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A COARSE-GRAIN MOLECULAR DYNAMICS MODEL FOR SICKLE HEMOGLOBIN FIBERS AND THEIR INTERACTIONS

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INTRODUCTION

As sickle hemoglobin fibers (HbS) play a very important role in causing sickle cell disease, the material properties and thermal behavior of HbS during the polymerization process have been widely studied for an extended period of time. Bending rigidities and persistence lengths of a group of HbS fibers with different thickness were measured by differential interference contrast (DIC) microscopy in [1]. The measured persistence length of a single HbS fiber was $0.24\,mm$ and the associated bending rigidity was $8.3 \times 10^{-25}\ Nm^2$. The twist and bend in single HbS fibers were studied in [2], where measurements of spontaneous thermal fluctuations showed that the bending rigidity of a single HbS fiber was approximately $5.2 \times 10^{-25}\ N\,m^2$ and the torsional rigidity was approximately $6 \times 10^{-27}\ J\,m$. The interactions between HbS fibers were investigated in [3]. The authors found that HbS gels and fibers were fragile and easily broken by mechanical perturbation. They also observed different types of fiber cross-links in gel and the process of fibers zippering.

In this work, a coarse-grain model of a single HbS fiber is introduced. The model is able to generate the material properties of single fibers, namely the bending and torsional rigidities, as they have been measured experimentally [1, 2]. At last, the interactions of two HbS fibers are investigated and one case of fiber zippering is studied.

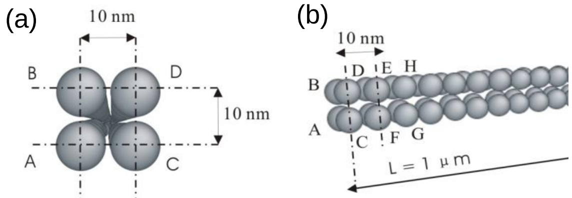


FIGURE 1. (a) TOP VIEW AND (B) SIDE VIEW OF THE HbS FIBER MODEL.

MODEL AND METHOD

The single HbS fiber studied in this work is modeled as four tightly bonded chains, each of which is composed of 100 soft particles. The cross-section of the HbS fiber model is shown in Fig.1 (a). The diameter of each particle is $10\ nm$ and the distance between the centers of neighboring particles is also $10\ nm$. The total length of the simulated HbS fiber is $1\ \mu m$ and the radius of the fiber is approximately $10\ nm$ (see Fig. 1(b)). The displacements of all particles are governed by the Langevin equation $m_i \frac{d^2\boldsymbol{r}_i}{dt^2} = \mathbf{F}_i - f\frac{d\boldsymbol{r}_i}{dt} + \mathbf{F}_i^B$, where $\boldsymbol{F}_i = -\partial U/\partial \boldsymbol{r}_i$ is the deterministic force produced by the implemented total potential U. $\boldsymbol{F}_i^B$ is Gaussian white noise that obeys the fluctuation-dissipation theorem [4, 5] .

Five different potentials are applied in the model. First, a harmonic spring potential is introduced between adjacent particles that belong to the same chain and between particles that belong to different chains that are initially in the same cross-section. The spring potential is described by $U_s = \frac{1}{2}K_s(r_{ij} - r_0)^2$, where K_s is the spring constant and r_0 is the equilibrium distance between particles. Second, a truncated Lennard-Jones potential is applied between two particles in the same fiber and it is given by $U_{TLJ}(r_{ij}) = 4\left[(1/r_{ij})^{12} - (1/r_{ij})^6\right] + 1$ for $r_{ij} < r_{cut}^{tr} = 2^{1/6}$.
When $r_{ij} \geq r_{cut}^{tr}$, $U_{TLJ}(r_{ij}) = 0$. A bending potential is employed to describe the bending rigidity of the HbS fiber and is defined as $U_b = \frac{1}{2}K_b(\theta - \theta_0)^2$, where K_b is the parameter that directly regulates the bending stiffness of the HbS fiber and θ is the angle formed by three consecutive particles in the same chain, as illustrated in Fig. 2(a). θ_0 is the equilibrium angle and it is chosen to be $180°$. The torsional rigidity of the proposed model is introduced via a torsional potential between particles belonging to consecutive cross-sectional planes defined by four particles. The potential is expressed as $U_t = \frac{1}{2}K_t(\Phi - \Phi_0)^2$, where K_t is the parameter that regulates the torsional stiffness of the HbS fiber and Φ is the angle between two directional vectors defined in two consecutive cross-sectional planes, as it is illustrated in Fig. 2 (b), Φ_0 is the equilibrium angle and it is initially equal to $0°$. At last, the Lennard-Jones potential is

employed between particles that belong to different fibers to produce attractive interfiber forces when two fibers are close.

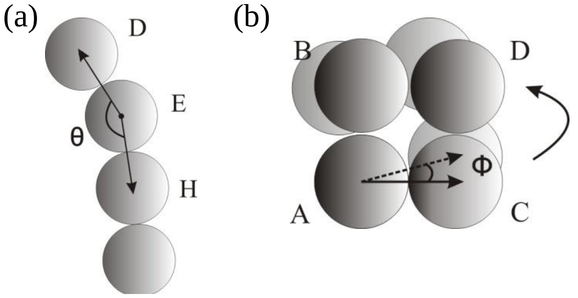


FIGURE 2. (A) BENDING AND (B) TWIST OF THE HbS FIBER MODEL

RESULTS AND DISCUSSION

Measurements of material properties of HbS fiber

We showed that the proposed model was able to simulate a single HbS fiber with the appropriate mechanical properties. In particular, by tuning the parameters K_b and K_t, the model reproduced the experimental values for the bending rigidity κ, and the torsional rigidity c, of a single HbS fiber [2].

It has been proven that the bending rigidity of the HbS fiber can be calculated via $\kappa = k_B T l_p = \frac{k_B T L^3}{48\langle (u_x(L/2))^2\rangle}$ where l_p is the persistence length of the HbS fiber, L is the length of the fiber, and $< u_x(L/2)^2 >$ is the average of the fiber square midpoint displacement from the central axis [1]. The numerical results showed that a single HbS fiber subjected to only thermal forces behaved as a stiff rod. The measured bending rigidity of a single HbS fiber with respect to time is plotted in Fig. 3(a). The bending rigidity at the equilibrium was approximately $\kappa = 5 \times 10^{-25}\ Nm^2$ which is very close to the experimental value and it moved as an almost rigid body because of the large persistence length.

As for the torsional rigidity, it has been shown in [1] that $c = \frac{k_B T \lambda}{\langle \Delta\theta^2 \rangle}\ [1 - \frac{L}{\lambda}(1 - e^{-\frac{\lambda}{L}}),$ where $\Delta\lambda = \lambda\Delta\theta/\pi,\ \lambda = 135\ nm$ and it is half of the average pitch length for the HbS fiber, $\Delta\theta$ is the twisted angle in half pitch length and L is the length of the HbS fiber. Fig.3 (b) shows that the measured torsional rigidity of the HbS fiber model is very close to the experimentally measured value of $c = 6 \times 10^{-27} J\ m$ [2].

Modeling of two HbS fibers zippering

Individual HbS fibers interact with each other through different mechanisms and form various X-shaped junctions, Y-shaped branches, and side-to-side coalescence ("zippering") cross-links [3, 6]. We applied the developed model to study the formation of bundles by zippering fibers. In this part, two fibers in a Y-shaped cross-link zippering from their contacting tips (see Fig. 4) were simulated. The weak interfiber force was represented by a L-J potential that was applied between particles that belonged to different fibers.

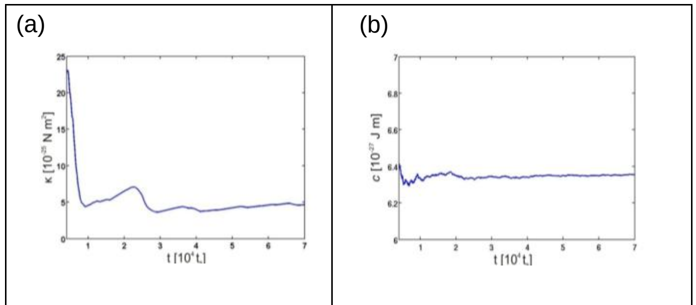
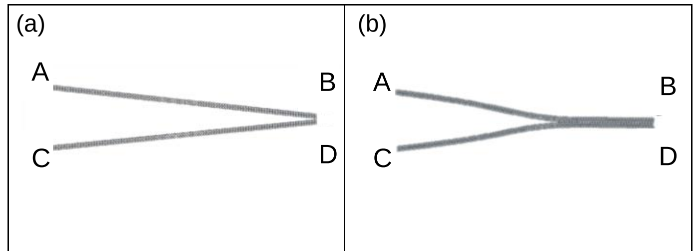


FIGURE 3. (A) BENDING RIGIDITY AND (B) TORSIONAL RIGIDITY OF THE HbS FIBER MODEL AS FUNCTION OF TIME.



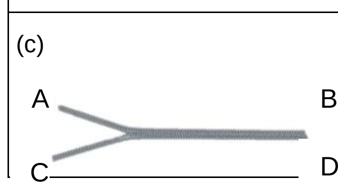


FIGURE 4. (A) INITIAL (B) INTERMEDIATE AND (C) EQULIBRIUM STATE OF TWO HbS FIBERS DURING ZIPPERING.

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