

Thesis synopsis

Thesis title: Phase transition in soft condensed matter fluids and contribution to enzyme kinetics including kinetic proofreading

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The thesis involves computer simulation and theoretical studies of phase transition in soft-condensed matter systems and theoretical understanding of enzyme kinetics along with kinetic proofreading of tRNA-aminoacylation in biological systems. Based on the system and phenomena of interest, the work has been classified into the following **four major parts**:

- I.** Surface phenomena and surface energy of vapor-liquid interface.
- II.** Condensation of vapor in two and three dimensions.
- III.** Liquid-solid phase transition in polydisperse systems.
- IV.** Enzyme catalysis and kinetic proofreading in biosynthesis.

Above mentioned four parts have further been divided into **thirteen chapters**. In the following we provide a brief chapter-wise outline of the thesis.

Part I deals with surface tension and interfacial properties of vapor-liquid interface for Lennard-Jones (LJ) fluid in both two and three dimensions. In **Chapter 1**, we provide a brief overview of vapor-liquid interface and existing theoretical and computer simulation studies of surface/line tension. In this chapter we also discuss about the existing experimental studies. In **Chapter 2**, we present computer simulation studies of surface tension in two dimensional Lennard-Jones system. The sensitivity of line tension on range (potential cut-off) of interparticle interaction is discussed in this chapter. We present Density Functional Theory (DFT) of line tension of vapor-liquid interface based on Weeks-Chandler-Anderson (WCA) and Barker-Henderson (BH) perturbation techniques. We compare the DFT prediction with the computer simulation results. In general, WCA approach has been found to be successful for 3D system in predicting the surface tension. In 2D, however, it does not give good agreement either for phase diagram or for the line tension. In fact, BH also does not give accurate values of the coexistence parameters, however, it predicts better line tension compared to WCA. In **Chapter 3** we present both theoretical and computer simulation studies of gas-liquid surface tension for three dimensional Lennard-Jones fluid. We perform non-equilibrium computer simulation study following Transition Matrix Monte Carlo (TMMC) method to obtain surface tension for various ranges of potential and introduce a new scaling relation of surface tension in order to capture both the temperature and interparticle interaction range dependence. The scaling shows excellent agreement with the simulation result and it can also predict the critical temperature with sufficient

accuracy. The width of the gas-liquid interface is found to be insensitive to the range of the potential, whereas the density separation of the bulk vapor and liquid phases increases with increasing range of potential. Thus, the major contribution comes from the increasing density separation of the bulk vapor and liquid phases.

Part II consists of four chapters, where we focus on the age old problem of nucleation, from the perspective of thermodynamics and kinetics. We account for the rich history of the problem in the introductory **Chapter 4**. In this chapter we describe various types and examples of the nucleation phenomena, and a brief account of the major theoretical approaches used so far. We begin with the most successful Classical Nucleation Theory (CNT), and then move on to more recent applications of Density Functional Theory (DFT) and other mean-field types of models. We present various experimental techniques used in the literature to obtain rate of nucleation. We conclude with a comparison between the experiments, theories and computational studies.

In the next chapter (**Chapter 5**) we attempt to understand the mechanism of the gas-liquid nucleation in three dimension at large metastability from microscopic point of view. Here we study the nature of sequential growth of all liquid-like clusters (not just the largest cluster) at different degrees of metastability. Therefore, we have ordered the clusters according to their decreasing sizes and identified them in terms of k^{th} largest cluster where, $k = 1$ denotes the largest cluster in the system, $k = 2$ represents the second largest and $k = 3$ is the third largest and so on. We have studied both the free energies and the trajectories of the liquid-like clusters in this extended set of order parameters. We further define $F_k^l(n)$ as the free energy of the k^{th} largest cluster with size n . Classical nucleation theory provides an expression of unconditional free energy of a single cluster, $F(n)$ (the free energy of formation of a cluster of size n), which is an intensive property of the system. The study of our conditional free energy surfaces, $F_k^l(n)$, reveals a more detailed, microscopic picture of the system's cluster size distribution that is necessary to understand the kinetics of nucleation and growth at large metastability. The rate of nucleation shows a cross over at kinetic spinodal (the limit of metastability, $\Delta F_1^l = 0$). Below kinetic spinodal only one (largest) cluster crosses the critical size through activation whereas above this point more than one cluster grow simultaneously through barrierless diffusion. We present a theoretical analysis of the free energy of k^{th} largest cluster based on order statistics. The theoretical predictions are in excellent agreement with computer simulation results for the range of supersaturation we studied.

While the previous chapter focuses on relatively well-studied nucleation mechanism in 3-dimensional (3D) LJ system at large metastability, in **Chapter 6** we present our studies on the characteristics of the nucleation phenomena in two dimensional Lennard-Jones fluid for different ranges of interparticle interaction. Using various Monte Carlo (MC) methods, we calculate the free energy barrier of nucleation and bulk densities of equilibrium liquid and vapor phases, and also investigate the size and shape of the critical nuclei. We find an interesting interplay between the range of interaction potential and the extent of metastability. The free energy barrier of nucleation strongly depends on the range of interaction potential.

The study is carried out at an intermediate level of supersaturation (away from the kinetic

spinodal limit). A surprisingly large cutoff ($r_c \geq 7.0\sigma$, where σ is the diameter of LJ particles) in the truncation of the LJ potential is required to obtain converged results. A lower cutoff leads to a substantial deviation in the values of the nucleation barrier, and characteristics of the critical cluster (with respect to full range of interaction). We observe that in 2D system CNT fails to provide a reliable estimate of the free energy barrier. While it is known to slightly overestimate the nucleation barrier in 3D, it underestimates the barrier by $\sim 50\%$ at the saturation ratio $S = 1.1$ (defined as $S = P/P_c$, where P_c is the coexistence pressure) and at the reduced temperature $T^* = 0.427$ (defined as $T^* = k_B T/\epsilon$, where ϵ is the depth of the potential well). The reason for the marked inadequacy of the CNT in 2D can be attributed to the non-circular nature of the critical clusters. Although the shape becomes increasingly circular and the clusters become more compact with increase in cutoff radius, an appreciable non-circular nature remains even for full potential (without truncation) to make the predictions of CNT inaccurate.

In **Chapter 7** we report the computer simulation study of nucleation in three dimensional LJ system. At a fixed supersaturation the free energy barrier of nucleation increases with increasing range of interparticle interaction. On increasing range of intermolecular interaction, the kinetic spinodal where the mechanism of nucleation changes from activated barrier crossing to barrierless diffusion, shifts towards the deep metastable region. Both the critical cluster size and pre-critical minimum in the free energy surface of k^{th} largest cluster shift towards the smaller size at their respective kinetic spinodal as we increase the range of potential. We find only a weak non-trivial (other than supersaturation and surface tension) contribution to the free energy barrier of nucleation.

Part III consists of two chapters and focuses on the liquid-solid phase transition of polydisperse fluid. In **Chapter 8** we introduce polydisperse systems and their classification based on different identities. We describe the importance and abundance of polydisperse system in nature. The theoretical modeling of different polydisperse systems and their extent of applicability have also been presented. We have discussed about the various factors which control the phase diagram and various phenomena related to the structure and phase transition.

In **Chapter 9** we present computer simulation study on freezing/melting of Lennard-Jones (LJ) fluid at different polydispersities. The freezing/melting of polydisperse LJ fluids presents an interesting case study, because, as the polydispersity increases the energy-entropy balance becomes increasingly unfavorable for the solid to exist as a stable phase. The energy of the solid increases due to build up of strain energy because of increasing mismatch in size of the neighbors, while the entropy of the liquid increases. These two factors lead to the existence of a terminal polydispersity. We find beyond the terminal polydispersity, $\delta \simeq 0.11$, the system remains in the disorder state even at very high pressure and low temperature. The terminal polydispersity obtained in the present study is close to the experimental value ($\delta_t \approx 12\%$). Interestingly, contrary to hard sphere polydisperse fluid, LJ fluid does not exhibit reentrant melting.

The last part (**Part IV**) of the thesis consists of three chapters that deal with the enzyme catalysis and kinetic proofreading of tRNA-aminoacyl synthetases. In **Chapter 10** we describe protein synthesis process in biological system and corresponding two processes:

aminoacylation of tRNA and translation of amino acid in ribosome. Our interest is to understand the enzyme catalysis involved in aminoacylation of tRNA in the process of protein synthesis. We present the classification of 20 aminoacyl-tRNA synthetases into two classes based on their structure and mode of binding to ATP and tRNA. We discuss all the steps involved in whole tRNA-aminoacylation process. Then we introduce kinetic proofreading during aminoacylation reaction. In **Chapter 11** we theoretically analyze the single turn over and steady state reaction mechanism of two classes of aminoacyl-tRNA synthetases. Class I enzymes not only differ in their structure but they also differ with respect to the pre-steady kinetics compared to class II enzymes. We find that the strong binding of product to class I enzymes causes the product release step to be rate limiting step leading to the burst of product formation in pre-steady reaction. On the other hand class II enzymes do not show any burst kinetics. The present study based on time dependent probability statistics is successful in explaining all the experimental results quantitatively. In **Chapter 12** we present an augmented kinetic scheme and then employ methods of time dependent probability statistics to understand the mechanism of kinetic proofreading of isoleucyl-tRNA synthetase (IRS) which belongs to class I. We investigate that the enhanced hydrolysis of wrong substrate (Val) enables IRS to discriminate the correct substrate (Ile) and wrong substrate (Val) efficiently. It has been observed that an extra CP1 editing domain serves as an activating domain towards enhanced hydrolysis of Val. The present study is able to explain most of the existing experimental observations. In the concluding note, **Chapter 13** lists a few relevant problems that may prove worthwhile to be addressed in future.

In the **Appendices**, we present two of the techniques used in our present computer simulation and theoretical studies. **Appendix A** describes Grand Canonical Transition Matrix Monte Carlo (GC-TMMC) method which is employed in computer simulation studies of nucleation and surface tension. In **Appendix B** we present the probabilistic method of waiting time distribution computation used in enzyme catalysis and kinetic proofreading.