Patient-specific modeling and predicting blood viscosity in sickle cell anemia

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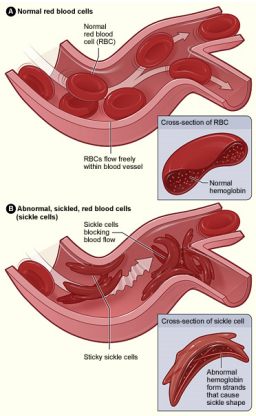
Motivation

Sickle cell anemia (SCA): a highly complex, inherited blood disorder exhibiting hetero-geneous cell morphology and abnormal rheology.



Normal RBCs and sickle cells

http://www.nhlbi.nih.gov/health/health-topics/topics/sca/

Sequence of events in sickle patients proceeds from sickle hemoglobin polymerization, to cell deformation, to vaso-occlusion and then to sickle cell disease.

Vekilov, *Br. J. Haematol.*, 2007, ***139***, 173.

SCA is often characterized as a rheological disease.

Kaul & Xue, *Blood*, 1987, ***77***, 1353.

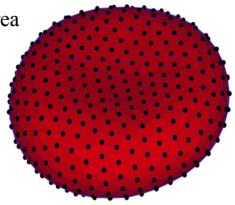
Individual patients with SCA have highly variable clinical phenotypes, and the clinical severity of symptoms can range from mild to very severe.

Ware, *Blood*, 2010, ***115***, 5300.

By using a multiscale red blood cell (MS-RBC) model based on parameters derived from patient-specific data, we present a mesoscopic simulation study to explore the rheological and hemodynamic characteristics of blood SCA.

Multiscale RBC Model

The MS-RBC model is constructed by a network of viscoelastic springs combined with bending energy and constraints for surface-area and volume conservation.



Triangular mesh:

- each vertex – a coarse-grained particle
- each edge – a viscoelastic bond

$$U_{POW-WLC}(x) = \frac{k_p}{(n-1)x^{n-1}} + \frac{k_B T L_m}{4p} \times \frac{3(x/L_m)^2 - 2(x/L_m)^3}{1 - x/L_m} + U_{visc}$$

- bending resistance of lipid bilayer

$$U_{BEND}(\theta_{\alpha\beta}) = k_b\left[1 - \cos(\theta_{\alpha\beta} - \theta_0)\right]$$

- shear resistance of cytoskeleton
- constant surface area

$$U_{AREA}(A) = \frac{k_A(A - A_0^{tot})^2}{2A_0^{tot}} + \sum_{j \in 1 \ldots N_f} \frac{k_d(A_j - A_0)^2}{2A_0}$$

- constant volume

$$U_{VOLUME}(V) = \frac{k_V(V - V_0^{tot})^2}{2V_0^{tot}}$$

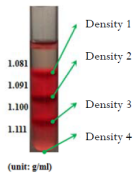
Fedosov, Caswell & Karniadakis, *Biophys. J.*, 2010, ***98***, 2215.

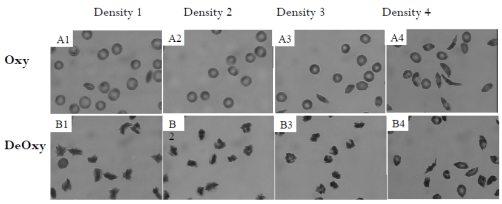
Clinical / Experimental Data

Selected hematologic parameters obtained from clinical / experimental data of sickle patients are summarized here:

	Normal blood	Sickle patients		Sickle patients with hydroxyurea	
		mild	severe	mild	severe
Hct (%)	40.0 ~ 45.0	22.9	18.6	21.9	29.2
MCV (fL)	92.4	83.0	83.3	99.1	99.0

Cell density	1	2	3	4
MCHC (g/dL)	27.3	30.9	34.9	50.0



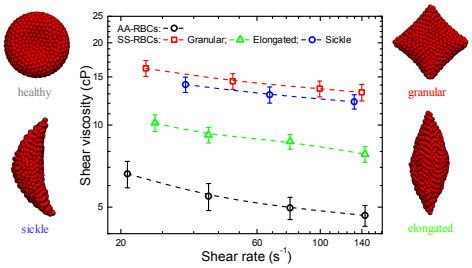


General characteristics and morphologic analysis of sickle RBCs in sickle patients:

Condition		Symptom	Sickling (%)	Cell density group	Percentage of sickled cells in all cells		
					G	E	S
Short-term hypoxia (40 seconds)	Sickle patients	mild	20.2	1	-	-	-
				2	4.4	-	-
				3	5.8	1.8	-
				4	2.5	5.1	0.6
		severe	39.0	1	-	-	-
				2	-	-	-
				3	12.5	-	0.3
				4	13.1	5.9	7.2
	Sickle patients treated with hydroxyuea	mild	9.4				
				2	3.1	-	-
				3	4.4	-	-
				4	1.4	0.5	-
		severe	3.1	1	-	-	-
				2	-	-	-
				3	2.5	-	-
				4	-	0.6	-
Long-term hypoxia (4 minutes)	Sickle patients	mild	59.5	1	-	-	-
				2	21.5	-	5.0
				3	18.1	-	5.9
				4	3.4	4.3	1.3
		severe	80.4	1	-	0.7	0.9
				2	17.4	-	15.4
				3	18.5	0.3	-
				4	10.9	6.9	9.4
	Sickle patients treated with hydroxyuea	mild	34.4	1	1.3	-	2.0
				2	4.6	-	2.8
				3	16.6	-	3.9
				4	2.0	1.2	-
		severe	57.6	1	-	-	-
				2	7.5	-	7.5
				3	31.3	-	4.4
				4	5.0	1.9	-

Blood Viscosity in SCA

We first examine the shear viscosity of sickle blood flow at Hct = 40% with three distinct types (granular, elongated and classic sickle types) of sickle RBCs:

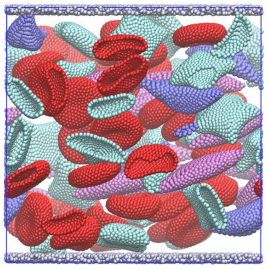


Sickle RBC suspensions exhibit different viscosity values for different cell morphologies.

We then carry out numerical simulations to probe the shear viscosity of patients in SCA based on the clinical/experimental data with four different cases at three different conditions (oxygenation state, short-term hypoxia and long-term hypoxia).

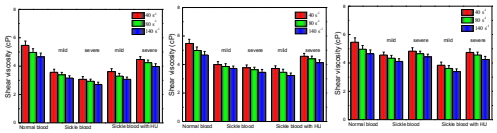
Simulation setup:

- Cell mixtures:
  - Normal RBCs
  - Sickle RBCs
  - Sickle RBCs with HU treatment
- Different cell shape:
  - Biconcave (red)
  - Granular (cyan)
  - Elongated (purple)
  - Typical sickle (blue)



Sickle blood in shear flow

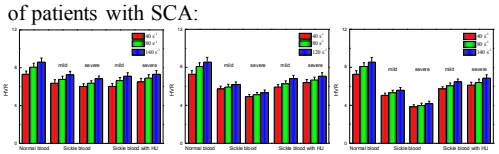
Calculated shear viscosity values of patients with SCA:



Oxygenation condition | Short-term hypoxia | Long-term hypoxia

- Blood viscosity increase with the deoxygenation time.
- Compared to the shear viscosity of other groups, the severe SCA has lowest viscosity at oxygenation condition, but largest viscosity values after long-term deoxygenation.

Calculated hematocrit-to-viscosity ratio (HVR) values of patients with SCA:



Oxygenation condition | Short-term hypoxia | Long-term hypoxia

- HVR level increases as shear rate increases.
- HVR level decreases with deoxygenation time development.
- Severe SCA has lowest HVR levels.

Summary

■ Our results show that treatment with hydroxyuea (HU) may alter rheological behaviors of sickle blood depending on the degree of hypoxia;

■ SCA patients treated with HU always have higher levels of hematocrit–to–viscosity ratio (HVR) than those for untreated patients, indicating that HU can indeed improve oxygen transport potential of blood and therefore improve blood flow;

■ The determination of HVR level rather than shear viscosity of sickle RBC suspensions is suggested to be a more reliable indicator in monitoring the response to HU treatment.

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