1
Introduction

Soft matters are the state of materials which neither fall into the class of simple liquids nor can be classified as crystalline solids [Jones, 2002]. They can be broadly classified into four domains: colloidal dispersions, amphiphilic molecules, polymers and liquid crystals. The colloidal dispersions are generally solids or liquids of sub-micrometer dimensions which are dispersed in some other liquid medium. Amphiphilic molecules such as surfactants or lipids self-assemble in presence of water to form macro-aggregates of variable shapes. Polymers are formed by the chemical or physical interactions between same or different types of monomeric units. Biologically existing polymers include nucleic acids, peptides, proteins and polysaccharides. Liquid crystals are the substances which possess some degree of ordering which lies intermediate between a crystalline solid and a liquid and show response to electric fields [Yang and Wu, 2014].

There are a number of properties followed by "soft matters" which are different than solids or liquids [Jones, 2002]. These properties are described as follows,

- Length scales of soft matters fall in the mesoscopic range. They are much larger in dimensions as compared to the size of atoms, yet quite smaller in size compared to the macroscopic material. The sizes of polymer chains and the self-assembled amphiphilic molecules generally lie in the range of tens of nanometers. The size of colloidal particles vary from nanometers to micrometers.

- Structures are affected by thermal fluctuations and continuous Brownian motions. These systems are involved in random motions; the polymeric chains tend to fold or writhe in solutions. Similarly, the membranes formed by amphiphilic molecules show flexible movements owing to the Brownian motions.

- Soft matters have strong tendencies for spontaneous formations of self-assembled structures [Whitesides and Grzybowski, 2002]. The simplest examples include formations of micelles or bilayers by the amphiphilic molecules. Self-assembly leads to complex supra-structures in biological systems, such as collagen fibres which are hierarchically organized, or complexes of DNA-enzyme which lead to DNA replication etc. [Capito *et al.*, 2008].

- Alterations in the temperature or mechanical stress can lead to alterations or deformations in the structures.

With these common features, soft matters contribute to a wide range of applications. They show their utilities in adhesives [Chipara *et al.*, 2020], bio-mimetic and bio-inspired materials [Fan and Gong, 2020], cosmetic products [Priestley and Prud'homme, 2020], micro-lasers [Ta *et al.*, 2019], drug delivery [Zhang *et al.*, 2019], hydrogels [Ye *et al.*, 2020], food science [van der Sman, 2012], lubricants [Apóstolo *et al.*, 2019], tissue engineering [Huang and Chu, 2019], etc. Liquid crystals are responsible to the electric fields and popularly used in display devices such as televisions, cellular phones, calculators, etc [Yang and Wu, 2014].

Since a wide range of materials with wide applications belong to soft matters which have unique characteristics, the soft matter science naturally becomes an interdisciplinary field. It involves concepts and theories of natural sciences such as as physics, chemistry, biology and

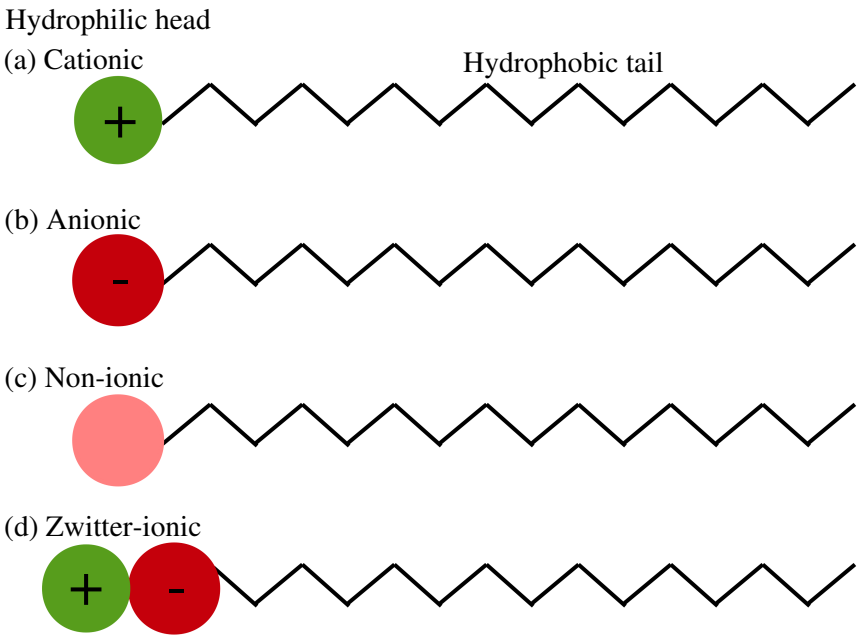

Figure 1.1: A schematic diagram showing amphiphilic surfactant molecules with a hydrophilic head-group and a hydrophobic tail. The surfactants are classified into four major categories based on the head-group charge.

advance sciences such as materials science, nanoscience, nanotechnology and engineering [van der Gucht, 2018; Mashaghi *et al.*, 2013]. Thus, in order to make full use of the potential applications of soft matters, it becomes important to gain molecular level insights on their properties. An understanding of the structural properties of the self-assembled macro-aggregates of soft matters and the interactions governing the self-assembly can thus be useful to modulate and control the features of soft-matters. Since soft matter science is a highly broad and diverse field, in this thesis, studies are devoted to understand the self-aggregation mechanisms of amphiphilic molecules and bio-inspired peptide derivatives employing computational methods. Here the aim is to recognize the key parameters which govern the self-assembly and the specific architectures of these aggregates with desired functionalities.

1.1 SELF-ASSEMBLY OF AMPHIPHILIC MOLECULES

Amphiphilic molecules are composed of two distinct components which differ in their affinity towards different solvents. Surfactants are one such class of amphiphilic molecules. They are made up of two chemically distinct parts; a polar head-group and a non-polar tail. The chemical structure of a surfactant molecule is in close resemblance with a lipid molecule. The head-group, due to its polar nature, has more affinity towards water whereas the tail being long chain hydrocarbon is hydrophobic in nature. On the other hand, the head groups can vary in terms of bearing charges. Thus, surfactants are classified into four categories based on the charges of the head-groups; (a) cationic surfactants having positively charged ammonium group (b) anionic surfactants which have negatively charged heads such as, sulphate, phosphate or carboxylate, (c) non-ionic surfactants having an alcoholic head and (d) zwitter-ionic surfactants which bear both positive and negative moities constituting the head-group. The schematic representations of these four types of surfactants is shown in figure 1.1. Due to the differences in the head-group types and affinities towards different solvents, surfactants self-assemble into aggregates of distinct phases and topologies in the solvent medium. The aggregates can be spherical micelles, reverse micelles,

cylindrical micelles, vesicles or bilayers, as shown in figure 1.2.

The features responsible for the formation of these shapes can be understood from few governing parameters. The driving force of the molecular self-assembly is the minimization of free-energy [Jones, 2002]. However, these amphiphilic molecules do not rapidly self-assemble to form aggregates. Instead, aggregates are formed when the concentration of these molecules increases above the critical micellar concentration (CMC). When the concentration is below the CMC, the entropy of mixing is the governing factor, due to which the molecules simply remain as a part of the solution. Above the CMC, the molecules tend to reduce their free-energies via the self-assembly mechanism. The major interactions which govern the self-assemblies of amphiphilic molecules are hydrophobic attractions which operate at the water-hydrocarbon interface. These interactions induce the association of the molecules. The second major contributions to the self-assemblies come from the hydrophilic or the steric repulsions from the headgroups which impose the reverse requirement that the headgroups remain in contact with water. Both these opposing forces are mainly operative at the interface region [Israelachvili, 2011].

Further, the factors determining the shape and size of the aggregates are characterized by three geometric parameters, v_0, a_h and l_c. v_0 signifies the critical hydrocarbon chain volume, a_h is the optimal head-group area and l_c is the critical chain length.

1.1.1 Packing parameter

Molecular packing features are associated with the three geometric parameters discussed above. These three parameters altogether constitute a dimensionless quantity called as the packing parameter. An intricate balance in the packing parameter dictates the shape of the aggregate. This dimensionless quantity is given as the ratio of the critical tail volume to the projected volume by the optimal head-group area [Israelachvili, 2011]. Mathematically it is represented as,

$$\text{Packing parameter} = \frac{v_0}{a_h l_c} \tag{1.1}$$

The above relationship denotes that a small packing parameter is an outcome of small v_0 and a large a_h. In other words, the packing parameter would be smaller if a small tail is attached to a larger head-group, resulting into curved aggregates. Whereas in the reverse case, when a large tail is connected to a smaller head-group, the packing parameter is higher and favors the formation of aggregates with a less curvature (for example bilayers or vesicles). A schematic representation of the shape of the amphiphilic molecule, shape of self-assembled aggregate and the respective packing parameter is shown in figure 1.2. A detailed insight relating to the packing parameter with the aggregate shape is discussed in the next section [Israelachvili, 2011; Jones, 2002].

Spherical micelles

For any spherical micelle with aggregation number N and radius r, the surface area and the volume can be written as

$$4\pi r^2 = N a_h \tag{1.2}$$

$$\frac{4}{3}\pi r^3 = N v_0 \tag{1.3}$$

From the above two equations, the radius r comes out to be $3v_0/a_h$. The radius of a spherical micelle cannot be higher than the critical chain length l_c. Thus, determining l_c from equation 1.1 and treating $r \leq l_c$ gives the following condition,

$$\frac{v_0}{a_h l_c} \leq \frac{1}{3} \tag{1.4}$$

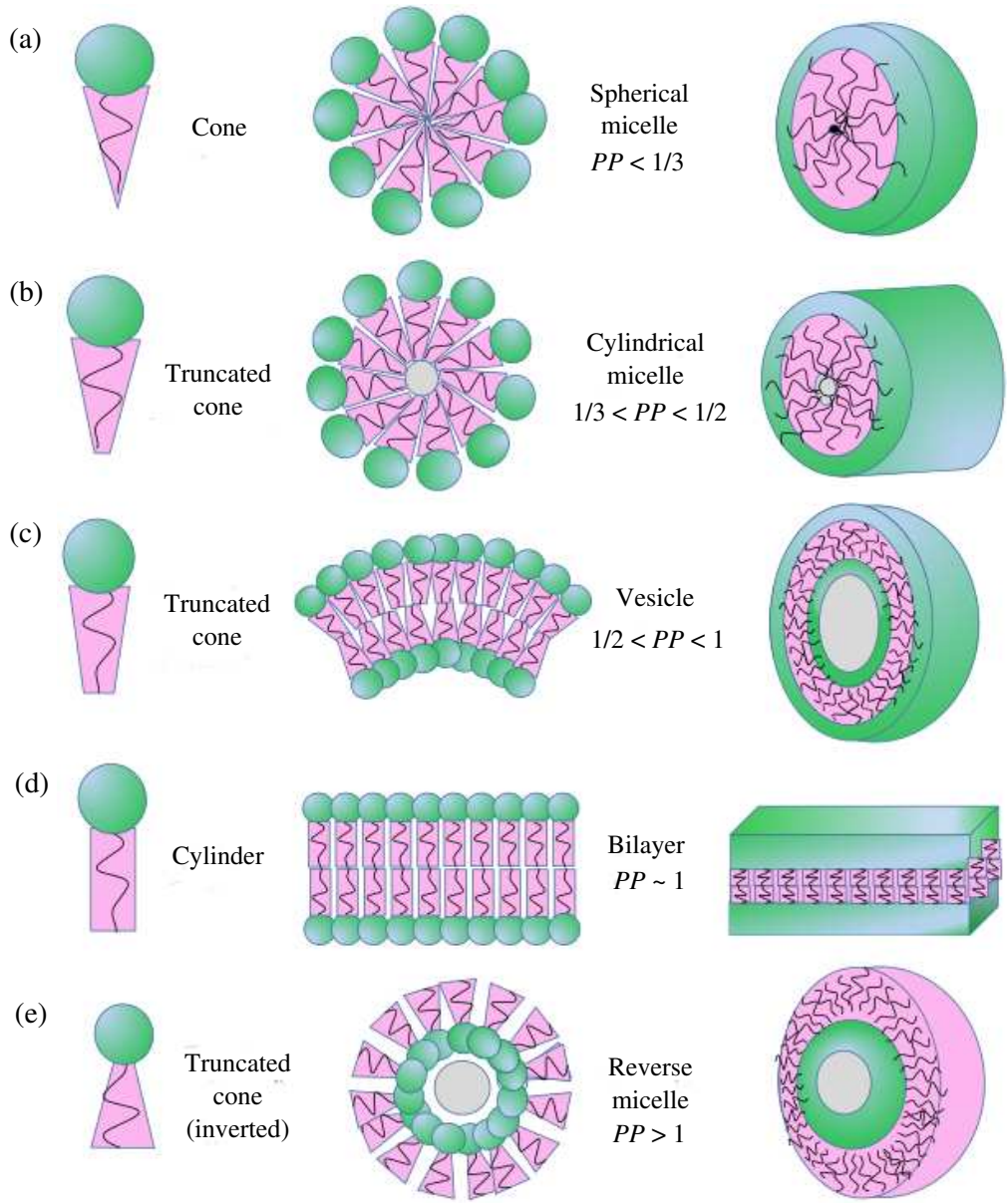

Figure 1.2: A schematic diagram showing the amphiphile shape, the self-assembled structure and the respective packing parameter which is denoted by PP ($=\frac{v_0}{a_h l_c}$). This figure has been taken from [Lombardo *et al.*, 2015].

where $v_0/a_h l_c$ is the packing parameter. Thus, the formation of spherical micelles is favorable at a lower value of a packing parameter.

Cylindrical micelles

For any cylindrical aggregate composed of N molecules, with length l and radius r the surface area and the volume can be written as,

$$2\pi r l = N a_h \tag{1.5}$$

$$\pi r^2 l = N v_0 \tag{1.6}$$

Upon solving the above two equations, the radius r comes out to be $2v0/a_h$. With a similar concept as followed for the spherical micelle, boundary of the packing parameter for the formation

of a cylindrical micelle is found to be,

$$\frac{1}{3} \leq \frac{v_0}{a_h l_c} \leq \frac{1}{2} \tag{1.7}$$

Bilayers and vesicles

The self-assembled aggregates resulting into a bilayer lack curvature and the area which is occupied per molecule in the upper and the lower leaflets are equal. Thus, the space occupied by the molecules is of a cylindrical or a shape similar to a rectangular prism [Mosley *et al.*, 2013]. The volume equation for such a configuration can be written as,

$$v_0 = a_h l_c \tag{1.8}$$

$$\frac{v_0}{a_h l_c} = 1 \tag{1.9}$$

Thus, the bilayers are formed when the packing parameter is near unity. Since the vesicular aggregates have a morphology in between cylindrical micelles and bilayers, the packing parameter for a vesicle is given as,

$$\frac{1}{2} \leq \frac{v_0}{a_h l_c} \leq 1 \tag{1.10}$$

Thus, the packing parameter foregrounds in predicting the shape of the self-assembled aggregate. The knowledge and understanding of the geometric variables and constraints of the packing parameter are therefore essential to develop a control over the shape of the aggregate. A systematic tuning of the packing parameter can be applied to get aggregates of desirable morphologies and applications.

1.1.2 Different non-covalent interactions

The non-covalent interactions play a major role in formation of supramolecular assemblies, specially in biologically relevant macromolecules including proteins, DNA, RNA, etc. The most important non-covalent interactions include electrostatic interactions, π-π interactions and van der Waals interactions. The electrostatic interactions arise due to the attractive forces operating between the charged molecules or ions. Such interactions are also observed if there is a molecule having a charge on any atom [Ciferri and Perico, 2012] or it has a permanent dipole moment. Due to the interactions between two oppositely charged atoms or ions, these interactions are strong and attractive in nature. The polarizability of the other molecule interacts with the electric field generated due to the charge or dipole of the first molecule. This gives rise to an induction energy [Levine, 2009]. The electric field due to the charge at a distance r is given as $E = q/r^2$ which is used to calculate the induction energy as, ($V_{ind}(r)$),

$$V_{ind}(r) = -\frac{1}{2}\alpha E^2 = -\frac{\alpha q^2}{2r^4} \tag{1.11}$$

where α is the polarizability of the second particle and q is the charge of the first particle. If the system bears a permanent dipole, the the electric field is given as $E = \mu/r^3$ and the induction energy arising due to the interaction of this dipole with the polarizability of the second particle is,

$$V_{ind}(r) = -\frac{\alpha \mu^2}{2r^6} = -\frac{A_{ind}}{r^6} \tag{1.12}$$

here A_{ind} is a constant and the induction energy has an inverse relation with the sixth power of the distance. Thus the electrostatic interactions are relatively stronger if a charge is present on any particle.

An important class of the electrostatic interactions include hydrogen-bonding. Hydrogen bonding arises due to the interactions between a hydrogen atom which is covalently bonded to any molecule and an electronegative or partially electronegative atom (for example O, N, S, F or Cl) having a lone pair [Pauling, 1941]. Here it is important that the electronegative atom and the said hydrogen atom do not form a covalent bond, but instead interact via the electrostatic interactions [Anslyn and Dougherty, 2004; Raevsky and Skvortsov, 2005]. The electronegative atom is termed as the acceptor while the atom bonded to the hydrogen atom serves as the donor. There are a number of factors which operate in a molecule for hydrogen bond formation. These include, (a) the electrostatic interactions between the negatively charges atoms and hydrogen atoms, (b) the directionality of the covalent attractions as H-atom is covalently bonded to one atom and is simultaneously attracted to an electrongative atom. This asymmetric situation is responsible for a directionality in hydrogen bonding, and (c) electronic interactions emerging from the overlap of electron clouds of negatively charged atom of one molecule with the hydrogen atoms of another neighbour molecule. A geometric criteria to compute hydrogen bonding between a donor-acceptor pair considers a distance $< 3.5\mathring{A}$ and an angle of $< 30^{\circ}$ formed due to the hydrogen-donor-acceptor triplet [Luzar and Chandler, 1996b; Rey *et al.*, 2002; Lawrence and Skinner, 2003; Eaves *et al.*, 2005]. Hydrogen bonding plays a very important role in the secondary structure of proteins. Proteins are known to exist in two common secondary structures, α-helix and β-sheets, where both these structures are formed by the hydrogen-bonding between the oxygen atom of the carbonyl group and hydrogen atom of the another amino group [Hubbard and Kamran Haider, 2010]. Similarly the helices of DNA and RNA are held together by forming hydrogen bonds.

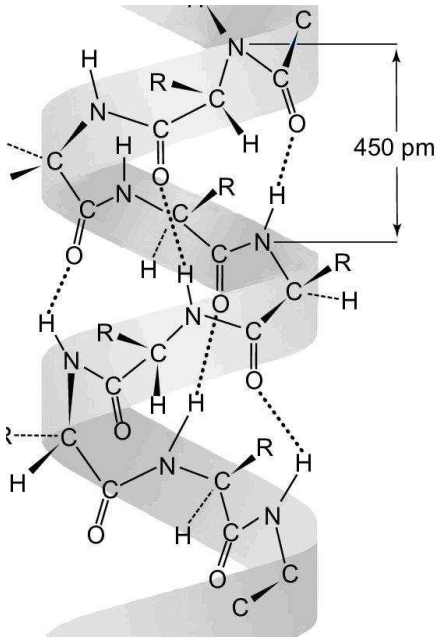

Figure 1.3: Structure of protein α-helix, assisted by hydrogen bond formations between the oxygen atom of the carbonyl group and the hydrogen atom of the amino group. This image has been taken from [Georgiev and Glazebrook, 2019].

van der Waals interactions are another important category of non-covalent interactions which can be understood as weak electrostatic interactions. They are further classified into three sub-divisions: (a) dipole-dipole interactions which occur when there is a permanent dipole, (b) dipole-induced dipole interactions which take place when atoms or molecules with no dipole are induced by the permanent dipole of another atom or molecule, and (c) dispersion forces which are very weak yet important non-covalent interactions arising in molecules or atoms with no dipoles but originate due to the interactions between their instantaneous dipoles [Israelachvili, 2011; Schneider, 2015]. In the absence of any permanent dipole in any molecule, a fluctuating dipole can exist in

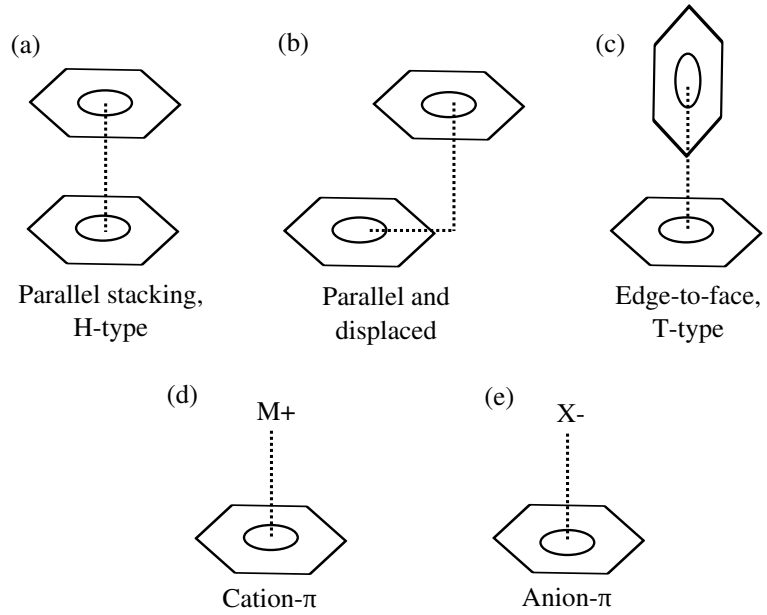

Figure 1.4: Schematic representation of different types of $\pi-\pi$ interactions in aromatic ring systems. M+ and X- denote the cation and anion respectively.

the system which averages out to be zero, resulting in an overall no dipole moment [Levine, 2009]. Assuming a single excited state for any pair of atoms, the transition dipole moment is referred to as μ. The electric field due to this dipole at some distance r from the first atom is $E_1 = \mu_1/r^3$. The induction energy due to the polarization effect of the second atom is $-\alpha_2 E_1^2/2$. A similar term is obtained when the polarizability of first atom interacts with the electric field generated due to the second atom. Thus the overall expression for the gain in the induction energy can be written as,

$$V_{disp}(r) = -\frac{1}{2}(\alpha_2 E_1^2 + \alpha_1 E_2^2) = -\frac{\alpha_2\mu_1^2 + \alpha_1\mu_2^2}{2r^6} = -\frac{A}{r^6} \tag{1.13}$$

The energy hence obtained by the interaction of transition dipole of one molecule or atom with the polarizability of the other is called as the dispersion energy. The constant A in the above equation ranges from 10^{-57}-10^{-59} erg cm^6. These interactions are important in cross-linking of polymers, hydrogels, proteins, etc.

π-π interactions arise due to the interactions between the π-orbitals of molecules having unsaturated bonds [Anslyn and Dougherty, 2004]. Such interactions are well known in aromatic ring systems which exhibit a high polarizability leading to dispersive interactions. The ring systems can interact with each other via a parallel (H-type), parallel and displaced or edge-to-face (T-type) configurations. These interactions are further divided into cation-π or anion-π interactions. The cation-π interactions are facilitated by the interactions of any positively charged metal ion with an electron rich π-system [Gallivan and Dougherty, 2000]. On the other side, an electron deficient aromatic ring interacts with a negatively charged species forming anion-π interactions [Kan *et al.*, 2018]. A schematic representation of different types of $\pi - \pi$ stackings is shown in figure 1.4. Altogether, the π-π interactions play important roles in holding the structures of nucleic acids or in supramolecular assemblies [Ashton *et al.*, 1989; Gallivan and Dougherty, 2000; Riley and Hobza, 2013].

1.2 MOLECULAR DYNAMICS SIMULATIONS

As discussed earlier, amphiphilic molecules can assemble to form broad spectra of topologically distinct mesoscopic aggregates. Study of these meso-structures has been extremely fascinating via established experimental methods. However, the bigger challenge lies in understanding the controlling factors which lead to these distinct phases. Complementary to the well established experimental techniques, molecular dynamics (MD) simulations are very well potent in providing molecular level insights on the interactions responsible for formation of a thermodynamically stable phase.

MD simulations are applied to investigate trajectories of atoms or molecules. In classical MD, the atoms under consideration are treated with the laws of classical mechanics which interact with each other for a certain period of time and thus giving a trajectory which demonstrates the evolution of a system with respect to time. Force (F) acting on each particle are determined from the following equation,

$$F = -\nabla U(r) = ma \tag{1.14}$$

where force is the negative gradient of potential ($U(r)$), m is mass and a denotes acceleration. The potentials are computed using the force-fields which describe the mathematical form of the potential energy. The force-field parameters contain a set of parameters like charges, bond lengths, angles or dihedrals along with the associated force constants which enables to compute the energy of the system. The accuracy of the MD simulations depends upon the quality and accuracy of these parameters. The system's total potential energy is a contribution due to bonds (U_{bonds}), angles (U_{angles}), dihedrals ($U_{dihedrals}$) and other non-bonded interactions arising from Lennard Jones interactions (U_{LJ}) and Coulombic interactions ($U_{Coulombic}$) [Durrant and McCammon, 2011].

$$U = U_{bonds} + U_{angles} + U_{dihedrals} + U_{LJ} + U_{Coulombic} \tag{1.15}$$

$$\begin{aligned} &= \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_{torsions} k_\phi [1 + cos(n\phi - \phi)] \\ &+ \sum_{improper} \frac{1}{2} k_\phi (\phi - \phi_0)^2 + \sum_{LJ} 4\epsilon_{ij} [(\frac{\sigma_{ij}}{r_{ij}})^{12} - (\frac{\sigma_{ij}}{r_{ij}})^6] + \sum_{Coulombic} \frac{q_i q_j}{4\pi\epsilon_0 r} \end{aligned} \tag{1.16}$$

where k_b, k_θ and k_ϕ are the force constants due to bonds, angles and torsions respectively, r_0, θ_0 and ϕ_0 signify the equilibrium bond lengths, bond angles and dihedral angles respectively, σ_{ij} and ϵ_{ij} denote the distance of closest approach and interaction strengths between the particles i and j. $q_i q_j$ are the product of charges on particles i and j, r and ϵ_0 signify the distance and permittivity due to free space. Once the potential energy is known, the force on each atom is computed by equation 1.14. The forces are then integrated using Newton's equations of motion to compute new positions and velocities using time-steps in the order of a few femto-seconds (fs). There are some well known algorithms which enable to integrate the equations of motions, for example leap-frog integrator, velocity Verlet integrator etc. [Hockney *et al.*, 1974; Swope *et al.*, 1982]. A brief flowchart of the steps followed in the MD simulation is shown in figure 1.5.

1.2.1 Multiscale simulations

In recent years, multiscale modeling has been instrumental to understand phenomena occurring at different length and time scales. This approach utilizes a combination of a variety of scientific methods and connects different hierarchies to fill up the gaps between the wide ranges of length and time scales. The multiscale simulations are useful in a wide variety of researches in science and engineering. This approach deals the concepts of quantum mechanics, Newtonian physics depending upon the length and time scales of the system of interest. It can operate in various ways to bridge different levels of resolutions [Golan *et al.*, 2018; Karplus, 2014; Levitt, 2014; Noid,

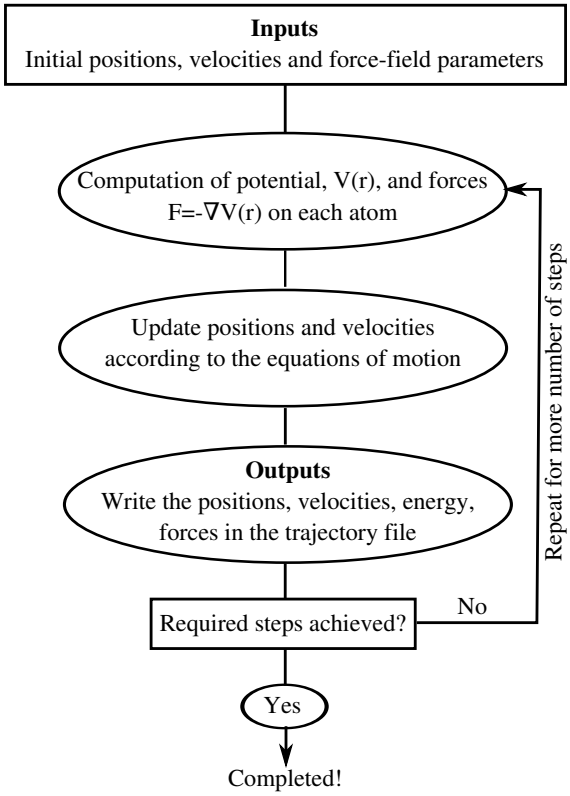

Figure 1.5: Flowchart of the steps performed in the molecular dynamics simulations.

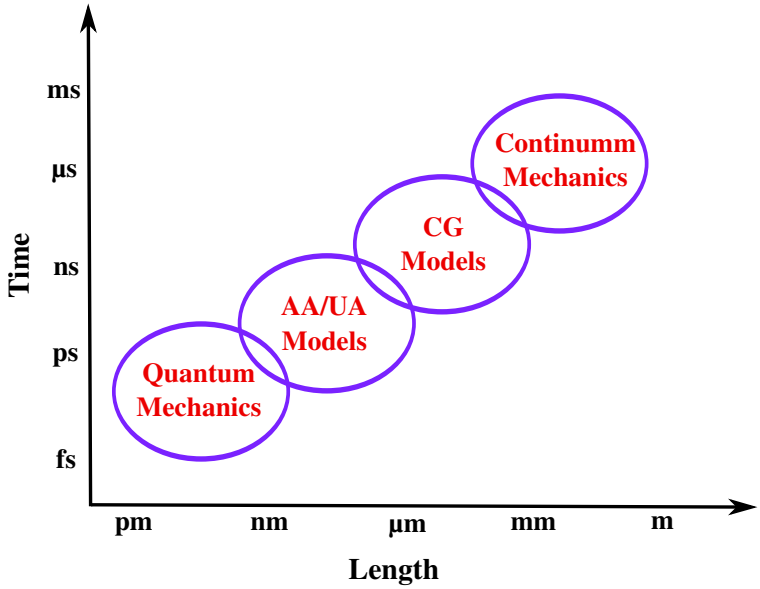

Figure 1.6: A schematic representation of the hierarchy of the multiscale modelling based on the length and time scale of the system. AA, UA and CG stand for all-atom, united-atom amd coarse-grained models respectively.

2013; Peter and Kremer, 2009; Liang *et al.*, 2014; Farah *et al.*, 2011; Masia *et al.*, 2014; Agrawal *et al.*, 2014]: (a) a sequential approach where the models at different resolutions are separately treated by using the informations like parameters, structures, etc. from one level to another, (b) a

hybrid approach where systems at different resolutions simultaneously interact, and (c) an adaptive approach which allows the particles to switch between different levels of resolutions. A schematic diagram of the multiscale approach is shown in the figure 1.6. The systems with size in the range of pm to nm showing their dynamics in the scale of fs to ps are treated with the laws of quantum mechanics. The study primarily focuses on determining the molecular energies along with the electronic structures of a system determining its chemical properties. Within the chemical precision, the energies and the electronic structures of the system are computed by solving the Schrödinger's equation. These calculations enable to construct an understanding of medicines, condensed matter physics and industrially important materials or catalysts [Wei *et al.*, 2020]. For a system composed of a group of atoms or molecules falling in the sizes of nm to μm with dynamics relevant within the time scales upto ns are treated with the laws of classical mechanics using molecular dynamics (MD) simulations. The MD method utilizes different types of models for simulating the particles falling in these length and time domains. These are all-atom (AA) models or united-atom (UA) models. The all-atom model is the finest among all as each and every bonded and non-bonded interaction is computed in an explicit manner. Since it explicitly computes all the interactions, this model is computationally expensive to explore the longer length and time scales. To overcome this, a united-atom model is often used where a particle is treated as a group of atoms. The computation time is reduced by grouping each C-atom with its bonded H-atoms. This model is widely acceptable due to its lower computational cost than the AA model and results agree well with the experiments [Chen *et al.*, 2006]. Both these models are utilized to study physical movements of the constituents. The constituents are allowed to interact for a time period which is sufficient enough to observe their dynamic evolution and structural features. These models are widely applicable to understand the systems falling within the domains of biophysics, material science or chemical physics.

Certain phenomena such as phase transitions, polymer dynamics, etc. are relevant to time scales in the range of ns-μs and require longer length scales, inaccessible to AA or UA simulations. For these cases, coarse-grained (CG) models serve as reliable platforms. There are several approaches by which coarse-graining is performed. One popular approach is a systematic conversion of an AA scale to a CG scale. In that case, the coarse-grained model is obtained by mapping few atomistic fragments and grouping them as a single bead or super-atom. The CG simulations are performed by considering larger pseudo-atoms, often called as super-atoms or beads [Kmiecik *et al.*, 2016]. Thus a reduction in the number of degrees of freedom results into a smooth potential energy landscape, enabling to explore the phenomena which are relevant to longer length and time scale. Due to a reduction in the degrees of freedoms, the systems can be simulated using the principles of classical mechanics with a larger time step (10-40 fs) [Marrink *et al.*, 2007] in comparison to the smaller time steps of atomistic simulations ($\sim$2 fs). This model is capable to capture the length and time scales of phase-transition, properties of polymers or complex biological events [Siewert *et al.*, 2009; Marrink *et al.*, 2007; Xue *et al.*, 2018; Duncan *et al.*, 2011]. However, the finer details like hydrogen bondings are not explicitly measured in the CG simulations but are treated in an implicit manner. The derivation of CG potentials between the beads may be focused on reproducing thermodynamic properties like free-energies and the overall properties of the system or the reproduction of structural distributions obtained from atomistic simulations [Peter *et al.*, 2008].

Further, to understand the mechanical behavior of materials, the systems are studied using the concepts of continumm mechanics. The mechanical behavior of the systems fall in the lengths of mm-m and time scales of μs-ms. The systems are modeled by assuming that the constituents fully fill up the space they occupy [Ranganathan and Murshed, 2018]. This method is independent of any co-ordinate system unlike the other models. The physical properties are denoted by tensors. Continumm models rely on some of the fundamental laws of physics such as the conservation of momentum, mass and energy. This approach is suitable to study solid and fluid mechanics, elastic or rheological properties [Dill, 2006]. Thus the multiscale modeling enables to capture the wide length and time scales to understand the phenomena occurring at a microscopic to a macroscopic level.

1.3 LITERATURE REVIEW ON SURFACTANT AGGREGATES

Due to huge contributions of surfactants in industries, medicines or in daily commodities, it becomes a necessity to look for a flexible and reversible methodology via which the existence of these mesoscopic phases can be controlled. Several studies conducted by molecular dynamics (MD) simulations have enabled the researchers to understand the shape and size of the surfactant aggregates. MD simulations of double chain surfactants in water and carbon dioxide have resulted into the formation of a reverse micelle where the results are in good agreement with the experimental findings. The shape and size of the aggregates are found to be dependent upon the ratio of water-to-surfactant where an increase in water content leads to the formation of more number of aggregates with larger size [Salaniwal *et al.*, 2001]. Atomistic models have been utilized to study the topological features of sodium dodecylbenzenesulfonate (SDBS) micelles under varying concentrations in the presence of oil/water mixture. Once the CMC is achieved, the SDBS molecules self-assemble into distinct shapes forming spherical, rod-like, worm-like and bilayer micelles. The transition in the micellar shape is characterized by the changes in the principle moments of inertia of the aggregates. The study enables to relate the micelle aggregation number with the SDBS concentration, which holds a power-law dependence [Jian GAO, 2005].

The shape transitions in surfactants also occur upon changing the ratio of the surfactant molecules. Simulations have been performed for mixed surfactant systems composed of a cationic cetyltrimethylammonium bromide (CTAB) and anionic sodium octyl sulfate (SOS) in aqueous medium by varying the surfactant ratios. The results show a shape transition from sphere to disc to rod shape micelles when CTAB concentration is higher, whereas in the reverse case a rod to spherical micelle formation is seen [Chen and Hao, 2013]. Counterions also play an important role in studying the compactness of the aggregate. The effect of three ions Li^+, Na^+ and NH_4^+ have been investigated for the micelles composed of dodecyl sulphate (DS) in presence of water. The trajectories show that the radii of gyration is smallest for $LiDS$. The radial distribution function of the ions with respect to the center of mass of the micelle reveals that Li^+ stays nearest to the micellar core. Thus the Li^+ ion penetrates deeper into the SD micelle than rest of the ions giving into the most compact structures [Rakitin and Pack, 2004a].

The aggregation behavior is also dependent upon the type of side chains which results into differences in interactions and size of the aggregates as seen in the case of perylene bisimide-based polyaromatic (PA) surfactants. Using organic solvents, the aggregation behavior has been studied for PA surfactants with different functional group using both MD and dynamic light scattering (DLS) method. The results have shown differences in the association of molecules, dynamics of aggregation and the structure of the aggregate. Treatment with different organic solvents like toluene and heptane show the existence of large size aggregates in the presence of toluene. The aromatic solvent toulene is found to hinder the $\pi - \pi$ stackings of PA. Thus, along with the substitutions in PA, solvent also acts as a controlling parameter for self-aggregation [Teklebrhan *et al.*, 2012].

Although the atomistic simulations serve as a promising method to capture the surfactant phases, they are still limited by the larger system size effects and the time scales. To overcome this, the coarse-grained (CG) models have served as a relevant choice with a modest computational price. CG-MD simulations have been performed for sodium dodecyl sulfate (SDS) with some modifications in the Dry MARTINI force-field. The simulations are carried out in the presence of implicit water. The force-field enables to capture the exchange of SDS molecules among the micellar aggregate, fission and fusion of micelles and micelle size distribution, shape transition upon addition of salt or increasing SDS concentration. Thus, the method redirects to the idea of simulating systems to study shape transitions [Wang and Larson, 2015]. Coarse-graining techniques have been well suited to provide the observations from the experimental analysis. CG simulations by decreasing the spacer length in Gemini surfactant (based on alkanediyl-a,w-bis (dimethylcetylammonium bromide)) in presence of water shows morphological changes from spherical to wormlike micelles

to vesicular shape. These findings are in good match with the experimental results [Wang *et al.*, 2017]. CG simulations have been performed for mixed surfactant systems to study the vesicles formed by a cetyltrimethylammonium chloride (CTAC) in the presence of sodium dodecyl sulfate (SDS). The vesicular shape has been a matter of contention due to its wide applicability in drug delivery process. Changing the surfactant ratio enables to obtain a wide spectrum of morphologies. At equal ratios of CTAC and SDS, a vesicle formation takes place via curling of the lamellar phase and entropy being the driving force for the mechanism [Wang *et al.*, 2016b]. Similar to this, CG simulations are performed for a surfactant dodecyltrimethylammonium bromide (DTAB) and an anionic poly-electrolyte polyacrylamide which is partially hydrolyzed (HPAM). The study reveals the change in shape of spherical aggregate to a rod-like structure with increasing DTAB concentration, which is even more promoted upon increasing the degree of hydrolysis of HPAM. Electrostatic interactions between the head-groups of the respective components are seen to be important for the structural transition [Hu *et al.*, 2018].

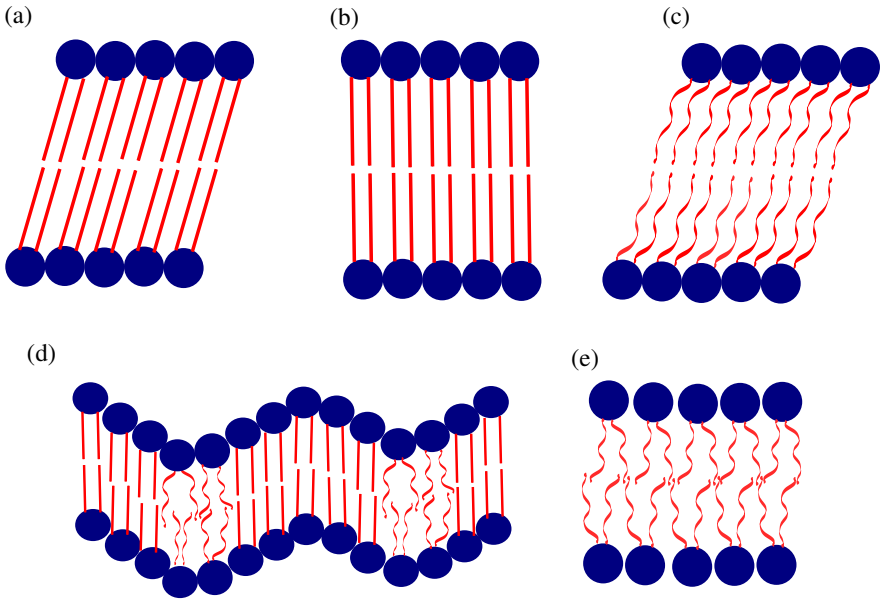

Figure 1.7: A schematic diagram showing different phases of a bilayer (a) Liquid crystalline phase (L_c), (b) Gel phase (L_β), (c) Tilted gel phase ($L_{\beta'}$), (d) Ripple phase (P_β) and fluid phase (L_α).

Surfactants are also well known to form bilayers which show similar phase behavior like lipid bilayers. These phases include liquid crystalline (L_c), gel (L_β), ripple (P_β) and fluid phases (L_α). A schematic representation of the bilayer phases is shown in figure 1.7. Molecular dynamics has shown its potentials to capture these distinct bilayer phases with structural properties similar to the experiments. Atomistic simulations conducted for SDS in water using the NAMD package and the CHARMM-27 force-field produce a liquid crystalline phase. Analyses as area per molecule or the parameters of hydrocarbon chain packing are well reproduced from simulations as obtained from the experimental analysis [Poghosyan *et al.*, 2007]. The ripple phase of a double chain cationic surfactant dioctadecyldimethylammonium bromide (DODAB) is well captured using atomistic simulations. The Berger lipid force-field is parameterized for DODAB molecule and a simulation carried out at 298 K leads to the formation of a tilted ripple phase ($P_{\beta'}$). Initial fragments of the surfactant chains near the heads are seen to be less ordered than the remaining chain fragments which are more ordered and give an alignment of $\sim 15^\circ$ with respect to the normal. The average density of the bilayer and area per molecule are similar to the experimental values [Jamróz *et al.*, 2010]. Efforts have also been made to develop a coarse-grained model for surfactant bilayers using the atomistic model. AA-MD simulations are carried out for an anionic surfactant Erucate (COO^- head) and a cationic surfactant EHAC ($-N^+(CH_2CH_2OH)_2CH_3$ head) where the hydrophobic

chains of both these surfactants are same. The objective to simulate these systems is to determine the stability and mechanical properties of the bilayers in the absence of any experimental evidence. Atomistic simulations show the formation of a stable lamellar phase for Erucate while the EHAC membrane is unstable. Systematic parameterization of the CG model by tuning the head-group size (σ) and interaction potential (ϵ) result into well reproducing the structural features as area per head group or the mechanical features as bending rigidity [Boek *et al.*, 2005b]. United atom (UA) and AA simulations have been performed for sodium dioctyl sulfosuccinate (AOT) in water. The molecular arrangements have been deeply investigated by the MD technique to study the anomaly in the structure. The curvature and structural defects in the middle region of AOT bilayer lead to the origin of a rippled defective membrane, which further induces a link and reduces mobility of water molecules. The AA simulations are found to very well complement the experimental results [Poghosyan *et al.*, 2019].

Next, the gel phase of the surfactants is known to be used in the cosmetic industry [Colafemmina *et al.*, 2020], atomistic simulations have been performed for systems composed of cetyl and stearyl alcohols in presence of CTAC. In absence of CTAC, there is a transition from the gel to the fluid phase, similar to the experimental findings. The simulation has shown the phase transition upon varying temperatures [de Oliveira *et al.*, 2020]. Thus, from the existing studies, it can be concluded that the surfactant self-assembly is a very sophisticated process which can be alerted by even a slight change in the physical conditions. Hence, it requires extreme vigilance to design the desired mesoscopic structure for the desirable functionalities.

1.4 SELF-ASSEMBLY IN PEPTIDES

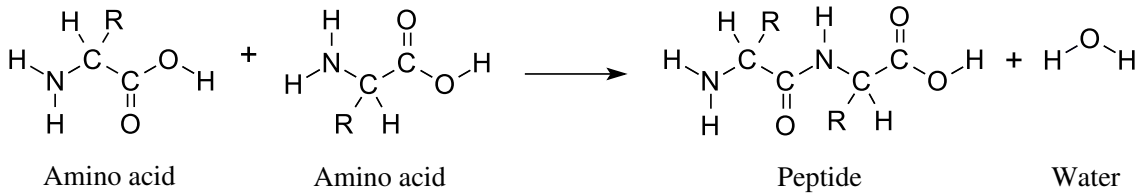

Figure 1.8: A schematic diagram showing the formation of a peptide by the linkage of amino acids and is facilitated by the elimination of water molecule.

Peptides are chains formed by the linkage of amino acids which are connected via peptide bonds ($CO-NH$ bond) as shown in figure 1.8. Peptide chains with around ten to fifteen amino acids are called as oligopeptides whereas the ones with larger amino acid sequences are termed as polypeptide. The longer polypeptide chains are responsible to make up a protein structure which are the vital components of all organisms. Similar to surfactant and lipid molecules, short chain peptides too can self-assemble forming nanostructures with a wide range of biological [Lee *et al.*, 2019] and non-biological applications [Hu *et al.*, 2020; Ahmed *et al.*, 2017]. In presence of aqueous solvents, these small peptide molecules adopt different structural conformations in order to minimize their free energies. The driving forces leading to the different structural frameworks are inter-molecular interactions which are also supported by intramolecular forces. These intramolecular interactions are the non-covalent interactions like hydrogen bonding, $\pi-\pi$ interactions, hydrophobic interactions or the metal-ion co-ordination [Wang *et al.*, 2016a]. It is also possible that these non-covalent interactions work in a co-operative manner leading to peptide self-assembly. Thus the linear peptides or their derivatives have a general tendency to self-assemble into nanotubes, nanoribbons or nanofibres [Tao *et al.*, 2016]; the branched peptides assemble into micellar or vesicular shapes [He *et al.*, 2018] and the cyclic peptides may stack as nanotubes [Chapman *et al.*, 2013]. These nano-structures often work as building blocks of different molecular assemblies which range from nanometers to microns in size. These structures are quite sensitive to physical conditions

and these assemblies can be perturbed by altering pH, solvent type, temperature, ionic strength, irradiation with light etc, metal-ion complexation etc. [Zou *et al.*, 2015]. With the tendency to form distinct phases and configurations, the peptide nano-structures show their usefulness in different areas. The short chain amphiphilic peptides can form nano-domains which can serve as nano-carriers in the fields of gene and drug delivery [Avila *et al.*, 2016]. Similarly, the nanotubes have been explored to work as ion channels in lipid membranes [Ghadiri *et al.*, 1994] or helpful as drug carriers [Chen *et al.*, 2016]. The nanostructures can also result into percolated structures, resulting into the formation of hydrogels which too have wide applications in biological fields [Cox *et al.*, 2019]. The helical nano-assemblies having π-conjugations have drawn attention due to their contributions in electronic devices [Ball *et al.*, 2016; Ahmed *et al.*, 2017]. The novel applications of peptide self-assemblies have inspired the researchers to explore the self-assembly mechanisms to design the application based nano-structures. Along with experimental methods to synthesize and characterize the peptide assemblies, electronic structure calculations and molecular dynamics simulations have been instrumental in studying such systems.

1.4.1 Molecular simulations based studies for self-assemblies of small peptides

Peptides being biologically active molecules, when incorporated with electronic functionalities, provide the potential to design bio-electric nano-devices [Aida *et al.*, 2012; Stupp and Palmer, 2014; Ahmed *et al.*, 2017]. The non-covalent interactions operating between the molecules are quite prevalent and a control over these interactions results in a desirable self-assembly [González-Rodriguez and Schenning, 2011; Jatsch *et al.*, 2010]. In previous years, a variety of well-structured molecular assemblies have been studied where the mode of molecular packing is responsible for the electronic properties within the designed nano-materials [Kim *et al.*, 2011; Noriega *et al.*, 2013; Ahmed *et al.*, 2017]. Hydrogen-bonding and $\pi - \pi$ interactions are found to play an important role in the synthesis and development of supramolecular assemblies with opto-electronic properties. Hydrogen bonds can provide a good alignment within molecular aggregates due to their directionality [González-Rodriguez and Schenning, 2011].

Similarly, optical and conducting properties of aromatic systems can be attributed to the extended π-conjugation. Self assemblies of oligothiophenes, oligophenyl, phenylenevinylenes, polydiacetylenes, diimide conjugates and larger aromatic systems such as hexa-peri-hexabenzocoronenes (HBC) are the examples of π conjugated ring systems which are widely used in electronic devices [Ardona and Tovar, 2015; Kim and Parquette, 2012; Ardona and Tovar, 2015]. Molecular dynamics simulations conducted to study the self-assembly of 2,5-dialkoxy-phenylene-thiophene-based oligomers (TBT) on the graphene monolayer for a wide temperature range (300K-600 K) reveals that the local structure of TBT assembly is dependent upon electrostatic interactions [Borzdun *et al.*, 2019]. The dominant electrostatic interactions result in a liquid-crystalline type of assembly of TBT on the graphene monolayers. The stability of the longer oligomer chain is seen to be higher at high temperatures which can be applicable as molecular wires over a wide temperature range. Spectroscopic methods and computational studies have been employed to investigate the desirable nano-fibril assembly using oligopeptide-substituted perylene bisimides and quaterthiophenes which can also serve as nanowires and can be used as charge transporters in organic semiconducting devices [Marty *et al.*, 2013]. Electronic structure calculations and AA-MD simulations have been useful in understanding the electronic properties in Asp-X-X-quaterthiophene-X-X-Asp oligopeptides, where X is an amino acid residue (X=Ala, Phe, Val, Ile, Gly) [Thurston *et al.*, 2019]. Oligopeptides comprised of these smaller amino acids (Ala and Gly) favor into a linear stack, while the remaining amino acids induce twist angles in between the peptides. Absorption spectra from electronic structure calculations reveal a better electron delocalization in linearly stacked oligomers which in turn show better conductivity than the twisted oligomers. Thus, a connection between the peptide configuration and the electron delocalization can be utilized to tune conducting properties in peptide based devices.

CG simulations have also been performed to study the peptide assemblies with optoelectronic properties. A CG model has been parameterized for DFAG-OPV3-GAFD peptides with OPV3 (distyrylbenzene) π-conjugated core [Mansbach and Ferguson, 2017]. The results show that two to eight peptides self-assemble into stacks by aligning their aromatic cores. The stacks further arrange themselves into aggregates of elliptical shape via interactions among the π-cores. The CG model developed in this study of optoelectronic peptides serves as a foundation to understand the molecular mechanisms at a larger length and time scales which can be useful in tuning the structure and optoelectronic properties of such systems. Coarse-grained molecular dynamics studies have also been employed for DXXX-π-DXXX oligopeptides which have a Asp-terminated tetrapeptide wings and the self-assembly is mediated via pH. The core and side chain interactions are analyzed in this study along with the kinetics of self-assembly. The CG simulations enable to simulate ten thousand oligopeptides of length of hundreds of nanometer and time scale of hundreds of microsecond, which were otherwise unexplored. The results obtained from the simulations lead to an understanding of peptide chemistry to design self-assemblies of required optoelectronic devices [Mansbach and Ferguson, 2018].

Along with the notable applications of peptide assembly in the field of material science and technology, some peptide molecules self-assemble to form hydrogels. The mechanism of hydrogelation is mostly driven by non-covalent forces of interactions [Raghavan and Douglas, 2012; Du *et al.*, 2015]. Generally, hydrogels can be understood as the supra-structures formed from colloidal solutions of a solid dispersed in a liquid [Yan and Pochan, 2010; Dong *et al.*, 2015; Li *et al.*, 2015]. Small peptides with low molecular weights are a preferred choice for a building block for supra-molecular hydrogels [Du *et al.*, 2015; Johnson *et al.*, 2011; Tomasini and Castellucci, 2013]. They possess a well defined peptide chemistry and compatibility with biological systems [Schneider *et al.*, 2002; Ozbas *et al.*, 2004; Smith *et al.*, 2008; Adams, 2011]. The operative non-covalent forces such as $\pi-\pi$ stacking, dipole interactions, electrostatic interactions, hydrogen-bonding, hydrophobic interactions and steric forces are responsible for the stability of these hydrogels [Hartgerink *et al.*, 2002; Fichman and Gazit, 2014]. The entropic cost of hydrogelation is counter-balanced by the effect of these interactions. The lengths of these self-assembled hydrogels can range upto hundreds of micrometers [Du *et al.*, 2015]. This supra-structure is a result of cross-linking and entanglement of molecules via non-covalent forces which further leads to a self-supported network [Du *et al.*, 2015; Raeburn *et al.*, 2013; Tomasini and Castellucci, 2013; Appel *et al.*, 2012].

A methodical variation in the monomer unit, also called as gelator, and an understanding of interplay among the driving forces of hydrogelation can be used in designing highly complex materials. A systematic approach can hence lead to a variety of hydrogel nano-structures, such as, micelles, nanofibres, nanosheets, nanotubes, etc. [Zhao *et al.*, 2010; Fleming and Ulijn, 2014; Zelzer and Ulijn, 2010]. Thus, to design a proficient hydrogel with high mechanical and structural properties strongly depends upon the choice of gelator and the physical conditions. In this background, a lot of studies have been performed via recognized experimental approaches. However, a few but yet quite promising studies have been conducted using molecular dynamics simulations. MD techniques have been useful in describing the key features of hydrogelation and explaining fundamental properties of hydrogels under variable physical conditions. The utmost virtue of MD simulations to study hydrogelation mechanism is that it can handle a lot of atoms, specially the solvent molecules [Alegre-Requena *et al.*, 2019]. The properties like diffusion, hydrogel swelling, volume transition, encapsulation or adsorption of materials, etc. have been studied by simulations as observed from the experimental methods [He *et al.*, 2011; Mann *et al.*, 2011; Walter *et al.*, 2012; Ou *et al.*, 2015].

The self-assembly phenomena for peptide amphiphiles (PA) has been studied using the CG simulations. The aggregation mechanism is found to be dependent upon the electrostatic parameters and temperature which produce a variety of aggregates including cylindrical micelles, spherical micelles, non-spherical morphologies and the amorphous structures. Identification of fundamental interactions and the effect of temperature on the morphology of the aggregate found from the CG

study can provide a direction to the experimental approaches for PA hydrogels [Fu *et al.*, 2013]. MD simulations have also been used to monitor the branching and entanglements in the hydrogels composed of β-hairpin MAX1 peptide. The peptide formed nano-fibrils with a cross-section having two folded peptide molecules with hydrophobic cores rich in valine and polymerized fibrils organized as β-sheets with hydrogen bonding. Inter-peptide interactions found from MD simulations are in good agreement with the experiments [Sathaye *et al.*, 2014]. The pH is also seen to be an important parameter which can influence the shape and size of the hydrogel. MD simulations have been carried out for a hydrogel composed of trastuzumab and PVA, modified with peptide at variable pH. Conformational changes in the gelator molecule is monitored by the changes in the radius of gyration (R_g) and the solvent accessible surface area (SASA). Both R_g and SASA decrease upon lowering the pH which signifies the shrinking of the hydrogel, which can be attributed to the changes in the hydrophilic environment [Sun *et al.*, 2014].

1.5 OBJECTIVES

The present thesis investigates self-assemblies of surfactants and peptide-based molecules and their structural organizations using multiscale simulation techniques. The aim of the work performed here is to understand the parameters to control the topological features of these assemblies in order to design functionally relevant supra-structures. Following are the objectives that have been looked into details in this thesis,

- Understanding the role of water content on self-assembled phases of mixed surfactant systems to construct a water driven phase diagram at the AA level.
- Using the phase diagram, derivation of a coarse-grained (CG) model for the micellar phase and find the factors responsible to obtain the desirable micellar size.
- Using the phase diagram, investigate the influence of compositional asymmetry, per chain configurational entropy and interdigitation on the lateral symmetries of the bilayers at AA and CG scales.
- Understanding the non-covalent interactions responsible for a preferred geometry of peptide-based molecules as a building block for a supra-structure with electronic properties at AA level.
- Understanding the unusual compartmentalization in an amphiphilic peptide-based hydrogel and the factors responsible for its prolonged stability in water using AA simulations.

1.6 THESIS OUTLINE

In chapter 2, the influence of water concentrations on phase transformations of a surfactant/co-surfactant/water system is investigated by using all atom molecular dynamics simulations. At higher water concentrations, where cationic surfactant (behenyl trimethyl ammonium chloride, BTMAC) to co-surfactant (stearyl alcohol, SA) ratio is fixed, BTMAC and SA self-assemble to form spherical micelles, which transform into an interdigitated one dimensional rippled lamellar phase upon decreasing water concentrations. Fusions or fragmentations of spherical micelles of different sizes are visible from the aggregation numbers at different temperatures. However, at lower water concentrations, the rippled bilayer transforms into an interdigitated gel phase ($L_{\beta I}$) phase upon increasing the temperature. The simulations reveal that the water concentrations can influence space available around the head-groups which couple with critical thickness to match the packing fraction required for respective phases. This leads towards obtaining

water as a controlling parameter to design the desirable phases with industrial and medical applications in the future.

Chapter 3 attempts to understand the controlling parameters which play roles in shape transformations of micelles using a multi-scale approach. AA and CG simulations are carried out for BTMAC in water which upon self-assembly form a cylindrical micelle. Addition of SA in the system leads to the transformation of cylindrical micelles into spherical micelles. The CG bonded potentials are derived by the Boltzmann Inversion of the respective atomistic distributions. MARTINI non-bonded potentials are found to reproduce the desirable cylindrical micelle at the CG level, similar to that obtained from AA simulations, but it does not capture the spherical micellar phase for the BTMAC/SA/water system. A systematic tuning of the MARTINI non-bonded parameters enables to get the desired size distributions of the spherical micelle, similar to that obtained from the AA simulations. The CG simulations demonstrate that an intricate balance between the size of the head-group and hydrophilicity is necessary to obtain a size distribution in micelles. Thus, this study sheds light on the controlling parameters which govern the cylindrical to spherical shape transformations of the micelles. It also reflects that multi-scale ansatz are suitable to access the relevant length and time scale of shape transformations which are, otherwise, inaccessible to the experiments.

Chapter 4 discusses self-assemblies of BTMAC and SA at a ratio of 2 : 1 in presence of water at 283 K by employing subsequent AA and CG molecular dynamics simulations. Differences in initial configurations lead to the formation of bilayers at ripple or square phase or interdigitated gel phase of varying trans-leaflet asymmetry. The AA ripple and gel phases are reproduced well at the CG level using bonded potentials from Boltzmann inversion of AA canonical sampling and non-bonded potentials from MARTINI. Inhomogeneous populations of disordered chains with higher per chain configurational entropy and tilt result in rippling stabilized by periodic hydrophobic energy barrier and strong interdigitation. Order parameters of the asymmetric bilayers are sufficiently coupled to the per chain entropies at both levels of resolutions to serve as a reflector of the per chain configurational entropy inaccessible by experiments. Thus trans-bilayer asymmetry may be a controlling parameter to induce rippling in a bilayer of industrial importance. This work will be useful for future investigation on domain associated transport and signaling in biomembranes at low temperature. The understanding of origin and stability of asymmetric bilayers can be extended to study mixed lipid bilayers. The combined results from AA and CG simulations of mixed surfactant bilayers will be useful to understand the rippling in lipid membranes which can nucleate poration and will be helpful to calculate the permeability across the membranes at low temperatures.

In Chapter 5, understanding of intermolecular interactions among supramolecular self-assembled organization is discussed. Identification of the molecular structure relevant to the self-assembly is crucial for designing materials with desired functionalities. Interactions of aromatic rings in a peptide- perylenediimide conjugate (P-1) are investigated using dispersion corrected density functional theory. The binding energies of fully optimized dimeric P-1 are calculated to identify the most stable conformation of the dimer. We show that the dispersion correction terms have significant contributions to the total energies of the dimers. The combined results from electronic structure calculations and AA-MD demonstrate that the stacked dimer with negative interplanar angle with clock-wise rotation has stronger binding energy than the dimer with positive inter-planar angle. The excess stability of the dimer with clock-wise rotation is attributed to the intra and inter-molecular $\pi - \pi$ stacking of the side aromatic rings of the dimer facilitated by formations of less numbers of hydrogen bonds. Potential of mean forces of these two dimers with negative and positive interplanar angles in presence of 10% THF-water and 100% THF respectively confirm the thermodynamic stability of the negative angle dimer compared to the positive angle dimer, similar to the experimental findings. The stacked P-1 dimer with negative inter-planar angle with stronger binding energy is identified as the building block of a super structure with left handed helical arrangements. The calculations build the first step towards understanding the molecular origin of the stability of a specific super structure of P-1 over the other as obtained in

the experiment relevant to material science and technology.

Chapter 6 focuses on understanding hydrogelation mechanism formed by small amphiphilic peptide-conjugate molecules. Previous experiments reveal that the high insolubility and high durability of the hydrogel networks are effective in protection of enzymes and other molecules. To gain a molecular insight, electronic structure calculations are performed which describe the folded dimer as a stable building block over the open chain dimer due to the effective $\pi - \pi$ stacking. AA-MD simulations of the folded conformers in water show the formation of a layer like structure. $\pi - \pi$ interactions and hydrogen bond formations are found to be responsible for the extra-ordinary characteristics of the hydrogel. The aromatic fragments of the dimers are exposed towards water and shield the amphiphilic groups, attributing to a low solubility in water. The amphiphilic moities bring few water molecules inside the hydrogel core which remain trapped inside the core. They show slow dynamics than the bulk water with strong hydrogen bonds which is responsible for less exchange of water molecules across the hydrogel. Thus MD simulations demonstrate that the restricted transport of water molecules leads to a unique compartmentalization in small peptide-based hydrogels. Our findings can be extended to study the activities of different enzymes or drugs by entrapping them inside the hydrogel core. This work will enable to learn the factors which are responsible for protecting the enzymes from denaturation or the drugs from external conditions.