Abstract

Structured nanoparticles are important for various scientific and industrial applications. For example, Janus particles can act as pigments in electronic paper, interfacial stabilizers, optical probes and catalysts; core-shell particles are useful in drug delivery; patchy particles can self-assemble into hierarchical structures. These applications require nanoparticles with a narrow size and morphology distribution, which needs to be addressed by the fabrication methods. In addition, a method which is simple and scalable is also desirable in order to achieve commercial applications of the nanoparticles. Flash Nanoprecipitation (FNP), which involves the rapid mixing of polymers in solution with a miscible non-solvent, is a continuous and scalable process that offers independent control over nanoparticle size, morphology, and composition.

To understand the assembly mechanism of FNP and to make quantitative predictions for experiments, I performed molecular dynamics (MD) and kinetic Monte Carlo (KMC) simulations. On the nanoscale, the MD simulations studied the assembly mechanism and revealed how nanoparticles with a range of surface structures, including Janus, core-shell and patchy, arise from different processing conditions. The simulations also indicated that nanoparticle morphologies and other properties such as the composition and patchiness can be reliably tuned. To reach macroscopic length- and time-scales, I performed KMC simulations and studied how nanoparticle size and size distribution can be controlled by processing parameters specific to FNP, such as the mixing rate and the feed concentration. The model produced results in quantitative agreement with experiments and also provided insights on particle aggregation mechanism through the solvent displacement process. This multi-scale simulation approach allows predictions for the FNP process from a given set of feed polymers and processing parameters. The results demonstrate that the process is highly promising for the production of structured nanoparticles with various surface features in a scalable and controlled way. These results also provide guidelines for fu-
ture design and preparation of polymeric nanoparticles with desired properties using FNP techniques, and thus facilitate their applications in various areas.
When I think back on the past four and half years I spent at Princeton which lead to this dissertation, I start to realize that I only made it to this point because of the guidance, help, and support from many people. I would like to express my sincere gratitude to them here.

I would like to thank my adviser, Professor Panagiotopoulos, for his knowledge and guidance. I came into graduate school not knowing exactly what was expected from a PhD student. For the first year in the group, I spent most of my time in confusion and self-doubt, and encountered many difficulties. Professor Panagiotopoulos helped me with his immense knowledge and expertise, and taught me the important scientific questions to ask. I benefited greatly from our meetings. His mentorship and guidance are invaluable to me as a researcher.

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My sincere thanks also goes to the rest of my thesis committee, Professor Robert K. Prud’homme and Professor Lynn Loo. They asked many thought provoking questions during my committee meetings, which helped me think more deeply about my research.

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Chapter 1

Introduction

Structured nanoparticles are important for many applications, including pharmaceuticals,\(^1,2\) electronics,\(^3,4\) photonics,\(^5,6\) etc. For example, Janus nanoparticles, which are characterized by their two distinct domains, can be used as interfacial stabilizers and pigments in electronic paper,\(^7–9\) while core-shell particles find application in bioimaging and as carriers in drug delivery systems.\(^10\) Patchy particles which possess discrete surface domains are promising building blocks for hierarchical structures.\(^11–15\) Nanoparticles with concentric lamellae may have applications as waveguides and other photonic materials.\(^16\) However, these applications require well-defined properties with narrow particle size and morphology distributions, which needs to be addressed by the manufacturing techniques. In addition, manufacturing techniques also need to be scalable to move beyond laboratory scales and to achieve commercially driven applications of these nanoparticles.

Various experimental methods have been successfully developed for the fabrication of structured nanoparticles, such as seeded polymerization (lacks size and structure control),\(^17–19\) templating (good size and shape control, but involves multiple manual steps),\(^20,21\) particle lithography (allows coating of particles, while it is limited by scale-up issues),\(^22,23\) synthesis in microfluidic reactors (can scale up and oper-
ate in a continuous fashion, while particle size distribution is wide and morphology control is difficult, \textsuperscript{24–26} and internal phase separation, \textit{e.g.}, Self-Organized Precipitation (SORP) method\textsuperscript{27} and miniemulsion polymerization.\textsuperscript{28} In particular, the SORP method is able to produce Janus and core-shell particles from different combinations of homopolymers depending on their solubilities in the poor solvent,\textsuperscript{29} and lamellar and onion-like structures from block copolymers.\textsuperscript{30–32} However, most of the aforementioned processes involve batch processing steps and the fabricated nanoparticles cannot always be readily available with high accuracy. It is thus clear that further research is required to develop fabrication methods which are both scalable and allow for precise control over particle size, morphology and composition.\textsuperscript{11,33}

The present work has been motivated by an experimental approach for creating structured particles, namely Flash NanoPrecipitation (FNP),\textsuperscript{34,35} where a polymer solution is rapidly mixed with an excess amount of a non-solvent to induce aggregation into nanoparticles. Compared to other competing methods, FNP stands out as an one-step continuous process that operates at room temperature, consumes little energy, and has potential to scale up. Previously, FNP was used to embed small hydrophobic drug molecules into nanoparticles, stabilized \textit{via} amphiphilic block copolymers,\textsuperscript{36–39} and to produce homopolymer nanoparticles.\textsuperscript{40,41} Recently, it has been experimentally demonstrated that the FNP technique can be used to produce various morphologies, \textit{e.g.}, Janus, patchy, concentric lamellar, etc. from different polymer feed materials, such as homopolymer blends and hydrophobic block copolymers.\textsuperscript{42–45} In contrast to previous FNP experiments which involved either amphiphilic block copolymers\textsuperscript{36–39} or charged polymers,\textsuperscript{40} this process makes use of electroneutral polymers with no stabilizing agents. The stability of the hydrophobic particles arises from a constant negative $\zeta$-potential between -30 to -40 mV, which was determined from electrophoretic light scattering measurements for the precipitated nanoparticles between 45 nm and
135 nm in radii.\textsuperscript{41} Most importantly, the process provides precise and independent control over particle size, morphology and composition.

Despite the above-mentioned experimental efforts to understand and realize the potential of the FNP technique, the underlying microscopic mechanisms responsible for the self-assembly are still elusive. This is because the FNP process takes place on nanometer length scales and millisecond time scales, which makes the experimental study of this process difficult. Furthermore, it is an expensive and time-consuming task to systematically search and screen in the experiments all relevant process parameters, such as feed ratio, feed concentration, mixing rate, molecular properties, etc. Computer simulations can provide considerably more microscopic level information than experiments, and are therefore useful tools in the study of complex mechanisms and morphologies. They also offer advantages in efficient parameter space searching.

Previous computational efforts to understand FNP have focused on the self-assembly of polymer-protected nanoparticles\textsuperscript{38,39} and homopolymers in FNP\textsuperscript{41} using methods such as Brownian dynamics (BD), dissipative particles dynamics, and molecular dynamics (MD) simulations. They focused on understanding the microscopic assembly mechanism, and produced results in qualitative agreement with the experiments. However, these studies were not able to access macroscopic length- and time-scales. Researchers also employed macro-scale simulations by solving the population balance equation using the method of moments within a computational fluid dynamics code to study the FNP of poly-\textgreek{e}-caprolactone.\textsuperscript{46–49} Results from these simulations were directly compared to experimental measurements. However, the macroscopic models presented in some of these earlier works were not parameterized according to the appropriate microscopic details of the system. In addition, charge stabilized nanoparticles obtained from FNP feed materials such as polymer blends and block copolymers have not been studied.
FNP spans over a wide range of length- and time-scales, which poses a significant challenge to computational studies. For example, the length-scales of the process range from a few Å for the size a solvent particle to a few hundreds nm for the radius of a precipitated nanoparticle. For the timescales, the relaxation time of a polymer chain is on the order of ns, the time to achieve homogeneous mixing in the FNP mixer is a few ms, and the typical growth time of the precipitated nanoparticles is on the order of tens or hundreds of ms. Therefore, to analyze the structures of the precipitated nanoparticles and the assembly mechanism in detail, and to make quantitative predictions for the experiments, it is crucial to study FNP both on microscopic and macroscopic levels.

In this dissertation, I study the self-assembly of various polymer feed materials through FNP on both microscopic and macroscopic levels. On the microscopic level, I use MD simulations to investigate how various surface structures of the precipitated nanoparticles, such as Janus, core-shell and patchy, etc, arise from different polymer feed materials and processing conditions. On the macroscopic scale, I perform kinetic Monte Carlo (KMC) simulations to reach macroscopic length- and time-scales. The goal of this study is to gain an understanding on particle aggregation mechanism through the solvent displacement process and to make quantitative predictions for the FNP process from a given set of feed polymers and processing parameters. The results from the simulations are also compared and verified with experiments. The structure of this dissertation is as follows.

From Chapter 2 to 5, MD simulations are used to study how different surface structures of the precipitated nanoparticles arise from various feed materials, which include a binary polymer blend with two rubbery components (Chapter 2), a binary polymer blend with one rubbery component and one glassy component (Chapter 3), block copolymers (Chapter 4), and a binary polymer blend with inorganic nanoparticles (Chapter 5).
For a binary polymer blend with two rubbery components (Chapter 2), MD simulations reveal that either Janus or core-shell structures can be obtained depending on the ratios between the polymer-solvent and polymer-polymer surface tensions. When the difference between the ratios for the two homopolymers is small, \textit{i.e.}, the two homopolymers like the solvent to a similar extent, Janus structures are obtained. When the difference between the two ratios is large, core-shell nanoparticles with the more solvophobic polymer as the core are obtained. When the abosolute values of both ratios are small, \textit{i.e.}, the two homopolymers show much stronger affinity for the solvent than for each other, separate homopolymer aggregates are obtained. In addition, the effects of mixing rate, polymer feed concentration and ratio on the final nanoparticle size, composition and distribution are also studied, and the results are in qualitative agreement with the experimental.

When one component of the binary polymer blend is glassy instead of rubbery (Chapter 3), kinetic trapping freezes nanoparticle morphology along the path to the equilibrium structure, leading to patchiness. Using MD simulations, I investigate the mechanism of patch formation, and explain how the number of patches can be tuned by the nanoparticle size and the blend ratio.

In addition to homopolymer blends, I also extend the MD model to study feed streams that consist of block copolymers in Chapter 4. In agreement with experiments, concentric lamellar structures are obtained for a symmetric low molecular weight diblock copolymer. However, for its high molecular weight counterpart, disorder in the lamellar structures arises as a result of the higher energy barrier to defect annealing and the slower dynamics of the longer chains. The MD model is also extended to study a blend of diblock copolymers and homopolymers, and the morphologies obtained are in qualitative agreement with experimental observations.

Lastly, hybrid structures obtained from a binary polymer blend and inorganic nanoparticles are considered in Chapter 5. Using MD simulations, I explore the
range of hybrid morphologies that can be obtained as function of the affinities between different components of the system. I also study how the loading and surface density of the inorganic nanoparticles can be tuned by various parameters, such as the feed concentration and ratio, as these properties are crucial in determining the performance of the hybrid structures.

In the above-mentioned chapters, MD simulations are used for morphology predictions from different feed materials. They are also effective tools for analyzing nanoscale structures in detail. The results demonstrate that FNP can access a wide range of morphologies with good control over the size, surface structures, and composition by simply altering the polymer feed materials.

However, due to computational limitations, these MD simulations probed nanoparticles at least 10 times smaller than in experiments and accessed mixing times in the order of a few $\mu$s compared to ms employed in the experiments. This discrepancy in length- and time-scales prevents quantitative comparisons of experimental data to the MD simulations. Therefore, in Chapter 6 and 7, I will present computational works done to access macroscopic length- and time-scales.

Chapter 6 presents an implicit solvent BD algorithm in an attempt to access larger length- and time-scales compared to the explicit solvent MD simulations. The standard BD algorithm neglects hydrodynamic interactions, which gives rise to incorrect dynamics of the aggregates, and effectively slows down aggregation. In order to reproduce the correct dynamics, a method is outlined which corrects the size dependent diffusion coefficients of aggregates by rescaling the friction coefficient for each aggregate individually to match the diffusion dictated by the Stokes-Einstein relationship. The enhanced BD algorithm produces aggregation dynamics in agreement with MD simulations, and is approximately 30 times faster in simulating the FNP systems. However, this speed up is still insufficient to access the length- and time-scales employed by the experiments.
In Chapter 7, a KMC model which is derived based on microscopic details obtained from MD simulations is presented. The KMC model is able to access macroscopic length- and time-scales, and allows direct comparison with experiments. In addition, the model provides insights on the aggregation mechanism on both microscopic and macroscopic levels, and determines the dependence of nanoparticle size on processing parameters such as the mixing rate and the polymer feed concentration. It also provides an estimate for the characteristic growth time of nanoparticles in the FNP process.

The contents of this dissertation are based on the following publications with the corresponding chapter denoted:


* denotes equal contribution.
Chapter 2

Self-assembly of two rubbery homopolymers*

As mentioned previously, a coarse-grained molecular dynamics (MD) model which incorporates surface potential has been developed to study hydrophobic homopolymers. With this model, the dependence of nanoparticle size on the polymer feed concentration, mixing rate, and surface potential was investigated and the results are in qualitative agreement with the experiments.

In this chapter, the MD model for homopolymers is extended to study the self-assembly of a binary homopolymer blend which consists of two rubbery components. Experimentally, it has been found that a blend of polyisoprene and low molecular weight polystyrene (PS) gave rise to Janus structures. The objective of this chapter is to understand the assembly mechanism and obtain a phase diagram which allows us to predict the morphology of the precipitated nanoparticles given any pair of homopolymers.

*This chapter is based on: Nannan Li, Athanassios Z. Panagiotopoulos, and Arash Nikoubashman, Structured nanoparticles from the self-assembly of polymer blends through rapid solvent exchange. *Langmuir* 2017, 33, 6021-6028.
The present work explores systematically how different processing parameters in FNP such as the hydrophobicity and chemical compatibility of the polymers, mixing rate, polymer feed concentration and ratio affect the size and morphology distributions of the precipitated nanoparticles. The structure of this chapter is as follows: we will first summarize the MD simulation model and methods used in the present work. Next, we present and analyze our simulation results, focusing on how particle morphology, size and composition can be independently tuned by the aforementioned parameters. Lastly, we summarize our results and comment on their implications.

2.1 Simulation model and methods

Our previous MD model for homopolymers undergoing the FNP process serves as a foundation for our study of polymer blends. In this model, a polymer is described as a linear bead-spring chain with $N$ beads, each with unit diameter $\sigma$ and mass $m$. Each bead represents a Kuhn segment of the polymer chain. In the experiments, the PS chains have a molecular weight of $16.5 \text{ kg/mol}$. Since the mass of a PS Kuhn segment is $M_k = 0.72 \text{ kg/mol}$, we obtained $N = 23$, which was used for all homopolymer chains in our simulations.

The bonded interactions between polymer beads are modeled via the finitely extensible nonlinear elastic (FENE) potential. The standard Kremer-Grest parameters were adopted to prevent unphysical bond crossing. Other than the bonded interactions, polymer beads also interact with one another via the standard Lennard-Jones (LJ) potential:

$$U_{\text{LJ}}(r_{ij}) = 4\varepsilon_{\text{LJ}} \left[ \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^6 \right], \quad (2.1)$$

with $r_{ij}$ being the interparticle distance between bead $i$ and $j$. Binary polymer blends have been considered in the current work and we set the prefactor $\varepsilon_{\text{LJ}}$ for the inter-
traspecies interaction of both polymer A and polymer B equal such that $\epsilon_{AA} = \epsilon_{BB} = k_B T$, with Boltzmann constant $k_B$ and temperature $T$. The interspecies AB interaction strength, $\epsilon_{AB}$, was varied between $0.9 \epsilon_{AA}$ and $0.01 \epsilon_{AA}$, to mimic the chemical incompatibility of the two polymer types. The cutoff radius was set to $r_{\text{cut}} = 3.0 \sigma$.

Following Ref. 41, solvent particles are modeled explicitly as LJ particles with the same size and mass as the polymer beads. A reduced number density of $\rho_S = 0.66$ has been chosen, which leads to a dynamic solvent viscosity of $\eta = 1.01$. Similar to previous computational studies on FNP,\textsuperscript{38,39,41} non-bonded interactions on all particles were varied simultaneously over a certain period of time, $\tau_{\text{mix}}$, to mimic the transition from good to poor solvent conditions. In our studies, we control the interaction between solvent particles and monomers by a dimensionless parameter $\lambda^57$

\[ U_{\text{MS}}(r_{ij}) = \lambda U_{\text{WCA}}(r_{ij}) + (1 - \lambda) U_{\text{LJ}}(r_{ij}), \tag{2.2} \]

where $U_{\text{WCA}}(r_{ij})$ is the purely repulsive Weeks-Chandler-Anderson (WCA) potential.\textsuperscript{58} As $\lambda$ increases from 0 to 1, the solvent quality changes from good to poor.

In order to make meaningful comparisons between our simulations and experimental results, it is important to establish a connection between units of energy, length and time in the two domains, which has been done in Ref. 41 for the homopolymer-solvent model. The experiments were performed at room temperature $T = 298$ K, and thus $\epsilon = k_B T = 4.11 \times 10^{-21}$ J for the characteristic energy. For the length scale, the radius of gyration of a single polymer chain in a $\Theta$-solvent, $R_{g,\Theta} = 2.35 \sigma$, was compared to $R_{g,\Theta}$ of the corresponding PS chain (3.5 nm), leading to $\sigma = 1.5$ nm. For the time scale, the diffusion coefficient of a polymer chain in good solvent conditions, \textit{i.e.}, $\lambda = 0$, was compared to the experimental diffusion coefficient of a PS chain (extrapolated to the same molecular weight as in the simulations) in THF at
room temperature \((1.4 \times 10^{-6} \text{ cm}^2/\text{s})\),\(^59\) which led to a time conversion factor of \(\tau = 0.28\) ns.

During the FNP process, the polymer chains aggregate to nanoparticles in order to minimize the contact surface with the surrounding poor solvent. Without a stabilizing mechanism, all polymers eventually form a single aggregate, as this configuration provides the lowest surface tension. However, in our case, nanoparticle stability is provided by a negative surface potential between -30 to -40 mV, which was measured experimentally on particles of radii between 45 nm and 135 nm using electrophoretic light scattering.\(^41\) Therefore, in addition to the bonded and non-bonded potentials between polymer beads, we also included a surface potential of \(\zeta = -33\) mV on the nanoparticles. This effect was mimicked by placing a virtual particle at the center of each aggregate, which carried the equivalent surface charge. Electrostatic interactions are switched off at good solvent conditions \((\zeta = 0\) mV). As the solvent quality worsens, the buildup of surface charges is mimicked by linearly decreasing \(\zeta\) to its final value \((\zeta = -33\) mV). In our previous work,\(^41\) we found that the precipitated nanoparticles became smaller as the \(\zeta\)-potential became more negative, whereas pH had only a minimal effect on the final aggregate size. More details on this method can be found in prior work by Nikoubashman \textit{et al.}\(^41\)

The MD simulations were run using the HOOMD simulation package.\(^60,61\) A cubic box with an edge length of 80\(\sigma\), containing 337,920 solvent particles and a total of up to 1,024 polymers at various A:B ratios was adopted. We have checked the influences of box sizes on simulation results at selected state points and did not find any appreciable finite size effects when the box edge length is above 80\(\sigma\). It is noted that the total number of 1,024 polymers in our systems limits the maximum nanoparticle size to \(a \approx 21\) nm, which is one order of magnitude smaller than those produced in the experiments. To realize in the simulations a nanoparticle with a radius of \(a = 100\) nm, approximately \(10^5\) polymers are required, which is computationally unfeasible. De-
spite this limitation, however, the model is able to reproduce the most important trends observed in the experiments. A Nosé-Hoover thermostat was employed to maintain the temperature at $T = 1$ and the equations of motion were integrated using the velocity Verlet algorithm at a timestep of $\Delta t = 0.01$ in the reduced units defined earlier.

2.2 Results and discussion

Torza and Mason investigated the equilibrium morphology of droplets in systems consisting of three immiscible liquids using the Neumann triangle. Depending on the value of the surface tensions, core-shell, acorn-shaped or separated droplets were obtained. These predictions were based on theoretical calculations on macroscopic systems, and it is not immediately clear whether these considerations are directly transferable to the nanoscale systems at hand. Subsequent studies have also used surface tensions to interpret the phase-separated structures of polymer blends in aqueous solutions. Therefore, to understand the different particle morphologies produced from the FNP process, we first determined the surface tension between our constituents. To this end, we performed simulations on systems consisting of two homopolymer slabs, as well as a homopolymer slab surrounded by solvent particles at $T = 1$. Surface tensions between the two polymers and between polymers and the solvent were calculated using the standard mechanical definition,

$$\gamma = \frac{L_z}{2} \left\langle P_{zz} - \frac{P_{xx} + P_{yy}}{2} \right\rangle,$$

where $L_z$ is the length of the simulation box along the $z$-axis, which was allowed to vary. $P_{xx}$, $P_{yy}$ and $P_{zz}$ are the diagonal components of the pressure tensor along the $x$-, $y$-, and $z$-axis, respectively, and the brackets denote an ensemble average.
As seen in Figure 2.1, the polymer-polymer surface tension, $\gamma_{\text{AB}}$, decreases with increasing $\varepsilon_{\text{AB}}$ and vanishes as expected when $\varepsilon_{\text{AB}}$ becomes identical to $\varepsilon_{\text{AA}}$ and $\varepsilon_{\text{BB}}$. Meanwhile, the polymer-solvent surface tension, $\gamma_{\text{AW}}$, decreases when the polymer-solvent interaction becomes less repulsive, and reaches 0 when $\lambda = 1$, i.e., when the polymer-solvent interaction is purely LJ. Our calculated surface tensions are comparable to those of real systems, e.g., $\gamma_{\text{PS,PMMA}} = 3.2$ mN/m and $\gamma_{\text{PS,water}} = 15.0$ mN/m, when the conversions described earlier from experimental to simulation energy and length scales are used. Since our coarse-grained model was not parameterized using surface tensions of specific polymers and solvents (e.g., PS and THF), the calculated values are not expected to agree quantitatively with experimental measurements. However, as will be shown in Figure 2.2, the phase behavior of the polymer blends is predominantly dictated by the ratio of surface tensions, and not their absolute values. In this respect, our model produces quantitatively similar values for $\gamma_{\text{AW}}/\gamma_{\text{AB}}$ and $\gamma_{\text{BW}}/\gamma_{\text{AB}}$ as for typical materials in experiments.

Figure 2.1: (a) Polymer-polymer surface tension, $\gamma_{\text{AB}}$, as a function of the reduced polymer cross interactions, $\varepsilon_{\text{AB}}/\varepsilon_{\text{AA}}$ ($\varepsilon_{\text{AA}} = \varepsilon_{\text{BB}}$). $\varepsilon_{\text{AB}}/\varepsilon_{\text{AA}}$ was varied between 0.01 to 1.0. (b) Polymer-solvent surface tension, $\gamma_{\text{AW}}$, as a function of the solvent quality parameter, $1 - \lambda$. 


Having obtained the surface tensions of the polymer blend and solvent systems, we used Torza and Mason’s criteria to explain the different particle morphologies from FNP. Here, we adopted the phase diagram reported in Ref. 67 to draw the solid lines in Figure 2.2. State points highlighted by the closed circles have been examined in our simulations on FNP systems at $\tau_{\text{mix}} = 21 \mu s$, and since $\varepsilon_{AA} = \varepsilon_{BB}$, symmetrical state points have also been labeled by the open circles. We obtained particle morphologies consistent with predictions from Torza and Mason’s criteria, i.e., dumb-bell shaped Janus particles in region I, acorn-shaped Janus particles in region II, core-shell particles in region III and completely phase separated aggregates in region IV. It is noted that, however, when a negative surface potential was applied to mimic the effect of charge stabilization during FNP, the boundary between regions II and IV shifted slightly upward as represented by the dashed line. The positions of the lines drawn in Figure 2.2 will be further studied by our analysis of an isolated nanoparticle (see ensuing discussion).

To differentiate the assembly mechanisms that lead to the different particle morphologies, we present simulation snapshots for both the Janus and core-shell particles in Figure 2.3. In case (a), when the difference in the solvophobicity of A and that of B was small, polymers A and B formed separate aggregates first, and the homogeneous aggregates merged to form Janus particles as mixing proceeded. When the difference in the solvophobicity of A and that of B was large as in case (b), the more solvophobic polymers aggregated first, and the less solvophobic polymers then spread out on the surface of the aggregates to form core-shell particles.

Next, we examined the self-assembled Janus and core-shell structures in more detail. We obtained an isolated Janus particle (the middle nanoparticle structure in Figure 2.4) with 93 A chains and 93 B chains from a simulation with $\varepsilon_{AB} = 0.9\varepsilon_{AA}$ and $\lambda_{AW} = \lambda_{BW} = 0.5$ and studied how the structure changed as we varied polymer-solvent and polymer-polymer interactions. We first kept $\varepsilon_{AB}$ and $\lambda_{BW}$ constant ($\gamma_{AB}$ =
Figure 2.2: Equilibrium morphologies of nanoparticles as a function of the ratios of surface tensions. Solid lines are reproduced from Ref. 67, and they are based on predictions by Torza and Mason using the Neumann triangle. The positions of the lines are verified by our analysis of an isolated nanoparticle. Cross sections of Janus and core-shell particles (region I-III) are shown here to reveal the internal structure. The dashed line represents the boundary between regions II and IV if a negative surface potential of $\zeta = -33 \text{ mV}$ is applied. Closed circles are state points examined in our MD simulations on FNP systems at $\tau_{\text{mix}} = 21 \mu\text{s}$. Open circles are symmetrical state points. Points (a) and (b) are chosen from the Janus and core-shell regions for studies on particle size and composition as will be explained later.
Figure 2.3: Simulation snapshots over time which represent two selected assembly parameters for a polymer blend undergoing the FNP process with $\tau_{\text{mix}} = 21 \mu s$. Case (a) leads to the formation of Janus particles, and case (b) leads to core-shell particles.
0.9 mN/m and $\gamma_{BW} = 2.4$ mN/m). By varying $\lambda_{AW}$ systematically from 0 to 1, which can be represented by a horizontal move from left to right across Figure 2.2, we observed particle structures as shown in Figure 2.4. Here, two structural properties were used to characterize the varying degree of encapsulation, i.e., the surface coverage of A-type beads, $S_A$, and the fraction of beads that belong to the A-B interface, $f_i$. The quantity $S_A$ was obtained by identifying and constructing the convex hull of the surface beads. To calculate $f_i$, we first identified the A-B interface by taking all the beads that have at least one bead of an opposite type in their immediate neighborhood, and then divided this number by the total number of beads in the particle.

As shown in Figure 2.4, $S_A$ increases as $\lambda_{AW}$ decreases, which results from an increasing degree of encapsulation by A. The dashed line at $S_A = 0.5$ is the predicted surface coverage by assuming that the area scales as a power of 2/3 of the number of beads; this line intersects the data at $\gamma_{AW} - \gamma_{BW} = 0$ mN/m, when the nanoparticle is dumb-bell shaped with no encapsulation. At $\gamma_{AW} - \gamma_{BW} = -0.94$ mN/m as predicted by the lines drawn between regions II and III in Figure 2.2, the particle undergoes a transition from Janus to core-shell, which is in agreement with measurements presented in Figure 2.4. Lastly, when $\gamma_{AW} - \gamma_{BW} = -2.4$ mN/m, i.e., $\gamma_{AW} = 0$ mN/m, polymer chains of type A dissolve in the solvent. It is also clear that calculations of $f_i$ support the same observations.

Next, we fixed both $\lambda_{AW}$ and $\lambda_{BW}$ at 0.5, and decreased $\varepsilon_{AB}$ from 0.9 to 0.01. In addition to $f_i$, we also computed the asphericity of the single Janus particle, $\alpha$. The quantity $\alpha$ characterizes the shape of the particle and is defined by

$$\alpha = \frac{(L_1^2 - L_2^2)^2 + (L_1^2 - L_3^2)^2 + (L_2^2 - L_3^2)^2}{2(L_1^2 + L_2^2 + L_3^2)^2} \tag{2.4}$$
Figure 2.4: Surface coverage of polymer A, $S_A$, and the fraction of beads that belong to the AB interface, $f_i$, as a function of $\gamma_{AW} - \gamma_{BW}$.

where $L_1, L_2$ and $L_3$ are the eigenvalues of the particle’s radius of gyration tensor. The shape of the particle is a sphere when $\alpha$ is 0.

As shown in Figure 2.5, the dumb-bell shaped Janus particle became more elongated with a decreasing interfacial area. In the absence of the negative surface potential, at $\varepsilon_{AB} = 0.01\varepsilon_{AA}$ which corresponds to a $\gamma_{AB}$ value of 4.8 mN/m, the Janus particle separates into two homopolymer aggregates (not shown in Figure 2.5), which is in agreement with Torza and Mason’s prediction and the solid line drawn between region II and region IV in Figure 2.2.

When a negative surface potential of $\zeta = -33$ mV is applied, the separation occurs at $\varepsilon_{AB} = 0.3\varepsilon_{AA}$ which corresponds to $\gamma_{AB} = 4.2$ mN/m and $\gamma_{AW}/\gamma_{AB} = \gamma_{BW}/\gamma_{AB} = 0.57$, leading to the dashed line drawn in Figure 2.2.

Having understood the relationship between particle structures and surface tensions, we moved on to study the processing parameters specific to the FNP process, such as mixing rate and polymer feed concentration. An advantage of the FNP
technique is the ability to independently control particle size and morphology, as demonstrated by recent experiments, where the size of the patchy particles was tuned by the mixing rate or polymer feed concentration. In the following section, we will present results from varying these two parameters in our simulations.

Two state points have been chosen from the phase diagram [(a) and (b) in Figure 2.2], which belong to the Janus and core-shell regions, respectively. It has been suggested by the experiments and previous simulations of homopolymers, that the particle size remains approximately constant at short mixing times, \( i.e. \), fast mixing, but increases when the mixing time exceeds a specific threshold. It was argued that micro-mixing only affects the final nanoparticle size when the collapse time of polymer chains during the solvent displacement is slower than the average contact time for two polymer chains. Ref. 41 provides details on estimating the average contact time and thus the threshold mixing time, which has been indicated by the
dashed line in Figure 6 for the studied system. Figure 2.6 also shows the average size of Janus and core-shell particles as a function of $\tau_{\text{mix}}$, and it is clear that polymer blends exhibit a similar trend as homopolymer systems. Interestingly, at fast mixing, precipitated Janus or core-shell particles are smaller than their homopolymer counterparts ($\varepsilon_{\text{AA}} = \varepsilon_{\text{BB}} = \varepsilon_{\text{AB}}$) at the same overall polymer concentration. This discrepancy stems from $\varepsilon_{\text{AB}} < \varepsilon_{\text{AA}} = \varepsilon_{\text{BB}}$ in our simulations, which leads to a smaller enthalpic gain when polymers of different types aggregate. This effect vanishes, however, at longer $\tau_{\text{mix}}$ and the particle diameters approach each other, despite the slightly unfavorable $\varepsilon_{\text{AB}}$; at such long mixing times, the polymers have enough time to aggregate before the good solvent is displaced by the poor one and the stabilizing surface charge builds up. Recent self-consistent field theory calculations of a similar system have indicated that $a \sim \tau_{\text{mix}}^{1/6}$ in this growth regime, which is in line with our observations.

Figure 2.6: The average size of nanoparticles (Janus, core-shell and homopolymers), $a$, plotted as a function of mixing time, $\tau_{\text{mix}}$. The dashed line indicates the estimated threshold mixing time for the homopolymers at the studied concentration of 8.2 mg/ml. Error bars are shown only when they are larger than symbol size.
Unlike systems of homopolymers undergoing FNP, $\tau_{\text{mix}}$ not only affects the final particle size in the case of polymer blends, it also leads to different compositions of the final system at equilibrium. During Janus particle formation, at fast mixing, a certain fraction of precipitated nanoparticles remains as homopolymer aggregates as shown in Figure 2.7. As $\tau_{\text{mix}}$ increases, the fraction of Janus particles, $f_{\text{JP}}$, increases and approaches 1. Figure 2.7 also shows the standard deviation of nanoparticle compositions from a 50:50 A:B ratio, $SD_{\text{JP}}$. As $\tau_{\text{mix}}$ increases, $SD_{\text{JP}}$ decreases as a result of the longer diffusion and aggregation time allowed before charge stabilization sets in.

The effect of mixing time on the final systems of core-shell particles have also been examined. As shown in Figure 2.8, at small $\tau_{\text{mix}}$, a large fraction of the less solvophobic chains remain dissolved in the solvent. Therefore, the average composition of A chains in the precipitated nanoparticles, $f_A$, deviates from 0.5, and the amount of surface coverage by A particles, $S_A$, is significantly larger than zero as the core is not completely covered by the less solvophobic B chains. However, as $\tau_{\text{mix}}$ increases, the number of free chains in the final system decreases, and $f_A$ and $S_A$ approach 0.5 and 0, respectively. It should also be noted that the number of the dissolved less solvophobic chains could be overestimated in our simulations, as they were assigned a larger artificial charge due to their large radius of gyration. While the origin of the negative surface potential is still unclear,$^{71-73}$ it is conceivable that only highly hydrophobic, collapsed aggregates carry such a surface potential. However, the general trends in our observations and the studied metrics should still hold as demonstrated through the analysis of the single isolated aggregates, where the surface charge was switched off.

In addition, it can be seen in both Figure 2.7 and Figure 2.8, that the studied metrics remain relatively constant at short mixing time, and start to vary more prominently after a threshold value. This observation can be understood with the concept of the
aforementioned threshold mixing time, which has been used to explain the trend in final nanoparticle size in Figure 2.6.

Figure 2.7: The fraction of Janus particles, $f_{JP}$, and the standard deviation from a 50:50 A:B ratio in the precipitated particles, $SD_{JP}$, plotted as a function of mixing time, $\tau_{mix}$. The dashed line indicates the estimated threshold mixing time for the homopolymers at the studied concentration of 8.2 mg/ml.

In addition to $\tau_{mix}$, we have also studied the effect of polymer feed concentration, $\Phi$, on the average nanoparticle size, $a$, as shown in Figure 2.9. We obtained good agreement with results from previous MD simulations on homopolymers for $\tau_{mix} = 21 \mu s$. The data can be fitted through $a \propto \Phi^n$ with $n \approx 0.3$ as in the experiments. The fact that nanoparticle size increases with polymer feed concentration confirms that the process is growth-controlled, which compares to a nucleation-controlled pro-
Figure 2.8: The average composition of A chains, $f_A$, and the amount of surface coverage of A particles in the precipitated particles, $S_A$, plotted as a function of mixing time, $\tau_{\text{mix}}$. The dashed line indicates the estimated threshold mixing time for the homopolymers at the studied concentration of 8.2 mg/ml.

cess, where the final nanoparticle size was found to decrease with polymer concentration, because polymers deposit on a larger number of nuclei that are formed.\textsuperscript{40} In our previous work, we studied the size distribution of the precipitated nanoparticles for homopolymeric systems \textit{via} experiments and simulations, and we found normal size distributions with polydispersity indices of approximately 0.1.\textsuperscript{41} We did not make such a quantitative analysis of the size distribution in the case of polymer blends due to the small number of samples, but visual inspection revealed a qualitatively similar behavior as in the homopolymer case.
Lastly, we investigated the effects of polymer feed ratio on the final nanoparticle composition profile at $\tau_{\text{mix}} = 21 \mu s$ and $\Phi = 8.2 \text{ mg/ml}$. Three different A:B feed ratios, i.e. 1:1, 1:2 and 1:4, were studied for both the Janus and the core-shell regimes. It was found that feed ratio, $f_{A,\text{feed}}$, had no effect on the nanoparticle size. At long mixing time, the average composition of A in precipitated nanoparticles at equilibrium, $f_{A,\text{particle}}$, converged to $f_{A,\text{feed}}$ as shown in Figure 2.10. This is because the polymers are homogeneously distributed, and when they are allowed long enough time to aggregate before the good solvent is displaced by the poor one, the compositions of individual nanoparticles should approach that of the feed stream. In experiments, $\tau_{\text{mix}}$ is typically on the order of milliseconds, which is 1 to 2 orders of magnitude larger than the $\tau_{\text{mix}}$ studied in our simulations. The experimentally studied polymer concentrations range from 0.1 to 2 mg/ml, which is 1 order of magnitude lower than the polymer concentration range studied by our simulations. At such lower concentrations in the experiments, the threshold mixing time is raised by approximately a factor of 5 to $\sim 5 \mu s$, which is still well below the characteristic mixing time of $\sim 3 \text{ ms}$. Hence, the effect of a lower polymer concentration can still be offset by the
much larger \( \tau_{\text{mix}} \), and nanoparticles produced in the experiments should belong to the regime where their compositions converge to the feed composition, which is consistent with experimental observations.\(^{42} \) Therefore, we can conclude that the FNP technique can reliably control the composition of the fabricated nanoparticles through polymer feed ratio.

![Diagram](image)

**Figure 2.10:** The average fraction of polymer A in equilibrium particles, \( f_{A,\text{particle}} \), as a function of the fraction of polymer A in the feed stream, \( f_{A,\text{feed}} \) at \( \tau_{\text{mix}} = 21 \mu s \). The dashed line represents \( f_{A,\text{particle}} = f_{A,\text{feed}} \). Examples of particle cross sections from each feed ratio are also shown in the figure.

### 2.3 Conclusions

In this work, MD simulations have been carried out to systematically explore how polymer-polymer and polymer-solvent surface tensions control the internal structures of nanoparticles (Janus and core-shell) produced from the FNP process. It was found that the final equilibrium structure can be predicted by the surface tensions be-
tween the polymer blend and between the polymers and the solvent, which qualita-
vitively agree with previous experimental and computational studies on phase-separated
structures of polymer blends in aqueous solutions. \textsuperscript{29,63–67}

We have also demonstrated the ability of the FNP process to independently tune
particle size through the mixing time of the solvent-nonsolvent streams and the overall
polymer concentration, as well as the particle composition through the polymer feed
ratio. Our simulations show that particle size remains relatively constant for fast
mixing, and increases with mixing time beyond a certain threshold time, as well as
the overall polymer concentration in the feed stream. The above relations agree with
experimental results and MD simulations on homopolymer systems. \textsuperscript{41,42} The average
particle composition was also found to approach the feed ratio at long mixing time.
Lastly, we were also able to elucidate the mechanism of Janus or core-shell particle
formation in our simulations, \textit{i.e.}, the homopolymers form separate aggregates first
before they merge to form structured particles.

The experimental technique and the generic simulation model should be generally
applicable to many other polymer blend systems undergoing a rapid solvent exchange.
We have thus demonstrated FNP as a simple, continuous and scalable process to
produce structured nanoparticles with nanoscale control. Our results also provide
guidelines for future design and preparation of polymeric nanoparticles with desired
properties using FNP techniques, and thus facilitate their applications in areas such as
drug delivery, sensors and emulsion stabilization. Our future work will be interested
in accounting for vitrification of the precipitated polymers, since recent experiments\textsuperscript{42}
suggested that this effect might lead to multifaced nanoparticles.
Chapter 3

Self-assembly of a rubbery and a glassy homopolymers*

Patchy particles which possess discrete surface domains are promising building blocks for hierarchical structures, with potential applications in photonic crystals, sensors, and targeted drug delivery.\textsuperscript{5,11–15,74,75} Since the particle size and surface properties are often the key parameters determining their functionality, it is highly desirable to develop facile and scalable routes for fabricating patchy particles with tunable and well-controlled dimensions.

Over the past decades, many experimental techniques have been developed for fabricating patchy particles, including templating,\textsuperscript{21,76} colloidal assembly,\textsuperscript{77,78} particle lithography,\textsuperscript{79,80} glancing-angle deposition,\textsuperscript{81} and capillary fluid flow.\textsuperscript{24} However, these processes either lack the ability to fabricate multi-patch particles of controlled morphologies, or involve multiple steps which limit their scalability. It is also possible to obtain patchy particles from microphase separation of block copolymers in a selective solvent; numerous experimental and computational studies have been dedi-

*This chapter is based on: Nannan Li, Arash Nikoubashman, and Athanassios Z. Panagiotopoulos, Controlled production of patchy particles from the combined effects of nanoprecipitation and vitrification. \textit{Soft Matter} \textbf{2017}, \textit{13}, 8433-8441.
cated to this approach.\textsuperscript{51,82–86} For example, it has been demonstrated that the slow addition of water into a solution of polystyrene-\textit{block}-poly(4-vinylpyridine) leads to the formation of patchy particles, and the number of patches depends on the diblock copolymer composition.\textsuperscript{87} Nevertheless, such procedures involve multiple steps and slow solvent evaporation, which pose a problem for scale-up, and also require chemical synthesis of new starting materials to access different particle structures.

The work presented in this chapter is motivated by the experimental observations which suggested that vitrification of one species in a binary polymer blend undergoing FNP can lead to complex multi-patch structures, due to kinetic trapping into metastable states.\textsuperscript{42,43} It was observed in the experiments that using a blend of polyisoprene (PI) and high molecular weight polystyrene (PS) ($M_w = 1600$ kg/mol), nanoparticles with multiple surface patches were obtained. In comparison, Janus structures were obtained when a low molecular weight PS ($M_w = 850$ g/mol) was used instead. In addition, the number of patches can be tuned by the $M_w$ and the fraction of PS in the feed polymer blend. These findings demonstrated the capability of FNP to produce patchy nanoparticles with independent control of size and patch distribution in a single and continuous route without redesigning the starting materials.

In this chapter, we use molecular dynamics (MD) simulations to investigate patchy particle formation in FNP from a binary polymer blend with one component being glassy. In particular, we focus our attention on how patchiness can be controlled through the various process parameters, since the dependence of nanoparticle size on mixing time and polymer feed concentration has been elucidated in Chapter 2. The structure of this chapter is as follows: we will first introduce the MD simulation model and methods used in the present work. Next, we present our simulation results, and examine the dependence of patchiness on nanoparticle size and composition, which
can in turn be independently tuned. Lastly, we summarize our results and comment on their implications on patchy particle production through the FNP process.

### 3.1 Simulation model and methods

Our previous MD model presented in Chapter 2 for binary polymer blends with two rubbery components undergoing the FNP process serves as a foundation for our current study.\(^8\) In this model, a polymer is described as a linear bead-spring chain with \(N\) beads, each with unit diameter \(\sigma\) and unit mass \(m\). Each bead represents a Kuhn segment of the polymer chain. We chose \(N = 23\) for all homopolymer chains (of type A and B) in our simulations.

The bonded interactions between polymer beads are modeled \textit{via} the FENE potential.\(^5\) The standard Kremer-Grest parameters were adopted to prevent unphysical bond crossing.\(^6\) Other than the bonded interactions, polymer beads also interact with one another \textit{via} the standard LJ potential [Eqn. (2.1)]. We set the prefactor, \(\varepsilon_{\text{LJ}}\), for the intraspecies interaction to \(\varepsilon_{\text{AA}} = 3\varepsilon\) and \(\varepsilon_{\text{BB}} = 2\varepsilon\), where \(\varepsilon\) is the unit of energy for our simulations.

We first performed MD simulations to determine the glass transition temperatures, \(T_g\), of polymers A and B, both in bulk and in aggregates under poor solvent conditions. The simulations were carried out at constant temperature and constant pressure \(p = 0\).

To calculate \(T_g\) in the bulk, we study the specific volume, \(v\), and the Lennard-Jones energy per bead between non-bonded monomers, \(E_{\text{NB}}\), during cooling, and \(T_g\) is indicated by a change of slope in the temperature dependence of these quantities. The system contained 500 polymer chains with \(N = 23\) beads. The system was initially equilibrated at \(T = 2.0\), and \(T\) was then lowered every 50,000 MD steps by 0.02 until
the final value of $T$ was reached. From Figure 3.1, it is clear that both $v$ and $E_{NB}$ indicate $T_{g,A} = 1.3$ for polymer A, and $T_{g,B} = 0.9$ for polymer B.

![Figure 3.1: Specific volume, $v$, and Lennard-Jones energy per bead between non-bonded monomers, $E_{NB}$, of polymers in bulk vs. temperature, $T$. The circles represent polymer type A, and the squares represent polymer type B. The positions of the kinks indicate that $T_{g,A} = 1.3$, and $T_{g,B} = 0.9$.](image)

In addition, we studied aggregates of polymers A and B, and found that they undergo glass transition at the same temperatures as in the bulk. We prepared a cubic box with an edge length of $30\sigma$ which contained an aggregate of 64 polymer chains and 17,820 solvent particles in poor solvent conditions, i.e., $\lambda = 0.5$. Figure 3.2 shows the Lennard-Jones energy per bead between non-bonded monomers, $E_{NB}$, vs. $T$ upon cooling, and a kink can be found at $T = 1.3$ and 0.9 for polymers A and B, respectively.

Having determined the glass transition temperatures of polymers A and B, we determine the simulation temperature by considering the experiments. In the experiments of Refs. 42 and 43, PI ($T_g \approx 198$ K) and PS ($T_g \approx 380$ K) were mixed at room temperature. In order to achieve similar conditions in our simulations, we set the temperature to $T = 1.1$, so that polymer A is glassy, while polymer B is rubbery.
Figure 3.2: Dependence of Lennard-Jones energy per bead between non-bonded monomers, $E_{NB}$, of an aggregate in poor solvent conditions on temperature, $T$, for (a) polymer A and (b) polymer B. The positions of the kinks indicate that $T_{g,A} = 1.3$, and $T_{g,B} = 0.9$.

Following Refs. 41 and 88, solvent particles are modeled explicitly as LJ particles with the same size and mass as the polymer beads. A reduced number density of $\rho_S = 0.66$ has been chosen, which leads to a dynamic solvent viscosity of $\eta = 0.92$. Similar to previous computational studies on FNP, the transition from good to poor solvent conditions was mimicked by varying the non-bonded particle interactions. The interaction between solvent particles and monomers is controlled by a dimensionless parameter $\lambda$:

$$U_{MS}(r_{ij}) = p_M[\lambda U_{WCA}(r_{ij}) + (1 - \lambda)U_{LJ}(r_{ij})], \quad (3.1)$$

where $U_{WCA}(r_{ij})$ is the purely repulsive Weeks-Chandler-Andersen (WCA) potential. Note that in contrast to our previous simulations, $\varepsilon_{AA} \neq \varepsilon_{BB}$, so the monomer-solvent interaction has to be tuned independently for the A and B species to achieve similar solvent conditions. The prefactor $p_M$ for polymers A and B was chosen so that a single chain of each polymer type collapses in a similar way as $\lambda$ increases. As shown in Figure 3.3, $p_{M,A} = 2.5$ and $p_{M,B} = 1.7$ lead to good agreement between the radius of gyration, $R_g$, of a single chain of polymers A and B at different $\lambda$ values.
addition, during FNP, feed streams are mixed at different rates, which was taken into account in our previous simulations by varying $\lambda$ from its initial to its final values over a period of time.\textsuperscript{41,88} Since our current study focuses on nanoparticle patchiness, all our simulations are conducted under instantaneous mixing, which means that the systems are initially well equilibrated in good solvent conditions at $\lambda = 0$, followed by an immediate increase to the final $\lambda$ value.

![Figure 3.3: Radius of gyration, $R_g$, of a single polymer chain of type A and B vs. the dimensionless solvent quality parameter, $\lambda$, when $p_{M,A} = 2.5$ and $p_{M,B} = 1.7$.](image)

Similar to the work presented in the previous chapter, the HOOMD-blue simulation package\textsuperscript{60,61} was used for the MD simulations. A Nosé-Hoover thermostat was employed to maintain the temperature at $T = 1.1$, and the equations of motion were integrated using the velocity Verlet algorithm at a timestep of $\Delta t = 0.01$ in the reduced unit of time, $\tau = \sigma \sqrt{m \varepsilon}$, where $\sigma$, $m$ and $\varepsilon$ are the characteristic length, mass and energy of our simulations. The methods to determine $\sigma$, $m$ and $\varepsilon$ have been outlined in the previous chapter. For the system studied in this chapter, we obtained $\varepsilon = 3.74 \times 10^{-21}$ J, $\sigma = 1.5$ nm, and $\tau = 0.28$ ns.

In addition, it should also be noted that unlike the work presented in the previous chapter, where an electrostatic repulsion was applied to stabilize the precipi-
tated nanoparticles, such a repulsion is disabled in the current study, since we are mainly concerned here with the effect of vitrification on patch formation of a single nanoparticle. For a detailed discussion regarding the effects of electrostatic charge on nanoparticle size and composition, we refer the reader to Refs. 41 and 88.

3.2 Results and discussion

We first studied the self-assembled structures from a binary blend of polymers A (glassy) and B (rubbery) undergoing a rapid solvent exchange for two different compositions, $f_g = 0.1$ and 0.8, where $f_g$ is the fraction of the glassy (A) component. A cubic box with an edge length of $80\sigma$, containing 337,920 solvent particles and 512 polymers was adopted. The systems were equilibrated at $\lambda_A = \lambda_B = 0$, and we set $\lambda_A = \lambda_B = 0.5$ to represent the final poor solvent conditions. This choice of $\lambda$ leads to a Janus morphology at equilibrium, and it has been verified by repeating our simulations at $T = 2.0$, which is above the $T_g$ of both polymers A and B. The systems were allowed to evolve for up to $10^8$ timesteps, which corresponds to approximately 0.3 ms in physical time. Snapshots at different times are shown in Figure 3.4. At low $f_g = 0.1$, upon a change in solvent quality at $t = 0$, homopolymer chains first self-assembled separately before they merged to form smaller patchy particles. The smaller patchy particles then aggregated further to form a single spherical particle. The number of patches of this single aggregate decreased gradually with time from 7 to 4. In contrast, at high $f_g$, small Janus and patchy nanoparticles formed initially. However, as aggregation proceeded, the larger aggregates were not able to evolve into a spherical shape within our accessible simulation time, which can be attributed to the low mobility of the glassy component.

We studied the size distribution of the surface patches for nanoparticles obtained at small $f_g$, since in many practical applications nanoparticles with highly symmetric
surface patches are desirable. We computed $f_{a,p}$, which is the area a single surface patch over the total area of all patches of a nanoparticle. For 2-patch, 3-patch and 4-patch nanoparticles, $f_{a,p}$ can be fitted through Gaussian distributions with means at 0.5, 0.33 and 0.25, respectively. The standard deviations are approximately 0.1, which is rather small. The uniform size distribution of surface patches can be explained by the formation of aggregates with a narrow size distribution as a result of the rapid precipitation, which leads to uniformly-sized surface patches.

To understand the evolution of nanoparticle shape in more detail, we calculated the aspect ratio, $\alpha$, as a function of time for a single nanoparticle obtained from self-assembly. This quantity $\alpha$ is defined by $\alpha = \frac{L_3}{L_1}$ where $L_3$ and $L_1$ are the largest and smallest eigenvalues of the particle’s radius of gyration tensor, respectively. As shown in Figure 3.5, $\alpha$ decreases more rapidly at first, but the decrease slows down significantly at long times. It can also be seen that higher $f_g$ leads to more aspherical nanoparticles.

It is thus evident from the above-mentioned results that vitrification can kinetically trap nanoparticle morphologies along the path to the final equilibrium configuration, giving rise to patchiness. However, the low mobility of glassy polymers and the limited simulation timescales prevent us from investigating larger nanoparticles with high $f_g$ if they are self-assembled from a polymer solution. To study more systematically patchy morphologies with respect to nanoparticle size and composition, we performed simulations starting from preformed spherical nanoparticles with homogeneously mixed glassy and rubbery components. This scenario also corresponds to the situation when nanoparticles obtained from the FNP process are subject to thermal annealing above the glass transition temperatures of both polymers, and are then cooled down to $T_{g,B} < T < T_{g,A}$.

The preformed nanoparticles consisted of between 64 to 1,024 polymer chains, and their radii, $a$, ranged between 8.3 to 21.0 nm, with the fraction of the glassy
Figure 3.4: Time evolution of a system of 512 polymer chains undergoing an instantaneous change in solvent quality at time 0 for two different compositions: (a) $f_g = 0.1$, and (b) $f_g = 0.8$. Snapshots rendered using Visual Molecular Dynamics 1.9.2.
component, $f_g$, chosen between 0.1 to 0.9. In experiments, the size of the precipitated nanoparticles can be controlled by the mixing rate and polymer feed concentration, while the composition of the particles can be tuned by the polymer feed ratio\textsuperscript{41,42}.

The structures at various nanoparticle sizes and compositions were allowed to evolve at $\lambda_A = \lambda_B = 0.5$ for at least 0.3 ms in physical time, and the morphologies are shown in Figure 3.6(a). It can be seen that in agreement with experimental observations\textsuperscript{43}, the minority component always forms the surface patches, irrespective of whether it is glassy or not. An examination on the inner structures in Figure 3.6(b) reveals that the composition at the core did not change much from the initial state and the polymers remained entangled. In contrast, patchy particles assembled from a polymer solution have homogeneous cores which consist of only the majority component (see snapshots in Figure 3.4). This difference can be explained by the well-mixed starting configurations, which limit the movement of polymer chains. Patches are mainly formed from movement of polymer chains near the surface. Polymers at nanoparticle cores are unable to make it to the surface, which explains why the
number of patches, $N_p$, only depends on $a$, but not $f_g$ as shown in Figure 3.7(a). In addition, $N_p$ can be fitted through $N_p \propto a^c$, where $c = 3.0 \pm 0.2$. Since for each composition the number of beads that can form patches, $N_{pp}$, is estimated to scale as the the volume of the nanoparticle, \textit{i.e.}, $N_{pp} \propto V \propto a^3$, the size of the patches, $N_{pp}/N_p$, thus should remain constant with respect to $a$. We confirmed this hypothesis by plotting the average patch diameter, $d$, \textit{vs.} $a$, which is approximately constant for a given $f_g$. This observation can be explained by the limited mobility and growth of the patches once they are formed. Therefore, starting from well-mixed nanoparticles leads to a larger number of patches compared to nanoparticles of the same size and composition obtained from self-assembly in solution. Moreover, the above results support the observation from Figure 3.4 that during self-assembly, polymer phase separation occurs before aggregation, because the low mobility of the glassy component prevents complete phase separation to be reached from a well-mixed nanoparticle.

It is thus clear that patchy particle formation due to vitrification is a dynamical process, and the resulting structures strongly depend on the initial configuration. Starting from states where polymer blends are well-mixed limits subsequent chain movement, and results in nanoparticles with entangled inner structures, which are different from those obtained from self-assembly from solution. During self-assembly, larger nanoparticles are formed from either smaller homopolymer aggregates or partchy particles, which means polymer blends are already phase separated. This difference is similar to the one between solvent casting and spray coating of polymer films; in the former, a homogeneous polymer film slowly phase separates as solvent is evaporated, whereas in the second case small (microphase-separated) units self-assemble into a film.\textsuperscript{91–93} We thus prepared another type of initial structures, which are preformed spherical nanoparticles with core-shell configurations. Interaction parameters are kept the same as systems studied previously, so that Janus struc-
Figure 3.6: (a) Morphology diagram obtained at various nanoparticle size, $a$, and composition, $f_g$, after the systems were allowed to evolve for at least 0.3 ms in physical time. Glassy polymers A are represented by cyan beads, while rubbery polymers B are shown in red. The starting structures are preformed spherical nanoparticles with well-mixed polymers A and B. (b) Typical nanoparticle morphologies with the internal structures revealed on the right.

The core-shell structures are made up of either glassy shells with rubbery cores, or rubbery shells with glassy cores. Two quantities are varied in each case, i.e., the size of the nanoparticle, $a$, and the composition of it, which is represented by the ratio between the number of core polymers and the number of shell polymers, $N_c/N_s$. All nanoparticles were allowed to evolve for at least 0.3 ms in physical time, and the morphology diagrams are presented in Figure 3.8. It can be observed that when the shell is thick, i.e., $N_c/N_s$ is small, or when $a$ is large, the core polymers are trapped
Within the shells, a greater extent of trapping is seen with glassy shells than rubbery shells, which is represented by the larger area marked by red squares in Figure 3.8(a) than 3.8(b). Janus structures are only obtained for the smallest nanoparticles studied ($a = 8.3 \text{ nm}$) when glassy polymers are the minority component. Similarly in the experiments, multi-patch nanoparticles started to emerge for radii greater than 75 nm, and only Janus structures were obtained below this value.\textsuperscript{43} However, the minimum radius obtained in the experiments is much larger because the longer timescale allows surface patches to diffuse over a larger distance and coalesce. Moreover, surface structures with elongated domains, or “ribbons” have also been observed for more symmetric blend ratios. Similar shapes have been reported in previous computational studies on patchy particle formation through block copolymers.\textsuperscript{51,86} Lastly, patchy structures are obtained at larger $a$ and more asymmetric blend ratios.

To elucidate the effect of kinetic trapping, we calculated the surface coverage of patch particles, $S_p$, defined as the fraction of surface beads that belong to the patches. This quantity was obtained by identifying and constructing the convex hull of the surface beads. The value for each $N_c/N_s$ and $a$ is compared to the corresponding equilibrium $S_p$ value obtained at $T = 2.0$. The deviations from the equilibrium

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**Figure 3.7:** (a) Number of patches, $N_p$, and (b) patch diameter, $d$, vs. size of the nanoparticle, $a$, at various compositions, $f_g$. Error bars are shown only when they are larger than symbol size.
Figure 3.8: Morphology diagram for various nanoparticle size, $a$, and composition, $N_c/N_s$, after the systems were allowed to evolve for at least 0.3 ms in physical time. The starting configurations consisted of glassy shells and rubbery cores in (a), and rubbery shells and glassy cores in (b).
values, $\delta$, are plotted in Figure 3.9. It can be seen that when the initial structures consist of glassy shells with rubbery cores [see Figure 3.9(a)], $\delta$ increases with increasing $a$ and decreasing $N_c/N_s$. This behavior can be explained by an increasing degree of kinetic trapping for larger nanoparticles and larger fractions of glassy shells. In contrast, for initial structures with glassy cores and rubbery shells, $\delta$ values do not show a significant dependence on $a$ or $N_c/N_s$, and the values of $S_p$ are much closer to their equilibrium values at $T = 2.0$. It is easier for the polymer chains at the core to escape rubbery shells than glassy ones on the path to the equilibrium Janus morphology. It is thus obvious that kinetic trapping is responsible for the different surface morphologies observed in Figure 3.8, and the degree of kinetic trapping increases with the nanoparticle size, the fraction of glassy polymers and also depends on the starting configuration.

Figure 3.9: Deviation, $\delta$, of surface coverage of patches from the values at equilibrium vs. size of the nanoparticle, $a$, at various compositions, $N_c/N_s$ when the starting configurations consisted of (a) glassy shells with rubbery cores and (b) rubbery shells with glassy cores. The dashed line in (b) represents data from $N_c/N_s = 1$ for glassy shells and it is plotted in the same graph for comparison purposes.

Next, we studied the number of surface patches, $N_p$, for patchy nanoparticles obtained from the core-shell start configurations in more detail. We hypothesize that patchiness arises when the distance between spontaneously formed patches is larger than their average displacement on the nanoparticle surface through Brownian
motion in a given time interval. In principle, the individual patches should coalesce to a single patch for $t \to \infty$, but this limit might not be reached at the accessible time scales due to the glassy nature of the A component. This hypothesis can be supported by plotting the time evolution of $N_p$ for nanoparticles with $a = 13.2$ nm and $N_c/N_s = 4$ and 8 in Figure 3.10. It can be seen that $N_p$ decreases rapidly at first, because there is a large number of small patches on the nanoparticle surface, which are close to each other and diffuse fast. As patch coalescence continues (indicated by the decrease of $N_p$), patches become larger, more sparsely distributed and they also diffuse more slowly. The decrease of $N_p$ with time can be fitted through $N_p \propto t^b$, where $b = -0.07 \pm 0.01$ and $-0.11 \pm 0.01$ for $N_c/N_s = 4$ and 8, respectively. The exponent, $b$, is expected to be -1 if the collision and coalescence of surface patches is assumed to be second-order. However, coalescence slows down with time as larger patches are farther apart and diffuse more slowly, which should lead to a smaller prefactor over time. Therefore, when the data are fitted with a power law function with a constant prefactor, the effective exponent appears to be smaller than -1.

![Figure 3.10: Time evolution of the number of patches, $N_p$, for $a = 13.2$ nm and $N_c/N_s = 4$ and 8. The solid lines are power law fits to the data.](image-url)
To characterize the \textit{spatial} properties of the patches, we studied the number of patches, $N_p$, their shape and diameter $d$, and their mean free path, $l$, as a function of nanoparticle size, $a$. It is possible to derive scaling relationships for these quantities if one of the properties is kept fixed, \textit{i.e.}, (1) constant $N_p$, (2) constant $d$, and (3) constant $l$, respectively. Because diffusion and coalescence of patches occur on the nanoparticle surface, \textit{i.e} in two dimensions, we can approximate the mean free path as

$$l \propto (dN_p/a^2)^{-1}. \quad (3.2)$$

Further, the number of beads that can form patches scales as $N_{pp} \propto a^3$, leading to $N_{pp}/N_p$ particles per patch for a monodisperse patch size distribution. The diameter of a patch scales then as

$$d \propto (N_{pp}/N_p)^e \propto (a^3/N_p)^e, \quad (3.3)$$

with $e = 1/2$ for flat patches and $e = 1/3$ for spherical patches.

(1) In the case of constant $N_p$, Equation (3.3) simplifies to $d \propto a^{3e}$, and we obtain $d \propto a^{3/2}$ for flat patches and $d \propto a$ for spherical patches. The mean free path between patches becomes $l \propto a^{1/2}$ for flat patches, and $l \propto a$ for spherical patches.

(2) If the patch size, $d$, is constant, Equation (3.3) leads to $N_p \propto a^3$, and Equation (3.2) simplifies to $l \propto a^{-1}$. This is the situation in Figure 3.6, when the starting structures are well-mixed and entangled. Surface patches show limited mobility and growth in size once they are formed.

(3) Lastly, we consider the scenario when the mean free path, $l$, is constant with respect to $a$, which leads to $N_p \propto a^2/d$ from Equation (3.2). By substituting Equation (3.3) into this expression, we obtain $N_p \propto a$ and $d \propto a$ for flat patches and $N_p \propto a^{3/2}$ and $d \propto a^{1/2}$ for spherical patches.

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Having considered these three scenarios analytically, we now study the dependence of \( N_p \), \( d \) and \( l \) on \( a \) in the simulations to determine which case best describes our data.

In Figure 3.11(a), we computed \( N_p \) at \( t = 0.3 \) ms for two compositions and reduced \( N_p \) by the corresponding value at the smallest nanoparticle size (\( a = 8.3 \) nm). Our simulations show that \( N_p \) increases as \( a \) increases, which is consistent with experimental observations.\(^{43}\) In Figure 3.11(b), we show the measured patch diameter, \( d \), which was computed by taking the square root of surface area per patch, and reduced by \( d_0 \) measured at \( a = 8.3 \) nm for each composition. Lastly, we plotted in Figure 3.11(c) the reduced mean free path, computed using Equation (3). It is thus clear that, from the above analysis, the scaling between \( N_p \) and \( R \) can be best explained by Scenario (3) where the mean free path of patches is independent of \( a \). The data for \( N_p \) and \( d \) suggest a value of \( e \) between 1/3 (spherical patches) and 1/2 (flat patches), which is also supported by visual inspection of the nanoparticle snapshots shown in Figure 3.11.

Lastly, we determined the dependence of \( N_p \) on polymer blend ratio. Having obtained a linear relationship between \( N_p \) and \( a \), we plot \( N_p / a_r \) vs. \( N_c / N_s \) in Figure 3.12, where \( N_p \) is obtained at 0.3 ms, and \( a_r \) is \( a \) reduced by the smallest radius at which multi-patch nanoparticles start to emerge (8.3 nm). Data for different \( a \) values collapse onto the same curve, and \( N_p \) increases as the blend ratio becomes more asymmetric. Results from our simulations also compare reasonably well with experimentally measured \( N_p \), which were obtained by manually counting the number of patches for nanoparticles of an average radius of 100 nm.\(^{43}\) The experimental results are reduced by 75 nm, which is the minimum radius multi-patch nanoparticles were observed.
Figure 3.11: (a) Number of patches, $N_p$, (b) patch diameter, $d$, and (c) patch mean free path, $l$, estimated using Equation (3.2), reduced by their respective values at $a = 8.3$ nm vs. size of the nanoparticle, $a$, at various compositions, $N_c/N_s$. The snapshots are taken at $N_c/N_s = 8$. The data were obtained for patchy nanoparticles obtained from core-shell start configurations with rubbery shells at $t = 0.3$ ms. Predictions from Scenarios (1), (2) and (3), which assume constant $N_p$, $d$ and $l$ with respect to $a$, respectively, are plotted with lines of different colors specified in the legend of panel (a). The dashed lines are predictions for spherical patches, the dotted lines are for flat patches, and the solid lines are for the cases independent of patch geometry.
Figure 3.12: Number of patches, $N_p$, reduced by $a_r$ vs. composition, $N_c/N_s$, at various $a$. $N_p$ values are obtained at $t = 0.3$ ms. $a_r$ is a reduced by the smallest radius multi-patch nanoparticles start to emerge. Experimental results are represented by the filled triangles.\textsuperscript{43}

### 3.3 Conclusions

In summary, we have studied through MD simulations of a generic polymer model relevant for understanding of FNP, a continuous and scalable method to fabricate patchy particles with independent control over particle size, composition and the number of surface patches. We were able to elucidate the mechanism of patchy particle formation in our simulations, \textit{i.e.}, the homopolymers form separate aggregates first before they merge to form structured particles. Our results show that kinetic trapping freezes particle morphology along the path to the equilibrium structure, leading to patchiness. Monitoring the time evolution of patches reveals that patch diffusion and coalescence occurs, but vitrification renders these processes slow. The patches are uniformly sized. The number of patches can be independently controlled by the size and the composition of the nanoparticles, both of which can be reliably tuned through process parameters specific to the FNP process. In agreement with previous experiments, more patches can be observed on the surface of a larger nanoparticle...
with a more asymmetric composition. A scaling analysis has been proposed to understand the relationship between the number of patches and the nanoparticle size. In addition, we have also observed novel structures with elongated surface domains for more symmetric nanoparticle compositions.
In the previous two chapters, the self-assembly of a binary polymer blend through FNP has been investigated using molecular dynamics (MD) simulations. In this chapter, we study polymer feed materials which consist of block copolymers. The phase separation of block copolymers has been studied in both bulk and confined systems and can be described by the Flory-Huggins interaction parameter, $\chi$, the degree of polymerization, $N$, and the composition of the block copolymer, indicated by $f = N_B / N$ where $N_B$ is the degree of polymerization of one block of the copolymer. By varying these parameters, bulk systems of diblock copolymers can adopt lamellar, spherical, or cylindrical morphologies when the system is equilibrated below its order-disorder temperature. As we study the phase separation behavior of block copolymer systems under the confinement of a colloid, we will explore the effects of these same parameters and use previous knowledge of bulk systems to guide our understanding.

The ability of FNP to advance structured colloid formation by exploiting the microphase separation of diblock copolymers has been demonstrated through experi-

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ments. With short symmetric block copolymers in the feed stream, it was found, for example, onion-like colloids consisting of concentric shells were obtained. However, an increase in polymer molecular weight, \( M \), led to disorder in the lamellar orientation. It was also demonstrated that colloid complexity can be enhanced by the addition of low-\( M \) homopolymer to the feed stream, swelling the lamellae at low weight percent but inducing a transition to a micellar morphology above a threshold concentration.

In this chapter, MD simulations are performed on low-\( M \) and high-\( M \) diblock copolymers, and a blend of diblock copolymers and homopolymers, to allow a more detailed analysis and understanding of the structures obtained in the experiments.

4.1 Simulation model and methods

In the MD model, a polymer chain was described as a bead-spring chain with a total number of \( N \) beads of either type A (PS) or B (PI). Each A bead represents one Kuhn segment of the PS chain, which led to \( N_A = 23 \) when simulating the low-\( M \) PS-b-PI \((M_n = 16.1 - b - 11.2 \text{ kg/mol})\) block copolymer used in experiments. The mole fraction of the PI block was matched to the experimental value, \( f = 0.52 \), leading to \( N_B = 25 \) \((N = 48 \text{ total beads per polymer})\). The bonded interactions between polymer beads were modeled via the FENE potential\textsuperscript{55} with the standard Kremer-Grest parameters.\textsuperscript{56} In addition, the polymer beads interact with one another through standard LJ potentials [Eqn. (2.1)]. Simulations of these chains in a bulk system resulted in a phase separated system with a lamellar period of \( L = 20 \text{ nm} \), which is in good agreement with the experiments.

In previous simulation studies, the \( \chi N \) parameter was calculated by obtaining an effective \( \chi_{\text{eff}} \) and then multiplying it by the chain length, \( N \). While this approach has been used successfully to simulate diblock copolymer systems, it becomes difficult to assess the chemical incompatibility between different monomer types independent
of the molecular architecture. With this approach, each change to the molecular composition requires a reevaluation of $\chi_{\text{eff}}$, necessitating additional and expensive simulations. Therefore, for this simulation model, we use the Flory-Huggins interaction parameter, $\chi$, between monomeric units, and then derive the effective $\chi N_{\text{eff}}$ of the block copolymers through the effective length of the chain $N_{\text{eff}}$ (as opposed to the effective $\chi_{\text{eff}}$) using the method outlined by Chremos et al. We obtained a $\chi N_{\text{eff}}$ value of 22.5 for chains where $N = 48$. Both $L$ and $\chi N_{\text{eff}}$ matched the low-$M$ PS-$b$-PI block copolymer used in experiments, indicating that the interactions in the simulation are representative of those in the experimental system.

Solvent particles are modeled explicitly as LJ particles with the same size and mass as the polymer beads. A reduced number density of $\rho_S = 0.66$ has been chosen, which leads to a reduced dynamic solvent viscosity of $\eta = 1.01$. In our studies, we control the effective solvent quality through the interaction between solvent particles and monomers using Eqn. (2.2). The system was initially equilibrated at $\lambda = 0$ to represent good solvent conditions.

In a previous simulation study, we have demonstrated that the morphology of the self-assembled nanoparticles from a binary polymer blend is dictated by the ratio of polymer-polymer and polymersolvent surface tensions. Therefore, to determine the rest of the interaction parameters in the current study, we matched the ratios of surface tensions, $\gamma$, to experimentally measured values: $\gamma_{\text{PS,PI}} = 3.2 \text{mN/m}$, $\gamma_{\text{PS,water}} = 15 \text{mN/m}$ and $\gamma_{\text{PI,water}} = 16.9 \text{mN/m}$. We chose the cross-interaction between polymers A and B, $\varepsilon_{\text{AB}}$, and $\lambda$ at poor solvent conditions, $\lambda_{\text{AW}}$ and $\lambda_{\text{BW}}$, so that $\lambda_{\text{AW}}/\lambda_{\text{AB}} = 5$ and $\lambda_{\text{BW}}/\lambda_{\text{AW}} = 1.1$. From measurements of polymer-polymer and polymer-solvent surface tensions using the method outlined by Li et al., we obtained $\varepsilon_{\text{AB}} = 0.9$, $\lambda_{\text{AW}} = 0.6$ and $\lambda_{\text{AW}} = 1.0$.

In order to make meaningful comparisons between our simulations and experimental results, it is important to establish a connection between the units of energy,
length and time in the two domains. FNP experiments were typically performed at room temperature $T = 298$ K, and thus $\varepsilon = 4.11 \times 10^{-21}$ J for the characteristic energy. For the length scale, the radius of gyration of a single chain in a $\Theta$-solvent, $R_{g,\Theta}$, from the simulation was compared to $R_{g,\Theta}$ of the corresponding PS-$b$-PI chain (16.1-$b$-11.2 kg/mol), which was obtained via $R_{g,\Theta} = (b_k \rho_{PS} N_{k,PS}^{0.5} + b_k \rho_{PI} N_{k,PI}^{0.5})/\sqrt{6}$, where $b_k$ is the Kuhn length and $N_k$ is the number of Kuhn segments of the respective polymers. We obtained $\sigma = 1.6$ nm for the characteristic length scale. For the time scale, the diffusion coefficient of a diblock copolymer chain ($N = 48$) under good solvent conditions, i.e., $\lambda = 0$, was compared to the experimental diffusion coefficient of a PS-$b$-PI chain (extrapolated to the molecular weight of 16.1-$b$-11.2 kg/mol) in toluene at room temperature (approximately $1.8 \times 10^{-7}$ cm$^2$/s), which led to a time conversion factor of $\tau = 0.23$ ns.

Typical simulation boxes had an edge length of 100 to 400 nm and contained up to 2,000,000 interaction sites. All simulations were performed in the canonical ensemble with a Nosé-Hoover thermostat. The velocity Verlet algorithm with a time step of $\Delta t = 0.01$ was employed to solve the equations of motion. Simulations were carried out using the HOOMD-blue simulation package. In addition, it should be noted that unlike our previous simulations, where an electrostatic repulsion was applied to stabilize the precipitated nanoparticles, such a repulsion was not utilized in the current study. Since the effect of surface charge on nanoparticle size has been elucidated in our previous studies, we are mainly concerned here with understanding and controlling the formation of colloids using block copolymer blends of different molecular weights and compositions.

Next, we tune the intraspecies interaction parameters, $\varepsilon_{AA}$ and $\varepsilon_{BB}$, so that the copolymers consist of a glassy block and a rubbery block at $T = 1.0$. We set $\varepsilon_{AA} = 3k_B T$ and $\varepsilon_{BB} = 2k_B T$, which results in glass transition temperatures of A and B of $T_{g,A} = 1.3$ and $T_{g,B} = 0.9$, respectively, from measurements of specific volume in the
bulk. Having determined $\varepsilon_{AA}$ and $\varepsilon_{BB}$, we chose $\varepsilon_{AB}$, $\lambda_{AW}$, and $\lambda_{BW}$ by matching the ratios of equilibrium surface tension values at $T = 2.0$ to experimental values similar to the previous section, which leads to $\varepsilon_{AB} = 2.2$, $\lambda_{AW} = 0.8$, and $\lambda_{BW} = 1.0$. We have also verified that this set of interaction parameters results in equilibrium concentric lamellae at $T = 2.0$, which is above the glass transition temperatures of both A and B blocks.

### 4.2 Results and discussion

We mapped the low-$M$ PS-b-PI to our model and obtained $N = 48$ with $N_A = 23$ and $N_B = 25$. Simulations of these chains in a bulk system resulted in a phase separated system with a lamellar period of $L = 20 \text{nm}$, which is in good agreement with the experiments. For the sake of computational efficiency, we performed the majority of our simulations with slightly shorter chains where $N = 23$, $N_A = 11$, and $N_B = 12$ (A$_{11}$B$_{12}$) with the same interactions as the longer chains. While these shorter chains result in a system with a smaller lamellar period of $L \approx 13.6 \text{nm}$, the morphologies produced are in qualitative agreement with those observed experimentally. The smaller chain length enables us to access the morphologies and dynamics of larger colloids over longer times to allow more direct comparisons with experimental results. Simulations of an increasing number of chains in the system, from 256 to 65,536 chains, are presented alongside the experimental data in Figure 4.1(a). It can be seen that the lamellar period remained constant at $L = 13.6\pm 0.4 \text{nm}$ [Figure 1(c)] as the particle diameter increased, qualitatively matching the results of experiments using low-$M$ block copolymer in the FNP feed stream.

With agreement between experiments and simulations for a low-$M$ block copolymer system, the agreement of higher $M$ systems was then tested. It was observed in the experiments that for a solution of a higher $M$ PS-b-PI block copolymer ($M_n =$
Figure 4.1: (a) In experiments and simulations of low-\(M\) diblock copolymers, as colloid radius (\(a, \text{nm}\)) increased, the lamellar period (\(L, \text{nm}\)) remained nearly constant. Red scale bars in transmission electron microscopy (TEM) images are 200 nm, and blue scale bars in simulation snapshots are 50 nm. (b) In experiments, lamellar period remained constant at \(L \approx 18.2 \text{ nm}\), indicated by the red arrows, and (c) in simulations remained constant at \(L \approx 13.6 \text{ nm}\), indicated by the black arrows. The smaller lamellar period in simulations is due to the shorter chains used. Dark gray regions in TEM images are PI stained with OsO\(_4\). In MD simulations, PS is blue and PI is red. Snapshots rendered using Visual Molecular Dynamics 1.9.2.\(^{89}\)

118-\(b\)-107 kg/mol) with an increase in \(\chi N\) to approximately 174, the resulting colloids adopted lamellar structures with a constant lamellar period of \(L \approx 71.0 \text{ nm}\) at all concentrations tested (Figure 4.2b), consistent with small-angle X-ray scattering measurements of \(L \approx 77 \text{ nm}\). However, the lamellae were no longer consistently oriented in concentric layers, as they were when prepared from lower-\(M\) block copolymer. Rather, defects in the phase separated structures led to a disordered lamellar morphology, as has been previously observed in block copolymer films.\(^{99-101}\) In one example, spin-coated films of cylinder-forming polystyrene-\(b\)-poly(n-hexyl methacrylate) block copolymers (PS-\(b\)-PHMA) formed polygrain structures with defects.\(^{102,103}\) In our system, the change in morphology from concentric lamellar to disordered lamel-
lar upon an increase in $M$ with no change in the chemical identities of the two blocks may have its roots in the increase in $\chi N$ and the resulting slower chain diffusion.

Figure 4.2: (a) Colloid radius ($a$, nm) increased with concentration of polymer in the FNP feed stream, for high-$M$ diblock copolymer. Red scale bars in TEM images are 200 nm. (b) In experiments, lamellar period remained constant at $L \approx 71$ nm, indicated by the red arrows. (c) Simulation results show a disordered lamellar internal structure at various particle sizes, corresponding to different numbers of high-$M$ diblock copolymer chains in the initial simulation box. Blue scale bars in the simulation snapshots are 50 nm. (d) The lamellar period in simulations remained constant at $L \approx 13.6$ nm, indicated by the black arrows. $L$ is smaller than the experimentally observed value because a shorter chain of $N = 23$ was studied here in order to access the range of particle sizes studied in the experiments. Dark gray regions in TEM images are PI stained with OsO$_4$. In MD simulations, PS is blue, and PI is red.

In order to elucidate the mechanism behind this change in morphology upon increasing $M$, we again turned to MD simulations. When simulating the phase separation of block copolymers in bulk, we observed three stages of phase separation from a disordered state: microphase separation, domain coarsening, and defect annealing, illustrated in Table 1 (a-d). Microphase separation, where there is clear separation of A and B domains in the system, and domain coarsening, where lamellar structures start to emerge on a local scale, were complete on the order of 110 s for the systems studied. In contrast, defect annealing could take up to several milliseconds, or
34 orders of magnitude longer than initial microphase separation, to achieve longer-ranged order and a perfect lamellar structure. We compared time scales for phase separation of block copolymers with increasing values of $\chi N_{\text{eff}}$ by increasing either the chain length, $N$, or the incompatibility between A and B blocks (decreasing $\varepsilon_{\text{AB}}$). As shown in Table 4.1, increasing values of $\chi N$ lead to slower defect annealing, which can be explained by a higher energy barrier.\textsuperscript{104} In addition, we also studied chains with lengths between $N = 23$ and 64 at constant $\chi N_{\text{eff}} = 16.8$ since previous simulations\textsuperscript{105,106} have indicated that the reduced parameter $\chi N$ is not sufficient to describe different block copolymers. Here, we found that the time required for all stages of phase separation increased with $N$, which can be attributed to the slower dynamics of longer chains. These two effects slow down phase separation and explain the disordered lamellar structures observed for high-$M$ block copolymers in the experiments. The time scales reported in Table 4.1 were estimated both by visual inspection and by tracing the structure factor of the system.\textsuperscript{107,108} Each value was obtained from 3 independent runs.

While it is computationally too taxing to directly simulate colloid formation from the high-$M$ block copolymer where the chain length would be $N = 350$, the slower dynamics of the high-$M$ system can be mimicked by imparting glassy dynamics to one of the blocks. Here, the glassy dynamics mimic the increase in viscosity that chain entanglements would cause at higher $M$. Glassy dynamics were achieved by tuning the intraspecies interaction parameters of A and B blocks so that B was glassy, while A remained rubbery at the temperature of the simulations. The glassy dynamics were assigned to only the PS blocks although both PS and PI of the high-$M$ block copolymer should exhibit slower dynamics in the experiments compared to their low-$M$ counterpart. This approximation was done because having both blocks glassy would slow down the dynamics too much and thus limit the degree of phase separation accessible to the simulation time scale. Therefore, only the PS blocks, which have
a significantly higher glass transition temperature than PI, were made glassy in the simulations to illustrate the effect of slow dynamics on phase-separated morphologies. Preformed spherical colloids with well-mixed, disordered A and B segments were prepared as the initial structures and allowed to evolve for up to 0.5 ms in physical time. As can be seen in Figure 4.2(c) and 4.2(d), the structures were unable to evolve to concentric lamellae, and they matched the experimentally obtained morphology of disordered lamellar colloids with a constant lamellar period as the colloid diameter increased. We therefore conclude that the slower dynamics of the higher $M$ chains, due to the higher viscosity of the system, impede the defect annealing necessary to form concentric lamellar colloids in the limited mixing time provided by FNP, thus leading to colloids with disordered lamellar internal morphologies.

Having examined the effect of varying $\chi N$ in systems of pure block copolymers by increasing $M$ and slowing the chain dynamics, we then added complexity to our system by incorporating homopolymers in the feed stream. While extensive research has been performed on the phase behavior of block copolymer and homopolymer blends in thin films and in bulk, less has been done to exploit the confinement of a colloid to generate new morphologies.

The effect of added homopolymer was explored in the experiments by introducing a homopolymer polystyrene (hPS, $M_n = 16.0$ kg/mol) into the feed stream with the low-$M$ PS-\textit{b}-PI block copolymer ($M_n = 16.1$-$b$-$11.2$ kg/mol) so that the $M$ of the hPS was matched to the $M$ of the PS block of the copolymer. The volume fraction of homopolymer in the system, $\Phi$, was varied from 0, where there is no hPS, to $\Phi = 0.414$ with $\alpha$ held constant at 0.482. As seen in Figure 4.3(a), for values of $\Phi$ from 0 to 0.2, the morphology remained concentric lamellar, while for $\Phi > 0.25$, the morphology transitioned into disordered and then micellar morphologies. In Figure 4.3(b) TEM images of over 100 particles, within the range of ratios for which a concentric lamellar morphology was observed. As homopolymer was added to the system, the lamellar
Table 4.1: Cross Interaction of Phases ($\varepsilon_{AB}$), $\chi$, Chain Length ($N$), and $\chi N_{\text{eff}}$ and Estimated Time ($\mu$s) To Achieve Each Stage of Phase Separation$^a$

<table>
<thead>
<tr>
<th>$\varepsilon_{AB}$</th>
<th>$\chi$</th>
<th>$N$</th>
<th>$\chi N_{\text{eff}}$</th>
<th>Microphase Separation</th>
<th>Domain Coarsening</th>
<th>Defect Annealing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>3.4</td>
<td>12</td>
<td>22.2</td>
<td>0.08</td>
<td>0.3</td>
<td>390</td>
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<tr>
<td>0.7</td>
<td>3.4</td>
<td>23</td>
<td>36.3</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>3.4</td>
<td>48</td>
<td>68.5</td>
<td>0.6</td>
<td>5</td>
<td>1000</td>
</tr>
<tr>
<td>0.7</td>
<td>3.4</td>
<td>64</td>
<td>89.2</td>
<td>4</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>0.92</td>
<td>0.8</td>
<td>48</td>
<td>16.8</td>
<td>0.5</td>
<td>7</td>
<td>157</td>
</tr>
<tr>
<td>0.9</td>
<td>1.1</td>
<td>48</td>
<td>21.5</td>
<td>0.35</td>
<td>10</td>
<td>330</td>
</tr>
<tr>
<td>0.8</td>
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<td>48</td>
<td>36.3</td>
<td>0.3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>3.4</td>
<td>48</td>
<td>68.5</td>
<td>0.6</td>
<td>5</td>
<td>1000</td>
</tr>
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<td>4</td>
<td></td>
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<td>0.3</td>
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<td>43</td>
</tr>
<tr>
<td>0.92</td>
<td>0.8</td>
<td>48</td>
<td>16.8</td>
<td>0.5</td>
<td>7</td>
<td>157</td>
</tr>
<tr>
<td>0.94</td>
<td>0.6</td>
<td>64</td>
<td>16.8</td>
<td>6</td>
<td>19</td>
<td>800</td>
</tr>
</tbody>
</table>

$^a$Illustrations show the stages in bulk phase separation of block copolymers: (a) initial disordered state, (b) microphase separation, (c) domain coarsening, and (d) annealing of defects. The estimated time scales have a 10% to 30% statistical uncertainty. $\chi N_{\text{eff}}$ values were calculated using the method outlined by Chremos et al., and they are the effective segregation parameter of our coarse-grained model.

The spacing increased from $L_0 = 18.2$ nm to $L = 25.7$ nm when $\Phi$ was raised to 0.2, an increase of 41%.

A similar trend in the lamellar period was observed when increasing $\Phi$ in the MD simulations for blends of a rubbery block copolymer, $A_{11}B_{12}$, and homopolymer $A_{11}$. Results are shown side by side with experimental data in Figure 4.3(a) and 4.3(b). Upon close examination, snapshots of the MD simulation reveal that the homopolymer chains were located within the PS lamellar domains at low volume fractions of PS, which can also be seen by plotting the fraction of PS and PI components, $F$, vs distance to the colloid center, $R$, in Figure 4.3(c). This finding is also consistent with
experimental studies in bulk films where the addition of low concentrations of hPS in the system swells the lamellar period. The transition from a lamellar to disordered or micellar morphology with increasing Φ was also observed in our MD simulations where the homopolymer chains encapsulated the block copolymer micelles. This transition has been predicted and observed for moderate values of $\chi N$ in bulk and can be explained by free energy arguments. In bulk systems, the addition of a small amount of homopolymer to a block copolymer first swells the similar block, creating undulations in the lamellar structure and incurring free energy penalties. At a tipping point, the penalty from perturbing the copolymer chains is greater than the penalty from the curvature produced, and the morphology transitions first to a disordered and then a micellar phase as the interface between the phases adopts a more extreme curvature.

4.3 Conclusions

Using a simple system of homopolymers and symmetric diblock copolymers, a wide variety of colloid morphologies has been generated via the cost-effective, scalable, and flexible FNP process. For example, concentric lamellar and disordered lamellar structures were obtained from low-$M$ and high-$M$ symmetric diblock copolymers. Adding a low-$M$ homopolymer at high volume fraction to the diblock copolymers in the feed stream gave rise to micellar structures. MD simulations have been employed to provide a microscopic understanding of the phase separation behavior observed in experiments on length and time scales that cannot be directly observed experimentally. Future studies will aim to further explore the morphology space by varying the number of blocks, the length, and the ratio of the blocks in the copolymer and to move toward using these complex colloid morphologies for encapsulation and controlled release applications.
Figure 4.3: (a) TEM images and cross sections of MD simulated colloids at increasing volume fractions of homopolymer, $\Phi$. Colloids from experiments are shown for $\Phi = 0.12, 0.38$, and 0.57. Cross sections of colloids from MD simulations are shown for $\Phi = 0.15$ and 0.60. At $\Phi \approx 0.1$, colloids were concentric lamellar. As $\Phi$ increases, colloids transitioned to disordered and then micellar morphologies where the homopolymer encapsulated micelles of the block copolymer. The PS and PI chains from the block copolymers are colored blue and red, respectively, and the PS homopolymers are colored yellow. In TEM images, scale bars are 200 nm, and dark gray regions are PI domains stained with OsO$_4$. (b) Lamellar period, $L$, reduced by its value at $\Phi = 0$, vs. $\Phi$ for concentric lamellar structures. (c) Fraction of each species (PS and PI in block copolymers, and PS homopolymers), $F$, vs distance to the nanoparticle center, $R$, for $\Phi = 0.1$ from MD simulations.
Chapter 5

Self-assembly of a binary homopolymer blend and inorganic nanoparticles*

Hybrid nanomaterials which consist of metal, semiconducting or magnetic nanoparticles (NPs) dispersed in various polymeric matrices have potential applications in a broad range of areas, including optics, electronics, sensors, catalysis, imaging, and pharmaceuticals. \textsuperscript{112–115} The selective localization of NPs in different domains of the aggregates, such as cores, surfaces, and interfaces between polymer domains, may critically affect the properties and applications of these materials. For example, encapsulation of quantum dots (QDs) in the core of polymer micelles improves their stability and reduces their toxicity in biological environments. \textsuperscript{116} Such hybrid materials are also potentially useful in labeling and imaging applications. Further, Janus nanoparticles with one or both domains modified with metal NPs are excellent interfacial catalysts for reactions in biphasic systems with controlled phase selectivity. \textsuperscript{7–9}

*This chapter is based on: Nannan. Li, Arash Nikoubashman, and Athanassios Z. Panagiotopoulos, Self-assembly of polymer blends and nanoparticles through rapid solvent exchange. \textit{Langmuir} \textbf{2019}, \textit{in press}. 
Two primary methods have been widely employed for incorporation of NPs into polymeric aggregates. The first one involves \textit{in situ} formation of metal NPs using chemical reactions,\textsuperscript{117–119} and the second one is the co-assembly of polymers and NPs.\textsuperscript{13–15,120–122} The second approach is suitable for a wider range of polymer and NP systems, and offers more precise control in NP size and position. In this work, we study a co-assembly technique named Flash NanoPrecipitation (FNP), where a polymer solution and NPs are rapidly mixed with an excess amount of a miscible non-solvent to induce supersaturation and aggregation.\textsuperscript{34,35,40} FNP is a continuous and scalable process which has low energy consumption, and is able to produce narrowly distributed aggregates with tunable size, morphology, and NP loading.

Previous efforts have focused on studying the incorporation of hydrophobic drugs, QDs, and metal NPs into either the core or the surface of block copolymer micelles using FNP.\textsuperscript{36,37,123–125} Recently, it was demonstrated that, Janus nanocolloids with controlled surface decoration could also be obtained from the FNP process using commercially available homopolymer blends and gold NPs (AuNPs).\textsuperscript{44} In addition to Janus structures, it has been shown in both experiments and simulations that FNP can also be used to generate core-shell and patchy structures with reliable control over size, composition, and morphology,\textsuperscript{42,43,45,88,126} which greatly expands the number of accessible hybrid architectures if NPs are included in the feed streams.

Given the extensive parameter space involved, such as polymer and solvent types, NP chemistry and size, polymer and NP feed concentrations, etc., simulations are a useful tool for guiding experiments and predicting assembly morphologies. Numerous theoretical and computational studies have been reported, mainly focusing on the self-assembly of block copolymers and NPs through solvent evaporation or gradual addition of a poor solvent to a solution of polymers and NPs.\textsuperscript{127–135} For example, a study which combined experiments and self-consistent field theory calculations showed that the location of AuNPs in vesicle walls or spherical micelles depends on the size...
of NPs and is an entropically driven process.\textsuperscript{128} In another study, molecular dynamics (MD) simulations were used to relate molecular design of block copolymers and NPs, such as the solvophobicity and composition of block copolymers, and NP size and concentration, to the location and quantity of NPs in the hybrid micell structures.\textsuperscript{131} However, systems which involve binary hydrophobic polymer blends and NPs have not been studied before.

In the present work, we are inspired by the wide range of structures that can be potentially obtained from binary polymer blends and NPs undergoing the FNP process,\textsuperscript{42–44,88,126} and use MD simulations to explore the parameter space. Our previous computational studies on binary polymer blends undergoing FNP in the absence of NPs have explained how the morphology, size and composition of the polymeric aggregates can be controlled through the types of feed polymers, and processing parameters specific to the FNP technique, \textit{e.g.}, mixing rate and polymer feed concentration and ratio.\textsuperscript{88,126,136} In the present study, we shift our focus to how NP localization, loading and surface density can be tuned in the precipitated hybrid structures. These factors will play significant roles in determining the properties and performance of the hybrid colloids. The remainder of this paper is structured as follows: we first introduce the MD simulation model and methods used in the present work. Next, we present our simulation results, and examine how the above-mentioned properties of the hybrid structures can be independently controlled by the interaction strengths between different species and the feed concentrations of polymers and NPs. Lastly, we summarize our results and comment on their implications.

### 5.1 Simulation model and methods

Our previous MD model for binary polymer blends undergoing the FNP process serves as a foundation for our current study.\textsuperscript{88} In this model, a polymer is described as a
linear bead-spring chain with $N$ beads, each with unit diameter $\sigma$ and unit mass $m$. Each bead represents a Kuhn segment of the polymer chain. We used $N = 23$ for all homopolymer chains in our simulations, which corresponds to, e.g., polystyrene (PS) chains with a molecular weight of 16.5 kg/mol. 42,44

The bonded interactions between polymer beads are modeled via the FENE potential 55 with the standard Kremer-Grest parameters to prevent unphysical bond crossing. 56 In addition to the bonded interactions, polymer beads also interact with one another via the standard LJ potential.

Binary polymer blends (of type A and B) have been considered in the current work. We set the prefactor of the LJ potential, $\epsilon_{\text{LJ}}$, for the intraspecies interaction of both polymer A and polymer B equal such that $\epsilon_{\text{AA}} = \epsilon_{\text{BB}} = k_B T$, with Boltzmann constant $k_B$ and temperature $T$. The interspecies A-B interaction strength, $\epsilon_{\text{AB}}$, was varied between $0.9\epsilon_{\text{AA}}$ and $0.3\epsilon_{\text{AA}}$, to represent the chemical incompatibility of the two polymer types. The cutoff radius of the LJ potential was set to $r_{\text{cut}} = 3.0\sigma$.

Following Ref. 41, solvent particles are modeled explicitly as LJ particles with the same size and mass as the polymer beads. A reduced number density of $\rho_S = 0.66$ has been chosen, which leads to a dynamic solvent viscosity of $\eta = 1.01$. Similar to previous computational studies on FNP, 38,39,41,88,126 the transition from good to poor solvent conditions was mimicked by varying the non-bonded particle interactions. In our studies, we control the interaction between solvent particles and monomers by a dimensionless parameter $\lambda$ according to Eqn. (2.2). In this work, we chose the values of $\lambda$ for good and poor solvent conditions to be 0 and 0.5, respectively.

In order to make meaningful comparisons between our simulations and experimental results, it is important to establish a connection between units of energy, length, and time in the two domains, which has been done in Ref. 41 for the homopolymer-solvent model. For our model, we found $\epsilon = 4.11 \times 10^{-21}$ J, $\sigma = 1.5$ nm, and $\tau = 0.28$ ns for the characteristic energy, length, and time scales, respectively.
NPs are modeled as spherical clusters of LJ beads of the same size and mass as chain monomers and solvent particles, forming spheres of diameter $\sigma_{NP}$. In experiments, the diameter of AuNPs is approximately 10 nm, $^{44}$ which corresponds to roughly 6 $\sigma$ in simulation units. However, the typical radii of the polymeric aggregates, $a$, obtained in the simulations (assumed to be approximately 1.3 times the radius of gyration $^{41}$) are between 25 to 30 nm, which are significantly smaller than the values of 100 to 200 nm obtained in the experiments. We have thus chosen $\sigma_{NP} = 2\sigma = 3.0$ nm in the simulations (2 times the diameter of a monomer or a solvent particle), so that $\sigma_{NP}/a$ is approximately 0.1, which is close to the experimental values.

The NP clusters are considered to be uniform spheres of unit reduced density, $\rho_* = \rho_{NP}/\sigma^3$, where $\rho_{NP}$ is the number density of LJ beads within each NP, and set to $\sigma^{-3}$. The potential between NPs is determined by integrating over all LJ particles in the two interacting NPs and has the form: $^{137}$

$$U_{NP,NP}(r) = U_A(r) + U_R(r). \quad (5.1)$$

The attractive component, $U_A(r)$, is

$$U_A(r) = -\frac{H_{NP,NP}}{6} \left[ \frac{\sigma_{NP}^2}{2(r^2 - \sigma_{NP}^2)} + \frac{\sigma_{NP}^2}{2r^2} + \ln \left( \frac{r^2 - \sigma_{NP}^2}{r^2} \right) \right], \quad (5.2)$$

and the repulsive component, $U_R(r)$, is

$$U_R(r) = \frac{H_{NP-NP}}{37800} \sigma^6 \left[ \frac{r^2 - 7r\sigma_{NP} + 27\sigma_{NP}^2/2}{(r - \sigma_{NP})^7} + \frac{r^2 + 7r\sigma_{NP} + 27\sigma_{NP}^2/2}{(r + \sigma_{NP})^7} - \frac{2(r^2 - 15\sigma_{NP}^2/2)}{r^7} \right]. \quad (5.3)$$

The cut-off radius of $U_{NP,NP}$ was set to $5.5\sigma$. $H_{NP-NP}$ is the Hamaker constant and $H_{NP-NP} = 4\pi^2\varepsilon_{NP}$, where $\varepsilon_{NP}$ is the prefactor of the LJ interaction between the constituent beads of the NPs. To determine the value of $H_{NP-NP}$, we considered
the equivalent Hamaker constant between polymeric aggregates in our simulations, which has a value of $4\pi^2 k_B T$, because polymeric aggregates consist of standard LJ beads with $\varepsilon_{AA} = \varepsilon_{BB} = k_B T$. Since the experimentally measured Hamaker constant of Au is approximately 5 times that of PS,$^{138}$ we chose $\varepsilon_{NP} = 5k_B T$, which led to $H_{NP-NP} = 20\pi^2 k_B T$.

The potential between an NP and a polymer bead or a solvent particle is given by:\(^{137}\)

$$U_{NP,P/S}(r) = \frac{\sigma_{NP}^3}{36(\sigma_{NP}^2/4 - r^2)^3} \left[ 1 - \frac{(5\sigma_{NP}^6/64 + 45\sigma_{NP}^4 r^2/16 + 63\sigma_{NP}^2 r^4/4 + 15r^6) \sigma_{NP}^6}{15(\sigma_{NP}/2 - r)^6 (\sigma_{NP}/2 + r)^6} \right],$$

(5.4)

where $H_{NP-P/S} = 24\pi \varepsilon_{NP-P/S}$. The cutoff radius of $U_{NP,P/S}$ was set to $5.0 \sigma$. Experimentally, the surface of NPs can be modified by different chemical groups, which gives rise to either hydrophobic or hydrophilic NPs.$^{113}$ In our simulations, we varied $\varepsilon_{NP-P}$ and $\varepsilon_{NP-S}$ between $0.025k_B T$ and $5k_B T$ to control the NP-polymer and NP-solvent affinities. When $\varepsilon_{NP-S} = k_B T$ and $\varepsilon_{NP-P} = k_B T$, i.e., the LJ beads that formed the NPs interact with the solvent particles and monomers with an equal strength as the solvent particles and monomers interact with themselves, the NPs aggregate in the solvent and the polymer matrix. NP-solvent and NP-polymer miscibility occur at approximately $\varepsilon_{NP-S} = 1.5k_B T$ and $\varepsilon_{NP-P} = 2.5k_B T$ for the chosen $H_{NP-NP}$ of $20\pi^2 k_B T$.

In addition to electroneutral NPs and polymers, we also considered charged NPs and polymers with charged end groups. In previous experiments, AuNPs stabilized by citrate groups were shown to electrostatically interact with amine-terminated PS polymer chains, so that the NPs were dispersed exclusively on the PS domain of the aggregates.$^{44}$ In our simulations, the end groups were modeled by the last bead of every polymer chain. The screened electrostatic interaction between the NPs and the
charged end groups is given by:\textsuperscript{139}

\[
U_{\text{Yukawa}}(r) = \lambda_B \left( \frac{Z_{\text{EG}} e^{\kappa \sigma/2}}{1 + \kappa \sigma/2} \right) \left( \frac{Z_{\text{NP}} e^{\kappa \sigma_{\text{NP}}/2}}{1 + \kappa \sigma_{\text{NP}}/2} \right) e^{-\kappa r} \frac{1}{r},
\]  (5.5)

where \( \lambda_B \) is the Bjerrum length, and \( \kappa \) is the inverse Debye screening length, \( \lambda_D \). For water with pH = 7 at room temperature, we used \( \lambda_B = 0.7 \text{nm} \), and \( \lambda_D = 0.15 \mu\text{m} \).\textsuperscript{41} The parameters \( Z_{\text{EG}} \) and \( Z_{\text{NP}} \) denote the charges of the end groups and the NPs, respectively. For amine end groups and citrate stabilized AuNPs studied in the experiments, \( Z_{\text{EG}} = +e \) and \( Z_{\text{NP}} = -3e \). These values translate to 6.1 and -18.3 in our simulations, respectively, where the unit of charge is \((4\pi E_0 \sigma \varepsilon)^{1/2}\), and \( E_0 \) is the vacuum permittivity.

The MD simulations were run using the HOOMD-blue simulation package.\textsuperscript{60,61} A cubic box with an edge length of 80\( \sigma \) was adopted, containing a total of up to 2,048 polymers. An A:B ratio of 1:1 was chosen throughout this paper. The only exception was the simulation snapshot shown in Figure 5.5(c), where a ratio of 2:1 was chosen to facilitate a comparison with previous experiments also performed with a 2:1 ratio.\textsuperscript{44} The number of NPs in the system varied between 100 to 2000 (the remaining volume of the box was filled with solvent particles to reach the desired density of \( \rho_S = 0.66 \)). We have checked the influences of box size on simulation results at selected state points and did not find any appreciable finite size effects when the box edge length is above 80\( \sigma \). It is noted that the total number of 1,024 polymers in our systems limits the maximum aggregate size to \( a \approx 28\text{nm} \), which is one order of magnitude smaller than those produced in the experiments. To realize in the simulations an aggregate with a radius of \( a = 100\text{nm} \), approximately \( 10^5 \) polymers and \( 10^7 \) solvent particles are required, which is computationally infeasible. Despite this limitation, however, the employed model is useful for predicting morphologies and it is able to reproduce the most important trends observed in the experiments.\textsuperscript{41,88}
thermostat was employed to maintain the temperature at $T = 1.0$ and the equations of motion were integrated at a timestep of $\Delta t = 0.01$ in the reduced units defined earlier. Measurement uncertainties of the results presented in the following section were determined from the standard error of the mean from three independent runs.

In our previous MD simulations,\textsuperscript{41,88} a negative surface potential was applied to all the aggregates to mimic the effect of charge stabilization on the precipitated aggregates. Since the effect of this surface potential on aggregate size has been elucidated in our previous studies and we are mainly concerned with understanding the equilibrium morphologies that can arise from the polymer-NP-solvent systems, such a negative surface potential is not included in the current work. In our simulations, the systems were allowed to evolve until one single polymeric aggregate remained, and this approach enabled us to access larger aggregates with a wider range of NP loading and surface density despite the limited system size accessible to our simulations. Typical simulations were run up to $10^7$ timesteps until equilibrium structures were achieved, which corresponds to approximately 28 $\mu$s, using the time scales developed in Ref. 88 for the homopolymer-solvent model.

### 5.2 Results and discussion

We first present results on particle morphology as a function of affinities between the different constituents in the system. Affinities are represented by the values of the Hamaker constant, which can be calculated using the relationship $H = 4\pi^2\varepsilon$ as mentioned in the previous section, where $\varepsilon$ is the prefactor of the LJ interaction between the constituent beads of the two interacting bodies. Considering the large parameter space, we first kept the A-B cross interaction and polymer-solvent interaction constant at $H_{A-B} = 1.5 \times 10^{-19}$ J, and $H_{A-S} = H_{B-S} = 8 \times 10^{-20}$ J. Here, we chose polymers A and B to have equal affinities to the solvent (the effect of $H_{P-S}$ on the equilibrium
morphologies will be discussed further below). Therefore, we use the notation $H_{P-S}$ to represent the identical Hamaker constants between both types of polymer beads and the solvent in the remainder of this paper, i.e., $H_{A-S} = H_{B-S} = H_{P-S}$. This combination of interaction strengths gives rise to Janus aggregates in the absence of NPs.$^{88}$ In this work, we focus on the dispersion of NPs in Janus aggregates, because such particles have been produced in previous experiments using FNP,$^{44}$ and they have potential applications in catalysis. $H_{NP-NP}$ was set to $8.1 \times 10^{-19}$ J as explained in the previous section. We varied systematically the NP-polymer and NP-solvent Hamaker constants, i.e., $H_{NP-P}$, and $H_{NP-S}$. The NPs are first chosen to be non-selective to either polymer A or B, as we are interested in controlling the radial distribution of NPs in the polymer matrix, i.e., surface, interior or A-B interface. The case when NPs are selectively localized on one polymer domain will be studied in a subsequent section.

The initial configurations consisted of polymer chains and NPs homogeneously distributed in the solvent. After an equilibration period at good solvent conditions ($\lambda = 0$), $\lambda$ was set to 0.5. Unlike our previous studies,$^{41,88}$ we changed the solvent conditions instantaneously, and did not consider the effect of mixing rate. We followed this procedure, because the mixing rate has been shown to affect only the final size of the aggregates for the FNP process.$^{41,88,136}$ In the current work, we are interested in the equilibrium morphologies of the hybrid aggregates, and have thus chosen the instantaneous mixing condition for simplicity.

The morphology diagram obtained from varying NP-solvent affinity ($H_{NP-S}$) and NP-polymer affinity ($H_{NP-P}$) is presented in Figure 5.1. Each point in the morphology diagram corresponds to a simulation result. It can be seen that NPs are distributed either (1) on the surface, (2) in the interior of the polymeric aggregates, or (3) they remain dispersed in the solution. When the difference between $H_{NP-S}$ and $H_{NP-P}$ is small, NPs locate on the surface, as shown by regions (I) and (II). Within regions

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(I) and (II), the degree of dispersion can be controlled by the values of $H_{\text{NP-S}}$ and $H_{\text{NP-P}}$. When both values are large, NPs are uniformly dispersed on the surface of the aggregates to maximize contact with both the polymers and the solvent. However, for small $H_{\text{NP-S}}$ and $H_{\text{NP-P}}$, NPs aggregate on the surface of the polymeric aggregate. When either $H_{\text{NP-S}}$ or $H_{\text{NP-P}}$ is significantly higher than the other, NPs are distributed in the energetically more favorable domain, i.e., inside the polymer aggregate (III) or in the solvent (IV).

![Morphology diagram](image)

Figure 5.1: Morphology diagram for different values of $H_{\text{NP-S}}$ and $H_{\text{NP-P}}$. Other interaction parameters are kept constant at $H_{\text{NP-NP}} = 8.1 \times 10^{-19}$ J, $H_{\text{A-A}} = H_{\text{B-B}} = 1.6 \times 10^{-19}$ J, $H_{\text{A-B}} = 1.5 \times 10^{-19}$ J, and $H_{\text{P-S}} = 8 \times 10^{-20}$ J. The triangles and the circles represent equilibrium morphologies with NPs dispersed and aggregated on the surface of the aggregates, respectively. The pentagons represent morphologies with NPs distributed in the interior, and the squares represent no aggregation between polymers and NPs. Approximate boundaries between the regions are indicated by dashed lines for visual clarity. Beads of polymers A and B are represented by the red and blue particles, respectively, while the AuNPs are shown as golden spheres. The same coloring scheme has been used for all other simulation snapshots as well. The snapshots show the cross sections of the equilibrium morphologies, and are produced using VMD.

To understand the morphology diagram in more detail, we consider the following structural properties of the aggregates:
(1) Fraction of NP uptake from the solution, \( f_{\text{NP}} = \frac{N_{\text{NP}}}{N_t} \), where \( N_{\text{NP}} \) is the total number of NPs that are attached to the aggregate, and \( N_t \) is the total number of NPs in the simulation box.

(2) Surface density of NPs on the aggregates, \( S_{\text{NP}} = \frac{N_{\text{NP},s}}{A} \), where \( N_{\text{NP},s} \) is the number of NPs on the surface of an aggregate, and \( A = 4\pi a^2 \) is the surface area of the aggregate. The surface NPs were identified by counting the number of surrounding monomers. For our systems, we determined that NPs are located on the surface when they have 20 or fewer nearest neighbors.

(3) Volume fraction of NPs at the A-B interface, \( f_i = \frac{8N_{\text{NP},i}}{N_{M,i}} \), where \( N_{\text{NP},s} \) and \( N_{M,i} \) are the numbers of NPs and monomers at the A-B interface region, respectively. The factor 8 arises from the volume ratio of a single NP and a single monomer in our simulations. The interface monomers were identified by taking all the monomers that have at least one bead of an opposite type in their immediate neighborhood. We divided \( N_{\text{NP},s} \) by \( N_{M,i} \) to take into account the decreasing A-B interfacial area in the aggregates with decreasing A-B interaction strength.

(4) Aspect ratio of the aggregates, \( \alpha = \frac{L_3}{L_1} \), where \( L_3 \) and \( L_1 \) are the largest and smallest eigenvalues of a particle’s radius of gyration tensor, respectively. A spherical aggregate has \( \alpha = 1 \).

In Figure 5.2, we plot the fraction of NP uptake, \( f_{\text{NP}} \), as a function of \( H_{\text{NP-P}} \) for different \( H_{\text{NP-S}} \) values. The results were obtained from initial configurations with a constant polymer feed concentration of \( 5.7 \times 10^{-4} \text{ nm}^{-3} \), and NP concentration of \( 5.6 \times 10^{-4} \text{ nm}^{-3} \), which leads to a pure polymeric aggregate to NP volume ratio of approximately 3. It can be seen that \( f_{\text{NP}} \) increases monotonically with \( H_{\text{NP-P}} \), and lower \( H_{\text{NP-S}} \) leads to more efficient NP uptake from the solution.

Next, we study the effects of \( H_{\text{NP-S}} \) and \( H_{\text{NP-P}} \) on the surface density of NPs, \( S_{\text{NP}} \). It can be seen in Figure 5.3 that a decrease in \( H_{\text{NP-S}} \) leads to higher \( S_{\text{NP}} \), which is similar to the trend in \( f_{\text{NP}} \). However, the maximum NP surface density only occurs
Figure 5.2: Fraction of NP uptake from the solution, $f_{NP}$, as a function of $H_{NP-P}$ for different $H_{NP-S}$ values, as indicated. Error bars are shown only when they are larger than symbol size.

at a $H_{NP-P}$ value comparable to the corresponding $H_{NP-S}$. Further increase in $H_{NP-P}$ results in an increasing number of NPs locating in the interior of the aggregates and a decrease in $S_{NP}$ as shown by the simulation snapshots.

In addition, higher $H_{NP-P}$ also gives rise to larger and more spherical aggregates as shown in Figure 5.4. When the NPs are dispersed on the surface of the aggregates, they lower the surface tension between polymers and solvent, and increase the area of contact between the aggregate and the solvent, which explains the higher $\alpha$ compared to polymeric aggregates without NP (indicated by the dotted line). However, as $H_{NP-P}$ increases, NPs locate increasingly at the interior of the aggregates, which gives rise to larger aggregates. The internal NPs, which show equally high affinities to both polymer types, improve the compatibility between the immiscible polymer blend and lead to more spherical aggregates.

So far, we have kept the polymer-solvent interaction ($H_{P-S}$) and polymer cross interaction ($H_{A-B}$) constant. To study the effect of these two parameters, we varied them systematically for two sets of $H_{NP-S}$ and $H_{NP-P}$ values, i.e., $H_{NP-S} = H_{NP-P} =$
Figure 5.3: Number density of NPs on the surface of the aggregates, $S_{NP}$, as a function of $H_{NP-P}$ for different $H_{NP-S}$ values, as indicated. The snapshots show the cross sections of the aggregates taken for $H_{NP-S} = 3.2 \times 10^{-19}$ J. The maximum values of $S_{NP}$ occur at $H_{NP-P} = 3.2 \times 10^{-10}$ J for $H_{NP-S} = 2.8 \times 10^{-10}$ J, $H_{NP-P} = 4.9 \times 10^{-10}$ J for $H_{NP-S} = 3.2 \times 10^{-10}$ J, and $H_{NP-P} = 6.5 \times 10^{-10}$ J for $H_{NP-S} = 4.9 \times 10^{-10}$ J, respectively.

Figure 5.4: Aspect ratio of the aggregates, $\alpha$, as a function of $H_{NP-P}$ for $H_{NP-S} = 3.2 \times 10^{-19}$ J. The dotted line indicates $\alpha$ of an aggregate with the same interactions in the absence of NPs.
3.2 \times 10^{-19} \text{ J}, and \( H_{\text{NP-S}} = 3.2 \times 10^{-19} \text{ J}, H_{\text{NP-P}} = 6.5 \times 10^{-19} \text{ J} \), which correspond to the equilibrium morphologies in regions (I) and (III) shown in Figure 5.1. \( H_{\text{P-S}} \) and \( H_{\text{NP-P}} \) were tuned by the dimensionless solvent parameter, \( \lambda \), and the strength of the A-B cross interaction, \( \varepsilon_{\text{A-B}} \), respectively. From Figure 5.5(a), it can be seen that increasing \( H_{\text{P-S}} \), i.e., decreasing hydrophobicity of the polymers, leads to a decrease in the density of NPs on the surface of the aggregates. In addition, a decrease in \( H_{\text{NP-P}} \) results in A-B interfacial regions more densely occupied by the NPs as shown in Figure 5.5(b).

For the experimental system studied in Ref. 44, which consisted of electroneutral PS, polyisoprene (PI), and AuNPs, with water used as the non-solvent, typical values of Hamaker constants are \( H_{\text{PS-PS}} = 8 \times 10^{-20} \text{ J}, H_{\text{Au-PS}} = 1.7 \times 10^{-19} \text{ J}, H_{\text{Au-Water}} = 1.4 \times 10^{-19} \text{ J}, \) and \( H_{\text{PS-PI}} = 6 \times 10^{-20} \text{ J} \).\(^{138}\) Since \( H_{\text{Au-PS}} \) and \( H_{\text{Au-Water}} \) are similar, our simulations indicate that NPs is expected to be distributed on the surface of the polymeric aggregates (see Figure 5.1). In addition, \( H_{\text{Au-PS}} \) is approximately 3 times larger than \( H_{\text{PS-PI}} \), indicating that a large fraction of NPs on the surface of the aggregates should be at the PS-PI interface. Indeed, it was observed in the experiments that such a PS-PI-Au system gave rise to Janus structures with NPs aligned on the PS-PI interface as shown by the scanning electron microscopy (SEM) image in Figure 5.5(c).

In order to reproduce this structure, we performed additional simulations, where we used the same ratios between the Hamaker constants as in the experiments. (Note that the absolute values of \( H \) in the experiments and simulations differ by a factor of \( H_{\text{PS-PS}}/H_{\text{KT}} \approx 0.5 \).) Similar to the experiments, an A:B ratio of 2:1 was also adopted. It can be seen in Figure 5.5(c) that a structure in qualitative agreement with the experiments was obtained in the simulations. In this case, an increase in polymer-polymer cross interaction relative to the polymer-NP interaction will lead to more uniformly dispersed NPs over the entire surface of the aggregates. An increase in
Figure 5.5: (a) Density of NPs on the surface of the aggregates, $S_{NP}$, as a function of $H_{P-S}$. (b) Volume fraction of NPs at polymer-polymer interface, $f_i$, as a function of $H_{A-B}$. The snapshots show the external views for $H_{NP-S} = H_{NP-P} = 3.2 \times 10^{-19}$ J, which corresponds to the structures with NPs dispersed on the surface of the aggregates. (c) SEM image of colloids obtained from an electroneutral PS/PI homopolymer blend and citrated-stabilized AuNPs undergoing FNP. (Copyright 2017, American Chemical Society.) A snapshot from the MD simulations in this work is also included for comparison. The scale bar is 200 nm for the SEM image and 8 nm for the simulation snapshot.
NP-polymer interaction and a decrease in NP-water interaction, e.g., by using AuNPs functionalized with a hydrophobic group, will lead to an increase in NP uptake from the solution and more NPs at the interior of the polymers.

Having understood the range of morphologies that can arise from the polymer-NP-solvent system by varying the interactions between different constituents, we then studied how NP loading and surface density can be controlled by processing parameters such as polymer feed concentration ($\Phi_P$), NP feed concentration ($\Phi_{NP}$), and polymer to NP volume ratio in the feed streams. Here, we focus on the structures from regions (I) and (III) shown in Figure 5.1, i.e., NPs dispersed either exclusively on the surface or throughout the entire volume of the aggregate.

For structures with NPs dispersed on the surface of the aggregates [region (I) in Figure 5.1], we chose $H_{NP-S} = 3.2 \times 10^{-19}$ J, and $H_{NP-P}$ between $1.2 \times 10^{-19}$ J and $3.2 \times 10^{-19}$ J. Other interaction parameters were chosen to be consistent with those in Figure 5.1. Figure 6(a) shows the dependence of $f_{NP}$ on $\Phi_{NP}$. Here, we prepared initial configurations with a fixed number of polymer chains and varying number of NPs between 100 and 2000. Similarly, we kept the number of NPs constant at, $N_t = 1000$, and varied the number of polymer chains in the range of 288 and 2,048 to understand the dependence of $f_{NP}$ on $\Phi_P$ [see Figure 5.6(b)].

In order to understand the results shown in Figure 5.6, we consider the adsorption of NPs on the surface of the polymeric aggregates:

$$\text{NP + SP } \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \text{NP-SP}, \quad (5.6)$$

where SP are the polymer beads on the surface of the aggregates, which are available for adsorption, and $k_{+1}$ and $k_{-1}$ are the rate constants of adsorption and desorption, respectively. The rate of adsorption, $r_{+1}$, can be represented as $r_{+1} = k_{+1}(1 - f_{NP})\Phi_{NP}(\Phi_{SP} - Bf_{NP}\Phi_{NP})$, where $(1 - f_{NP})\Phi_{NP}$ is the concentration of free NPs in
the solution, and \((\Phi_{SP} - Bf_{NP}\Phi_{NP})\) is the concentration of unoccupied polymer beads on the surface of the aggregates. The parameter \(B\) is a geometric constant which takes into account that a single NP binds to multiple polymer beads, since the NP diameter is twice the monomer diameter. The rate of desorption is \(r_{-1} = k_{-1}f_{NP}\Phi_{NP}\), where \(f_{NP}\Phi_{NP}\) is the concentration of NPs which are adsorbed on the surface of the polymeric aggregate. At equilibrium, \(r_{+1} = r_{-1}\), which leads to

\[
k_{+1}(1 - f_{NP})(\Phi_{SP} - Bf_{NP}\Phi_{NP}) = k_{-1}f_{NP}.
\]  

(5.7)

Solving Eqn. (5.7) for \(f_{NP}\), and choosing the solution which is 0 for \(\Phi_{SP} = 0\) gives rise to

\[
f_{NP} = \frac{(\Phi_{SP} + B\Phi_{NP} + k_{-1}/k_{+1}) - \sqrt{(\Phi_{SP} + B\Phi_{NP} + k_{-1}/k_{+1})^2 - 4B\Phi_{SP}\Phi_{NP}}}{2B\Phi_{NP}}.
\]  

(5.8)

Having derived the dependence of \(f_{NP}\) on \(\Phi_{NP}\) and \(\Phi_{SP}\), we fitted the data in Figure 5.6(a) and (b) according to this relationship. Here, we assumed \(\Phi_{SP} = C\Phi_{P}^{2/3}\), where \(C\) is also a fitted constant. It can be seen from Figure 5.6 that good agreement was obtained between the results from our MD simulations and Eqn. (5.8). We obtained \(B = 5.5 \pm 0.5\), which is close to the ratio of the surface area of an NP to that of a monomer, \(\sigma_{NP}^2/\sigma^2 = 4\). The fitted constant \(C\) can be considered as \(N_{SP}/(V^{1/3}N_{P}^{2/3})\), where \(V\) is the system volume; \(N_{SP}\) and \(N_{P}\) are the numbers of monomers on the surface of the aggregate, and in the entire volume of the aggregate, respectively. We obtained \(N_{SP}/N_{P}^{2/3} = 6.2 \pm 0.6\) from fitting. This value is consistent with the number of surface monomers for aggregates obtained from our simulations. The fitted values of the constants in Eqn. (5.8) are summarized in Table 5.1.

Results in Figure 5.6 show that an increase in the concentration of polymers in the feed stream leads to a more efficient uptake of NPs from the solution. However, increasing the NP concentration results in an increase in the absolute number of ad-
Table 5.1: Estimates for the parameters $B$, $C$, and $k_{-1}/k_{+1}$ and fitted values obtained from fitting the data in Figure 6 according to Eqn. (5.8). The value of $B$ was estimated from the ratio of the surface area of an NP to that of a monomer. $C$ was estimated from counting the number of surface monomers for aggregates obtained from our simulations.

<table>
<thead>
<tr>
<th>Constants</th>
<th>Fitted values</th>
<th>Estimated values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B$</td>
<td>$5.5 \pm 0.5$</td>
<td>4</td>
</tr>
<tr>
<td>$C$</td>
<td>$(6.2 \pm 0.6)/V^{1/3}$</td>
<td>$6/V^{1/3}$</td>
</tr>
<tr>
<td>$k_{-1}/k_{+1}$</td>
<td>0.0005 to 0.1, decreases with increasing $H_{NP-P}$</td>
<td>$&lt; 1$, decreases with increasing $H_{NP-P}$</td>
</tr>
</tbody>
</table>

sorbed NPs as shown by the snapshots in Figure 5.6(a), but a decrease in the relative fraction of uptake. This is because an increase in NP concentration at a constant polymer concentration leads to fewer monomers available for interactions with solvent and other monomers. In addition, the more saturated surface of the aggregate makes it increasingly difficult to take up additional NPs due to the repulsions between NPs. This also explains why the decrease in $f_{NP}$ is more pronounced at higher $H_{NP-P}$, because the surface is more densely occupied by NPs. Therefore, the number of NPs adsorbed does not increase proportionally with the total number of NPs in the system, which gives rise to a decrease in $f_{NP}$. Eqn. (5.8) also allows us to predict the dependence of $S_{NP}$ on $\Phi_{NP}$ and $\Phi_{P}$, since $S_{NP}$ can be estimated to be proportional to $f_{NP}N_{NP}/N_{SP}$.

In addition, we also plot in Figure 5.7 the Gibbs free energy change of the adsorption per NP, $\Delta G$, vs. the strength of NP-polymer interaction, $H_{NP-P}$. $\Delta G$ was calculated using the relationship $k_{-1}/k_{+1} = e^{\Delta G/k_B T}$, and we obtained two sets of values of $k_{-1}/k_{+1}$ from the two independent fitting procedures shown in Figure 5.6(a) and 5.6(b) using Eqn. (5.8). It can be seen that $\Delta G < 0$, which indicates that adsorption is energetically more favorable than desorption for our system. The two sets of data show good agreement, and they can be fitted according to a linear relation-
Figure 5.6: Fraction of NP uptake from the solution, $f_{NP}$, as a function of (a) $\Phi_{NP}$ for constant $\Phi_P$, and (b) $\Phi_P$ for constant $\Phi_{NP}$ for different values of $H_{NP-P}$, as indicated. The solid lines are fits according to Eqn. (5.8). The snapshots in (a) are the external views of the aggregates obtained for $H_{NP-P} = 3.2 \times 10^{-19}$ J and $\Phi_{NP} = 0.0002$ and $0.001$ nm$^{-3}$.

When $H_{NP-P}$ increases further, the NPs aggregate simultaneously with the polymers, and equilibrium structures with NPs dispersed throughout the entire volume of the aggregates are obtained [region (III) in Figure 5.1]. To study the spatial distribution of NPs in this case, we chose the same value of $H_{NP-S} = 3.2 \times 10^{-19}$ J, and $H_{NP-P}$ between $5.6 \times 10^{-19}$ J and $8.1 \times 10^{-19}$ J. We varied systematically the volume fraction of NPs in the final polymer aggregates by increasing the number of NPs while keeping the number of polymer chains constant in the initial configurations.

In Figure 5.8(a), we plot the surface density of NPs on the surface of the aggregates, $S_{NP}$, vs. the volume fraction of NPs in the aggregate, $f_v$. We determined $f_v$ using the relationship $f_v = \frac{8N_{NP}}{8N_{NP} + N_M}$, where $N_M$ is the total number of monomers in the aggregate. The factor 8 that appears in this relationship arises from the volume
Figure 5.7: Gibbs free energy change of adsorption per NP, $\Delta G$, obtained from fitting the two independent sets of data in Figure 5.6(a) and (b), respectively, as a function of $H_{\text{NP-P}}$. The dotted line represents a linear fit to the data. The red data points were obtained from fitting the data shown in Figure 5.6(a), and the blue data points were obtained from fitting the data shown in Figure 5.6(b).

It can be seen that the results for $H_{\text{NP-P}} = 5.6 \times 10^{-19} \text{ J}$ follow the prediction for uniform distribution very well. For higher values of $H_{\text{NP-P}}$, $S_{\text{NP}}$ is zero for nonzero $f_v$, which means that for small $f_v$, the NPs are distributed exclusively in the interior. The behavior can be explained by the competition between enthalpic and entropic effects. The larger $H_{\text{NP-P}}$ with respect to $H_{\text{NP-S}}$ leads to NPs which prefer the interior of the aggregates. However, as more NPs are incorporated to the interior of the aggregates, i.e., $f_v$ increases, it results in a larger conformation entropy loss of the ratio of a single NP and a single monomer in our simulations. The dotted line indicates the prediction for $S_{\text{NP}}$ if the distribution of NPs is uniform throughout the entire volume of the aggregate with the assumption that the aggregate is spherical. This prediction was derived from the relationship between the number of NPs on the surface of the aggregate, $N_{\text{NP,s}}$, and $N_{\text{NP}}$, which is $N_{\text{NP,s}} = N_{\text{NP}}V_{\text{ss}}/V_a$. Here, $V_a$ is the volume of the aggregate, $V_a = 4/3 \pi a^3$, and $V_{\text{ss}}$ is the volume of a spherical shell on the surface of the aggregate with a thickness of an NP diameter, $\sigma_{\text{NP}}$. 

It can be seen that the results for $H_{\text{NP-P}} = 5.6 \times 10^{-19} \text{ J}$ follow the prediction for uniform distribution very well. For higher values of $H_{\text{NP-P}}$, $S_{\text{NP}}$ is zero for nonzero $f_v$, which means that for small $f_v$, the NPs are distributed exclusively in the interior. The behavior can be explained by the competition between enthalpic and entropic effects. The larger $H_{\text{NP-P}}$ with respect to $H_{\text{NP-S}}$ leads to NPs which prefer the interior of the aggregates. However, as more NPs are incorporated to the interior of the aggregates, i.e., $f_v$ increases, it results in a larger conformation entropy loss of the ratio of a single NP and a single monomer in our simulations. The dotted line indicates the prediction for $S_{\text{NP}}$ if the distribution of NPs is uniform throughout the entire volume of the aggregate with the assumption that the aggregate is spherical. This prediction was derived from the relationship between the number of NPs on the surface of the aggregate, $N_{\text{NP,s}}$, and $N_{\text{NP}}$, which is $N_{\text{NP,s}} = N_{\text{NP}}V_{\text{ss}}/V_a$. Here, $V_a$ is the volume of the aggregate, $V_a = 4/3 \pi a^3$, and $V_{\text{ss}}$ is the volume of a spherical shell on the surface of the aggregate with a thickness of an NP diameter, $\sigma_{\text{NP}}$. 

It can be seen that the results for $H_{\text{NP-P}} = 5.6 \times 10^{-19} \text{ J}$ follow the prediction for uniform distribution very well. For higher values of $H_{\text{NP-P}}$, $S_{\text{NP}}$ is zero for nonzero $f_v$, which means that for small $f_v$, the NPs are distributed exclusively in the interior. The behavior can be explained by the competition between enthalpic and entropic effects. The larger $H_{\text{NP-P}}$ with respect to $H_{\text{NP-S}}$ leads to NPs which prefer the interior of the aggregates. However, as more NPs are incorporated to the interior of the aggregates, i.e., $f_v$ increases, it results in a larger conformation entropy loss of the
polymer chains that distribute around the NPs. When this entropy loss outweighs the enthalpic gain due to the more favorable NP-polymer interactions, NPs are driven to the surface of the aggregates. In addition, for the same value of $f_v$, stronger NP-polymer interactions lead to higher NP internal density, and a smaller number of NPs on the surface. This is because the stronger enthalpic attraction between NPs and polymers can afford a larger entropy loss and allow more NPs to be incorporated to the interior of the aggregates, i.e., a higher threshold $f_v$ before NPs start to emerge on the surface.

When we plot in Figure 5.8(b) $S_{NP}$ vs. $f_v$ shifted by its value when $S_{NP}$ first becomes nonzero, results for different values of $H_{NP-P}$ collapse onto the dotted line, which means that the distribution of NPs is uniform when $f_v$ is above its corresponding threshold value, $f_{v,0}$. These findings provide guidelines for tuning the internal and surface density of NPs via $f_v$, which can in turn be controlled by the ratio of NPs and polymers in the feed streams and the size of the NPs during the experiments.

We now move on to study how NP loading and localization are affected when NPs selectively interact with one polymer domain. With only van der Waals interactions between NPs and polymers, selective localization can be achieved by choosing different

![Figure 5.8: Surface density of NPs on the aggregates, $S_{NP}$. (a) volume fraction of NPs, $f_v$, and (b) $f_v$ minus its value when $S_{NP}$ first becomes nonzero for different values of $H_{NP-P}$. The dotted line represents prediction for $S_{NP}$ if NPs are uniformly distributed throughout the entire aggregate.](image-url)
state points for NP-A and NP-B interactions in Figure 5.1. For example, by choosing a state point for NP-A interaction in region (I), and a state point for NP-B interaction in region (IV), NPs will be dispersed exclusively on the surface of polymer A domain [Figure 5.9(a)]. Similarly, a combination of state points in regions (III) and (IV) will lead to aggregates with NPs dispersed exclusively in the interior of the polymer A domain [Figure 5.9(b)].

Figure 5.9: Cross sections of the precipitated aggregates, which demonstrate selective localization of NPs, by choosing (a) NP-A interaction in region (I), NP-B interaction in region (IV), and (b) NP-A interaction in region (III), NP-B interaction in region (IV). Other interaction parameters are kept constant at $H_{\text{NP-NP}} = 8 \times 10^{-19}$ J, $H_{\text{A-A}} = H_{\text{B-B}} = 1.6 \times 10^{-19}$ J, $H_{\text{A-B}} = 1.5 \times 10^{-19}$ J, and $H_{\text{P-S}} = 8 \times 10^{-20}$ J, which are consistent with Figure 5.1.

In addition to van der Waals interactions, other polymer-NP interactions have also been used experimentally to achieve selective localization, such as hydrogen bonding, electrostatic interactions, and ligand replacement. Motivated by this procedure, we consider electrostatic interactions in addition to the van der Waals attraction between NPs and polymers. In the experiments, such electrostatic interaction was achieved by incorporating charged amine end groups to PS chains.

It can be seen from the snapshot in Figure 5.10(a) that the negatively charged NPs are selectively localized on the polymer A domain, where the positively charged end beads are incorporated into. The general trends in $f_{\text{NP}}$ and $S_{\text{NP}}$ remain the same as the case with uncharged polymers and NPs. However, the stronger electrostatic interactions between NPs and polymers increase NP uptake for small $H_{\text{NP-P}}$. In addition, the charged end groups are distributed on the surface of the aggregates.
to minimize the electrostatic repulsion among themselves, resulting in an increased surface density of NPs compared to the electroneutral case. Therefore, our results show that incorporating electrostatic interactions between polymers and NPs can enhance NP loading and surface density in the polymeric aggregates.

Figure 5.10: (a) Fraction of NP uptake, $f_{NP}$, and (b) surface density of NPs, $S_{NP}$, vs. $H_{NP-P}$ for $H_{NP-S} = 3.2 \times 10^{-19}$ J and different values of $H_{NP-P}$. Results for both the charged and uncharged cases were obtained from initial configurations with a constant polymer feed concentration of $5.7 \times 10^{-4}$ nm$^{-3}$, and NP concentration is $2.2 \times 10^{-4}$ nm$^{-3}$. An A:B ratio of 1:1 leads to a concentration for the charged end groups of $2.9 \times 10^{-4}$ nm$^{-3}$. A simulation snapshot is included in (a) which shows the external view of the Janus hybrid aggregate obtained at $H_{NP-P} = 3.2 \times 10^{-19}$ J for the charged case. The charged end beads of polymer A are represented by the green particles.

5.3 Conclusions

In this work, MD simulations were carried out to study the assembly of a binary polymer blend and NPs under a rapid solvent exchange, a process experimentally realizable as Flash Nanoprecipitation (FNP). We systematically varied the interaction strengths between the different constituents, i.e., NP-solvent, NP-polymer, polymer-solvent, and polymer-polymer cross interaction, and demonstrated how the morphologies and the selective localization of the NPs can be tuned in the final structures. From our simulation results, we observed that three types of hybrid structures
can arise with NPs distributed (1) on the surface, (2) throughout the entire volume of the polymeric aggregates, or (3) aligned at the interface between the two polymer domains. The loading and surface density of the NPs in the polymeric aggregates for each of these three cases can also be reliably tuned by the polymer and NP feed concentrations, and their volume ratio in the feed streams. In addition, we have also demonstrated that electrostatic interactions between polymers and NPs can enhance NP loading and surface density. We have thus demonstrated FNP as a simple, continuous and scalable process to produce polymer-NP hybrid materials with nanoscale control over particle properties, \textit{i.e.}, size, morphology, NP loading, surface density and localization. Our results also provide guidelines for future design and preparation of polymer-NP hybrid materials with desired properties, and thus facilitate their applications in areas such as drug delivery, sensors and catalysis.
Chapter 6

Enhanced Brownian dynamics algorithm for FNP

Compared to explicit solvent molecular dynamics (MD), implicit solvent methods, such as Brownian dynamics (BD), can potentially speed up simulations of FNP. In BD simulations, the solvent degrees of freedom are integrated out and instead mimicked through the stochastic movements of the solute particles. By coarse-graining out the fast modes of the solvent, it is possible to simulate much longer time scales than with explicit-solvent simulations.

However, the standard BD simulations neglect hydrodynamic interactions (HI), an important effect that needs to be included in simulations of aggregation processes, when the dynamics of nanoparticles in solutions are concerned. HI are long-ranged effects induced by the motion of other particles and mediated by the fluid. HI are usually completely neglected when considering particle assembly in quiescent solvents, particularly when only the final, equilibrium configuration rather than the aggregation kinetics is of interest.\textsuperscript{140} Nevertheless, there are many systems for which non-equilibrium effects are important, particularly in driven systems, \textit{e.g.}, when a shearing force is applied externally.\textsuperscript{141–145} Dynamic effects are crucial in FNP; simula-
tions neglecting HI led to smaller nanoparticles than those obtained in explicit-solvent simulations, as demonstrated in Ref. 39 and in the present work.

In addition to explicit solvent molecular dynamics (MD) simulations, various mesoscopic simulation methods are available to account for HI in colloidal dispersions. The first category of methods includes dissipative particle dynamics (DPD), the hybrid lattice Boltzmann-molecular dynamics (LB-MD), and multi-particle collision dynamics (MPCD) which treat solvent particles explicitly. Therefore, HI between aggregating entities (e.g., polymer chains) arise naturally through the exchange of momentum between the solute beads and solvent particles.

The second category of methods involves implicit solvent simulations. Stokesian dynamics is a simulation technique that accounts for full HI. It includes the many-body interactions and the near-field lubrication forces, but both effects require $O(N^3)$ operations for a system of $N$ particles, which render Stokesian dynamics computationally intensive. On the other hand, many researchers have approached the problem from the dilute Brownian limit, and accounted for only far-field interactions by adopting e.g., the Rotne-Prager-Yamakawa tensor, the construction of which scales as $O(N^2)$. This approach is generally known as Brownian dynamics (BD). Despite the substantial computational savings from this incomplete treatment of HI, the calculation of hydrodynamically correlated random displacements, which requires taking the square root of the hydrodynamic mobility tensor, still incurs a significant cost. One common technique to determine the random displacements is by Cholesky factorization, which results in a runtime of $O(N^3)$. Other BD-HI methods are available, e.g., through the adoption of Ewald summation techniques, and these implementations reduce the overall scaling to $O(N\log N)$ or $O(N)$ in their most efficient versions. However, they are better suited for specific applications, e.g., homogeneous systems or non-Brownian suspensions. For the assembly of colloidal particles in dilute solutions, some of the suitable methods are the Chebyshev-expansion Fixman
procedure \( (O(N^{2.25})) \)\textsuperscript{165} and the Truncated Expansion Ansatz \( (O(N^2)) \).\textsuperscript{166} They are usually limited to small systems with a few thousand solute particles owing to the less favorable scaling.

In this chapter, I present a BD method to study FNP, that avoids the expensive calculation of hydrodynamically correlated displacements. Instead, the method corrects the size dependent diffusion coefficients of aggregating entities by rescaling the friction coefficient for each aggregate individually to match the diffusion dictated by the Stokes-Einstein relationship. I argue that although this method does not reproduce full hydrodynamics, correcting the diffusion coefficients is nevertheless a necessary condition for obtaining the correct dynamic evolution of an aggregating system. Furthermore, this method retains the advantage of BD simulations in computational efficiency through the implicit treatment of solvent particles, but also scales more favorably with the number of particles compared to other BD methods with HI. It is thus a promising approach for studying aggregation processes with larger systems for longer times.

The structure of this chapter is as follows. I first discuss the details of the proposed BD method and compare the algorithm to other well established simulation methods which take into account HI. The main test here is the center-of-mass diffusion coefficient of aggregates, a central dynamic property I wish to reproduce. Next, I present and analyze results from simulating the FNP process. I compare the enhanced BD model with the explicit-solvent MD model in terms of aggregation dynamics, as well as their relative computational efficiency. I conclude with a summary of the results and assess the possibility of applying this method for studies of FNP.
6.1 Methodology

6.1.1 Enhanced BD algorithm

The Langevin equation of motion for a Brownian particle is

\[ m_i \ddot{r}_i = -\gamma v_i + F^C_i + F^R_i, \]  \hspace{1cm} (6.1)

where \( m_i \) is the mass, \( r_i \) and \( v_i \) are the position and velocity of particle \( i \), respectively. Each particle experiences a conservative force \( F^C_i \) due to the intra- and intermolecular interactions, a random force \( F^R_i \) with zero mean, and a friction force proportional to the particle velocity. The friction force dampens the particle motion as a result of the surrounding viscous environment. The magnitude of this effect is controlled through the friction coefficient \( \gamma \), which usually (but not exclusively) depends on the shape, size, and surface of the solute particle and the viscosity of the surrounding solvent. According to Stokes Law, the friction for a sphere of radius \( R \) is given by

\[ \gamma = c \pi \eta_s R, \]  \hspace{1cm} (6.2)

where \( \eta_s \) is the solvent viscosity, and \( c \) is a constant determined by the choice of hydrodynamic boundary conditions. In addition, the friction force and the random force satisfy the fluctuation dissipation theorem

\[ \sigma_R^2 = 2\gamma kT, \]  \hspace{1cm} (6.3)

which implies that the noise amplitude \( \sigma_R \) for \( F^R_i \) is balanced by \( \gamma \) in a way that determines the thermal energy of the system, \( kT \).

In the standard BD algorithm, particles experience the stochastic random force independently and thus neither local nor global momentum is conserved. Therefore,
the total friction coefficient of the aggregate $\gamma_{agg}$ is the sum of the contribution of $N_b$ beads, $\gamma_{agg} = N_b \gamma$. According to the Einstein relation, the center-of-mass diffusion coefficient of the aggregate is $D_{\text{COM}} = \frac{kT}{\gamma_{agg}}$, and I thus obtain the Rouse behavior

$$D_{\text{COM,Rouse}} = \frac{kT}{N_b \gamma}. \quad (6.4)$$

However, in the presence of HI, the aggregate of radius $R$ moves collectively as a solid object, and effectively drags some solvent with it. The Stokes-Einstein relation should be obeyed and the diffusion coefficient of the aggregate is thus

$$D_{\text{COM,SE}} \propto \frac{kT}{\eta_s R} \propto \frac{1}{N_b^{1/3}}, \quad (6.5)$$

with $R \propto N_b^{1/3}$ for a close packed aggregate under poor solvent conditions.

Therefore, as aggregation proceeds and clusters grow in size, their Rouse diffusion coefficients become progressively smaller with respect to those given by the Stokes-Einstein relationship. For example, for an aggregate with $N_b = 1000$ beads, $D_{\text{COM,Rouse}}$ will be 100 times smaller than $D_{\text{COM,SE}}$. This large discrepancy can lead to an erroneous aggregation behavior, when the dynamics of the system are governed by multiple timescales.$^{39,41}$ To obtain physical aggregation dynamics in BD simulations, I propose to reproduce the Stokes-Einstein scaling by tuning the bead friction coefficient $\gamma$ accordingly as aggregates grow in size. If a value $\gamma_0$ is chosen for an isolated bead, the number of beads in each cluster $N_b$ needs to be calculated and $\gamma$ of every bead in the cluster can be adjusted as aggregation proceeds. Since $D_{\text{COM}} \propto \gamma_{agg}^{-1} = (N_b \gamma)^{-1}$ as previously mentioned, $\gamma$ can be updated according to $\gamma = \gamma_0 N_b^{-2/3}$ to achieve an overall scaling of $D_{\text{COM}} \propto N_b^{-1/3}$. A similar approach has been proposed in Ref. 167 to account for local many-body lubrication interactions in dense colloidal solutions.
To execute this BD method, an algorithm that identifies all aggregates and calculates their sizes at every timestep is required. In this implementation, the center-of-mass of each aggregating entity is first calculated, and neighboring entities within a certain cutoff radius are grouped into the same cluster. \( N_b \) and the corresponding \( \gamma \) value can thus be computed.

To verify the proposed algorithm, I studied the center-of-mass diffusion coefficients \( D_{\text{COM}} \) of aggregates of various sizes, and the results were compared to those from three other methods, \textit{i.e.}, explicit-solvent MD, MPCD and BD with Cholesky factorization. The system consisted of a single spherical aggregate made up of \( N_b = 1 \) to 5000 beads (see Figure 6.1), which interacted with each other \textit{via} the LJ potential [Eqn. (2.1)] with \( \epsilon = 5.0 k_B T \) and \( r_{\text{cut}} = 3.0 \sigma \).

![Figure 6.1: Snapshots of aggregates with size \( N_b \) of 1, 20 and 1000 respectively, showing the surface getting rougher, which explains the transition from slip to no-slip boundary conditions in the explicit-solvent MD simulations.](image)

The edge length of the simulation box was set to \( 40 \sigma \). In the case of MD simulations, the surrounding solvent was modeled explicitly as a liquid of LJ particles with the same size and mass as the solute beads. I set \( \epsilon_{\text{solvent}} = 1.0 k_B T \) and chose a reduced number density of \( \rho = 0.66 \), resulting in a dynamic viscosity of \( \eta_s = 1.01 \). Solvent particles and solute beads interacted through the purely repulsive Weeks-Chandler-
Andersen (WCA) potential:

\[
U_{\text{WCA}}(r) = \begin{cases} 
4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6 + 1/4] & r \leq 2^{1/6}\sigma \\
0 & r > 2^{1/6}\sigma 
\end{cases}.
\] (6.6)

Both MD and BD simulations were performed via HOOMD-blue\textsuperscript{61} in the \textit{NVT} ensemble, and MD simulations adopted the Nosé-Hoover thermostat. The equations of motion were integrated by a velocity-Verlet algorithm with a timestep of 0.01. BD simulations with Cholesky factorization were run via BD\textsc{box}.\textsuperscript{168} To calculate \(D_{\text{COM}}\), I performed a linear fit of their center-of-mass mean-squared displacements versus time and used multiple time origins to increase the number of samples.

\(D_{\text{COM}}\) as a function of aggregate size is presented in Figure 6.2(a). The data have been reduced by the diffusion coefficient of a single bead \(D_0\). It appears at first that results from the explicit-solvent MD simulations fall below the Stokes-Einstein prediction of \(D_{\text{COM}} \propto N_b^{-1/3}\). This mismatch can be explained by the transition from slip (single bead) to no-slip (aggregates) boundary conditions as the aggregate grows in size (see Figure 6.1). Slip and no-slip boundary conditions are achieved by setting \(c = 4\) and \(c = 6\) in Eqn. (6.2), respectively.\textsuperscript{169} To approximate the effective radius of the spherical aggregate, I used the relation \(R_g/R_h = 0.77\) for hard spheres,\textsuperscript{54} and obtained good agreement with theoretical predictions as shown in Figure 6.2(b).

On the other hand, it is obvious from Figure 6.2(a) that Rouse scaling was reproduced in the standard BD simulations without HI, where the bead friction coefficient remained constant irrespective of the size of the cluster it belonged to. In contrast, the Stokes-Einstein scaling was reproduced in both the enhanced BD algorithm and BD with Cholesky factorization.

Lastly, aggregate \(D_{\text{COM}}\) was computed via MPCD, a \(O(N)\) method where the solvent is modeled by \(N\) point-like particles which move in continuous space with a
continuous distribution of velocities.\textsuperscript{170,171} The solvent particles exchange momentum with each other and the solute particles through stochastic collisions, which conserve energy, and local and global momentum. Here, the stochastic rotation dynamics (SRD) variant of the MPCD algorithm was used, and a grid size of $\sigma$ for the collision cells was chosen to resolve the HI on the bead level. Galilean invariance was restored by shifting the grid cells before each collision step.\textsuperscript{172} More detailed information on the MPCD algorithm can be found in Refs. 170 and 171. As shown in Figure 6.2(a), diffusion coefficients from MPCD simulations do not follow Stokes-Einstein scaling, and can be fitted by $D_{\text{COM}}/D_0 \propto N_b^{-0.54}$.

![Figure 6.2](image)

Figure 6.2: (a) Reduced diffusion coefficient $D_{\text{COM}}/D_0$ of unbonded bead aggregates of various sizes $N_b$ from the enhanced BD simulations, standard BD simulations (no HI), MD simulations, BD simulations with Cholesky factorization and MPCD simulations. (b) Results from MD simulations compared against Stokes-Einstein slip and no-slip boundary conditions predictions.

\subsection*{6.1.2 Runtime considerations}

Without HI, the BD algorithm scales linearly with the number of particles, \textit{i.e.}, $N_b$, due to the implementation of cell and neighbor lists in the simulations.\textsuperscript{173} These runtimes were obtained by adopting the system described in the previous section and running each of the simulations for at least $1 \times 10^7$ timesteps to ensure sufficient statistical accuracy.
On the other hand, to perform the enhanced BD algorithm, a custom plug-in to HOOMD-blue was utilized to identify clusters and update bead friction coefficients at every timestep. As shown in Figure 6.3, the enhanced BD simulations slowed down the simulations at every $N_b$ by a constant factor, but the overall scaling remained approximately the same. This scaling is more favorable than other BD simulations with analytical hydrodynamic corrections. It thus allows for even larger aggregating systems to be handled efficiently when it is not necessary to make calculations of full HI.

Figure 6.3 also presents runtimes from explicit-solvent MD simulations. Since the number of solvent particles was an order of magnitude larger than that of solute particles, the runtimes of the explicit-solvent MD simulations remained relatively constant in the range of $N_b$ studied. It is obvious that these simulations required more computation time than both the standard and the enhanced BD simulations, and intersect the enhanced BD simulations at approximately $N_b = 10^4$. However, it is worth noting that the plug-in which identified the clusters in the enhanced algorithm was not optimized for speed, which could explain the apparent degradation in performance.

## 6.2 Enhanced Brownian dynamics on FNP

### 6.2.1 Polymer model and potential parameters

Having verified that the enhanced BD algorithm reproduces Stokes-Einstein scaling \[ \text{cf. Eqn. (6.5)} \], I applied this method to study colloidal assembly in FNP. As will be shown in the following section, dynamics play an important role in this process. BD simulations which neglect HI produce smaller nanoparticles than those obtained from MD simulations.
Figure 6.3: Comparison of the runtime behavior of enhanced, standard BD (no HI) and MD simulations vs. the number of solute particles, $N_b$. All simulations in this figure were performed on CPUs.

The MD simulation model developed by Nikoubashman et al. for studies of FNP systems served as a foundation for the BD model. In this model, a polymer was modeled as a linear bead-spring chain with 23 beads, each with diameter $\sigma$ and mass $m$.

The bonded interactions between polymer beads were modeled via the FENE potential. The standard Kremer-Grest parameters were adopted to prevent unphysical bond crossing.

In BD simulations, solvent molecules were modeled implicitly. Similar to previous computational studies on FNP, non-bonded interactions on all particles were varied simultaneously over a certain period of mixing time to mimic the rapid homogeneous solvent displacement. The non-bonded potential between polymer beads was chosen as outlined in the work by Huissmann et al.

$$U_{NB}(r, \lambda) = U_{WCA}(r) + \lambda U_{att}(r),$$

(6.7)
where $U_{\text{att}}$ is an attractive potential:

$$U_{\text{att}}(r) = \begin{cases} 
-\epsilon & r \leq 2^{1/6}\sigma \\
4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6] & r > 2^{1/6}\sigma 
\end{cases}$$  \hspace{1cm} (6.8)

The parameter $\lambda$ controls the strength of the attraction, and $U_{\text{NB}}$ becomes the standard LJ potential for $\lambda = 1$. As solvent quality worsens during solvent displacement, polymer beads experience stronger effective attraction. To make a quantitative comparison between BD simulations and the previous MD simulations, $\lambda$ was chosen so that the radius of gyration values of a single polymer chain at each mixing step from the two models agree with each other as shown in Figure 6.4. I used $\lambda = 0.2$ at the starting good solvent conditions and $\lambda = 0.7$ at the final poor solvent conditions.

![Figure 6.4: Radius of gyration $R_g$ of a single polymer chain in solution as a function of solvent quality, which worsens as $\lambda$ increases. The data from explicit-solvent simulations are taken from Ref. 41.](image)

During the FNP process, neutral polymer chains aggregate to form nanoparticles without the need of an external stabilizing agent. Nanoparticle stability is provided by a negative surface potential between -30 to -40 mV, which was measured experimentally on particles of radii between 45 nm and 135 nm using electrophoretic light
scattering. Therefore, in addition to the bonded and non-bonded potentials between polymer beads, I also mimicked the effect of charge stabilization on the nanoparticles. This effect was achieved by placing a virtual particle at the center of each aggregate, which carried the equivalent surface charge. More details on the method can be found in prior work by Nikoubashman \textit{et al.} Importantly, the size of the nanoparticles was already computed during this step, and as a result, performing the enhanced BD simulations on the FNP system caused only minimal increase in computation time.

To make a meaningful comparison between results from BD and previous MD simulations, it is necessary to calculate the length- and time-scales of BD simulations. Using the methods outlined in Chapter 2, I obtained $\sigma = 1.5\,\text{nm}$ for the length-scale and $\tau = 0.86\,\text{ns}$ for the time-scale. $\tau$ compares to the time-scale of 0.28 ns in MD simulations, which shows that by coarse-graining out the solvent particles, a speedup of approximately 3.5x has been achieved in the BD simulations.

### 6.2.2 Dynamics of aggregation in FNP system

The simulations were carried out in a cubic box with edge length of $80\sigma$ containing up to 1024 polymer chains. The system was equilibrated at good solvent conditions ($\lambda = 0.2$) for 5000 timesteps, and then $\lambda$ was increased linearly within a certain amount of mixing time to 0.7, which was chosen as the final poor solvent conditions. Mixing time is directly related to the inlet flow rates in the experiments, and it is used as a measurement of mixing rate in simulations. From these simulations, I was interested in studying the dependence of the final nanoparticle size on different processing parameters and reproducing results obtained in previous explicit-solvent MD simulations.

Figure 6.5 shows the time evolution of average nanoparticle radius, $a$, in a sample FNP system. The growth curves of the explicit-solvent model and the enhanced
BD model show good agreement. In these two models, the average nanoparticle radius of the system started increasing as solvent displacement was initiated at time zero, and plateaued as the electrostatic repulsion between clusters prevented further aggregation. In contrast, the standard BD model produced nanoparticles that stopped growing at a smaller value. In fact, it was run for as long as 1 ms in physical time and the average cluster radius remained approximately constant at 6.1 nm. This is because polymers and small aggregates diffused too slowly to merge before the mixing time was over. As a result, nanoparticles became trapped at a smaller size before the negative charge could fully build up and stabilize the colloids.

![Figure 6.5: Average cluster size, \(a\), vs. time, \(t\), for the enhanced and standard BD (no HI) models, as well as the explicit-solvent model for \(\zeta = -75\) mV and \(\tau_{\text{mix}} = 6\) µs at polymer concentration of 8.2 mg/mL. The growth curves were obtained from 3 to 5 independent runs for each model.](image)

Next, I systematically studied the dependence of nanoparticle size on mixing time and polymer concentration, which are key measurements from the FNP process. It was indicated in MD simulations that the radius of nanoparticles increases with increasing polymer concentration. Furthermore, \(a\) can be controlled by mixing time. The nanoparticle radius increases with slower mixing rate (longer mixing time), as
nanoparticles stay longer in the growth regime. However, there exists a threshold mixing time $\tau_{\text{thr}}$, below which $a$ remains approximately constant. It was shown by Nikoubashman et al. in explicit-solvent simulations, when the nanoparticle radius $a$ reduced by its value at $\tau_{\text{mix}} = 0$ is plotted against the normalized mixing time $\tau_{\text{mix}}/\tau_{\text{thr}}$, simulation data from different polymer concentrations should collapse onto one single curve as can be seen in Figure 6.6. A similar behavior of nanoparticle size with respect to solvent mixing rate was also observed in recent mean-field calculations of on nanoparticle precipitation through solvent mixing.$^{175}$ For more details on obtaining an estimate of $\tau_{\text{thr}}$, I refer the reader to Ref. 41.

However, it is evident from Figure 6.6 that the data from the standard BD model do not show this universal behavior. The nanoparticle radius does not increase as expected with higher polymer concentration and mixing time. The failure of the standard BD algorithm originates from the fact that the diffusion coefficients of larger aggregates become progressively smaller, and aggregation proceeds mainly by addition of unimers or small aggregates. In contrast, in the enhanced BD model, larger aggregates also have enough time to merge, which produces a larger increase in cluster size with respect to increasing polymer concentration and mixing time.

### 6.2.3 Computational efficiency

Experimentally, FNP is performed in dilute solutions with polymer concentrations between 0.1 mg/mL to 2 mg/mL. Explicit-solvent simulations would spend most of the time simulating the solvent particles, which are only of minor interest for the final aggregates. While implicit-solvent models seem to be a promising alternative, as previously discussed, standard BD simulations are unable to reproduce the diffusion coefficients of aggregates that obey the Stokes-Einstein relation. The slow diffusion in standard BD simulations not only produces unphysical aggregation behavior as
Figure 6.6: Nanoparticle radius $a$, reduced by its value at $\tau_{\text{mix}} = 0$, vs. the normalized mixing time $t_{\text{mix}}/t_{\text{thr}}$ for (a) the standard BD model and (b) the enhanced BD model. The solid line corresponds to the results from explicit-solvent MD simulations, while symbols are the data from implicit-solvent BD simulations.
shown in the previous section, but also prevents simulations of larger systems for longer times as will be discussed in the next paragraph.

For a system of 100 polymer chains in a simulation box of $80\sigma \times 80\sigma \times 80\sigma$, the standard BD model ran at a speed of 340 seconds per $10^4$ timesteps on a NVIDIA GTX 580 graphics processing unit (GPU), whereas the enhanced BD model ran at a speed of 530 seconds per $10^4$ timesteps. However, as previously mentioned, the nanoparticle diffusion coefficients in the standard BD simulations are substantially smaller than those given by the Stokes-Einstein predictions. For a particle with a radius of 20 nm, the uncorrected BD diffusion coefficient is roughly 500 times smaller than the Stokes-Einstein value. If one were to study FNP using larger systems for longer mixing times, the average size of the nanoparticles was expected to be approximately 50 nm. To reach this value, the standard BD model needs to be run for significantly longer, and based on the scaling of diffusion coefficients seen in the simulations, its small computational efficiency over the enhanced BD model would be cancelled out when the cluster radius reached $\approx 5$ nm.

Next, I compare enhanced BD simulations to explicit-solvent MD simulations, and the enhanced BD simulations show a clear advantage in computational efficiency. Both simulation models were run on a GPU for more than $10^6$ timesteps, and I calculated how long they have progressed in physical time. As presented in Figure 6.7, the enhanced BD model is always faster than the MD model in the concentration range of interest, achieving on average a speedup of 3x at a polymer concentration of $\Phi = 8.2$ mg/mL. While the computation time scales approximately linearly as the number of interaction sites in the explicit-solvent MD model as shown in the inset, the computation time of BD simulations remains approximately constant with respect to concentration. Therefore, it can be estimated that at 1 mg/mL, which is the polymer concentration used in the FNP experiments, the enhanced BD model will become 28 times faster than the explicit-solvent model.
Figure 6.7: Computation time required to simulate 10 ns in physical time. At lower polymer concentration, the enhanced implicit model becomes increasingly more efficient than the explicit-solvent MD model. The inset shows that computation time scales linearly as the number of solvent particles, $N_{\text{solvent}}$ in the MD model. The number of polymer beads is one or two orders of magnitude smaller than the number of solvent particles, and is thus not included.

### 6.3 Conclusions

In summary, I have presented a BD algorithm that corrects the unphysical aggregation dynamics in standard BD simulations without HI by tuning the bead friction coefficient to obtain the correct size-dependent diffusion coefficients. This method was used to simulate colloidal aggregation under a rapid solvent displacement. With the enhanced BD model, I obtained results in good quantitative agreement with explicit-solvent simulations, but with significantly reduced computation time. However, it should be noted that an approximate 28 times decrease in computation time from MD simulations is still insufficient to reach the length- and time-scales employed in the experiments of FNP.
Chapter 7

Kinetic Monte Carlo simulations of FNP on macroscopic length- and time-scales*

As shown in the Chapter 2 to 5, the molecular dynamics (MD) model we developed previously\textsuperscript{41,45,88,126} has proven to be useful in morphology predictions and producing trends in qualitative agreement with the experiments. MD simulations provide considerably more microscopic level information than experiments, and are therefore efficient tools in the study of complex mechanisms and morphologies involved in FNP. Due to computational limitations, however, these MD simulations probed nanoparticles at least 10 times smaller and accessed mixing timescales in the order of a few $\mu$s compared to ms employed in the experiments.\textsuperscript{41} This gap in length- and time-scales prevents quantitative comparisons of experimental data to the MD simulations.

In this chapter, we develop a kinetic Monte Carlo (KMC) model, which makes use of the microscopic details obtained from MD simulations, to investigate nanoparticle

formation in FNP up to macroscopic length- and time-scales by solving stochastically the population balance equation. Other computational approaches capable of reaching experimental scales have also been reported for the study of the FNP process, such as solving the population balance equation using the method of moments within a computational fluid dynamics code.\textsuperscript{46–49} The novelty of the present work consists of the explicit incorporation of the charge stabilization mechanism into the aggregation kernel, which is a key element for studying, \textit{e.g.}, polymers with charged end groups.\textsuperscript{40,44} The effect of charge stabilization was not included in previous works, as they either dealt with nanoparticles stabilized \textit{via} amphiphilic block copolymers or assumed an aggregation efficiency of either zero or one. Furthermore, our approach allows us to carry out a detailed analysis of the aggregation dynamics, and thus to make predictions for important properties relevant to the FNP system, such as the threshold mixing time, the characteristic aggregation time, and nanoparticle stability from any given set of operating conditions.

The structure of this chapter is as follows: we first introduce the simulation model and methods used in the present work. Next, we present our simulation results, and focus on understanding the aggregation mechanism and explaining the dependence of nanoparticle size and distribution on processing parameters, such as polymer feed concentrations and characteristic mixing timescale. Lastly, we summarize our results and comment on their implications on controlled particle production through the FNP process.

### 7.1 Simulation model and methods

Our simulation model consists of a combination of MD and KMC simulations. The microscopic model used in the MD simulations has already been discussed extensively
elsewhere,\textsuperscript{41} and therefore we concentrate in this manuscript only on aspects relevant for coupling to the KMC algorithm.

We adopted the KMC algorithm outlined by Gillespie,\textsuperscript{176} which has been applied extensively in studying the kinetics of chemical reactions and aggregation processes.\textsuperscript{177–181} The KMC simulations can be summarized in the following three major components: (1) an event, $k$, is chosen to occur, so that its probability, $P_k = \frac{R_k}{R_T}$, where $R_k$ and $R_T$ are the rate of event $k$, and the sum of the rates of all possible events for the system at the current time, respectively. (2) The time of the system is advanced by $\tau = -\frac{\ln(u)}{R_T}$, where $u$ is a uniform random number in the interval $(0,1]$. (3) The system and the rate database are updated.

For the systems of interest for the present work, we consider the relevant events to be particle aggregation due to Brownian diffusion. Nucleation and growth is not included in our description because the aggregation process has been shown experimentally to be growth-controlled.\textsuperscript{40} Particle breakage is also assumed to be negligible. In addition, turbulent shear can cause particles to collide and aggregate. Using the turbulent shear kernel outlined by Saffman and Turner,\textsuperscript{182} its magnitude only becomes comparable to that of Brownian aggregation for $a \gtrsim 300$ nm. For the range of particle size studied in this work, the effect of turbulent shear is thus negligible and therefore has not been considered. The rate constant for Brownian aggregation between particle $i$ and particle $j$, $K_{i,j}$, can be calculated as follows:\textsuperscript{183}

$$K_{i,j} = \frac{4\pi}{W} (a_i + a_j)(D_i + D_j),$$

where $a_i$ and $a_j$ are the radii, and $D_i$ and $D_j$ are the diffusion coefficients of particles $i$ and $j$, respectively. $W$ is the Fuchs stability ratio which takes into account inter-
particle interactions:\(^{184}\)

\[ W = (a_i + a_j) \int_{a_i+a_j}^{\infty} \frac{e^{U/k_{B}T}}{r^2} \, dr, \tag{7.2} \]

where \( U \) is the total energy of interaction, and \( r \) is the center-to-center distance between the two particles. \( W = 1 \) when every collision leads to an aggregation event.

It should be noted that the following assumptions were made with the use of the rate constant in Eqn. (7.1): (a) Particles diffuse towards each other under steady-state conditions. (b) The system is dilute so that only binary collisions are considered. (c) The particle densities are uniform throughout the entire system. (d) Particles are assumed to be spherical.

The state of the KMC system changes after every event, and \( K_{i,j} \) needs to be calculated and updated accordingly. To solve for \( K_{i,j} \) in Eqn. (7.1), \( a, D \) and \( W \), are derived from MD simulations. Since the rate constant, \( K_{i,j} \), is derived from MD simulations, the characteristic energy- (\( \varepsilon \)), length- (\( \sigma \)) and time-scales (\( \tau \)) of the KMC simulations in real units are identical to those of the MD simulations, i.e., \( \varepsilon = 4.11 \times 10^{-21} \text{J} \), \( \sigma = 1.5 \text{nm} \), and \( \tau = 0.28 \text{ns} \).\(^{41}\)

The radius of particle \( i \), \( a_i \), can be estimated using

\[ a_i = c R_{\text{g},i} = \frac{c \sigma}{2} (N_b N_i)^{\nu}, \tag{7.3} \]

where \( c = 1.3 \) from our previous study,\(^{41}\) and \( R_{\text{g},i} \) is the radius of gyration of the particle. \( \sigma/2 \) is the radius of a single bead in the coarse-grained bead-spring MD model used to describe the polymer chains (\( \sigma/2 = 0.75 \text{nm} \)). \( N_i \) is the number of chains which belong to particle \( i \), and \( N_b \) is the number of beads in a single chain. \( \nu \) is the Flory exponent, which depends on solvent conditions. For the polystyrene chains with a molecular weight of 16.5 kg/mol studied in the experiments,\(^{41-43}\) our coarse-graining method leads to \( N_b = 23 \).\(^{41}\) In addition, the values of \( \nu \) for different solvent conditions...
have been calculated from MD simulations, and presented in Figure 7.1. Here, $\lambda$ is a dimensionless solvent quality parameter in our MD model, which represents the transition from good solvent ($\lambda = 0$) to poor solvent conditions ($\lambda = 0.5$).

The diffusion coefficient of particle $i$, $D_i$, can also be calculated from MD simulations. From Figure 7.1, it can be seen that the diffusion coefficient of a single polymer chain, $D_1$, in different solvent conditions shows good agreement with the Stokes-Einstein relation. Therefore, the diffusion coefficient of particle $i$ can be approximated by

$$D_i = \frac{k_B T}{6\pi \eta_s a_i},$$

(7.4)

where $k_B$ is the Boltzmann constant, $T$ is the temperature, and $\eta_s$ is the dynamic viscosity of the solvent.

Figure 7.1: Dependence of Flory exponent, $\nu$, and diffusion coefficient, $D_1$, of a single polymer chain of length $N = 23$, on the dimensionless solvent quality parameter, $\lambda$, from MD simulations. The line represents predictions from the Stokes-Einstein relation in Eqn. (7.4).

Having obtained Eqns. (7.3) and (7.4), we now discuss the interaction potentials between the particles, required for calculating, $W$, in Eqn. (7.2), which will then
allow us to obtain the rate constant, $K_{i,j}$, between any given pair of particles. Here, we consider that $U$ is the sum of the van der Waals attraction, $U_A$, the depletion interaction, $U_D$, and the electrostatic repulsion, $U_R$.

In our MD model, the polymer chains consist of Lennard-Jones (LJ) particles that are tethered through massless springs. To reproduce the attractive LJ interaction between the precipitated particles in KMC simulations, we represented $U_A$ as follows:

$$U_{A,i,j}(r) = -\frac{H}{6} \left( \frac{2a_ia_j}{r^2 - (a_i + a_j)^2} + \frac{2a_ia_j}{r^2 - (a_i - a_j)^2} + \ln \left( \frac{r^2 - (a_i + a_j)^2}{r^2 - (a_i - a_j)^2} \right) \right), \quad (7.5)$$

where $H$ is the Hamaker constant, and $H = 4\varepsilon\pi^2 = 1.6 \times 10^{-19}$ J, where $4\varepsilon$ is from the coefficient of the LJ interaction and $\pi^2$ arises from integrating all the monomer-monomer interactions over the volumes of the interacting particles. From our MD model, $\varepsilon = k_BT_{\text{room}} = 4.11 \times 10^{-21}$ J, since the experiments were performed at room temperature $T_{\text{room}} = 298$ K. Values of $H$ calculated for polystyrene in water depend on the methods used and typically lie between $10^{-20}$ and $10^{-19}$ J. For our system, we found that the radius of the precipitated nanoparticles, $a$, is not strongly influenced by the magnitude of $H$, and $a$ decreased by approximately 10 nm for a 40-fold decrease in $H$ over a broad range of mixing times, while the qualitative behavior remained the same. We have thus used the value of $H$ directly derived from the LJ interaction in all our simulations to be consistent with our MD model. The implication of using this slightly higher $H$ on quantitative comparisons with experiments will be discussed later.
between two spherical particles $i$ and $j$ was approximated by the Asakura-Oosawa model:

$$U_{D, i,j}(r) = \begin{cases} \infty, & r < 2a_p \\ -\frac{4P\pi(a_s+a_p)^3}{3} \left[ 1 - \frac{3r^2}{4(a_s+a_p) + \frac{r^3}{10(a_s+a_p)^2}} \right], & 2a_p < 2 < 2a_p + 2a_s \\ 0, & 2a_p + 2a_s < r \end{cases} \quad (7.6)$$

where $a_p$ is the mean radius of particles $i$ and $j$, and $a_s$ is the radius of solvent particles ($a_s = 0.75$ nm in our MD model). $P$ is the osmotic pressure, and $P = \rho_s k_B T$, where $\rho_s$ is the number density of solvent particles, and $\rho_s = 0.2$ nm$^{-3}$ from our MD model.

The third component of $U$ is the screened electrostatic repulsion $U_R$. We adopted the Yukawa potential used in our MD model:

$$U_{R, i,j}(r) = \lambda_B \left( \frac{Z_i e^{\kappa a_i}}{1 + \kappa a_i} \right) \left( \frac{Z_j e^{\kappa a_j}}{1 + \kappa a_j} \right) e^{-\kappa r}, \quad (7.7)$$

where $\lambda_B$ is the Bjerrum length, and $\kappa$ is the inverse Debye screening length, $\lambda_D$. For water with pH = 7 at room temperature, we used $\lambda_B = 0.7$ nm, and $\lambda_D = 0.15$ µm. The parameter $Z_i$ denotes the size-dependent charge of particle $i$, which can be estimated using Gauss’s Law for a spherically symmetric environment within linear-screening theory and at low particle concentrations:

$$Z_i = \frac{(1 + \kappa a_i)a_i e\zeta}{\lambda_B k_B T}, \quad (7.8)$$

where $\zeta$ is the zeta potential, and $\zeta \approx -30$ to $-40$ mV from experimental measurements using electrophoretic light scattering. For more details on obtaining the values of these parameters, we refer the reader to Ref. 41.

The effect of solvent displacement was accounted for in our KMC simulations in the following two aspects. First, we varied parameters such as $\lambda_B$, $\kappa$ and $\zeta$ between their
values for good solvent conditions and poor solvent conditions linearly within a certain period of time, $\tau_{\text{mix}}$. This procedure mimics the effect of increasing surface potential when the polymer solution in the good solvent is rapidly mixed with water. A larger $\tau_{\text{mix}}$ corresponds to slower mixing in the experiments, and vice versa. It should be noted that in the experiments, the mixing timescale is controlled by the flow rates of the inlet streams. The micromixing time of the multi-inlet vortex mixer used in the experiments has been studied using competitive reactions, and it was found to be in the range of milliseconds for Reynolds number larger than 1600. \textsuperscript{187,188} This quantity is the characteristic timescale for molecular diffusion across fluid lamellae during mixing. Note, however, that the mixing time in our simulations has a slightly different physical meaning: here, $\tau_{\text{mix}}$ can be understood as the time before the surrounding non-solvent to solvent ratio has reached its final value in the non-solvent reservoir and surface charge is fully built up. Therefore, $\tau_{\text{mix}}$ cannot be compared directly to the experimentally measured quantity in Refs. \textsuperscript{187} and \textsuperscript{188}. However, $\tau_{\text{mix}}$ studied in our simulations still reflects the rate of mixing in the experiments, and can provide useful insights on aggregation dynamics and the characteristic aggregation time required to obtain nanoparticles of a certain size as will be shown in the next section.

Secondly, the effect of solvent should also be reflected in the effective inter-particle interaction, $U$. For example, in $\Theta$ conditions, which occur at approximately $\lambda = 0.05$ for our model, the LJ interaction between monomers is identical to the monomer-solvent interaction, and the chains are effectively inert to one another. We have studied polymer chain aggregation using MD simulations for different $\lambda$ values, and the average particle size, $a$, vs. time, $t$, is shown in Figure 7.2. It can be seen that for $\lambda \leq 0.08$, no aggregation occurred despite the presence of van der Waals attraction between polymer chains. The aggregation rate then increased gradually for increasing $\lambda$ until it reached its full value for $\lambda \geq 0.18$. To account for this solvent effect in our KMC model, we modified the aggregation rate constant, $K_{i,j}$, by a prefactor, $f$, so
that \( f = 0 \) for \( \lambda \leq 0.08 \), and \( f = 1 \) for \( \lambda \geq 0.18 \). In the intermediate region for \( 0.08 < \lambda < 0.18 \), \( f \) increases linearly from 0 to 1. This modification of the KMC aggregation rate constant produced good agreement with MD simulations as shown by the comparison shown in Figure 7.2.

![Figure 7.2: Average radius of nanoparticles, \( a \), vs. time, \( t \), for different \( \lambda \) values from MD simulations (points) and KMC simulations (lines), which used a linearly increasing prefactor, \( f \). There is no electrostatic repulsion between aggregates in these simulations.](image)

### 7.2 Results

We first verified our KMC model by comparing aggregation dynamics from KMC with results from MD. In Figure 7.3, we plot the time evolution of the average particle radius, \( a \) for polymer feed concentration, \( \Phi = 8.2 \text{ mg/mL} \) and different \( \tau_{\text{mix}} \) and \( \zeta \) values in 3(a) and 3(b), respectively. Good agreement between KMC and MD results can be seen in all cases, except for small \( \tau_{\text{mix}} \) value of 7 \( \mu s \) [dashed line in Figure 7.3(a)].

This discrepancy arises from the stability ratio, \( W \), which assumes that particles approach each other from infinity with zero interaction. However, for large \( \Phi \) and
small $\tau_{\text{mix}}$, high surface charge is fully built up when there are still small particles in the system, and particles do not approach each other from zero interaction due to the long-ranged nature of the electrostatic repulsion. A correction to $W$ was applied, so that the integral in Eqn. (7.2) was bounded between $[a_i + a_j, l]$. $l$ is the mean free path between the particles, and can be estimated as $l \approx \rho_p^{-1/3}$, where $\rho_p$ is the number density of the precipitated particles in the system. It can be seen that better agreement for $\tau_{\text{mix}} = 7 \mu s$ was achieved as shown in Figure 7.3(a). However, such a correction to the KMC algorithm is only required for comparisons with the high $\Phi$ and small $\tau_{\text{mix}}$ employed in our previous MD simulations.\(^\text{41}\) In contrast, typical FNP experiments operate in the range of much smaller $\Phi$ (<1 mg/mL) and larger $\tau_{\text{mix}}$ (>100 $\mu$s). It can be seen from Figure 7.3 that in this case, the particle concentration of the system is low when surface charge is fully built up and the assumption that particles approach each with zero interaction becomes valid.

Figure 7.3: Average nanoparticle radius, $a$, vs. time, $t$, from MD and KMC simulations for polymer feed concentration of 8.2 mg/mL and (a) $-33$ mV and different $\tau_{\text{mix}}$ values, and (b) $\tau_{\text{mix}} = 42 \mu s$ and different $\zeta$ values. The points are from MD simulations. The thin solid lines and dashed lines are from KMC simulations with and without corrections for the stability ratio, respectively.

Having verified the agreement of the KMC model with our previous MD simulations, we first studied the aggregation mechanism by plotting nanoparticle radius, $a$, vs. $t$ for $\tau_{\text{mix}} = 14$ ms and $\zeta = -33$ mV and different polymer feed concentrations.
in Figure 7.4. To describe the time evolution of $a$ at short times, we consider the diffusion limited aggregation (DLA) dynamics.\textsuperscript{189} The DLA model gives the change in the average aggregation number, $N$, with respect to time, $t$, according to

$$\frac{N}{t} = 1 + \frac{1}{2} K_{\text{DLA}} \Phi t,$$

(7.9)

where $\Phi$ is the initial concentration. $K_{\text{DLA}}$ is the rate kernel from the DLA approximation, and

$$K_{\text{DLA}} = 16\pi a_1 D_1,$$

(7.10)

where $a_1$ and $D_1$ are the radius and diffusion coefficient of unimers, respectively. Equation (10) assumes $W = 1$, and the rate kernel for aggregation is independent of particle size. It is a good approximation for aggregation between particle $i$ and $j$ when $1 < m_i/m_j < 2$, where $m_i$ and $m_j$ are the masses of particles $i$ and $j$, respectively.

To compare our KMC results to DLA approximation, we fit the data in Figure 7.4 using the relationship $a = (At + B)^{1/3}$, since $a \propto N^{1/3}$ for spherical close-packed particles. It can be seen that at short times before mixing is complete, the time evolution of $a$ can be well described by DLA. The reason is twofold. First, there is a large number of similarly sized particles in the early stage of aggregation, and the condition $1 < m_i/m_j < 2$ can be satisfied for most of the aggregation events that take place. Therefore, the $(a_i + a_j)(D_i + D_j)$ term in Eqn. (7.1) is approximately constant. Secondly, at the early stage of aggregation when the electrostatic repulsion is still small, $W$ is also close to 1. The dynamics can thus be approximated by a constant $K_{i,j}$, and fitted through the relationship $a = (At + B)^{1/3}$.

When we plot $A$, vs. $\Phi$ in Figure 7.5, the data can be fitted through a relationship $A \propto \Phi^b$, where $b = 0.98 \pm 0.02$. This scaling relationship is in good agreement with predictions from DLA, i.e., $A \propto \Phi$. However, as shown in Fig. 5, the values of $A$
calculated from DLA are slightly smaller than the fitted values, because at the early stage of aggregation when the electrostatic repulsion is small, $W$ is dominated by attractive potentials, i.e., $U_A$ and $U_D$, and $W$ is smaller than 1. Aggregation is thus slightly faster than DLA predictions, which assume $W = 1$. As mixing proceeds and surface charge builds up on the precipitated nanoparticles, aggregation enters a slow-growth regime and deviates from the DLA approximation. In Figure 7.6, $a$ is plotted against $t$ up to macroscopic timescales for two different $\Phi$ values. It can be seen that small nanoparticles are less stable after mixing is complete, and they continue to grow at a slower rate and gradually converge on a much larger timescale. To understand the convergence, we consider the rate of aggregation. Unlike the rate of aggregation in the DLA regime [Eqn. (7.9)], which is directly proportional to $\Phi$ as $K_{DLA}$ is constant, the rate of aggregation in the slow growth regime is largely determined by the magnitude of $W$. Smaller particles as a result of smaller $\tau_{\text{mix}}$ or $\Phi$ experience a weaker electrostatic repulsion, which leads to a smaller $W$ and higher rate constant, and vice versa. Therefore, growth curves for
Figure 7.5: Fitted parameter, $A$, vs. $\Phi$ from KMC simulations for $\zeta = -33$ mV and different $\tau_{mix}$ values. The solid line shows predicted $A$ from the DLA approximation.

Different $\tau_{mix}$ and $\Phi$ in Figure 7.6 eventually converge to a similar value of $a$ when they are allowed to evolve in the slow growth regime for a sufficiently long time. In contrast, larger particles are more strongly stabilized by charge, and their growth is less appreciable on macroscopic timescales up to $10^8$ s. This observation is consistent with experimental measurements, which indicate a 10% to 15% increase in radius for nanoparticles obtained from FNP with $a > 50$ nm after one month.\(^1\)

Figure 7.6: Average nanoparticle radius, $a$, vs. time, $t$, for (a) 0.018 mg/mL and (b) 8.2 mg/mL for different $\tau_{mix}$. The $\zeta$-potential is $-33$ mV. Growth curves for $\tau_{mix} > 14$ ms are not shown in (b) for clarity, because they lead to much larger $a$ values.
From Figure 7.6, it can be seen that for any chosen cut-off time, $t_f$, growth curves of $a$ below a threshold $\tau_{\text{mix}}$ value converge. We thus define the threshold $\tau_{\text{mix}}$ as $\tau_{\text{thr}}$. We are interested in $\tau_{\text{thr}}$ because for $\tau_{\text{mix}} \leq \tau_{\text{thr}}$, $a$ calculated at $t_f$ is independent of $\tau_{\text{mix}}$. Experimentally, this finding suggests that there exists a threshold mixing rate, and any further increase in this rate does not produce smaller nanoparticles. It is evident that $\tau_{\text{thr}}$ depends on the $t_f$ value chosen. For larger $t_f$, more growth curves converge within the given time, which means larger $\tau_{\text{thr}}$. Furthermore, it can be seen from Figure 7.6 that larger $\Phi$ leads to smaller $\tau_{\text{thr}}$. This is because larger $\Phi$ results in higher aggregation rate in the DLA regime, and larger difference in $a$ for different $\tau_{\text{mix}}$ values at the start of the slow growth regime. Fewer growth curves thus converge within the given time.

To understand the dependence of $\tau_{\text{thr}}$ on different parameters, we plot $\tau_{\text{thr}}$ for two different $t_f$ values in Figure 7.7. As expected, $\tau_{\text{thr}}$ increases with decreasing $\Phi$ and increasing $t_f$. On the other hand, $\tau_{\text{thr}}$ can also be predicted from the DLA model. It can be seen from Figure 7.6 that for a given $t_f$ value, there is a minimum $a$, $a_{\text{thr}}$, that cannot be undercut by further decrease in $\tau_{\text{mix}}$. $\tau_{\text{thr}}$ is thus the characteristic growth time in the DLA regime to form a particle of radius $a_{\text{thr}}$. Using the fitted parameters $A$ and $B$ we obtained previously, we plot predictions from the DLA approximation in Figure 7.7, and they show good agreement with $\tau_{\text{thr}}$ obtained from performing multiple KMC simulations for different $\tau_{\text{mix}}$ values.

Having understood the aggregation dynamics, we then performed KMC simulations for more $\tau_{\text{mix}}$ and $\Phi$ values, and results are shown in Figure 7.8(a). Values of $a$ were calculated at a “final” time $t_f$ arbitrarily set to $10^4$ s. The choice of $t_f$ affects the minimum nanoparticle radius, $a_{\text{thr}}$. However, it does not affect significantly $a$ for $\tau_{\text{mix}} > \tau_{\text{thr}}$, since larger $\tau_{\text{mix}}$ leads to larger $a$, which is stabilized up to $10^8$ s as shown in Figure 7.6.
Several features of the aggregation process can be observed from Figure 7.8. (a) Nanoparticle radius, $a$, increases with $\tau_{\text{mix}}$ because the particles stay longer in the DLA growth regime before charge builds up and slows down growth significantly. (b) $a$ increases with $\Phi$ for a given $\tau_{\text{mix}}$ above its corresponding $\tau_{\text{thr}}$, because $a$ is dictated by growth in the DLA regime for $\tau_{\text{mix}} > \tau_{\text{thr}}$. As shown in Eqn. (7.9), larger $\Phi$ leads to larger particles in this regime. (c) Below $\tau_{\text{thr}}$, the initial concentration, $\Phi$, has little effect on the final $a$, because the $t_f$ chosen, i.e., $10^4 \text{s}$, is much larger than $\tau_{\text{mix}}$. In other words, particles stay much longer in the slow growth regime than in the DLA regime. The initial difference in size as a result of different $\Phi$ in the DLA regime becomes insignificant and particles eventually converge to a similar size. These trends are in qualitative agreement with previous studies on the self-assembly of amphiphilic block copolymers using FNP, which also involves fast unimer addition, followed by a much slower aggregate fusion process due to the formation of coronas of overlapping soluble brushes.

In addition, if $a$ is plotted against $\tau_{\text{mix}}$ reduced by its corresponding $\tau_{\text{thr}}$ in Figure 7.8(b), all data collapse onto the same master curve. For $\tau_{\text{mix}}/\tau_{\text{thr}} > 1$, the data can
be fitted through a relationship \( a \propto (\tau_{\text{mix}}/\tau_{\text{thr}})^c \), where \( c = 0.3 \pm 0.02 \). The scaling relationship can be explained by the DLA growth model, which predicts \( a \propto t^{1/3} \) for spherical close-packed particles.

Figure 7.8: Average nanoparticle radius, \( a \), vs. (a) \( \tau_{\text{mix}} \) and (b) \( \tau_{\text{mix}} \) reduced by \( \tau_{\text{thr}} \), for different \( \Phi \) and -33 mV. Values of \( a \) were measured at \( t_f = 1 \times 10^4 \) s. The solid line represents \( a \propto (\tau_{\text{mix}}/\tau_{\text{thr}})^{1/3} \).

Lastly, we compare the dependence of \( a \) on \( \Phi \) from KMC simulations to experimental measurements. A multi-inlet vortex mixer was used for the experiments, which contained four inlet ports controlled by digital syringe pumps and a single effluent stream. Mixing was performed at a rate which led to a Reynolds number of approximately 2200. More details on the experimentals can be found in Ref. 41. In Figure 7.9, it can be seen that results from simulations obtained for \( \tau_{\text{mix}} = 850 \) ms and \( \zeta = -33 \) mV are in quantitative agreement with those from the experiments,\(^41\) and \( a \) increases with \( \Phi \) according to a relationship \( a \propto \Phi^{1/3} \). Therefore, our KMC model deduced that for the particle sizes obtained in the experiments, the characteristic growth time is approximately 850 ms, which can also be interpreted as the time it takes for the non-solvent to solvent ratio to reach its final value in the non-solvent reservoir in the experiments. However, since the Hamaker constant used in our simulations is at the upper end of the range of values calculated for the experimental system, the actual characteristic growth time can be higher than 850 ms. The lowest Hamaker constant reported for polystyrene in water is approximately \( 10^{-20} \) J.\(^{138} \)
which, according to our KMC approach, leads to an upper limit for the characteristic growth time of approximately 1 s. This 18% increase in time as a result of a more than 10 times decrease in $H$ shows that the size of the precipitated nanoparticles is not strongly influenced by the value of Hamaker constant used in our simulations. It has been previously estimated in the experiments that, for systems of hydrophobic core material and amphiphilic block copolymer, the FNP mixer can achieve homogenous mixing on the order 1.5-3 ms.\textsuperscript{34} Subsequent assembly of the supersaturated core material and hydrophobic block of the copolymer follows diffusion-limited aggregation, and characteristic particle formation time occurs on the order of 10-100 ms.\textsuperscript{52,53} However, nanoparticles obtained from homopolymers undergoing FNP, which are stabilized by a constant $\zeta$-potential have not been studied previously. Our KMC simulations provide insights into the characteristic timescale of this process.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{nanoparticle_size.png}
\caption{Average radius of nanoparticles, $a$, obtained from the experiments and from KMC simulations for $\tau_{\text{mix}} = 850$ ms, $\zeta = -33$ mV, and different concentrations. The solid line is the fit to experimental data, which represents $a \propto \Phi^{1/3}$.}
\end{figure}

Figure 7.10 shows the size distribution of the precipitated nanoparticles for $\zeta = -33$ ms, $\tau_{\text{mix}} = 850$ ms and $\Phi = 0.018$ and 0.067 mg/mL. Results from KMC can
be fitted through Gaussian distributions, with standard deviations of approximately 15%, which are also in good agreement with experimental measurements.\textsuperscript{41}

![Size distributions for nanoparticles obtained for Φ = 0.018 mg/mL and 0.067 mg/mL, τ_{mix} = 850 ms and ζ = -33 ms from KMC simulations. The lines are Gaussian distribution fits.](image)

7.3 Conclusions

In summary, we have developed a multi-scale model, which combines both MD and KMC simulations, and allows us to simulate the formation of charge-stabilized polymeric nanoparticles through rapid solvent exchange up to macroscopic length- and time-scales. This model is derived based on microscopic details from MD simulations, and produces results which are in quantitative agreement with experiments.

Based on the results from our simulations, we were able to elucidate the aggregation mechanism, consisting of a fast growth regime when the surface charge is still small, which can be approximated by the DLA mechanism, and a slow growth regime, when the surface charge is fully built-up. For slow mixing, nanoparticles stay longer in the DLA regime, and are mostly stabilized in the subsequent slow growth
regime. Therefore, nanoparticle size can be predicted from the DLA approximation. On the other hand, for fast mixing, growth in the DLA regime is small. Nanoparticle sizes are thus dictated by the slow growth regime, and they eventually converge over macroscopic timescale, \textit{i.e.}, size is independent of the mixing rate and feed concentration. From our simulations, we have also derived and explained the dependence of nanoparticle size on processing parameters, \textit{e.g.}, polymer feed concentration and characteristic mixing timescale. This knowledge demonstrates that the rapid mixing of a polymer solution with a non-solvent through FNP produces uniformly sized nanoparticles with reliable control. Together with our previous MD studies,\textsuperscript{45,88,126} our results allow us to predict the range of operating conditions required to obtain nanoparticles of a certain size and morphology, and thus provide useful guidelines for fabricating nanoparticles with desired properties for applications in various areas.
Chapter 8

Concluding remarks and future directions

8.1 Concluding remarks

In this dissertation, various simulation techniques, including molecular dynamics (MD) and kinetic Monte Carlo (KMC), were applied to study the assembly of polymers through rapid solvent exchange. The main objectives of this work were to develop a simulation model to (1) understand the assembly mechanism, and (2) make quantitative predictions for the experiments for a given set of process parameters.

From Chapter 2 to Chapter 5, MD simulations were used to study the assembly of different polymer feed materials, i.e., a binary polymer blend with two rubbery components, a binary polymer blend with one glassy component, block copolymers, and a polymer blend with inorganic nanoparticles.

In Chapter 2, I studied systematically how polymer-polymer and polymer-solvent surface tensions control the internal structures of nanoparticles (Janus and core-shell) produced from two rubbery homopolymers undergoing the FNP process. It was found that the final equilibrium structure can be predicted by the surface tensions between
the polymer blend and between the polymers and the solvent, which qualitatively agrees with previous experimental and computational studies on phase-separated structures of polymer blends in aqueous solutions. The results have also demonstrated the ability of the FNP process to independently tune particle size through the mixing time of the solvent-nonsolvent streams and the overall polymer concentration, as well as the particle composition through the polymer feed ratio.

A binary polymer blend with a glassy component was investigated in Chapter 3 using MD simulations. I was able to elucidate the mechanism of patchy particle formation in our simulations, i.e., the homopolymers form separate aggregates first before they merge to form structured particles. Results show that kinetic trapping freezes the particle morphology along the path to the equilibrium structure, leading to patchiness. The number of patches can be independently controlled by the size and the composition of the nanoparticles, both of which can be reliably tuned through process parameters specific to the FNP process, i.e., polymer feed concentration, mixing rate, and polymer feed ratio.

In Chapter 4, MD simulations were employed to study diblock copolymers of low and high molecular weights, and a blend of diblock copolymers and homopolymers undergoing FNP. Morphologies such as concentric lamellar, disordered lamellar, and micellar structures, which were in qualitative agreement with the experiments, were obtained. In addition, simulations also provided a microscopic understanding of the phase separation behavior observed in experiments on length- and time-scales that cannot be directly observed experimentally.

The assembly of a rubbery binary polymer blend and inorganic nanoparticles through FNP was studied using MD simulations in Chapter 5. The interaction strengths between the different constituents were systematically varied, and three different hybrid structures were obtained with inorganic nanoparticles distributed (1) on the surface, (2) throughout the entire volume of the polymeric aggregates, or (3)
aligned at the interface between the two polymer domains. Furthermore, the loading and surface density of the inorganic nanoparticles in the polymeric aggregates for each of these three cases were also analyzed. Results showed that these quantities can be reliably tuned by the polymer and NP feed concentrations, and their volume ratio in the feed streams. It was also demonstrated that electrostatic interactions between polymers and inorganic nanoparticles can enhance NP loading and surface density.

MD simulations proved to be useful for analyzing mechanisms and morphologies on a microscopic level. They were also efficient in morphology prediction from a given type of feed materials. However, MD simulations accessed nanoparticle sizes 10 times smaller and mixing times at least 1000 times smaller than experimental values, which prevented quantitative predictions.

Chapter 6 presents an attempt to access larger length- and time-scales by adopting implicit solvent Brownian dynamics (BD) simulations. An algorithm was outlined, which corrected the slower dynamics as a result of neglecting hydrodynamic interactions in the standard BD simulations. This algorithm corrected the size dependent diffusion coefficients of aggregates by rescaling the friction coefficient for each aggregate individually to match the diffusion dictated by the Stokes-Einstein relationship, and produced aggregation dynamics in agreement with our MD simulations. However, the computational speed up (approximately 30 times) was still insufficient to access length- and time-scales employed by the experiments.

In Chapter 7, a KMC model which used the microscopic details from MD simulations was employed to study FNP on macroscopic length- and time-scales. A direct comparison with experimental results was made, and quantitative agreement was achieved. A detailed analysis on the aggregation mechanism was included, consisting of a fast growth regime when the surface charge is still small, which can be approximated by the diffusion limited aggregation model, and a slow growth regime when the
surface charge is fully built-up. In addition, I also derived and explained the dependence of nanoparticle size on processing parameters, *e.g.*, polymer feed concentration and characteristic mixing timescale.

This dissertation provides a deep understanding on the FNP process on both microscopic and macroscopic levels. The potential of FNP to access a wide range of morphologies with good control by using different feed materials was demonstrated in Chapter 2 to Chapter 5. A detailed analysis on the aggregation mechanism is presented in Chapter 7, which shows that nanoparticle size can be reliably tuned by feed parameters, such as the mixing rate, polymer feed concentration, and surface potential. This multi-scale simulation model allows us to predict the range of operating conditions required to obtain nanoparticles of a certain size and morphology, and thus provide useful guidelines for fabricating nanoparticles with desired properties for applications in various areas. The model is also generic, and can be extended to other feed materials such as block copolymer blends and polymers with charged end groups for future studies.

## 8.2 Future directions

In addition to the structures discussed in this dissertation, such as charge stabilized hydrophobic Janus, core-shell, and patchy nanoparticles, FNP can potentially be used to fabricate other nanoparticle products for various applications. For example, amphiphilic Janus particles which consist of a hydrophobic domain and a hydrophilic domain can act as interfacial stabilizers for Pickering emulsions. They have been shown to adsorb on an oil/water interface with an adsorption energy three times stronger than that of homogeneous particles.\textsuperscript{191} In addition, amphiphilic Janus particles also show interesting self-assembly behavior, leading to aggregates such as micelles,\textsuperscript{192–195} chains,\textsuperscript{196} and mesoscale structures such as membranes.\textsuperscript{194,195,197} It has been shown
experimentally that with FNP, amphiphilic Janus colloids can be obtained from a homopolymer blend and an amphiphilic block copolymer which selectively adsorbs onto one homopolymer domain. Our MD model can be used to study how the size and morphology of the amphiphilic Janus nanoparticles can be tuned by various process parameters, such as the composition of block copolymers and the ratio of homopolymers to block copolymers in the feed stream. Simulations can also shed light on how such nanoparticles can improve the stability of Pickering emulsions.

There are also some ongoing experimental efforts which involve self-assembly of charged polymers, such as amine-terminated polystyrene and carboxyl-terminated polyisoprene. It is of great interest to produce charge functionalized nanoparticles with tunable size, charge, and morphology from this process. Our MD model can be extended to charged polymers, and help us understand how electrostatic interactions affect the assembly mechanism, and how the size, morphology and charge of the precipitated nanoparticles can be controlled.

A modification on FNP, which involves the encapsulation of hydrophilic compounds such as biologics using amphiphilic block copolymers, was recently developed. During this process, which is named inverse Flash NanoPrecipitation (iFNP), a hydrophilic compound and amphiphilic block copolymers are dissolved in a polar solvent, and they are rapidly mixed with a miscible non-polar non-solvent. iFNP was shown to have higher loadings and encapsulation efficiencies than the traditional double emulsion process. To prepare these inverted nanoparticles for drug delivery in an aqueous phase, they undergo further processing which involves either coating with another amphiphilic block copolymer or incorporation into a matrix of hydrophobic polymers.

It has been shown in the experiments that the size of the precipitated nanoparticles can be controlled by the concentration of the hydrophilic drugs, the ratio of drugs to polymers, the choice of non-solvent, and the water content of the solvent stream.
Additional points such as the use of biocompatible and biodegradable polymers also need to be addressed. Simulations can provide insights on the assembly mechanism in order to achieve high drug loading and encapsulation efficiency.

Another possible area of interest is Flash NanoComplexation (FNC),\textsuperscript{200,201} and it involves the rapid mixing of aqueous solutions of polyelectrolytes which are oppositely charged in a jet mixer. Compared to solvent displacement in FNP, FNC makes use of electrostatic attractions between the polyelectrolytes, which cause complexation, leading to the fabrication of uniform polyelectrolyte complex nanoparticles. These nanoparticles are suitable for encapsulating water soluble, charged macromolecular therapeutics such as plasmid DNA and proteins. The FNC technique is promising for producing such nanoparticles in a scalable way with control over size, charge ratio, and charge density. Simulations can be used to understand and achieve better control over this process.
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