# Computationally Assisted Design and Experimental Validation of a Novel 'flow-focussed' Microfluidics Chip for Generating Monodisperse Microbubbles.

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**Abstract:** Whilst initially developed as a diagnostic aid to improve echogenicity in ultrasound imaging, gas-filled lipid microbubbles are now emerging as a next generation 'theranostic' tool in the medical arena. Here, their therapeutic potential has now been realized through their unique capability to deliver molecular species such as drugs and genes by means of disrupting the cell membrane in response to ultrasound wave stimulus[1].

This paper presents the development of a finite element model used to validate an in-house design for a novel microfluidic microbubble generator. The design features a distinctive junction geometry, wherein the liquid and gas phases meet, and more importantly, produce stable monodisperse microbubbles. COMSOL Multiphysics v4.1 Laminar Multi-Phase Flow, Level-Set physics was used to generate a two-dimensional model which was firstly compared directly against our observational results to confirm its accuracy and furthermore to form parameterized studies in order to characterize the chip design.

**Keywords:** Two-phase, Level Set, Bubble, Microfluidics.

## 1. Introduction

Microbubbles may perhaps be most well known for their current clinical use as ultrasound contrast agents where due to their high degree of echogenicity they offer a solution to overcome a limitation to detect slow flow in small deep vessels. Recently however, much promise has formed for their use in therapeutic applications, such as in targeted drug delivery or gene therapy [2]. However, in order to support this development, there has emerged an appreciated need for more advanced bubble preparation techniques, that facilitate more control over size, composition and stability. Of key importance is the monodispersity of the generated microbubble population due to the relationship between bubble diameter, resonant frequency and susceptibility to radiation force.

There are various techniques available for microbubble preparation, however in this research we focus on a novel microfluidic based flow focusing approach. Such devices allow the strict control of the dispersion of two immiscible fluids enabling the producing of monodisperse bubble populations in the desirable range of 2-10µm[3].

Stable ultrasound micrbubbles are generally created using a distinct lipid shell and gas core components. We accomplished this by utilizing a mother liquor of PEGylated-lipid mixed with cholesterol, and forming a gas core with either nitrogen or perfluorobutane. Figure 1 shows a schematic illustration of the system we used for our preparation. A continuous liquid flow rate is controlled by a high precision syringe pump and the gas pressure was varied using a gas regulator.

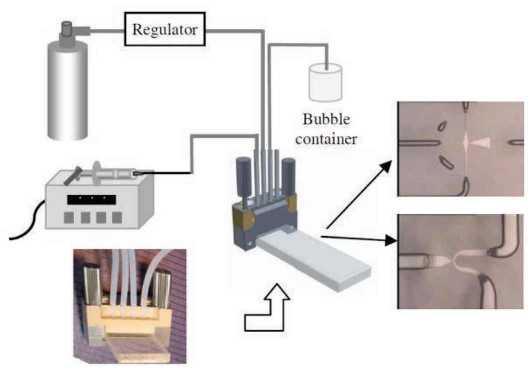


**Figure 1.** Schematic of Dundee microfluidic system.

The microfluidic chips are fabricated on a 15mm x 15mm x 4mm block of Superwite glass (Dolomite Ltd, UK) and channels were etched using soft-lithography at two depths, 2µm in the area extending ~0.5mm around the liquid (continuous phase) and gas (dispersed phase) junction and to 50µm depth in the rest of the channel network. The chip features several novel features including;

- Gas inlet entering at 120$^{o}$ on curved wall to promote lipid flow behind forming bubble to increase shear forces thus increasing break-off speed and in turn reduce size.
- Constricted liquid flow channel at gas inlet to increase flow velocity at gas injection.
- Glass construction as opposed to traditional PDMS (silicone), allowing elevated gas pressures and solvent resistance.

## 2. The Use of COMSOL Multiphysics

A simulation of the dynamic process of bubble generation is completed using the Laminar Two-Phase Flow, Level Set physics in COMSOL Multiphysics 4.1. This approach calculates the flow field using the incompressible form of the Navier-Stokes equation and is coupled to the level set method available in COMSOL Multiphysics 4.1. The level set method was chosen for its accuracy in tracking the interface between two immiscible fluids undergoing topological changes on a fixed Cartesian grid.

Owing to the intense computational demands of simulating two phase flows in three dimensions, a 2D model accurately simulating our system was advantageous. Due to the constrained height aspects of our microfluidic channels, the bubble pinch off process is approximately restricted to a plane, therefore in order to compute a quasi 3D flow a "shallow channel" term is added :

$$F_{\mu} = -12\frac{\mu \boldsymbol{u}}{h^2} \qquad (1)$$

where $F_{\mu}$ represents a body force to account for drag effects from the top and bottom boundaries, $h$ is the channel depth, µ is the fluid viscosity and **u** is fluid velocity.

### 2.1 Computational Domain and Grid Generation

Due to the extended length of microchannels on our chip it was not feasible to model the entire system. Figure 2 (Bottom) shows the reduced computational domain used which incorporated the design features salient to the point of bubble generation, including the curved continuous phase channel and angled dispersed phase inlet. A grid convergence study was conducted to find the required mesh quality to accurately describe the moving interface. Using a mapped mesh it was found that a maximum element size of 1µm, resulting in 20,365 mesh elements was acceptable.

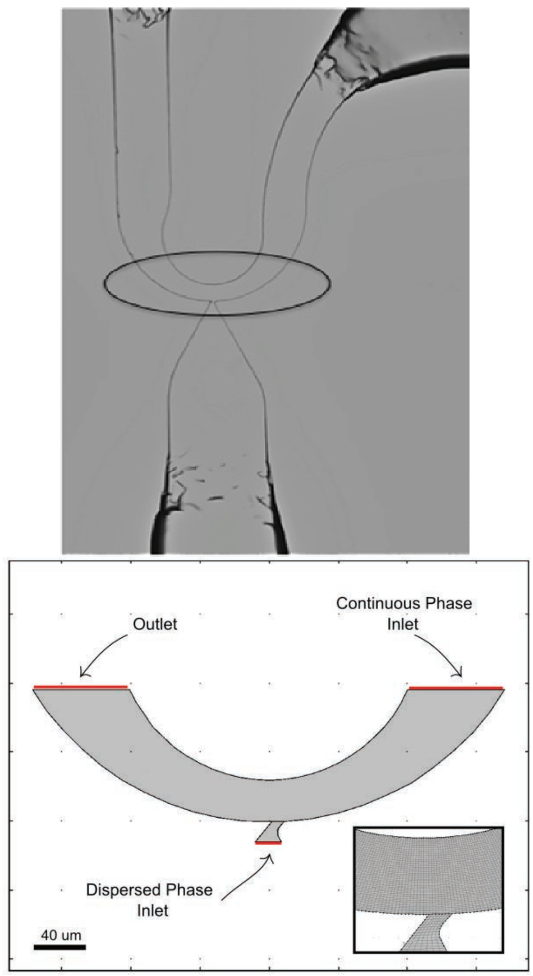


**Figure 2.** Top: Optical micrograph of physical microfluidic channels, black ellipse indicates simulation domain. Bottom: Computational domain geometry with inset showing mesh quality.

### 2.2 Boundary Conditions

The side boundaries of the channels are defined as wetted walls, to which we assigned a contact angle of 150$^o$, this value was estimated from a direct visual observation of our chip in operation with our lipid formula. As the physical system incorporates a mixture of volume flow rate (liquid) and pressure driven inlets (gas) and in our experience the computational model being more stable when inlets are defined with fluid velocity boundary conditions, it was required to estimate a gas inlet velocity from driving pressures utilizing the Hagen-Poiseuille equation[4]:

$$Q = \frac{\Delta P \pi r^4}{8\mu L} \qquad (2)$$

where $Q$ is the volume flow rate (m$^3$/s), $\Delta P$ represents the pressure drop in the channel, r is the channel radius and L is the channel length.

**Table 1:** Properties of the fluids used in this study

| **Lipid Liquid** | |
|---|---|
| Density | 1000 kg/m$^3$ |
| Viscosity | 2x10$^{-3}$ Pa.s |
| **Gas** | |
| Density | 1.2 kg/m$^3$ |
| Viscosity | 2x10$^{-5}$ Pa.s |
| **Surface Tension** | 3x10$^{-2}$ N/m |

## 3. Results

The simulation was first compared directly against our observational results to validate it's accuracy, Figure 3 shows the bubble formation process as observed with a high speed camera and as modeled in COMSOL. The close relationship between the two sets of data justified the model and its use for further investigations.

At the high flow rates required (152 kPa gas pressure and 1.5-2 uL/min liquid flow rate) for reasonable throughput, specific nuances of the bubble formation process such as pinch-off and location within the flow arc of the microfluidic channels not easily observed in our experimental data could be readily discerned in our model. Figure 4 shows the instance of bubble pinch off and how angled gas inlet combined with the curved channel encourage the liquid flow to accelerate the pinch process.

Through parameterized studies it was possible to characterize the relationship between inlet flow rates and bubble size. Figure 5 shows a brief example of this where by varying the liquid flow rate one can tailor bubble diameters to suit specific applications.

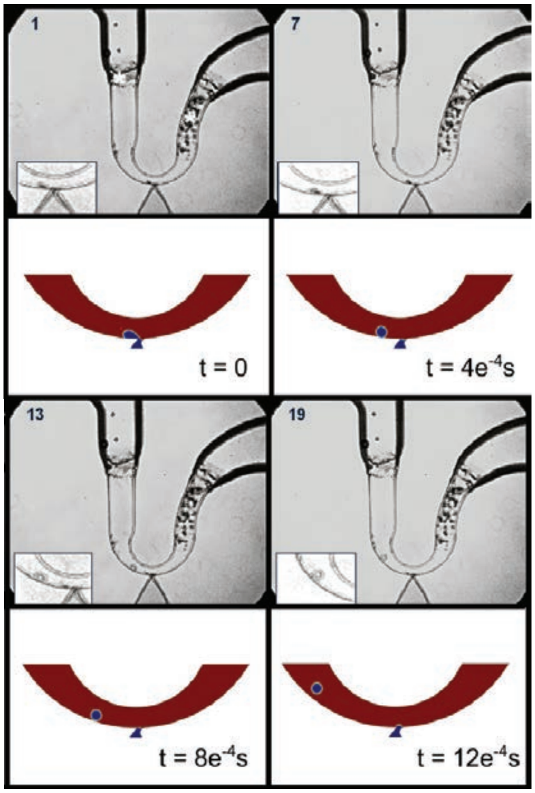


**Figure 3**. Comparison of experimental data from high speed camera and numerical model results.

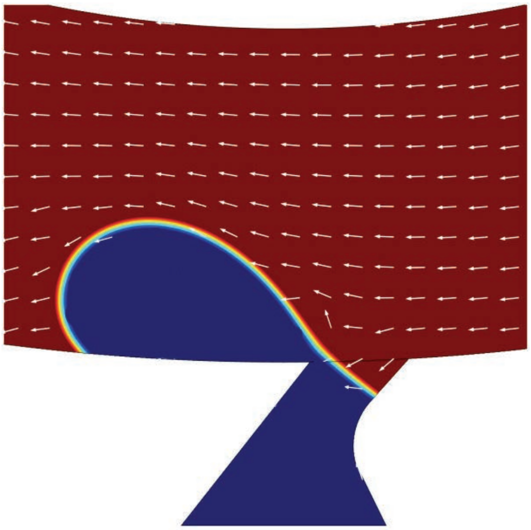

**Figure 4**. Snapshot, a short time before bubble pinch off. Arrows represent normalized liquid velocity field in main channel.

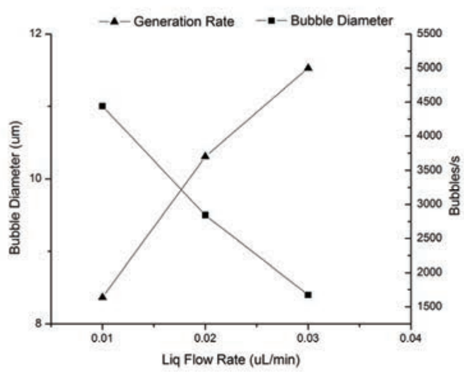


**Figure 5**. Plot depicting how varying the liquid inlet flow rate affects bubble diameters and production rates. Gas flow rate was held constant at 0.085μL/min.

## 4. Conclusion

Controlled microbubble generation is fundamental for the progressive development towards functionalized bubbles that will act as targeted therapeutic systems for a range of conditions. Microfluidic technologies with tight control over inlet flow rates and optimised geometries prove promising in this regard and coupled with their compact dimensions can offer multiple processes in single devices that may feature in future fully automated, point of care instruments to be used by clinicians working under personalized medicine regimes.

In this study, we have developed a numerical model to validate an in-house designed novel microfluidic chip bubble generator. Through parameterized studies easily implemented in COMSOL Multiphysics, factors that will inform next generation designs for our chip and the optimum operational parameters for said chip can be rapidly investigated, significantly accelerating development.

## 8. References

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