the spring elongation/contraction.

**Spring Constant of an AFM Cantilever**

Manufacturers report a range for the spring constant values for the cantilevers, which provides information on the serviceable range of the cantilever for the user. It is difficult to maintain close tolerances on the properties that affect the spring constant of the cantilever. For example, the thickness of the cantilevers can vary significantly from one to another. Consequently, the nominal value of the spring constant reported by the manufacturer is usually not accurate enough for force curve measurement.

Determining the correct spring constant is critical for obtaining accurate force curves. Clifford et al. [35] reviewed the methods that use the geometry and mechanical properties of the cantilever to determine its spring constant. Briefly, the spring constant of a rectangular cantilever is given by:

$$k = \frac{Ewt^3}{4L^3}$$  \hspace{1cm} (3.1)

Here, $E$, $w$, $t$ and $L$ are the elastic modulus, width, thickness and length of the rectangular cantilever, respectively. Cleaveland [36] replaced the thickness in the above formula by an expression in terms of the resonance frequency of the cantilever as follows:

$$f_o \approx \frac{t}{2\pi L^2} \left(\frac{E}{\rho}\right)^{1/2} \quad \Rightarrow \quad k \approx \frac{2\pi^3 w}{\sqrt{E}} \left(\frac{f_o L\sqrt{\rho}}{3}\right)^3$$  \hspace{1cm} (3.2)
Here, \( f_0 \) is the resonance frequency and \( \rho \) is the density of the cantilever. The resonance frequency can be obtained from the power spectral density of thermal fluctuations of the cantilever. For V-shaped cantilevers the method proposed by Sader [37] can be used.

\[
k = \frac{Ewt^3}{2L^3} \cos \theta \left[ 1 + \frac{4w^3}{b^3} (3 \cos \theta - 2) \right]^{-1}
\]

(3.3)

Here, \( b \) is the width of the base of cantilever and \( \theta \) is the half-angle between the legs. A more accurate but complex method developed by Neumiester [38] can be used for V shaped cantilevers.

Although used by manufacturers, the geometric methods of spring constant determination are limited by accurate knowledge of the thickness and the elastic modulus of the cantilever. It is hard to determine the thickness of cantilevers accurately. The elastic modulus of cantilevers can only be approximated by the bulk value of the material that may not be true for the cantilever. Additionally, the presence of the chromium and gold coating on the back-side of the cantilever also affect the spring constant. Usually the uncertainty in the measurement using this method is about 16 to 25%.

Senden et al. [39] determined the spring constant from the cantilever bending, measured under optical microscope, caused by placing 10-50 \( \mu \)m tungsten balls at the end of the cantilever. Sources of uncertainty in this method are the correct diameter of tungsten balls, deflection calibration and the exact location of the ball on the cantilever. Practically it is tedious to place the ball on the cantilever and there is possibility of damaging the cantilever.

A popular method for determining the cantilever spring constant is by pressing it against a cantilever of known spring constant [40, 41].

\[
k = \frac{k_{\text{ref}}}{\cos \theta} \left( \frac{\delta_{\text{ref}}}{\delta_{\text{total}}} - 1 \right)
\]

(3.4)

Here, \( k \) is the spring constant of the test cantilever, \( k_{\text{ref}} \) is the known spring constant of the reference cantilever, \( \delta_{\text{ref}} \) is the deflection sensitivity of the test cantilever against the reference cantilever, \( \delta_{\text{total}} \) is
the deflection sensitivity of the test cantilever against a hard surface and \( \theta \) is the angle between the test and reference cantilever. The test cantilever should be positioned close to the end of the reference cantilever. Care should be taken to avoid the inaccuracy caused by torsion if the test cantilever is not placed at the center of the reference cantilever. The slip at the contact between the test and reference cantilever is a source of error in the measurement. It is desirable that \( k \) is close to \( k_{\text{ref}} \), which in some cases might not be estimated a priori.

A widely used method called Cleveland’s added-mass method [36] is based on the principle that adding mass to a spring alters its resonance frequency. The cantilever spring constant is given by the following relationship:

\[
 k = \frac{2\pi^2 M}{\frac{1}{f_1^2} - \frac{1}{f_o^2}} 
\]  

(3.5)

Here, \( M \) is the mass added by placing the tungsten ball at the end of the cantilever, and \( f_1 \) and \( f_o \) are the resonant frequencies with and without \( M \), respectively. The position of the ball on the cantilever and its correct mass are the main sources of uncertainty in the measurements made using this method.

Another widely used method to determine the spring constant of a rectangular cantilever utilizes thermal fluctuations [42]. The spring constant is given as follows:

\[
 k = \frac{k_b T}{\left\langle x_{\text{thermal}}^2 \right\rangle} 
\]  

(3.6)

Here, \( k_b \) is the Boltzmann’s constant, \( T \) is the temperature and \( \left\langle x_{\text{thermal}}^2 \right\rangle \) is the mean squared thermal fluctuation. This method does not compensate for the fact that the cantilever is not an ideal spring and that the deflection measured by an optical lever system using a laser and photodiode is not same as the actual deflection of the cantilever because this is based on angular displacements. Butt et al. [43] introduced a correction to this formula as follows:
Here, $\langle x^2_{\text{thermal}} \rangle$ is the mean squared thermal fluctuation recorded by photodetector. The uncertainty in this method comes from the uncertainty in the measurement of the deflection sensitivity. Once established, this method is quick and easy to use.

Burnham et al. [44] compared the added-mass method of Cleveland [36], Sader’s method [45] for rectangular cantilevers, Hutter and Bechhoefer’s method of thermal vibrations [42] and their own modified thermal vibration method and found that all these methods agree with 17% of the value reported by manufacturer. The non-existence of a method that can determine the exact value of the spring constant prevents the direct comparison of the methods. The precision of a given method, applicability of the method to the test cantilever and the ease of use are the criteria that are usually considered in choosing a method to calibrate the spring constant.

Applications of Force Curves

In the last two decades AFM has been a vital tool for researchers to study interactions at molecular level and a large body of research on CFM has been published. Some of the important applications of CFM have been briefly discussed below; for more detailed and comprehensive information on CFM the reader is referred to excellent reviews written by Noy et al. [3] and Takano et al. [4]. Butt et al. [46] published a review on the measurement of force curves in liquid environments.

Approach Force Curves

Approach force curves measured using AFM are used to characterize short and long-range forces like van der Waals, electrostatic and electrical double layers formed in liquids in the presence of ions and charged probe and substrate.

Gauthier-Manuel [47] measured the van der Waals force between a tungsten tip and mica surface from the approach curve. A homemade AFM based on magnetic levitation designed to prevent the tip snapping in during the approach to the mica surface was used.
The van der Waals force between tip and substrate is proportional to the Hamaker constant, which depends upon the dielectric constant and refractive index of the tip, substrate and the medium. Therefore, the nature of van der Waals forces can be tuned from attractive to repulsive by choosing the medium appropriately. Hutter et al. [48] observed that van der Waals force between a Si$_3$N$_4$ tip and a mica surface changes from attractive in ethanol medium to repulsive in 1-bromonaphthalene and 1-methylnaphthalene. The repulsive force between the tip and sample enhances the resolution in AFM images compared to the attractive force between the tip and sample.

AFM is a vital tool for studying the interactions between two charged surfaces in an electrolytic environment. Butt et al. [49] analyzed the approach force between negatively charged substrates, glass and mica, and Si$_3$N$_4$, Al$_2$O$_3$, glass and diamond tips in liquid media of varying salt concentrations and pH. As the salt concentration is increased or the pH is decreased the electrostatic interaction becomes weaker and van der Waals forces become larger for all the tips. Hydration forces were measured by making the salt concentration greater than 1 M. In a similar work, Lin et al. [50] studied the double layer interactions between Si$_3$N$_4$ AFM tips and SiO$_2$ surface in an electrolyte medium. The isoelectric point (IEP) of Si$_3$N$_4$ probe was determined by monitoring the double layer force by varying the pH.

**Retraction Force Curves**

The retraction force curve provides the information about adhesive forces between two surfaces, chemical composition of the surfaces, binding strength between the molecules on the AFM tip and substrate.

The plot of force of adhesion between the tip as a function of the surface coordinates (X,Y) yields information about the chemical composition of the surface. Burnham et al. [10] observed that surfaces with monolayers of stearic acid and $\omega_3\omega_3\omega_3$-trifluorostearic acid can be differentiated by looking at the approach or retraction well depths of the force curves obtained with AFM tips. Both kinds of monolayers are exactly the same except for the terminal group and a topography map cannot distinguish between them. In a similar work, Frisbie et al. [11] mapped the surface patterned with monolayers terminating in COOH and CH$_3$ groups by measuring the adhesive and friction forces between AFM tips modified with COOH and CH$_3$ groups.
Nakagawa et al. [12] observed that compared to an unmodified AFM tip, an AFM tip functionalized with a monolayer of octadecyltrichlorosilane was more sensitive in detecting alkyltrichlorosilane monolayers of different carbon chain lengths adsorbed on the substrate. Radmacher et al. [17] measured the viscosity and Young’s modulus of a lysozyme protein and observed that at pH of 4.0 they could identify single protein molecules on the mica surface from adhesion force maps of the surface.

Another interesting application of AFM retraction force curves is the measurement of interaction forces between individual molecular pairs. Hoh et al. [51] studied the adhesive interactions between the Si$_3$N$_4$ AFM tips and glass surface in water. The pH of the solution was kept at 8.5 – 9 by adding sodium hydroxide. The histogram of adhesive forces obtained revealed the quantized nature of adhesive forces. They appeared to vary in steps of 0.1 nN. This quantization was attributed to the ordered layers of water at the substrate.

Florin et al. [15] determined the binding force between individual avidin-biotin and avidin-iminobiotin (ligand – receptor) pairs to be 160 pN and 85 pN respectively. This was accomplished by functionalizing the AFM tip with avidin and the surface with biotin or iminobiotin and measuring the adhesive force from the retraction force curve using AFM. They found that the adhesive forces measured multiple times were quantized by 160 pN and 85 pN for avidin-biotin and avidin-iminobiotin pairs. In an extension of this work they also determined the pair rupture lengths [52].

Lee et al. [16] measured the adhesive forces between single DNA strands from the retraction force curves by functionalizing the AFM probe and substrate with oligonucleotides. The distribution of adhesive forces between DNA strands showed peaks at 1.52, 1.11 and 0.83 nN corresponding to 20, 16 and 12 base pairs respectively. van der Vegte et al. [13] studied the interactions between alkanethiol monolayers terminating with -CH$_3$, -OH, -NH$_2$, -COOH and -CONH$_2$ functional groups by measuring the force curves between the monolayer-functionalized AFM tips and substrates in an ethanol medium. The distributions of the measured adhesive forces between monolayers with these above-mentioned terminal groups were used to obtain single pair interactions. These interactions agreed well with the JKR theory of adhesion. The friction coefficients between the tip and the sample were found to be directly correlated to the adhesive force between them.
Colloidal Probes and Force Curves

In their pioneering work, Ducker et al. [29, 30] measured the force between a 7.0-μm (diameter) silica particle and flat silica surface in a sodium chloride solution. The measured forces were in good agreement with electrical double layer theory. The technique of attaching particles to AFM probes made it possible to study the forces between colloidal particles. Thus, such probes are known as colloidal probes. Following this technique, Li et al. [33] analyzed the approach force curves between two 2-μm polystyrene spheres at varying concentrations of KCl. The force curves appeared to possess short-range attractive force at high salt concentrations with smaller or no long-range force. On the other hand, at lower salt concentrations, the attractive force became almost indiscernible while a long-range repulsive force became evident. These results are in agreement with results obtained by Butt et al. [49].

Miling et al. [53] measured the effect of the medium on the van der Waals forces between gold microspheres and a polyterafluoroethylene surface. In low polarity solvents the interaction was found to be repulsive van der Waals, corresponding to a negative composite Hamaker constant. Larson et al. [54] measured the force between a 9-μm TiO₂ sphere and a flat TiO₂ surface in the presence of an electrolyte. At the isoelectric point, the interaction between these surfaces was deemed to be van der Waals type and the measured Hamaker constant compared well with Lifshitz theory.

Considine et al. [27] observed that the range of attractive force between two 6-μm polystyrene particles, which was 20 – 400 nm, was greater than that expected for van der Waals forces. The forces were measured in high purity water with varying salt concentration. This behavior was attributed to the bridge formed by gases dissolved in water around the micro-contact between the rough hydrophobic polystyrene particles on the tip and substrate. Using degassed water resulted in a decrease in the range of attractive force.

While the above mentioned work was primarily based on measuring the interactions between particles using approach curves, Hodges et al. [31, 32] measured and modeled the adhesive force between polystyrene particles.
Summary

The atomic force microscope (AFM) has been widely used to study the forces between a variety of surfaces due to its unique ability to measure the force between its probe and the substrate as a function of separation between them. The approach curve measures van der Waals and electrostatic forces; on the other hand adhesive forces are measured by retraction curves. By attaching a colloidal particle to the probe and/or to the substrate the force between two colloidal particles and a particle and surface can be measured.

All the force measurements between two colloidal particles or a colloidal particle and a flat substrate reported in the literature are limited to particles of size 2-μm or larger. This is because particles of size smaller than 2 μm are difficult to manipulate under an optical microscope using micromanipulators as an objective lens of sufficiently large magnification makes the working distance between the lens and substrate very small. Moreover, putting the adequate amount of adhesive on a cantilever for smaller particles becomes increasingly difficult as the particle size decreases. However, many colloids are smaller than 1 μm; therefore, to characterize the interaction between such colloidal particles, the present method of measuring forces between colloidal particles needs to be extended to nanoparticles.

Systematic Coarse-Graining Techniques

Introduction

Molecular simulations are computer experiments that are used to compute desired properties of a system of ‘atoms’ based on the nature of the interaction between atoms. Atoms usually refer to the individual entities in the system and can represent individual atoms, molecules or nanoparticles, etc. Molecular simulations require the input of potential functions describing the nature of interactions between the atoms.

In molecular dynamics (MD) simulations [55, 56], a system of atoms is evolved in time by solving their equation of motion \( \vec{F}_i = m \ddot{r}_i \), where \( \vec{F}_i \) is the net force acting on particle \( i \), which depends on the relative positions of all other particles with respect to particle \( i \), and \( \ddot{r}_i \) represent the second derivative of the position of atom \( i \) w.r.t time. On the other hand, the Monte Carlo (MC) [55, 56] technique is stochastic by nature. A computer experiment using MC is conducted by obtaining the acceptable
configurations of the system according to the probability distribution that governs the system, usually Boltzmann distribution.

Depending upon the nature of problem to be studied, one technique might be better than the other. However, according to the ergodic hypothesis [55, 56], the time average of a property over a long time is equal to its ensemble average, therefore, in majority of computer experiments both MD and MC should yield same result. One advantage of MD over MC is that by using MD the dynamics of a system, such as diffusion coefficients, can be studied. Pair potentials are believed to be adequate to simulate the desired systems accurately and are computationally faster than more accurate potentials involving many body interactions. A majority of molecular simulations are carried out using pairwise interaction potentials. If there are $N$ atoms in a system then at each step of MD, $N(N-1)/2$ pair potentials need to be evaluated or, in other words, evaluation of forces in MD scales as $N^2$. However, in MD algorithms using the technique of cell lists and neighbor lists, force evaluation scales as $N$ [55, 56].

**Need for Coarse-Graining**

Even with the most efficient MD algorithms, prohibitively large computation time and memory are required to study the systems of macromolecules due to vastly varying time and length scales involved. In a molecular system, typical bond lengths are of the order of angstroms and bond vibrations take place at the time scale of $10^{-13}$ s. Therefore, the equations of motion have to be integrated with the time steps of the order of $10^{-15}$ s. On the other hand, most of the interesting phenomena in macromolecules take place at much larger length (µm) and time scales (ms) [57-60]. Given these challenges associated with simulations of macromolecules it is impossible to simulate aggregation of nanoparticles at atomistic detail due to limited computational resources. Consequently, the nanoparticles are generally simulated by modeling their interaction as a pair-wise potential and the parameters of the LJ potential are chosen qualitatively to resemble the real systems [61-69] because of the lack of systematic, general and reliable computational or experimental techniques to determine the pair potentials. Therefore, the results obtained from these molecular simulations offer qualitative insights but not reliable, quantitative results.

Usually, when studying phenomena occurring at timescales of the order of $10^{-6}$ - $10^{-1}$ s, the behavior of fast degrees of freedom, like bond fluctuations, are not of interest. Therefore, a systematic method of
Coarse-graining a system by eliminating the unimportant degrees of freedom and at the same time retaining the physics that governs the phenomena at larger length and time scales is needed.

In the pioneering work published in 1991, Baschnagel et al. [57] demonstrated the ability of the coarse-grained representation to preserve the physics of an atomistic system at the length scales relevant to the coarse-grained representation. It was found that distribution functions of the bonds, $P(l)$, and angles, $P(\theta)$, between the CG sites, obtained from the atomistic simulations of linear flexible polymers (polyethylene and bisphenol-A-polycarbonate), were able to capture the essential features of the chemical structure and effective potential at length scales greater than the persistent length, $(<l^2>)^{1/2}$, and the features that occur at the length scales smaller than the persistent length were averaged out.

**Coarse-Graining Techniques**

The aim of the coarse-graining techniques is to find the effective interaction potentials between the coarse-grained sites such that the simulation of a system using the coarse-grained potentials yields the properties that compare favorably with the corresponding atomistic system.

Usually, coarse-graining an atomistic system is a two step process, grouping the atoms to be represented as single sites and determining the effective bonded and non-bonded potentials between the CG sites. Most of the coarse-graining procedures reported in the literature can be classified into three categories, namely, optimization of potential parameters by fitting it to a desired property, structure matching and force matching.

**Optimization of Potential Parameters by Fitting to a Desired Property**

In a frequently referenced study, Shelley et al. [70, 71] coarse-grained the important and complex biological system of phospholipids. Coarse-grained potentials were generated in such a way that they reproduced key physical or structural properties in accordance with experiments or atomistic simulations. Three water molecules were represented as one site using LJ 6-4 type of potential, where $\sigma$ was chosen to satisfy the bulk density of water and $\varepsilon$ was determined from the vapor pressure. Choline, phosphate, glycerol backbone, ester groups, $(\text{CH}_2)_3$ and $(\text{CH}_2)_2\text{-CH}_3$ were represented as one site. The parameters of the harmonic bond and the bending potential were fitted to the corresponding mean and the deviation from atomistic simulations. The non-bonded interactions
were determined such that the RDF from the coarse-grained simulation matched the atomistic RDF using the Inverse Monte Carlo method of Lyubartsev et al. [72], which will be discussed later. The coarse-grained system was faster and captured the properties of the bilayer, for example, the density profile of aqueous DMPC bilayer, in semi-quantitative manner. However, the coarse-graining procedure is tedious and not automatic because a different strategy was used for different coarse-grained sites. Marrink et al. [73, 74] used the coarse-grained models to study the aggregation of dipalmitoylphosphatidycholin (DPPC) into a bilayer. Applicability of coarse-grained model to different head groups (ethanolamine) and tail groups (lauroyl, stearoyl and oleoyl) was also discussed. Aggregation of dodecylphosphocholine (DPC) into micelles and of dioleoylphosphatidylethanolamine (DOEP) into inverted hexagonal phase was also addressed. The coarse-grained model was comprised of four types of interaction sites: polar, nonpolar, apolar and charged, to represent various molecules. The charged sites were further divided into four types: a site incapable of forming a hydrogen bond, the donor of hydrogen bond, the acceptor of hydrogen bond and the sited capable of being a donor and acceptor. All the interaction sites were assigned the same mass, which was equal to the mass of four water molecules. The non-bonded interactions were modeled as LJ 12-6 potential with a cut-off of 1.2 nm. The \( \varepsilon \) values for non-bonded interaction were chosen from a set of five possible values (5, 4.2, 3.4, 2.6 and 1.8 kJ/mol) depending on the nature of interaction being modeled. The \( \sigma \) for all the interaction was kept the same for all the types of interaction and was set equal to 0.47 nm. A trial and error approach was employed to optimize the \( \sigma \) and \( \varepsilon \) values such that densities, mutual solubility and relative diffusion were matched to corresponding experimental values for water and alkanes system. Partial charges were assumed to be incorporated in LJ interactions. The bonded/bending interactions were optimized using the data from atomistic simulations. Four water molecules were represented by one site. Simulation of water using the optimized parameters gave the isothermal compressibility and diffusivity comparable to experiments. For alkanes (especially the longer alkanes) the experimental densities were reproduced within 5%. Diffusion coefficients for smaller alkanes were 2-3 times smaller, however, for larger alkanes they were in good agreement with experiments. The chain stiffness (constant of bending potential) from coarse-grained simulations was in good agreement with atomistic simulations. Solubility of alkane in water and vice-versa also compared favorably with experiments. Relative density of alkane-water interface was also in good agreement with atomistic simulations. The magnitude of charges was optimized to reproduce the radial distribution function obtained from atomistic simulations. The coarse-grained model was able to reproduce the correct aggregating
structures like micelles (DPC) and inverted hexagonal phase. The hexagonal spacing obtained compared well with experiments. Although, the model was able to predict the properties that are in good agreement with experiments, the unsystematic method of optimizing and an extensive set of experimental properties required make this methodology less appealing for more complex systems.

Harmandaris et al. [75] coarse-grained atactic polystyrene such that each styrene monomer was represented as two beads. The bond, bending and dihedral interaction potentials were derived as the potential of mean force from the probability distributions \( P(r,T) \), \( P(\theta,T) \) and \( P(\phi,T) \) obtained from multiple independent united atom simulation of polystyrene dimers. The non-bonded interactions were modeled using an offset and shifted LJ potential as follows:

\[
u(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r - r_{ij}} \right)^{12} - \left( \frac{\sigma}{r - r_{ij}} \right)^{6} + \frac{1}{4} \right]
\]

Here, \( \sigma \) for CH\(_2\) was obtained from the van der Waals radii of the united atom model and for CH-Ph it was obtained by bringing the two toluene molecules close to each other and looking at the potential for all orientations and distances between them. The strength of potential was scaled to temperature, i.e. \( \varepsilon = kT \). Distribution of bond, angle and dihedral distributions and the radius of gyration and end to end distance obtained using the coarse grained model were in excellent agreement with atomistic simulation.

**Structure Matching**

This class of methods is based on determining the potentials between the coarse-grained sites such that structural properties, mostly radial distribution function, obtained from coarse-grained potential match with the corresponding atomistic system. Two methods most frequently used to achieve this are the inverse Monte Carlo and the Boltzmann inversion. These methods stem from a simulation technique known as Reverse Monte Carlo (RMC) [76], which is used to simulate a system using the experimental radial distribution function data as input without even knowing the interaction potentials. This is accomplished by accepting a MC move if there is a negative change in \( \chi^2 \), given as follows,
Here, \( g^{MC}(r) \) and \( g^{exp}(r) \) are the Reverse Monte Carlo and experimental radial distribution functions, respectively, and \( \varepsilon(r) \) is the assumed error bar. Both of these methods are similar and in fact, for the case of a system with only one kind of coarse-grained site they are the same.

**Inverse Monte Carlo Method of Coarse-Graining**

Lyubartsev and Laaksonen’s [72] Inverse Monte Carlo scheme optimizes the coarse-grained potential in tabulated form, thus it is independent of the functional form of the potential, making this method generally applicable. The distance is represented as \( M \) grid points extending from 0 to \( r_{cut} \) and the corresponding potential in the \( i^{th} \) grid is represented as \( V_i \). If \( S_i \) is the number of particles in \( i^{th} \) grid, then \( <S_i> \) is related to radial distribution function in the \( i^{th} \) grid, \( g_i \), according to following relationship,

\[
\frac{nV_{bin}}{V_{total}}
\]  

(3.10)

where \( n \) is the total number of pairs in the system, \( V_{bin} \) and \( V_{total} \) are the volumes of the \( i^{th} \) bin and system respectively. Also, as \( S_i \) depends upon \( V_i \), the change in \( <S_i> \), neglecting the higher order terms, is given as follows,

\[
\Delta<S_i> = \sum_j \frac{\partial<S_i>}{\partial V_j} \Delta V_j \quad \text{and} \quad \frac{\partial<S_i>}{\partial V_j} = -\frac{\langle S_i S_j \rangle - \langle S_i \rangle \langle S_j \rangle}{k_bT} \]  

(3.11)

Here, \( k_b \) is the Boltzmann’s constant and \( T \) is the temperature. Therefore, the initial guess potential \( V^0 \), the potential of mean force, which can be used as initial guess, is iteratively refined using the relationship \( V^1 = V^0 + \Delta V^0 \) in conjunction with Equation (3.11). All the potentials in the system corresponding to various coarse-grained sites are determined simultaneously and for each iteration a simulation using \( V^0 \) needs to be run to obtain \( g(r) \) in order to determine \( \Delta V^0 \). The fact that three body and higher order potentials have been neglected may lead to the concentration and temperature
dependence of effective pair-wise potentials. This may also prevent reliable evaluation of thermodynamic properties. Using this approach, Lyubartsev and Laaksonen successfully derived the effective interaction potentials for Na⁺ and Cl⁻ ions in water [72] and studied the ion distributions and relative binding affinities of different alkali ions to DNA [77].

Murtola et al. [78] studied the structural properties of large scale Dipalmitoylphosphatidylcholine (DPPC)/cholesterol bilayer. Using the data obtained from the atomistic (united atom model) simulation of hydrated DPPC/cholesterol bilayer system at six different concentrations inverse Monte Carlo technique was employed to coarse-grain all the molecules, DPPC and Cholesterol, to one site such that they interact in 2D plane. The coarse-grained interactions were constructed such that the radial distribution functions for the coarse-grained sites, center of masses projected on a 2D plane of bilayer, from atomistic simulations are reproduced. The water molecules were eliminated in the coarse-grained model. The coarse-grained potentials were able to reproduce the radial distribution functions very well and the domains of large and small cholesterol concentrations were observed. An improvement of eight orders of magnitude in time of simulations was observed. The coarse-grained potentials were found to depend upon the concentration, so they could only be used to simulate the systems at the concentrations at which they were derived.

In the subsequent paper, Murtola et al. [79] studied the effect of putting a thermodynamic constraint, area compressibility, to reproduce its experimental value while coarse-graining the DPPC/cholesterol bilayer using the inverse Monte Carlo method. The organization of cholesterol rich and poor domains was much clearer with the new and improved potential compared to the previous one. They also observed that inverse Monte Carlo method requires the adequate sampling of the four particle correlations functions during each iteration. Thus this method becomes increasingly difficult to be applied systems with large number of interactions. A good initial approximate potential is needed for the convergence. For complex systems, it was suggested that Boltzmann inversion method might be computationally more feasible compared to inverse Monte Carlo.

**Iterative Boltzmann Inversion Method of Coarse-Graining**

Iterative Boltzmann inversion method [80, 81] is an alternative coarse-graining method that works by iteratively refining the tabulated coarse-grained potential according to following relationship,
where \( V_{i+1}(r) \) is the coarse-grained potential at the \( i^{th} \) iteration, \( g_i(r) \) is the radial distribution function obtained from the simulation using \( V_i(r) \), and \( g_{\text{target}}(r) \) is the radial distribution function obtained from atomistic simulations or experiments. A merit function is used to evaluate the convergence,

\[
f = \int_{r_{\text{min}}}^{r_{\text{max}}} w(r) \left( g_{\text{target}}(r) - g_i(r) \right) ; \quad w(r) = e^{-r/\sigma}
\]

Here, \( w(r) \) is the weighting function to penalize large fluctuation at small distances. The potential of mean force can be used as an initial guess, given according to the following relationship,

\[
F(r) = -k_b T \ln(g(r))
\]

Here, \( k_b \) is the Boltzmann’s constant and \( T \) is the temperature. Since the distribution functions are dependent on each other, individual potentials cannot be iterated individually, however, while refining one potential others can be kept constant. Consequently, it is better to refine the potentials which don’t depend much on the changes in others first, for example bonded potentials followed by non-bonded potentials. For optimizing the bond, angle and dihedral potentials appropriate distribution functions are used instead of the radial distribution function. Soper [81] applied the idea of Iterative Boltzmann Inversion to derive the effective potential between the water atoms using the experimental radial distribution functions and compared with the SPC/E potential of water and found qualitative but not quantitative similarity between them. Reith et al. [80] used systems of WCA and LJ particles to validate the Boltzmann inversion method and then the systems of polyisoprene melt and solution in cyclohexane were studied. The dependence of the coarse-grained potential on the cut-off distance of \( g(r) \) was also observed. The initial estimates of bond, bending (angle) and dihedral potentials, found to be adequate without further optimization, were as follows,

\[
V_{\text{bond}}^0(l) = -k_b T \ln(P(l)), \quad V_{\text{bend}}^0(\theta) = -k_b T \ln(P(\theta)/\sin \theta), \quad V_{\text{dihedral}}^0(\phi) = -k_b T \ln(P(\phi))
\]
Here, $V^\theta$ is the Boltzmann inverted potential analogous to the potential of mean force, $P(l)$, $P(\theta)$ and $P(\phi)$ are probability distribution functions of bond stretching, angle bending and dihedral angle, respectively.

In an earlier work, Tschop et al. [82] extended the work done by Baschnagel et al. [57] by determining the bond, angle and torsion potentials between the CG sites by inverting the corresponding probability distribution functions determined from the atomistic simulation of the single chains of the different modifications of polycarbonates. Their approach was fundamentally the same as that of Reith et al. [80]. However, Tschop et al. [82] did not coarse-grain the intermolecular potentials systematically, which were instead modeled as repulsive LJ hard-core potentials. For short polymer chains such treatment of non-bonded potential will be inadequate as non-bonded interactions become more important in the short chain system. The advantage of this method is that it does not require the functional form of the potential to be known a priori. The results obtained from the simulations employing CG potentials were found to be in semi-quantitative agreement with the experiments. They were also able to map the atomistic details back into the coarse-grained simulations [83].

Depa et al. [84] coarse-grained a polyethylene melt with chains containing fifty united carbon atoms. Each coarse-grained bead contained four united atoms. The coarse-grained bond and bending potentials were obtained by Boltzmann inversion of the distributions of bond length and angles between the coarse-grained sites. The non-bonded interaction were modeled as LJ 12-6 potential with $\sigma$ and $\epsilon$ chosen such that the radial distribution function was reproduced. The coarse-grained potential was able to reproduce radial distribution function, radius of gyration and end-to-end distance. The dynamic properties also agreed with united atom simulation with time scaled by $\alpha = 4.5$, which was in good agreement with $\alpha = 4.2$ predicted by the theory of accelerated molecular dynamics. Owing to faster dynamics and smoother coarse-grained potentials, a reduction in computation time by a factor of 10 was observed. In the following publication, the authors [85] used the coarse-grained the potential derived from the atomistic simulation of polyethylene chains of length 50 to simulate systems with chains of length in the range 76 – 300 and observed that the static and dynamic properties were in agreement with atomistic simulations and experiments.
Li et al. [86] applied the method of iterative Boltzmann inversion to coarse-grain cis-poly(1,4-butadiene). They fitted an analytical function to the bond, bending and torsion distributions and then employed Boltzmann inversion to obtain corresponding coarse-grained potentials and used the same procedure as Reith et al. [80] to obtain the coarse-grained non-bonded potential. The coarse-grained simulation exhibited faster dynamics but when time was rescaled by appropriate speed-up factor, the mean squared displacement from the coarse-grained system coincided with the one from atomistic simulations as has been observed by other researchers [84, 85]. Similar results were seen for the coarse-grained system of poly(styrene-β-butadiene) [87].

Instead of using the iterative Boltzmann inversion, Meyer et al. [88] derived the non-bonded coarse-grained potential of LJ liquids, diphenyl carbonate, tetrahydrofurane and monomers of polyisoprene by using Simplex optimization technique. The parameters of the chosen functional form of the coarse-grained non-bonded potentials are optimized in a semi-automatic manner so that derived potential reproduced the atomistic \( g_{\text{target}}(r) \), the radial distribution function (RDF). The criterion for optimization was the minimization of the following merit function,

\[
f = \int_{r_{\text{min}}}^{r_{\text{max}}} w(r) \left( g_{\text{target}}(r) - g_i(r) \right) \; ; \quad w(r) = e^{-r/\sigma} \quad (3.16)
\]

Here, \( g_i(r) \) is the radial distribution function obtained from the simulation using the coarse grained-potential at the \( i^{th} \) iteration and \( w(r) \) is the weighting function to penalize large fluctuation at small distances. The coarse-grained potential thus obtained was able to reproduce the structural properties of the system correctly. However, the quality of the coarse-grained potential depended upon the choice of model potential and in general, adjusting more than 4-5 parameters was a tedious task because at each iteration, a simulation using the coarse-grained potential needed to be run to obtain the updated merit function. For the same reason it was time consuming to evaluate different potential models to find the best model for potential.

**Force Matching**

In the force matching method [89, 90], the effective pair-forces between coarse-grained sites are derived from the net force acting on chosen CG sites along an MD trajectory obtained from a short atomistic MD. A suitable model for pair-force \( f_{ij}(r, r_j, p_1, p_2, ..., p_m) \) acting between two CG sites \( i \) and \( j \)
with positions at $r_i$ and $r_j$ respectively is chosen. $p_1, p_2 \ldots p_m$ are the unknown parameters that need to be determined. Often the functional form of a CG pair-force is not known \textit{a priori}; therefore $f_{ij}$ can be modeled using cubic splines. The unknowns $p_1, p_2 \ldots p_m$ can are obtained by solving the set of equations is generated by equating the net force acting on a site $i$ from CG pair-force to the corresponding net force obtained from atomistic MD as follows,

$$\sum_{j=1}^{N} f_{ij} = F_i, \quad i = 1, 2, 3 \ldots N$$

(3.17)

where $N$ is the number of CG sites in the atomistic MD. The force-matching method has the advantage of being systematic and automatic because the CG pair forces are evaluated from the data gathered along the atomistic trajectory and there is no need to run multiple simulations. The force matching method has been successfully applied to study condensed phase liquids [89-91], ionic liquids [92, 93], C$_{60}$ nanoparticles [94, 95] and dimyristoylphosphatidylcholine (DMPC) lipid bilayers [96, 97].

**Comparison of Coarse-Graining Methods**

An effective coarse-graining method is desired to be systematic, fast, automatic, flexible enough handle different kind of potentials, and capable of predicting accurate coarse-grained potentials which are able to reproduce properties that match the experimental values or the properties obtained from an atomistic simulation.

Both the inverse Monte Carlo and iterative Boltzmann inversion methods are semi-automatic because at each iteration, the radial distribution needs to be re-evaluated and convergence can be a problem in cases where potential of mean force does not serve as a good initial guess. Inverse Monte Carlo method evaluates all the potentials at the same time and requires adequate sampling of the four particle correlations functions during each iteration, which becomes time consuming if there are a few different kinds of pair potentials. On the other hand, in Boltzmann inversion method, potentials can be refined one at a time by keeping the rest of them constant. However, as the potentials depend upon each other it is important to ensure that they have not changed due to the optimization of others. The advantage of these methods is that they result in potentials that will reproduce the correct structural
properties. The frequent re-evaluation of radial distribution functions and increasing complexity for a system with more than five coarse-grained sites are its main disadvantages.

The force-matching method has the advantage of being very systematic and automatic because the coarse-grained pair-force is evaluated from the data gathered along the atomistic trajectory and there is no need to run multiple simulations. However, like inverse Monte Carlo, all the pair-forces are evaluated at the same time making computation time consuming for a system with a few types of coarse-grained sites. Another limitation of the force-matching method is its inability to treat the pair-forces that cannot be expressed as linear functions of unknown parameters, for example, a dihedral potential.

All the coarse-grained systems exhibit faster dynamics compared to the equivalent atomistic system because of the missing random forces due to eliminated degrees of freedom. Therefore, one needs to be careful about deriving inferences about the dynamics from coarse-grained simulations. Usually coarse-grained potentials are applicable at the concentrations at which they were derived. To reproduce the thermodynamic properties the coarse-grained potentials can be constrained to do that, but at the cost of making them more non-transferable. Despite these shortcomings, coarse-graining is a vital tool to understand phenomena happening at large length and time scales.

**Summary**

The time and length scales at which interesting phenomena take place in the systems of macromolecules, such as polymers, lipids and nanoparticles, prohibit a molecular simulation study at atomistic detail due to enormous CPU time and memory requirements. Using a suitable coarse-graining method, the uninteresting degrees of freedom can be eliminated while retaining the important physics. The reduction in degrees of freedom reduces the demand for the computing resources, thus making molecular simulations feasible.

Most of the research published in the literature utilizing molecular simulation to study the aggregation of nanoparticles has been carried out in reduced units using pair-wise interaction potentials whose parameters are chosen to mimic the real systems in a qualitative manner [61-69]. Consequently, the insights obtained from these simulations are qualitative in nature. Therefore, a systematic approach
needs to be formulated to systematically derive the interaction potential between nanoparticles from the quantum mechanical data of the molecules that are the building block of the nanoparticles.

Coarse-graining techniques, such as Inverse Monte Carlo [72, 77], iterative Boltzmann inversion [80, 81] and force-matching [89, 90], can be employed to systematically obtain the interaction potential between the nanoparticles, however, force-matching is the most appealing compared to the other two because it is more systematic and automatic. Therefore, a force-matching approach will be used in this research.

**Diffusion of Fractal Aggregates**

**Introduction**

The nanoparticle aggregates are self-similar objects known as fractal aggregates [98]. The morphology of a fractal aggregate is characterized by its fractal dimension $d_f$, which relates the mass of an aggregate ($N$) to its radius of gyration ($R_g$) as $N \propto R_g^{-d_f}$. Strongly attractive nanoparticles aggregate in the diffusion-limited regime and form open aggregates [99] and weakly attractive nanoparticles aggregate in the reaction-limited regime and form compact aggregates [100]. The diffusion of nanoparticle aggregates, which depends upon their mass and morphology, plays an important role in the aggregation kinetics and the final cluster size distribution in a system of aggregating nanoparticles. At the reactor scale, nanoparticle aggregation is usually modeled using the population balance equations. For example, in a system undergoing irreversible aggregation, the particle size distribution is governed by the Smoluchowski equation,

$$\frac{dc_k}{dt} = \frac{1}{2} \sum_{i+j=k} K_{ij} c_i c_j - c_k \sum_{j=1}^{\infty} K_{kj} c_j$$

(3.18)

where $c_k$ is the concentration of aggregates containing $k$ primary particles ($k$-mer) and the aggregation kernel $K_{ij}$ is a symmetric matrix of rate constants describing reactions between $i$-mers and $j$-mers. The aggregation kernel for nanoparticles undergoing Brownian aggregations is given as [101, 102],

$$K_{ij} = 4\pi \left( R_i + R_j \right) \left( D_i + D_j \right)$$

(3.19)
where the sum of the radii $R_i+R_j$ represents the effective collision cross-sectional radius and $D_i$ is the diffusion coefficient of an $i$-mer. While $R_i$ can be evaluated from the geometry of fractal aggregates, $D_i$ of fractal aggregates is not known a priori. Therefore, it is necessary to study the diffusion of nanoparticle aggregates as a function of their mass and fractal dimension.

**Experimental Measurements**

The systematic experimental measurement of the diffusion coefficient for fractal aggregates using methods such as dynamic light scattering, settling velocity, and differential electrophoretic mobility analysis, is a challenging problem [103]. It is a near impossible to generate monodisperse aggregates with precisely known mass and fractal dimension, therefore this polydispersity must be taken into account [104, 105]. Experimentally measured diffusion is also convoluted by contributions from rotational diffusion, which is very difficult to account for [106, 107]. Nonetheless, the ratio of hydrodynamic radius to the radius of gyration of fractal aggregates ($R_h/R_g$) has been shown to be independent of their mass for a given fractal dimension [99, 100, 105, 108, 109]. The values reported for $R_h/R_g$ range between 0.71 - 0.93 for DLA aggregates and 0.83 - 1.0 for RLA aggregates [99, 100, 105, 108, 109]; clearly there is significant overlap and this ambiguity needs to be addressed.

**Theoretical Models**

Theoretical models for predicting diffusion coefficients have been developed by approximating the fractal aggregates as porous objects [110-112]. In these models, the fluid motion on the outside of an aggregate is modeled using Stokes' equation and inside the pores with Brinkman's equation. The $R_h/R_g$ predicted by these models is, in general, greater than the experimental measurements. In contrast, the predictions from models based on Kirkwood-Riseman hydrodynamic theory [113] generally agree well with experiments [103, 114-116].

**Molecular Simulation Study of Aggregate Diffusivity**

Moskal et al. [117] employed Brownian dynamics to obtain the diffusion coefficient of aerosol particle aggregates in the continuum regime. The particle aggregates were constructed in separate simulations where two particles bond rigidly on the close approach and the fractal dimension is controlled by using a smaller sticking probability for dense internal structure. A simulation of 100 aggregates (with normally distributed fractal dimensions) with 100 particles each was conducted and mean diffusivity as a function of mean $d_f$ and $N$ was calculated. The results indicate that the diffusivity predicted by theories using equivalent radii methods are consistently larger than the ones
obtained using these simulations. However, because BD simulation is an implicit solvent method and it therefore requires as an input the solute mobility, the usefulness of BD simulations for computing diffusivities is questionable. Furthermore, BD simulations do not conserve momentum transport through the solvent phase, and therefore they do not correctly account for hydrodynamic interactions. Therefore, diffusion coefficients obtained using BD are useful only for qualitative comparison.

On the other hand, Heyes et al. [118-122] studied the diffusivity of compact spherical clusters using molecular dynamics simulations. However, they used ad-hoc velocity rescaling to thermostat the system which is known to alter the dynamics. Additionally, the results were not properly corrected for finite size effects. Therefore, these results are not reliable even though they provide valuable information about the diffusion of spherical aggregates. Since the nature of a dense and spherical cluster is expected to be significantly different from the fractal aggregates, the diffusion of fractal aggregates needs to be studied in a systematic manner.

**Generating Aggregates of Given Size and Fractal Dimension**

The fractal aggregates with precisely known mass and fractal dimension are obtained in a hierarchical manner according to the recipe of Thouy and Jullien [123, 124]. Starting with $2^n$ particles, at the first step monomers are combined to form $2^{n-1}$ dimers; at the second step dimers combine to form $2^{n-2}$ tetramers and so on until an aggregate with $2^n$ is obtained. The aggregates are oriented and connected to each other such that each step the desired fractal dimension is preserved by choosing the appropriate distance between the centers of mass (COMs) of the two clusters.

The center of mass of an aggregate of $N$ particles is given by:

$$r_c = \frac{1}{N} \sum_{i=1}^{N} r_i$$  \hspace{1cm} (3.20)

Here, $r_i$ is the position of the $i^{th}$ particle in an aggregate. The radius of gyration of the aggregate is then defined as,

$$R_N^2 = \frac{1}{N} \sum_{i=1}^{N} (r_i - r_c)^2$$  \hspace{1cm} (3.21)

Equivalently in terms of particle position only,
\[
R_N^2 = \frac{1}{2N^2} \sum_{i=1}^{N} \sum_{j=1}^{N} (r_i - r_j)^2
\]  
(3.22)

Therefore the radius of gyration of an aggregate with \(2N\) particles formed by joining of two \(N\) particle aggregates ‘\(a\)’ and ‘\(b\)’ can be expressed as,

\[
R_{2N}^2 = \frac{R_{aN}^2 + R_{bN}^2}{4} + \sum_{i=a}^{a,N} \sum_{j=b}^{b,N} (r_{a,i} - r_{b,j})^2
\]  
(3.23)

Here, \(R_{aN}\) and \(R_{bN}\) are the radii of gyration of clusters ‘\(a\)’ and ‘\(b\)’ with \(N\) particles each and the indices \(i\) and \(j\) run over the particles belonging to clusters ‘\(a\)’ and ‘\(b\)’ respectively. If \(\Gamma = r_{a,c} - r_{b,c}\) and \(r_{a,i} - r_{b,j} = (r_{a,i} - r_{a,c}) + (r_{b,j} - r_{b,c}) + \Gamma\), then

\[
R_{2N}^2 = \langle R_N^2 \rangle + \frac{\Gamma^2}{4}, \quad \langle R_N^2 \rangle = \frac{R_{aN}^2 + R_{bN}^2}{2}
\]  
(3.24)

For fractal aggregates \(N \propto (R_N)^d\) therefore \(\Gamma\) and \(R_N\) are related as,

\[
\Gamma = k\sqrt{\langle R_N^2 \rangle}, \quad k = 2\sqrt{\frac{1}{d_f}} - 1
\]  
(3.25)

To make sure that this method works for constructing dimers from monomers the following expression for \(\Gamma\) is used,

\[
\Gamma = \sqrt{k^2 \langle R_N^2 \rangle + 1}
\]  
(3.26)
Figure 3.4: Schematic illustration of how two clusters are combined hierarchically, preserving fractal dimension

For combining two clusters $A$ and $B$, with COMs $C1$ and $C2$, containing $N$ particles each with fractal dimension $d_f$, the distance $C1C2$ is determined using the Equation (3.26). Two particles, $I1$ in $A$ and $I2$ in $B$, which will form the bond between $A$ and $B$ are chosen randomly, as shown in Figure 3.3.1. A site $J1$ in $A$ around $I1$ is obtained such that $IIJ1 = 1$ and the direct angle between $IIJ1$ and $C1C2$ is given by,

$$\theta = \pi \xi^{\sqrt{2/\Gamma}}$$

(3.27)

$\xi$ is chosen randomly between 0 and 1. The azimuthal angle of the $IIJ1$ vector is chosen randomly between 0 and $2\pi$. $I2$ will be placed at $J1$ eventually. To check if the chosen particles $I1$ and $I2$ will be able to form the bond between $A$ and $B$ given that $C1C2 = \Gamma$, the triangle condition is verified, $\Gamma > C1J1+C2I2$. If the condition fails then $I1$ and $I2$ are chosen again and the above procedure is repeated.
With $C1J1$ as an axis a circle is drawn such that any point on this circle $M$ satisfies following conditions,

$$\Gamma = C1M \text{ and } J1C2 = I2C2 \quad (3.28)$$

The cluster $B$ is now oriented such that $I2$ coincides with $J1$ and $C2$ coincides with $M$. The cluster $B$ is rotated with $J1M$ as the axis by an angle chosen randomly between 0 and $2\pi$. Now the final cluster $AB$ is checked for any overlap between constituting $2N$ particles. If any particles overlap then the whole process is repeated again, else the clusters $A$ and $B$ have aggregated successfully to form an aggregate of $2N$ particles and $d_f$ fractal dimension.

**Summary**

To model the cluster size distribution in an aggregating system using a population balance, information about the diffusivity of the aggregates is required as input. Diffusion of nanoparticle aggregates has been studied via experiments, theoretical models based on simplifying hydrodynamics and molecular simulations, but there is disagreement in results reported in the literature. Therefore, in this work the diffusion of fractal aggregates as a function of their mass and fractal dimension is systematically studied using molecular dynamics simulations, thus ensuring that no assumptions about hydrodynamic interactions are invoked.

**References**


CHAPTER 4: MEASURING FORCES BETWEEN POLYSTYRENE MICRO- AND NANOPARTICLES USING ATOMIC FORCE MICROSCOPY

Based on a manuscript in preparation for *Langmuir*

Gaurav Pranami, Qingze Zou and Balaji Narasimhan

**Abstract**

The force between a 300 nm polystyrene (PS) nanoparticle and a PS film was measured using AFM and compared with the force between a 2 µm PS particle and a PS film. Layer-by-layer assembly was used to functionalize silica colloidal probes (5-30 µm) with a monolayer of 300 nm PS nanoparticles and the force corresponding to a single nanoparticle is deduced from the variation of force between functionalized silica probes and a PS film as a function of the diameter of silica particle. The measured nanoparticle force was predominantly van der Waals force with a well depth of ~ 0.39 nN. The ratio of microparticle to the nanoparticle forces was ~ 3.5 and is in good agreement with the prediction of ~ 6.7 based on a continuum model. These force measurements are valuable for the development and validation of molecular-based models derived from multi-scale simulations for predicting the nanoparticle interaction potentials.

**Introduction**

Nanoparticles have a wide range of exciting applications as basic building blocks in catalysts, magnetic devices, polymer composites, sensors, paints, pharmaceuticals, coatings and adhesives [1-5] and the forces between these particles play a vital role in phenomena such as colloidal stability and aggregation that govern the properties of these materials. Many applications require nanoparticles with well-controlled particle size distributions, especially in the biomedical field [6-8]. Therefore, a thorough understanding of interaction potentials between colloidal micro- and nanoparticles is essential for the rational development of novel advanced materials with desired properties. Experimental knowledge of the forces between colloidal particles is also valuable in guiding modeling efforts that are directed toward understanding advanced materials [9-13], which often
involve approximate stochastic or scaling arguments to model the effect of nanoparticle interactions [14-18].

Atomic force microscopy (AFM) [19] is an experimental method to measure forces between microscopic objects of sub-micron sizes. AFM has the unique ability to measure the force exerted on an AFM probe (an optical lever) by a substrate as a function of the separation between them, i.e. a force curve. It is sensitive enough to measure the forces of the order of $10^{-9}$ N, which are typical of forces between colloidal particles [20-25]. In their pioneering work, Ducker et al. [21] measured the force between a single 3.5 µm silica particle by attaching it to an AFM cantilever (colloidal probe) and a flat silica surface in a salt solution and showed that DLVO model was able to explain the measurements. Since then, AFM has become a quintessential tool for the measurement of forces between colloidal particles. Li et al. [26] measured the forces between a pair of PS particles (2 and 16 µm) as a function of salt concentration and found that DLVO potential was not able to explain all the measured forces. While Li et al. [26] do not mention the effect of dissolved gases in the water on the measured forces, Considine et al. [27] argued that dissolved gases significantly alter the forces between PS (6 µm) particles in water. This was attributed to the bridging between nanobubbles of dissolved gases that form on the hydrophobic surfaces. They also asserted that the DLVO theory is inadequate to explain the observed double layer repulsion because the roughness of the particle surfaces. The formation of nanobubbles on the hydrophobic surface of PS has also been convincingly shown by Simonsen et al. [28]. While these studies utilized the force curves measured during the approach of the probe to the surface, Hodges et al. [22, 23], utilized the retraction force curves to study the adhesion between a pair of PS particles of size ~ 2-100 µm in degassed water. They found that the JKR model [29], without accounting for surface roughness, was not adequate to explain the observed adhesive forces.

There are a number of studies reported in the literature on the use of colloidal probes for measuring forces between a variety of materials, however, almost always, the size of the colloidal particle attached to the AFM cantilever is greater than 3-5 µm. While the research involving large particles (> 5 µm) provides invaluable insights on the interactions between microparticles, it is important to systematically study the forces between smaller particles because a large number of advanced materials utilize particles that are much smaller than 5 µm.
Ong et al. [30] measured the force between ceria nanoparticles and polyurethane pads using AFM by functionalizing an AFM probe with ceria nanoparticles. They applied a two-component epoxy adhesive to the AFM cantilever and placed the cantilever on the dry ceria particles placed on a substrate, resulting in multiple nanoparticles attached to the probes. The ceria colloidal probe was imaged using AFM to ascertain that a single nanoparticle was present at the apex. To ensure that the apex was not contaminated with adhesive, the forces measured with the ceria probe were compared to the force measured with a probe coated with only the adhesive, which were found to be significantly different. It is important to recognize that due to capillary forces, the adhesive creeps up through the voids between nanoparticles. In addition, most quick setting and two-component adhesives, outgas and contaminate the nearby region, which may affect the measured forces. Therefore, a more controlled approach for preparing probes functionalized with nanoparticles is necessary.

![Diagram](image)

**Figure 4.1:** Schematic describing the approach followed in this work to estimate the force corresponding to a single polystyrene nanoparticle from the relationship of the force ($F$) with a polystyrene film as a function of the diameter of core silica particle ($d$)

In this work, the forces between a pair of 2 µm PS particles and a 2 µm PS particle and a PS film were measured in air using AFM from the approach force curves. The results obtained were compared to existing continuum models [31]. The force between a 300 nm PS particle and a PS film
is estimated from the variation of the force between a silica microparticle coated with a monolayer of nanoparticles and a PS film as shown in Figure 4.1. This idea is a variation of the approach proposed by Golovko et al. [32], in which the force between silica microparticles (10 µm) coated with a monolayer of latex nanoparticles (70 nm) and ZnO was measured. Golovko et al. did not explore the variation of the force with the size of core silica particle. As the size of silica particle is varied the number of nanoparticles at the apex that interact with the substrate varies and this variation can be utilized to estimate the force corresponding to a single nanoparticle. To our knowledge this is the first experimental attempt to study nanoparticle forces in this manner.

Materials and Methods

Preparation of 2 µm Polystyrene Colloidal Probes

Surfactant-free carboxylated polystyrene (PS) particles (2 µm diameter, 4% v/v, product number 7-2000) were purchased from Interfacial Dynamics (www.idclatex.com). The manufacturer reported the standard deviation of the particle diameter as 0.092 µm and the surface charge density due to carboxyl groups as 11.1 µC/cm². These particles come as a colloidal suspension in distilled and de-ionized water with 4.4% solids (weight/volume). NOA 68 adhesive, which is a UV-curing clear and colorless liquid photopolymer was purchased from Norland Corporation (www.norlandprod.com)

V-shaped tipless silicon nitride (Si₃N₄) cantilevers (NP-O20) purchased from Veeco Probes (www.veecoprobes.com) were used for the measurement of the force between a 2 µm PS particle and a PS film. A single 2 µm PS particle is attached to a cantilever of a nominal spring constant of 0.12 N/m using NOA 68 adhesive with the help of two micromanipulators (PPM-5000, www.wpiinc.com) viewed with an upright optical microscope with 10x and 50x magnification objectives as shown in Figure 4.2. The amount of adhesive used was carefully controlled to avoid contaminating the apex of the PS microparticle attached to the AFM cantilever known as a colloidal probe.

For the force measurements between a pair of 2 µm PS particles, colloidal probes from Novascan (www.novascan.com) were used. The 2 µm PS particles (as mentioned above) were supplied to Novascan in order to maintain the consistency in the materials used in force measurements. The nominal spring constant of these cantilevers was 0.08 N/m.
Preparation of 5 – 30 μm Silica Colloidal Probes

Uniform silica microparticles (dry, SS05N) of diameter ~4.8 μm were purchased from Bangs Laboratories (www.bangslabs.com) and were used without further treatment. Soda lime glass beads of diameter in the range 10 – 30 μm (product number 07668-1) were purchased from Polysciences (www.polysciences.com).

V-shaped tipless silicon nitride (Si₃N₄) cantilevers (MLCT-O20) were purchased from Veeco Probes. Cantilevers of nominal spring constants $k = 0.03$ and 0.05 N/m were respectively used for making 5 μm silica and 10-30 μm glass colloidal probes using NOA 68 adhesive for the measurement of force against a PS film. The cantilevers were heated for 12 h at 50 °C to optimize the bonding between the silica/glass bead and the cantilever with the use of NOA 68.

Coating Silica Colloidal Probes with a monolayer 300 nm Polystyrene Nanoparticles

Poly (allylamine hydrochloride) (PAH, MW 70,000, product number 283223-5G), was purchased from Sigma Aldrich (www.sigmaaldrich.com). Surfactant-free 300 nm diameter carboxylated PS particles of (4% v/v, product number 7-300) were purchased from Interfacial Dynamics. The standard
deviation of the diameter of the particles reported by the manufacturer was 10 nm and the surface charge density due to carboxyl groups was 9.9 μC/cm².

A layer-by-layer assembly procedure from the literature [33] was modified to coat a monolayer of PS nanoparticles on silica colloidal probes. The negatively charged silica/glass probes were coated with a layer of positively charged PAH, thus rendering the surface positively charged. When the probes are introduced into a suspension of negatively charged PS nanoparticles, a monolayer of PS nanoparticles self-assembled on the positively charged silica surface as shown in Figure 4.3.

Figure 4.3: Scanning electron micrographs of silica colloidal probes coated with a monolayer of 300 nm polystyrene nanoparticles

Ten silica colloidal probes were immobilized on a glass cover slip using minimal amount of NOA 68 adhesive and were gently rinsed with 18.2 MΩ nanopure water (Milli Q). The glass cover-slip was then placed in a 100 mL beaker containing 60 mL of 0.05 M PAH and 0.03 M KCl solution in nanopure water for 30 min to coat a layer of positively charged PAH on the silica colloidal probe. The cover slip was tilted by leaning it against a stirrer-bar at the bottom the beaker. In order to flush the beaker with a desired solution or solvent, the beaker was connected with an inlet and outlet tube. A peristaltic pump (4 channel SCI-Q 200 series pump, Watson-Marlow Inc., www.watson-marlow.com) was used to simultaneously introduce the desired solution into and withdraw the solution from the beaker. An inlet/outlet flow rate of ~15 mL/min was utilized; however, the inlet flow rate obtained was slightly smaller (< 1 ml/min) compared to the outlet flow rate. The level of the inlet tube was maintained at ~ 80 mL and that of the outlet tube was maintained at ~60 mL (by taping the tubes on
the outside of the beaker), which ensured that the volume of solution in the beaker was constant at 60 mL. The beaker was flushed with 0.06 M KCl solution for 60 min to remove excess PAH and to stabilize the PAH coating on the silica microparticles. The beaker was flushed with nanopure water for 180 min to remove excess KCl. A 300 µL PS nanoparticle suspension (4% v/v) was introduced into the beaker and allowed to stand for 30 min, after which the beaker was flushed with nanopure water to remove excess PS nanoparticles. The beaker containing the cover slip was autoclaved for 1 min (the complete cycle lasted ~ 15 min) to fuse the PS nanoparticles to the silica/glass microparticle. During the entire process, the cover slip was completely immersed in the solution in the beaker. After autoclaving, the cover slip was air-dried and AFM probes were detached from cover slip by gently pushing the probes along the plane of cover slip from the side using a tweezer. It is necessary to fuse the PS particles to silica by autoclaving to prevent any damage to the PS nanoparticle coating from the adhesive force between the probe and the substrate during force curve measurements. Additionally, drying the PS nanoparticle coated colloidal silica probes in air without autoclaving results in a non-uniform coating due to the capillary forces resulting from water removal as shown in Figure 4.4.

![Figure 4.4](image)

**Figure 4.4:** Representative comparison of the quality of PS nanoparticle monolayer coating on silica microparticles resulting from autoclaving followed by air drying (left) and air drying without autoclaving (right)
Preparation of Polystyrene Film

PS films on silicon wafers were spin coated (spin coater model PWM 32, Headway Research Inc., www.headwayresearch.com) at 600 – 1000 rpm using a solution of ~40 mg of air-dried 2 μm PS particles dissolved in 1 mL of toluene. The typical film RMS roughness was measured to be 0.34 nm over an area of 15 μm², indicating that the film surface is atomically smooth.

![AFM image of 2 μm PS particles immobilized on a surface](image)

Figure 4.5: AFM image of 2 μm PS particles immobilized on a surface

Immobilizing 2 μm Polystyrene Microparticle

A PS film was coated on a silicon wafer at 750 rpm from a solution of ~40 mg PS per mL of toluene. A dilute suspension was prepared by adding 30 μL of 4% v/v suspension of 2 μm PS particles to 40 mL water. Approximately 50 μL of this suspension was placed on the PS film and allowed to dry. Due to the hydrophobic nature of the PS, the dried particles form an island of closely-packed PS particles and the region near the edge is essentially a closely packed monolayer of PS particles. The PS particles are fused into the PS film by heating the substrate at 110 °C for 4 min, thus immobilizing the PS particles on the substrate as shown in Figure 4.5.
**Force Curve Measurements using AFM**

All the force curves were recorded in air (at ambient conditions) with a tip velocity of ~ 1 µm/s for both the approach and retraction from the substrate. There was no delay between consecutive approach and retract force curves. The deflection sensitivity was calibrated from the force curve against a silicon wafer, which is a hard substrate.

The forces between 2 µm PS colloidal probes and PS film were measured using a Dimension 3000 AFM with Nanoscope IV controller from Digital Instruments (www.di.com). Seven colloidal probes were made with a single 2 µm PS particle attached to each tipless AFM cantilever. Two PS films were spin coated on a silicon wafer at 600 (Film A) and 1000 rpm (Film B) as mentioned above. For each probe force curves were measured in air, at five different locations on each film; at each location five force curves were measured. The spring constants of the cantilevers were calibrated using the method of thermal vibrations proposed by Hutter et al. [34], corrected by Butt et al. [35] (deviations from a simple harmonic oscillator) and by Stark et al. [36] (for cantilevers with a triangle geometry). The spring constants of the tips were found to be in the range 0.14 – 0.21 N/m whereas the nominal value of spring constant reported by manufacturer is 0.12 N/m.

The forces between a pair of 2 µm PS particles were measured in air using a Dimension 3100 AFM with a hybrid head and a Nanoscope IV controller from Digital Instruments. Six 2 µm PS colloidal probes obtained from Novascan (www.novascan.com) were used to measure the force with another 2 µm PS particle immobilized on a surface as described above. In order to measure force between two particles, the PS colloidal probe was required to be aligned vertically on top of a particle immobilized on a substrate. This can be achieved by successive imaging in contact mode and by zooming on the particles on substrate with the colloidal probe. In practice, this resulted in frequent detachment of the PS particles from the AFM cantilevers due to lateral friction force, rendering the colloidal probe useless. Moreover, using the offset function to move the probe to a desired location based on an already captured image is not precise. In order to circumvent this problem, an image of a 6 × 6 µm² area was obtained and force curves were measured on a fine square grid with a spacing of 100 nm over the desired particles in the scan. The distance between the starting point and the contact point of the approach force curves was used to reconstruct the image of the substrate and force curves precisely at the apex were selected for analysis. This eliminated the need for repeated scanning, minimized the detachment of the PS particles from the cantilever, and ensured precise vertical
alignment between the PS colloidal probe and the PS particle on the substrate. The spring constants were calibrated using the reference cantilever method [37] and a total of 141 force curves were used for the analysis.

The forces between silica microparticles coated with a monolayer of PS nanoparticles and a PS film were measured in air using the Dimension 3100 AFM with a hybrid head and a Nanoscope IV controller from Digital Instruments. Ten colloidal silica probes of diameters 5 µm and 10-30 µm each were coated with a monolayer of 300 nm PS particles using the procedure described above. A PS film was spin coated on a silicon wafer at 750 rpm, as described above. The spring constants were calibrated using the reference cantilever method [37] and 49 force curves were recorded at different locations on the PS film with each probe.

**Results and Discussion**

A typical approach force curve obtained between a 2 µm PS particle and a PS film is shown in Figure 4.6. Though the PS particles used here are reported as negatively charged by the manufacturer due to the presence of carboxyl group and the PS film is prepared from the same particles, there is no evidence of long range electrostatic repulsion in the measured force curves. The most likely reason for this is that carboxyl groups on the surface exist as COOH in air as opposed to COO⁻ in water. However, a short range attractive force typically acting over a distance of ~8 nm indicates that the force between the PS particle and the PS film is dominated by van der Waals interactions. It is well-known that van der Waals and electrostatic forces usually act at distances of 10 nm and 100 nm, respectively [38].

The strength of the van der Waals force can be characterized by the maximum attractive force ‘well-depth’, as shown in Figure 4.6. The difference in the mean of well depths obtained from the force curves measured between 2 µm PS particles and PS films (Film A and Film B, Table 4.1) were found to be statistically insignificant, indicating that the PS films were thick enough so that the silicon wafer underneath the film did not affect the force measurements. The average well-depth between a 2 µm PS particle and a PS films was found to be ~1.35 nN. Similarly, the average ‘well-depth’ of the force between a pair of 2 µm PS particles was found to be 1.31 nN with a standard deviation of 0.57 nN.
Figure 4.6: A typical approach force curve between a 2-μm PS particle and PS film

Table 4.1: Mean and standard deviation of well-depth of the approach force curves between a 2 μm PS particle and a PS film

<table>
<thead>
<tr>
<th>Film</th>
<th>Mean (nN)</th>
<th>Standard Deviation (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (spin coated at 600 rpm)</td>
<td>1.31</td>
<td>0.40</td>
</tr>
<tr>
<td>B (spin coated at 1000 rpm)</td>
<td>1.41</td>
<td>0.29</td>
</tr>
</tbody>
</table>

While a micron sized particle can be attached to an AFM cantilever using adhesive with the help of micromanipulators while viewing through an optical microscope, it is not possible to use the same
procedure to attach a nanoparticle to an AFM probe. Therefore, in this work the force between a 300 nm PS particle and a PS film was deduced from the variation of the force between silica particles (5-30 µm) coated with a monolayer of PS nanoparticles and a PS film as a function of the diameter of core silica particle. The surface density \( \rho_s \) of PS nanoparticles as evaluated from scanning electron microscopy images was found to be \( \sim 1.3 \) particles/\( \mu \)m\(^2\). The measured force curves did not exhibit any long-range electrostatic forces and the force was dominated by short-range van der Waals forces. The average well depths thus obtained are plotted in Figure 4.7 as a function of the diameter of silica particle attached to the AFM cantilever. Despite the scatter in the data, there is a significant statistical evidence \( R^2 = 0.81 \) of a linear relationship over the range of the sizes of silica particles studied as shown in Figure 4.7. It can be argued that intercept represents the force contribution from the core silica particle, but this is unlikely because neither electrostatic nor van der Waals forces from silica particles are expected to extend beyond 300 nm, the diameter of the PS nanoparticle at the apex. In order to decipher the force corresponding to a single nanoparticle, it is essential to estimate the number \( N \) of PS nanoparticles on a silica colloidal probe that contribute to the measured force. Given the surface density of PS nanoparticles on silica probes, \( N \) can be readily obtained if the effective contact area \( A \) of a given silica colloidal probe is known, \( N = A/\rho_s \). The contact area can be estimated using JKR theory [29] for zero applied load because there is no external load before the contact between the probe and the substrate in the approach force curves. The contact area \( A \) based on JKR theory for zero load is:

\[
A = \left( \frac{6\pi R^2 W}{K} \right)^{1/3}
\]

Here, \( R \) is the radius of the colloidal probe, \( W \) is the work of adhesion between the probe and substrate and \( K \) is the effective modulus. The work of adhesion \( W \) for the PS-silica interface is 0.32 J/m\(^2\) [39]. The effective modulus is given by:

\[
\frac{1}{K} = \frac{3}{4} \left( \frac{1 - \nu_{probe}^2}{E_{probe}} + \frac{1 - \nu_{substrate}^2}{E_{substrate}} \right)
\]

In this expression, \( \nu \) is the Poisson’s ratio and \( E \) is the Young’s modulus. The Poisson’s ratio and the Young’s modulus for PS and Silica were taken to be 0.33 and 3.3 GPa, and 0.165 and 7.3 GPa.
respectively. Based on the contact areas evaluated using these representative values, approximately 9
PS nanoparticles will contribute to the measured force for silica particles of diameter 30 µm and 1 PS
nanoparticle will contribute to the measured force for silica particles of diameter 5 µm. This is under
the assumption that the surface distribution of PS nanoparticles on silica particles of various
diameters is uniform – this was confirmed from the SEM images of the PS nanoparticle-decorated
silica particles. Therefore, in Figure 4.7, for μm an estimated well depth of ~ 0.39 nN can be
obtained for the force between one PS nanoparticle and a PS film.

According to continuum theory [31], the van der Waals force between a spherical particle and a film
is expected to be half the force between a pair of spherical particles of same size, which are given
according to Equations (4.3) and (4.4).

\[ F(D) = -\frac{AR}{6D^2} \]  
\[ F(D) = -\frac{AR}{12D^2} \]

Here, \( F(D) \) is the van der Waals force acting between two surfaces at a separation \( D \), \( A \) is the
Hamaker constant which depends of the materials of interacting surfaces and the medium and \( R \) is the
radius of the spherical particle.

For PS in air (or vacuum) the Hamaker constant equals \( 6.6 \times 10^{-20} \) J [31]. Therefore, a well depth of ~
68 nN and ~ 34 nN is expected between a 2 µm PS particle and a film and between a pair of 2 µm PS
particles respectively, assuming that \( D \sim 4 \) Å (based on the excluded volume of a benzene molecule
[40]) at the contact between them. However, the experimentally measured well depths of the forces
between a 2 µm PS particle and PS film and a pair of 2 µm PS particles are ~ 20 - 50 times smaller
than the theoretical predictions and the difference between them is statistically insignificant.
Likewise, from Equation (4.3), a well depth of ~ 10 nN is expected for force between a 300 nm PS
nanoparticle and a PS film, which is ~ 25 times larger than the measured force.

The theoretical models represented by Equations (4.3) and (4.4) assume the surfaces to be perfectly
smooth. Based on Equation (4.3), a well depth of 1.35 nN will exist between a PS particle of diameter
\( \sim 40 \text{ nm} \) and a PS film at \( D \sim 4 \text{ Å} \), which is much smaller compared to a 2 \( \mu \text{m} \) PS particle used in these experiments. This observed discrepancy is most likely due to the roughness of the PS microparticle surface. PS microparticles are known to possess rough surfaces and the JKR model [29] was found to be inadequate for modeling the adhesion between PS microparticles in water [22, 23]. In addition to the surface roughness, the humidity in the ambient air and contamination, which are difficult to control and characterize for volumes of the order of 1 \( \mu \text{m}^3 \), may also cause the observed deviation from the model. The humidity may result in capillary condensation, which is likely to occur at nanometer length scales and will affect the value of \( D \) in Equation (4.3). Like with the forces due to the 2 \( \mu \text{m} \) PS particles, the discrepancy between the continuum theory prediction and the experimental results with the nanoparticles is likely due to the deviation of the experimental system from the model in terms of particle surface roughness and humidity in ambient air.

The insignificant difference between particle-particle and particle-film force can be attributed to the large uncertainties associated with the spring constant calibration in addition to roughness and humidity as discussed before. The variability in the spring constants of the cantilevers (same nominal spring constant) evaluated using thermal vibration [34-36] and reference cantilever [37] methods was as much as 100\% in some cases and similar variability was observed in the values obtained from a specific method of cantilever calibration, which limits the experimental resolution and prevents the observation of forces that are expected to within 100\% of each other. This essentially means that for the resolution of force measurements using AFM, the force between a pair of particles can be approximated by the force between a particle and a film.

According to Equations (4.3) and (4.4), the force is proportional to the diameter of the particles, analogously, the force between silica microparticles functionalized with a uniform monolayer of PS nanoparticles and a PS film can be expected to vary approximately linearly as a function of the diameter of silica microparticles. Thus, the ratio of the well depth for a 2 \( \mu \text{m} \) PS particle and a 300 nm particle for their force with a PS film is expected to be \( \sim 6.7 \). This ratio compares well with the experimental estimate of 3.5 given the uncertainty in choosing the diameter of core silica sphere corresponding to a single PS nanoparticle.
Figure 4.7: Variation of the well-depth obtained from the force curves measured between silica microparticles coated with 300 nm PS nanoparticles as a function of the diameter of core silica particles. In the linear fit, $Y$: Well depth (nN) and $X$: Diameter of core silica particle

It is important to note that the validity of continuum models at nanometer length scales is questionable. Nonetheless the scaling of force with the size of particle is in reasonable agreement with the theoretical prediction. Alternatively, models to predict the nanoparticle interactions can be based on multiscale simulations and the experimental measurements in this work can be used for validating such molecular based models.

**Conclusions**

In this work, the force between a submicron PS particle (300 nm) and a PS film was measured using AFM. The nanoparticle force was deduced from the variation of force between silica colloidal probes (5-30 µm) functionalized with a monolayer of the PS nanoparticles and a PS film as a function of the diameter of the silica particle. The measured nanoparticle force was dominated by van der
Waals force with a well depth of \( \sim 0.39 \) nN. The forces between a pair of 2 µm PS particles and a 2 µm PS particle and PS film were measured to be \( \sim 1.3 \) nN, indicating that AFM force measurements are not sensitive enough to distinguish between the two geometries. The ratio of the microparticle force to the nanoparticle force was \( \sim 3.5 \) and is in good agreement with that based on a continuum model of van der Waals force. These force measurements are valuable for the development and validation of molecular-based models derived from multi-scale simulations for predicting nanoparticle interaction potentials.

Acknowledgements

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References


CHAPTER 5: COARSE-GRAINED INTERMOLECULAR POTENTIALS DERIVED FROM THE EFFECTIVE FRAGMENT POTENTIAL: APPLICATION TO WATER, BENZENE, AND CARBON TETRACHLORIDE


Gaurav Pranami, Lyudmila Slipchenko, Monica H. Lamm and Mark S. Gordon

Abstract

A force matching technique based on previous work by Voth and co-workers is developed and employed to coarse grain intermolecular potentials for three common solvents: carbon tetrachloride, benzene, and water. The accuracy of the force-matching approach is tested by comparing radial distribution functions (RDF) obtained from simulations using the atomistic and coarse-grained potentials. Atomistic molecular dynamics simulations were performed using the effective fragment potential method (EFP). The RDFs obtained from molecular dynamics simulations of EFPs for carbon tetrachloride, benzene and water are in a good agreement with the corresponding experimental data. The coarse-grained potentials reproduce the EFP molecular dynamics center-of-mass RDFs with reasonable accuracy. The biggest discrepancies are observed for benzene, while the coarse-graining of water and spherically symmetric carbon tetrachloride is of better quality.

Introduction

In the molecular dynamics (MD) [1, 2] technique, a system of particles evolves in time according to the equation of motion, \( \vec{F}_i = m_i \vec{a}_i \), where \( \vec{F}_i \) is the net force acting on particle \( i \), and \( m_i \) and \( \vec{a}_i \) are the mass and acceleration of particle \( i \), respectively. In a molecular system, typical bond lengths are of the order of angstroms while bond vibrations take place at the time scale of \( 10^{-13} \) s. Therefore, the equations of motion for atoms have to be integrated with time steps on the order of \( 10^{-15} \) s. However, many important chemical and biological phenomena in macromolecules take place at much larger time scales, as shown in Table 5.1.
Table 5.1: Characteristic time scales of different events in macromolecular systems

<table>
<thead>
<tr>
<th>System / Phenomena</th>
<th>Characteristic time scales (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion of micelles [3]</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>Self-assembly of diblock copolymers [4]</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>Entanglement of a polymer chain [5]</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>Protein folding [6]</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>DNA replication [6]</td>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>Membrane fusion [6]</td>
<td>$10^{-1}$</td>
</tr>
</tbody>
</table>

Large time and length scales of characteristic events in macromolecular systems, such as polymers, lipids and nanoparticles, prohibit a molecular simulation study at the atomistic level due to enormous CPU time and memory requirements. Moreover, when studying phenomena occurring at timescales on the order of $10^{-6}$ to $10^{-1}$ s, the behavior of the fast degrees of freedom, like bond fluctuations, are not always of interest. Therefore, a systematic approach to coarse-graining is needed, in which the unimportant degrees of freedom are eliminated, but the underlying physics governing the phenomena at larger length and time scales is retained.

Thus, the aim of coarse-graining techniques is to determine the effective interaction potentials between the coarse-grained sites such that the simulation of the coarse-grained (CG) system using the CG potentials yields properties that compare favorably with those of the corresponding atomistic system. An effective coarse-graining method should be systematic, automatic, and fast. Moreover, it should be flexible enough to handle different kinds of potentials and capable of generating CG potentials that would reproduce properties matching experimental data or the properties obtained from an atomistic simulation.
In general, coarse-graining an atomistic system requires a two step process, i.e., first, grouping the atoms into CG sites, as shown in Figure 5.1, and second, determining the effective bonded and non-bonded potentials between the CG sites. Most of the coarse-graining procedures reported in the literature can be classified into three categories: (i) optimization of potential parameters by fitting them to a desired property [7-11], (ii) structure matching [5, 12-22], and (iii) force matching [23, 24].

Systematic structure matching and force matching methods are preferable to the method of ad hoc parameter guessing. In structure matching methods, potentials between the CG sites are determined by fitting structural properties, typically radial distribution functions (RDF), obtained from MD employing the CG potential (CG-MD), to those of the original atomistic system. This is often achieved by either of two closely related methods, Inverse Monte Carlo [16-19] and Boltzmann Inversion [12-15, 20-22]. Both of these methods refine the CG potentials iteratively such that the RDF obtained from the CG-MD approaches the corresponding RDF from an atomistic MD simulation.

Both the inverse Monte Carlo and iterative Boltzmann inversion methods are semi-automatic since the radial distribution function needs to be re-evaluated at each iteration. Moreover, convergence can be a problem if the potential of mean force (PMF) does not serve as a good initial guess. The inverse Monte Carlo method evaluates all the potentials at the same time and requires adequate sampling of
the four-particle correlation functions during each iteration. The latter becomes time consuming if there are several different kinds of pair potentials. On the other hand, in the Boltzmann inversion method, potentials can be refined one at a time by keeping the rest of them constant. However, as the potentials depend upon each other, it is important to ensure that each potential does not change during the optimization of others. The advantage of the structure matching methods is that they result in potentials that will reproduce the correct structural properties; however, their main disadvantages are the necessity for frequent re-evaluation of radial distribution functions and the increasing complexity for a system with more than five coarse-grained sites.

In the force matching method, the effective pair-forces between coarse-grained sites are derived from the net force acting on chosen CG sites along an MD trajectory obtained from a short atomistic MD. The force-matching method has the advantage of being systematic and automatic because the CG pair forces are evaluated from the data gathered along the atomistic trajectory and there is no need to run multiple simulations. The force matching method has been successfully applied to study condensed phase liquids [24-26], ionic liquids [27, 28], C_{60} nanoparticles [23, 29] and dimyristoylphosphatidylcholine (DMPC) lipid bilayers [30, 31].

In order to ensure accurate CG potentials, one needs to conduct MD simulations with a reliable atomistic potential model. The most desirable theoretical approach for the atomistic-scale simulations would be to use a level of quantum mechanics (QM) that can treat both intermolecular and intramolecular interactions with acceptable accuracy. Realistically, the minimal QM levels of theory that can adequately treat all different types of chemical forces are second order perturbation theory [32], (MP2) and, preferably, coupled cluster (CC) theory with some accounting for triples; i.e., CCSD(T) [33]. Unfortunately, a sufficiently high level of QM comes at a significant computational cost; for example, CCSD(T) scales \( \sim N^7 \) with a problem size, where \( N \) is the number of atomic basis functions. This places serious limitations on the sizes of accessible molecular systems. Moreover, in order to obtain the CG potentials including the three-body terms, one needs to perform an extensive sampling of the atomistic-level system, which at present is impractical even for very short time-scales. Successful examples of QM-based coarse-graining have been presented based on Car-Parrinello simulations of atomistic systems [25].
An alternative approach is to replace an accurate but expensive first-principle-based technique by a reliable model potential. Such potentials, broadly referred to as molecular mechanics (MM), generally cannot account for bond-breaking, but can, in principle, account for the range of intermolecular interactions. However, using a fitted pair-wise potential may result in losing quantitative accuracy, predictability, and the underlying physics.

This contribution pursues a different approach for preserving the accuracy of the atomistic level, by using a model potential that is exclusively derived from first principles, the effective fragment potential method (EFP). The original EFP1 method [34, 35] was developed specifically to describe aqueous solvent effects on biomolecular systems and chemical reaction mechanisms, and contains fitted parameters for the repulsive term. A general (EFP2) method [36] is applicable to any solvent; it includes all of the essential physics and has no empirically fitted parameters. A force matching technique is applied to derive a coarse-grained potential from the molecular trajectories generated with EFP MD simulations. The quality of the EFP force matching is tested on carbon tetrachloride, benzene, and water systems. This contribution is the first application of a coarse-graining procedure to the EFP method.

Theory

Effective Fragment Potential method

The effective fragment potential method is a first-principles based model potential for describing intermolecular forces. The interaction energy in EFP1, specifically designed for modeling water, consists of electrostatic, induction, and fitted exchange-repulsion terms. Presently, three different EFP1 models are available, with fitting done to represent Hartree-Fock (HF), DFT/B3LYP, and MP2 levels of theory. These models are called EFP1/HF [34], EFP1/DFT [37], and EFP1/MP2 [38], respectively. In EFP1/MP2, fitted dispersion terms are also included.

The general EFP2 model can be applied to any solvent and includes electrostatic, induction, exchange-repulsion, dispersion, and charge-transfer components, all of which are derived from first-principles using long- and short-range perturbation theory. Charge-transfer interactions are not included in this work, since they are primarily important for charged species. All of the EFP2 parameters are generated during a MAKEFP run, performed for each unique molecule; e.g., benzene
and CCl₄. Once EFP parameters for a particular fragment are generated for a given atomic basis set, they can be used in a variety of applications. The various components of the non-bonded interactions between molecules are evaluated using the EFP2 generated parameters. The procedure has been described in elsewhere [36]; only the main points are summarized below.

The electrostatic energy is calculated using the distributed multipolar expansion introduced by Stone [39, 40], with the expansion carried out through octopoles. The expansion centers are taken to be the atom centers and the bond midpoints. So, for water, there are five expansion points (three at the atom centers and two at the O-H bond midpoints), while in benzene there are 24 expansion points. The induction or polarization term is represented by the interaction of the induced dipole on one fragment with the static multipolar field on another fragment, expressed in terms of the distributed localized molecular orbital (LMO) dipole polarizabilities. That is, the number of polarizability points is equal to the number of bonds and lone pairs in the molecule. One can opt to include inner shells as well, but this is usually not useful. The induced dipoles are iterated to self-consistency, so some many body effects are included.

The Coulomb point multipole model breaks down when fragments approach too closely, since then the actual electron density on the two fragments is not well approximated by point multipoles. Thus, electrostatic interactions become too repulsive whereas the induction energy is too attractive if fragments approach each other too closely. In order to avoid this unphysical behavior, electrostatic and induction energy terms are modulated by exponential damping functions with parameters being obtained from fitting the damped multipole potential to the Hartree-Fock one [41, 42]. In EFP2, the induction energy terms are damped in a similar way [43].

The exchange repulsion energy in EFP2 is derived as an expansion in the intermolecular overlap. When this overlap expansion is expressed in terms of frozen LMOs on each fragment, the expansion can reliably be truncated at the quadratic term [44]. This term does require that each EFP carries a basis set, and the smallest recommended basis set is 6-31++G(d,p) [45] for acceptable results. Since the basis set is used only to calculate overlap integrals, the computation is very fast and quite large basis sets are realistic.

The dispersion interaction can be expressed as the familiar inverse R expansion,
The coefficients \( C_n \) may be derived from the (imaginary) frequency dependent polarizabilities summed over the entire frequency range [46]. If one employs only dipole polarizabilities the dispersion expansion is truncated at the leading term, with \( n = 6 \). In the current EFP2 code, an estimate is used for the \( n = 8 \) term, in addition to the explicitly derived \( n = 6 \) term. Rather than express a molecular \( C_6 \) as a sum over atomic interaction terms, the EFP2 dispersion is expressed in terms of LMO-LMO interactions. In order to ensure that the dispersion interaction goes to zero at short distances, the damping term proposed by Tang and Toennies [47] is employed.

The effective fragment potential method is several orders of magnitude less computationally expensive than \textit{ab-initio} methods because it evaluates intermolecular interactions by simplified formulas derived from perturbation series in terms of intermolecular distances and orbital overlap integrals. The most time-consuming terms in EFP2 are the charge-transfer (omitted in the current work) and the exchange-repulsion, which is evaluated using calculated on the fly orbital overlap integrals between different fragments. EFP2 can be used in MD simulations of moderately sized systems. For example, calculation of the energy and gradient for a system of 64 waters with periodic boundary conditions (PBC) requires about 2 sec. on one Opteron 2600 MHz processor. Despite its low computational cost, the accuracy of EFP in predicting structures and binding energies in weakly-bonded complexes and liquids is very high and comparable with that of MP2 [42].

**Force Matching Procedure**

The aim of the force matching procedure is to obtain the effective pair-force between CG sites using the force data obtained from a detailed atomistic molecular dynamics (MD) trajectory. The current implementation of the force-matching method closely follows the formulation from Refs. [24, 25].

The first step of the systematic force matching procedure is to define the CG sites, which are generally the centers of mass or geometric centers of groups of atoms, as illustrated in Figure 5.1, thus eliminating the group’s internal degrees of freedom. In the next step, the forces and positions of
atoms from the detailed atomistic MD are converted to forces and positions of CG sites as depicted in Figure 5.2.

Figure 5.2: Conversion of forces from atomistic MD to forces on coarse-grained sites

Assume that there are a total of $N$ coarse-grained sites in the system for any one MD snapshot ($p = 1$), with coordinates $(r_i = x_i, y_i, z_i)$ and net forces, $F_i$ (where $i = 1 \rightarrow N$) acting on them, and that these are known from the atomistic MD trajectory data. If $f_{ij}(r_i, r_j)$ represents the force acting on the $i$th CG site due to the $j$th CG site, then each snapshot from the MD trajectory results in the following $n$ (= $N$ for one snapshot) equations:

$$
\sum_{j=1}^{N} f_{ij} = F_i \quad i = 1,2,3 \ldots N
$$

Here the pair-force $f_{ij}(r_i, r_j)$ is unknown, so a model pair-force $f_{ij}(r_i, r_j; p_1, p_2 \ldots p_m)$ is chosen, which depends linearly upon $m$ unknown parameters $p_1, p_2 \ldots p_m$. Consequently, the set of equations (5.2) is a system of linear equations with $m$ unknowns $p_1, p_2 \ldots p_m$. The system (5.2) can be solved using the singular value decomposition (SVD) method if $n > m$ (over-determined system), and the resulting solution will be unique in a least squares sense. If $m > n$, more equations from later snapshots along the MD trajectory should be added to the current set so that the number of equations is greater than the number of unknowns. Mathematically, $n = qN > m$ where $q$ is the number of MD snapshots used to generate the system of equations.

It is important to note that model pair-forces for the interactions $A-A$, $A-B$, $A-C$, etc. are different from each other although they may have the same functional form. If required, the interaction between two
non-bonded A CG sites ($A_{\text{A(non-bonded)}}$) can be treated differently from the interaction between two bonded A CG sites ($A_{\text{A(bonded)}}$). In a system with $A$, $B$, ..., $E$ as chosen coarse-grained sites,

$$f_{ij} = \begin{cases} f_{ij}^{AA}(p_1^{AA}, p_2^{AA}, \ldots, p_u^{AA}) & \text{if } ij = AA \\ f_{ij}^{AB}(p_1^{AB}, p_2^{AB}, \ldots, p_b^{AB}) & \text{if } ij = AB \text{ or } BA \\ \vdots & \vdots \\ f_{ij}^{EE}(p_1^{EE}, p_2^{EE}, \ldots, p_z^{EE}) & \text{if } ij = EE \end{cases} \quad (5.3)$$

Clearly, the total number of unknowns that need to be determined is $m = a + b + \ldots + z$ and a solution set for parameters $p_1, p_2, \ldots, p_m$ is determined using the singular value decomposition or any other suitable method. The mean pair-force can be obtained in a systematic manner by averaging a number of sets of solutions for parameters $p_1, p_2, \ldots, p_m$ obtained along the atomistic MD trajectory in which the phase space is sampled extensively.

**Figure 5.3:** $f_{ij}(r_{ij})$ as cubic splines. The distance, $r_{ij}$ between atoms $i$ and $j$ is divided into the mesh as shown. In each mesh, the pair-force $f_{ij}$ is modeled as a cubic polynomial.

A convenient and systematic way to represent $f_{ij}(r_{ij})$ ($r_{ij}$ is the distance between particles $i$ and $j$) as a linear function of unknowns is to employ cubic splines [48], as shown in Figure 5.3. The advantage of using cubic splines is that the function is continuous not only across the mesh points, but also in the
first and second derivatives. This ensures a smooth curvature across the mesh points. The distance $r_{ij}$ is divided into 1-dimensional mesh points, thus, $f_{ij}(r_{ij})$ in the $k^{th}$ mesh ($r_k \leq r_{ij} \leq r_{k+1}$) is described by Equations. (5.4), (5.5) and (5.6) [48].

\[
f_{ij}(r_{ij}) = A(r_{k+1}, r_{k+1})f_{ij, k+1} + B(r_{k}, r_{k+1})f_{ij, k+1} + C(r_{k}, r_{k+1})f_{ij, k} + D(r_{k}, r_{k+1})f_{ij, k+1}
\]

(5.4)

\[
A = \frac{r_{k+1} - r_{ij}}{r_{k+1} - r_k} \quad B = 1 - A \quad C = \frac{1}{6}(A^3 - A)(r_{k+1} - r_k)^3 \quad D = \frac{1}{6}(B^3 - B)(r_{k+1} - r_k)^3
\]

(5.5)

Here, $f_{ij, k}$, $f'_{ij, k}$ and $f''_{ij, k}$ are the values of the pair-force $f_{ij}(r_{ij})$ and its first and second derivatives, respectively, at mesh point $r_k$. Equation (5.4) ensures the continuity of the function and its second derivative at the mesh points. In order to make the first derivatives continuous across the mesh points $r_k$, an additional set of Equations (5.6) is needed:

\[
\frac{r_k - r_{k+1}}{6} f''_{ij, k+1} + \frac{r_{k+1} - r_k}{3} f''_{ij, k} + \frac{r_{k+1} - r_k}{6} f''_{ij, k+1} = \frac{f_{ij, k+1} - f_{ij, k}}{r_{k+1} - r_k} - \frac{f_{ij, k} - f_{ij, k-1}}{r_k - r_{k-1}}
\]

(5.6)

At the end points of the mesh, Equation (5.6) cannot be applied. Instead, one needs to introduce boundary conditions, for instance, at large $r_{ij}$ the pair-force $f_{ij}$ is usually zero. It is important to note that the mesh sizes should not necessarily be uniform. For example, at those separations for which the pair-force varies rapidly with distance the mesh size can be chosen to be small enough to capture all of the variations.

If some meshes do not get sampled in the set of Equations (5.2), i.e., if the coefficients of the corresponding $f_{ij, k}$ and $f''_{ij, k}$ are zero, then these unknowns are removed from the set of equations and set equal to zero. By solving the set of Equations (5.2) in the least squared sense, the unknowns $f_{ij, k}$ and $f''_{ij, k}$ can be determined. Solutions obtained for a large number of such sets of equations are averaged to reduce statistical noise in the CG pair-force. Then, a suitable analytic function should be fitted to the tabulated $f_{ij}(r_{ij})$. If no distinction is made between $A-A_{bonded}$ and $A-A_{non-bonded}$ interactions in the force matching procedure the resulting coarse-grained $A-A$ pair-force will have the combined
effect of bonded and non-bonded interactions. In a typical atomistic MD simulation, bonded and non-bonded interactions both occur at short $A-A$ distances. Therefore, the coarse-grained $A-A$ interaction force may not be physically correct. In general, separate treatments of bonded and non-bonded interactions are preferred even though it increases the total number of unknowns and the size of the linear least squared problem.

Once all the coarse-grained interactions are determined using the force-matching procedure, they need to be validated by running a MD simulation of the coarse-grained system. Comparing properties such as pair correlation function(s) obtained from the coarse-grained and original atomistic MD is a direct test of the quality of coarse-graining.

The reduction in the number of degrees of freedom can lead to an incorrect pressure in the simulation of the coarse-grained systems in NVT ensembles or to an incorrect density in NPT ensembles [24]. The pressure depends linearly on the pair-forces in the system, hence the effect of the reduced number of degrees of freedom can be accounted for during the force matching procedure [24]. If $T$ is the temperature, $V$ the volume, $N$ the number of degrees of freedom of the system, and $k_b$ the Boltzmann constant then the pressure $P$ of a system is given by

$$P = \frac{Nk_bT}{3V} + \frac{1}{3V} \sum_{i<j} \vec{\mathbf{f}}_i \cdot \vec{\mathbf{r}}_i$$

In order to compensate for the reduced number of degrees of freedom in the coarse-grained system, the set of Equations (5.2) should be solved with the following constraint:

$$\sum_{i<j} \vec{\mathbf{f}}_i \cdot \vec{\mathbf{r}}_i = 3P^{At-MD} V^{CG} - N^{CG} k_b T$$

Here, $P^{At-MD}$ is the pressure in the system in detailed atomistic MD and $V^{CG}$ and $N^{CG}$ are the volume and number of degrees of freedom of the coarse-grained system. The left side of this equation is evaluated for the coarse-grained system for each snapshot during force-matching.
Computational Details

EFP MD Simulations

Molecular dynamics simulations of liquid carbon tetrachloride, benzene, and water were performed using the effective fragment potential method, as implemented in the GAMESS (General Atomic and Molecular Electronic Structure System) electronic structure package [49] . EFP2 parameters for benzene were obtained using the 6-311++G(3df,2p) basis set at the MP2/aug-cc-pVTZ [50] geometry of the benzene monomer, with C-C and C-H bond lengths of 1.3942 Å and 1.0823 Å, respectively. EFP2 parameters for CCl₄ were generated by using the 6-311++G(d,p) basis [51-53] , with the monomer geometry optimized at the MP2/6-311G(d,p) level (C-Cl bond length of 1.772 Å). The EFP1/MP2 [38] potential was used for water.

Table 5.2: EFP-MD simulation parameters*

<table>
<thead>
<tr>
<th>System</th>
<th>Potential</th>
<th>Box Length (Å)</th>
<th>Timestep (fs)</th>
<th>Frequency (fs)</th>
<th>Sample</th>
<th>Simulation Time (ps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl₄</td>
<td>EFP2</td>
<td>21.77</td>
<td>0.3</td>
<td>30</td>
<td>1200</td>
<td>36</td>
</tr>
<tr>
<td>Benzene</td>
<td>EFP2</td>
<td>21.20</td>
<td>0.5</td>
<td>50</td>
<td>500</td>
<td>25</td>
</tr>
<tr>
<td>Water</td>
<td>EFP1/MP2</td>
<td>12.40</td>
<td>0.3</td>
<td>30</td>
<td>1000</td>
<td>30</td>
</tr>
</tbody>
</table>

*For each system, columns specify the type of the potential, simulation box size, time step of MD integration, frequency at which data is sampled for force-matching, total number of configurations sampled in MD simulations and the total time of equilibrated MD simulations.

The MD simulations were carried out in an NVT ensemble at ambient conditions; each simulation contained 64 molecules in a cubic box with periodic boundary conditions. Table 5.2 summarizes details of the EFP-MD simulations used for force-matching. In particular, the type of the potential, box size, time step of integration, frequency of data sampling, total number of sampled configurations, and the total time of the equilibrated MD simulation are listed for each system. Initial equilibration of the systems was performed before recording the data for force matching. In order to ensure good energy conservation in the MD simulations, switching functions were employed for all
EFP interaction terms at long distances [54]. Additionally, in simulations of water, Ewald summations were used to treat long-range electrostatic interactions (charge-charge, charge-dipole, dipole-dipole, and charge-quadrupole).

Since EFP employs frozen internal geometries of fragments, during the MD simulations, CCl$_4$, benzene and water molecules are treated as rigid bodies with a net force and torque acting on each center of mass (COM). Thus, the net forces acting on COMs required for force matching are directly available from the EFP MD simulations. The information about torques is not used in force-matching because each molecule is represented as a point at its COM.

**Force Matching**

Carbon tetrachloride, benzene and water molecules have been coarse-grained to their COM using the force matching technique described earlier. The effective COM pair-force was modeled using cubic splines over a range of distances, described by an inner cutoff and an outer cutoff, with the mesh sizes summarized in Table 5.3. The outer cutoff of the model pair-force was set such that it never exceeded half of the simulation box length and large enough to ensure that the effective pair-force obtained from force-matching naturally approaches zero at the chosen outer cutoff. The inner cutoff can be safely chosen as zero or it can be approximated as a distance which is smaller than the smallest separation between a pair of CG sites sampled in the atomistic MD. The mesh-size should be small enough to capture all the features of the effective pair-force but, as mentioned earlier, smaller mesh-sizes result in more unknowns. Consequently, a smaller mesh is used in the regions where the CG pair-force is sharply repulsive and varies rapidly with distance. A total of $k$ meshes are used to model an interaction that is expressed in $2k+2$ unknowns.

The net forces acting on the COMs of all molecules in a given MD snapshot were equated to the corresponding net force obtained from the model pair-force; consequently, each configuration yields 64 equations since each EFP-MD simulation contains 64 molecules. Three or four (see Table 5.3) MD configurations were used to generate a set of equations such that the number of equations was greater than the number of unknowns. Solutions for a number of such sets were averaged to obtain the effective mean COM pair-force. In the results reported here, the pressure is not constrained.
Table 5.3: Force matching details

<table>
<thead>
<tr>
<th>System</th>
<th>Distance (Å)</th>
<th>Mesh-Size (Å)</th>
<th>Unknowns</th>
<th>Configurations per Set</th>
<th>Number of Sets Averaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl₄</td>
<td>4 – 6</td>
<td>0.05</td>
<td>178</td>
<td>3</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>6 – 10.8</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>3 – 6</td>
<td>0.05</td>
<td>202</td>
<td>3</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>6 – 10</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>2 – 3.5</td>
<td>0.025</td>
<td>222</td>
<td>4</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>3.5 – 6.0</td>
<td>0.050</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For each studied system, the range of distances at which pair-forces are modeled as cubic splines is given, as well as mesh sizes and the number of resulting unknowns, the number of configurations included in a set to generate an over-determined system of equations, and the number of sets for which the least squared solution is averaged.

At short distances, approximately equal to the excluded volume diameter, effective pair forces obtained from force matching exhibit unphysically large fluctuations. This is largely due to inadequate sampling of configurations at short distances in the EFP-MD simulation. These short-range pair-force data were ignored in further analysis. Ignoring the force data may lead to some inconsistency in the agreement of properties of atomistic and CG systems; however, as very few CG sites exist at such small separations in the EFP-MD simulation, this should not lead to significant error if averaging is done over a large number of sets during force matching. The remaining pair-force data, \( f(r) \), obtained from force-matching, are fitted to the following function:

\[
F(r) = \sum_{n=2}^{16} \frac{A_n}{r^n}
\]  

(5.9)

The fitting coefficients \( A_n \) for CCl₄, benzene, and water are listed in Table 5.4 and the units of \( r \) and \( F(r) \) are Å and kcal/mol-Å, respectively. The corresponding effective COM pair-potential, \( U(r) \), was obtained by integrating \( F(r) \) with the condition that the potential is zero at the outer cutoff:

\[
U(r) = -\int F(r)dr
\]

(5.10)
Table 5.4: Fitting coefficients $A_n$ corresponding to Equation (5.9).

<table>
<thead>
<tr>
<th></th>
<th>Carbon Tetrachloride</th>
<th>Benzene</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_2$</td>
<td>$-1.969 \times 10^{21}$</td>
<td>$1.244 \times 10^{21}$</td>
<td>$2.175 \times 10^{17}$</td>
</tr>
<tr>
<td>$A_3$</td>
<td>$4.306 \times 10^{21}$</td>
<td>$-2.620 \times 10^{21}$</td>
<td>$-8.551 \times 10^{17}$</td>
</tr>
<tr>
<td>$A_4$</td>
<td>$-4.333 \times 10^{21}$</td>
<td>$2.545 \times 10^{21}$</td>
<td>$1.550 \times 10^{18}$</td>
</tr>
<tr>
<td>$A_5$</td>
<td>$2.659 \times 10^{21}$</td>
<td>$-1.511 \times 10^{21}$</td>
<td>$-1.719 \times 10^{18}$</td>
</tr>
<tr>
<td>$A_6$</td>
<td>$-1.112 \times 10^{21}$</td>
<td>$6.129 \times 10^{20}$</td>
<td>$1.302 \times 10^{18}$</td>
</tr>
<tr>
<td>$A_7$</td>
<td>$3.356 \times 10^{20}$</td>
<td>$-1.795 \times 10^{20}$</td>
<td>$-7.124 \times 10^{17}$</td>
</tr>
<tr>
<td>$A_8$</td>
<td>$-7.528 \times 10^{19}$</td>
<td>$3.918 \times 10^{19}$</td>
<td>$2.903 \times 10^{17}$</td>
</tr>
<tr>
<td>$A_9$</td>
<td>$1.276 \times 10^{19}$</td>
<td>$-6.468 \times 10^{18}$</td>
<td>$-8.957 \times 10^{16}$</td>
</tr>
<tr>
<td>$A_{10}$</td>
<td>$-1.642 \times 10^{18}$</td>
<td>$8.117 \times 10^{17}$</td>
<td>$2.100 \times 10^{16}$</td>
</tr>
<tr>
<td>$A_{11}$</td>
<td>$1.596 \times 10^{17}$</td>
<td>$-7.706 \times 10^{16}$</td>
<td>$-3.728 \times 10^{15}$</td>
</tr>
<tr>
<td>$A_{12}$</td>
<td>$-1.155 \times 10^{16}$</td>
<td>$5.446 \times 10^{15}$</td>
<td>$4.928 \times 10^{14}$</td>
</tr>
<tr>
<td>$A_{13}$</td>
<td>$6.026 \times 10^{14}$</td>
<td>$-2.779 \times 10^{14}$</td>
<td>$-4.704 \times 10^{13}$</td>
</tr>
<tr>
<td>$A_{14}$</td>
<td>$-2.144 \times 10^{13}$</td>
<td>$9.678 \times 10^{12}$</td>
<td>$3.066 \times 10^{12}$</td>
</tr>
<tr>
<td>$A_{15}$</td>
<td>$4.658 \times 10^{11}$</td>
<td>$-2.058 \times 10^{11}$</td>
<td>$-1.221 \times 10^{11}$</td>
</tr>
<tr>
<td>$A_{16}$</td>
<td>$-4.660 \times 10^{09}$</td>
<td>$2.018 \times 10^{09}$</td>
<td>$2.241 \times 10^{09}$</td>
</tr>
</tbody>
</table>
The coarse-grained pair-force and pair-potential were used for carrying out the molecular dynamics simulations (coarse-grained MD, CG-MD) of 64 points, each point representing a COM of a CCl₄ or benzene or water molecule, at the same conditions as used for the corresponding atomistic MD (Table 5.2). All CG-MD simulations were run using the LAMMPS [55] (Large-scale Atomic/Molecular Massively Parallel Simulator) molecular simulation code available at http://lammps.sandia.gov. LAMMPS is capable of running MD simulations using tabulated pair-forces and pair-potentials. Therefore, the CG pair-forces obtained from force matching can be directly used to run the CG MD simulations. The integration timestep was 1 fs. Each equilibrated CG-MD simulation was 3 ns long and the position data was collected every 1 ps. In order to test the ability of coarse-grained potentials to reproduce properties of atomistic systems, RDFs obtained from CG-MD are compared below to the corresponding COM-COM RDFs from atomistic EFP-MD.

Results and Discussion

EFP MD Simulations

EFP radial distribution functions for liquid CCl₄, benzene, and water are presented in Figure 5.4, Figure 5.5 and Figure 5.6. EFP2 and experimental [56] C-Cl and Cl-Cl RDFs for liquid carbon tetrachloride are shown in Figure 5.4. The Cl-Cl EFP2 RDFs are in good agreement with the experimental data. The discrepancies in the C-Cl RDF curves are more significant, although the qualitative features of the experimental RDF are reproduced. It is possible that the strong structural enhancement observed in the experimental CCl₄ RDFs is an artifact that arises due to numerical instabilities when specific atom-atom RDFs are obtained from X-ray and neutron analysis data [57]. To confirm this the so-called $G_d(r)$ functions were calculated. The $G_d^X(r)$ and $G_d^n(r)$ functions are Fourier transforms of the X-ray and neutron diffraction distinct structure functions, respectively; the latter are unambiguously determined experimentally [56]. For CCl₄, $G_d^X(r)$ and $G_d^n(r)$ functions are connected to specific atom-atom RDFs in the following way:

$$
G_d^X(r) \approx 0.00 g_{CC}(r) + 0.12 g_{CCl}(r) + 0.88 g_{ClCl}(r),
$$

$$
G_d^n(r) \approx 0.02 g_{CC}(r) + 0.25 g_{CCl}(r) + 0.75 g_{ClCl}(r),
$$

(5.11)

where $g_{CC}(r)$, $g_{CCl}(r)$, and $g_{ClCl}(r)$ are C-C, C-Cl, and Cl-Cl RDFs, respectively.
Experimental and EFP-MD $G_d^u(r)$ and $G_d^X(r)$ functions are shown in Fig. 4c and 4d, respectively. The agreement between the EFP2 and experimental $G_d^u$-functions is better than that between specific RDFs, although some discrepancies remain. EFP2 overestimates the heights of the peaks at 4.0 Å in both $G_d$ graphs, and the peaks at 6.2 Å are slightly shifted to longer distances.

Figure 5.4: Comparison of EFP2 and experimental RDFs and $G_d$-functions for liquid carbon tetrachloride: (a) C-Cl and (b) Cl-Cl RDFs, (c) $G_d^u$, (d) $G_d^X$

Figure 5.5 shows the EFP2 and experimental [58] C-C RDFs for liquid benzene. The EFP2 RDF is in reasonable agreement with the experimental curve, with three distinct peaks in the 4 – 7 Å region. These peaks might correspond to different orientations of neighboring benzene molecules in solution, e.g., T-shaped-like and parallel-displaced configurations are possible. Compared to experiment, the EFP2 RDF features are slightly more pronounced, suggesting that EFP2 over-structures liquid benzene. This may be due to the fact that EFP2 slightly overestimates the interactions between benzene molecules [42].
Figure 5.5: Comparison of EFP2 and experimental C-C RDFs for liquid benzene

The EFP1/MP2 oxygen-oxygen RDF for water is shown in Figure 5.6. The positions of the peaks in the EFP1/MP2 and experimental RDFs are in excellent agreement [59], but the intensities of the EFP peaks are overestimated, i.e., EFP1/MP2 over-structures the water RDF. Some degree of over-structuring has been attributed to omitting quantum affects [60], although such affects are likely to be very small when no H atoms are involved. Over-structuring could arise due to intrinsic inaccuracies in the EFP1/MP2 potential, for example, water-water interactions that are too strong. A detailed analysis of the performance of different EFP models for liquid water can be found elsewhere [61].
Because carbon tetrachloride is a spherically symmetric molecule, it is logical to coarse-grain it to its COM and represent it as a single point. The effective pair-force and pair-potential for the CCl$_4$ COM obtained from force matching are shown in Figure 5.7. The CG pair-potential was obtained by integrating the pair-force according to Equation (5.10). The potential, $U(r)$, becomes sharply repulsive below $r \sim 4\text{Å}$ indicating that the CCl$_4$ excluded volume corresponds to the diameter $\sim 4\text{Å}$. This is reasonable given that the C-Cl bond length in CCl$_4$ is 1.767Å and the excluded volume diameter should be slightly larger than twice the C-Cl bond length ($\approx 3.534$ Å). Therefore, the force matching method has taken excluded volume into account. The potential $U(r)$ is smooth and slowly varying with a wide minimum at $r \sim 7\text{Å}$.
The comparison of the CG and EFP RDFs clearly indicates that the coarse-grained potential is able to reproduce the liquid structure of \( \text{CCl}_4 \) reasonably well. The locations of the CG RDF peaks are in good agreement with those in the EFP RDF, although the CG peaks are a bit higher. This may be attributed to an overly steep repulsive CG pair-force (at \( r \sim 4.5 \) Å) used in the CG MD. There is an uncertainty about the nature of the repulsive CG pair-force at short distances, where the pair-force obtained from force-matching exhibits large unphysical fluctuations due to insufficient sampling of pairs at short separations (\( r \sim 4.5 \) Å) in the atomistic MD. Ignoring the data with large unphysical fluctuations in CG pair-force and replacing it with a fit through the remaining pair-force data may make the pair-force strongly repulsive at \( r \sim 4.5 \) Å as shown in Figure 5.7. This repulsion may be stronger than the repulsion in the corresponding EFP-MD. Strong repulsion at close separations (\( r \sim 4.5 \) Å) in the CG MD at the same density as the EFP-MD probably results in a more structured liquid, so sharper peaks are observed.

Figure 5.7: Coarse-graining of \( \text{CCl}_4 \). (a) Black: COM-COM RDF from EFP-MD, (b) red: RDF from CG-MD, (c) orange circles: the effective COM pair-force, (d) green: polynomial fit of the force matching data, (e) blue: the effective COM pair potential
Favorable coarse-graining results for CCl$_4$ are not surprising because this molecule is symmetric in three dimensions. Planar benzene presents a more stringent test for the force-matching approach. Figure 5.8 shows the effective pair-force and pair-potential for the benzene COM.

The locations of the peaks in the benzene CG RDF are in good agreement with the EFP RDF, but the heights of the peaks consistently exceed that of the EFP RDF. Moreover, the first peak in the CG RDF is not as broad as the first peak in the EFP RDF. This indicates that the coarse-grained pair-potential produces a more structured liquid compared to that of the EFP. It is possible that these discrepancies arise due to the use of a system (64 molecules) that is too small and a 25 ps EFP MD run that is too short. This might result in inadequate configuration sampling. For example, as noted above for CCl$_4$, inadequate configuration sampling at short distances, $r \sim 4 - 4.5$ Å, the CG leads to unphysically large fluctuations in the CG pair force. Therefore the data in this range has to be neglected. This leads to the loss of information relating to the minimum energy parallel displaced
benzene dimer configuration, see Figure 5.9. Fitting a curve using the remaining \( f(r) \) data makes the interaction at short distances more repulsive, resulting in a larger excluded volume and a narrower first peak. The 5.0 Å shoulder in the first peak of the EFP RDF can be associated with the T-shaped benzene dimer structure, Figure 5.9. Due to inadequate sampling and repulsion at short distances, the peak in the CG RDF lacks this shoulder and is narrower and higher than the corresponding EFP RDF peak. Additionally, due to the short EFP run, the coarse-grained potential has been averaged over only 150 sets, compared to 250 and 400 sets for water and CCl\(_4\), respectively (Table 5.3). This is because the EFP MD simulations of liquid benzene are more computationally demanding than the simulations for water or CCl\(_4\) (see Table 5.5).

![Figure 5.9: The minimum energy configurations of benzene dimer: (a) T-shaped, (b) parallel-displaced, and (c) edge-to-edge structures](image)

Water is a very important and widely used solvent. Many of the unique properties of water are the result of the complex interactions that occur among water molecules. A water molecule is planar and highly polar, so it is an important system to test with the force matching approach. The coarse-graining results for water are summarized in Figure 5.10. The CG pair-force and pair potentials match qualitatively with the results reported in the literature [24].
Figure 5.10: Coarse-graining of water. (a) Black: COM-COM RDF from EFP-MD, (b) red: RDF from CG-MD, (c) orange circles: the effective COM pair-force, (d) green: polynomial fit of the force matching data, (e) blue: the effective COM pair potential

The CG RDF is in reasonable agreement with the EFP MD COM-COM RDF. In particular, the first peak is in excellent agreement, while the second peak is slightly off (4.2 Å vs. 4.5 Å and slightly too low compared to the EFP RDF). After about 5 Å there is almost no structure in the CG RDF. Water is a complicated molecule to coarse-grain to a single site due to the presence of Van der Waals and coulombic interactions. Moreover, as it is a highly polar molecule, coarse-graining it to a single point at its COM may not be the best choice. Despite these shortcomings, the one-site coarse-grained potential is able to reproduce the first and second peaks, indicating that the force matching technique works reasonably well even for polar non-symmetric molecules.

The real advantage of coarse-graining is the speed up due to the reduction in the number of degrees of freedom and due to substituting a complex EFP potential by a simpler polynomial one. The speed-ups achieved for the three studied systems are listed in Table 5.5.
Table 5.5: CPU time per timestep for EFP-MD and CG-MD simulations and CPU speed-up due to coarse-graining

<table>
<thead>
<tr>
<th>System</th>
<th>EFP-MD</th>
<th>CG-MD</th>
<th>Speed-up**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPU-Time (s)</td>
<td>Timestep (fs)</td>
<td>CPU-Time (s)</td>
</tr>
<tr>
<td>CCl₄</td>
<td>24.80</td>
<td>0.3</td>
<td>0.000238</td>
</tr>
<tr>
<td>Water</td>
<td>117.30</td>
<td>0.5</td>
<td>0.000249</td>
</tr>
<tr>
<td>Benzene</td>
<td>1.03</td>
<td>0.3</td>
<td>0.000239</td>
</tr>
</tbody>
</table>

*All CPU times reported are for MD simulations carried out on one AMD 280 Opteron 2.4 GHz processor

** Speed-up = EFP-MD (CPU time/time step)/CG-MD (CPU time/time step)

Conclusions

In the work presented here, the force matching technique is used to coarse-grain three typical solvents, carbon tetrachloride, benzene, and water, to their centers of mass. The accuracy of the force-matching is tested by comparing structural properties, namely, the radial distribution functions, of the underlying atomistic and coarse-grained systems. The atomistic MD simulations were performed using the effective fragment potential method. The EFP is a first-principles-based method designed for describing intermolecular interactions.

The RDFs for all three systems obtained from coarse-grained MD compare favorably with RDFs from EFP MD. Owing to its spherical symmetry, CCl₄ was found to be the most amenable to coarse-graining using the force matching method. For benzene, the coarse-grained MD produced a more structured liquid than that obtained with the atomistic MD. This might be attributed to a limited sampling of configuration space in the atomistic MD that is required for force matching. This issue needs to be explored further. On the other hand, the coarse-grained RDF of water is in reasonably good agreement with the corresponding atomistic RDF.
The quality of coarse-grained potentials critically depends on the accuracy of the underlying atomistic MD from which the data required for force matching are generated. EFP, used for “atomistic” MD simulations in this work, is a promising technique for capturing the chemistry of liquids and solvents. Most of the previous applications of the EFP method focused on analysis of reactions and properties in complexes and clusters. This work presents the results of EFP MD simulations on liquid CCl₄, benzene, and water. In all cases, the EFP RDFs are in reasonable agreement with the available experimental data. EFP does tend to produce sharper peaks in RDFs, suggesting that some overstructuring of liquids may occur. For coarse-graining, the quality of the sampling of conformational space in an EFP MD simulation can be an issue. For example, more extensive sampling of conformational space in benzene could potentially improve the quality of its coarse-graining. Because it is a first principles-based technique, EFP is significantly more expensive than other force fields. This makes long EFP-MD simulations computationally demanding. These issues will be addressed in future work. Future contributions will also extend the methodology presented here to coarse-graining polymers, in order to study the mechanisms of their aggregation.

Acknowledgements

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CHAPTER 6: MOLECULAR DYNAMICS SIMULATION OF FRACTAL AGGREGATE DIFFUSION

Based on the manuscript submitted to Physical Review E

Gaurav Pranami, R. Dennis Vigil and Monica H. Lamm

Abstract

The diffusion of fractal aggregates comprised of $N_p$ spherical primary particles was studied as a function of the aggregate mass and fractal dimension ($d_f$) using molecular dynamics simulations. It is shown that finite size effects have a strong impact on the apparent value of the diffusion coefficient ($D$), but these can be corrected by carrying out simulations using different simulation box sizes. Specifically, the diffusion coefficient is inversely proportional to the length of a cubic simulation box, and the constant of proportionality appears to be independent of the aggregate mass and fractal dimension. Using this result, it is possible to compute infinite dilution diffusion coefficients ($D_o$) for aggregates of arbitrary size and fractal dimension, and it was found that $D_o \propto N_p^{-d_f}$, as is often assumed by investigators simulating Brownian aggregation of fractal aggregates. The ratio of hydrodynamic radius to radius of gyration is computed and shown to be independent of mass for aggregates of fixed fractal dimension, thus enabling an estimate of the diffusion coefficient for a fractal aggregate based on its radius of gyration.

Introduction

The formation of fractal clusters due to aggregation of compact spherical primary particles is an important process that occurs in many physical situations, such as during the synthesis of particulate material in aerosol and colloidal reactors. Because the resulting particle morphology and size distribution can have a strong impact on product quality, for example in biomedical drug delivery applications that may require specific particle size and shape [1-3], it is necessary to develop accurate models of particle aggregation for the purposes of prediction and control. At the reactor scale, these models are usually formulated in terms of population balance equations, which are simply statements of continuity for the density of particles with specific properties. For example, in a closed system
undergoing irreversible aggregation, the particle size distribution is governed by the Smoluchowski equation,

\[
\frac{dc_k}{dt} = \frac{1}{2} \sum_{i+j=k} K_{ij} c_i c_j - c_k \sum_{j=1}^{\infty} K_{kj} c_j
\]  

(6.1)

where \(c_k\) is the concentration of aggregates containing \(k\) primary particles (\(k\)-mer) and the aggregation kernel \(K_{ij}\) is a symmetric matrix of rate constants describing reactions between \(i\)-mers and \(j\)-mers.

The functional form for \(K_{ij}\) depends upon many microscopic details of aggregation events including the transport mechanism responsible for particle collisions, the collision efficiency (fraction of collisions that lead to an aggregation event), and particle morphology. In some cases \(K_{ij}\) can be derived analytically by invoking simplifying assumptions and applying physical reasoning. A particularly important example is the case of particles undergoing diffusion-limited aggregation under the influence of Brownian motion, which includes colloidal dispersions of particles that are too small to be influenced by fluid shear, as in the case of nanoparticles. The relevant Brownian kernel, first derived by Smoluchowski [4, 5], is given by

\[
K_{ij} = 4\pi(R_i + R_j)(D_i + D_j)
\]  

(6.2)

where the sum of the radii \(R_i + R_j\) represents the effective collision cross-sectional radius and \(D_i\) is the diffusion coefficient of an \(i\)-mer. It follows from Eq. (6.2), that in order to express \(K_{ij}\) explicitly in terms of \(i\) and \(j\), the dependencies of \(R_i\) and \(D_i\) on the particle mass \(i\) must be known. For compact spherical aggregates, these relations can be obtained from simple geometrical considerations and by invoking the Stokes-Einstein relation so that

\[
R_i = \left( \frac{3i}{4\pi \rho_p} \right)^{1/3}
\]  

(6.3)

and
where \( \rho \) is the particle density and \( \eta \) is the viscosity of the suspending fluid.

Many processes, however, result in aggregates with non-Euclidean size scaling and they therefore cannot be described by Eqs. (6.3) and (6.4). For example, in the absence of cluster restructuring, particles produced by diffusion limited aggregation (DLA) possess ramified morphology characterized by a low mass fractal dimension \( d_f \sim 1.8 \), where \( d_f \) is defined by \( i \propto (R_g)^{d_f} \) [6, 7]. Here, \( i \) is the number of primary particles in the aggregate and \( R_g \) is the radius of gyration of the cluster. Reaction limited aggregation (RLA) produces more compact aggregates \( (d_f \sim 2.5) \) [7, 8], but even these clusters are significantly different than spheres and therefore may not obey Eqs. (6.3) and (6.4).

The most straightforward and commonly used method for generalizing the Brownian kernel to include non-spherical fractal aggregates is to assume that the appropriate particle radius to be used in Eqs. (6.2) and (6.4) can be obtained directly from the fractal dimension (i.e. \( R_i \approx R_g \propto i^{1/d_f} \)). However, the validity of this assumption has not been rigorously established, and substantial conflicting information derived from experimental, theoretical, and molecular simulations has been reported concerning the dependence of the diffusion coefficient on the radius of gyration for fractal aggregates. Furthermore, the relationship between \( R_g \) and the hydrodynamic radius, \( R_h \) (radius of a sphere with equivalent mobility) is also not well understood for fractal aggregates.

The systematic experimental measurement of the diffusion coefficient for fractal aggregates using methods such as dynamic light scattering, settling velocity, and differential electrophoretic mobility analysis, is a challenging problem [9]. For example, an inherent difficulty with any experiment is the near-impossibility of obtaining homogeneous samples of aggregates with specific mass and fractal dimension at the desired solvent density. Consequently, experimental measurements are convoluted by the existence of a distribution of aggregate sizes and shapes, and this polydispersity must be taken into account while interpreting the data by either determining these distributions independently or by assuming a distribution [10, 11]. It is also non-trivial to decouple contributions from translational and rotational diffusion components to the measured diffusivity [12, 13]. Despite these difficulties, it has
been demonstrated that in the continuum regime the ratio $R_h/R_g$ approaches a fixed value, $\beta$, for aggregates containing sufficiently large numbers of primary particles [6, 8, 11, 14, 15]. However, the values of $\beta$ reported by various investigators can vary widely, as illustrated by the results summarized in Table 6.1. Specifically, the values reported for $\beta$ range between 0.71 - 0.93 for DLA aggregates and 0.83 - 1.0 for RLA aggregates.

Table 6.1: The ratio of the hydrodynamic radius to the radius of gyration ($R_h/R_g = \beta$) of fractal aggregates in the continuum regime measured using light scattering (SLS/DLS) as reported in the literature.

<table>
<thead>
<tr>
<th>Author</th>
<th>Primary Particle</th>
<th>Size (nm)</th>
<th>$d_f$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al. [6]</td>
<td>Gold</td>
<td>7.5</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Silica</td>
<td>3.5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polystyrene</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. [11]</td>
<td>Polystyrene</td>
<td>28</td>
<td>1.75</td>
<td>0.71±0.05</td>
</tr>
<tr>
<td>Kaetzel et al. [14]</td>
<td>Pyrogenic silica</td>
<td>1.5 - 1.85</td>
<td></td>
<td>0.79 - 0.99</td>
</tr>
<tr>
<td>Wiltzius [15]</td>
<td>Silica</td>
<td>50-700</td>
<td>2.1</td>
<td>0.72±0.02 (0.83*)</td>
</tr>
<tr>
<td></td>
<td>Gold</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. [8]</td>
<td>Silica</td>
<td>3.5</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Polystyrene</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. [11]</td>
<td>Polystyrene</td>
<td>28</td>
<td>2.15</td>
<td>0.97±0.05</td>
</tr>
</tbody>
</table>

* as corrected by Wang et al. [11]

Theoretical models for predicting diffusion coefficients have also been developed by approximating the fractal aggregates as porous objects [16-18]. In these models, the fluid motion on the outside of an aggregate is modeled using Stokes' equation and inside the pores with Brinkman's equation. The $R_h/R_g$ predicted by these models is, in general, greater than the experimental measurements and the predictions from models based on Kirkwood-Riseman hydrodynamic theory [19]. The results from models based on Kirkwood-Riseman theory generally agree well with experiments [9, 20-22].
However, there are some exceptions as summarized in Table 6.2, where the theoretical predictions for the value of $\beta$ can be up to an order of magnitude greater than experimentally measured values. Clearly, it is important to address the inconsistencies in the observed experimental and theoretical values for $R_h/R_g$ reported in the literature.

Table 6.2: The ratio of the hydrodynamic radius to the radius of gyration ($R_h/R_g = \beta$) of fractal aggregates in the continuum regime derived from theoretical models as reported in the literature. KR: Kirkwood - Riseman hydrodynamic theory. SB: Aggregates modeled as porous bodies, and flow inside and outside the pores is modeled using the Stokes and Brinkman equations. G: General solution of Stokes equation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Aggregate Model</th>
<th>$d_f$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hess et al. [21]</td>
<td>KR</td>
<td>Spherically symmetric fractal; Number density, ( c(r) = A r^{-\beta} )</td>
<td>1.8</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
<td>1.46</td>
</tr>
<tr>
<td>Chen et al. [20]</td>
<td>KR</td>
<td>Off-lattice cluster-cluster aggregates</td>
<td>1.8</td>
<td>0.875</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Rogak et al. [22]</td>
<td>KR</td>
<td>Self-similar aggregates with uniform porosity</td>
<td>1.79</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Lattuada et al. [9]</td>
<td>KR</td>
<td>Uses radial distribution function of an aggregate</td>
<td>1.86</td>
<td>0.765</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.05</td>
<td>0.831</td>
</tr>
<tr>
<td>van Saarloos [17]</td>
<td>SB</td>
<td>Porous sphere model of Debye Bueche</td>
<td></td>
<td>1.23</td>
</tr>
<tr>
<td>Tandon et al. [16]</td>
<td>SB</td>
<td>Radially uniform and spherically porous aggregate</td>
<td></td>
<td>$R_h/R_g$ is 20% larger than [20]</td>
</tr>
<tr>
<td>Veerapaneni et al. [18]</td>
<td>SB</td>
<td>Constant volume averaged porosity</td>
<td>2.1</td>
<td>1.03</td>
</tr>
<tr>
<td>Filippov et al. [23]</td>
<td>G</td>
<td>Numerically generated fractal aggregates with specified pre-factor</td>
<td>1.8</td>
<td>0.9 - 1.0</td>
</tr>
</tbody>
</table>

Particle-based molecular simulations offer a promising route to systematically study fractal aggregate diffusion because practical difficulties associated with carrying out experiments and some simplifying assumptions associated with purely theoretical models can be avoided. Recently Moskal et al. [24] employed Brownian dynamics (BD) to obtain the diffusion coefficient of aerosol particle aggregates.
in the continuum regime. Their simulations consisted of 100 aggregates (with normally distributed fractal dimensions) containing 100 primary particles each. The BD trajectories thus generated were used to evaluate mean diffusivity as a function of mean fractal dimension $d_f$ and size $N$. The diffusivities obtained from these BD simulations are consistently smaller than diffusion coefficients predicted by theories using equivalent radii methods. However, because BD simulation is an implicit solvent method and it therefore requires as an input the solute mobility, the usefulness of BD simulations for computing diffusivities is questionable. Furthermore, BD simulations do not conserve momentum transport through the solvent phase, and therefore they do not correctly account for hydrodynamic interactions. Therefore, diffusion coefficients obtained using BD are useful only for qualitative comparison.

In contrast, molecular dynamics (MD) simulations directly account for solute-solvent interactions because solvent molecules are represented explicitly, and hence the diffusion coefficients obtained can be expected to be more accurate. However, because MD simulations include an explicit solvent, simulation of large aggregates or populations of aggregates can become computationally intractable. Although no MD simulations of fractal aggregates have been reported, Heyes et al. [25-29] have used MD simulations to study translational and rotational diffusion of spherical clusters using purely repulsive pair potentials, and it was found that the difference in the translational diffusivity of rigid and dynamic clusters was statistically negligible [26]. It was also shown that both the translational and rotational diffusivities increased with increasing simulation box size [26], which is a manifestation of finite size effects. At high solvent densities of $0.8 - 0.9$ (reduced units) both the translational diffusivity and rotational diffusivity were found to be independent of the mass ratio of the cluster primary particle and solvent particle [27, 28]. The translational and rotational diffusivities decreased with increasing solvent density and cluster size [27]. As the solvent density was increased, the reorientation relaxation time also increased [27]. However, these simulations were run using an ad-hoc velocity rescaling technique to thermostat the system, which can introduce deviations in the system dynamics. Additionally, the results were not properly corrected for finite size effects, and simulations were performed only for dense spherical clusters.

In this work we compute the diffusivity ($D$) of nanoparticle aggregates in the limit of infinite dilution as a function of their size ($N_p$) and fractal dimension ($d_f$) using MD simulations in the presence of explicit solvent molecules in the continuum regime. We find that $D$ scales as $N_p^{-1/d_f}$ and that the
ratio of hydrodynamic radius to the radius of gyration attains a fixed value, \( \beta \), for sufficiently large aggregate size. The resulting values of \( \beta \) for fractal dimensions of 1.8 and 2.5 are found to be 0.76 and 0.98 respectively. These results are then compared with corresponding values based on experiments and hydrodynamic theory reported in the literature.

**Computational Details**

**Generation of Fractal Aggregates**

Off-lattice fractal aggregates with precisely controlled mass and fractal dimension were generated using the recipe proposed by Thouy et al. [30, 31]. In the first step of this hierarchical method, \( 2N \) monomers (primary particles) are paired to form \( N \) dimers. Similarly, in the second step the \( N \) dimers are paired to form \( N/2 \) tetramers and so on, until a single aggregate with \( 2N \) primary particles remains.

At each step of the cluster pairing process, the clusters are connected and oriented so that the resulting aggregate maintains the desired fractal dimension. Even within the constraint of constant fractal dimension there are several degrees of freedom in combining two clusters, so the process is carried out stochastically. Hence, it is possible to generate a large number of unique fractal aggregates with specific size and fractal dimension, and the number of such isomers increases rapidly with increasing cluster size.

In order to verify that the aggregates produced by using the above methodology have the desired fractal dimension, we generated six aggregates of sizes \( N = \{32, 62, 128, 256, 512, 1024\} \) corresponding to each of the fractal dimensions \( d_f = \{1.8, 2.5\} \). As expected, a plot of \( \ln(N) \) vs \( \ln(R_g) \) for these clusters yields straight line fits with slopes 1.8 and 2.5, as shown in Figure 6.1. Two dimensional projections for two fractal clusters (each of size \( N \)) with fractal dimensions \( d_f = 1.8 \) and 2.5 produced using the method of Thouy et al. are shown in Figure 6.2.
Figure 6.1: Plot of $N$ versus $R_g$ for clusters of fractal dimensions 1.8 and 2.5 generated using the hierarchical method of Thouy et al. [30, 31]. The straight line fits through the data yield the slopes 1.8 and 2.5, thereby validating this method for generating fractal aggregates of precisely controlled $N$ and $d_f$.

Simulation Details

In MD simulations a system consisting of a collection of particles (which may represent atoms, molecules, or larger entities) is evolved in time by solving the equations of motion for each particle:

$$m \ddot{r}_i = \mathbf{F}_i$$  \hspace{1cm} (6.5)

Here $\mathbf{F}_i$ is the net force acting on particle $i$, which depends on the relative positions of all other particles with respect to particle $i$, and $r_i$ represent the position of atom $i$. Therefore, by neglecting multibody interactions, the net force on particle $i$ can be obtained by summing the pairwise interactions between that particle and all of the other particles in the system.
Figure 6.2: Two-dimensional projections of fractal clusters generated using the hierarchical method of Thouy et al. [30, 31]

Usually these forces are expressed in terms of the gradient of the pairwise interaction energy potential $U$ so that the total force acting on a given particle is given by
In the above expression $n$ is the total number of particles in the system and $|\mathbf{r}_i - \mathbf{r}_j|$ is the distance separating particles $i$ and $j$. The result of integrating the equations of motion over small time intervals is a record of the system trajectory (i.e. positions and momenta of all constituent particles). Using this information, a variety of structural, dynamical and thermodynamic properties can then be calculated.

In this work, a system comprised of $N_s$ solvent particles and a single fractal aggregate (consisting of $N_p$ primary particles) residing in a cubic simulation box of length $L$ with periodic boundaries was evolved in time using MD simulation. In all simulations, $L$ was chosen to be at least six times the radius of gyration of the chosen solute cluster. The fractal aggregates were represented in the simulations as rigid bodies, and consequently it was not necessary to define interaction energy potentials between the primary particles that comprise an aggregate. Interactions between two solvent particles and between solute particles and fractal aggregate primary particles were modeled using a Lennard-Jones (LJ) potential,

$$U(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

where $r$ is the distance separating two particles, $\sigma$ is the size of the interacting particles (assumed to be equal), and $\varepsilon$ is the well-depth that characterizes the strength of their attraction.

All simulations were carried out in reduced units, as indicated in Table 6.3, using the LAMMPS molecular dynamics program available from Sandia National Laboratory [32]. As was mentioned previously, the size ($\sigma$) and mass ($m$) of the aggregate primary particles and the solvent particles were chosen to be identical and set to unity, i.e. $\sigma_p = \sigma_s = 1$ and $m_p = m_s = 1$. To ensure that LJ solvent particles were in the liquid state, the number density of solvent particles ($\rho_s$) and the temperature ($T$) were fixed at values of 0.85 and 1.2, respectively [33]. In all simulations the solvent-solvent and solvent-primary particle interactions were identical, i.e. $\varepsilon_{ss} = \varepsilon_{sp} = 1$, and the system was equilibrated in the canonical ensemble (NVT) for 2500 reduced time units using a Nose-Hoover thermostat to ensure that all systems studied were at an identical temperature. After the completion of this initial
equilibration, the thermostat was turned off to avoid artificially altering the system dynamics [33]. Subsequently, a production run in the microcanonical ensemble (NVE) was carried out for 50000 reduced time units, and the resulting trajectories of the fractal aggregates were recorded at an interval of one time unit. A time step of 0.005 was found to be suitable for solving the equations of motion for all systems studied in this work.

**Table 6.3: Reduced units used in the MD simulations.**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>$\sigma_s$</td>
</tr>
<tr>
<td>Energy</td>
<td>$\varepsilon_s$</td>
</tr>
<tr>
<td>Mass</td>
<td>$m_s$</td>
</tr>
<tr>
<td>Temperature</td>
<td>$\varepsilon_s/k_B$</td>
</tr>
<tr>
<td>Time</td>
<td>$\sigma_s\sqrt{m_s/\varepsilon_s}$</td>
</tr>
<tr>
<td>Diffusivity</td>
<td>$\sigma_s\sqrt{\varepsilon_s/m_s}$</td>
</tr>
<tr>
<td>Viscosity</td>
<td>$\sqrt{m_s\varepsilon_s/\sigma_s^2}$</td>
</tr>
</tbody>
</table>

The diffusion coefficient of fractal aggregates can be computed from trajectories generated by MD simulation using the Einstein relation [34]

$$D = \frac{1}{6} \lim_{\tau \to \infty} \left\{ \frac{\langle r(\tau) - r(0) \rangle^2}{\tau} \right\}$$  (6.8)
where $D$ is the diffusion coefficient, $\overline{r(\tau)}$ is the cluster position at time $\tau$, $\tau = 0$ refers to a time origin and the operator $<>$ represents the average over time origins. For particles undergoing diffusion, the mean squared displacement grows linearly with time for sufficiently large values of $\tau$, and therefore $D$ can be obtained from a plot of $\langle [\overline{r(\tau)} - \overline{r(0)}]^2 \rangle$ vs $\tau$. Alternatively, the diffusion coefficient can be computed from the aggregate velocity autocorrelation function using the Green-Kubo formula [34],

$$D = \int_0^\infty \frac{\langle \overline{v(\tau)} \cdot \overline{v(0)} \rangle}{3} \, d\tau$$

(6.9)

where $\overline{v(\tau)}$ is the velocity at time $\tau$. However, due to uncertainty associated with the behavior of the velocity autocorrelation at long times and inaccurancy in evaluating the integral numerically, the diffusion coefficients reported in this work were obtained using Einstein's relation, i.e. Eq. (6.8).

**Finite Size Effects**

As stated previously, the MD simulations were carried out in periodic boxes with lengths $L \geq 6R_g$. Nevertheless, finite size effects due to long-range hydrodynamic interactions can be expected to be important because they decay as the inverse of distance, which is evident from the $1/r$ dependence of the Oseen tensor. Therefore, the dynamic properties of a finite system modeled with periodic boundary conditions are affected by interactions between the system and its periodic images. Yeh et al. [35] and Dunweg et al. [36, 37] have proposed the following correction to account for these finite size effects on the diffusion coefficient:

$$D_o = D + \frac{k_b T}{6 \pi \eta L}$$

(6.10)

In Eq. (6.10), $D_o$ is the corrected diffusion coefficient, $D$ is the diffusion coefficient obtained from MD simulation in a periodic box with sides of length $L$, $\xi = 2.837297 \ [35, 36]$ (constant), $k_b$ is the Boltzmann constant, $T$ is temperature, and $\eta$ is the dynamic viscosity of the solvent. This relation has been shown to hold for Lennard-Jones fluids [35, 37] and TIP3P water [35]. In addition, Yeh et al. [35] have shown that the variation in viscosity with changes in $L$ is statistically negligible.
Results and Discussion

Finite Size Effects for Fractal Aggregates

Based on Eq. (6.10), it can be expected that at fixed temperature the constant of proportionality between the diffusion coefficient and the inverse box length is independent of the mass and fractal dimension of the diffusing cluster. However, because this equation was not developed specifically for fractal clusters, it is possible that the slope of the linear fit of $D$ versus $L^{-1}$ data could depend upon $N_p$ and $d_f$. In order to determine whether or not this is the case, several MD simulations were carried out using various simulation box lengths, aggregate sizes, and fractal dimensions, and the data were plotted as shown in Figure 6.3. For each aggregate considered, simulations were carried out using several different box sizes. For each such simulation box, ten multiple independent simulations were carried out by randomly varying the initial velocities assigned to all particles. As expected, it was found that $D$ varies linearly with $L^{-1}$. In addition, the slope appears to be independent of the aggregate size and fractal dimension. It is also evident from the scatter in the data shown in Figure 6.3 that in order to deduce the correct slope (and hence the correct diffusion coefficient), it is crucial to carry out multiple independent simulations. Although it would be desirable to carry out ten multiple independent simulations for several box lengths for every aggregate considered in this work, the computational cost would severely restrict the maximum aggregate size that could be considered, because the number of solvent particles required increases as $R_g^3$. However, in view of the fact that Figure 6.3 suggests that a universal slope exists for the dependence of the diffusion coefficient on inverse box length, we have made use of this slope to compute diffusion coefficients at infinite dilution for all aggregate sizes and fractal dimensions considered. In particular, for each aggregate a single simulation was conducted for each of the different box sizes listed in Table 6.4. The diffusion coefficients obtained for each box size were then extrapolated linearly to $L^{-1} = 0$ (infinite dilution) using the mean value of the slopes shown in Figure 6.3, and the finite size corrected diffusion coefficient, $D_0$, was obtained from the mean of these extrapolated values. Alternatively, one can determine the mean diffusion coefficient for multiple independent simulations carried out at a single computationally feasible box size and then extrapolate to infinite dilution using the universal slope.
Figure 6.3: Variation of the diffusion coefficient ($D$) of fractal aggregates as a function of the inverse simulation box length ($L^{-1}$). For an aggregate placed in a box of a given size, ten independent MD simulations were conducted by randomly varying the initial velocity of all particles. The slopes of the least squared straight line fits through the data are indicated in the legend.

**Diffusion Coefficient Scaling with Mass and Fractal Dimension**

Figure 6.4 illustrates the relationship between the corrected diffusion coefficient and the aggregate mass ($N_p$) for clusters having fractal dimensions of 1.8 and 2.5. Note that each point on this plot required carrying out numerous simulations using different box sizes in order to correct for finite size effects as was discussed above. As expected, for a given fractal dimension, the diffusivity of the aggregates decreases with increasing mass, and the linearity of the plots suggests a power law relationship between $D_0$ and $N_p$. The slopes of the best straight line fits through these data were found to be -0.59 and -0.43 for fractal dimensions 1.8 and 2.5, respectively, and these values compare very well with $-1/d_f = -0.56$ and -0.40. Hence, it appears that the appropriate scaling relation is given by
Table 6.4: List of the systems studied in this work. $L$ is the length of the cubic simulation box and is given in the units of $R_g$ of the corresponding fractal aggregates. Each cluster # indicates a unique aggregate. *Ten multiple independent simulations were conducted for each box size.

<table>
<thead>
<tr>
<th>$N_p$</th>
<th>Cluster #</th>
<th>$d_f$</th>
<th>$L \times R_g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>64'</td>
<td>1</td>
<td>1.8</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td>64'</td>
<td>2</td>
<td>2.1</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>8, 10, 12.5, 15</td>
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<td>2.5</td>
<td>8, 10, 12.5, 15</td>
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<tr>
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<td>8, 10, 12.5, 15</td>
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<tr>
<td>64'</td>
<td>3</td>
<td>2.1</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3</td>
<td>8, 10, 12.5, 15</td>
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<td></td>
<td>2.5</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8*</td>
<td>6, 7, 8, 10</td>
</tr>
<tr>
<td>64'</td>
<td>4</td>
<td>2.1</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3</td>
<td>8, 10, 12.5, 15</td>
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<tr>
<td></td>
<td></td>
<td>2.5*</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td>64'</td>
<td>5</td>
<td>2.1</td>
<td>8, 10, 12.5, 15</td>
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<tr>
<td></td>
<td></td>
<td>2.3</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>8, 10, 12.5, 15</td>
</tr>
<tr>
<td>128</td>
<td>1</td>
<td>1.8*</td>
<td>6, 7, 8, 9, 10</td>
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<td></td>
<td></td>
<td>2.5</td>
<td>7, 8, 10, 12.5</td>
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<tr>
<td>256</td>
<td>1</td>
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<td></td>
<td></td>
<td>2.5</td>
<td>6, 7, 8, 10</td>
</tr>
<tr>
<td>512</td>
<td>1</td>
<td>1.8</td>
<td>6, 6.5, 7, 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>6, 7, 8, 9, 10</td>
</tr>
</tbody>
</table>
\( D_0 \propto N_p^{-1/d_f} \)  \hspace{1cm} (6.11)

Since the intercepts of the straight line fits in Figure 6.4 are given by -2.66 and -3.16 for fractal dimensions 1.8 and 2.5, respectively, it can be concluded that the proportionality constant for the relation given by Eq. (6.11) also depends on the fractal dimension.

Eq. (6.11) shows that as the cluster mass increases, the diffusivity of ramified aggregates with a low fractal dimension decreases more quickly than does the diffusivity of compact clusters with a high fractal dimension. This trend can be explained by the fact that the open structure of low fractal dimension clusters provides solvent particles access to nearly all of the primary particles comprising the aggregate, thereby decreasing the Brownian mobility. In contrast, interior primary particles in compact clusters with high \( d_f \) are largely shielded from solvent particles.
Figure 6.5: Variation of the diffusion coefficient with fractal dimension for aggregates containing 64 primary particles. For each fractal dimension considered, five independent aggregates were simulated. The data point indicated by \( \times \) is the diffusion coefficient of a packed spherical aggregate containing 64 particles as calculated using the Stokes-Einstein relation.

The dependence of the diffusion coefficient on fractal dimension for fixed aggregate mass \((N_p = 64)\) is depicted in Figure 6.5. Five unique aggregates were simulated for each of the four fractal dimensions considered \((d_f = 1.8, 2.1, 2.3, 2.5)\). It can be seen that for fixed aggregate mass, \(D_o\) increases approximately linearly with \(d_f\). Not surprisingly, aggregates with higher values of \(d_f\) diffuse faster because the compact morphology results in fewer interactions with solvent particles. The data in Figure 6.5 also show significant variation of the diffusivity within clusters that have the same fractal dimension, which suggests that morphological factors other than fractal dimension may be important for predicting the mobility of an aggregate.

The diffusivity of a spherical aggregate \((d_f = 3)\) with mass \((N_p = 64)\) was calculated using the Stokes-Einstein formula for a stick boundary condition [38] and this point is also plotted in Figure 6.5. It is clear that the location of this point is consistent with an extrapolation of the values of \(D_o\) found for the fractal clusters, and therefore it appears that the diffusivity approaches the correct limit as \(d_f \to 3\).
order to obtain the Stokes-Einstein prediction for the spherical aggregate, it was necessary to obtain estimates of the viscosity of the solvent and the hydrodynamic radius of a spherical cluster comprised of 64 spherical primary particles. The viscosity of the solvent (3.12 in reduced units) was inferred using Eq. (6.10) and the slope reported in Figure 6.3. The hydrodynamic radius of the spherical cluster of spherical particles was approximated by the radius of gyration. The latter quantity was obtained by using Monte Carlo simulation to generate an optimally packed spherical aggregate with 64 primary particles. Specifically, the primary particles interacted repulsively according to a Lennard Jones potential with a cutoff at $2^{1/6}\sigma$, and the spherical aggregate was produced by ramping the pressure to a high value while simultaneously decreasing the temperature.

**Ratio of Hydrodynamic Radius to Radius of Gyration**

The hydrodynamic radius $R_h$ of the fractal aggregates was computed using the Stokes-Einstein relation

$$R_h = \frac{k_BT}{6\pi\eta D_o}$$

and the resulting values for the ratio $\beta = R_h/R_g$ are plotted as a function of aggregate mass in Figure 6.6 for clusters with fractal dimensions 1.8 and 2.5.

In both cases, within statistical uncertainty $\beta$ remains constant even for the smallest aggregates comprised of 64 primary particles, and the mean values of $\beta$ for $d_f = 1.8$ and 2.5 were found to be 0.76 and 0.98 respectively. An aggregate formed in the RLA regime has a compact morphology and approaches a spherical aggregate in the limit as $d_f \to 3$. Our result of $\beta$ for aggregates of $d_f = 2.5$ agrees well with experimental measurements [8, 11] and theoretical predictions [18, 20, 22] reported in the literature for RLA aggregates. The value of $\beta$ obtained for aggregates formed in the DLA regime ($d_f = 1.8$) also agrees with previous experimentally determined [11] and theoretically derived [9] values. However, these results should be interpreted with the understanding that in this work a solvent particle represents many solvent molecules in a real system. Therefore, we expect the diffusion coefficients obtained from our simulations to be larger (hence, underpredicting the hydrodynamic radius) than real systems with inherent solute-solvent size separation.
Figure 6.6: Ratio of hydrodynamic radius to radius of gyration ($\beta$) as a function of the mass of aggregate ($N_p$) for fractal dimensions ($d_f$) of 1.8 and 2.5. Within statistical uncertainty $\beta$ is fixed for a given fractal dimension irrespective of the size of the aggregate. For $d_f$ of 1.8 and 2.5, $\beta$ is found to be 0.76 and 0.98 respectively.

Conclusions

In this work MD simulations were used to study the diffusion of fractal aggregates as a function of their mass and fractal dimension. Because aggregates with carefully controlled mass and fractal dimensions were generated, it was possible to compute diffusion coefficients without having to perform difficult deconvolutions associated with data obtained from experiments, which by necessity employ polydisperse samples of aggregates. Moreover, because solvent particles were represented explicitly, hydrodynamics effects are computed directly and therefore there is no need to invoke simplifying assumptions that are associated with purely theoretical approaches.

The diffusion coefficient of a fractal aggregate has been found to vary linearly with the inverse of the simulation box length ($L$). Therefore, the intercept of a plot of $D$ vs $L^{-1}$ is the diffusion coefficient corrected for finite size effects (infinite dilution limit). However, it was shown that multiple
independent simulations for each simulation box size are required in order to correctly compute this value. Nevertheless, it appears that at constant temperature, the slope of a plot of $D$ vs $L^{-1}$ is independent of the aggregate mass and fractal dimension, and therefore multiple independent simulations need not be performed for every aggregate size and fractal dimension considered.

The infinite dilution diffusion coefficient was also found to scale with aggregate mass according to $D_0 \propto N_p^{-1/d_f}$, which validates an assumption commonly invoked to compute aggregation rate kernels for Brownian aggregation. The ratio of hydrodynamic radius to radius of gyration ($R_h/R_g$) of fractal aggregates sheds the light on dynamic properties and can be measured experimentally. Consequently, $R_h/R_g$ for fractal aggregates has been investigated extensively both theoretically and experimentally in the literature. Unfortunately, there is significant ambiguity in the dependence of $R_h/R_g$ on $N_p$ and $d_f$ in the results reported. In this work, we have shown that $R_h/R_g$ approaches a constant value ($\beta$) for even relatively small aggregates of fixed fractal dimension. The value of $\beta$ for fractal dimensions of 1.8 and 2.5 was found to be 0.76 and 0.98 respectively, which is in good agreement with other published results.

It has been established in the literature that experimentally measured diffusion coefficients of fractal aggregates are convoluted by rotational diffusion. We are currently working on understanding the coupling of rotational and translational diffusion. The diffusion of fractal aggregates also depends on whether the primary particles comprising the aggregates are solvophilic or solvophobic, which in turn governs the aggregation kinetics. This aspect of the diffusion of fractal aggregates has not yet been addressed systematically, and simulations are underway to explore how the diffusion of fractal aggregates varies as the interactions between the aggregate and solvent particles are changed.

**Acknowledgments**

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References


CHAPTER 7: STATISTICAL ERROR IN THE PROPERTIES DERIVED FROM TIME CORRELATION FUNCTIONS FROM MOLECULAR DYNAMICS SIMULATIONS

Based on manuscript prepared to American Institute of Chemical Engineers Journal

Gaurav Pranami, Rastko Sknepnek and Monica H. Lamm

Abstract

The minuscule length- (nanometer) and time-scales (nanosecond) accessible through computationally demanding molecular dynamics (MD) simulations result in approximate equilibrium properties compared to the corresponding experimental systems, which warrants the estimation of statistical error associated with them. With the exception of systems known to have metastable states, the desired properties are usually estimated by time averaging the measurements (which may be correlated) from a single MD simulation based on the assumption of the validity of the ergodic hypothesis. In this work, the mean squared displacement of Lennard-Jones particles obtained from MD simulations (5-10 times longer than typical simulations of such systems reported in the literature) is shown to depend on the initial state of the system which is contrary to the ergodic hypothesis. Therefore, the diffusion coefficient ($D$) and other properties should be estimated by averaging the measurements from multiple independent simulations and the associated statistical uncertainty in $D$ should be reported as at least a 95% (or $\alpha = 0.05$) confidence interval, $\bar{D} \pm t_{N-1,1-\alpha/2} S/\sqrt{N}$, where $N$ is the number of independent measurements of $D$, $S$ is the estimate of the standard deviation and $t_{N-1,1-\alpha/2}$ is obtained from one-sided Student's $t$-distribution.

Introduction

Molecular dynamics (MD) simulations are commonly used to study microscopic phenomena in complex fluids and advanced materials which are difficult to probe experimentally. In addition to gaining molecular insights to understand bulk structural properties of novel materials, molecular dynamics can be used to calculate important thermodynamic and transport properties. However, due
to the computationally intensive nature of MD simulations the typical length- and time-scales that can be accessed are of the order of few nanometers and nanoseconds respectively, resulting in properties that are only approximations to the corresponding experimental measurements. Therefore, it is essential to estimate the statistical uncertainty associated with the properties evaluated from MD simulations.

In MD simulations, the desired properties are evaluated at regular intervals as the trajectory of a system of atoms evolves in time. A small time-interval between two successive samples may result in measurements that are correlated with each other. This prohibits a simple statistical analysis assuming that the measurements are independent. The statistical error in static properties that are likely to be correlated can be estimated using the method of block averages [1] or the method proposed by Flyvbjerg et al. [2]. On the other hand, the error in the time correlation functions can be estimated using the method proposed by Zwanzig et al. [3]. Often the interest is not only in the time correlation functions but also the properties that are deduced from them; for example diffusion coefficient and viscosity, which are obtained from mean squared displacement and stress autocorrelation respectively. However, to the best of our knowledge, there is no rigorous statistical approach for using the estimated error in a time correlation function to estimate the error in the properties evaluated from them.

In this work, the calculation of diffusion coefficient ($D$) of Lennard-Jones (LJ) fluid particles from their mean squared displacement (MSD) is used as a model problem to show that the ordinary linear regression analysis of MSD vs time data cannot be used to estimate the statistical uncertainty in $D$. It is also shown that two independent MD simulations of a system can result in MSDs that are statistically different from each other. Therefore, a rigorous way to estimate the statistical error in the mean diffusion coefficient is through statistical analysis of the diffusion coefficients obtained from multiple independent simulations of the same system. The importance of running multiple independent simulations is demonstrated for a system of pure LJ fluid and a system of anisotropic fractal aggregate undergoing Brownian diffusion in the presence of explicit LJ fluid, where the diffusivity shows dependence on the system size. The ideas presented here can be analogously extended to other time correlation functions.
**Computational Details**

**Simulation Details**

In MD simulations [1] a system consisting of a collection of particles (which may represent atoms, molecules, or larger entities) is evolved in time by numerically integrating the Newton's equations of motion for each particle:

\[ \vec{F}_i = m\dddot{\vec{r}}_i \]  \hspace{1cm} (7.1)

Here \( \vec{F}_i \) is the net force acting on particle \( i \), which depends on the relative positions of all other particles with respect to particle \( i \), and \( \dddot{\vec{r}}_i \) represent the second derivative of the position of atom \( i \) w.r.t time. Therefore, by neglecting multibody interactions, the net force on particle \( i \) can be obtained by summing the pairwise interactions between that particle and all of the other particles in the system. Usually these forces are expressed in terms of the gradient of the pairwise interaction energy potential \( U \) so that the total force acting on a given particle is given by

\[ \vec{F}_i = -\sum_{j=1,j\neq i}^{n} \nabla U(|\vec{r}_i - \vec{r}_j|) \]  \hspace{1cm} (7.2)

In the above expression \( n \) is the total number of particles in the system and \( |\vec{r}_i - \vec{r}_j| \) is the distance separating particles \( i \) and \( j \). The result of integrating the equations of motion over small time intervals is a record of the system trajectory (i.e. positions and momenta of all constituent particles). Using this information, a variety of structural, dynamical and thermodynamic properties can then be calculated.

In this work, the pair-interactions between all the particles are modeled by Lennard-Jones (LJ) potential which is given as follows,

\[ U(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right] \]  \hspace{1cm} (7.3)
where \( r \) is the distance separating two particles, \( \sigma \) is the size of the interacting particles (assumed to be equal), and \( \varepsilon \) is the well-depth that characterizes the strength of their attraction.

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All the simulations have been carried out in reduced units, as indicated in Table 7.1, using the LAMMPS molecular dynamics program available from Sandia National Lab [4]. The size (\( \sigma \)) and mass (\( m \)) of the particles are set to unity, i.e. \( \sigma = 1 \) and \( m = 1 \). To ensure that LJ fluid is in liquid phase [1], the number density of particles (\( \rho \)) and the temperature (\( T \)) are respectively set to 0.7 and 2.75. All the simulations are carried out in the canonical ensemble (NVT) using a Nose-Hoover thermostat to ensure that all the systems are studied at identical temperature. It is known that application of a thermostat alters the dynamics in the MD simulation [1], and introduces a bias into the calculated transport properties. However, this bias does not pose a problem for the present work because we are interested in a comparative study, not the exact values of the diffusion coefficient. An equilibration run of 100,000 timesteps is followed by a production run of 1 million timesteps (or 5 million timesteps, where explicitly stated). The trajectory of the system is recorded at an interval of
200 timesteps. A timestep of 0.005 was found suitable for solving the equations of motion for all the systems of LJ liquid studied in this work.

**Statistical Uncertainty**

The population parameters of a random variable $X$, such as its population mean $\mu$ and variance $\sigma^2$, are rarely known because it is impossible to sample the entire population of $X$ for all practical purposes. The point estimates of these parameters are given by the mean $\bar{X}$ and variance $S^2$ of a sample of $N$ independent measurements of the variable $X$ as given by Equations (7.4) and (7.5) [5].

\[ \bar{X} = \frac{\sum_{i=1}^{N} X_i}{N} \]  
(7.4)

\[ S^2 = \frac{\sum_{i=1}^{N} (X_i - \bar{X})^2}{N - 1} \]  
(7.5)

The uncertainty associated with the estimate of population mean based on a one-sided Student's $t$-distribution is given by a 100(1-$\alpha$) confidence interval where $0 < \alpha < 1$, Equation (7.6).

\[ \bar{X} \pm t_{N-1,1-\alpha/2} S/\sqrt{N} \]  
(7.6)

Often researchers report the error to be $\bar{X} \pm S/\sqrt{N}$, which is equivalent to a 68.2% confidence interval for a sufficiently large sample, e.g. $N \geq 50$. A 68.2% confidence interval severely underestimates the statistical error, therefore, it is highly recommended to report at least 95% confidence interval i.e. $\alpha = 0.05$. It is important to be careful while interpreting the meaning of a confidence interval. A 95% confidence interval means that 95% of such intervals are likely to contain population mean $\mu$ not that there is a 95% probability that the population mean lies in this interval.

**Results and Discussion**
Diffusion Coefficient

We calculated the diffusivity of LJ fluid particles from their trajectories generated by MD simulations using Einstein's relation [6],

\[
D = \frac{1}{6} \lim_{\tau \to \infty} \langle [\overline{r(\tau)} - \overline{r(0)}]^2 \rangle \tag{7.7}
\]

where \(D\) is the diffusion coefficient, \(\overline{r(\tau)}\) is the cluster position at time \(\tau\), \(\tau = 0\) refers to a time origin and the operator \(< >\) represents the average over time origins. For particles undergoing diffusion, the mean squared displacement grows linearly with time for sufficiently large values of \(\tau\), and therefore \(D\) equals one sixth of the slope of the plot of \(\langle [\overline{r(\tau)} - \overline{r(0)}]^2 \rangle\) vs \(\tau\).

![Figure 7.1: Schematic describing the calculation of mean squared displacement, MSD(\(\tau\)), for a given time \(\tau\). A: represents the MD trajectory with the coordinates recorded at the time interval of \(\Delta t\), as indicated by vertical tick marks. B: represents the time intervals (\(\tau = 4\Delta t\)) sampled along the MD trajectory over which the displacement is evaluated. The difference between the time origins of two consecutive samples is denoted by \(Lag = 2\Delta t\). Mean squared displacement is obtained by taking the mean of the square of these displacements. It is obvious that for large \(\tau\) and small \(Lag\) the squared displacement samples will be heavily correlated, therefore, the statistical uncertainty in estimated \(MSD(\tau)\) cannot be evaluated using Equation (7.6).]
A schematic illustrating the calculation of mean squared displacement of particles from their MD trajectory is shown in Figure 7.1. MSD for a given \( \tau \), \( \text{MSD}(\tau) \), is obtained by taking the average of the square of displacements over time-intervals of length \( \tau \). Usually, the difference between two consecutive time origins, i.e. \( \text{Lag} \), is kept minimum in order to obtain maximum averaging. However, it is obvious that for a large \( \tau \) and small \( \text{Lag} \), the squared displacements will be heavily correlated which leads to severely biased estimates and the statistical analysis as discussed in the Section ‘Statistical Uncertainty’ is not applicable.

![Figure 7.2](image_url)

**Figure 7.2:** The normalized autocorrelation of the squared displacements over a time-interval \( \tau \) as a function of \( \text{Lag} \). For a given \( \tau \), the autocorrelation function decays to its average value as \( \text{Lag} \to \tau \). Therefore, squared displacements can be sampled independently by ensuring that \( \text{Lag} \geq \tau \), and the error in corresponding \( \text{MSD} \) is given by Equation (7.6).

The normalized autocorrelation of the squared displacements over a time-interval \( \tau \) as a function of \( \text{Lag} \) decays to its average value in time \( \tau \), as shown in Figure 7.2. This important result indicates that
in order to ensure that the squared displacement samples are not correlated, they should not be overlapping i.e. \( \text{Lag} \geq \tau \), and the uncertainty associated with \( \text{MSD}(\tau) \) is simply given according to Equation (7.6).

Figure 7.3: Squared displacements \( (SD) \) vs. time \( (\tau) \). The least squares method gives the best straight line fit, \( \text{MSD}(\tau) = \bar{SD} = A_0 + A_1 \tau \), where \( A_0 \) and \( A_1 \) are the regression parameters. The diffusion coefficient is given as, \( D = A_1/6 \). The statistical uncertainties obtained from ordinary linear regression analysis are invalid because the assumption of homoscedasticity i.e. constant variance in \( SD \) for all \( \tau \) is severely violated as evident from increasing spread of \( SD \) with increasing \( \tau \). Alternatively, a rigorous way to estimate the uncertainty is by using Equation (7.6) on the diffusivities obtained from multiple independent simulations.

The diffusion coefficient is equal to 1/6 of the slope of the straight line fit of \( \text{MSD}(\tau) \) vs \( \tau \) after the initial ballistic regime. The best fitting straight line, \( \text{MSD}(\tau) = \bar{SD} = A_0 + A_1 \tau \) where \( A_0 \) and \( A_1 \) are the regression parameters, is readily obtained by the least squared method [5]. The statistical uncertainties in the estimated \( A_0 \) and \( A_1 \) can be readily obtained by linear regression analysis, if the
associated assumptions are valid. Assumptions of the existence of $SD$ with certain probability distribution having finite mean and variance and normal distribution of $SD$ for a given $\tau$ are naturally valid. Assumption of the existence of a linear relationship between $SD$ and $\tau$ is valid based on Equation (6.8) and the assumption of the independence of $SD$ samples can be ensured by following the approach previously discussed. Unfortunately, the assumption of homoscedasticity i.e. constant variance in $SD$ for any $\tau$ is severely violated as evidenced by the increasing spread in $SD$ with increasing $\tau$, as shown in Figure 7.3. One can attempt to account for heteroscedasticity by suitably transforming the data, e.g. $\log(SD)$, but the linear regression will result in an inappropriate relationship, $\log(SD)$ vs. $\tau$. Alternatively, weighted least squares can be used, which often work well in the circumstances where the assumption of homoscedasticity is violated [5]. In the following section, however, it is shown that the uncertainty in the diffusion coefficient is more rigorously obtained from the statistical analysis of diffusion coefficients obtained from multiple independent simulations of same system.

**Need for conducting MIS**

The ergodic hypothesis states that time average and ensemble average of a property of a multi-particle system in equilibrium are identical. Subsequently, the properties of simple systems which are not expected to have metastable states, e.g. LJ fluid, are almost always estimated as time-averages from a single MD simulation and are assumed to be independent of the initial state of the system based on the ergodic hypothesis. In order to assess the effect of initial state on the mean squared displacement of LJ particles, we conducted two independent MD simulations of a system of 64 LJ particles. Two simulations were identical except the initial velocities assigned to the particles. The mean squared displacement was calculated from the equilibrated run of 5 million time steps of size 0.005 in reduced time units and are shown in Figure 7.4. The error bars represent 95% confidence intervals and were calculated by sampling non-overlapping squared displacements as described earlier. The non-overlapping error bars in Figure 7.4 indicate that the two mean squared displacements are significantly different from each other even though these simulations are 5-10 times longer than typical simulations reported in the literature for similar systems. This is contrary to the ergodic hypothesis which is most likely because of insufficient sampling of phase space in these simulations of finite length, and clearly demonstrates the need to average the properties from multiple independent MD simulations in addition to time-averaging. The effect of initial state may be mitigated by running a sufficiently long MD simulation but running very long MD simulations is not
advisable because the finite numerical precision in the computations results in energy drift leading to altered dynamics in the system. Therefore, it makes more sense to conduct computationally manageable multiple independent simulations.

**Figure 7.4:** Plot of mean squared displacement vs $\tau$ obtained from two independent long MD simulations of an identical system for 5 million timesteps. The error bars indicate 95% confidence intervals. The mean squared displacements from these two runs are statistically different as indicated by non-overlapping error bars.

**Diffusion vs Simulation Box Length**

The spread in the properties resulting from multiple independent simulations has important implications on deciphering their relationship with other variables, for instance, the dependence of diffusion coefficient ($D$) on the simulation box length ($L$). It is well-known that the hydrodynamic interactions are long range interactions and they decay as the inverse of distance which is evident from the $1/r$ dependence of the Oseen tensor. Therefore, the dynamic properties of a finite system
modeled with periodic boundary conditions are affected by the interactions between the system and its periodic images. Dunweg et al. [7, 8] and Yeh et al. [9] have proposed a correction to account for these finite size effects on the diffusivity,

\[
D_o = D + \frac{k_B T}{6 \pi \eta L}
\]  

(7.8)

![Figure 7.5: Variation of the diffusion coefficient (D) of LJ fluid particles as a function of the inverse of the simulation box length (L⁻¹). For each box length, a hundred independent MD simulations are conducted by varying the initial velocity of LJ particles. The spread in the diffusion coefficient data clearly illustrates that if only one simulation was conducted for each box length, the linear relationship between D and L⁻¹ may not be apparent or the estimated D₀ (intercept) may be severely inaccurate. It is necessary to conduct multiple independent simulations in order to rigorously estimate the slope and intercept and the associated uncertainty.](image)
Here, $D_o$ is the diffusion coefficient corrected for finite size effects, $\xi = 2.837297\$ (constant), $k_b$ is the Boltzmann constant, $T$ is temperature, and $\eta$ is the dynamic viscosity of the solvent and $L$ is the length of cubic simulations box. Therefore, the correct diffusion coefficient, $D_o$, is given by the intercept of a straight line fit through $D$ vs $L^{-1}$ data.

A plot of $D$ of LJ fluid particles as a function of $L^{-1}$ is shown in Figure 7.5. One hundred multiple independent simulations were carried out for each $L$ by varying the random seed to generate the initial velocity (based on the Boltzmann's distribution) of the LJ particles. Therefore, finding $D_o$ is a simple matter of fitting a straight line through $D$ vs $L^{-1}$ data and recording the intercept. On the other hand if
only one simulation was conducted for each box length, the linear relationship between $D$ and $L^{-1}$ may not be apparent or the estimated $D_o$ may be severely inaccurate.

This problem is much more acute when calculating the diffusivity of a macromolecular body undergoing diffusion in a fluid. In case of LJ fluid, even in the systems of modest sizes (containing 50 - 100 particles) SD sampling is quite extensive because it includes contributions from all the identical particles, which is not possible, for e.g., in a system of a nanoparticle aggregate undergoing diffusion in a solvent at infinite dilution. To illustrate this point, a nanoparticle aggregate undergoing Brownian diffusion was simulated using molecular dynamics.

An off-lattice fractal aggregate of a fractal dimension ($d_f$) of 2.5 containing 64 primary particles ($p$) was generated using the recipe proposed by Thouy et al. [10, 11]. The aggregate was treated as a rigid body and was placed in a cubic simulation box containing explicit solvent particles ($s$) at density of 0.85 in reduced units as listed in the Table 7.1. $s$-$s$ and $s$-$p$ interactions are modeled with LJ potential with $\sigma = 1$ and $\epsilon = 1$. The equilibrium temperature of 1.2 (reduced units) was achieved by running the MD simulations for 2500 time units in canonical (NVT) ensemble, after which thermostat was switched-off and the production run was carried out in microcanonical ensemble (NVE) for 50000 time units. The diffusivity of fractal aggregate was calculated from the mean squared displacement of its center of mass obtained from MD simulation. Figure 7.6 shows the variation of diffusion coefficient (obtained from ten multiple independent simulations for each $L$) of the aggregates as a function of $L^{-1}$. Clearly, if only one simulation was conducted for each $L$, the linear dependence of $D$ on $L^{-1}$ would possibly be severely incorrect or completely absent if the diffusion coefficients obtained fell on lines $l_1$, $l_2$, and line $l_3$ respectively in Figure 7.6. Therefore, it is necessary to conduct multiple independent simulations. Moreover, the uncertainties associated with $D_o$ and slope can simply be obtained from the regression analysis of the least squared straight line fit through $D$ vs $L^{-1}$ data.

**Conclusions**

Using the example of the diffusivity ($D$) of Lennard-Jones (LJ) fluid, it is shown that the properties obtained from a single long MD simulation may depend on the initial state of the system which is contrary to the ergodic hypothesis, usually assumed to be valid for such systems. This is most likely due to minuscule length- (nanometer) and time-scales (nanoseconds) accessible through computationally demanding molecular dynamics simulations compared to the realistic experimental
systems, which warrants the estimation of statistical error associated with properties obtained from such simulations. Specifically, mean squared displacements of LJ particles obtained from the MD simulations of a system of LJ liquid have been shown to depend on the initial velocity assigned to the particles. Therefore, the diffusion coefficient ($D$) and other properties should be estimated by averaging over the measurements from multiple independent simulations and the associated statistical uncertainty in $D$ should be reported as at least a 95% (or $\alpha = 0.05$) confidence interval, $D \pm t_{N-1,1-\alpha/2} S/\sqrt{N}$, where $N$ is the number of independent measurements of $D$, $S$ is the estimate of the standard deviation and $t_{N-1,1-\alpha/2}$ is obtained from one-sided Student's $t$-distribution.

Acknowledgments
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References
CHAPTER 8: CONCLUSIONS AND FUTURE WORK

Nanoparticles have a wide range of exciting applications in catalysts, magnetic devices, polymer composites, sensors, paints, pharmaceuticals, coatings and adhesives. The nanoparticle interaction potential significantly influences its aggregation characteristics, which in turn play a vital role in governing the properties of advanced materials based on nanoparticles. Therefore, an understanding of the forces between nanoparticles and their role in nanoparticle aggregation is essential for rationally designing and developing advanced nanomaterials. This knowledge is of profound importance in the design of processes for high throughput synthesis of nanoparticles with well-controlled properties. The overall goal of the research presented in this thesis is to advance our understanding of nanoparticle aggregation in the regime of Brownian aggregation without shear (length scales of 0.1-100 nm) by combining molecular simulations and atomic force microscopy (AFM) experiments. Monodisperse polystyrene (PS) micro- (2 µm) and nanoparticles (300 nm) were chosen as the model systems because they are widely used to study colloidal aggregation.

AFM was used to directly measure the force (in air) between a 300 nm polystyrene (PS) nanoparticle and a PS film which has been compared with the force measured between a 2 µm PS particle and a PS film. While a vast literature exists on the usage of AFM for the measurement of forces between a variety of microparticles (> 5 µm), literature on the use of AFM to examine the forces between nanoparticles is non-existent. This is primarily due to the lack of a robust technique to attach nanoparticles to an AFM probe. In this work, a novel approach based on layer-by-layer assembly to functionalize an AFM probe was developed and applied to the measurement of the force between nanoparticles. Specifically, the nanoparticle force was deduced from the variation of force between a silica colloidal probe (5-30 µm) functionalized with a monolayer of 300 nm PS particles and a PS film as a function of the diameter of the silica particle. The measured nanoparticle force was found to be predominantly van der Waals force with a well depth of ~ 0.31 nN. The forces between a pair of 2 µm PS particles and those between a 2 µm PS particle and a PS film were measured to be ~1.3 nN, indicating that AFM force measurements are not sensitive enough to distinguish between the two geometries. The ratio of the microparticle force to the nanoparticle force was ~ 4.4, and is in good agreement with the value ~6.67 based on a continuum model of the van der Waals force. However, the magnitude of the measured well depths was found to be 20-50 times smaller than the theoretical
predictions; this discrepancy was attributed to the rough surfaces of PS particles and the humidity in the ambient air, which are not accounted for in the theoretical model. Moreover, the suitability of continuum models to explain the experimental observations is questionable because at the nanometer length scales of the roughness features, the continuum theory breaks down. In this regard, these force measurements are valuable for the development and validation of molecular-based models derived from multi-scale simulations for predicting the nanoparticle interaction potentials.

While the approach used in this work to deduce the nanoparticle interaction potential from multiple nanoparticle forces using AFM worked well, it is important to verify these results by direct measurement of the force between a nanoparticle and a PS film by attaching a single nanoparticle to an AFM probe. In order to achieve this, a silica probe with a flat apex (instead of round colloidal silica particles) can be used for layer-by-layer assembly procedure to functionalize the probe with PS nanoparticles. This is a promising approach as shown by preliminary experiments in which probes with a flat top of area ~ 500 nm × 500 nm were used, as shown in Figure 8.1. A single 300 nm PS nanoparticle is likely to be placed on the apex successfully by using a probe with a flat area of ~ 1 µm × 1 µm.

Figure 8.1: Layer-by-layer assembly of 300 nm PS nanoparticles on AFM probes with flat top. The likelihood of obtaining a single nanoparticle on the apex is higher for a larger flat area.

Force measurements in this work were carried out in ambient air. However the humidity was not controlled, which is expected to affect the measured forces. It would be useful to study the effect of humidity on the measured forces in a systematic manner by carefully controlling the humidity with a
customized apparatus. The forces measured in air did not exhibit any electrostatic repulsion, but these forces are responsible for the stability of the colloidal suspension of PS particles in water. Therefore, it will be interesting to measure these forces in water for comparison with the corresponding measurements presented in this work. This will also require a customized setup to pump degassed water through the AFM liquid cell during force measurements to prevent bridging of nanobubbles formed on hydrophobic PS surfaces resulting from dissolved gases.

The inadequacy of continuum models to predict nanoparticle forces clearly demonstrates the need to develop better theoretical models. One promising route to tackle this problem is via molecular-based models derived from multi-scale simulations. Quantum chemical \textit{(ab-initio)} calculations provide highly accurate quantitative information about a system consisting of a few molecules but such computations are very expensive and cannot be used to study nanoparticles, which contain millions of molecules. Therefore, a systematic methodology for coarse-graining (based on the method of force-matching) the quantum chemical data was developed to make the simulations of systems containing larger number of molecules computationally feasible. Specifically, three common solvent molecules (carbon tetrachloride, benzene and water) modeled using a first principles based Effective Fragment Potential (EFP) were coarse-grained to their center of mass. These coarse-grained potentials representing each molecule as point mass at their center of mass were able to produce the correct radial distribution function compared to the corresponding EFP radial distribution function while the simulation time was reduced by a factor of $10^4$. Therefore, a multi-scale simulation framework is now in place for deriving nanoparticle interaction potential from the quantum chemical data of styrene molecules.

EFP treats molecules as rigid bodies circumventing the determination of coarse-grained bond and angle potentials that are necessary for obtaining the PS nanoparticle interaction potential. Efforts are underway in Professor Gordon’s group to develop a first principles based Fragment Orbital Method, which will enable the derivation of bond and angle potentials needed for obtaining the coarse-grained potential of PS nanoparticle according to the scheme shown in Figure 8.2.
Figure 8.2: Coarse-graining scheme to obtain the effective PS nanoparticle pair potential

While specific nanoparticles form aggregates of defined morphologies depending on their interaction potential, it is essential to understand the diffusion of aggregates over the entire spectrum of their morphologies. Significant work has been done to study the diffusion of nanoparticle aggregates using experimental, theoretical and particle-based simulation methods, but there is still considerable ambiguity in the results reported in the literature. This is mainly due to difficulties associated with controlling experimental conditions and from simplifying assumption to account for hydrodynamic interactions in theoretical models. To this end molecular dynamics simulations were employed to study the diffusion of fractal aggregates as a function of their mass \( N \) and fractal dimension \( d_f \). The diffusion coefficient \( D_o \) for aggregates was found to scale as \( D_o \propto N^{-d_f} \). The ratio of the hydrodynamic radius to the radius of gyration was found to be independent of mass for aggregates of a given fractal dimension, thus enabling an estimate of the diffusion coefficient for a fractal aggregate based on its radius of gyration. The results obtained in this work are necessary for studying the nanoparticle aggregation kinetics through population balance methods.

It is well known that experimentally measured diffusivity of nanoparticle aggregates is convoluted by rotational diffusion. Therefore, it would be useful to understand the coupling of rotational and translational diffusivities of anisotropic nanoparticle aggregates as a function of their mass and fractal dimension. It is also important to study how the diffusion coefficient of nanoparticle aggregates varies
as the interaction between solvent and nanoparticle is changed. In this work, the interaction between solvent and nanoparticle was identical; in future studies, the interaction could be varied systematically from solvophobic to solvophillic to examine its effects on the scaling relations.

In conclusion, the research presented in this dissertation provides an integrated framework of modeling and experiments which is applied to study the nanoparticle aggregation. The methodologies developed in this work are applicable to a variety of multi-scale macromolecular systems.