SELF-ASSEMBLY AND MECHANICS INTERPLAY IN CYCLIC PEPTIDE NANOTUBES

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Summary: Cyclic peptide nanotubes (CPNs) have unique chemical and mechanical features that are promising for sensor technologies, tissue scaffolds, templates for organic and hybrid electronics, as well as ultra-small electromechanical systems. In this study, we demonstrate a multi-scale approach for investigating the mechanics of cyclic peptide based organic nanotubes (CPNs), mapping out the elastic range of intersubunit interactions along with the large deformation and fracture regimes. Our studies illustrate the potential of atomistically informed multi-scale models for predicting elastic as well as large deformation behavior of high aspect ratio self-assembling nanostructures.

INTRODUCTION

Self-assembly facilitated through weak interactions has been recently applied to artificially create biomimetic molecular assemblies such as cyclic peptide nanotubes [1]. Peptide nanotubes are very intriguing from a mechanics perspective because they are the stiffest biomolecular assemblies known that employ only secondary interactions [2]. Here we investigate the elasticity and fracture behavior of individual cyclic peptide nanotubes (CPNs), a new type of organic nanotubes consisting of stacks of cyclic peptides (CP) stabilized by inter-chain backbone-backbone hydrogen bonds parallel to the growth direction of the nanotube [3]. These remarkable structures have shown great promise as antimicrobials [4], selective transmembrane transport channels [5], and thin subnanoporous films [6] due to their precise structural features, diverse chemical functionalization capabilities and exceptional stability arising from the arrangement of hydrogen bonds into cooperative clusters [7]. In this paper, the elasticity and fracture behavior of the organic nanotubes are examined, which are of great significance for the self-assembly process and are crucial for the successful implementation of these structures in nanotechnology and biological applications [8]. We calculate the potential of mean force (PMF) of a peptide dimer using atomistic simulations. From this analysis we obtain the tensile elastic behavior and fracture of a dimer composed by two CPs. Leveraging the simplicity of the system, we apply the Cauchy-Born rule for small linear elastic deformations, and compare the results with the full energy landscape to shed light on the valid ranges of key simplifying assumptions.

RESULTS AND DISCUSSION

The first step in our approach is to run MD simulations applying nonequilibrium thermodynamics theories to obtain the PMF along selected reaction coordinates. For this purpose, we carry out ten SMD simulations, as described above, and use Jarzynski's equality using the second cumulant expansion averaging scheme to compute the PMF along the intersubunit distance (Fig. 1)[9]. One of the major advantages offered by the method is that material behavior under a wide range of conditions, including large deformation and fracture can be elucidated using the PMF profiles along selected reaction coordinates. The multiscale strategy proposed here uses the free energy along key reaction coordinates at a finer scale as the basic input to build coarser scales, avoiding the explicit definition of constant parameters to define the material behavior. While the linearity assumption is adequate for extremely small strains around equilibrium, our results show that it may lead to loss of accuracy in hierarchical simulations of large deformation for nanostructures that exhibit softening even at small deformation. The fully nonlinear constitutive laws that determine the mechanical behavior of the material can be captured with our approach, providing a means for achieving higher fidelity descriptions of encompassing also large deformation behavior.

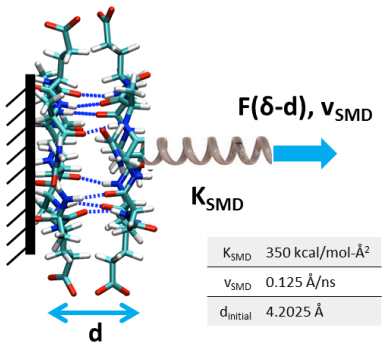

Figure 1. SMD Simulation Setup

The constitutive thermomechanical behavior of CPNs under axial stress is derived from the free energy profile with respect to the intersubunit distance (Fig. 2). From the free energy curves we identified the equilibrium state of the system at $d \approx 4.63$ Å and a metastable state around $d \approx 7.5$ Å. The equilibrium state corresponds to the situation where the two CPs are bound by backbone-backbone hydrogen bonding and in the metastable state we find the CPs separated in solution. The free energy difference reported here between these two states is $\Delta E_d \approx 5.5$ kcal/mol, in good agreement with experimental measures [10]. A system composed of CPs in solution, under favorable conditions, would evolve toward the equilibrium state, self-assembling CPs in nanotubes. The constitutive laws obtained for the CPNs indicate a nonlinear elastic behavior with marked softening until fracture. We identify the fracture strain ε_f in a range from 31 to 36 % approximately. This relatively high fracture strain compared to those values observed for other materials based on β–sheets secondary structures is due to the structural characteristics and boundary conditions of our system, a defect free small crystalline unit cell with the movement

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constrained to the axial dimension. The fracture event is associated with the energy barrier observed in the free energy profile. It is observed that once the system is driven over the energy barrier, it disassembles and evolves towards the metastable state that is observed due to hydrogen bond interactions with explicit water molecules. In the elastic range, we observe nonlinear behavior with softening for all the ranges of strain. We reported a value of the Young's modulus in the axial direction of the CPNs, defined as the tangent modulus to the initial point of the stress versus strain curve, of E = 19.9 GPa. This measure is in good agreement with previously reported values for other biological materials based on β-sheet architectures [11, 12].

In order to describe the material behavior in situations corresponding to states far from equilibrium, such as large deformation and fracture, we need a more elaborated approach than Cauchy-Born rule, such as the full energy landscape obtained from MD simulations. In this approach, we use the complete PMF profile rather than the vicinity of the equilibrium state to fit 9th degree polynomials, which are used to obtain the best approximation of the PMF profiles. Using thermodynamics concepts applied to elasticity, we can derive the stress versus strain and the Young's modulus versus strain as a function of interdimer distance. A strong nonlinear elastic behavior is observed with a marked softening of the material until failure. Values of the Young's modulus obtained from the tangent modulus vs. initial modulus obtained via the Cauchy-Born approximation illustrate reasonable agreement in the small deformation regime but diverging at large deformation. Therefore, we argue that the full-energy landscape of the materials, which can be obtained from MD simulations, has to be considered when the interplay of assembly and breaking of protein fibrils are to be captured in coarser descriptions.

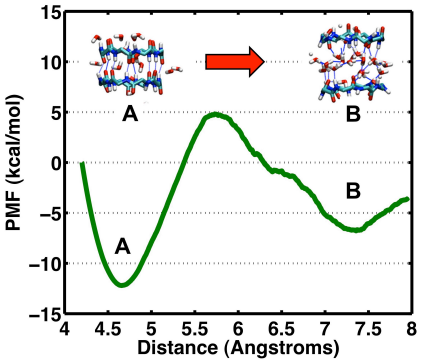

Figure 2. Potential of mean force profile from simulations.

CONCLUSION

In conclusion, we lay the foundations for a multiscale modeling approach that overcomes limitations of the models used to date. The complexity of the materials can be captured with any desired degree of accuracy by increasing the number of reaction coordinates used to map the free energy surface of the material. The approach described here can also be used to assess how the mechanical behavior of self-assembling peptide materials change with variations of the ambient conditions such as solvent polarity and ionic concentration. Multi-scale simulations informed from atomistic trajectories can be used to gain insight into the mechanical behavior of complex hierarchical materials and develop high-fidelity models that would lead to the development of a new generation of self-assembling biomimetic materials by simultaneously capturing underlying principles of material propagation, processability and failure.

References

[1] M. R. Ghadiri *et al.*, NATURE **366**, 324 (1993).
[2] S. Scanlon, and A. Aggeli, in *Nano Today*2008), pp. 22.
[3] M. R. Ghadiri *et al.*, Nature **366**, 324 (1993).
[4] S. Fernandez-Lopez *et al.*, Nature **412**, 452 (2001).
[5] M. R. Ghadiri, J. R. Granja, and L. K. Buehler, Nature **369**, 301 (1994).
[6] T. Xu *et al.*, Acs Nano **5**, 1376 (2011).
[7] R. Hourani *et al.*, Journal of the American Chemical Society **133**, 15296 (2011).
[8] L. Ruiz, and S. Keten, Int J Appl Mech **3** (2011).
[9] S. Park *et al.*, J Chem Phys **119**, 3559 (2003).
[10] M. R. Ghadiri *et al.*, Angewandte Chemie International Edition in English **34**, 93 (1995).
[11] T. P. J. Knowles, and M. J. Buehler, Nat Nano **6**, 469 (2011).
[12] S. Keten *et al.*, Nat Mater **9**, 359 (2010).