Computationally Assisted Design and Experimental Validation of a Novel ‘Flow Focussed’ Microfluidics Chip for Generating Monodisperse Microbubbles

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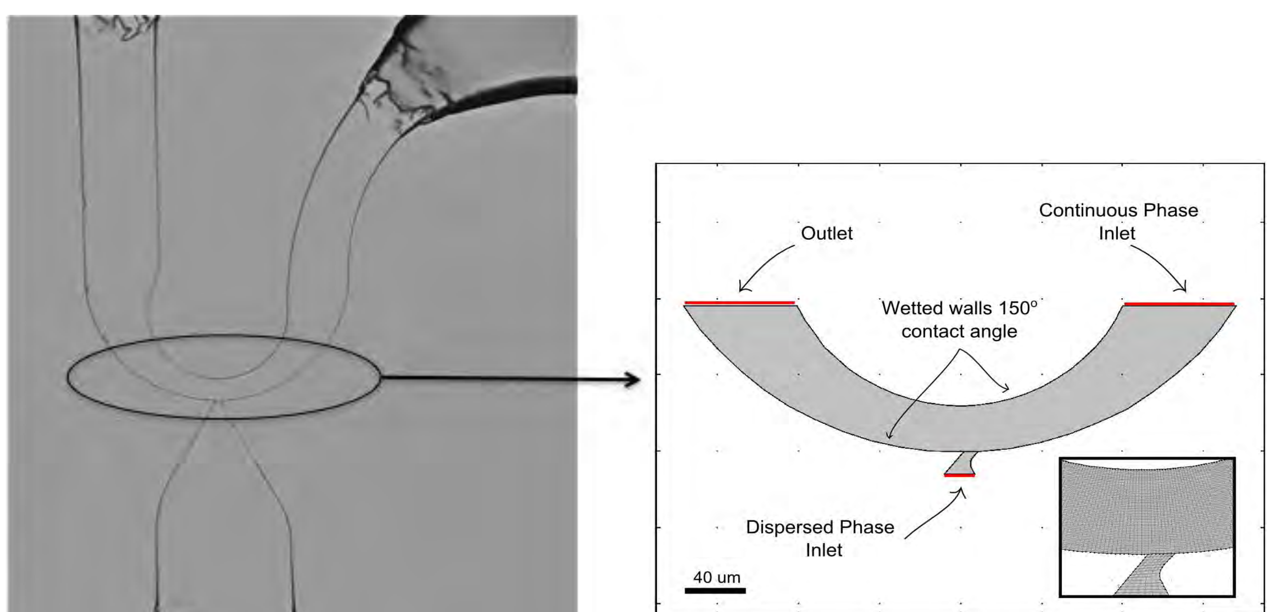
Gas-filled lipid microbubbles are emerging as a next generation **‘Theranostic’** tool in the medical arena. Initially developed as a ***diagnostic*** aid to improve echogenicity in ultrasound imaging, their ***therapeutic*** potential has now been realized also, through their unique ability to deliver molecular species such as drugs and genes by disrupting the cell membrane in response to ultrasonic stimulation.

‘Flow-focusing’ is one technique employed to generate micrometer-scale gas bubbles in liquid (microbubbles), with a comparatively tight (monodisperse) size distribution. This technique utilizes the focusing of a gas stream by a liquid stream driven by a pressure drop. The gaseous thread breaks close to the gas-inlet, releasing a bubble into the outlet channel. The size of these microbubbles can be controlled primarily by gas and liquid flow rates and the nozzle size at the liquid-gas junction.

DropGen 1 Chip Design and Computational Model



Model domain and boundary conditions

- **DropGen 1** is a glass etched microchannel with a 35 x 4 µm main channel (radius of curvature of 140 µm) and a gas nozzle of 6 x 4 µm dimension entering at 120° on the curved wall.

- It features a constricted liquid flow channel at gas inlet to increase flow velocity at gas injection point and encourage bubble pinch off.

- The level-set (1) method was utilized to track the interface between the liquid and gas phases on a fixed grid mesh.

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (\phi \mathbf{u}) + \gamma\left[\left(\nabla \cdot \left(\phi(1-\phi)\frac{\nabla \phi}{|\nabla \phi|}\right)\right) - \varepsilon \nabla \cdot \nabla \phi\right] = 0 \qquad (1)$$

- The 0.5 contour of the level-set function φ is defined as the phase interface where 0 = "Continuous Phase" (liquid shell material) and 1 = "Dispersed Phase" (air). This interface propagates with the fluid velocity **u**.
- **u** is solved for through the incompressible Navier-Stokes equation (2)

$$\rho\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u}\right) - \nabla \cdot (\mu(\nabla \mathbf{u} + \nabla \mathbf{u}^T)) + \nabla p = \mathbf{F}_{st} \qquad (2)$$

$$(\nabla \cdot \mathbf{u}) = 0$$

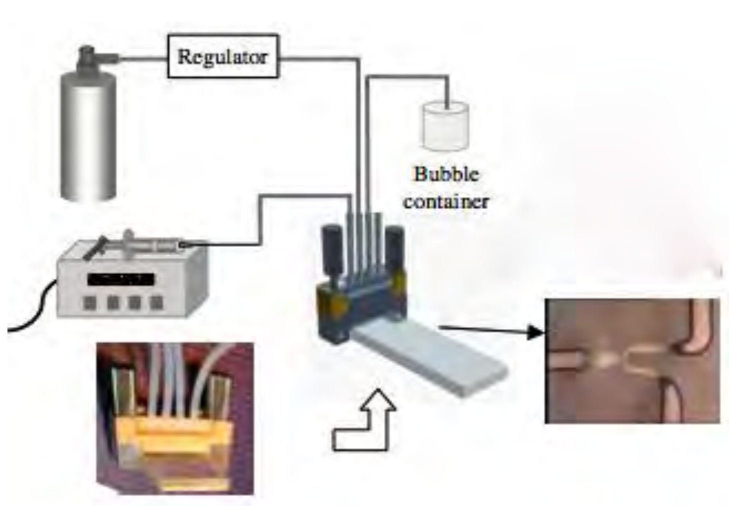
where, ρ = density, µ = dynamic viscosity, *p* = pressure, T = transpose, **u** = velocity and $\mathbf{F}_{st}$ = surface tension.

- To approximate a quasi 3-D flow more closely, a 'shallow channel' term (3) incorporates a volume force to the fluid flow equation to account for drag effects of the top and bottom boundaries.

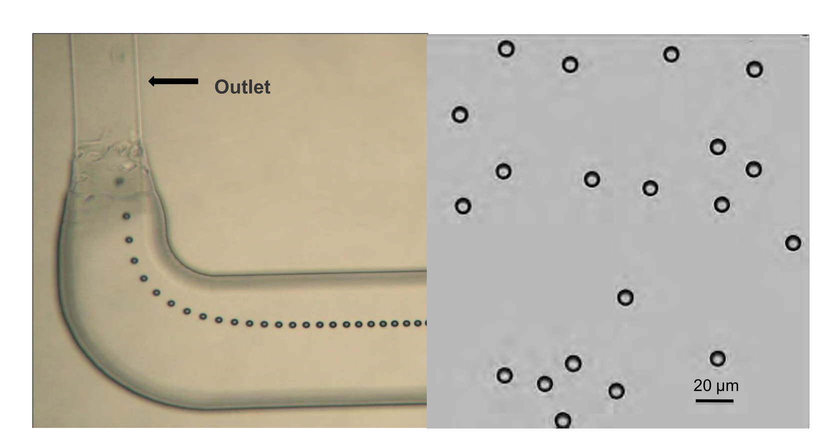
$$\mathbf{F}_{\mu} = -12\frac{\mu \mathbf{u}}{h^2} \qquad (3)$$

where, h = channel depth.

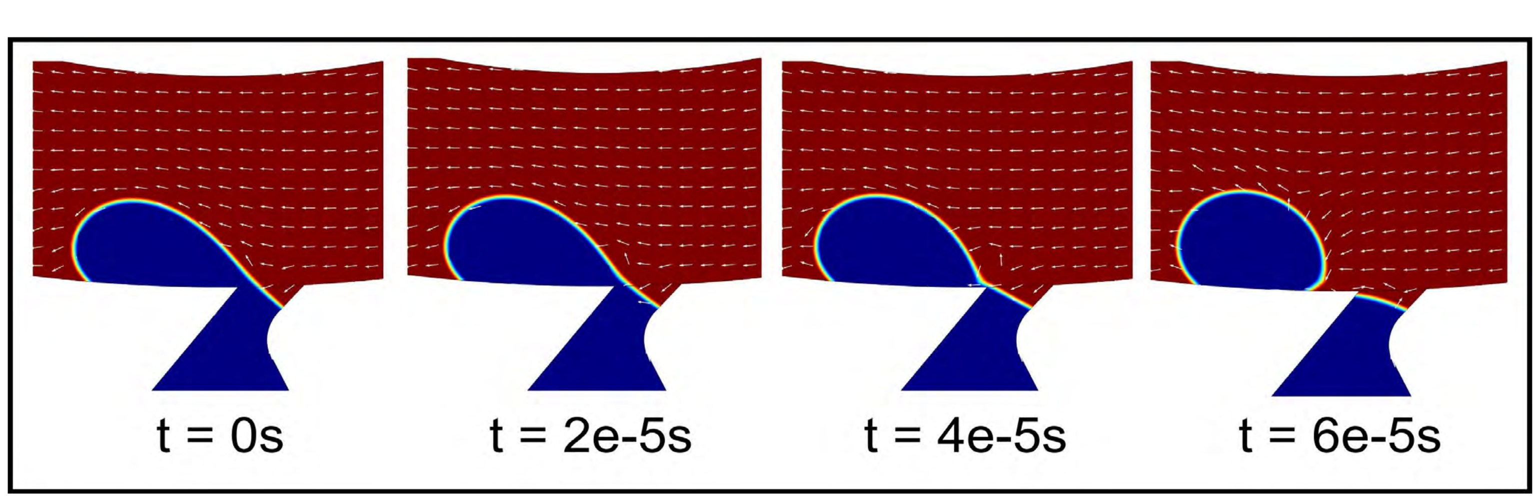
Microbubble Synthesis



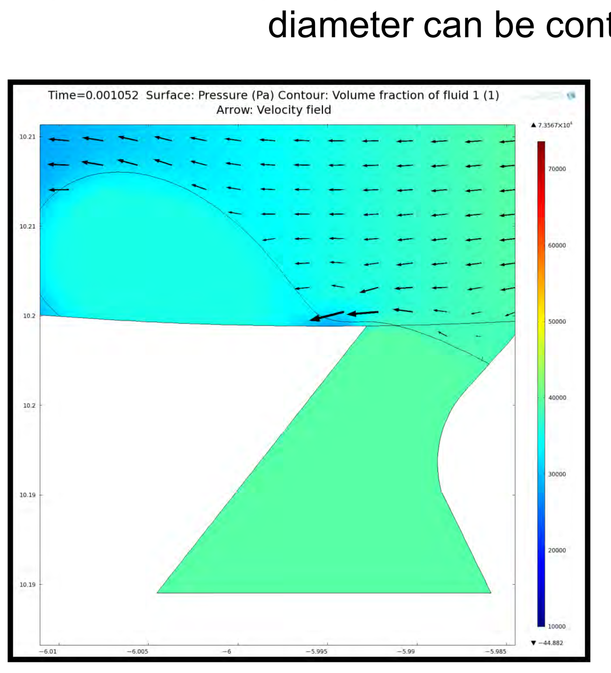
Microbubbles were prepared using specific lipid shell and gas core components and by lipid film hydration method. The microfluidic chip (DropGen1) was held by a specially made chip holder and was placed on an inverted fluorescence microscope before external fluidic connections were made. A syringe driver pumped the lipid solution present in the sterile syringe into the chip at constant flow rates ranging from 1.5 – 2 µl min^{-1}. The gas core component used was either hydrogen or perfluorobutane and was supplied from pressurized tanks by maintaining uniform gas pressure of up to 22psi. HPV-1 (Shimadzu, Japan) high-speed camera was used to capture still images and record movies. The images were taken at 16,000 frames s^{-1}.

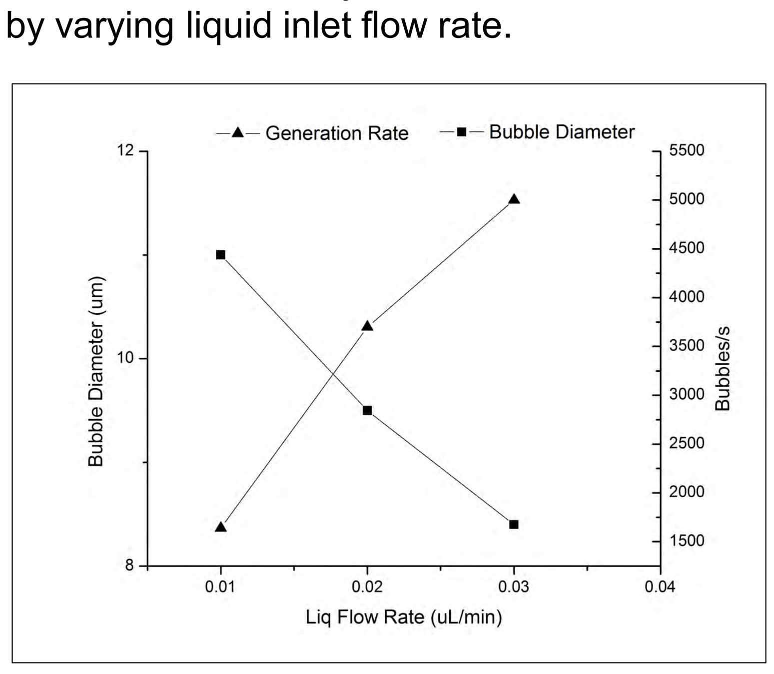


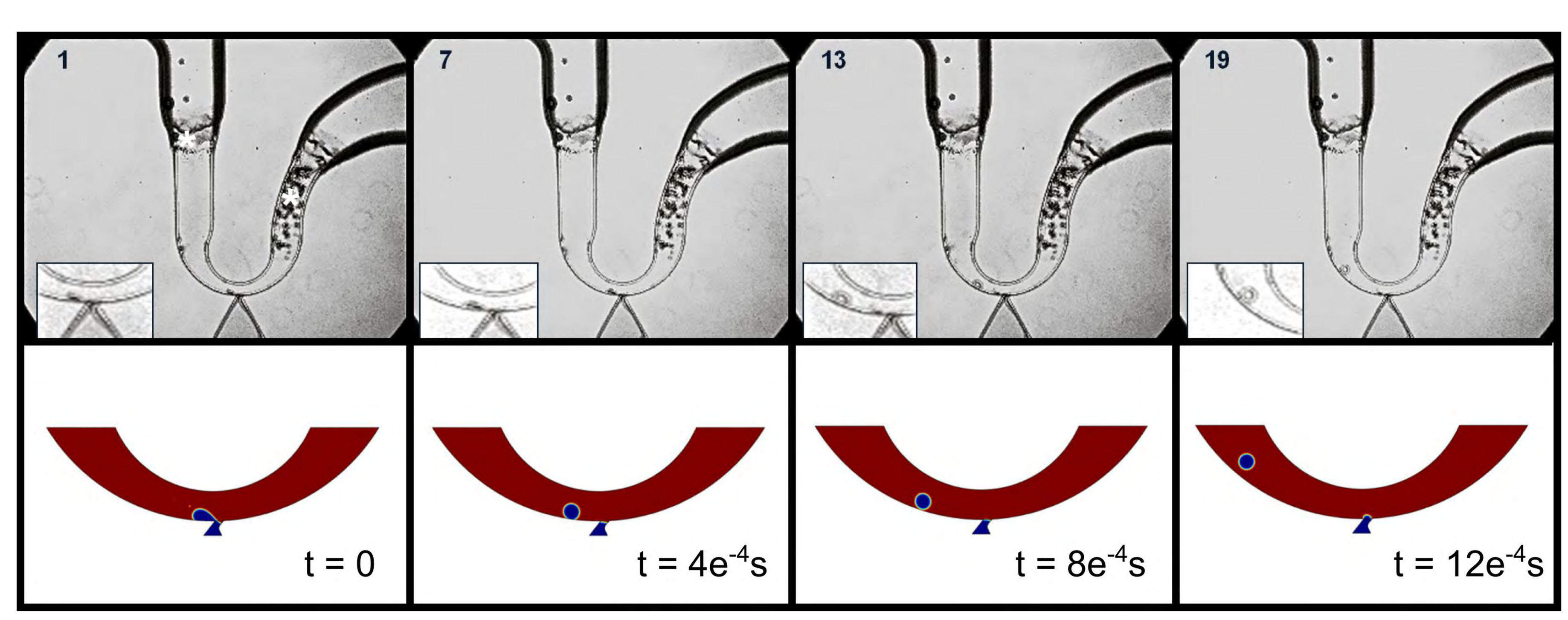
Computational Results



Above: Short time steps reveal subtle nuances in bubble pinch off, including effect of angled gas inlet and curved main channel. Below Left: Pressure field analysis highlights pressure drop at pinch site. Below Right: Parameterized study illustrated how bubble diameter can be controlled by varying liquid inlet flow rate.







These results point to the promise of using the COMSOL Multiphysics model to optimize the chip design and performance, revealing factors that will inform next generation designs for our chip, greatly accelerating development.

Future works: Further parameterized studies, including; running the system in the reverse flow direction, altering the gas inlet angle and at extended inlet flow rates could potentially offer wider range of control over bubble size.

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