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Topical White Paper

Title: Coupling non-Newtonian interfacial and bulk flows in reduced gravity

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Abstract:

Non-Newtonian fluids with a free surface are widely studied due to their prevalence in space-based applications including food processing, 3D-printing, and sampling of biological fluids for health monitoring, where reduced gravity can unmask the interaction of bulk and interfacial stresses. Significant resources have been spent on coupled problems in systems with negligible inertia. Predictive modeling of coupled systems that include fluid inertia is lagging behind, impacting progress in both Earth and space-based science and technology, including manufacturing of pharmaceuticals.

Background:

Interfacial hydrodynamics can drastically alter the transfer of mass, momentum, and energy across the surface of a liquid due to the coupling to the bulk hydrodynamics. The importance of interfacial hydrodynamics is evident everywhere in nature, ranging from small scale systems such as the alveoli in the lungs to CO_2 transfer between the atmosphere and the oceans.[1] In manufacturing, interfacial hydrodynamics impacts everything from wet processing of micro-electronics to the production of polyurethane foam. A recent development in the pharmaceutical manufacturing industry is the increased utilization of interfacial processing.[2] Yet, extraordinary little is understood regarding the prediction, and ultimately control, of interfacial hydrodynamics.

In reduced gravity, numerous processes are dominated by free surface phenomena, including food processing, 3D printing, energy and environmental controls, biological sampling/health monitoring, and pharmaceutical handling and storage, to name a few. Reduced gravity can make free surfaces more prevalent and dynamically more important than on Earth, where solid containment is generally the norm. Consequently, understanding two-way coupling is an essential feature for surface tension dominated systems. These include capillary and wetting phenomena, surface tension gradients with their associated surface elasticity and Marangoni phenomena, all or some of which can become comparable if not larger than other forces considered in fluids, including pressure forces and viscous forces.

Our understanding of interfacial hydrodynamics has come a long way from just knowing that oil can calm troubled waters, but there is still a long way to go. A major challenge for our times is the manufacturing of pharmaceuticals, in particular monoclonal antibodies, at global scales. For more than 50 years, pharmaceuticals have been produced using batch manufacturing, which is a multi-step process involving synthesis, crystallization, blending, granulation and tableting. In between each stage, the products are tested, shipped and stored from one batch processing location to another. More recently, there has been a slow shift toward continuous manufacturing, where the pharmaceuticals are produced simultaneously on a single process line, increasing both product quality and cost efficiency.[2] Among the many challenges in designing these new processors for each manufacturing stage is how to mitigate adverse effects from hydrodynamic and interfacial stresses.[2-6] For example, in bioreactors where microbial factories such as *E. coli* and *S. cerevisiae* are used to over-express therapeutic proteins, such as insulin via recombinant technologies, one must limit the range of shear stress imposed on the micro-organisms. After the protein is extracted, it must be purified and utilized at large concentrations—such as in injectable monoclonal antibodies. Proteins can denature and aggregate as a result of exposure to hydrodynamic shear and/or hydrophobic interfaces.

The current state-of-the-art in pharmaceutical manufacturing resembles the aeronautics industry 30 years ago, which then relied on wind tunnel tests, as opposed to predictive computational fluid dynamics today.

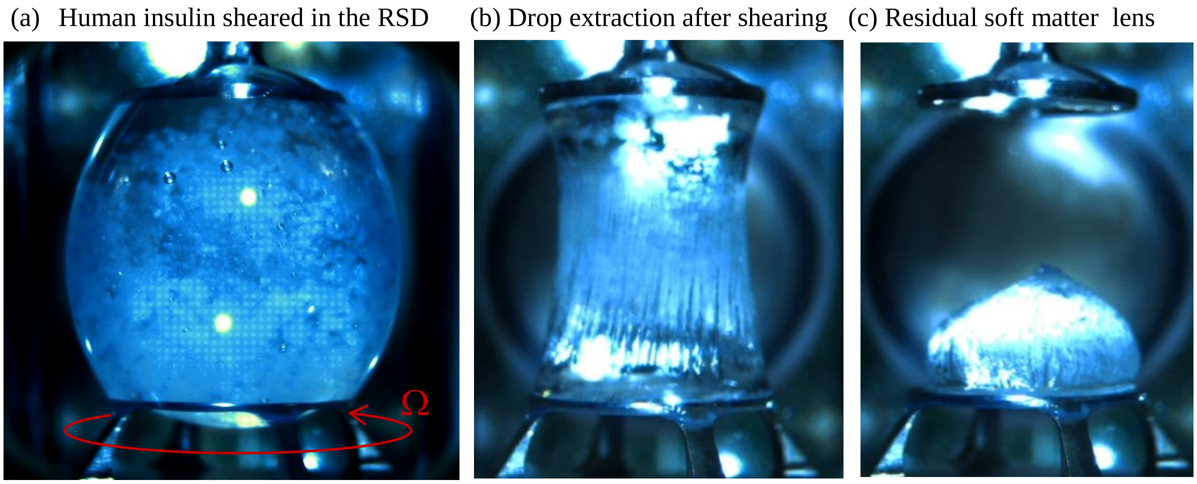
(a) Human insulin sheared in the RSD (b) Drop extraction after shearing (c) Residual soft matter lens

Figure 1 The ring-sheared drop (RSD), a 1-inch diameter containerless bio-chemical reactor for the study of mixing and interfacial stresses aboard the ISS. Containment is via surface tension, and the drop is constrained by a stationary contact-ring in the northern hemisphere and a rotating one in the south. Mixing is primarily conveyed by the action of surface shear viscosity. (a) Snapshot of a video (link to movie) showing a drop of pre-sheared, Human insulin (4 mg/mL, pre-sheared) forming amyloid fibrils, a pathological state of protein associated with many diseases. By this time (~ 3.5 days of shearing at 30 rpm) the northern hemisphere has transitioned from a clear aqueous solution to a gel-state while the south remains fluid. (b) Shows a bridge made of soft mater during drop extraction (from the deployment tube on top). Note, the ring was stopped long before the extraction started and the helical shape of the wrinkled skin on the bridge is apparently due to residual stresses and spatial non-uniformities within the drop. (c) Shows the soft matter left on the bottom ring after the material had been extracted and the bridge ruptured.

Some of the opportunities and challenges in describing and modeling the flow of soft matter in reduced gravity environment are demonstrated in Figure 1. This figure shows images obtained in September/October 2021 in the ring-sheared drop (RSD) module aboard the International Space Station. RSD provides an example of a platform for taking the first steps towards answering fundamental questions about soft matter.

State-of-the-art:

The state-of-the-art in predictive modeling includes quantification of the transition from Newtonian to non-Newtonian flow.[1] These transitions have been documented and studied on Earth using open flow systems with a flat free surface, including phospholipids[7] and soluble proteins[8]. In reduced gravity environments the interface is not flattened by gravity, but is generally curved by the action of surface tension and pinning, thus transition to non-Newtonian bulk flow can introduce many complications, including normal stresses (classically demonstrated by fluid climbing a rotating rod). Predictive modeling capabilities must be further developed.

Next steps:

Missing pieces for modeling and experimental validation and verification include:

1) Detailed flow experimentation and measurement are needed, especially for systems with disparate time scales: e.g. protein in solution can change structure over months or years under quiescent conditions but can do so over hours and days when forced to flow, whereas the viscous time scale can be on the order of seconds. Predictive models are beginning to be developed for "living polymers" namely, polypeptides and proteins.[9]
2) The next challenge is to develop computational models and experiments capable of head-to-head comparisons. Consequently, the challenge is developing modeling capabilities for handling both physical and biological systems, as their distinctions vanish. [9]

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