

I. NEED

The use of targeted molecular level contrast agents offers unique imaging possibilities in the field of cardiovascular research. In traditional pathological diagnoses, abnormalities indicating disease have been interpreted by careful examination of MRI or ultrasound images. The difference between the image contrast of abnormal and normal tissue is often the only non-invasive method available for disease diagnoses. Thus, clinical assessment is difficult, requiring a great deal of subjectivity, skill, and past experience. In addition, the identification of a pathological process can not occur without the abnormal tissue reaching some detection level limited by the imaging tool resolution. This, unfortunately means that the diseased tissue can't be detected immediately; rather, detection is prolonged until a critical detection size is reached [1]. One solution to this paradox is to make use of micro and nanoscale contrast agents. In the case of ultrasound imaging, tiny microbubbles are conjugated with targeting antibodies to attach to pathologic tissue. As a result, the effective imaging modality resolution can be improved to sizes approaching the molecular level. Our group has been successful at creating microbubbles, however, the manufacturing process (high energy sonication) leaves much to be desired when the ability to control size and polydispersity are considered (Figure 1a).

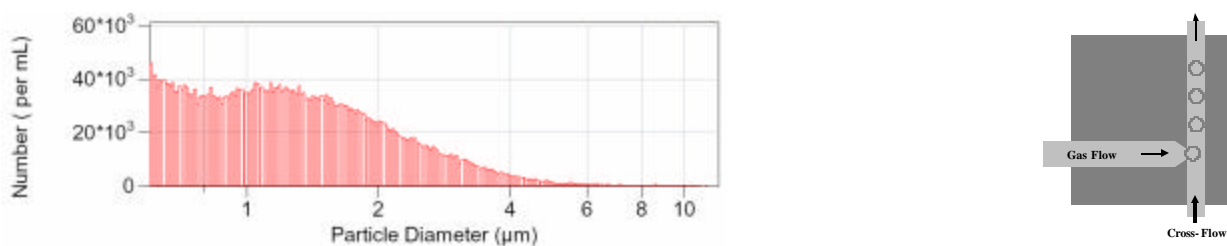


Figure 1. (a) Histogram showing the polydisperse nature of current bubble processing protocol. (b) Proposed microfluidic device.

II. PROBLEM STATEMENT & SOLUTION REVISITED

In the previously submitted Project Proposal, a continuous manufacturing approach to make nanoscale bubbles using a microfluidic device was proposed. In contrast to the batch fabrication processes, this approach provides continuous supply of newly generated nanobubbles using cross-flow and channel geometry to size the bubbles. As mentioned previously, it is well understood that cross-flow configurations are known to produce smaller bubbles when compared with formation conditions under stagnant liquid conditions [2]. In addition, cross-flowing liquids sweep away detached bubbles from the orifice region, thereby minimizing the chances of bubble coalescence (Figure 2). Given what I have discovered about the capabilities of Coventorware®, the proposal is still to develop a microfluidic device capable of continuously manufacturing nanoscale bubbles using cross-flow in conjunction with a submicron orifice to template the bubble size. Schematically illustrated in Figure 1b (for reference), the proposed device introduces a perfluorocarbon gas through a nanoscale orifice into a continuously flowing surfactant solution.

The modeling of this device has been separated into two different phases. The first involves BubbleSim using the 'Free Surface Flow' (FSF) physics solver to model individual bubbles in a simple channel (channel layout not shown for space constraint reasons). This solver allows for air bubbles defined by internal pressure and surface energy to be modeled flowing through a channel with coalescence and pressure gradients driving the bubble motion (Figure 2). The FSF physics solver was initially going to be used to model the entire design; however, after experimenting with the solver, there are some shortcomings that appear to necessitate using the 'Two Immiscible Liquids' (TIL) physics engine. While these shortcomings require the use of the second physics solver, there is important information that has been derived from the FSF. Among these, bubble coalescence can be modeled as shown in Figure 2. This is important to derive the minimum distance in fluid flow to prevent any collisions that may preclude bubbles from coalescing. In addition, as can be seen in the figure, the three equi-spaced (in the direction of flow) bubbles travel at different speeds depending on their position transverse to the flow (because of the flow profile and wall drag). It should be noted that the bubble

MEMS II Progress Report – Alex Barker

is not allowed to leave the control volume; hence they coalesce on the right as the bubbles are stopped by the right boundary. Other simulations were performed in which the bubble was placed along the mid-line of the channel and no collisions (therefore no coalescence) occurred until they collided with the right boundary.

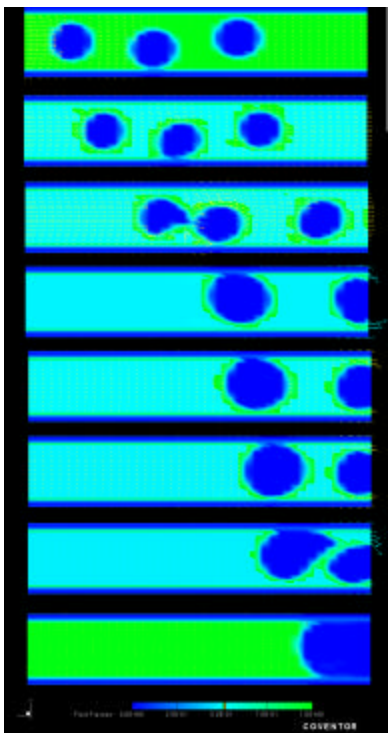


Figure 2. Three equi-sized, equi-spaced (in the flow direction) bubbles showing coalescence as a function of transverse position. Here, wall drag and velocity profile cause the left two bubbles to join. Edited for clarity.

III. LOGISTICS

Given results from the preliminary simulation described above, there is a major shortcoming in the FSF physics engine which prevents the ability to design the gas supply channel, labeled ‘Gas Flow’ in Figure 1(b). The FSF only allows for the flow of one phase to be assigned (in Figure 2, the liquid was given a pressure gradient, which subsequently moved the air bubbles). Thus if we were to use this solver to try and model the gas channel, there would be no way to indicate that: (1) the gas injection channel composed of a gas phase, and (2) that the gas phase channel had a pressure gradient. Therefore, the next phase of this project involves the use of the TIL physics engine to mimic a gas/fluid interaction. In order to simulate the design shown in Figure 1(b), one liquid phase will represent the water in the cross-flow channel, and the other ‘liquid’ phase will represent the gas injection channel (the ‘liquid’ can be made gas-like by altering the Materials Property Database). With the MPD alterations, the bubbles should be able to be modeled.

It should be noted that by choosing the TIL engine, there may be a risk that coalescence is not capable of being modeled. More importantly, it may prove difficult to break the ‘gas’ fluids into individual bubbles. With this in mind, the backup plan is to return to the FSF engine and focus on how to sort different size bubbles by channel geometry engineering [3].

IV. SCHEDULE

The schedule indicating the current progress is indicated in Chart 1. Included in this outline is the progress to date as well as the next phase which incorporates the ‘Two Immiscible Fluids’ physics engine to develop a turn-key approach to making tiny bubbles.

	15-Oct	31-Oct	15-Nov	30-Nov	15-Dec
Prior Art & Training	[Bar spanning 15-Oct to 15-Nov]				
Design considerations	[Bar spanning 15-Oct to 31-Oct]				
Understand Conventor Capabilities	[Bar spanning 15-Oct to 31-Oct]				
Complete appropriate tutorials	[Bar spanning 15-Oct to 15-Nov]				
Design and Test					
Phase 1 - Free Surface Flow				[Bar spanning 15-Nov to 30-Nov]	
Phase 2 - Two Immiscible Fluids				[Bar spanning 15-Nov to 30-Nov]	
Complete Report					[Bar spanning 30-Nov to 15-Dec]

Chart 1. Gantt chart showing proposed schedule and milestones

1. Wickline, S.A. and G.M. Lanza, *Molecular imaging, targeted therapeutics, and nanoscience*. Journal of Cellular Biochemistry, 2002: p. 90-97.
2. Tan, R.B.H., W.B. Chen, and K.H. Tan, *A non-spherical model for bubble formation with liquid cross-flow*. Chemical Engineering Science, 2000. **55**(24): p. 6259-6267.
3. Link, D.R., S.L. Anna, D.A. Weitz, and H.A. Stone, *Geometrically mediated breakup of drops in microfluidic devices*. Physical Review Letters, 2004. **92**(5).