Microcanonical thermostatistics of aggregation transition in a system with anisotropically interacting molecules

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Abstract. Microcanonical thermostatistics analysis has been introduced as an important method in the study of phase transitions observed in intrinsically small systems, such as folding transitions in proteins and surface adsorption transitions of polymeric chains. Here we consider a lattice model and apply microcanonical analysis to investigate the aggregation transition of a system with anisotropically interacting molecules. By performing multicanonical Monte Carlo simulations we are able to obtain free-energy profiles from where we extract physical quantities related to the aggregation transition such as its transition temperature, latent heat, and free-energy barriers. Our results confirms that the aggregation transition is a first-order type of transition and that it is related to the nucleation of molecules into elongated aggregates. Also, our analysis revealed an unexpected non-monotonic behavior for the free-energy barrier as a function of the anisotropic ratio $\xi$ between strong and weak interactions of the molecules, indicating that the nucleation kinetics might be also influenced by $\xi$.

1. Introduction

Microcanonical thermostatistics analysis has been used to reveal fundamental aspects of phase transitions in intrinsically small systems [1, 2]. The determination of the microcanonical entropy $S(E)$ and the inflexion points of its derivative, which is the inverse of the microcanonical temperature, $\beta(E) = dS(E)/dE$, allows one to obtain important information about the thermodynamic stability regions [3, 4], e.g., coexisting temperatures, spinodal lines, and free-energy barriers. Such approach has been applied to the characterization of phase transitions in many systems, from protein folding [5, 6, 7] and peptide aggregation [8, 9, 10, 11, 12] to vapour-water condensation [13] and order-disorder transitions in magnetic systems [14, 15, 16].

Recently, Janke and co-workers [17] have applied microcanonical analysis to determine free-energy barriers in the study of nucleation in systems with both Lennard-Jones particles and polymeric chains. As discussed in Ref. [17], such methodology can be considered a powerful numerical tool to estimate stationary nucleation rates, $R \propto \exp(-\beta^*\Delta F^*)$, as the evaluation of the free-energy barrier, $\beta^*\Delta F^*$, does not rely on any information about the shape of the aggregates. Such methodology is of particular interest for systems with anisotropically interacting molecules. This because the anisotropic interactions leads to the formation of elongated aggregates, and the classical nucleation theory (CNT) may have limitations in describing the nucleation of non-spherical aggregates. Indeed, there are already studies that
confirm the limitations of CNT in describing the nucleation of molecules with anisotropic interactions [18, 19].

Since one need to deal with several time and length scales to simulate aggregation processes, a variety of modeling approaches should be considered, this includes full atomistic models, coarse-grained models, and lattice models. While full atomistic models include a detailed description of the molecules in the system, they are restricted to small time and length scales where the aggregation process is difficult to be observed. Simulations using coarse-grained models seems to be a better option as they allow one to explore the aggregation transitions, but usually they require large concentrations of molecules in order to observe their aggregation (still with a relative large computational cost). Lattice models, in particular, have been shown to reproduce several experimental features and they can be used to explore relevant time and length scales. Thus, although they might not include all details of the system at the molecular level, they allow one to explore experimentally relevant concentrations and have been used in many studies on aggregation [20, 21, 22, 23].

Here we apply microcanonical analysis to study a lattice model similar to those considered in Refs. [18, 19], where the interactions between molecules are anisotropic, mimicking, for instance, the (weak) hydrophobic and (strong) hydrogen bond interactions observed between amyloid peptides [24]. In Sec. 2 we describe the lattice model, the implementation details of the Monte Carlo simulations, as well as the relevant aspects of microcanonical thermostatistics analysis. The results and discussions are presented in Sec. 3, while our concluding remarks are included in the last section.

2. Methods

2.1. Lattice model

The model system used here is defined as a lattice gas model similar to those used in Refs. [18, 19, 23, 24]. The whole system is defined by a two-dimensional square lattice with linear size \( L \) where \( N \) molecules can randomly diffuse and rotate without overlapping each other. Each molecule can occupy a single site of the lattice and the number density \( \rho = N/L^2 \) (molecules per sites) is fixed. We consider that only nearest neighbour molecules interact with attractive bonding energies. As shown in Fig. 1, the interaction between two neighbour molecules can be strong, with energy \( \psi_s \); or weak, with energy \( \psi_w \), depending on their relative orientation. Thus, one can define the ratio \( \xi = \psi_s/\psi_w \) as the anisotropy of the interaction between molecules, and this is the main parameter of the lattice model.

Figure 1. Schematic representation illustrating two nearest neighbour molecules interacting in the system. Each molecule is denoted by a square with a two-sided (blue) arrow indicating its orientation. (a) shows aligned neighbour molecules which present strong interactions (pink dotted lines) while (b) displays configurations of non-aligned molecules that present weak interactions (yellow plus symbols).
2.2. Multicanonical Monte Carlo simulations

In order to obtain microcanonical thermostatistics we have implemented Monte Carlo simulations using the multicanonical (MUCA) algorithm [25], since estimates for the microcanonical entropy \( S(E) \) can be directly evaluated from the MUCA sampling weights \( w(E) \). Like other flat histogram algorithms, MUCA sampling weights are defined as \( w(E) = e^{-S(E)} \) and require a priori determination of \( S(E) \) from intermediary simulations using recursive relations (see Ref. [26] for details). In MUCA, the recursive relations are required to obtain the multicanonical parameters, \( a(E) \) and \( b(E) \), which are used in determination of the microcanonical entropy, which is given by \( S(E) = b(E)E - a(E) \). Importantly, there is an equivalence between the multicanonical parameter \( b(E) \) and the inverse microcanonical temperature \( \beta(E) \) (also named statistical temperature and which can be obtained from energy histograms [27]). We note that, as it is demonstrated in Ref. [14], this equivalence is valid even in regions close to first-order type of phase transitions.

For the specific lattice model described above, the multicanonical Monte Carlo simulations are used to sample independent configurations in order to evaluate the energy histograms \( H(E) \) that are needed to obtain MUCA parameters. By initiating the system with a completely random configuration, i.e., all molecules are randomly placed in the lattice sites with random orientations, new configurations are obtained using the Kawasaki algorithm [28], as described in the following. First, we try to move a randomly selected molecule to another site and check if the new site is occupied. If that new site is already occupied by any other molecule we reject the movement and select other molecule. If the new site is not occupied, a random number \( r \) between zero and one is drawn and the new configuration is accepted if \( r < \min[1, w(E')/w(E)], \) where \( E \) and \( E' \) are the total energy of the configurations before and after the displacement, respectively. A Monte Carlo sweep is defined as \( N \) attempts to change the positions of molecules plus \( N \) attempts to rotate them. Rotations are accepted (or not) depending on the same acceptance criteria based on energy differences.

2.3. Free-energy profiles

Figure 2 illustrates the main quantities that are evaluated for the microcanonical thermostatistics analysis. The primary quantity is the inverse microcanonical temperature, which is given by the multicanonical parameter \( b(E) \). When the system displays a first-order type of phase transition \( b(E) \) is characterized by a \( S \)-shaped curve, as shown in Fig. 2(a), from where one can use a Maxwell-like construction (i.e., equal areas criteria) to extract the inverse temperature \( \beta^* \) where the two phases coexist. As \( b(E) \) is related to the microcanonical temperature \( T(E) = 1/b(E) \), one can estimate the transition temperature as \( T^* = 1/\beta^* \) (see the inset of Fig. 2(a)). Figure 2(b) shows the free-energy profile, which is obtained from the the microcanonical entropy \( S(E) \) and is given by [5]

\[
\beta^* \Delta F(E) = \tilde{S}(E) - S(E),
\]

where \( \beta^* \) is the inverse of the transition temperature \( T^* \) obtained from the Maxwell-like construction and which can be evaluated as

\[
\beta^* = \frac{S(E_+) - S(E_-)}{E_+ - E_-},
\]

and \( \tilde{S}(E) = \beta^*E + C \) is a canonical-like entropy that is a linear function of the energy, and \( C \) is an arbitrary constant that is fixed in order to set the minima of the free-energy profile at zero. The two minima of the free-energy profile in Fig. 2(b) correspond to the two different phases observed in the system. One phase, at high energies close to \( E_+ \), is dominated by free molecules, i.e., monomeric units, and the other at lower energies near \( E_- \) is characterized by the presence of an aggregate of molecules. As it can be seen from the free-energy profile,
Figure 2. (a) Microcanonical temperature $T(E)$ (inset) and its inverse $b(E) = 1/T(E)$. Horizontal dashed lines indicate transition temperatures, $T^*$ and $\beta^* = 1/T^*$.

(b) Free-energy profile with two minima (at energies $E_-$ and $E_+$) obtained from $b(E)$ in a region of phase coexistence. The physical quantities $\lambda$ and $\beta^* \Delta F^*$ denote the latent heat and the free-energy barrier, respectively. Vertical dashed lines indicate energies $E_-$ and $E_+$.

Results were obtained for a system with anisotropy $\xi = 3$, $N = 400$ molecules in a lattice with linear size $L = 200$ (i.e., $\rho = 10^{-2}$).

3. Results

Next we include results exploring systems with a fixed number density $\rho = 10^{-2}$ (molecules per site) with different values of anisotropy $\xi$. This value of $\rho$ was chosen because at this density (and temperatures and system sizes), the formation of more than one aggregate or an aggregate that stretches across the entire lattice is not observed in the system [29]. The multicanonical parameters $a(E)$ and $b(E)$ used in the microcanonical thermostatistics analysis were obtained considering from 300 up to 800 recursion steps with $10^6$ sweeps each. Following Refs. [18, 19, 23], we set $\psi_w = 1$ (in arbitrary energy units) so changes in $\xi$ correspond to changes in $\psi_s$.

In Fig. 3 we present results on the influence of the system size on the transition temperature $T^*$, the latent heat $\lambda$, and the free-energy barrier $\beta^* \Delta F^*$, for different values of the anisotropy $\xi$. Following the finite-size scaling analysis proposed in Ref. [29] for the isotropic system ($\xi = 1$) at a fixed density, we show in Fig. 3(a) that the transition temperature $T^*$ is a linear function of $L^{-2/3}$. For systems with isotropic interactions, there is an equivalence between the lattice gas model and the Ising model, which has an analytic scaling relation for the transition temperature ($T_\infty$) in the limit of large systems [29]. For $\xi = 1$, the extrapolation of the aggregation temperature for large systems obtained from our numerical results is $T^*_\infty \simeq 0.3997$, which is in fair agreement with the analytical estimate $T^*_\infty \simeq 0.3988$ from Ref. [29]. Importantly, the results in Fig. 3(a) indicate that the same scaling behavior is also valid for systems with anisotropically interacting molecules and, as it is shown in the inset of Fig. 4, the aggregation temperature $T^*$ increases linearly with anisotropy $\xi$.

In Figs. 3(b) and 3(c) we show that both latent heat $\lambda$ and free-energy barrier $\beta^* \Delta F^*$ present a linear dependence with the lattice size $L$ for all values of the anisotropy considered. These results indicate that the aggregation transitions occurring in the systems considered here are first-order-like phase transitions [30], corroborating the S-shaped curves observed in $b(E)$ for all
Figure 3. System size effects on (a) the transition temperature $T^*$, (b) the latent heat $\lambda$, and (c) the free-energy barrier $\beta^*\Delta F^*$ for a system with $\rho = 10^{-2}$ and different values of the anisotropy $\xi$. Lines correspond to linear regression curves.

Figure 4. Dependence on anisotropy $\xi$ of the free-energy barrier $\beta^*\Delta F^*$ and the transition temperature $T^*$ (inset). Results obtained for a system with $\rho = 10^{-2}$ using $L = 200$. The dotted line in the main panel is only a guide to the eyes, while the straight line in the inset corresponds to a linear regression curve: $T^* = 0.26 + 0.138 \xi$

cases (data not shown).

We note that the results presented in Fig. 3(c) revealed an interesting behavior where $\beta^*\Delta F^*$ is higher for the system with anisotropy $\xi = 3$. Indeed, as illustrated in Fig. 4, the free-energy barrier $\beta^*\Delta F^*$ displays a non-monotonic dependence on the anisotropy with a maximum localized at $\xi = 3$. As it can be inferred from Fig. 3(c), such behavior does not change for large lattice sizes. We note that, as suggested in Ref. [17], higher values of the free-energy barrier $\beta^*\Delta F^*$ may lead to lower aggregation rates, thus one might expect slower kinetics for molecular systems with anisotropy around $\xi = 3$.

4. Concluding remarks

In this work we present a microcanonical thermostatistics analysis to explore the aggregation transition of molecules described by a lattice model for molecules with anisotropic interactions. Unlike the usual numerical methods to obtain free-energy profiles, microcanonical analysis is a shape-free method that can be applied to the aggregation of molecules interacting with high anisotropies and which yield elongated aggregates. Our results indicate that the free-energy barrier is a non-monotonic function of the anisotropy. According to the nucleation theory based on microcanonical thermostatistics presented in Ref. [17], the free-energy barrier can be directly related to the aggregation rate and our analysis might be useful in understanding the kinetics of the aggregation process. In the case of peptide aggregation [31], for instance, changes in solution, e.g., pH and salt concentration, might promote or inhibit nucleation since it can alter
the bonding energies, thus the anisotropy.

Acknowledgement
The authors acknowledge Prof. Nelson A. Alves for careful reading of the manuscript, the financial support by the Brazilian agencies FUNARBE, FAPEMIG, CAPES, and CNPq (Grant No. 306302/2018-7), and also the computational infrastructure made available by GISC-UFV.

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