Title: 'Ugly' nanoparticle/aggregate characterization: What you don't know can't help you
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Number of Graduate Students/Post Docs: 3 GS
Time span: Two years
Budget: $300,000

Abstract Paragraph:
Many complexes and molecular assemblies have irregular shapes, density profiles across the particle, and multiple components. While classic small molecule and polymeric amphiphiles make well know geometries (e.g. spherical, cylindrical particles, membranes), many new assemblies form unknown geometries when assembled and/or kinetically trapped. With a combination of real space/local cryoTEM characterization, reciprocal space/global SANS characterization, and computational modeling/simulation through computational reverse-engineering analysis for scattering experiments (CREASE), we are able to characterize the size, shape, and dispersity of novel particles made from the assembly, complexation, or processing of molecular mixtures to provide direct knowledge of particle structures on the nanoscale.

Summary of Project: Many small molecule drug compounds, protein therapeutics, flavors and scents in the food industry, pigments, and other important industrial products must be processed into particles for proper delivery (i.e., for small molecule drugs or protein therapeutics), proper storage, or desired dispersion in solution or mixtures. While small molecule surfactants or polymeric amphilphiles work well to co-assemble with many molecule products, particularly if they are hydrophobic, for encapsulation and delivery, many new assembled systems are being developed that are not based primarily on a hydrophobic, small molecule payload. Some examples of new delivery or dispersion needs are the need to keep a protein properly folded and properly separated from neighboring proteins, having a charged polymer be collapsed into a particle with oppositely charged molecules, or having unique molecular payloads such as a stiff, charged polysaccharide. All three of these examples, obviously, will not be forming a simple geometry of particle.

One must know what the nanostructure of final particles are in order to begin drawing structure-property relationships for the desired particles and their targeted use. The Pochan and Jayaraman labs have created a collaborative method of complex, novel particle characterization that can take solution-based particles produced through industrial processing and assembly and provide the nanoscale structure and dispersity of the particles. The method involves initial cryoTEM imaging of the particles in suspension so as to provide local, real-space structure of a collection of the particles. Subsequent SANS is then performed in order to observe what the structure of the particles looks like when globally averaged. Then, armed with the local structure of the particles with cryoTEM, simulated particles are used to calculated SANS scattering profiles in order to match the experimental data and provide quantitative, structural descriptions of the particle populations.

Armed with direct knowledge of particle sizes and shapes, one is then able to directly understand how the processing/assembly and molecular constituents of particles impacts the particle morphology as well as how the morphology affects the desired use/environment of the particles. Aqueous-based particles are straightforward to characterize with Pochan-Jayaraman methods while polar organics have also been characterized.

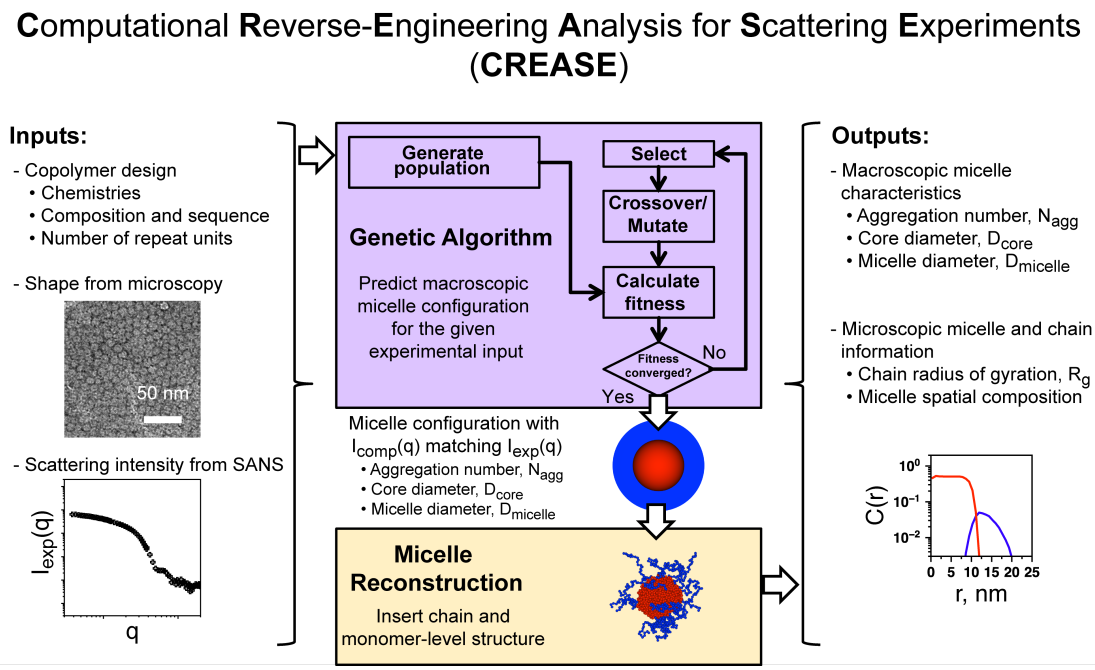

Figure 1. *Work flow of CREASE process. CREASE will be combined with cryoTEM and SANS for particle characterization*

Aims of Project:

1) direct characterization of nanoparticles via cryoTEM
2) SANS observations of global particle structures
4) Use of CREASE to calculate SANS profiles while iterating with particle simulations to quantify structure and dispersity of overall population of particles

Outcome of Work:

The project will provide direct knowledge of novel particle structure so as to provide structure-function relationships.

References:

Beltran-Villegas, D.J.; Wessels, M.G.; Lee, J.Y.; Song, Y.; Wooley, K.L.; Pochan, D.J.; Jayaraman, A. Computational Reverse-Engineering Analysis for Scattering Experiments on Amphiphilic Block Polymer Solutions, *J. Am. Chem. Soc.,* **2019**, 141, 14916-14930.

Lee, J.Y.; Wessels, M.G.; Song, Y.; Wooley, K.L.; Jayaraman, A.; Pochan, D.J.; Hierarchical Self-assembly of Poly(D-glucose carbonate) Amphiphilic Block Copolymers in Mixed Solvents, *Macromolecules*, in review.