

Patient-specific modeling and analysis of individual sickle cell behavior in transient hypoxia

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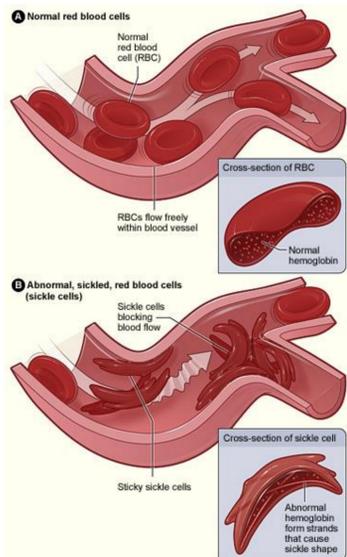
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Motivation

Sickle cell anemia (SCA): an inherited blood disorder exhibiting hetero-geneous cell morphology and abnormal rheology under hypoxic conditions.



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.

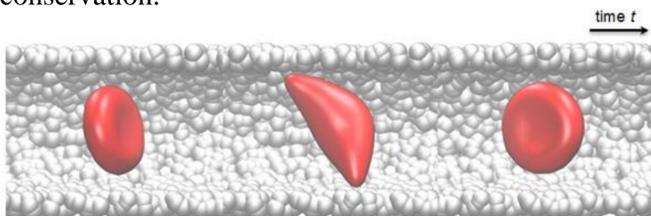
Ware, *Blood*, 2010, 115, 5300.

Normal RBCs and sickle cells
<http://www.nhlbi.nih.gov/health/health-topics/topics/sca/>

By using a kinetic cell sickling model based on parameters derived from *patient-specific* data, we present a computational study to investigate the dynamic and rheological behavior of individual sickle RBCs in microfluidic channel with obstacles.

Kinetic Cell Sickling Model

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



Triangular mesh:

➤ each vertex – a coarse-grained particle

➤ bending resistance of lipid bilayer

$$U_b = \sum_{j \in 1 \dots N_s} k_b [1 - \cos(\theta_j - \theta_0)]$$

➤ shear resistance of cytoskeleton

$$U_s = \sum_{j \in 1 \dots N_s} \left[\frac{k_B T l_m (3x[pO_2(t-t_D)]^2 - 2x[pO_2(t-t_D)]^3)}{4p(1-x[pO_2(t-t_D)])} + \frac{k_p}{(n-1)l_j^{n-1}} \right]$$

$$x[pO_2(t-t_D)] = x_0 \left\{ 1 - \left[\left(\frac{x_{ref}}{x_0} \right)_{max} - 1 \right] \left[\frac{pO_{2-ref} - pO_2(t-t_D)}{pO_{2-ref}} \right] \right\}$$

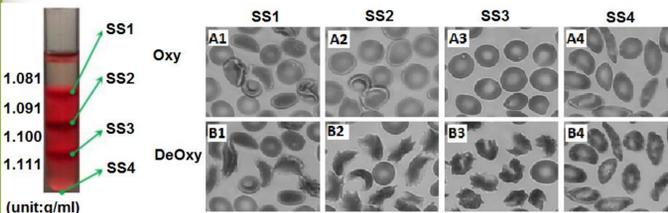
➤ constant surface area & volume

$$U_{a+v} = \sum_{j \in 1 \dots N_i} \frac{k_l (A_j - A_0)^2}{2A_0} + \frac{k_v (V^{tot} - V_0^{tot})^2}{2V_0^{tot}}$$

This kinetic cell model is able to simulate the dynamics processes of repeated sickling and unsickling of RBCs under transient hypoxic conditions.

Clinical/Experimental Data

Blood samples from patients with SCA have been collected for *in vitro* test. Each blood sample was fractionated into four density subpopulations using an Optiprep-based gradient medium.

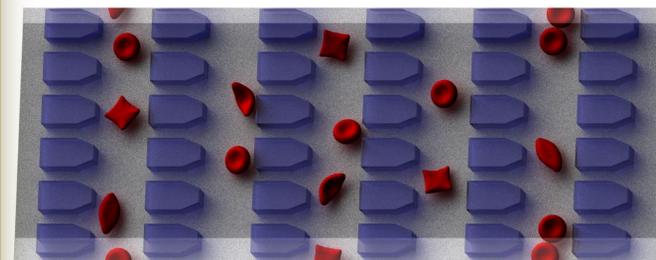


Typical shapes of sickle RBCs under Oxy/DeOxy states. These four samples included two with hydroxyurea treatment (On-HU) and two without HU treatment (Off-HU). Selected hematologic parameters are summarized here:

	Off-HU		On-HU	
	S-P-I	S-P-II	S-P-III	S-P-IV
Hct (%)	22.9	18.6	21.9	29.2
MCV (fL)	83.0	83.3	99.1	99.0
MCHC, g/dL	36.7	36.6	35.6	34.2
HbS, %	84.2	90.1	72.4	86.0
HbF, %	11.9	6.0	24.1	10.0
HbA, %	0.0	0.0	0.0	0.0
HbA ₂ , %	3.9	3.9	3.5	4.0

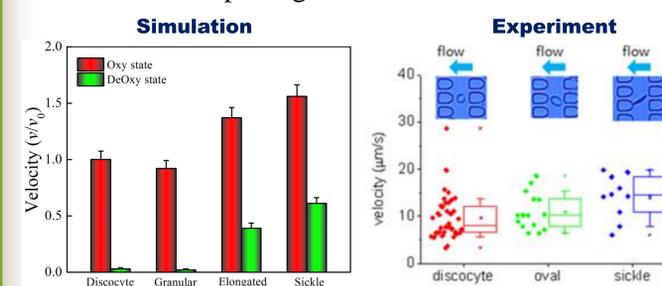
Sickle RBCs and Microfluidics

We modeled the dynamics and rheology of individual sickle RBCs flowing in microfluidic channel with small microgates without adhesion but considering different sickle RBC morphologies.



Sickle RBCs in microchannel with multiple microgates

Sickle RBCs exhibit different transit velocity for different cell morphologies:

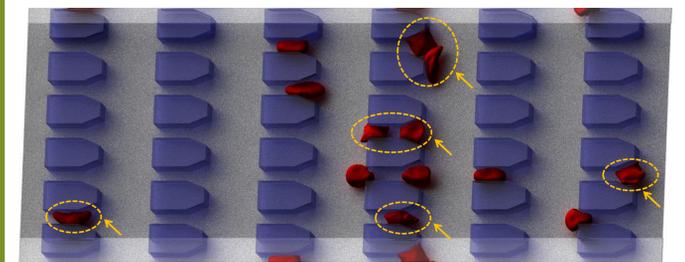
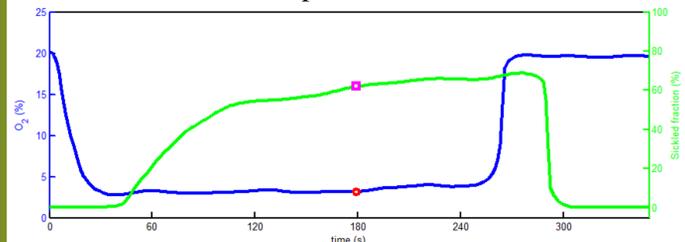


Dependence of cell transit velocity on sickle cell shapes

❖ Sickle RBCs with granular/disc shapes have lower transit velocity at Oxy state.

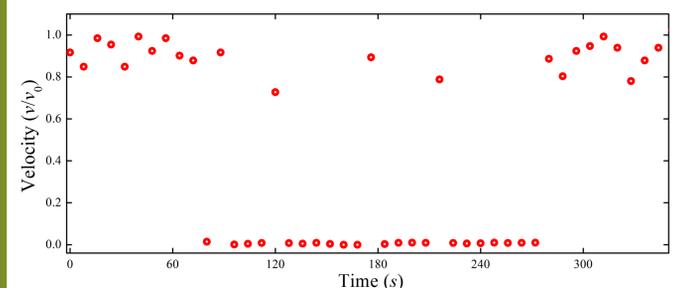
❖ Sickle RBCs show further increased flow resistance at Deoxy state; some sickle RBCs even get stuck in micropores.

We then carried out numerical simulations to probe the dynamic behavior of individual sickle RBCs based on the clinical/experimental data.

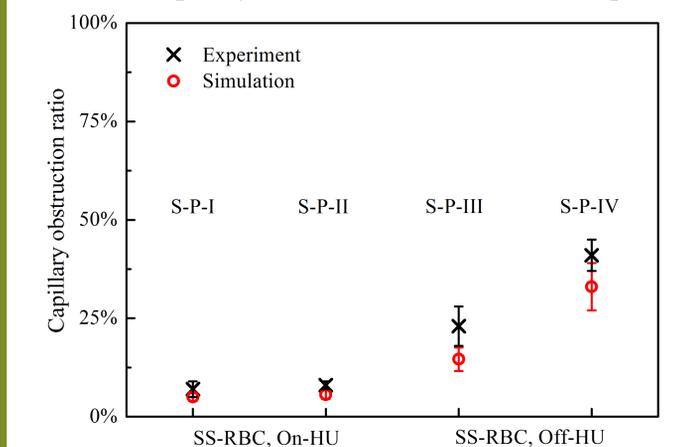


Sickle RBCs (indicated by arrows) get stuck in microgates

Calculated transit velocity of sickle RBCs:



Calculated capillary obstruction ratio of blood samples:



❖ Sickle RBCs treated with HU had less capillary obstructions, indicating that HU can enhance the dynamic performance of sickle RBCs in microcirculation.

Summary

■ We have systematically studied the dynamic behavior of sickle RBCs by using a kinetic cell sickling model under physiological conditions.

■ We investigated how sickle RBCs behave differently from healthy ones, and analyzed the alteration of cellular behavior and response to single-cell capillary obstruction under hypoxic conditions.

■ We simulated the flow dynamics of sickle RBCs with HU treatment, and quantified the relative enhancement of hemodynamic performance of HU.

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