Development of Sickled RBC Phase Field Model

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Abstract

Sickle cell anemia is a genetic illness caused by an HBB gene mutation that produces an abnormal version of beta-globin known as hemoglobin S (HbS). It affects millions of people worldwide, and some of the symptoms are fatigue, acute and chronic pain, bone pain, dactylitis (swelling and inflammation of the hands and/or feet), and pulmonary hypertension. The average life expectancy of sickle cell anemia patients is 40-50 years. The only potential cure is bone marrow or stem cell transplant, which have high risks and can cause severe side effects.

Many studies and much modeling of the dynamics of HbS polymer fibers have been done to better understand sickled red blood cells (RBC) [1,2,3]. However, integrating the dynamics and the interactions of the fibers and RBC membrane remains challenging as they occur at multispatial scales, ranging from nanometers to micrometers, and models introduced so far are computationally expensive and require substantial CPU hours. In this poster, we discuss the capability of phase-field method in modeling vesicle dynamics and introduce a potential HbS fiber - RBC membrane interaction model.

Phase-Field Method

Based on the elastic energy of closed lipid bilayer proposed by Helrich[4], the elastic energy of a vesicle is

$$E = \int_\Gamma \frac{k}{2}(H - c_0)^2 \, ds \qquad (1.1)$$

k: bending rigidity
H: mean curvature
c_0: Spontaneous curvature

In order to avoid interface tracking in numerical simulations, we describe the energy using a phase-field function $\phi = \phi(\mathbf{x})$ defined on a computational domain Ω, where the level sets $\{\mathbf{x} : \phi(\mathbf{x}) = 0\}$ represents the membrane Γ, $\{\mathbf{x} : \phi(\mathbf{x}) > 0\}$ represents the interior of Γ, and $\{\mathbf{x} : \phi(\mathbf{x}) < 0\}$ represents the exterior. Using $\phi(\mathbf{x}) = \tanh\left(\frac{d(\mathbf{x},\Gamma)}{\sqrt{2}\epsilon}\right)$, equation (1.1) becomes

$$E_M(\phi) = \frac{3k}{8\sqrt{2}\epsilon}\int_\Omega \left[\epsilon\Delta\phi + (\frac{1}{\epsilon}\phi + c_0\sqrt{2})(1-\phi^2)\right]^2 dx \qquad (1.2)$$

As $\epsilon \to 0$,

$$E_M(\phi) \to \int_\Gamma \frac{k}{2}(H - c_0)^2 \, ds$$

Phase-Field Simulations

Various equilibrium conformations of vesicles can be obtained by minimizing (1.2) with different surface areas and volume[5]. Furthermore, vesicle-vesicle adhesion[6] and dynamics of multi-component lipid membrane[7] can be simulated using multiphase-field methods.
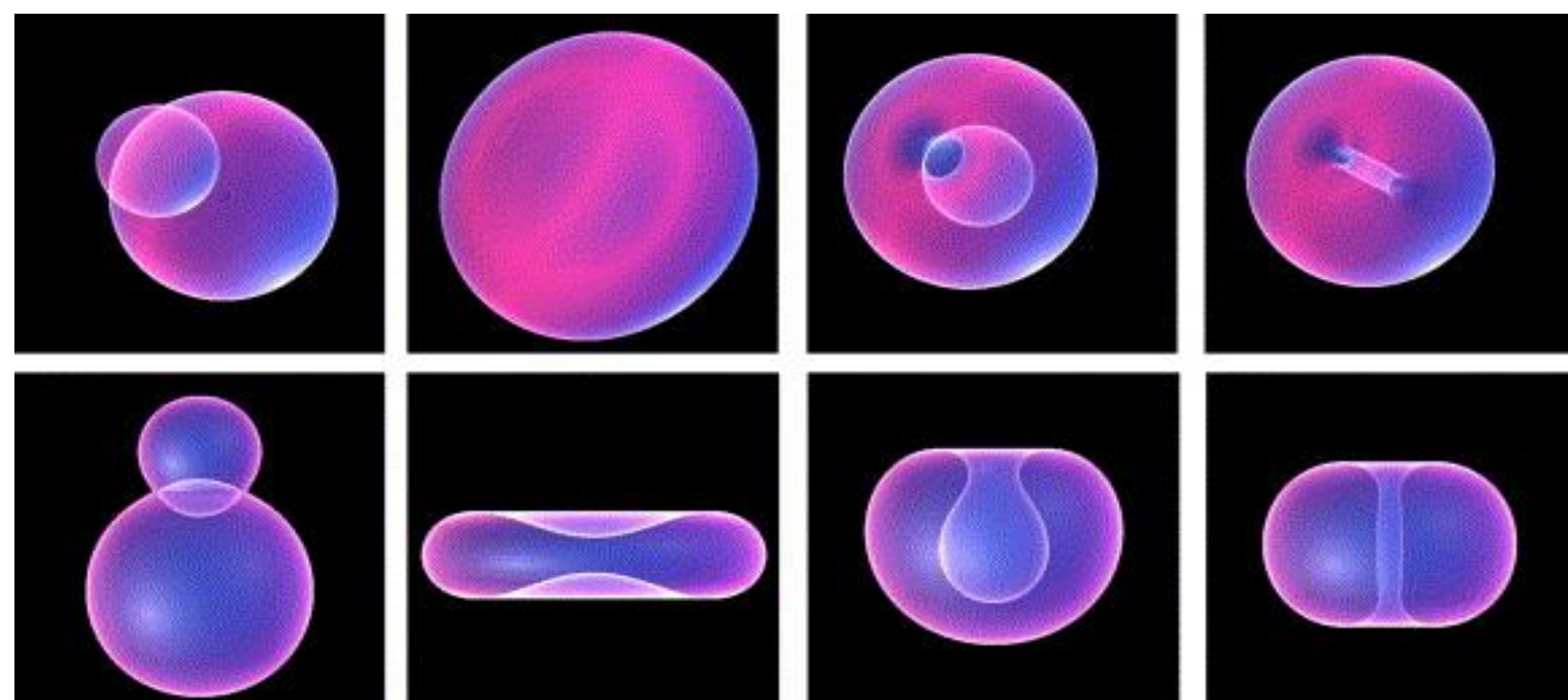

Figure 1. 3D views of equilibrium conformations obtained by minimizing (1.3) with different surface areas and volumes. From left to right: twin-bubble, dimpled-disc, round-pot torus.

HbS Polymer Model

We model the HbS fiber as a chain of N+1 particles, where the N-1 internal particles function as hinges that allow the chain to bend. By setting the chain segment lengths and the bending angles equal, we only need to store the first three particles' coordinates and can define the energy of HbS fiber as

$$E_C(\mathbf{P}_0, \mathbf{P}_1, \mathbf{P}_2) = K_b(N-1)(cos\theta + 1)^2 \qquad (2.1)$$

K_b: bending stiffness
$$cos\theta : \frac{(\mathbf{P}_1 - \mathbf{P}_0)\cdot(\mathbf{P}_2 - \mathbf{P}_1)}{l^2}$$
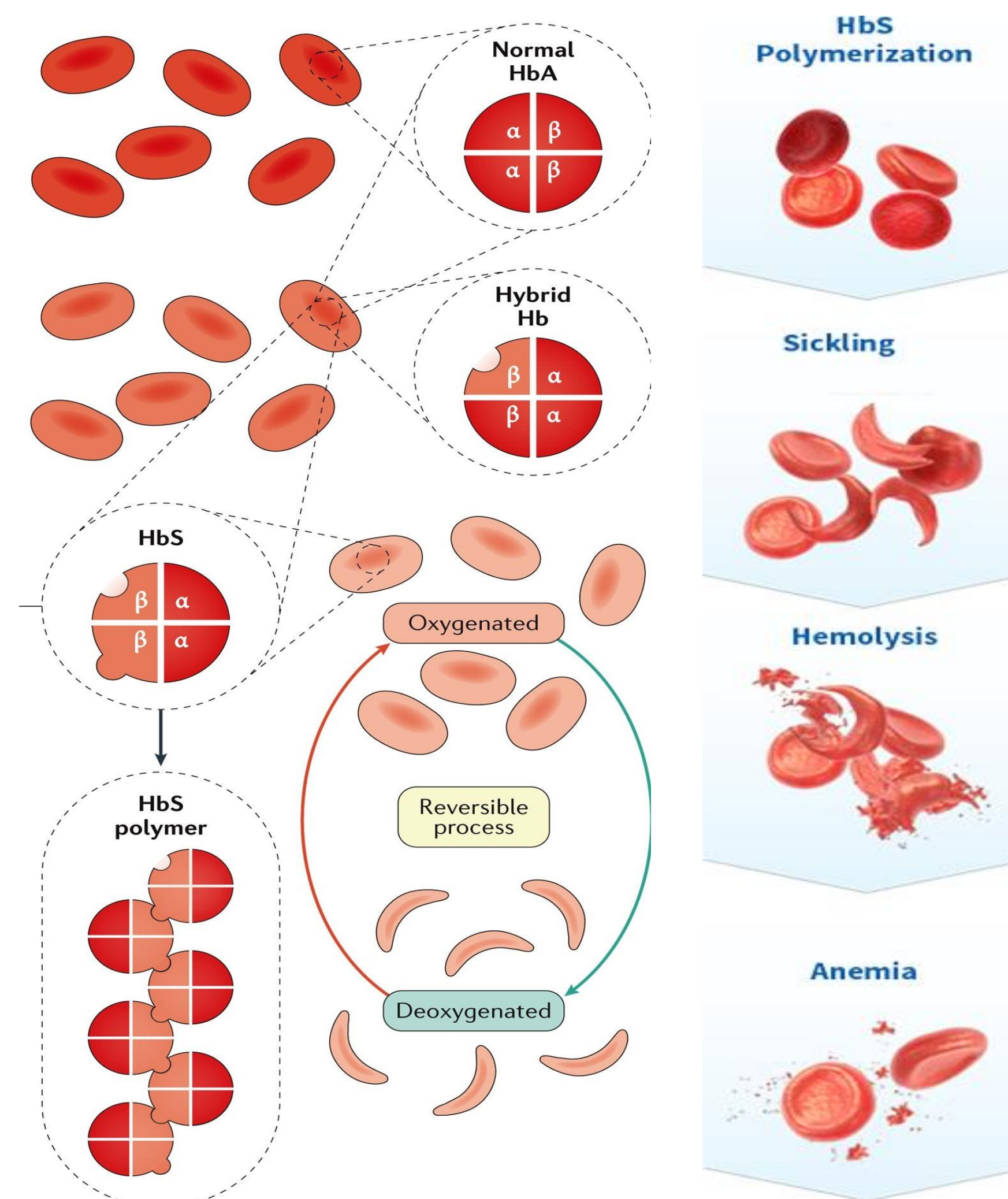

Figure 2. Simple illustrations of sickle cell cycle. A mutation in the HBB gene substitutes valine for glutamic acid as the sixth amino acid of beta globin chain, resulting in HbS molecules that polymerize and form stiff fibers in deoxygenated state. The sickled red blood cells have increased rigidity, which causes hemolysis and promotes vascular damage and vaso-occlusion. The reduction in blood flow then promotes hypoxic conditions that help induce HbS polymerization.

HbS – RBC Membrane Model

The interaction between HbS fiber and Γ should be distance-dependent, and since the distance information is contained in $\phi_{\mathbf{P}_i} = \tanh\left(\frac{d(\mathbf{P}_i, \Gamma)}{\sqrt{2}\epsilon}\right)$, we define the interaction energy between each HbS chain particle and Γ as

$$T(\phi_{\mathbf{P}_i}) = \frac{1}{\phi_{\mathbf{P}_i}} - 1 \qquad (2.2)$$

which increases asymptotically as $\mathbf{P}_i$ nears Γ but diminishes to zero as the distance increases.

Total Energy

The total energy of HbS fiber – RBC membrane model we want to minimize is

$$E_{total} = E_M(\phi) + E_C(\mathbf{P}_0, \mathbf{P}_1, \mathbf{P}_2) + \sum_{i=0}^{N} T(\phi_{\mathbf{P}_i}) \qquad (3.1)$$

with the constraints

$$A(\phi) = \alpha$$
$$V(\phi) = \beta$$
$$d(\mathbf{P}_0, \mathbf{P}_1)^2 = d(\mathbf{P}_1, \mathbf{P}_2)^2 = l^2$$

To enforce the constraints, we apply penalty method:

$$W = E_{total} + M_1(A(\phi) - \alpha)^2 + M_2(V(\phi) - \beta)^2 + M_3\sum_{i=0}^{1}[d(\mathbf{P}_i, \mathbf{P}_{i+1})^2 - l^2]^2 \quad (3.2)$$

where M_1, M_2, and M_3 are large penalty constants

Future Works

➢ Run various simulations
  ➢ Validate the model by comparing the computational results to experimental results
  ➢ Optimize our parameters

➢ Expand the model to include sickle cell -sickle cell and sickle cell – blood vessel interactions

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