Towards the understanding of structure formation and dynamics in bio-nano systems

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Abstract. This paper gives an overview of a number of key structure formation processes involving the well known biomolecular and nano objects such as fullerenes, nanotubes, polypeptides, proteins and DNA molecules. We formulate the problems, describe the main experimental observations and theoretical advances in the corresponding fields. We demonstrate the interconnection of various dynamic and thermodynamic problems involving very different nano and biomolecular systems.

1. Introduction
There is an increasing interest towards the understanding of structure formation and dynamics in Bio-Nano systems and their potential use for possible future applications.

The characteristic size of many biomolecular systems is at the nanometer scale, i.e. the same as for nanostructures. Therefore, it is natural that one can identify many similar phenomena being present in molecular systems of both biological and none-biological nature. A few examples of this kind dealing with the structure formation and dynamics of those systems are discussed in this paper. Among them is the problem of cooperative changes in Bio- and Nano- systems, which can be understood as phase transitions. The phase transitions (PhTs) in finite complex molecular systems, i.e. the transition from one well defined structural state to another one or to a random coil or a gas state, has a long standing history of investigation. The PhTs of this nature occur in many different complex molecular systems and in nano objects, such as polypeptides, proteins, polymers, DNA, nanoparticles, fullerenes, nanotubes [1–4]. They can be understood as first order PhTs, which are characterized by a rapid growth of the system free energy at a certain temperature. As a result, the heat capacity of the system as a function of temperature acquires a sharp maximum at the PhT temperature.

Other exciting examples of structure formation and dynamics in Bio-Nano systems include the problem of structure determination of unfolded proteins from measurements of the nuclear magnetic resonance residual dipolar couplings [5], the problem of pattern formation on a surface [6], dynamics of DNA unzipping and the strand breaking process [7,8], formation, growth and fragmentation of nanoparticles, fullerene-like structures, nanotubes [9,10], macromolecular complexes and nanoparticles association (dissociation) [11] and many more.

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The interdisciplinary approaches towards solution of all these problems bring many useful insights in the understanding of structure formation and dynamics in Bio-Nano systems. Below we discuss this on several such examples: helix–coil phase transitions in polypeptides, the process of fragmentation and reassembly of fullerenes, unzipping of DNA molecules, random walk dynamics in Bio-Nano systems and carbon nanotube growth, and draw the conclusions.

2. Structural transitions in Bio- Nanosystems

2.1. Helix ↔ coil transition in polypeptides

The helix-coil transition in polypeptides has been a subject of many experimental (see e.g. [12–15] and references therein) and theoretical [2,3,16–20] studies. Much of interest is due to a probable role of such transitions in the folding process of globular proteins [18,21]. Indeed, the structure of an α-helix is one of the most essential elements of protein secondary structure, which appears as a building block in a tertiary structure of these molecules [22,23].

In the course of the helix-coil transition the polypeptide undergoes a significant structural change. The helix conformation of the polypeptide has lower energy and lower entropy compared to the energy and the entropy of the coil state. For illustrative purposes in the upper part of Fig. 1 we show the characteristic change of the structure of alanine polypeptide experiencing an α-helix↔random coil phase transition.

![Image of helix-coil transition](image)

**Figure 1.** Dependencies of the heat capacity on temperature calculated for the alanine (plot a), leucine (plot b) and valine (plot c) polypeptides consisting of 30 amino acids. The results obtained using the derivative of the total energy on temperature are shown with the thick solid line, while the results obtained using fluctuations of the total energy are shown with the dots. The characteristic structural change of alanine polypeptide experiencing an α-helix↔random coil transition is illustrated in the upper part of the figure. The figure is adapted from Ref. [20].

For the description of phase transition in the mentioned molecular systems a novel *ab initio* theoretical method has been recently developed [1–3, 24]. In particular, it was demonstrated that in polypeptides one can identify specific twisting degrees of freedom responsible for the folding dynamics of the amino acid chain. The method has been proved to be applicable for
the description of the structural transitions in polyalanine of different length by the comparison of the theory predictions with the results of molecular dynamics simulations. Comparison of the results of this method with the results of molecular dynamics simulations allows one to establish the accuracy of the new approach for molecular systems of relatively small size and then to extend the description to the larger molecular objects, which is especially essential and interesting in those cases when molecular dynamics simulations are hardly possible because of computer power limitations.

The dependence of the heat capacity of a system on temperature is of primary importance because it can be measured experimentally (see e.g. [12–15] and references therein) and reveals important features of a phase transition (i.e. the phase transition temperature, temperature range for the phase transition, the maximum heat capacity). The heat capacity of a system can be calculated as a derivative of the system’s internal energy with respect to temperature or derived from the energy fluctuations. Both methods of calculation of heat capacity of the system were analyzed [20]. Figure 1 shows the dependencies of the heat capacity on temperature calculated using both methods for the alanine (plot a), leucine (plot b) and valine (plot c) polypeptides consisting of 30 amino acids. The peaks in the heat capacity on temperature dependence are the fingerprint of the existence of the first-order-like phase transition in finite systems.

In this particular example we illustrated that phase transitions can occur in polypeptides, however this phenomenon is rather general and can be expected in many other nano scale systems. In the next subsection we consider another manifestation of a very similar process occurring in fullerene molecules.

2.2. Fragmentation and reassembly of fullerenes

![Figure 2](image_url)

**Figure 2.** Plot (a): the total energy of a fullerene C\textsubscript{60} as a function of simulation time at T = 5800 K. Plot (b): the total energy of C\textsubscript{60} as a function of temperature for different values of single bond energy \(\epsilon_s = 2.38, 3.25, 3.81, 4.12\) and 4.99 eV. Each curve shows a distinct jump in energy corresponding to a phase transition in the system. The scattered plot is the time-average total energy and the solid thick line is the cubic B-spline interpolation. In the inset to the plot (b) the structure of a fullerene being in the cage and in the gaseous states are shown. The figure is adapted from Ref. [25].

Formation and fragmentation mechanisms of fullerenes have been intensely investigated over two decades. While it is known that fragmentation of the cage can be induced by pyrolysis [26],
laser-irradiation [27] or collisions with charged/neutral particles [28–30], the mechanism of formation has remained unclear [31,32]. The processes of thermal fragmentation and reassembly of fullerene molecules in the gas phase has been recently reconsidered [25]. It has been suggested that both processes occur in a course of a phase transition between gaseous state of carbon dimers and fullerene-state of the system.

The phase transition of fullerenes C_{60} and C_{240} is investigated by conducting constant-temperature molecular dynamics simulations [25]. The phase transition temperature of 5855 K for the C_{60} and 5500 K for the C_{240} has been reported. The simulations were conducted using a developed forcefield based on the Lennard-Jones potential with accounting for the correct bonding between atoms in the fullerene. During the course of 500 ns simulation the fission of C_{60} and the reassembly of the fullerene cage from a gas of 30 dimers has been observed, as illustrated in Fig. 2a. In that figure the states with energy of about -325 eV correspond to the C_{60} cage, while the states with the energy of about -180 eV to the gas of 30 dimers.

In certain temperature range (see Fig. 2), the fullerene is seen to continuously oscillate between two phases. The process of structural transition of fullerene between the cage and the gaseous state is accompanied by abrupt growth of internal energy of the system (see Fig. 2b). Therefore the dependence of the heat capacity on temperature has a prominent peak, indicating the first-order-like phase transition in the fullerene molecule.

### 2.3. Unzipping of DNA molecule

The transition of DNA macromolecule from the double-stranded (ds) state to the single stranded (ss) configuration occurs under a temperature increase, change of ion concentration in solution, interaction with proteins or action of some external forces. The characteristic structural change of a DNA molecule experiencing this transition is illustrated in Fig. 3. Under such processes the H-bonds in complementary pairs of dsDNA break out and the nucleic bases become open. The opening of the pairs in the double helix is the cooperative process that induces the separation of two DNA strands. In the native conditions the DNA opening is a key element of important biological processes, such as DNA transcription and replication.

During the last years there appeared a number of new experimental techniques for probing single-molecule micromechanics which have been used for studying the process of DNA double helix opening. Thus, there was developed a special system for the investigation of mechanical separation of the DNA strands (unzipping) [34]. The unzipping of the DNA helix occurs under the action of external force (optical or magnetic tweezers) applied to one of the strands of the double helix. Recently, this experiment was supplemented with measurements of the temperature dependence of DNA unzipping within the temperature interval from 15 up to 50 °C [33]. The results obtained were presented as the force-temperature phase diagram of DNA unzipping and are shown in Fig. 3. The experiment shows that the base pair opening by external force depends on temperature in a nontrivial manner [33]. Figure 3 shows that the existing theoretical approaches can not describe accurately the experimentally observed plateau in the force-temperature diagram at low temperatures.

Recently the mechanism of DNA unzipping has been considered theoretically [7] with account for possible conformational changes in dsDNA and formation of metastable states of base pairs under temperature increase. It has been suggested that the DNA double helix is a relatively soft structure which can be present in several metastable states, which are populated under temperature increase. The model is based on the normal mode analysis of dsDNA dynamics within the framework of the 4-mass model approach [35] and accounts for different possible pathways of DNA unzipping. The constructed model supports the common view that the observed process of DNA unzipping is the first order phase transition induced by applied force. The developed model leads to linear force-temperature dependence of unzipping at the temperatures interval 24-35 °C as described in Refs. [33,36] and explains the appearance of
Figure 3. The dependence of the unzipping temperature on the stretching force applied to the DNA molecule. Circles and squares are experimental results, which correspond to different DNA’s sample preparation techniques (see Ref. [33] for details). The line correspond to the results of theoretical model discussed in [33]. The characteristic structural motifs of the DNA molecule being in the double helix and unzipped states are shown in the insets.

3. Stochastic dynamics in Bio- Nano systems

3.1. Residual Dipolar Couplings in Unfolded Polypeptide Chain

Unfolded proteins have recently attracted a lot of attention when it became evident that the intrinsically unstructured proteins comprise a large part of the proteins being encoded in eukaryotic genomes [37]. The open question, which is important, e.g., for the protein folding studies, is how much of residual structure is actually present in the unfolded proteins. High-resolution, liquid-state nuclear magnetic resonance (NMR) spectroscopy is an ideal tool for answering this question. Several experimental observables (e.g., chemical shifts) can be used for this purpose [38]. One of such observables is the direct dipole-dipole interactions between nuclear spins (the so-called residual dipolar couplings, RDCs), e.g., between the spins of a $^{15}N$ and a $^1H$ nuclei. RDCs are expressed via the average orientation of internuclear vectors in an anisotropic environment (created by dissolving the polypeptide in a liquid crystal medium). As RDCs throughout the polypeptide chain are correlated, NMR spectroscopy makes it possible to deduce the persistent residual structure of the chain [39]. RDCs have been measured on a variety of unfolded proteins and small peptides.

Recently [5] a theoretical framework suitable for describing various characteristics of unfolded polypeptides including the prediction of RDCs has been developed. Within this framework amino acids in the polypeptide are modeled as beads with three degrees of freedom for each amino
Figure 4. Plot (a): NH residual dipolar couplings as a function of the segment number for random flight chains of different lengths: 11 segments, 21 segments, 51 segments, and 101 segments. Plot (b): Experimental NH residual dipolar couplings for the urea (bars) and predicted values for a chain of equal length (line). The figure is adapted from Ref. [5].

This allows one to reduce the number of degrees of freedom in the system significantly providing the possibility of an analytical description of its dynamics.

The developed framework is rather general and can serve as a basis for determining RDCs in unfolded polypeptide chains under a wide spectrum of experimental conditions. The framework allows one to employ various models for the polypeptide chains and for aligning media in order to find RDCs with the desired degree of accuracy. Using the framework it was showed that within a simple model which approximates the alignment media as infinite planes and in which unfolded polypeptides are described within the random walk formalism, it is possible to obtain an analytical result for the RDCs. The two general features predicted by the model are (i), RDCs in the center of the chain are larger than RDCs at the ends and (ii), RDCs are larger for shorter chains than for longer chains at a given liquid crystal medium concentration. These two features are illustrated in Fig. 4a. Experimental data available from the literature confirm the first prediction of the model (see Fig. 4b), providing, therefore, a tool for recognizing fully unfolded polypeptide chains. With less certainty experimental data appear to support the second prediction as well.

3.2. Nanotube growth

Chemical vapor deposition (CVD) is a standard technique for obtaining high quality carbon nanotubes in technologically significant quantities [41–43]. In catalytic CVD a patterned array of catalyst nanoparticles (typically, Ni, Co or Fe nanoclusters) is attached to a substrate. It allows one to grow vertically aligned nanotube arrays, very well suited for various applications in thin films development, electronics, biophysics, etc [44,45]. There are numerous empirical recipes for improving production efficiency and quality of the carbon nanotubes, such as, e.g., plasma-enhanced CVD [46]. However, in spite of intensive research and huge body of experimental knowledge, the physical mechanisms leading to the catalytically assisted carbon nanotubes growth remain a widely debated issue. It is evident that a breakthrough in understanding the growth mechanisms would facilitate further improvements in the growing techniques leading to a better quality of the nanotubes and to a better control over the nanotubes properties.

One of the possible descriptions of the process of catalytically assisted growth of carbon nanotubes is based on solving of kinetic equations. Recently a model to describe this process
Figure 5. Cross section of the nanotube attached to the catalytic nanoparticle. Arrows depict the flows of feedstock molecules and carbon atoms which are accounted in the kinetic model. Catalytically active part of the nanoparticle is denoted "c", "poisoned" by the products of feedstock pyrolysis or in any other way inactivated part of the nanoparticle surface is denoted "p", the growth region is "g", the nanotube base region is "b". The figure is adapted from Ref. [40].

has been developed [40]. The model describes the flow of carbon atoms starting from the catalytic decomposition of the feedstock molecules at the surface of the catalyst and ending at their embedding into the nanotube. The model is capable of reproducing any growth regime, depending on the input parameters such as CVD conditions and properties of the catalytic particles. The model allows one to predict with a reasonable accuracy the distribution of carbon between important regions of the catalytic nanoparticle, the relative significance of various growth mechanisms, the nanotube growth rate, etc. The input parameters (e.g., diffusion coefficients, activation energies for embedding into the nanotube) are to be obtained from accurate quantum mechanical calculations or from experiments.

To illustrate the kinetics of the nanotube growth in Fig. 5 the cross section of a nanotube attached to the catalytic nanoparticle is depicted. The catalytic particle (except for the part inside the nanotube and for the particle–substrate interface in the case of the base-growth mode) is exposed to the flow of the feedstock gas. The feedstock molecules hitting the surface of the catalytic particle are partially reflected and partially decomposed on the catalytically active part of the particle's surface, shown as region "c" in Fig. 5. The carbon atoms adsorbed in region "c" can evaporate or diffuse (either along the surface or through the bulk of the cluster) into the other parts of the catalytic particle. The growth region surrounding the nanotube walls (region "g") and the near-surface region inside the nanotube (region "b") are indicated.

From the region "b" carbon atoms can reach the growth region by surface or bulk diffusion or they can evaporate. Some of the evaporated atoms are deposited on the nanotube walls
and reach the growth region by surface diffusion. Region “g” represents a gate through which the carbon atoms embed themselves into the nanotube walls. The nanotube’s growth rate is proportional to concentration of carbon in the growth region.

4. Conclusion

We have described several examples of structure formation in the nanoscale molecular systems of both biological and none biological nature. We have elucidated the correspondence and the analogy of various problems that could be addressed to all of them. The similarity of the methods of description of bio- and nano- molecular systems and the experimental techniques for their investigation allows us to conclude that all these problems represent a common field of research which can be called the bio-nano science. This field of research is growing up rapidly during the last decade, but still leaves quite a number of open challenging problems for further investigations.

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