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Peptide–zinc oxide interaction: Finite element simulation using cohesive zone models based on molecular dynamics simulation

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ABSTRACT

In this study, a multiscale simulation approach of coupling molecular dynamics (MD) and finite element method (FEM) simulations was established to investigate the mechanical properties of a ZnO–peptide material. MD simulations of a single 6-mer peptide adsorbed on the polar ZnO(0001)–O surface were performed to calculate the adsorbed peptide conformations and their adsorption force parameters, which were used to estimate mechanical properties of the ZnO–peptide composite material in three point bending tests using FEM simulations. The results from the multiscale simulations revealed that the influence of the Elastic modulus of the peptide on the material properties of the composite differs depending on the elastic properties of the cohesive zone. For developing a nanocomposite based on ZnO and a peptide, this dependency should be carefully considered and used to create stronger nanocomposites. Based on these simulation results, a set of binding affinities of the peptide and mechanical properties like the crack opening displacement of ZnO–peptide material could be predicted.

1. Introduction

In material science, especially for metals, multiscale simulations have been recently applied to use the results of molecular dynamics (MD) simulations as input data for other simulation tools like finite element method (FEM) simulation or phase field simulations. Molnar et al. reported on multiscale simulations on the coarsening of Cu-rich precipitates in α-Fe using kinetic Monte Carlo, molecular dynamics and phase-field simulations [1]. Similar multiscale simulations were also performed on metal/ceramic materials where fracture on the metal/ceramic interface was analyzed [2]. In the present work, a method is developed to combine MD simulations of peptide binding to a ceramic surface with FEM simulations. Coupling molecular dynamics simulations to FE simulations is important for bridging the gap between nanoscale and micro- or macroscale. MD simulations have been successfully applied to study atomistic effects in nanoscale of biological molecules [3,4], although they are usually limited to microsecond timescale simulations for typical systems (10^6–10^5 atoms) [5], while FEM simulations in the framework of conventional continuum mechanics are used for macroscale material behavior [6]. A combination of the two simulation methods is able to predict mechanical properties of organic–inorganic nanocomposites as shown in [7].

A virtual ceramic composite material which consists of zinc oxide (ZnO) and peptides with a high binding affinity for ZnO was examined for its mechanical properties. The molecular binding mechanism of peptides to ZnO was studied by MD simulations and the binding affinities were evaluated.

The material properties of layered structures of peptides and zinc oxide are of high interest for the industry. The use of ZnO is based on its favorable properties making it well suited for many applications [8], which leads to the need to understand the mechanical properties of peptides adsorbed on the ZnO surface material. The use of ZnO includes construction of solar cells, luminescent materials and acoustic devices [8–11]. Within the last decade, many attempts have been made to study the adsorption of peptides to the ZnO surface to prepare nanostructured hybrid materials [12–17]. It was also demonstrated that ZnO-binding peptides could be used as bioactive layers for surface functionalization and modification [18] and that nano-sized structures of ZnO have unique material properties and a remarkable performance in electronics, optics, and photonics [19]. One major disadvantage of ZnO is that it is a relatively soft material [20]. A reinforcement of the mechanical properties of these nanomaterials could lead to longer life spans and an improved usability of these systems in

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environments where resistance against mechanical stress is essential [21]. An exciting hybrid material with superior mechanical properties can be found in nature: nacre, the inner layer of mollusk shells. Nacre contains a relatively brittle mineral phase that is combined with an organic microstructure resulting in an increase of toughness of the composite compared to the mineral phase alone which is reinforced through microstructures.

Nacre is hierarchically structured, it consist of a layered brick (95% aragonite – platelets) and mortar structure (5% organic components like proteins) [22]. Viewed in more detail, nano-mineral-bridges between the platelets get visible. Artificial nacre with material properties that are optimized for the respective application would be highly appreciated in engineering [23,24]. Based on a mechanical model derived from multiscale simulations, optimal peptides can be designed as a basis of future ZnO–peptide hybrid materials with optimized mechanical stabilities.

ZnO-binding peptides (6- to 12-mer) are usually selected through biopanning techniques of phage display [13,16] or bacterial surface display [25–27] peptide libraries. In a previous study [16], the adsorbed conformations and the adsorption free energy of peptide 31 (amino acid sequence HHGHSPTSPQVR) was investigated using MD simulations. Peptide 31 was previously identified by phage display [17]. It was found that the peptide preferred the negatively charged ZnO(0001)–O surface. To investigate peptide binding to this surface, peptide 31-6 with amino acid sequence HHGHSR was designed which was derived from peptide 31. In a first step, the adsorption properties of peptide 31-6 were studied by MD simulations to obtain mechanical properties on the atomic level. In a second step, the thus obtained nanoscopic mechanical properties were used for a three point bending test of a ZnO–peptide composite to characterize the macroscopic mechanical properties, thus bridging the gap between MD simulations and FEM simulations as within a multiscale approach.

The necessary parameters for FEM simulations were generated from the results of the MD simulations. Because the Elastic modulus (EM) of the peptide is not exactly known, a sensitivity analysis with different elastic moduli for the peptides layer was made for the peptide conformation.

In our study, crack propagation at the interface between ZnO and a peptide layer was studied, assuming that the crack will not primarily propagate within the peptide layer. Crack propagation in the peptide layer could be prevented by crosslinking the peptides or by using longer polypeptides rather than short peptides as in the model presented here.

2. Material and methods

2.1. Using MD simulations to estimate the adsorption affinity of the peptide

The adsorption force of peptide 31-6 on the ZnO surface were determined from the MD simulations of a single peptide adsorbed and desorbed on the negative polar ZnO(0001)–O surface. The MD simulation procedure involves three stages: first, the peptide was pulled slowly towards the surface using steered MD simulations. Second, the pulling force was removed after the peptide contacted the surface, and the peptide was equilibrated on the ZnO surface. Third, the peptide was pulled away from the surface in the desorption process using steered MD simulations, as described previously [16]. All MD simulations were performed in explicit water at constant temperature (300 K) and pressure (1 bar) using Berendsen's thermostat implemented in the simulation package GROMACS 4.5.3 [28]. Further details of the simulation can be found in the appendix.

To obtain different binding conformations of the peptide, three independent steered MD simulations were performed where peptide 31-6 was pulled towards the ZnO(0001)–O slab model and equilibrated at the surface. The last snapshot of each equilibrium simulation was chosen as the adsorbed conformation of the peptide.

To calculate the adsorption force, peptide 31-6 was pulled away from the ZnO surface in the desorption process using steered MD simulation. The external force applied in the steered MD simulation was monitored to measure the adsorption force. Three different conformations of the adsorbed peptide were used as starting conformations for the steered MD simulations. In order to evaluate the dependence of the potential of mean force (PMF) on different pulling velocities, the peptide was pulled with 4 different velocities (0.25, 0.5, 1.0, and 1.5 nm/ns). Each simulation was repeated 10 times with different initial velocities.

2.1.1. MD simulation details

All MD simulations were performed using the standard AMBER force field [29,30] for the peptide and TIP3P model for water [29]. Histidines and arginines were simulated in their protonated state, while the N-terminus and the C-terminus were simulated in their protonated and deprotonated state, respectively. The ZnO slab was modeled based on a wurtzite crystal structure with lattice parameters of $a = 0.3249$ nm and $c = 0.5207$ nm [16,31]. The force field parameters for ZnO were used based on initial computations by Raymand [32] using atomic partial charge values of $1.026e$ and $-1.026e$ for Zn and O atoms, respectively. To reduce the dipole moment of the polar ZnO(0001) surface, 25% of the negatively charged oxygen atoms on the O-terminated side and 25% of the positively charged Zinc atoms on the Zn-terminated side were removed, as described by Kornherr [33]. The negative surface charge of the O-terminated side is in agreement with the experimentally determined zeta potential at neutral pH [17]. In aqueous environment, water adsorbed to the negatively charged ZnO(0001)–O surface forming ordered water layers.

After equilibration of peptide 31-6 in explicit water for 5 ns at a distance of 6 nm from the ZnO surface, the adsorption was simulated by pulling the center of mass of the peptide along the z-axis towards the ZnO surface in a steered MD simulation of 20 ns, in which a spring constant of 3000 kJ mol^{-1} nm^{-1} and a decrease in pulling velocity from 0.5 to 0.1 nm ns^{-1} were used. When the peptide contacted the ZnO surface within a center of mass distance of 1.1 nm, the peptide was simulated for 5 ns without external forces to reach an equilibrium state for the system. The peptide conformation at the end of this equilibration time was used as an adsorbed conformation for the next MD simulations in the adsorption process. The adsorption force (f) during a steered MD simulation is monitored and can be represented at time t by the following equation:

$$f(t) = k[(Z_{\text{peptide}}(0) + vt) - Z_{\text{peptide}}(t)], \quad (1)$$

where k is the spring constant, v is the pulling velocity, and $Z_{\text{peptide}}(t)$ and $Z_{\text{peptide}}(0)$ are the z coordinates of the center of mass of peptide 31-6 at time t and initial time 0, respectively. The rupture event during the desorption process is recognized when an anchor residue is detached from the ZnO surface meanwhile the force reaches a peak in the adsorption force profile.

2.2. FEM simulations

FEM simulations of a three point bending test of a ZnO/peptide composite were conducted. The peptide was simulated as one averaged peptide, which was calculated from the results obtained from three adsorbed conformations of the MD simulations. In a real bulk material, which would consist out of the three or even more peptide confirmations, the material properties of all peptide