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Nanomechanics of macromolecules: Force-extension response of biological macromolecules

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The development in recent years of single-molecule force spectroscopy experiments allowed a better knowledge of macromolecules of biological interest, such as DNA and proteins. The work presented here describes the modelling of the macromolecules’ response to deformation and to thermal fluctuations with the help of the statistical mechanics, through comparison with the experimental results obtained by single-molecule force spectroscopy, providing valuable information on the static and dynamic responses induced by applied forces. These analyses are even more important for bistable macromolecules with conformational transitions, thus corresponding to folding/unfolding processes and to two stable positions (folded and unfolded).

In order to analytically obtain the force-deformation response of a chain composed of bistable units, it is necessary to calculate the partition functions, which are essential in the statistical mechanics and allow to obtain average values of parameters of interest. Thus, the bistable potential energy is decomposed into two parabolas, both corresponding to the folded and unfolded states and identified using the spin variable technique. Several extensions are added to this technique, in order to bring the model closer to reality, such as the extensibility of the bonds between the bistable units, the interactions existing among the bistable units, thanks to the Ising model, or again the heterogeneity, an important parameter to determine the unfolding sequence in proteins folding.

Finally, the influence of the pulling speed on the force peaks is considered in the dynamic study, provided with the help of the Langevin method.
The themo-mechanical response of macromolecules can be experimentally observed with single-molecule force spectroscopy (SMFS). Recent sophisticated experiments offer a wider comprehension of intra and intermolecular forces. The typical measure realized with the help of SMFS is the force-extension response. A broad class of biological polymers such as RNA, DNA and diverse proteins showed a non-linear elastic response. One of the most important experiment concerns the stretching of a double-stranded DNA. The aim of our work is to model this force-extension relation by using statistical mechanics. As we consider small systems, different conditions must be studied, namely the isothemal and the isometric conditions, respectively associated to the Gibbs and the Helmholtz ensembles.

### Extensibility and Interactions

- **Freely jointed chain model.**
- **Borel-unt units undergoing configurational transitions.**
- **Here, the bonds between the units are extensible (k > 0, finite value).**
- **We observe a cooperative (synchronized) process in the Gibbs ensemble and a non cooperative (unsynchronized) process in the Helmholtz ensemble, confirming the experimental results.**
- **We note the strong reduction of the force peaks with increasing the elastic constant.**
- **We studied the first time Hermite polynomials Hn with negative index to solve the partition function integral.**

### Ising Interactions

- To represent interactions existing among units, we chose the Ising model. The Ising coefficient, λ, allows us to take account of interactions between units, bringing our model closer to the reality. This term is directly included in the Hamiltonian and can be associated to affinity in chemistry.
- **If λ > 0, we consider that the interaction is positive, namely units in the same state (folded or unfolded) want to be close to each other.** This case can be associated to an ferromagnetic-like interaction.
- **If λ < 0, we consider that the interaction is negative, namely units in opposite state (folded and unfolded) want to be close to each other.** This case can be associated to an antiferromagnetic-like interaction.
- **It is possible to introduce in the spin variable model both the extensibility and the Ising interactions (see right panel).** We have studied to find completely analytical solutions and compare with our semi-analytical/semi-numerical model, for instance, strong ferromagnetic-like interactions.
- **The Ising interactions induce a specific cooperativity, which can be detected in the modification of the hierarchy of forces in the sawtooth-like response, as recently observed in force spectroscopy experiments of proteins (e.g., in Filamin A).**

### Heterogeneity and Dynamics

- **Another aspect to consider to be even closer to the reality concerns the heterogeneity in chains of bistable units.**
- The latter may concern elastic response, basal energy or other parameters characterizing the units. We suppose the system at thermodynamic equilibrium. In practice, this equilibrium corresponds to a very low pulling speed of extension of the chain.
- **In the homogenous case, all units are identical, so that all folded units have the same probability to fold or unfold at each event.** This means that we cannot obtain a folding/unfolding sequence because of the homogeneity of the chain. This is not the case in real experiments, where the folding/unfolding sequence can be exactly identified and depends on heterogeneous aspects of the chain (the quenched disorder breaks the symmetry). We propose this model to describe the actual folding/unfolding pathway and relative unfolding probabilities of units. We introduce the heterogeneity at the energetic level, using the Monte-Carlo method to generate basal energies.

### Spin variable model

- **We introduced a new technique called the spin variables method to theoretically analyze the behavior of bistable chains, exhibiting the so-called conformational transitions.** This method is based on the introduction of a sequence of n spin variables, able to describe the state of all elements of the chain. Indeed, the exact calculation of the Gibbs and Helmholtz partition functions is complicated because the potential energy is represented by a double-well energy potential. Therefore, to define the system in a simpler way, we add internal variables, belonging to the phase space and considered as standard variables of the statistical mechanics. These variables are discrete and behave as spin variables. The spin variables allows to identify the potential well explored by the domain under consideration and to know if the chain is folded or unfolded. Hence each potential well is now described by a quadratic potential, which simplifies calculations.

### Dynamics

- **We propose to study the unfolding processes under dynamic regime in order to better represent real SMFS experiments.** Indeed, about experiments in the Helmholtz ensemble, chains are often subjected to an increasing force (with a speed of around 1 μN/s), which can generate dynamic effects corresponding to an out-of-equilibrium statistical mechanics regime.
- **However, there are currently two methods to deal with this problem: the first one is the analytical calculation, which provides correct results only for very low extension speeds (equilibrium), and the second one is the numerical calculation (molecular dynamics), which can only be applied for high extension speeds, due to cost of calculation, which limits total time of simulation.** This implies that we can work not with intermediate extension speeds, which are necessary to interpret the SMFS experiments.
- **Therefore, we used the Langevin equation to study the out-of-equilibrium processes. As a result of the dynamics, force peaks depend on pulling velocity, and this dependence can be used to measure the energy barrier between folded and unfolded states, which play a crucial role in determining characteristic times of the process.**