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Regular Article

Comparison Between All-Atom and Coarse-Grained Dynamics Simulations for Predicting Mechanical Properties of Proteins

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Abstract: In this work, we perform all-atom and coarse-grained dynamics simulations to predict the mechanical properties of a typical synthetic protein system. Previous experiments showed that proteins with a larger molecular weight exhibit better mechanical performance. Our steered molecular dynamics (SMD) simulations at the all-atom level only capture intermolecular interactions and fail to reproduce this tendency. The results of the dissipative particle dynamics (DPD) simulations at the coarse-grained level are consistent with experiments. The comparison between two levels of resolution highlights the importance of simulation scales in predicting mechanical properties of complex systems. We also reveal some underlying factors correlated with the mechanical properties of synthetic proteins, such as molecular weights, fabrication processes, the ratio of hydrophobic to hydrophilic segments and their order in the amino acid sequences.

Key words: steered molecular dynamics, dissipative particle dynamics, mechanical property, silk protein, multiscale simulation.

One of the central tasks of computational chemistry is predicting physical and chemical properties. Since many chemical processes occur in a broad range of spatial and time scales, the level of resolution for simulations is crucial for computational models [1-5]. On one hand, predictions on optoelectronic properties of materials require explicit modelling of electronic degrees of freedom that are governed by quantum mechanics. On the other hand, thermodynamic properties such as the free energy changes during biological processes can be well predicted based on classical statistical mechanics via molecular dynamics (MD) simulations. How to improve the accuracy and efficiency of simulations with affordable computational resources has been a long-standing challenge. Compared with the all-atom computational model, the coarse-grained model reduces particular degrees of freedom and significantly saves computational cost, usually at the expense of prediction accuracy. In practice, all-atom MD simulation results can be utilized as the reference to validate the thermodynamic properties predicted at the coarse-grained level.

Aside from optoelectronic and thermodynamic properties, theoretical predictions on the mechanical properties of complex molecular systems are also an important task of computational chemistry, especially for the rational design of biomaterials. In recent years, various computational models at different levels of resolution have been developed and successfully applied to study the mechanical properties of proteins, microtubules and other types of polymers [6-10]. However, a comprehensive comparison of all-atom and coarse-grained simulation results has never been discussed in depth, at least to the best of our knowledge. In the present work, we

implemented molecular simulations for synthetic silk proteins to predict their mechanical properties at the all-atom and coarse-grained levels. The difference between these two computational models was illustrated in Figure 1.

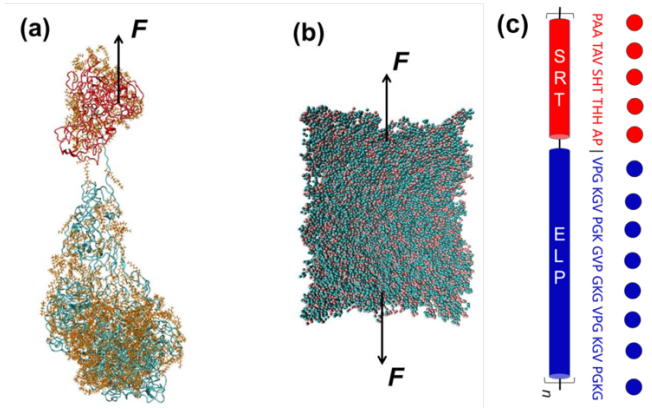

Figure 1. Computational models: SMD at all-atom level (a), DPD at coarse-grained level (b), and an example of mapping between two levels (c).

We employed recombinant chimeric proteins consisting of the squid ring teeth (SRT) and elastin-like polypeptide (ELP) sequences, which have been studied by Liu and coworkers in experiments [11-13], as our test systems. The SRT acts as a hydrophobic segment with the sequence of PAATAVSHTTHHAP, while the ELP is a hydrophilic sequence as $(VPGKG)_5$. These two segments repeat several times to construct silk proteins, such as $(SRT\text{-}ELP)_{12}$, $(SRT\text{-}SRT\text{-}ELP)_9$, $(SRT\text{-}ELP\text{-}ELP)_7$, $(SRT\text{-}ELP)_{24}$ and $(SRT\text{-}ELP)_{36}$. It was observed in experiments that the polymer of SRT-ELP with a larger molecular weight exhibits better mechanical performance, including a higher breaking stress and Young's modulus [11]. The impact of fabrication processes such as the introduction of glutaraldehyde crosslinking or non-covalent counterion surfactants was also well investigated experimentally and theoretically [11,14], revealing details of intermolecular interactions. However, the theoretical prediction of the mechanical properties of such complex systems is still challenging.

We first applied steered molecular dynamics (SMD) simulations to four systems: $(SRT\text{-}ELP)_{12}$, $(SRT\text{-}SRT\text{-}ELP)_9$, $(SRT\text{-}ELP\text{-}ELP)_7$ and $(SRT\text{-}ELP)_{24}$ with sodium dodecyl benzenesulfonates (SDBSs) at the all-atom level. The results were depicted in Figure 2. The standard deviations were small relative to the corresponding average values, justifying the setup of SMD simulations. The breaking stresses predicted for 12mer and 24mer were 315 and 227 kJ/mol/nm, respectively. Notably, the breaking stress decreases with the growing molecular weight, which is opposite to experimental observations [11]. Then we compared the results of $(SRT\text{-}SRT\text{-}ELP)_9$, $(SRT\text{-}ELP\text{-}ELP)_7$ and $(SRT\text{-}ELP)_{12}$ since their molecular weights are similar. The breaking stress was predicted as 344 and 278 kJ/mol/nm for $(SRT\text{-}SRT\text{-}ELP)_9$ and $(SRT\text{-}ELP\text{-}ELP)_7$, respectively, exhibiting an increased order of breaking stresses as $(SRT\text{-}ELP\text{-}ELP)_7 < (SRT\text{-}ELP)_{12} < (SRT\text{-}SRT\text{-}ELP)_9$. It suggests that the SRT segment with β-sheet structures may enhance the tensile strength of proteins via hydrogen bonds and hydrophobic interactions with other chains, while the ELP segment may be more relevant to conformational variability. Taking account of the serious deviation from experiments, however, any conclusion based on the present all-atom MD simulations is questionable in the absence of independent theoretical verifications.

The limitations of all-atom MD simulations, including molecular modelling, equilibrium sampling and umbrella pulling, may be responsible for the unsatisfactory results. First, the three-dimensional protein structures should be predicted from the amino acid sequence at the beginning. Such a homology modelling process is a nontrivial issue for synthetic proteins. Second, different protein force fields probably generate different conformational ensembles [15,16], but the influence on mechanical proteins still lies in the lack of research.

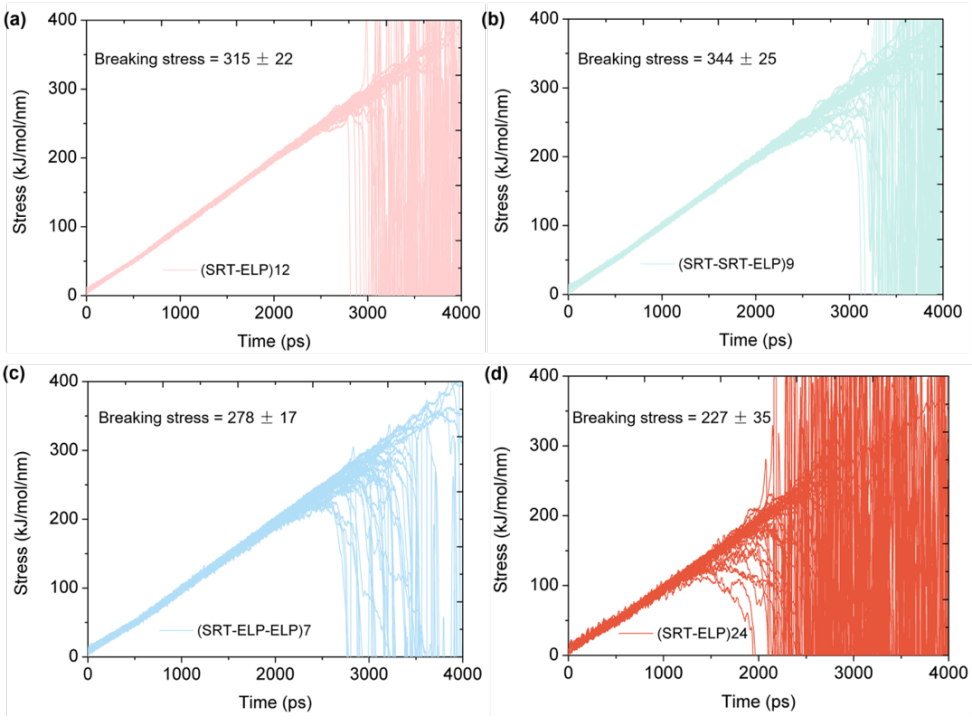

Figure 2. Stress curves as a function of SMD simulation time with breaking stresses of different systems: $(SRT\text{-}ELP)_{12}$ (a), $(SRT\text{-}SRT\text{-}ELP)_9$ (b), $(SRT\text{-}ELP\text{-}ELP)_7$ (c), and $(SRT\text{-}ELP)_{24}$ (d).