Accurate Coarse-Grained Potentials for Soft Matter Systems

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In this Chapter, we present the general statistical-mechanical theory for the derivation of effective Hamiltonians for arbitrary many-body systems in thermodynamic equilibrium. The approach towards a simplified, yet accurate, coarse-grained view of a many-body system has proven to be particularly fruitful in the realm of the Physics of Complex Fluids, a synonym for the broad research area of Soft Matter Science, which encompasses aspects of Physics, Chemistry, Materials Science and Bioscience. After the exposition of the general formalism, we present the methods by which one can derive, in a manageable and accurate way, effective Hamiltonians for a variety of physical systems, by exposing mutually complementary theoretical and computations techniques to this end. Further, we provide extensive exposures of specific and diverse examples from current research in soft matter systems, for which the coarse-graining approach has been applied with remarkable success.

1 Introduction

Soft matter is a subfield of condensed matter that deals with materials whose dominant physical behavior occurs on an energy scale of the order of thermal energy. Soft matter systems are extremely complex materials, typically composed of mesoscopic particles i.e., particles with sizes between the nanometer and the micrometer scale, dispersed into a solvent constituted by much smaller molecules (typically of atomic dimensions). These colloidal suspensions can, in turn, be complemented by co-solutes such as polymers, ions, etc. The huge difference in the length scales associated to the different species in solution results in a very large range of characteristic time scales, which span many orders of magnitude; the dynamics of the solvent molecules, which are very small and thus very fast, needs to be resolved on the time scale of ps, while the typical characteristic diffusion times of colloidal particles is of the order of \( \mu s \). On one hand, this makes it very impractical to keep track of the solvent degrees of freedom, numerically as well as theoretically. On the other hand, in the majority of the cases we are only interested in the structure and dynamics of the solute. We can thus think of an effective one-component description of the system, where the effect of the solvent can be taken into account indirectly by regarding it as a “mediator” of the colloid-colloid interaction.

The process of going from a full-detailed description to a simpler one, also known as coarse-graining, can be generalised to any kind of system, and can also be iterated to further reduce the complexity. For instance, polymer systems are good examples for the application of a hierarchical coarse-graining procedure: at the first level, the solvent molecules can be treated implicitly and the polymer monomers can be identified by their centres of mass only, obtaining a monomer-resolved description. The resolution, and thus the number of degrees of freedom, can be further lowered by considering polymeric chains as composed by several blobs, each containing a certain number of monomers.
Finally, one can go as far as describing a chain with its center of mass, so as to map each chain to a single soft sphere.\textsuperscript{6}

The two main strategies used to perform a coarse-graining are the \emph{top-down} and \emph{bottom-up} approaches. With the former, the matching between the original and coarse-grained systems is carried out in a heuristic way by mapping mesoscopic or macroscopic quantities, such as the persistence length, the melting temperature or the elastic modulus. Examples of top–down coarse-grained models can be found in Refs.\textsuperscript{7,8} By contrast, \emph{bottom-up} approaches start from the microscopic description of the system, usually given in the form of the full Hamiltonian, and rigorously trace out some of the microscopic degrees of freedom.\textsuperscript{1}

In this Chapter we first provide a theoretical basis for the bottom-up approach, and then describe in depth a few reliable computational methods that can be used to apply this concept to real-world soft-matter systems. The rest of this work is organized as follows: the general theory concerning the definition of the effective Hamiltonian and the structure of the resulting effective interactions is presented in Section 2. On the basis of the formalism and the properties of this effective interaction, we present in Section 3 the methods by which it can be calculated or measured by means of theoretical or computational techniques. In the following three sections, we present applications of the general formalism to specific soft-matter systems: generic mixtures of size-asymmetric, hard-soft colloidal particles are discussed in Section 4. Dendrimers of various generations, both neutral and charged, are discussed in Section 5, whereas in Section 6 we focus our attention on ring polymers. Finally, in section 7, we summarize and draw our conclusions.

2 The Effective Hamiltonian

2.1 General considerations and formal definitions

Consider a $\nu$-component ($\nu \geq 1$) classical many-body system. There exist $N_\alpha$ particles of species $\alpha$ enclosed in the macroscopic volume $V$ and the system is at thermodynamic equilibrium at absolute temperature $T$. The quantities $\rho_\alpha \equiv N_\alpha/V$ are the corresponding partial densities, whereas $\rho = \sum_{\alpha=1}^{\nu} \rho_\alpha$ is the total density of the mixture. Each particle of species $\alpha$ has mass $m_\alpha$, and the corresponding thermal de Broglie wavelength is $\lambda_\alpha = h\sqrt{2\pi/\beta} = h\sqrt{2\pi/\beta}$, where $\beta = (k_B T)^{-1}$, and $k_B$ is Boltzmann’s constant. Let, in addition, $\{s_{j\alpha}\}, \ j = 1, 2, \ldots, N_\alpha$, denote the coordinates of the particles of species $\alpha$ and $\{p_{j\alpha}\}$ be the corresponding momenta. The total Hamiltonian of the system, $\mathcal{H}$, can be written as the sum of the kinetic and interaction terms, $\mathcal{H} = K + U$. The kinetic energy is, of course, given as

$$K = \sum_{\alpha=1}^{\nu} \sum_{j=1}^{N_\alpha} \frac{p_{j\alpha}^2}{2m_\alpha},$$

and we will not specify any further the form of the potential energy function $U$ apart from reminding the reader that it depends on the set of all coordinates of all species. Let us also introduce a shorthand for the configurational integral over the coordinates of species $\alpha$ acting on any quantity $\mathcal{O}$ that depends on the coordinates:

$$\text{Tr}_\alpha \mathcal{O} \equiv \int ds_{1\alpha} \cdots \int ds_{N_\alpha \alpha} \mathcal{O}. \tag{2}$$
With these definitions, the canonical partition function $Z$ of the system takes the form

$$Z = \prod_{\alpha=1}^{\nu} \frac{1}{N_\alpha! A_\alpha^{3N_\alpha}} \text{Tr}_\alpha \exp (-\beta U). \quad (3)$$

Suppose now we wish to calculate the expectation value of some quantity $Q_\gamma$ whose instantaneous value depends solely on a subset $\{s_{1\gamma}, \ldots, s_{k\gamma}\}$, $k \leq N_\gamma$, of the coordinates of particles of the $\gamma$-species. This can be obtained easily as

$$\langle Q_\gamma \rangle = \frac{1}{Z} \prod_{\alpha=1}^{\nu} \frac{1}{N_\alpha! A_\alpha^{3N_\alpha}} \text{Tr}_\alpha \left[ Q_\gamma \exp (-\beta U) \right]. \quad (4)$$

Moreover, we can go one step further and formally fix the variables to some prescribed values, $s_i = S_i$, $i = 1, 2, \ldots, k$. In a similar fashion, we can then calculate a generalized $k$-body ‘connected correlation function’ $G^{(k)}_\gamma(S_1, S_2, \ldots, S_k)$ between particles of species $\gamma$ as:

$$G^{(k)}_\gamma(S_1, S_2, \ldots, S_k) = \frac{1}{Z} \prod_{\alpha=1}^{\nu} \frac{1}{N_\alpha! A_\alpha^{3N_\alpha}} \text{Tr}_\alpha \left[ \exp (-\beta U) \prod_{i=1}^{k} \delta (s_{i\gamma} - S_i) \right]. \quad (5)$$

The physical idea behind coarse-graining is, as mentioned at the Introduction, to go over from a full Hamiltonian that contains the coordinates of all particles and all species as degrees of freedom, to one that features only those of a selected species, say $\gamma$. In doing so, we wish to maintain exactly both the thermodynamics of the full mixture, i.e., its partition function $Z$, as well as all the expectation values of quantities involving the coordinates of species $\gamma$ and only of $\gamma$. Formally, this is achieved by defining the effective interaction $\hat{U}_\gamma(\{s_{i\gamma}\})$ between particles of species $\gamma$ through a partial trace in Eq. (3), in which the trace is carried out over all other species excluding $\gamma$, i.e.:

$$\exp (-\beta \hat{U}_\gamma) = \prod_{\alpha \neq \gamma} \frac{1}{N_\alpha! A_\alpha^{3N_\alpha}} \text{Tr}_\alpha \exp (-\beta U). \quad (6)$$

From Eqs. (3) and (6) it is evident that with this definition the partition function remains invariant under the elimination of the other species and it can be equally well expressed in the effective one-component Hamiltonian as:

$$Z = \frac{1}{N_\gamma! A_\gamma^{3N_\gamma}} \text{Tr}_\gamma \exp (-\beta \hat{U}_\gamma). \quad (7)$$

From the above definitions, it immediately follows that also the quantities of Eqs. (4) and (5) remain invariant if expressed now in the effective one-component description, i.e., we can write

$$\langle Q_\gamma \rangle = \frac{1}{Z} \frac{1}{N_\gamma! A_\gamma^{3N_\gamma}} \text{Tr}_\gamma \left[ Q_\gamma \exp (-\beta \hat{U}_\gamma) \right] \quad (8)$$

and

$$G^{(k)}_\gamma(S_1, S_2, \ldots, S_k) = \frac{1}{Z} \frac{1}{N_\gamma! A_\gamma^{3N_\gamma}} \text{Tr}_\gamma \left[ \exp (-\beta \hat{U}_\gamma) \prod_{i=1}^{k} \delta (s_{i\gamma} - S_i) \right]. \quad (9)$$
Formally, therefore, we have found a way to reduce the multicomponent system to a single-component one, which is described by the effective Hamiltonian $H_{\text{eff}}$ that features exclusively the coordinates and momenta of the species $\gamma$ on which we are mainly interested, namely:

$$H_{\text{eff}} = H_0 + \sum_{i=1}^{N_\gamma} \frac{p_i^2}{2m_i} + U_{\text{eff}}(\{s_{\gamma}\}), \tag{10}$$

where we have written $U_{\gamma} = H_0 + U_{\text{eff}}$, separating a term $H_0$ that does not depend on the coordinates $\{s_{\gamma}\}$, whose physical meaning and origing will be discussed later on.

What, if anything at all, have we achieved? Up to now, not much it seems, apart from writing down Eq. (6) and its immediate consequences. Indeed, from the practical point of view, one might say that exactly nothing has been achieved, for if we could carry out the integrations of Eq. (6), we might then as well carry out the remaining ones in Eq. (7) and obtain the partition function of the system. In such a case, the effective interaction would be just a trivial and unnecessary intermediate result. However, this is a too negative point of view and one that does not take into account that, of course, the integrations cannot be carried out in practice. The value of Eq. (6) lies therein that it provides us with an exact formal definition of the effective interaction, on which approximations of varying and, hopefully, increasing accuracy can be applied. Moreover, an effective interaction sheds light on the effects that the coarse-grained degrees of freedom have on the physics of the ones that remain in the description and, in this way, it also makes direct contact with experimental observations.$^1$

In the sections to follow, we will proceed with a more detailed analysis of various aspects of the effective potential, of particular properties of its structure depending on the physical systems at hand and of suitable approximation methods. Before doing so, let us set forth a few important points regarding important limitations it has and relevant difficulties associated with this theoretical tool.

1. The process of the coarse-graining generates, first of all, one additional, extensive term in the effective Hamiltonian, denoted $H_0$ in Eq. (10). Although this has no effect on the structural functions of $\gamma$-type-particles, it does influence the free energy, in which it appears as an additive constant that depends, however, on the mixture composition and on the nature of its constituent units.

2. Information on the densities of the species that have been coarse-grained, on the temperature and on the interactions they have among one another and with the remaining $\gamma$-species are all encoded in the effective potential $U_{\text{eff}}$. This makes the latter tunable by suitable choice of the composition and physical nature of the mixture.

3. The effective potential $U_{\text{eff}}$ is by no means pairwise additive. This is the price we have to pay for simplifying the system. This feature is strongly reminiscent of the problem of proliferation of interactions encountered when performing a (real-space), block-spin type renormalization-group coarse-graining of lattice Hamiltonians; note that also in that case we obtain extensive, additive terms akin to $H_0$ in the renormalized Hamiltonian. Still, a pairwise-additivity approximation can often be applied and it turns out to be quite accurate in some occasions. In the sections to follow, we will
see examples of pairwise-additivity approximations that range in their quality from excellent to hopeless.

4. The coarse-graining process does result into loss of information. In particular, any correlation function or any quantity that involves the coordinates of the coarse-grained degrees of freedom cannot be calculated any more within the framework of \( H_{\text{eff}} \).

5. The general approach to coarse-graining was presented above in the canonical ensemble. Depending on the physical situation at hand, working in different ensembles, such as the semi-grand or the grand canonical ones, when possible, could be advantageous.

Having thus set the stage for the effective Hamiltonian, we proceed in what follows with a more and more detailed examination of particular cases and physical systems.

2.2 Unconstrained systems

We consider for simplicity a binary mixture of two species of particles, 1 and 2, with populations \( N_1, N_2 \), and coordinates \( \{R_i\}, i = 1, 2, \ldots, N_1 \), and \( \{r_j\}, j = 1, 2, \ldots, N_2 \), respectively. We are further assuming that the constituent particles of the two species have no internal degrees of freedom and that the can be represented as point particles. In the opposite case in which, e.g., each species is some complex macromolecule, the considerations of this section should be preceded by the coarse-graining of the internal degrees of freedom and the substitution of the whole macromolecular aggregate by a single effective coordinate, as described in Section 2.3 that follows. Setting the masses of the two species to be \( m_1 \) and \( m_2 \), the Hamiltonian \( H \) of the mixture is expressed as the sum of the kinetic and interaction parts, \( H = K + U \). The kinetic energy is trivially expressed as:

\[
  K = \sum_{i=1}^{N_1} \frac{P_i^2}{2m_1} + \sum_{j=1}^{N_2} \frac{p_j^2}{2m_2},
\]

with the canonical momenta \( P_i \) and \( p_j \) of the two species. The interaction part, on the other hand, is conveniently separated into a sum of intra- and interspecies interactions, \( U_{\text{intra}} = U_{11} + U_{22} \) and \( U_{\text{inter}} = U_{12} \) respectively, whereby:

\[
  U_{11} = \sum_{i=1}^{N_1} \sum_{j>i}^{N_1} \phi_{11}(|R_i - R_j|),
\]

\[
  U_{22} = \sum_{i=1}^{N_2} \sum_{j>i}^{N_2} \phi_{22}(|r_i - r_j|),
\]

and

\[
  U_{12} = \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \phi_{12}(|R_i - r_j|),
\]

introducing the microscopic pair potentials \( \phi_{ij}(x) \), which are assumed to be isotropic.\(^a\)

\(^a\)This is not a restriction: the formalism can also be extended to anisotropic interactions but we refrain from examining this case in the present manuscript.
A comprehensive theoretical approach to coarse-graining such a system in eliminating component 2 and obtaining as a result an effective Hamiltonian for component 1 only was set forward by Dijkstra et al.,10 we summarize below the main results of this approach and discuss their physical meaning. To begin with, the most suitable statistical ensemble to treat this problem turns out to be not the canonical one, in which the particle numbers \(N_1, N_2\) are fixed together with temperature \(T\) and volume \(V\) but rather the semigrand one, in which the particle number \(N_2\) is allowed to fluctuate via a fixed chemical potential \(\mu_2\) of the second species. The corresponding thermodynamic potential in this ensemble is the semigrand free energy \(J(N_1, \mu_2, V, T)\), which is expressed as the Legendre transformation of the Helmholtz free energy \(F(N_1, N_2, V, T)\), viz:

\[
J(N_1, \mu_2, V, T) = F(N_1, N_2, V, T) - \mu_2 N_2.
\]  

(15)

The semigrand free energy is, of course, \(k_B T\) times the logarithm of the semigrand partition function, for which a sum upon all particle numbers \(N_2\) is performed:

\[
\exp(-\beta J) = \sum_{N_2=0}^{\infty} \exp[-\beta (F - \mu_2 N_2)],
\]

(16)

whereas

\[
\exp(-\beta F) = \frac{1}{N_1! N_1^3} \frac{1}{N_2! N_2^3} \text{Tr}_1 \text{Tr}_2 \exp(-\beta H).
\]

(17)

From Eqs. (15) and (16), and setting the activity of species 2 as \(z_2 = \Lambda_2^{-3} \exp(\beta \mu_2)\), we immediately obtain an effective, one-component version of the semigrand partition function as

\[
\exp(-\beta J) = \frac{1}{N_1! N_1^3} \text{Tr}_1 \exp[-\beta (U_{11} + \Omega)],
\]

(18)

where \(\Omega\) is the constrained grand partition function of the particles of species 2 under the condition that those of species 1 are held fixed at positions \((R_1, R_2, \ldots, R_{N_1})\):

\[
\Omega(\{R_i\}; N_1, z_2, V, T) = \sum_{N_2=0}^{\infty} \frac{z_2^{N_2}}{N_2!} \text{Tr}_2 \exp[-\beta (U_{12} + U_{22})].
\]

(19)

Following the notation introduced in Section 2.1, the effective potential function \(\tilde{U}_1\) is expressed as the sum \(U_{11} + \Omega\); the former quantity is the direct interactions between particles of species 1, whereas the latter represents the interactions that are mediated through the second component:

\[
\tilde{U}_1(\{R_i\}; N_1, z_2, V, T) = U_{11}(\{R_i\}) + \Omega(\{R_i\}; N_1, z_2, V, T).
\]

(20)

Of particular importance for the case of unconstrained systems is the remarkable fact that the induced interaction \(\Omega\) can be systematically decomposed into a sum of \(n\)-body terms, \(n = 0, 1, 2, \ldots\), by means of diagrammatic expansions based on 1-2 and 2-2 Mayer-function bonds defined as

\[
f(|R_i - r_j|) = \exp[-\beta \phi_{12}(|R_i - r_j|)] - 1,
\]

\[
g(|r_i - r_j|) = \exp[-\beta \phi_{22}(|r_i - r_j|)] - 1.
\]

(21)
For the details of the diagrammatic expansion, we refer the reader to the original publication.\textsuperscript{10} To illustrate the power of the formalism and the main results to which it leads, let us further define a subset of the cross-interaction term $U_{12}$, call it $U_{12}^{(n)}$, which involves \textit{precisely} $n$ particles of species 1 interacting with $N_2$ particles of species 2, namely

$$U_{12}^{(n)}(\mathbf{R}_1, \mathbf{R}_2, \ldots, \mathbf{R}_n) = \sum_{i=1}^{n} \sum_{j=i+1}^{N_2} \phi_{12}(|\mathbf{R}_i - \mathbf{r}_j|), \quad (22)$$

where, evidently, $U_{12} \equiv U_{12}^{(N_2)}$, cf. Eq. (14), and we have dropped from the list of arguments the coordinates $\{\mathbf{r}_j\}$ for parsimony in the notation (in what follows these will be integrated upon anyway). The induced interaction $\Omega(\{\mathbf{R}_i\}; N_1, z_2, V, T)$ can then be decomposed as a sum of $n$-body terms, each one involving thermodynamic averages that involve, respectively, only the $n$-body cross-interaction potentials $U_{12}^{(n)}$ defined above:

$$\Omega(\{\mathbf{R}_i\}; N_1, z_2, V, T) = \sum_{n=0}^{N_1} \Omega_n(\{\mathbf{R}_i\}; N_1, z_2, V, T). \quad (23)$$

It is particularly instructive to look into some more detail into the first three terms, $n = 0, 1$ and $n = 2$. The zeroth-order term, $\Omega_0$ involves a system that contains no particles of species 1 at all, and it is nothing else than the grand potential of a pure system of particles of type 2 at fixed chemical potential $\mu_2$. Accordingly, it is given as

$$\Omega_0(z_2, V, T) = -Vp(z_2, T), \quad (24)$$

where $p(z_2, T)$ is the pressure of a pure system of particles of species 2 with activity $z_2$. Since we are working at the semigrand ensemble, this term is, at the same time, the pressure of a reservoir of particles 2, which is at particle exchange equilibrium with the mixture at hand through the presence of a semipermeable membrane that allows the passage of particles of species 2 only, blocking the particles of species 1. The $\Omega_1$-term formally involves a single particle of species 1 inserted in the bath of particles of species 2. Through the homogeneity (translational invariance) of the bath of species 2, the dependence on the point of insertion disappears and $\Omega_1$ also becomes an extensive contribution which does not depend on the coordinates of species 1. In particular,

$$\Omega_1(N_1, z_2, T) = N_1 \omega_1(z_2, T), \quad (25)$$

where

$$\omega_1(z_2, T) = -k_B T \ln \langle \exp \left[ -\beta U_{12}^{(1)}(0) \right] \rangle_{z_2}, \quad (26)$$

where the notation $\langle \cdots \rangle_{z_2}$ denotes a grand canonical expectation value taken at the reservoir-Hamiltonian, i.e., within a system interacting by means of $U_{22}$ only. In other words, in Eq. (26), the particle of species 1 is inserted, without loss of generality, at the origin 0 and it acts as a ghost particle: it neither displaces particles of the bath nor does it affect their configuration. We thus have to perform a measurement of the quantity in the brackets without the quantity itself being active in determining physical correlation the system, which are dictated by $U_{22}$ alone. One immediately recognizes here the famous Widom insertion\textsuperscript{11} and Eq. (26) expresses $\omega_1(z_2, T)$ as one contribution of the sea of species 2 to the excess chemical potential of the particles of species 1.
Taken together, the terms $\Omega_0$ and $\Omega_1$ thus constitute the configuration-independent, extensive contribution $H_0$ to the effective Hamiltonian, cf. Eq. (10):

$$H_0 = -Vp_2(z_2, T) + N_1\omega_1(z_2, T),$$

(27)

the interaction terms involving all the higher-order contributions to $\Omega$:

$$U_{\text{eff}}([R_i]; N_1, z_2, T) = U_{11}([R_i]) + \sum_{n=2}^{N_1} \Omega_n([R_i]; N_1, z_2, T).$$

(28)

Eq. (28) manifests what has been mentioned previously: the effective interaction inadvertently generates $n$-body coupling terms in the Hamiltonian, going thus beyond pair-additivity. Still, effective pair potentials usually dominate and it is useful to look in more detail into the structure of the term $\Omega_2([R_i]; N_1, z_2, T)$. In analogy to the bare interaction $U_{11}([R_i])$, Eq. (12), this term is pair-decomposable as

$$\Omega_2([R_i]; N_1, z_2, T) = \sum_{i=1}^{N_1} \sum_{j>i}^{N_1} \omega_2([R_i - R_j]; z_2, T).$$

(29)

Setting $R \equiv |R_i - R_j|$, the species-2-induced pair interaction potential $\omega_2(R; z_2, T)$ is expressed as

$$\omega_2(R; z_2, T) = -k_B T \ln \left[ \frac{\left< \exp \left[ -\beta U_{12}^{(2)}(R_i, R_j) \right] \right>_{z_2}^{z_2}}{\left< \exp \left[ -\beta U_{12}^{(1)}(0) \right] \right>_{z_2}^{z_2}} \right].$$

(30)

The reduction of the dependence from $R_i, R_j$ to just the magnitude of their difference is the result of the averaging in an isotropic system.

It is worth taking a closer look at the denominator of Eq. (30) above. It expresses the expectation value of the Boltzmann-weighted cost of introducing a particle of type 1 in a sea of particles 2, squared. In other words, it can also be looked upon as the same cost for the introduction of two particles of type 1, separated by an infinite distance from one another. Certainly, if the two are infinitely far apart, the insertion of one of them is uncorrelated from the insertion of the other. Assuming, therefore, that one of the particles is inserted at the origin $0$ and the other at $S$, we can write

$$\left< \exp \left[ -\beta U_{12}^{(1)}(0) \right] \right>_{z_2}^{z_2} = \left< \exp \left[ -\beta U_{12}^{(1)}(0) \right] \right>_{z_2}^{z_2} \left< \exp \left[ -\beta U_{12}^{(1)}(S) \right] \right>_{z_2}^{z_2} = \left< \exp \left[ -\beta U_{12}^{(1)}(0) \right] \right>_{z_2, S \to \infty} \left< \exp \left[ -\beta U_{12}^{(1)}(S) \right] \right>_{z_2, S \to \infty} = \left< \exp \left[ -\beta U_{12}^{(2)}(0, S) \right] \right>_{z_2, S \to \infty}.$$  

(31)

In the first line above, we used the independence of the expectation value on the point of insertion. In the second one, we took the limit $S \to \infty$ and made use of the fact that in this case the two random insertions yield costs uncorrelated to one another, and thus
the expectation value of the product coincides with the product of the expectation values. Combining Eqs. (30) and (31), we can now express the induced pair potential as

\[
\omega_2(R; z_2, T) = -k_B T \ln \left\langle \exp \left[ -\beta U_{12}^{(2)}(0, R) \right] \right\rangle_{z_2} \\
+ k_B T \ln \left\langle \exp \left[ -\beta U_{12}^{(2)}(0, R \to \infty) \right] \right\rangle_{z_2}.
\] (32)

The induced interaction \(\omega_2(R; z_2, T)\) is therefore a difference between two semigrand free energy costs: the one that obtains by the (virtual) insertion of two type-1 particles, separated by \(R\), in a sea of small ones minus the same quantity when these particles are inserted at places infinitely far apart from one another. The procedure a generalized Widom insertion, in which two particles are virtually placed inside the system instead of just one. The induced interaction evidently fulfills the property \(\omega_2(R \to \infty; z_2, T) \to 0\).

Eq. (32) above is exact. Its value lies therein that it gives us a point of reference, a theoretical milestone to which we can refer when applying any further approximations to calculate the induced interaction, a quantity which, in the realm of the coarse-graining of binary, unconstrained systems is also called depletion interaction. However, its practical value for dense systems is very limited. To illustrate this point, imagine of a concrete physical system, i.e., a mixture of hard spheres, large (species 1) and small (species 2). Suppose that the small system is very dense and keep in mind that the expectation values of Eq. (32) are taken in an ensemble of pure small hard sphere systems, which are unaware of the existence of the large ones; the insertions are, as mentioned above, virtual. What is the chance that such a system will spontaneously create a void sufficiently large to accommodate one and two large hard spheres? It is ridiculously small! In the vast majority of cases, the attempt to insert one or two large hard spheres will result in overlaps with the small ones and both terms in the exponents of Eq. (32) will have the value minus infinity. What Eq. (32) actually does, is to take the difference between the logarithms of two numbers that are both extremely small; the difference, however, is a reasonable number of order unity. Attempting to do this in the way Eq. (32) suggests is hopeless at high densities of the small component, if the steric interactions with the big one are strong. Accordingly, one has to resort to other methods, in which the large particles are inserted in the fully interacting system from the outset. If this is the case, then the relative difference of the two logarithms (or, equivalently, the ratio of the two expectation values) is measured directly, and therefore the problem is circumnavigated in this way. We will return to this point in Section 3 below.

Finally, we briefly mention the higher-order interactions, taking the three-body term \(\Omega_3(\{\mathbf{R}\}; N_1, z_2, T)\) as a case in point: This term can be decomposed as

\[
\Omega_3(\{\mathbf{R}\}; N_1, z_2, T) = \sum_{i=1}^{N_1} \sum_{j>i}^{N_1} \sum_{k>j}^{N_1} \omega_3(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k; z_2, T),
\] (33)
with the three-body induced potential taking the form:

\[ \omega_3(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k; z_2, T) = -k_B T \ln \left\langle \exp \left[ -\beta U^{(3)}_{12}(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k) \right] \right\rangle _{z_2} \]

\[ + k_B T \sum_{(m,n)} \ln \left\langle \exp \left[ -\beta U^{(2)}_{12}(\mathbf{R}_m, \mathbf{R}_n) \right] \right\rangle _{z_2}, \quad (34) \]

where the sum at the second line runs over the combinations \((m, n) = (i,j), (j,k), (k,i)\).

The structure of Eq. (34) reveals the physical meaning of the three-body induced potential \(\omega_3(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k; z_2, T)\). In the first term, three particles of species 1 are Widom-inserted and the cost of this insertion relative to the case in which all three are infinitely far away from one another is calculated. The second term is, evidently, minus the sum of the three two-body interactions between the particles, cf. Eq. (30). Thus, \(\omega_3(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k; z_2, T)\) measures precisely the deviations of the free energy cost of insertion of three particles from those that would result from pair additivity. Such deviations are expected on physical grounds, if we think of three large hard spheres being really and not just virtually inserted in a sea of small ones. The distortions they cause on the density profile of the small spheres are not necessarily the superposition of the distortions caused by insertions in pairs. There are genuine three-body effects, which are not reducible to superpositions of pairs. This is a general characteristic of the effective, as opposed to fundamental (i.e., microscopic) interactions, such as the Coulomb potential. Even higher-order induced potentials follow the same logic; thus, \(\Omega_n\) counts the genuine \(n\)-body free energy insertion cost of \(n\) particles, which is not included in all lower-order terms. Their functional form follows from this statement and we will therefore not delve into this topic in any further detail.

Gathering the above results the effective, single-species Hamiltonian takes the form:

\[ \mathcal{H}_{\text{eff}}(\{\mathbf{P}_i\}, \{\mathbf{R}_i\}; V, N_1, z_2, T) = -V p(z_2, T) + N_1 \omega_1(z_2, T) \]

\[ + \sum_{i=1}^{N_1} \frac{\mathbf{P}_i^2}{2m_1} + \sum_{i=1}^{N_1} \sum_{j>i}^{N_1} \left[ \phi_{11}(\mathbf{R}_{ij}) + \omega_2(\mathbf{R}_{ij}; z_2, T) \right] \]

\[ + \sum_{i=1}^{N_1} \sum_{j>i}^{N_1} \sum_{k>j}^{N_1} \omega_3(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k; z_2, T) + \cdots \quad (35) \]

Excluding the two first terms on the right-hand side from the statistical mechanics of the system, we would obtain an apparent pressure \(\Pi(\rho_1, z_2, T)\) for the system as well as an apparent chemical potential \(\mu_1^*(\rho_1, z_2, T)\). From Eq. (35), it follows that the total pressure \(P(\rho_1, z_2, T)\) of the system and the total chemical potential \(\mu_1(\rho_1, z_2, T)\) of species 1 are given by the expressions:

\[ P(\rho_1, z_2, T) = \Pi(\rho_1, z_2, T) + p(z_2, T); \quad (36) \]

\[ \mu_1(\rho_1, z_2, T) = \mu_1^*(\rho_1, z_2, T) + \omega_1(z_2, T). \quad (37) \]

Accordingly, the quantity \(\Pi(\rho_1, z_2, T)\) is recognized as the osmotic pressure across a semipermeable membrane separating the system from a reservoir of species 2, which allows the exchange of this species only, setting its activity to \(z_2\) for both the system and the
reservoir. The reader should confirm that the terms \( p(z_2, T) \) and \( \omega_1(z_2, T) \) do not affect the location of possible phase boundaries \( (\rho_1^A, \rho_1^B) \) for the densities of species 1 between two coexisting phases A and B.

We conclude this Section with a remark regarding the correlations between particles of species 1, which are immersed in a fluid of species 2. As discussed above, the latter is described by its partial chemical potential \( \mu_2 \), or equivalently by its activity \( z_2 \), which can be thought of as that of a reservoir of the second species at the same chemical potential. Let us truncate the series of Eq. (35) at the pair potential level, for simplicity. Then, the total pair interaction potential, \( \phi_{\text{eff}}(r; z_2, T) \) is given as

\[
\phi_{\text{eff}}(r; z_2, T) = \phi_{11}(r) + \omega_2(r; z_2, T).
\]

The radial distribution function \( g_{11}(r; \rho_1, z_2, T) \) between particles of species 1 depends parametrically on the number density \( \rho_1 = N_1/V \) of the same, as well as on \( z_2 \) and the temperature; the \( z_2 \)-dependence comes from the induced interaction \( \omega_2(r; z_2, T) \). All techniques from the theory of the liquid state to calculate the correlation functions can be applied to the system interacting by means of the effective potential \( \phi_{\text{eff}}(r) \). In particular, at the limit of vanishing density of species 1, it holds:

\[
\lim_{\rho_1 \to 0} g_{11}(r; \rho_1, z_2, T) = \exp [-\beta \phi_{\text{eff}}(r; z_2, T)].
\]

Eq. (39) can be very useful for measuring the effective potential. We will return to this point in Section 3.

### 2.3 Constrained systems

Another broad class of soft matter systems for which coarse-graining is involved have mutual constraints in their number fluctuations, and therefore the semigrand ensemble formalism set forth in the preceding section cannot be applied in this case. Two categories of such common systems exist, namely the following.

1. Mixtures of entities that carry electric charge, such as ionic mixtures, liquid metals and charged colloidal suspensions, containing in general salt. In this case, one is dealing with a \( \nu \)-component mixture, each of the constituent particles carrying charge \( Z_{\nu} \). Since electroneutrality must be strictly obeyed so that the thermodynamic limit exists, the number densities \( \rho_{\nu} \) of the components are bound to fulfill the condition:

\[
\sum_{i=1}^{\nu} \rho_i Z_i = 0.
\]

In most cases, we are dealing with two-component mixtures, so that Eq. (40) above immediately implies that the particle number \( N_2 \) cannot fluctuate independently of \( N_1 \); the two are mutually constrained.

2. Systems that consist of macromolecular aggregates with internal fluctuations, each aggregate \( \mathcal{I} \) consisting of a fixed number of \( M_I \) microscopic units; a typical example are polymers of different architectures (chain, ring, star, brush, dendritic, cross-linked etc.) Here, one wishes to represent the full object in a coarse-grained fashion by reducing the \( M_I \) degrees of freedom to a much smaller number, typically just one
effective coordinate. Evidently, the number of effective coordinates is bound to the number of the microscopic ones by the architecture (chemistry), which is a quenched property of the system. The microscopic and the coarse-grained numbers of degrees of freedom cannot fluctuate independently of one another.

The first class of systems constitute one of the most well-studied category of colloidal suspensions and one that still is very much an active topic of research. Among the most celebrated results of the coarse-graining approach to charge-stabilized colloidal suspensions are the Poisson-Boltzmann theory and its linearized version, known as Debye-Hückel theory, as well as the associated Derjaguin-Landau-Verwey-Overbeek (DLVO) potential. We will not discuss any further these system at the present Chapter, referring the reader to some of the most representative articles on this subject in the literature.\textsuperscript{19} We focus, instead on the second class of systems. The formalism for deriving an effective interaction is set in the framework of the canonical ensemble, as shown in Section 2.1. In what follows, we will make the derivation tractable by considering just two macromolecules and formally tracing out the microscopic degrees of freedom, so that a pair effective interaction between the mesoscopic degrees of freedom remains.

We consider two star polymers with $f$ arms, see Figure 1, as a representative example. The average spherical symmetry of the monomer density profile around the central, anchoring point of the arms, makes the choice of the latter as an effective coordinate natural; however, the discussion is general and any other material coordinate or even the center of mass can be chosen as such. The goal of the coarse-graining is thus to canonically average out all the degrees of freedom of the monomers along the arms and be left with an effective interaction $\phi_{\text{eff}}(R)$ between the centers, whereby the first star is placed at the origin and the second at a position $\mathbf{R}$ from it.

Figure 1: Simulation snapshots of two model star polymers at moderate mutual overlap. The spheres denote monomers along the arms, whereas the two red balls are the centers of the stars, which are chosen as effective coordinates, as explained in the text.
We assume that each star contains $M + 1$ beads, one being the central one and $M$ along the arms. We denote the position of the $i$-th bead of the $\alpha$-star as $s_{i\alpha}$, $i = 0, 1, \ldots, M$ being the monomer index and $\alpha = 1, 2$ the molecule index, whereby $s_{0\alpha}$ and $s_{2\alpha}$ are the coordinates of the two central particles. The total potential energy $U$ of the two interacting stars can be written as the sum of intramolecular, $U_{\text{intra}}$, and intermolecular, $U_{\alpha\beta}$, $\alpha \neq \beta$ and $\alpha, \beta = 1, 2$, contributions as

$$U(\{s_{i1}\}, \{s_{j2}\}) = U_{11}(\{s_{i1}\}) + U_{22}(\{s_{j2}\}) + U_{12}(\{s_{i1}\}, \{s_{j2}\})$$

$$\equiv U_{\text{intra}}(\{s_{i1}\}, \{s_{j2}\}) + U_{12}(\{s_{i1}\}, \{s_{j2}\}),$$

where we have grouped together the two intramolecular terms in $U_{\text{intra}}$, which is free of interactions between the stars. The intramolecular potential energy functions contain contributions from both bonded and non-bonded monomers, whereas, evidently, the intermolecular one features exclusively non-bonded terms. Let us denote as $W_2$ the configuration part of the partition function of the two stars, expressed as [cf. Eq. (3)]:

$$W_2 = \int \cdots \int d s_{M2} \exp \left[ - \beta U(\{s_{i1}\}, \{s_{j2}\}) \right].$$

Moreover, let $W_1$ be the partition function of a single star with its center fixed at some position in space, namely

$$W_1 = \int \cdots \int d s_{M\alpha} \exp \left[ - \beta U_{\alpha\alpha}(\{s_{i\alpha}\}) \right],$$

where, in the last equation, it is irrelevant whether $\alpha = 1$ or $\alpha = 2$, since the two molecules are identical.

The key quantity is a constrained Helmholtz free energy $F(R)$ defined as the partial trace over all other degrees of freedom, with the two centers kept at positions $s_{01} = 0$ and $s_{2\alpha} = R$, viz.:

$$\exp \left[ - \beta F(R) \right] = \int \cdots \int d s_{M2} \exp \left[ - \beta U(\{s_{i1}\}, \{s_{j2}\}) \right] \delta(s_{01}) \delta(s_{02} - R) .$$

With $p(R)$ denoting the probability density of finding the center of the second star at position $R$ relative to the first, it holds by construction of the quantity $F(R)$ that:

$$p(R) \propto \exp \left[ - \beta F(R) \right],$$

the constant of proportionality being the inverse of the partition function, $W_2^{-1}$, which is irrelevant as long as we are interested in the relative probabilities:

$$\frac{p(R)}{p(R_0)} = \exp \left[ - \beta (F(R) - F(R_0)) \right],$$

where $R_0$ is some arbitrary reference vector. Of particular usefulness is the choice $R_0 \rightarrow \infty$. In this case, the quantity $\exp \left[ - \beta F(R_0) \right]$, Eq. (44), takes a simple form. Indeed, since every molecule has a finite spatial extension (of the order of its gyration radius), when the centers of the two are taken infinitely far apart, all intermolecular contributions

\[\text{Nothing changes in the formalism to follow if the two stars have different monomer numbers but we set them equal for simplicity in notation.}\]
vanish and the expression in Eq. (44) reduces to the product of the partition functions of two isolated stars, each with its center fixed in space, Eq. (43):

$$\exp [-\beta F(R_0 \to \infty)] = W_2^1.$$  (47)

We now define the effective interaction $\phi_{\text{eff}}(r)$ between the two macromolecules as

$$\phi_{\text{eff}}(r) = F(r) - F(R_0 \to \infty).$$  (48)

Combining Eqs. (46) and (48), we readily obtain

$$\exp [-\beta \phi_{\text{eff}}(r)] = \frac{p(r)}{p(R_0 \to \infty)}.$$  (49)

However, according to the discussion preceding Eq. (47), as $R_0 \to \infty$, the two stars become uncorrelated to one another. Accordingly, $p(R_0 \to \infty) = p_0(r)$ for any $r$, where $p_0(r)$ is the probability density in the Hamiltonian $U_0$ of two noninteracting stars; the latter form an ideal gas and therefore

$$\frac{p(r)}{p(R_0 \to \infty)} = \frac{p(r)}{p_0(r)} \equiv g(r),$$  (50)

introducing the infinite-dilution radial distribution function $g(r)$ of the centers of only two star polymers in the volume $V$, in the absence of any others. Accordingly, from Eqs. (49) and (50) we obtain that the effective interaction is isotropic and it can be expressed as

$$\lim_{\rho \to 0} g(r; \rho) = \exp [-\beta \phi_{\text{eff}}(r)],$$  (51)

which is identical to Eq. (39).

Contrary to the discussion in Section 2.2, we have not presented here a general scheme that generates at once expressions for all $n$-body interactions. However, the generalization to $n > 2$ is conceptually straightforward: one considers the constrained free energy $F(R_1, R_2, \ldots, R_n)$ of the centers of $n$ macromolecules and subtracts from it the sum of all contributions of the immediately lower, $(n-1)$-order effective potential, defining in this way the $n$-body interaction. Depending on the physical system, and in particular on the deformability of the macromolecules at hand, the higher-order interactions can become very important. We will return to this point in Section 6.

3 Methods of Calculating Effective Pair Potentials

3.1 Methods based on the radial distribution function

The most straightforward way for calculating the effective interaction in a simulation is offered by Eq. (39) or Eq. (51). Ideally, one would perform a standard Monte Carlo (MC) or Molecular Dynamics (MD) simulation of just two macromolecular aggregates in a sea of smaller particles [Eq. (39)] or just by themselves [Eq. (51)] and measure, by calculating the properly normalized histogram of separations $r$ the infinite-dilution limit radial distribution function $g(r; \rho \to 0)$; the limit $\rho \to 0$ is, of course, an idealization but having just two particles in a sufficiently large simulation box is sufficient. From that, the effective interaction can be obtained as

$$\phi_{\text{eff}}(r) = -k_B T \ln g(r; \rho \to 0).$$  (52)
The simplicity of this approach is deceptive. Regions in which the effective interaction attains values significantly higher than $k_B T$ will be rarely visited in an unbiased simulation and therefore sampling will be extremely poor there. In a similar spirit, if $\phi_{\text{eff}}(r)$ has deep negative minima, separated from the rest by high barriers, in a free simulation the two particles will be trapped or ‘locked’ into these and, again, it will be very hard to explore efficiently and accurately the whole range of separations $r$. One possibility to overcome this problem is to add a bias potential, $\Phi_{\text{bias}}(r)$, to the interaction and measure the modified radial distribution function, $\tilde{g}(r; \rho \to 0)$ given by

$$\phi_{\text{eff}}(r) + \Phi_{\text{bias}}(r) = -k_B T \ln \tilde{g}(r; \rho \to 0).$$

Ideal, one would like to choose $\Phi_{\text{bias}}(r)$ in such a way that all separations $r$ are sampled uniformly, i.e., $\tilde{g}(r; \rho \to 0) = 1$, which immediately implies, through Eq. (53), $\Phi_{\text{bias}}(r) = -\phi_{\text{eff}}(r)$. One would have to add a bias potential opposite to the unknown effective interaction, which, if we knew in advance, we wouldn’t need to make a simulation to find out what it is! Evidently, we have to resort to some more sophisticated approaches, in which the bias potential is determined in an iterative way or it is built-up locally during the simulation in a Wang-Landau-type simulation scheme.

To avoid iterative approaches, one may choose the bias potential to be local, constraining thereby $r$ within smaller regions or ‘windows’. The technique is thereby called ‘window sampling’ and the basic idea is the following: the interval $r \in [r_{\text{min}}, r_{\text{max}}]$ is separated into sub-intervals or windows of width $w$, which may vary from one window to the other. Within each window, the effective potential $\phi_{\text{eff}}(r)$ is supposed or expected to vary by at most a few $k_B T$, so that when $r$ is restricted to lie within any given window, statistics there is good and the whole width $w$ is sampled well. Common choices for the local bias potential are an infinite well that vanishes within $w$ and diverges elsewhere or a harmonic potential $\Phi_{\text{bias}}(r) = k_j (r - r_j)^2$ centered at the midpoint $r_j$ of the window. Separate histograms $\tilde{g}^{(j)}(r)$ within each of these windows are collected and at the end of the simulation the effective interaction results by merging together the pieces $\phi_{\text{eff}}^{(j)}(r)$ obtained in each window:

$$\phi_{\text{eff}}^{(j)}(r) = -k_B T \ln \tilde{g}^{(j)}(r) - \Phi_{\text{bias}}(r) + c_j,$$

where the $c_j$’s are arbitrary constants that are used to match the pieces of the effective potential. In particular, the various pieces are ‘vertically shifted’ via appropriate choices of the constants $c_j$ so as to obtain a smooth function $\phi_{\text{eff}}(r)$. To achieve this, some overlap between the windows is necessary. Alternatively, one can resort to more sophisticated methods, such as histogram reweighting to obtain a smooth ‘patching’ of the $\phi_{\text{eff}}^{(j)}(r)$ into $\phi_{\text{eff}}(r)$.

### 3.2 Methods based on the effective force

Instead of measuring directly the effective potential $\phi_{\text{eff}}(r; z_2, T)$, one can resort to measuring its gradient, which is the effective force $F_{\text{eff}}(r)$, namely

$$F_{\text{eff}}(r; z_2, T) = -\nabla_r \phi_{\text{eff}}(r; z_2, T).$$

In what follows, we will derive expressions for the effective force for both unconstrained [Section 2.2] and constrained [Section 2.3] systems.
3.2.1 Unconstrained systems

Our starting point is Eq. (32). Consider the first term in the brackets at the right-hand side of Eq. (32). Using Eq. (22) and setting $R \rightarrow r$, we have:

$$
\exp \left[ -\beta U_{12}^{(2)}(0, r) \right]_{z_2} \frac{1}{\Xi_2(z_2, T, V)} \sum_{N_2=0}^{\infty} \frac{z_2^{N_2}}{N_2!} \times \text{Tr}_2 \exp \left\{ -\beta \left( U_{22}(\{r_j\}) + \sum_{j=1}^{N_2} \phi_{12}(r_j) + \phi_{12}(|r - r_j|) \right) \right\},
$$

(56)

where $\Xi_2(z_2, T, V)$ is the grand partition function of the reservoir of particles 2. The term in the parentheses in the exponential of the right-hand-side of Eq. (56) above can be interpreted as the configurational part of a modified Hamiltonian, in which two type-1 particles, held fixed at positions $0$ and $r$ act as an external potential to the system of particle of type 2, namely

$$
\hat{U}_{22}(\{r_j\}; 0, r) = U_{22}(\{r_j\}) + \sum_{j=1}^{N_2} \phi_{12}(r_j) + \sum_{j=1}^{N_2} \phi_{12}(|r - r_j|).
$$

(57)

Accordingly, Eq. (56) can be expressed as

$$
\exp \left[ -\beta U_{12}^{(2)}(0, r) \right]_{z_2} = \frac{\hat{\Xi}_2(r; z_2, T, V)}{\Xi_2(z_2, T, V)},
$$

(58)

where $\hat{\Xi}_2(r; z_2, T, V)$ is the grand partition function of the system interacting with the Hamiltonian $\hat{U}_{22}(\{r_j\}; 0, r)$, and it depends only on $r = |r|$ as a result of the averaging. With this notation, Eq. (32) now takes the form

$$
\omega_2(r; z_2, T) = -k_B T \ln \left[ \frac{\hat{\Xi}_2(r; z_2, T, V)}{\Xi_2(r \rightarrow \infty; z_2, T, V)} \right],
$$

(59)

implying

$$
- \nabla_r \omega_2(r; z_2, T) = k_B T \frac{\nabla_r \hat{\Xi}_2(r; z_2, T, V)}{\Xi_2(r; z_2, T, V)}.
$$

(60)

Using Eqs. (56) and (57), Eq. (60) takes the form

$$
- \nabla_r \omega_2(r; z_2, T) = \left\langle \sum_{j=1}^{N_2} [-\nabla_r \phi_{12}(|r - r_j|)] \right\rangle_{\hat{U}_{22}, z_2} = \left\langle \sum_{j=1}^{N_2} f_{12}(|r - r_j|) \right\rangle_{\hat{U}_{22}, z_2},
$$

(61)

where the notation $\langle \cdots \rangle_{\hat{U}_{22}, z_2}$ denotes an expectation value carried in a system of particles 2 having activity $z_2$, and in which two particles of type 1 are physically inserted at positions 0 and r. The quantity $f_{12}(|r - r_j|) = -\nabla_r \phi_{12}(|r - r_j|)$ is the microscopic force acting
on particle 1 at position \( r \) due to a particle of type 2 at position \( r_j \). Denoting, in addition, as \( f_{11}(r) = -\nabla_r \phi_{11}(r) \) the microscopic force between particles of species 1, and taking into account Eqs. (38), (55), and (61), we obtain

\[
\mathbf{F}_{\text{eff}}(r; z_2, T) = f_{11}(r) + \left( \sum_{j=1}^{N_2} f_{12}(|r - r_j|) \right) \delta(z_2 - z_2).
\]

Eq. (62) above is an extremely useful result and a very elegant one in its simplicity and clarity: it states that the total effective force being experienced by a particle of species 1 at position \( r \), is the sum of the direct force acting upon it by the other particle of species 1 held fixed at the origin, plus the expectation value of all the microscopic forces acting on it by all the particles of species 2 present in the mixture. We emphasize, once again, a crucial difference with the results we obtained in Section 2.2. There, all expectation values were taken at the Hamiltonian of a system of a pure reservoir of species 2-particles. In that case, the only physically active interactions were those between particles of the reservoir and the insertions of particles of species 1 were virtual: expectation values of observables involving 1-2 interactions were calculated in the sense of Widom insertions, which do not alter the configurations of particles of species 2. Here, instead, the two particles of species 1 are physically inserted and their simultaneous presence at positions \( 0 \) and \( r \) creates an inhomogeneous density profile \( \rho_2(r'; 0, r, z_2, T) \) for the particles of species 2, the latter being the expectation value of the density operator \( \hat{\rho}_2 \) (\( \{ r_j \} \) = \( \sum_{j=1}^{N_2} \delta(r' - r_j) \)), viz:

\[
\rho_2(r'; 0, r, z_2) = \left( \sum_{j=1}^{N_2} \delta(r' - r_j) \right) \delta(z_2 - z_2).
\]

We can, thus, equivalently to Eq. (62) write

\[
\mathbf{F}_{\text{eff}}(r; z_2, T) = f_{11}(r) + \int f_{12}(|r - r'|) \rho_2(r'; 0, r, z_2, T) \, dr'.
\]

Eq. (64) is very useful for theoretical approaches, in which one employs, e.g., density functional theory\(^{30}\) or the superposition approximation\(^{31}\) to calculate the density profile \( \rho_2(r'; 0, r, z_2, T) \), from which the effective force results by performing (numerically) the integral of Eq. (64).

The virtual insertion formalism of Section 2.2 and the physical insertion formalism presented here are, of course, fully equivalent. Each one has its advantages and drawbacks, depending on what one wants to do. As previously mentioned, the virtual insertions are extremely inefficient in measuring directly the effective potential in a dense system with strong steric repulsions between the particles. Here, the physical insertion formalism is well-suited to deal with such problems. We just set up a MC or MD simulation, in which we first insert the two big particles into the empty box, and fix them at the desired positions, \( 0 \) and \( r \). Thereafter, the small particles are inserted sequentially, taking care of avoiding too strong overlaps. From then on, the system is equilibrated and the simulation, in which only particles of species 2 are moved, proceeds normally. At given intervals, the vector sum of the microscopic forces from all particles of species 2 on the big particle held fixed at position \( r \), \( \sum_{j=1}^{N_2} f_{12}(|r - r_j|) \), is measured and averaged at the end. A good check is to also measure the same forces \( \sum_{j=1}^{N_2} f_{12}(r_j) \) acting on the big particle at the origin, and
verify at the end of the run that the expectation values satisfy the *actio-reactio* law, as they should. Having gathered the statistics and calculated $F_{\text{eff}}(r; z_2, T)$ as given by Eq. (62), the effective potential $\phi_{\text{eff}}(r; z_2, T)$ follows by simple, one-dimensional integration:

$$\phi_{\text{eff}}(r; z_2, T) = \int_r^\infty |F_{\text{eff}}(r'; z_2, T)| \, dr'.$$

### 3.2.2 Constrained systems

It will come as no surprise that for the case of constrained systems we obtain the same result as Eq. (62); still, it is instructive to go through the steps and demonstrate this explicitly. From Eq. (48), we obtain

$$F_{\text{eff}}(r) \equiv -\nabla_r \phi_{\text{eff}}(r) = -\nabla_r F(r).$$

Set explicitly $s_{01} = 0$ and $s_{02} = r$ in Eq. (44) and define the constrained configuration partition function $W_2(r)$ as

$$W_2(r) = \int ds_{i1} \cdots \int ds_{iM} \int ds_{j1} \cdots \int ds_{jM} \times \exp[-\beta U_{11}(0, \{s_{i1}\})] \exp[-\beta U_{22}(r, \{s_{j2}\})]$$

$$\times \exp[-\beta U_{12}(0, r, \{s_{i1}\}, \{s_{j2}\})] = \exp[-\beta F(r)],$$

where $1 \leq i, j \leq M$. In analogy with the discussion in Section 3.2.1, define a modified interaction, $\hat{U}$, in which the coordinates $s_{01}$ and $s_{02}$ are clamped at the values $0$ and $r$, respectively:

$$\hat{U}(\{s_{i1}\}, \{s_{j2}\}; 0, r) = U_{11}(0, \{s_{i1}\}) + U_{22}(r, \{s_{j2}\}) + U_{12}(0, r, \{s_{i1}\}, \{s_{j2}\}).$$

The instantaneous value of the microscopic force $f_{\text{micro}}(r)$ acting on the effective coordinate located at $s_{02} = r$ is derived from the interactions as

$$f_{\text{micro}}(r) = -\nabla_r U_{22}(r, \{s_{j2}\}) - \nabla_r U_{12}(0, r, \{s_{i1}\}, \{s_{j2}\}),$$

i.e., it is the sum of all intramolecular and intermolecular microscopic forces. From Eqs. (66), (67), and (69) above, it immediately follows that the effective force is the expectation value of all microscopic forces taken in the Hamiltonian with interaction $\hat{U}$:

$$F_{\text{eff}}(r) = \langle f_{\text{micro}}(r) \rangle_{\hat{U}},$$

where we set $r \to r$ due to isotropy of space. Note that the microscopic force includes one term that is not fluctuating, and this is the direct interaction between the effective coordinate $s_{01}$ and the coordinate $s_{02}$; since they are clamped, the direct force between the two remains fixed. All other degrees of freedom fluctuate, and the averaging acts on those microscopic forces. This completes the analogy with the discussion in Section 3.2.1 and in particular with Eq. (62). For more details and applications of this method to polymeric systems, we refer the reader to Refs. 32, 33.
3.3 Generalized Widom insertion

A different possibility to compute the effective interaction between bonded and intrinsically fluctuating macromolecular aggregates is a generalization of the Widom insertion algorithm. Indeed, combining Eqs. (43), (47), (48), and (67), we obtain

\[
\exp \left\{ -\beta \phi_{\text{eff}}(r) \right\} = \frac{W_2(r)}{W_1^2}.
\]

(71)

By virtue of Eq. (68), we readily obtain

\[
\frac{W_2(r)}{W_1^2} = \langle \exp \left\{ -\beta U_{12}(0, r, \{s_{i1}\}, \{s_{j2}\}) \right\} \rangle_{U_{\text{intra}}},
\]

(72)

where the notation \( \langle \cdot \cdot \cdot \rangle_{U_{\text{intra}}} \) indicates that the expectation value has to be calculated in the ensemble of the Hamiltonian whose interaction part contains macromolecules that do not interact with one another; this is equivalent, of course, to just a single macromolecule. Finally, Eqs. (71) and (72) yield

\[
\phi_{\text{eff}}(r) = -k_B T \ln \langle \exp \left\{ -\beta U_{12}(0, r, \{s_{i1}\}, \{s_{j2}\}) \right\} \rangle_{U_{\text{intra}}},
\]

(73)

It might appear at first sight paradoxical that one is capable of expressing a constrained free energy as the expectation value of some quantity. However, as Eq. (48) readily shows, \( \phi_{\text{eff}}(r) \) is a difference between two constrained free energies, one at separation \( r \) and the other at infinite separation. Free energy differences can indeed be calculated very efficiently in computer simulations.

Widom insertion takes advantage of Eq. (73) in the following way. First, a very large number of independent and equilibrated single-molecule configurations are generated. Thereafter, these are combined in pairs by simply pulling one of the two is such a way that the effective coordinates lie at a distance \( r = |r| \) from one other, i.e., one molecule is inserted at a distance \( r \) from the other. From the ensemble of these inserted pairs, the expectation value appearing in Eq. (73) is computed. The method is simple and transparent; however, it is inefficient when the typical conformations of the interacting entities are markedly different from those generated within the non-interacting Hamiltonian. For instance, Widom insertion would not be appropriate to calculate the effective interaction of a dense polymer brush with a hard wall, since for close brush-wall approaches, the massive retraction of the brush hairs, enforced by the presence of the wall, would result in configurations that appear extremely rarely in the free-brush case. However, Widom insertion is well-suited for fractal, open, and penetrable macromolecules, whose effective interactions do not exceed a few \( k_B T \) even at the closest approaches. It has been successfully employed to linear chains, sparsely polyelectrolyte-coated colloids and dendrimers, as well as ring polymers, for which special care must be taken to preserve the topological constraint of no-concatenation.

4 Hard-Soft Colloidal Mixtures

Highly asymmetric binary mixtures have long been investigated as model systems for colloid-polymer suspensions. Indeed, when the polymer-to-colloid size ratio and polymer density are sufficiently small one can think of tracing out the microscopic degrees
of freedom of the polymer and thus obtain an effective isotropic potential for the polymer-polymer and polymer-colloid interactions. Performing a further coarse-graining on the small-component remaining degrees of freedom allows for the calculation of an effective colloid-colloid potential. The tunability of this depletion interaction, which depends on the polymer (also called depletant) nature, size and density, makes it possible to finely control the degree of association between large particles in solution. This is of great importance for both soft matter and biological systems.\textsuperscript{1,38}

In the approximation of hard polymer-colloid interaction and ideal (i.e. zero) polymer-polymer interactions the effective colloid-colloid potential can be derived analytically.\textsuperscript{13,14} This Asakura-Oosawa-Vrij formulation has become the reference model system for depletion interactions and its use is widespread.\textsuperscript{15,10,39–41,16} One can go one step further and calculate the effective interaction also for the case of non-ideal depletants interacting through a hard-sphere repulsion.\textsuperscript{42} However, it has been shown that both polymer-polymer and polymer-colloid effective potentials always show some degree of softness,\textsuperscript{34} which makes it extremely hard, if not impossible, to analytically calculate Eq. (19). It is thus more convenient to provide a numerical estimate of the effective interaction between the colloids. Given the extremely simple nature of the components, which interact only via isotropic potentials, the best approach is the one outlined in Section 3.1: the inversion of the radial distribution function $g(r)$ in the limit of infinite dilution, i.e. for $\rho \to 0$. In practice, this zero-density limit is reached when three-body effects are negligible\textsuperscript{c}. Care has to be taken in choosing the right simulation parameters.

In the following, $\sigma$ is the colloid diameter, $q$ is the depletant-to-colloid aspect ratio and $\sigma_d = q\sigma$ and $\rho_d$ are the depletant diameter and number density, respectively. For all but the simplest cases, computing the $g(r)$ with the required numerical accuracy in the whole $r$-range of interest is not as straightforward as it may seem at a first glance. Indeed, the most simple approach, i.e. performing an unbiased simulation of a very diluted suspension of colloids in a sea of small depletants, has several practical drawbacks, namely:

1. The number of depletants $N_d$ required to simulate the mixture becomes prohibitively large for small values of $q$. For example, computing the radial distribution function $g(r)$ of 100 colloids at a density $\rho\sigma^3 = 0.01$, with $q = 0.1$ and $\rho_d (q\sigma)^3 = 0.2$, would require to simulate no fewer than $10^7$ particles!

2. Since the number of depletants is proportional to the number of colloids, one could keep $N_d$ low by simulating just two colloids. However, in doing so, the numerical accuracy of the resulting $g(r)$, which depends on the number of pairs of colloids, would be severely hindered.

3. The probability $P(r)$ of finding two colloids at a distance comprised between $r$ and $r+dr$ is connected to the $g(r)$ via the relation

$$P(r) = P_{id}(r) \cdot g(r),$$

\textsuperscript{74}

\textsuperscript{c}This is not to say that having just two colloids in a sea of depletants is a sufficient condition to enforce the $\rho \to 0$ limit. Indeed, if the length of the simulation box side is comparable with the extent of the distortions induced by the presence of the colloids on the density profile of the depletants, a colloid could feel twice the presence of the second colloid thanks to periodic boundary conditions.
where \( P_id(r) \) is the corresponding quantity for an ideal gas. In three dimensions, 
\[ P_id(r) = 4\pi\rho_dr^2. \]
Since, for sufficiently large \( r \), \( g(r) \approx 1 \) and hence \( P(r) \sim r^2 \), it follows that colloids will more likely be far apart from each other, wasting compute time on configurations which are, sampling-wise, uninteresting.

4. As mentioned in Section 3.1, for even the most simple systems the \( g(r) \) will never be sampled uniformly: distances corresponding to peaks in the \( g(r) \), which translate to local minima in \( \phi_{\text{eff}}(r) \), will be visited with a larger probability than distances which correspond to maxima of the effective potential. On top of this, very attractive systems will end up trapping colloids in local minima, thus further hindering the sampling.

A simple, albeit both general and powerful, way of achieving a quasi-uniform sampling is to use the ‘window sampling’ presented in Section 3.1. In summary, the interval of interest \([r_{\text{min}}, r_{\text{max}}]\) is split into \( N_w \) windows. In each window \( j \), centered around its midpoint \( r_j \), the total potential felt by the two large particles has an additional term, \( \Phi_{\text{bias}}(r; j) \).

Splitting the region of interest into different windows has several advantages:

1. All the windows can be sampled separately, making the overall process inherently parallel.

2. The interval \([r_{\text{min}}, r_{\text{max}}]\) is not fixed once and for all: if need be, more windows can be added.

3. The width of each window, \( \Delta r_j \), can be chosen as to yield an as uniform sampling as possible. For example, if we observe that the \( g(r) \) within a given window varies substantially, we can decide to split the window up in order to achieve a better sampling.

4. We can control the convergence of the signal window by window. We can thus decide to increase the length of the simulation only for those windows having unsatisfactory statistics.

The choice of the local bias potential is not to be taken lightly, as different \( \Phi_{\text{bias}}(r; j) \) can have a different impact on the convergence, the numerical accuracy of the final \( g(r) \) and the required number of windows. The two most common choices are a harmonic potential and an infinite well. The former, also known as umbrella sampling,\(^\text{23}\) is most useful when performing molecular dynamics simulations and when large particles have internal degrees of freedom, e.g. star polymers. The infinite well bias is more suited when dealing with simple objects, such as spheres. This local bias is given by

\[
\Phi_{\text{bias}}(r; j) = \begin{cases} 
\infty & \text{if } r < r_j - \frac{\Delta r_j}{2} \\
0 & \text{if } r \in \left[ r_j - \frac{\Delta r_j}{2}, r_j + \frac{\Delta r_j}{2} \right] \\
\infty & \text{if } r > r_j + \frac{\Delta r_j}{2},
\end{cases}
\]  

(75)

where \( \Delta r_j \) is the width of the window. Neighboring windows \( j \) and \( j + 1 \) should be overlapping, i.e. \( r_j + \frac{\Delta r_j}{2} > r_{j+1} - \frac{\Delta r_{j+1}}{2} \). The bias potential (75) may be used only in conjunction with Monte Carlo simulations, since it is not derivable at the window boundaries. In what follows we will show how to use this infinite well potential to extract the
effective interaction between the large components of a mixture of soft colloids and polymers. The softness in the colloid-colloid and colloid-polymer interactions is provided by power-law potentials:

\[ V_{36}(r) = \epsilon \left( \frac{\sigma_{ij}}{r} \right)^{36}, \]  

(76)

where \( \epsilon \) sets the energy scale and \( \sigma_{ij} \) is the diameter associated to the specific interaction \( ij \). \( \sigma_{cc} = \sigma \) and \( \sigma_{cp} = \sigma(1 + q)/2 \) for colloid-colloid and colloid-polymer interactions, respectively. We model the polymers as weakly repulsive gaussian particles, with the polymer-polymer interaction potential given by

\[ V_{pp}(r) = 2k_B T \exp \left( - \frac{r^2}{(0.6q\sigma)^2} \right). \]  

(77)

We start off by noting that, without loss of generality, we can use Eq. (74) to our advantage by constraining the two large colloids to lie on the \( x \) axis, so that \( g(r) = F(r)/\rho_d \). This expedient simplifies the data analysis and may lead to a higher numerical accuracy when \( r \) is small, since we avoid dividing by \( r^2 \). Figure 2 shows a cartoon depicting the geometry and the employed method for a generic window \( j \). For this specific test case we set \( \rho_d \sigma_3^3 = 0.25, N_w = 21, \Delta r_1 = 0.02\sigma, \Delta r_{j>1} = 0.024\sigma, r_{\text{min}} = 0.92\sigma \) and \( r_{\text{max}} = 1.34\sigma \). The overlap between neighboring windows is set to 0.004\( \sigma \).

We start a simulation in each window \( j \) by placing the two colloids in their initial positions, \( r_1 = (0, 0, 0) \) and \( r_2 = (r_j, 0, 0) \), and the polymers in random positions, only taking care that no overlap with the colloids is generated. Then we run a regular Monte Carlo simulation with translational moves, with the constraints that
Figure 3: (a) Colloid-colloid distance histograms for all the investigated windows. The scale on the $y$ axis is arbitrary. (b) Total $H(r)$: all the histograms in (a) have been rescaled so as to superimpose the regions of overlap between the windows. This curve is proportional to the radial distribution function $g(r)$. Inset: the effective colloid-colloid potential $\phi_{\text{eff}}(r)$, calculated inverting the $H(r)$ and then shifting it up so that $\lim_{r \to \infty} \phi_{\text{eff}}(r) = 0$.

(i) trial displacements for colloids are parallel to the $x$ axis and (ii) trial moves for which $|r_2 - r_1| \notin [r_j - \frac{\Delta r_j}{2}, r_j + \frac{\Delta r_j}{2}]$ are outright rejected. We equilibrate the system for $10^6$ MC sweeps, each sweep being equivalent to $N = N_d + 2$ trial moves, and then start accumulating data by updating the histograms of the colloid-colloid distances, $H_j(r)$.
Figure 3(a) shows the output of a typical set of simulations, with a curve for each window. Once we have collected all the histograms, we have to stitch them together in order to obtain a function which is proportional to the \( g(r) \). The process begins from the first window and then joins subsequent windows by applying a least square method to each overlap region between neighbouring windows \( j \) and \( j + 1 \). In practice, adding \( H_{j+1}(r) \) to the total \( H(r) \) is done by rescaling the former by a factor

\[
c_{j,j+1} = \frac{\sum_k r_{k,j}^2}{\sum_k r_{k,j}^2 r_{k,j+1}},
\]

where \( k \) runs over all the points which are in the overlap region between the two windows. The result of this operation is shown in Figure 3(b). The output quantity of this procedure, namely the total \( H(r) \), is proportional to the \( g(r) \) of the system. One can either set the unknown proportionality constant by imposing the condition \( \lim_{r \to \infty} g(r) = 1 \) or, equivalently, by using Eq. (52) and then imposing \( \lim_{r \to \infty} \phi_{\text{eff}}(r) = 0 \). In this framework, the \( r \to \infty \) limit is effectively reached when the \( g(r) \) reaches its final value at large values of \( r \). If the \( g(r) \) does not display any plateau at large distances, more windows should be added in order to reach the asymptotic behavior.

Finally, we note that Eq. (19) can be rewritten as:

\[
\exp \left[ -\beta \Omega(\{ R_i \}; N_1, z_2, V, T) \right] = \exp \left[ z_2 \int dr \exp \left[ -\beta (U_{12} + U_{22}) \right] \right].
\]

If the depletants are ideal among themselves, from Eq. (79) follows that

\[
\Omega(\{ R_i \}; N_1, z_2, V, T),
\]

and hence the effective pair potential, depends linearly on the depletant density \( \rho_d \), \( \phi_{\text{eff}}(r; \rho_d) \), it immediately follows that the effective potential at a different depletant density can be obtained as

\[
\phi_{\text{eff}}(r; \rho_d) = \frac{\rho_d}{\rho_d^*} \phi_{\text{eff}}(r; \rho_d^*).
\]

Unfortunately, there are no available short cuts in the case of non-ideal depletants: we have to compute as many effective potentials as depletant densities we need to investigate.

The effective potential, shown in the inset of Figure 3(b), can now be used to simulate the one-component system and extract colloid-related structural and dynamical data. As an example, we simulate a one-component system made of 10000 colloids interacting through the effective potential and make a comparison with the full binary mixture (100 colloids and 250000 depletants). For this specific case, the simulation of the full binary mixture required a few days of computing time on a GPU. Simulating the same state point as a one-component system, on the other hand, took only a few hours on a single core. This is roughly equivalent to a \( 10^4 \)-fold performance increase.

Figure 4 shows the structure factors \( S(q) \) of the two systems. The two curves fall on top of each other within statistical accuracy. This result demonstrates that the choice of coarse-graining the interactions to obtain an effective pair-potential is justified: the excellent agreement between the one-component and full mixture results shows that many-body effects are negligible even for moderately high \( \rho_d \) values such as the one investigated here.
Figure 4: Structure factor \( S(q) \) of the one-component system (black line), where colloids interact through the computed effective potential \( \phi_{\text{eff}}(r) \), and of the full binary mixture (orange points).

5 Dendrimers

In considering polymers, one usually thinks about long chains of repeating units. However, in the late 1970's an interest arose in regular and highly branched structures that resulted in the first synthesis of dendrimers by Vögtle.\(^{44}\) A coarse-grained representation of such a macromolecule is provided in Figure 5. Similar to polymer chains there is a simple unit-structure that is repeated, but in the case of the dendrimer shown here it is chosen to be trifunctional and results in a network rather than a linear chain. The center or seed of the dendrimer is formed by a connected pair of the so-called generation 0 monomers and consecutive generation layers can be added by for instance a two step process. First the non-bonded ends need to be activated or unblocked by some agent which is removed from the environment afterwards. Now an excess of trifunctional units is added to the system and each of the four reactive ends in the seed can bind a single unit. Given enough time for all sites to react and removing the remaining, non-reacted trifunctional units, one is left with macromolecules that each consist of six units and of which only the outer four have two (eight in total) blocked ends. Repeating the same procedure allows one to add eight more units in the second generation shell, sixteen in the third, and so on. This results in macromolecules that will contain an exponentially growing number of units as function of the number of generation or iteration steps.

Since their first appearance, these type of macromolecules have received a considerable interest from both experimental and theoretical research.\(^{45}\) This is not only due to their role in applications such as solubility enhancement, drug-delivery vectors, or nano-carriers,\(^{46-49}\) but also from a fundamental point of view because they combine properties of colloidal and polymeric systems.\(^{50}\)
If we consider the interaction between two uncharged dendrimers we find an effective pair-potential with a Gaussian shape.\textsuperscript{51,52} Given the overall spherical shape, where the number of constituents grows exponential but, due to connectivity, the radius grows only linearly with increasing generation, one can control the softness from penetrable, low generation to almost hard-core, high generation dendrimers. The richness in behavior is increased further by allowing for different units, for instance by adding charge to the outer generation monomers but keeping neutral units in the center, which results in spherical particles that in a first order approximation have a homogeneous surface charge density.\textsuperscript{53} Accordingly, dendrimers\textsuperscript{54–57} play a prominent role in soft matter research.\textsuperscript{58–65}

A significant amount of research has been devoted to properties of neutral dendrimers, with the focus on internal structure, interactions, and phase behavior as function of the concentration of the solution.\textsuperscript{56–69} Polyelectrolyte dendrimers are less well studied, for the obvious reason that the addition of long range Coulomb interaction increase the complexity of the system. A good example is the fact that in a water-based solution of such dendrimers, the ionizable groups dissociate which results in charged macromolecules and oppositely charged counterions that can move freely in solution. Since the counterions are only weakly bound to the dendrimer, the internal structure responds to the internal charge distribution and this causes the molecule to swell.\textsuperscript{70,71} The interactions and behavior can be influenced and controlled further by screening the Coulomb interaction via the addition of salt, manipulating the charge distribution through a modification of pH, or adjusting the spacer length between the nodes in the dendrimer structure.\textsuperscript{72–75}

### 5.1 Simulation Model

An appropriate method to study polyelectrolyte dendrimers is by means of computer simulations, in particular monomer-resolved Molecular Dynamics simulations that are com-
implemented with the Ewald summation technique to treat the electrostatic interactions.\(^{76, 77}\) In order to concentrate on a qualitative behavioral description of these complex systems, we employ a coarse-grained model in which the atomistic structure and covalent bonds are replaced by a simple bead-spring model.

For the center of the dendrimer a single, bonded pair of monomeric units is chosen, which we can label as the two 0th generation building blocks. By assuming the usage of trifunctional units only, every particle in the most outer shell has two unused reaction sites. Hence, on augmenting the generation of the dendrimer, the number of particles in the next shell is twice as large, i.e., the \(g\)th shell of the dendrimer consists of \(2^{g+1}\) units. If we denote by \(G\) the generation of the most outer shell, we find by adding all shells that such a dendrimer of generation \(G\) contains a total of \(2^{G+2} - 2\) particles. In our case, we restrict ourselves to dendrimers of generation 4 and therefore will contain 62 units or nodes. We can modify the spacer length \(P\) (in terms of bondlengths), by inserting a short chain of \(P - 1\) bifunctional units between the nodes. In our case, this means that the total number of units (bi- and trifunctional) is given by \(61P + 1\), which follows from the realization that is we start with a single unit the addition of a node always increases the number of spacer chains by one as well.

By carefully selecting suitable constituents for their synthesis, dendrimers can be obtained that are charge neutral at large pH, but of which the nodes become ionized at low pH.\(^{50}\) During the synthesis process one is of course not obliged to use the same kind of building blocks at every reaction step. With the aid of functional groups, such as secondary and tertiary amines, one can obtain structures where the monomers in outer shells are already ionized for intermediate pH values. It is therefore possible to influence the charge contribution in polyelectrolyte dendrimers in a controlled fashion. Here we will focus on three different charge distributions, with ionizable groups located only at the nodes. These are the fully neutral case, only charged end-groups, and fully charged dendrimers, with an overall charge number of \(Z = 0\), \(Z = 32\), and \(Z = 62\) respectively. For computational reasons the spacers are chosen to be neutral and have a fixed length throughout the dendrimer that is restricted to a maximum of \(5\) (\(P = 1\) up to \(P = 6\)).

In the bead-spring model we employ here for athermal solvent conditions, all units, that are either nodes in the dendrimer or located within the inter-node chains, are represented by identical spherically symmetric monomers. The mutual interaction between any pair these monomers is modeled via the purely repulsive, truncated and shifted Lennard-Jones\(^{78}\) potential that only depends on the relative distance \(r\)

\[
V_{LJ}(r) = \begin{cases} 
4\epsilon \left( \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} + \frac{1}{4} \right) & r \leq 2^{1/6}\sigma \\
0 & r > 2^{1/6}\sigma, 
\end{cases} \tag{81}
\]

where \(\epsilon\) represents the strength of the interaction and \(\sigma\) is a measure for the diameter of the particles. It is convenient to use \(\epsilon\) and \(\sigma\) as the units of energy and length respectively. The chemical bonds between monomers that determine the connectivity in the dendrimer are typically covalent in nature and can be described by the so-called finite extensible nonlinear elastic (FENE) potential\(^{79}\)

\[
V_{FENE}(r) = \begin{cases} 
-U_{0} \left( \frac{R_{0}}{\sigma} \right)^{2} \ln \left[ 1 - \left( \frac{r}{R_{0}} \right)^{2} \right] & r \leq R_{0} \\
\infty & r > R_{0}, 
\end{cases} \tag{82}
\]
Note that the potential diverges at both distances \( r = 0 \) and \( r = R_0 \), which provides the minimum and maximum bond length respectively. The strength of this spring is measured by means of \( U_0 \). The particular values in the current model are chosen to be \( U_0 = 15 \varepsilon \) and \( R_0 = 1.5 \sigma \). This choice ensures that there will not be any unphysical crossing of bonds within the simulations, because the energy barrier that would be needed to overcome lies outside the range of the typical energy fluctuations found in these systems.\(^80\)

We have implemented the Ewald summation method to simulate the long range Coulomb interactions between charged particles that is given by

\[
V_{\text{Coulomb}}(r) = \frac{k_B T \lambda_B Z_i Z_j}{r}
\]

with \( Z_i \) and \( Z_j \) the charge numbers, \( k_B \) the Boltzmann constant, \( T \) the temperature and \( \lambda_B \) the Bjerrum length

\[
\lambda_B = \frac{\varepsilon^2}{\epsilon_r k_B T},
\]

where \( \epsilon_r \) is the relative permittivity. The charged dendrimers that we consider carry monovalent charges which are located on all the 62 nodes or on the 32 terminal monomers only. Their electrostatic interaction is added on top of the always present Lennard-Jones and FENE potentials. In order to guarantee charge neutrality of the full system 62 or 32 oppositely charged monovalent counterions respectively have to be added per dendrimer. In addition, various salt concentrations of positive/negative salt ion-pairs have been added, where both components are either monovalent or divalent in nature. The three representative salt concentrations that will be used are 0.05, 0.10, and 0.50 mol/l. In addition to their charge, all counter and salt ions interact stERICALLY with all other particles by means of the same shifted Lennard-Jones potential (81) used for the monomers within the dendrimers.

The solvent of the solution is chosen to be water at room temperature. The water molecules are not simulated explicitly, but only implicitly by imposing \( \epsilon_r = 80 \) and for which an interaction strength \( k_B T = 1.2 \varepsilon \) is chosen. The temperature is controlled via an Andersen thermostat. The corresponding Bjerrum length \( \lambda_B = 0.714 \text{ nm} \) is fixed to be \( \lambda_B = 3 \sigma \), which results in a monomer diameter \( \sigma = 0.238 \text{ nm} \) typical for the van-der-Waals radii of atoms that can be used in the framework of a bead-spring model for polymer molecules.\(^1,81\)

The shape of simulation box is cubic with periodic boundary conditions and sides of length \( L \equiv 11 R_g \), where \( R_g \) denotes the radius of gyration of a single isolated dendrimer. This quantity is a measure for the radius of extended objects, that in the case of \( P = 1 \) and \( P = 2 \) dendrimers in our model has typical values of 2.86\( \sigma \) or 4.55\( \sigma \), respectively. In order to measure the effective interaction between dendrimers a single pair of dendrimers, the corresponding counterions, and salt ions are placed in the simulation box. Rather than measuring the effective interaction potential, \( V_{\text{eff}}(D) \), as a function of the distance \( D = |\mathbf{R}_1 - \mathbf{R}_2| \) between the centers of mass, we consider here the effective force at fixed distances, which can be measured directly in MD-simulations. To this end we fix the centers of mass \( \mathbf{R}_1 \) and \( \mathbf{R}_2 \) of the two dendrimers and maintain their location by external force fields. A convenient choice is to place both centers of mass on the diagonal of the simulation box, because this will minimize finite size effects arising from the periodic boundary conditions.
The relation between the effective force and potential (66) is given by

\[ F_{\text{eff}}^\alpha (D) = -\nabla_{\mathbf{R}_\alpha} \phi_{\text{eff}} (|\mathbf{R}_1 - \mathbf{R}_2|), \]  

(85)

where the index \( \alpha = 1, 2 \) corresponds to either dendrimer. The effective interaction can be measured directly in the simulation, because it is the ensemble average of the total force acting on a dendrimer that follows from the addition of all forces \( F_{\text{eff}}^\alpha \) acting on monomers within the same molecule, i.e.,

\[ F_{\text{eff}}^\alpha = \left\langle \sum_{i=1}^{N_\alpha} F_{\text{eff}}^\alpha \right\rangle. \]  

(86)

Note that the total instantaneous force has the same magnitude but opposite direction of the constraining force that fixes the center of mass location. Although the instantaneous forces acting on both dendrimers can be different, their ensemble averages should be the same. In addition, for reasons of symmetry, the effective force should be along the relative distance. Deviations from either of these observations can be used as a measure to determine whether proper equilibrated values have been obtained.

The time is measured in units of \( \tau = \sqrt{m \sigma^2 / E} \) and the time-step used in solving the equations of motion is \( \delta t = 0.002 \tau \). Initially, the dendrimers are placed with random configurations at their designated positions, and all ions are inserted at random locations throughout the simulation box. After an equilibration time that is long enough to relax all stresses within and between the dendrimers, as well as for the ions to diffuse in to the dendrimers, equilibrium measurements are made over a time of typically \( 10^7 \) time-steps.

### 5.2 Neutral Dendrimers

In these complex systems we can investigate in detail the consequences of particular modifications in the architecture on the molecular level. In particular, the effects that changes in generation number, spacer length, and charge distribution have on the effective interactions. In the case of neutral dendrimers in athermal solvents, one finds that the effective interaction potential in general has a Gaussian-like shape.\(^{51,52}\) Its strength and range could be increased by for instance augmenting the generation number and introducing longer spacers respectively. In simulations by Götze et. al.,\(^{66}\) the spacer length was modified by adjusting the softness of the interaction between the nodes of the dendrimers. Rather than changing the monomer-monomer interaction, this effect can be reproduced by means of the addition of spacer monomers.\(^{53}\) It turns out that the radius of gyration \( R_g \) for fixed generation number scales with the spacer length \( P \) as \( R_g \propto P^{1/5} \). In addition, the density profiles, which are a measure for the internal structure of the molecule, can be scaled to collapse onto a master-curve. Here, we will examine whether a similar behavior can be found for the effective interactions.

Hereto we have performed simulations of two generation 4 dendrimers with spacer lengths \( P = 1 - 6 \) and measured the effective force at fixed relative distances. Typical snapshots of such a pair of neutral dendrimers interacting with each other are shown in Figure 6, where we let the centers of mass of both dendrimers coincide, i.e., \( D = 0 \). Since the mutual interaction has only steric components, it is not surprising that this limit corresponds to the maximum interaction. Rather than truly creating overlapping configurations,
where the two dendrimers penetrate each other, one mainly observes a segregation in different regions for either dendrimer, i.e., the dendrimers wrap around each other. This effect is strongest in the case of $P = 1$ with the shortest spacer length. On increasing the spacer length the overall size (radius of gyration) increases and the added flexibility allows more free volume to be explored by the individual monomers. Consequently a weaker overall interaction between the dendrimers is observed.

The radial component of the effective force between the dendrimers as a function of the relative distance $D$ is shown in Figure 7(a) for four different values of $P$. On approaching each other from the far distance, non-interacting range one observes a slow increase in the repulsive interaction between the macromolecules. When the dendrimers get closer, more intermolecular monomer pairs add their repulsive contribution to the total effective force. What might be surprising, however, is that the repulsive force attains a maximum value at a relative distance close to the radius of gyration. When the centers of mass of the dendrimers are forced closer together, the repulsive force diminishes and ultimately vanishes at zero distance. This effect is due to the fact that for such configurations a substantial number of monomers become surrounded by other monomers from either the same or the other dendrimer, and hence the forces that such a monomer experiences start to cancel out. Therefore these units contribute less to the total repulsive force between the dendrimers. In addition, some of the outer monomers that experience typically a force directed away from the center of mass of the dendrimer they belong to, will, when projected on the line connecting the centers of both, lie beyond the center of the other dendrimer and hence give an attractive contribution to the effective interaction. The results that the force at zero distance should vanish, follows from the realization that the effective interaction is an ensemble average. Since in such configurations there should therefore be no preferred direction, the average effective force needs to be disappear. Note that this does not imply that in a particular configuration there can not be an either attractive or repulsive force between the dendrimers.

The measured effective forces for different spacer lengths $P$ are very similar in shape and when scaled appropriately will collapse on a mastercurve as shown in the inset of Figure 7(a). This collapse is obtained when the force is scaled with a factor $P^{-0.65}$, where the scaling factor is fitted from the data presented here. In addition the distance $D$ is measured in units of the radius of gyration $R_g$ measured for a single, isolated dendrimer. It should be noted that the radius of gyration of the dendrimers on interacting is affected. On decreasing the relative distance, the radius of gyration increases with respect to that of an isolated dendrimer, obtaining a maximum value at zero center-to-center distance that is approximately 15% larger than its original size. This increase in dimensions is a direct
consequence of the fact that the mutual overlap results in an increased local monomer density and a corresponding higher internal pressure. The larger size of the dendrimer that follows is achieved by a combination of stretching bondlengths and increasing the effective persistence length in the polymeric structure.

The integration of the effective forces with respect to the distance is straightforward and results in the effective interaction potentials shown in Figure 7(b), that have the characteristic Gaussian-like shape. The maximum that we observed in the force, corresponds to the inflection point in the potential where the concave switches to the convex behavior. The maximum at zero separation distance are a measure for the energy cost of overlapping dendrimers, which not surprisingly is highest for the smallest spacer length. This was already anticipated from the snapshots of Figure 6 that reveal a more open structure on augmenting the spacerlength thereby facilitating such configurations with respect to that of the compact structure at \( P = 1 \).

5.3 Charged Dendrimers

If proper functional groups are incorporated during the synthesis procedure of dendrimers, it is possible to influence the interaction between these macromolecules. In particular, by employing groups that get protonated at low pH values, allow for an easy control of the internal charge distribution that range from neutral to fully charge objects. Since we consider an implicit solvent here, we mimic the effect of pH by adding charges to particular chosen node monomers. To simplify the study of such charged structures, we restrict ourselves to three cases only. The fully neutral dendrimer already discussed, a dendrimer where every node carries a charge, and an intermediate structure where only the most outer nodes are charged. In the case of our 4th generation dendrimers this means that they have a total valency \( Z = 0 \), \( Z = 62 \), and \( Z = 32 \) respectively. Without loss of generality, we assume the charges on a node will be a positive elementary charge. In order to maintain an overall neutral system, negatively charged counter ions have to be added to the system.

In Figure 8 the effect on the conformations of dendrimers caused by changes in the pH or charging the macromolecules, is illustrated by representative snapshots. The figure shows configurations of a pair of these particles with spacer length \( P = 4 \) for each of the three charge distributions and two different relative distances, i.e., the overlapping case of
zero distance, and a distance equal to that of the radius of gyration where there is only a partial overlap. From the snapshots one can already infer that increasing the charge results in a monotonic swelling of the dendrimers, which is simply due to the internal electrostatic repulsion between charged monomers. The counter ions can move freely in and out of the dendrimer and are only loosely bound to the molecule. Only a small fraction, that depends on the overall density, will leave the vicinity of either molecule. The presence of counterions within the complex will, at least partially, screen the Coulomb interactions between both dendrimers.

The electrostatic interactions not only result in a significant swelling for both types of charged molecules, but it also results in more intertwined rather than interpenetrating conformation if the two dendrimers approach each other. In the intermediate charged case, the stretching is less compared to the fully charged molecules. This is not only due to the weaker overall charge, but also caused by the fact that the core by itself will be neutral.

Figure 8: Snapshots from simulations of dendrimers with $G = 4$ and $P = 4$ at distance $D = 0\sigma$ for different pH values of the solvent: (a),(b) fully charged dendrimers, (c),(d) dendrimers with end-groups charged, and (e),(f) neutral dendrimers. The dendrimer's centers of mass either coincide, (a),(c),(e) or are separated at a distance $D \simeq R_g$, (b),(d),(f). Counterions are gray, neutral monomers are shown in pale colors, and charged monomers in dark colors.
and can facilitate some of the terminal monomers on back-folding. In fact in the case
of only terminally charged dendrimers the internal configurations of dendrimers become
approximately uniformly charged.\textsuperscript{53} The back folding of some of the branches is to a
lesser extent also found in the case of neutral dendrimers, where it is attributed to steric
interactions. Especially for higher generation dendrimers this effect is often encountered
due to the exponential growth of the density with generation shell.

It is not surprising that this visible change in structure is also reflected in the effective
interactions between charged dendrimers. The effective force, Eq. (86), can be measured
by the same method as discussed for the neutral dendrimers, except that now also the free
counterions contribute to the total force acting on the center of mass of each individual
dendrimer. In Figure 9 the results of these measurements are shown for the three types
of charge distribution, as well as for different spacer lengths. The shape of the forces
indicate that the underlying potentials are of Gaussian shape, in agreement with other work
published on this topic.\textsuperscript{51,52,66}

On raising the overall charge of dendrimers from $Z = 0$ to $Z = 62$, we observe a
monotonic increase in the effective force. Depending on the spacer length, the maximum
that the force attains lies between two and three times that of the force between neutral
dendrimers. At the same time its range is enhanced due to the swelling of the molecule
originating from the internal electrostatic repulsive interactions. At large separation, the
interaction shows the typical Yukawa-like decay found for charged molecules screened by
solvent and counterions. If the mutual distance between the dendrimers is decreased the
force rises until a distance of about $D \approx 1.2 R_g$ is reached. For shorter distances the force

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{The effective force, $F$, between $G = 4$ dendrimers with number of spacer segments (a) $P = 1$, (b)
$P = 2$, (c) $P = 4$, and (d) $P = 6$ at different pH values of the solvent. The total charge of a dendrimer is
denoted by $Z$.}
\end{figure}
decreases and drops to zero at zero distance. A change in the spacer length has relatively little effect on these observations. The main consequences of increasing the length of the chain segment between nodes in the dendrimer, is that it results in an increased overall size of the dendrimer and the corresponding change in range of the interaction. Closely related to that, is the fact that this also weakens the strength of the interactions, because the longer spacers allow more freedom to avoid both steric and electrostatic interactions as well as it makes it easier for the counterions to explore the inner regions and screen the bare interactions more efficiently.

5.4 Effect of salt

So far we only discussed the effect of the different charge distributions of dendrimers in an implicit solvent that, in order to maintain an overall charge neutrality, has been completed with the appropriate number of monovalent counterions. We can however still influence the interaction between the macromolecules further by for instance the addition of salt. Within the current model this means the addition of an equal number of positively and negatively charged ions with the same short-range, repulsive Lennard-Jones interaction (81) as all other monomers and counterions. Here we consider three different typical concentrations of the salt corresponding to 0.05, 0.10, and 0.50 mol/l. Note that the number of ion-pairs this corresponds to depends on the size of the simulation box.

The effective force measured for the different salt concentrations are shown in Figure 10: The effective force, $F$, between fully charged dendrimers with number of spacer segments $P = 1$ [(a),(c)] and $P = 2$ [(b),(d)] at different salt concentrations $c_s$, where the salt ions are either monovalently charged [(a),(b)] or divally charged [(c),(d)]. The forces for neutral dendrimers without salt are shown for comparison.

The effective force measured for the different salt concentrations are shown in
Figure 10(a) and (b) for the case of fully charged dendrimers with spacer length \( P = 1 \) and \( P = 2 \) respectively. In order to interpret the results, the interaction for uncharged dendrimers are also shown. For the case \( P = 1 \), we find that there is no dependence on the salt concentration, in fact the four salt concentrations, that is including no added salt, coincide over the whole range. For the longer spacer \( P = 2 \), we see that for the short distances the force is still unaffected, but for larger distanced decreases slightly upon increasing the salinity. This can be understood in the light of the fact the \( P = 1 \) dendrimers have a very compact structure that does not allow for additional salt ion-pairs the explore the interior of the structure. By increasing the spacer to \( P = 2 \), more volume is created that will be accessible to salt molecules, and more so in outer shells of the dendrimer. In so doing, the combined counterions and salt ion-pairs are capable of screening the electrostatic interactions more efficiently and reducing the effective force at larger separations.

A more interesting situation arises when we replace the monovalent salt used above by divalent salt. Upon increasing the concentrations, the effective forces are significantly reduced in the case of spacer length \( P = 1 \) approaching the interaction of neutral dendrimers. In the case \( P = 2 \) the forces for the three non-zero concentrations nearly collapse on the neutral case. The divalent ions are much more efficient in screening the interactions than the monovalent ones. In addition, a single divalent ion can replace two monovalent ions. What is happening here is that the monovalent counterions originally found within the dendrimer are expelled and replaced by divalent salt ions, because this reduces the steric interaction in the interior. This is advantageous for another reason, because by having two counterions in bulk rather than a single divalent ion the entropy is increased. The compact structure of the \( P = 1 \) dendrimer still obstructs this process, but already for the \( P = 2 \) spacer length this more efficient screening almost eliminates the Coulomb contribution to the effective interaction.

### 6 Ring Polymers

Ring polymers are macromolecules obtained by joining together the two free ends of a linear polymer chain. They are the most characteristic prototype of topologically constrained molecules,\(^{82}\) that allow to appreciate how the mere operation of “closing” a linear polymer chain has profound impact on the structural and dynamical properties of single molecules and concentrated solutions of the same alike.

Interest in ring polymers dates many decades ago, as is witnessed, e.g., in three pioneering papers on the subject: in the work of Frank-Kamenetskii et al.,\(^{83}\) the notion of the topological interaction between two rings has been introduced and analyzed quantitatively, which arises from the non-concatenation condition of the same; in the work of Grosberg et al.,\(^{84}\) the crumpled globule model of rings in the melt has been put forward, making a strong distinction between the structures of linear- and ring-polymer melts; and finally, Obukhov et al.\(^{85}\) have put forward an annealed lattice-animal picture of a ring polymer in a melt, deriving thereby novel scaling laws for the diffusion coefficient and the longest relaxation time of a ring, and thereby revising earlier predictions.\(^{86,87}\) Despite their conceptual simplicity and their highly interesting characteristics, the study of ring polymers, both experimentally and theoretically, is confronted with many obstacles.\(^{88}\) From the theoretical point of view, the main difficulty of rings in comparison to their linear counterparts lies indeed in the treatment of the topological constraints, which, inter alia,
prevents the formulation of the problem in terms of a field-theoretical approach that has proven extremely fruitful for the treatment of solutions or melts of linear chains. On the experimental side, the main problems are related to the difficulty of controlling the synthetic processes so as to obtain monodisperse rings of identical knottedness. Accordingly, computer simulations have emerged as an indispensable tool for the analysis of static and dynamic properties of ring polymers and their solutions. A great deal of interest in ring polymers is motivated by their biological relevance. Indeed, biopolymers such as DNA or chromosomes are often found in a topologically constrained state when they are packed within cells or eukariotes. In 1993, Grosberg et al. demonstrated that molecules that have a topological constraint appear to be able to survive longer in an out-of-equilibrium state that allows for more compact structures, therefore hypothesizing that the long-lasting problem of packing of, e.g., chromosomes in eukaryotes that could not be explained by packing of linear biopolymers, could be solved by adding a topological constraint. Proteins and DNA display a rich variety of topological effects, both structural and dynamic. For example, the DNA of bacteria is present in the traditional double-helix form, but contrarily to what happens for eukaryotes, they have circular chromosomes contained in a DNA helix closed into a ring. Formation of knots along the backbone of DNA and their location in dependence of the varying rigidity along the backbone of the macromolecule in the bulk and in confinement are another manifestation of the importance of topological concepts for biologically relevant processes.

At the single-molecule level (equivalent to the infinite-dilution limit of a polymer solution), topology manifests itself in various ways. Although the infinite-dilution gyration radius of the rings, $R_{g,0}$, scales with monomer number $N$ with the same Flory exponent $\nu = 0.588$ as the linear chains in athermal solvents ($R_{g,0} \sim N^\nu$), topology effectively expresses itself as a larger excluded-volume parameter, resulting into a lowering of the $\Theta$-temperature of the rings in comparison to that of the linear polymers. A related, remarkable effect is the fact that in contrast to ideal (i.e., without excluded volume) linear polymers, ideal ring polymers experience an effective repulsion between molecules that is purely due to the additional topological constraint of closing each chain into a loop, leading to a scaling $R_{g,0} \sim N^\nu$ that is identical to that of self-avoiding rings.

The effects of topology become even stronger at higher concentrations, and in particular at those exceeding the overlap density of the rings. Whereas the concentration screens out the excluded-volume interaction for linear chains, resulting into Gaussian statistics between the correlation blobs of the same, the topological potential between different rings cannot be screened out.

Solutions of ring polymers present a melt viscosity that is lower by one order of magnitude with respect to a solution of linear chains in the same density and solvent conditions. Investigations on melts of unknotted, non-concatenated rings have shown that they display a higher diffusivity and that the Rouse regime extends to larger scales than in their linear counterparts. Rheological experiments and simulations have revealed a power-law stress relaxation, instead of the usual reptation-like exponential behavior found for linear chains. Semiflexible rings, on the other hand, feature a particular form of self-organization in semidilute solutions, forming a disordered state of columnar clusters penetrated by other rings and displaying an unusual dynamic scenario in which the coherent and the incoherent correlation functions are decoupled from one another, resulting into a state that has been termed cluster glass.
Figure 11: A sketch of a coarse-grained polymer ring chain (red) in a solution of full monomer molecules (grey).

It is evident, thus, that the properties of topologically constrained molecules in the semi-dilute regime are extremely difficult to access, both via theoretical approaches and with computational studies. The difficulty of the latter increases with polymer size and density of polymers in solution, as the bigger the ring and the more rings in solution, the more the monomers to simulate, and the topological tests required in order to preserve the original topology of the system. It therefore becomes of crucial importance being able to analyze, simulate and access the semi-dilute regime for molecules with a ring architecture. A full-monomer detailed representation of semi-dilute solutions, due to both the high number of monomers that it would be necessary to simulate and the high number of topological checks that would be needed, appears to be quite prohibitive if simulations have to be performed for very large polymers in density regimes close and above the overlap concentration, and therefore a coarse-grained approach is called for.

The simplest coarse-graining strategy amounts to replacing the entire ring with a single effective coordinate, usually chosen to be the molecule’s center of mass, in close analogy with the case of linear chains. This single-blob representation of the rings already expresses some of the distinct features related with the ring topology: the resulting effective interaction has a very different amplitude and shape with respect to the Gaussian effective interaction of linear chains, a feature that has been recently rationalized in terms of the strong asymmetry in the sizes of two interpenetrating ring polymers, stemming from the threading of one through the other. Further, the single-blob approach is sensitive to the type of knottedness of the rings, at least for moderate sizes of the same.

6.1 The full-monomer models

To represent the ring polymers, monomers are modeled as hard-spheres of diameter $d$ and the connections among them are implemented as threads of maximal surface-to-surface
extension $\delta_d$ $(\delta > 1)$. Accordingly, the monomer-monomer interaction $V_{\text{mm}}(r)$ and the bonding interaction $V_{\text{bond}}(r)$, where $r$ is the distance between the monomer centers, read as:

$$V_{\text{mm}}(r) = \begin{cases} \infty & \text{for } \frac{\delta}{2} < 1 \\ 0 & \text{for } \frac{\delta}{2} > 1 \end{cases}$$

(87)

acting among all monomers and

$$V_{\text{bond}}(r) = \begin{cases} \infty & \text{for } \frac{\delta}{2} < 1 \\ 0 & \text{for } 1 < \frac{\delta}{2} < 1 + \delta \\ \infty & \text{for } \frac{\delta}{2} > 1 + \delta \end{cases}$$

(88)

for connected ones. Within this representation, we prevent crossing of the bonds of the rings and thus conserve all of the intra- and inter-molecular topology avoiding any accidental concatenations, by setting $\delta = 0.2$ and choosing the Monte Carlo (MC) displacement step to be less or equal to $\delta$.

6.2 Effective pair interactions between two rings

As mentioned in the introduction, properties of ring polymer solutions in the semi-dilute regime are very interesting. If big molecules have to be simulated, both the high number of monomeric units and the topological tests required to simulate the system grow with increasing molecule size and number of molecules in solution till becoming prohibitive. A possible way to simulate those systems is to extract effective interactions between the centre of masses of the molecules and then use such effective interactions to represent the polymer chains. We will in this section deeply analyse how to compute the enter-of-mass effective interactions between two ring polymers with the Widom insertion method\textsuperscript{101,102} $V_{\text{eff}}(R)$, non interacting two ring polymers, $\mathcal{H}$ have the general form:

$$\mathcal{H} = \mathcal{H}_{11}(\{r^N\}) + \mathcal{H}_{22}(\{s^N\}) + \mathcal{H}_{12}(\{r^N, s^N\}),$$

(89)

where $\{r^N\}$ and $\{s^N\}$ are the collective coordinates of the segments of polymer 1 and 2, respectively, $\mathcal{H}_{11}(\{r^N\})$ and $\mathcal{H}_{22}(\{s^N\})$ are the intra-ring parts of the Hamiltonian and $\mathcal{H}_{12}(\{r^N, s^N\})$ contains all the inter-ring interactions between the segments. The canonical and topologically faithful partition function $Z^T$ is given as

$$Z^T = \int \int dr^N ds^N \exp[-\beta \mathcal{H}]^T.$$  

(90)

Note the usage of the notation $Z^T$ and $\exp[-\beta \mathcal{H}]^T$ with the $T$-superscript. This indicates that, in addition to the usual Boltzmann weight, expressed in the exponential factor of the Hamiltonian, there is an explicit exclusion from the partition sum of all microstates that lead to concatenated rings. In what follows, a $T$-superscript will always be used to indicate the presence of this topological constraint, whereas its absence will denote a usual partition sum, in which concatenated configurations are allowed. Additional constraints on the coordinates can be formally handled by, e.g., introducing appropriate $\delta$-functions in the integrand of Eq. (90). The separation between the centers of mass, for instance, can be
formally fixed at a distance \( R = | \mathbf{R} | \) to define the constrained partition function \( Z^T(R) \) as:

\[
Z^T(R) = \int \int \mathcal{d}r^N \mathcal{d}s^N \exp[-\beta H] \delta \left( \frac{1}{N} \sum_{i=1}^{N} (r_i - s_i) - R \right). \tag{91}
\]

With the help of \( Z^T(R) \) given in Eq. (91), the effective interaction \( V_{\text{eff}}(R) \) between the centers of mass of the molecules is defined as:

\[
\exp[-\beta V_{\text{eff}}(R)] \equiv \frac{Z^T(R)}{Z^T(R \rightarrow \infty)} = \frac{Z^T(R)}{Z(R \rightarrow \infty)}, \tag{92}
\]

where we have taken into account that when two finite rings are infinitely far apart from one another, they are also non-concatenated, thus one can set \( Z^T(R \rightarrow \infty) = Z(R \rightarrow \infty) \). By multiplying and dividing the right-hand side with \( Z(R) \), one can decompose the effective interaction \( V_{\text{eff}}(R) \) into its steric part \( V_{\text{steric}}(R) \) and the topological potential \( V_T(R) \):

\[
V_{\text{eff}}(R) = V_{\text{steric}}(R) + V_T(R), \tag{93}
\]

the two terms on the right-hand side being expressed as

\[
\exp[-\beta V_{\text{steric}}(R)] = \frac{Z(R)}{Z(R \rightarrow \infty)} \tag{94}
\]

and

\[
\exp[-\beta V_T(R)] = \frac{Z^T(R)}{Z(R)}. \tag{95}
\]

The steric potential \( V_{\text{steric}}(R) \), Eq. (94), is thus expressed in the usual way in which effective interactions between macromolecular entities are defined in cases where topology plays no role. Eq. (93) above demonstrates however, that for ring polymers, \( V_{\text{steric}}(R) \) is only part of the full story: an additional, topological term \( V_T(R) \) must be added to it to obtain the full effective potential \( V_{\text{eff}}(R) \). Though, as it will be shortly shown, for two rings \( V_T(R) \) is only a small fraction of \( V_{\text{eff}}(R) \), in concentrated solutions where steric interactions are increasingly screened out, the topological interaction plays a very important role in determining the conformations of the molecules and the correlations between them.

To compute the two contributions to the effective pair potential in the simulation, we use a generalization of the Widom insertion algorithm.\textsuperscript{34,22,35} Our choice is guided by the fact that as \( R \rightarrow \infty \), and since the inter-monomer potentials are short-ranged, the interaction term \( H_{12}(\{r^N, s^N\}) \) vanishes identically and the denominator of Eq. (92) factorizes into the product of the partition functions of two noninteracting rings. Concomitantly, Eq. (92) can be re-expressed as

\[
\exp[-\beta V_{\text{eff}}(R)] = \langle \exp[-\beta H_{12}(\{r^N, s^N\})] \delta \left( \frac{1}{N} \sum_{i=1}^{N} (r_i - s_i) - R \right) \rangle_{\text{intra}}, \tag{96}
\]

where the notation \( \langle \cdots \rangle_{\text{intra}} \) indicates that the expectation value has to be calculated in the ensemble of the non-interacting intramolecular Hamiltonian \( H_{\text{intra}} \) of two independent rings:

\[
H_{\text{intra}} = H_{11}(\{r^N\}) + H_{22}(\{s^N\}). \tag{97}
\]
It might appear at first sight paradoxical that one is capable of expressing a constrained free energy as the expectation value of some quantity. However, as Eq. (92) readily shows, \( V_{\text{eff}}(R) \) is a difference between two constrained free energies, one at separation \( R \) and the other at infinite separation. Free energy differences can indeed be calculated very efficiently in computer simulations.

As mentioned in 3.3 the Widom insertion method has proven successful in extracting effective interactions between macromolecules. In the case of ring polymers, it must be emphasized that the arbitrary insertion of one ring in the neighborhood of another always entails the risk of producing a concatenated pair. Therefore, due care has to be taken \textit{a posteriori} to exclude such cases from the calculation of the expectation value in Eq. (97).

For the case at hand, we proceeded as follows. For each insertion step we randomly select two molecules from an ensemble of \( L = 10^4 \) isolated ring equilibrium configurations. We then compute, for all possible \( L = \binom{L}{2} \) combinations of the equilibrium configurations, the probability \( P_{\text{TS}}(R) \) of bringing the centers of mass of the two molecules at a distance \( R \), under the condition that both the topological (T) and the steric (S) constraints are fulfilled. To this end, the following procedure has been followed. Each microstate \( \mu(R) \) in which the centers of mass of the two rings are separated by \( R \) is first checked for steric interactions and it is provisionally accepted with a steric hindrance acceptance probability \( p_{\text{acc}}^S(\mu(R)) \) given by:

\[
p_{\text{acc}}^S(\mu(R)) = \exp[-\beta H_{12}(\mu(R))],
\]

which never exceeds unity, since all cross-ring interactions are repulsive. In this way, \( L_S(R) \) out of \( L \) configurations survive the steric test.\(^d\)

To account for inter-winding of the two rings, we compute the Gauss linking number, \( m \), which is a measure of the degree of concatenation of two molecules.\(^121,10^1\) For any microstate \( \mu(R) \), \( m \) is given by

\[
m(\mu(R)) = \frac{1}{4\pi} \oint_{C_1} \oint_{C_2} \frac{1}{|\mathbf{r} - \mathbf{s}|^3} \left( \mathbf{r} \times d\mathbf{s} \right) \cdot \mathbf{r} - \mathbf{s},
\]

where the \( r \)- and \( s \)-integrations run along the closed contours of the ring polymers \( C_1 \) and \( C_2 \), respectively. When \( m \neq 0 \) the two molecules are concatenated, while \( m = 0 \) implies non-concatenation.\(^e\) Accordingly, the probability of acceptance for the combination of steric and topological constraints, \( p_{\text{acc}}^{\text{TS}}(\mu(R)) \), reads as

\[
p_{\text{acc}}^{\text{TS}}(\mu(R)) = \delta_{m,0} p_{\text{acc}}^S(\mu(R)).
\]

In this way, the number of accepted configurations is further reduced from \( L_S(R) \) to \( L_{\text{TS}}(R) \) and the effective interaction is computed as

\[
\beta V_{\text{eff}}(R) = - \ln \left[ \frac{L_{\text{TS}}(R)}{L} \right] = - \ln [P_{\text{TS}}(R)].
\]

\(^d\)Note that for Model I the exponential factor at the right-hand side of Eq. (98) is either zero, if any two monomers of the two rings overlap, or unity, otherwise, and thus the survival of a microstate is not any more a matter of chance.

\(^e\)This is not entirely correct. Although \( m \neq 0 \) always implies the existence of concatenation, the opposite is not true, since there are some particular situations, such as the Whitehead link, for which \( m = 0 \). We have ignored these special cases here.
The steric part, $V_{\text{steric}}(R)$, is calculated as $-k_B T$ times the logarithm of the probability $\mathcal{P}_S(R)$ of passing the steric requirements, i.e.,

$$\beta V_{\text{steric}}(R) = - \ln \left[ \frac{\mathcal{L}_S(R)}{\mathcal{L}_T} \right] = - \ln \mathcal{P}_S(R). \quad (102)$$

The topological potential is now easily obtained with the help of Eqs. (93), (101) and (102) as $-k_B T$ times the logarithm of the ratio of the number of configurations fulfilling the combination of $T$- and $S$-conditions over those fulfilling only $S$:

$$\beta V_T(R) = - \ln \left[ \frac{\mathcal{L}_{TS}(R)}{\mathcal{L}_S(R)} \right] = - \ln \mathcal{P}_{T|S}(R). \quad (103)$$

In the last equation, we introduced the conditional probability $\mathcal{P}_{T|S}(R)$ that a given configuration will fulfill the topological constraints provided it fulfills the steric ones. This follows immediately from Eqs. (101)-(103) above as a corollary of the rule for calculating conditional probabilities:

$$\mathcal{P}_{T|S}(R) = \frac{\mathcal{P}_{TS}(R)}{\mathcal{P}_S(R)}. \quad (104)$$

For purely repulsive monomers, the contribution $V_{\text{steric}}(R)$ is positive, since the proximity of the two molecules restricts the number of conformers for both, thereby reducing the entropy of the system. This is also evident from Eq. (102) above, valid only for repulsive interactions, which expresses $\beta V_{\text{steric}}(R)$ as minus the logarithm of a probability and it thus implies $\beta V_{\text{steric}}(R) \geq 0$ for all $R$. However, in solvents of worsening quality, for which enthalpic terms would be present in the intermonomer interactions, this quantity can indeed develop attractive parts for some ranges of the intermolecular separation.\(^{22,111}\)

The topological potential, on the other hand, is given as $\beta V_T(R) = - \ln \left[ Z_T(R) / Z(R) \right]$, and the numerator of the ratio within the logarithm is always smaller than its denominator, since those microstates that violate the non-concatenation condition are included in the partition sum $Z(R)$ but excluded from $Z_T(R)$. Topology sets forth a constraint that inadvertently reduces the number of permissible microstates, therefore the topological contribution $\beta V_T(R)$ is non-negative at all $R$, independently of the microscopic details of the model. Still, a weakly attractive, topological effective force $F_T(R) = -\nabla V_T(R)$ can emerge between two rings at moderately small values of their separation, $R \leq R_{g,0}/2$, see below.

Results for the effective and topological potentials $V_{\text{eff}}(R)$ and $V_T(R)$ are reported in Figure 12. The topological effective potentials obtained are quantitatively comparable to those predicted by Hirayama et al.,\(^ {121}\) who employed the self-avoiding polygon model, by Bohn and Heermann,\(^ {101}\) who performed lattice simulations, as well as by Narros et al.\(^ {102}\) in their off-lattice simulations. As predicted by the various authors, $V_T(R)$ is positive and it displays a maximum at $R \equiv R_{g,0}/2$, which accounts for about 13% of the maximum value of the total effective potential.

Coarse-graining a ring polymer with a single effective potential has been proven to be a good approach up to densities of the order of the overlap density $\rho^*$. As soon as the concentration approaches $\rho^*$, the single blob representation loses its validity and many body effects start playing an important role.\(^ {102}\) It is possible to overcome the shortcomings of the single-blob representation by switching to a so-called “multi-blob” representation.\(^ {5,36}\)
each ring made of $N$ monomers will be “broken into” a number of $n_B$ blobs, every blob containing $g = N/n_B$ monomers. The number of blobs is chosen in such a way that each coarse-grained entity is sufficiently small to be below its own overlap concentration, so that many body effects play a minimum role and only pair overlaps are significant. Such a coarse-graining model is extremely powerful and allows to explore the semi-dilute regime of ring polymers without any loss of information with respect to full monomer simulations. Static properties, such as the pair distribution function can be obtained with this coarse-graining methodology for various densities and, as shown in Figure 13, the agreement between the two representations is striking. It is important to stress that the multiblob methodology allows to simulate arbitrarily long polymers at a small fraction of the computational cost that would have been required in a full-monomer representation. For more details, we refer the reader to Ref.36 and references therein.

7 Concluding Remarks

We have presented a concise exposure to the strategy of coarse-graining of complex fluids by means of systematic elimination (“integrating out”) of degrees of freedom that are small and fast in comparison to the ones in which we are interested. It must be emphasized, of
Figure 13: The pair distribution functions $g(R)$ between the centers of mass of unknotted, flexible and non-concatenated ring polymers at various polymer densities $\rho/\rho_\ast$. Shown are results from both the full-monomer simulations of Model I with $N = 100$ hard monomers per ring (for $\rho/\rho_\ast = 0.5, 1.0, 2.0, 3.0$ and $4.0$) and the multi-blob simulation with $n_B = 50$ blobs per ring. From bottom to top, densities are increased in steps of $\Delta \rho = 0.5 \rho_\ast$, starting from the value $\rho = 0.5 \rho_\ast$. For clarity, each curve has been shifted up by an amount of 0.5 from the preceding one.

course, that their presence has a profound influence in the structure and the dynamics of the bigger and slower degrees of freedom: therefore, they might be uninteresting but they are not irrelevant, and therefore they cannot be ignored! The general formalism has been put forward, which is valid for any classical system in thermodynamic equilibrium. In fact, the formalism leading to the derivation of the effective Hamiltonian does not distinguish at all between the small/fast and the big/slow degrees of freedom: the very same framework is equally valid in case one is interested in eliminating the big degrees of freedom in favor of the small. This unusual state of affairs is, however, just an academic exercise: on the one hand, it is of little or no practical advantage and on the other the effective interactions that would result in such a case would be heavily many-body in nature.

We have also presented some concrete examples of coarse-graining, in which a full bridging of the length scales has been achieved: from the monomer-monomer interactions (microscopic) to the effective interactions and structure (mesoscopic) all the way to the thermodynamic phase behavior (macroscopic). The microscopic interactions set forth were of some generic nature, based on a non-specific modeling of the steric and the dispersion
forces. A more detailed calculation there would begin at the level of quantum mechanics, and the solution of a many-body electronic-structure problem would be required to derive effective atom-atom potentials starting, essentially, from the Schrödinger equation, a topic which is beyond the scope of this Chapter. Finally, we emphasize that the contents of this Chapter are limited exclusively to equilibrium properties. For extensions of the notion of the effective interaction to systems out of equilibrium, we refer the reader to the literature and references therein.

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