Probing the Twisted Structure of Sickle Hemoglobin Fibers via Particle Simulations

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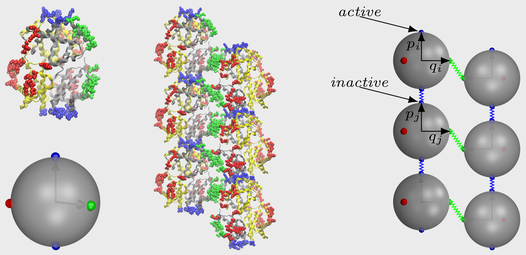
Introduction

Sickle cell disease (SCD) is an inherited anemia that arises from a single point mutation, from glutamate to valine, in the hemoglobin molecule. The primary pathophysiological event in SCD is that sickle hemoglobin (HbS) polymerizes into long fibers under deoxygenated conditions. The fibers distort the morphologies of red blood cells (RBCs) and dramatically alter their mechanical and rheological properties.

HbS molecule model

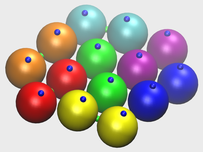
Hemoglobin (Hb) contains two a- and two b-globin subunits.
Three types of contacts:

- intra-double-strand axial contacts (blue);
- intra-double-strand lateral contacts (green);
- inter-double-strand contacts (red).



HbS fiber nucleus

In this study we focus on the growth dynamics of HbS molecules and the polymerized structure of HbS polymer fiber, so we assume that a sickle hemoglobin fiber nucleus already exists.

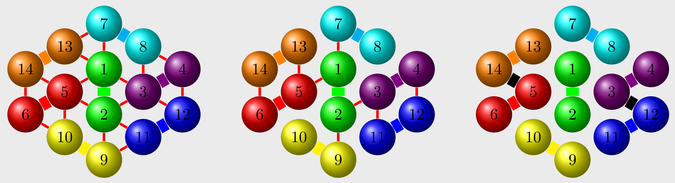


Interactions

- How do two HbS molecules combine to form a molecular contact?
  - Two HbS molecules interact through their patches, which are divided into two types (active and inactive) depending on whether the HbS molecule is attached to a site or not.
  - If an active site and an inactive site come into a close contact, i.e., less than a constant δ, an axial bond is built between the two HbS molecules.

Interactions

- Why is the HbS polymer fiber helically twisted?
  - Angle-bending potentials between axial vectors $\mathbf{p}_i$ and $\mathbf{p}_j$, and lateral vectors $\mathbf{q}_i$ and $\mathbf{q}_j$ of two neighboring HbS molecules in the same strand.
- The inter-double-strand contact holds the seven double strands together and stabilizes the HbS polymer fiber. There are three hypotheses for the possible inter-double-strand contact:



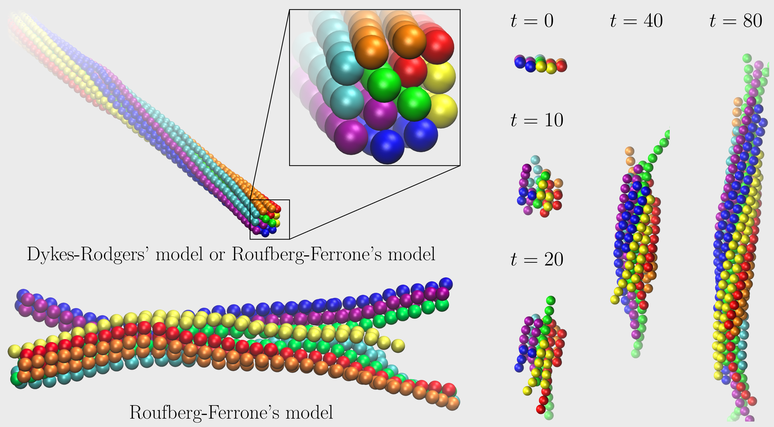
Dykes-Rodgers' model | Carragher's model | Roufberg-Ferrone's model

Simulation method

$$m_i \frac{d\boldsymbol{v}_i}{dt} = -m_i \zeta_i^T \boldsymbol{v}_i + \boldsymbol{F}_i + \boldsymbol{\xi}_i^T$$
$$I_i \frac{d\boldsymbol{\omega}_i}{dt} = -I_i \zeta_i^R \boldsymbol{\omega}_i + \boldsymbol{T}_i + \boldsymbol{\xi}_i^R$$

where $\boldsymbol{v}_i$ and $\boldsymbol{\omega}_i$ are center-of-mass linear velocity and angular velocity of particle i. $\boldsymbol{F}_i$ and $\boldsymbol{T}_i$ are force and torque exerted on particle i, and $\boldsymbol{\xi}_i^T$ and $\boldsymbol{\xi}_i^R$ are random force and torque, respectively. ζ_i^T and ζ_i^R are friction coefficients.

Formation dynamics of HbS polymer fiber

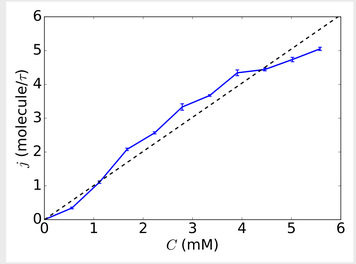


Dykes-Rodgers' model or Roufberg-Ferrone's model

Roufberg-Ferrone's model

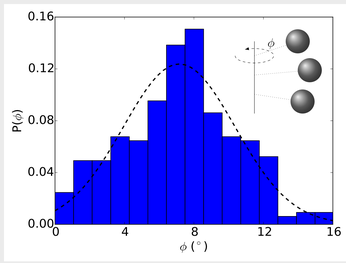
Influence of HbS monomer concentration on the growth rate of HbS fiber

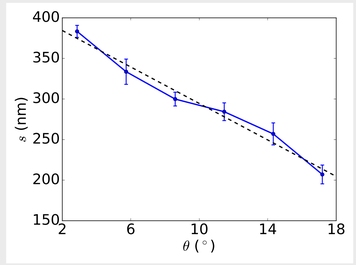
The growth rate j is expected to be a linear function of HbS activity a, which, in turn, is the product of the activity coefficient γ, and HbS concentration C, $a = \gamma C$. The coefficient γ is determined by the volume fraction of all Hb species in the growth medium.



Structural and mechanical properties of HbS polymer fibe

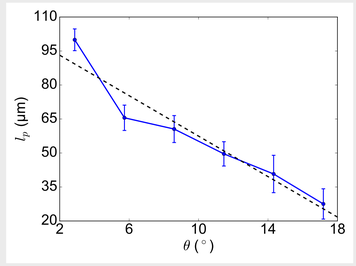
The mean value of ϕ is ∼7.4° with a standard derivation (SD) about 3.5°
Pitch length $s = \frac{2\pi}{\sum \phi} l \approx 270$nm





The bending rigidity and persistence length of the HbS fibe

$$\kappa = \frac{k_B T L^3}{3\langle \delta u(L)^2 \rangle}$$
$$l_p = \frac{\kappa}{k_B T}$$



References

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