



Hemoglobin diffusion and polymerization in HbF_xHbS_{1-x} compounds

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Sickle cell disease (SCD) is a genetic blood disorder, inducing severe anemia. It results from the polymerization of the oxygen-carrying protein hemoglobin found in red blood cells (RBC), which leads to a deformation of the cells to rigid, sickle-like shape under certain circumstances that will obstruct capillaries vessels, and will ultimately induce the disease of different organs. The hemoglobin (HbS), that is at the origin of this blood disorder, is a variant of normal human hemoglobin A0 (HbA0) whose sequence only differs by two amino acids over the 574 of the protein. Human that are homozygote of HbS gene (inherited from both parents) suffer from a severe anemia. SCD was the first identified molecular disease by Linus Pauling, in 1949 [1]. The pharmacological treatments for sickle cell disease include hydroxyurea, a molecule that promotes the synthesis of fetal hemoglobin (HbF) that leads to a hemoglobin mixture HbF_xHbS_(1-x) in blood with HbF partially or fully inhibiting HbS polymerization depending on its concentration. We have shown previously that diffusion inside the red blood cells is similar to that in solution at the same concentration [2]. From the concentration dependence of the diffusion coefficient and using a simple model developed for oxygen uptake in the lungs [3] we have stressed that not only the diffusion of hemoglobin is necessary to obtain the full oxygenation of the RBC during the limited time of transit in the capillary close to the alveolar sac [4] but the concentration of hemoglobin inside RBC corresponds to an optimum oxygen transport for an individual under physical activity. We investigated the structure and the dynamics of HbS and HbF mixtures to better understand 1- how HbF will inhibit HbS polymerization, under which concentration and partial oxygen pressure. The impact of oxygen partial pressure is fundamental, because in the body it differs from the alveoli (PO₂=160 mm.Hg) down to the heart (PO₂=10-20 mm.Hg). And 2- gain insight on the oxygen exchange process at the RBC level. We will present how the intermediate scattering function is strongly affected by the oxygen partial pressure and the fraction of HbF present in solution (x). Moreover, we will show how the free (non polymerized) Hb diffusion is affected by polymerization and discuss the physiological implications.

[1] L. Pauling et al. Science 110, 543–548 (1949).

[2] W. Doster and S. Longeville, Biophys. J. 93 (4) , 1360-1368 (2007)

[3] A. Clark et al., Biophys. J., 47, 171 (1985).

[4] S. Longeville et al., Scientific Report, 7, 10448 (2017)

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