UIC COLLOQUIUM
Department of Physics

Wednesday, October 2, 2019

"Using Physics and Physical Chemistry to Screen for a Drug to Treat Sickle Cell Disease"

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A single nucleotide change from A to T in the DNA coding for the beta chain of hemoglobin is responsible for sickle cell disease, the first disease for which a molecular cause has been identified. The change from a glutamate to a valine on the molecular surface creates a sticky patch that causes the protein to polymerize into 14-stranded helical fibers upon deoxygenation in the tissues. The fibers distort ("sickle") and stiffen the red cells, causing obstruction in the smallest vessels, organ damage and sporadic episodes of pain so severe that they are called a "sickle cell crisis." The kinetics of fiber formation are quite extraordinary, with the duration of a delay prior to the appearance of fibers that is inversely proportional to up to the 40^{th} power of the initial protein concentration, a nucleation rate proportional to up to the 80^{th} power, a universal relation between the delay time and the supersaturation expressed as activities instead of concentrations because of the large excluded volume effects, and stochastic fluctuations in the delay time in small volumes due to nucleation of a single fiber. All of these observations are quantitatively explained by a double nucleation mechanism in which secondary nucleation occurs on the surface of pre-existing fibers. The mechanism also explains the aggregation kinetics of the Alzheimer's peptide.

We have taken advantage of the enormous sensitivity of the delay time to develop a patho-physiologically relevant assay for high throughput screening of large compound libraries to find a potential drug to treat sickle cell disease by increasing sickling times. Longer sickling times allow more cells to escape the smallest vessels of the tissues before fiber formation has started. In our assay, fiber formation is induced by slow deoxygenation with nitrogen of sickle trait red cells in a 384 well plate in the chamber of an automated microscope system. Images are collected every 15 minutes and analyzed by robust automated image analysis that produces a record of the fraction sickled vs time for each well. A summary of our results so far will be presented.

The Department of Physics Colloquium will be held at 3pm in 238 SES.

**Refreshments will be served from 2:45 pm to 3pm outside of room 238 SES*