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Microbubble transport through a bifurcating vessel network with pulsatile flow

Doug T. Valassis[#], Robert E. Dodde[#], Brijesh Esphuniyani, J. Brian Fowlkes, Joseph L. Bull
Department of Biomedical Engineering, University of Michigan, Ann Arbor, USA

[#] These authors contributed equally to this work.

Abstract

Motivated by two-phase microfluidics and by the clinical applications of air embolism and a developmental gas embolotherapy technique, experimental and theoretical models of microbubble transport in pulsatile flow are presented. The one-dimensional time-dependent theoretical model is developed from an unsteady Bernoulli equation that has been modified to include viscous and unsteady effects. Results of both experiments and theory show that roll angle (the angle the plane of the bifurcating network makes with the horizontal) is an important contributor to bubble splitting ratio at each bifurcation within the bifurcating network. When compared to corresponding constant flow, pulsatile flow was shown to produce insignificant changes to the overall splitting ratio of the bubble despite the order one Womersley numbers, suggesting that bubble splitting through the vasculature could be modeled adequately with a more modest constant flow model. However, bubble lodging was affected by the flow pulsatility, and the effects of pulsatile flow were evident in the dependence of splitting ratio of bubble length. The ability of bubbles to remain lodged after reaching a steady state in the bifurcations is promising for the effectiveness of gas embolotherapy to occlude blood flow to tumors, and indicates the importance of understanding where lodging will occur in air embolism. The ability to accurately predict the bubble dynamics in unsteady flow within a bifurcating network is demonstrated and suggests the potential for bubbles in microfluidics devices to encode information in both steady and unsteady aspects of their dynamics.

Keywords

Gas embolotherapy; air embolism; decompression sickness; bubble dynamics; bubble logic

1 Introduction

In this study, the effects of pulsatile flow on the behavior of long gas bubbles suspended in liquid flowing through successive bifurcations were investigated experimentally and theoretically. This work is motivated by a variety of microfluidics and physiologic applications. The transport of gas bubbles and liquid droplets in microfluidics devices has received considerable interest in recent years in a variety of contexts, such as models of

vascular or pulmonary two-phase flow (Calderon, Heo et al. 2006; Huh, Fujioka et al. 2007; Qamar, Wong et al. 2010; Tavana, Zamankhan et al. 2011; Wong, Kripfgans et al. 2011), biomedical microdevices that use multiple phases as a key component to their desired function (Zhang, Wu et al. 2008; Baroud, Gallaire et al. 2010; Behzad, Seyed-allaei et al. 2010; Carlson, Do-Quang et al. 2010; Chung, Lee et al. 2010; Malsch, Gleichmann et al. 2010; Theberge, Courtois et al. 2010; Abate and Weitz 2011; Gu, Duits et al. 2011; Prakash and Bush 2011), and “bubble logic” devices that use bubbles to perform logic or computing processes (Epstein 2007; Fuerstman, Garstecki et al. 2007; Prakash and Gershenfeld 2007; Wang, Zhang et al. 2010). In the latter of these applications, bubbles or droplets are used to encode and decode information or perform logical operations. This application is described in more detail by Epstein (Epstein 2007). These processes involve bubble (or droplet) transport through a series of bifurcations such that the bubble “chooses” one of the two paths it encounters at a bifurcation with information encoded into the train of bubbles within the network (Fuerstman, Garstecki et al. 2007). Such an approach allows for Boolean AND, OR, and NOT operations (Prakash and Gershenfeld 2007). The work considered here provides scope for more complicated operations and more complex encoding and decoding by considering additional features of bubble splitting, e.g. the bubble does not have to “choose” a single path at a bifurcation and has the option of splitting with some fraction entering each branch, and time dependent flow rather than steady flow.

The dynamics of vascular microbubbles is central to a several biomedical phenomena, including air embolism, decompression sickness, and gas embolotherapy (Eckmann, Branger et al. 2000; Bull 2005; Bull 2007). Air embolism can occur accidentally in clinical procedures, and can have deleterious or even fatal effects. Decompression sickness occurs during rapid decompression, often due to surfacing too quickly in diving, when gasses come out of solution forming gas emboli in the blood. Microbubbles that are long compared to the vessel diameter may split as they pass through vessel bifurcations (Calderon, Fowlkes et al. 2005), and this splitting behavior determines where the microbubble ultimately lodge (Calderon, Heo et al. 2006). The lodging of microbubbles can occlude blood flow leading to tissue necrosis, myocardial infarction, stroke and other pathological conditions (Branger and Eckmann 1999; Branger, Lambertsen et al. 2001; Branger and Eckmann 2002; Galion, Do et al. 2010).

Another motivation for this work is gas embolotherapy, which is a developmental cancer therapy aimed at occluding blood flow to tumors. This occlusion therapy may also be coupled to localized drug delivery. Gas embolotherapy is a minimally invasive and highly selective therapy in which gas emboli occlude blood flow to tumors, inducing tumor necrosis. A brief overview the mechanics of the technique follows. Albumin- or lipid-encapsulated perfluorocarbon droplets are injected intravenously. The particular perfluorocarbon (fluoropentane C_5F_{12}) has a boiling point of $29^{\circ}C$ at atmospheric pressure and is consequently superheated at body temperature. The superheated liquid droplets are vaporized by focused ultrasound in the desired location to form long gas bubbles that are 125 to 150 times the initial droplet volume. The mechanics of acoustic droplet vaporization have been examined elsewhere (Kripfgans, Fowlkes et al. 2000; Kripfgans, Fowlkes et al. 2002; Kripfgans, Fabiilli et al. 2004; Ye and Bull 2004; Ye and Bull 2006; Qamar, Wong et al. 2010; Wong, Kripfgans et al. 2011). The present study is relevant to the transport and

lodging of microbubbles that occurs subsequent to their formation. Lodged bubbles are large enough in size to block blood flow through arterioles and capillaries. The bubble lifetime is on the order of hours to days, and lodged bubbles are sufficient to occlude blood flow (Kripfgans, Fowlkes et al. 2000; Kripfgans, Fowlkes et al. 2002; Kripfgans, Fabiilli et al. 2004; Calderon, Fowlkes et al. 2005; Kripfgans, Orifici et al. 2005; Calderon, Heo et al. 2006; Calderon, Eshpuniyani et al. 2010; Samuel, Fabiilli et al. 2010). The ability to predict bubble splitting and sticking behavior is essential to gas embolotherapy for two reasons. First, in order to successfully eliminate a tumor, at least 78% occlusion of blood flow to the tumor is necessary (Di Segni, Young et al. 1997). Second, bubbles with the size to occlude blood flow in the vasculature may pose a threat to other untargeted tissues in the body, i.e. brain, heart, and lungs.

Arteries, arterioles and capillaries exist in the body as a bifurcating network. Consequently, we have previously examined the effects of gravity and flow rate on bubble splitting and occlusion during steady flow. Using a bench-top model system of bifurcating tubes and a one-dimensional quasi-steady theoretical model, we have previously shown that gravity and flow rate play an important role in determining bubble splitting ratios and lodging (Calderon, Fowlkes et al. 2005; Eshpuniyani, Fowlkes et al. 2005). The capillary number may be considered to be a dimensionless form of flow rate, and the relation between flow rate and gravitational effects may be represented by capillary number and roll angle, where the roll angle is the angle that the plane of the bifurcating channel makes with the horizontal. When roll angle is zero, the plane of the bifurcation is horizontal and gravity does not favor transport of bubbles into one daughter branch of the bifurcation over the other. There exists a critical capillary number where bubbles do not split at the bifurcation and flow completely into the upper branch of a bifurcation when testing at nonzero roll angles at values below this number. The critical capillary number increases with roll angle and parent tube diameter (Calderon, Fowlkes et al. 2005). The experiments of (Calderon, Fowlkes et al. 2005) considered a single bifurcation. Subsequent experiments by (Eshpuniyani, Fowlkes et al. 2008) considered an arteriole bench-top model that utilized two bifurcations and concluded that faster flow rates cause more even bubble splitting within a bifurcating tube network and noted that the evenness of splitting ultimately affected the occurrence of bubble lodging within the network. In related work, we examined the ability to occlude model and actual microvessels using microbubbles (Calderon, Heo et al. 2006; Samuel, Fabiilli et al. 2010), and examined bubble splitting in a boundary element model (Calderon, Eshpuniyani et al. 2010). Our previous model studies have predicted the general trends observed in vivo (Galion, Do et al. 2010; Samuel, Fabiilli et al. 2010).

Until now, the effects of pulsatile flow on bubble splitting and lodging in a series of bifurcations have been unexplored. The present study incorporated pulsatile flow to better mimic the physiological setting and to explore a framework for predicting bubble behavior in time-dependent flow in biomedical microdevices. The effect of unsteady flow on bubble splitting and lodging was explored experimentally and a corresponding time-dependent, one-dimensional theoretical model was also developed to complement the experimental data and simulate untested situations.

2 Methods

2.1 Experiments

The bifurcating network (Figures 1–2) consisted of a single parent tube that splits into two identical daughter tubes, followed by a second bifurcation at the end of each first generation daughter tube. These two second generation bifurcations each split into two more second generation daughter tubes to create four total second generation daughter tubes. The parent tube has a diameter of 1 mm. Each set of successive generation daughter tubes has a diameter 0.78 times the diameter of the previous generation. The branching angle at all of the bifurcations is 78 degrees. The geometry was chosen match physiological values for arterioles (Fung 1997; Calderon, Fowlkes et al. 2005).

The bifurcating network was fabricated by machining semicircular channels in two identical acrylic 12.7 cm squares, 1.27 cm thick (McMaster-Carr, Chicago, IL), which composed the top and bottom halves of the planar bifurcating network. The two halves were then aligned with locator pins and secured together with bolts. To create the circular lumen, ball-end mills (Fullerton Tool Co. Saginaw, MI) of 1 mm, 780 μm and 608 μm in diameter were used to machine the channel branches of with the corresponding diameters. All machining was executed using a 3-axis mill (Chevalier Machinery Inc., Santa Fe Springs, CA) with programmable CNC (Milltronics Manufacturing, Waconia, MN). To secure the acrylic squares together, forty through-holes were drilled along the perimeter of the bifurcating channels. Screws, flat washers, and nuts (McMaster-Carr, Chicago, IL) were used to bolt the two halves together ensuring a tight seal to avoid any leakage.

Pulsatile flow through the parent tube of the model bifurcation was generated by a programmable linear actuator (Animatics, Santa Clara, CA) that drove a syringe plunger. The flow rate was measured by an electronic flow meter (Alicat Scientific, Tucson, AZ). Tygon tubing was used to connect the outlets of the daughter tubes to pressure reservoirs kept at a constant level above the bifurcation model. The reservoirs were open to the atmosphere and allowed to overflow, resulting in constant water level and consequently constant pressure in each reservoir. All experiments were conducted at room temperature. The blood phase was modeled by deionized water, and the vaporized perfluorocarbon bubble was simulated by air bubble. The bifurcating channel was cleaned thoroughly at regular periods using soap and water.

To prepare an experimental trial, a microliter syringe was inserted through an access port created by a luer lock fitted to the Tygon tubing upstream from the parent tube. This port gave access to the parent tube in order to prevent the bifurcating channel from having to be disconnected from the experimental circuit during the injection of an air bubble (Figure 1). When the syringe needle was properly placed in the parent tube, an air bubble was injected. The bubble was placed a sufficient distance upstream from the bifurcation so that the bubble and surrounding water could reach the desired pulsatile flow waveform far upstream from the bifurcation. The distance between the bubble and bifurcation was also calculated to allow the front meniscus of the bubble reach the bifurcation at the maximum flow rate of the, approximately sinusoidal, pulsatile flow waveform. Flow from the linear actuator driven syringe in the parent tube of the bifurcation varied from 0.06-0.30 ml/min. The motion of the

bubble through the channels and bifurcations was imaged by a CCD camera and recorded on digital videotape (DCR-PC110, Sony, Tokyo, Japan). These digital videos were then transferred to a computer (MacBook Pro, Apple, Cupertino, California, USA) and converted to a sequence of bitmap images for analysis using iMovie HD (Apple, Cupertino, California, USA).

The images were used to measure the length of the bubbles in each of the branches of the two bifurcations. Digital calipers were used to measure the bubble lengths. Length measurements were made before bubble splitting began and after splitting was complete. This included scenarios where a bubble was lodged and portions of it remained in the first and second-generation daughter tubes and scenarios when all bubbles had passed beyond the second bifurcation. Bubble volume was then computed by multiplying the length of the bubble by the cross-sectional area of the corresponding branch. A range of pulsatile flow frequencies and roll angles were investigated.

The flow rate waveform and frequency were specified by programming the linear actuator that drove the flow. The bifurcating channel was mounted on a tripod to allow for testing at multiple roll angles. Roll angle was set by first ensuring the plane of the bifurcation channels (all tubes are in the same plane) was level with the horizontal plane of the floor, then adjusting the tripod to the desired angle. The roll angle was changed by rotating the plane of the bifurcation about the axis that passes through the parent tube. The flow and frequency conditions were set to match non-dimensional parameter values observed in arterioles in a physiological situation. Changing the flow rate changes the capillary number, $Ca = \mu U / \sigma$, where U = characteristic fluid velocity, σ = surface tension, and μ = fluid viscosity. The capillary number is a non-dimensional representation of the ratio of viscous forces to surface tension forces, and may be considered a dimensionless flow rate. At each roll angle, bubble transport was studied at flow rates ranging from 0.06-0.30 ml/min and pulsatile frequencies of 80, 105, and 130 beats per minute (BPM). The average capillary number of the flow waveform is $5.71 \cdot 10^{-5}$. Figure 3 shows the range of Ca values for each of the roll angles tested in the current experimental pulsatile flow study. The range of capillary numbers measured in arterioles in the human circulation, based on properties of blood and perfluorocarbon, is $6.51 \cdot 10^{-4}$ – $4.89 \cdot 10^{-4}$ (Calderon, Fowlkes et al. 2005).

The Reynolds number, $Re = \rho U D_P / \mu$, represents the ratio of inertial to viscous forces and is also a function of the flow rate. D_P is the diameter of the parent tube, U is the average velocity (in the parent tube), and μ viscosity and ρ density of the core fluid (water), respectively. The average Reynolds number corresponding to the pulsatile waveform is 2.7. We previously estimated the range of Reynolds numbers anticipate in small arterioles in the human circulation, based on properties of blood and perfluorocarbon, to $2.9 \cdot 10^{-1}$ to 1.0 (Calderon, Fowlkes et al. 2005). The Strouhal number, $St = \omega D_P / U$, is a dimensionless parameter that indicates the ratio of unsteady inertial forces to steady inertial forces. A related non-dimensional parameter that is often used in biofluid mechanics is the Womersley number, $\alpha = D_P \sqrt{\omega \rho / \mu} = \sqrt{Re \cdot St}$, which indicates the ratio of unsteady inertial forces to viscous forces. The value of α in the experiments was approximately 1 for the 105 BPM

case, indicating the experimental range of α values is consistent with the $\alpha = O(1)$ in small arteries and large arterioles (Fung 1997).

The Bond number, $Bo = \Delta\rho g \cdot D_p^2 / \sigma$, where ρ is the density difference between the core fluid and the bubble, g is the gravitational acceleration, D_p is the parent tube diameter, and σ is the surface tension between the core fluid and bubble gas (water and air in this case). The Bond number is the ratio of the forces due to gravity over surface tension. Since roll angles are changed during this experiment, the effect of varying roll angles must be accounted for. This was accomplished by using a modified Bond number defined as $Bo^* = Bo \cdot \sin(\theta)$ (Calderon, Fowlkes et al. 2005). The modified Bond number is used to show that the experimental value matches the physiological value expected in arterioles. Therefore, the results of the experiment can be applied towards physiological situations. The experimental Bond number is obtained by using small values of the roll angle, θ . By using small values of θ , the modified Bond numbers mimic the physiological values of Bond numbers. The Bond number in this study is $Bo = 3.58 \cdot 10^{-2}$. Experiments are conducted at roll angles of 0, 15, 30, 45, and 60 degrees. This corresponds to modified Bond numbers, Bo^* , of 0 , $9.3 \cdot 10^{-3}$, $1.79 \cdot 10^{-2}$, $2.53 \cdot 10^{-2}$, and $3.10 \cdot 10^{-2}$. The range of Bond numbers anticipated in small arterioles in the human circulation, based on properties of blood and perfluorocarbon, is $2.0 \cdot 10^{-3}$ to $2.81 \cdot 10^{-4}$ (Calderon, Fowlkes et al. 2005). The values of Ca , Re , α , and Bo^* used in the bench top experiments were selected to approximate the values in the terminal arteries and start of the arterioles within the constraints imposed by the pumping system.

2.2 Theory

To elucidate the mechanisms responsible for the bubble behavior observed in the experiments, a theoretical model was developed. The results obtained from this model were compared with the experimental data. The current theoretical model is an extension of our previous quasi-steady single bifurcation model (Calderon, Fowlkes et al. 2005). The extended model can now be utilized to analyze steady and unsteady inertial force, varying flow rates and flow through the multiple bifurcations. Figure 4 shows the schematic of the bifurcation model. As depicted, the bubble travels along the parent tube (L_0) from left to right before initially separating into the upper (L_2) and lower (L_1) primary daughter tubes at time $t = 0$. For nonzero roll angle, the bubble does not split evenly and reaches the upper second bifurcation before reaching the lower second bifurcation, as shown in Figure 4. Assuming quasi-sinusoidal motion of the bubble with uniform bubble pressure, the pressure difference between the bubble (P_b) and the reservoir surface (P_e) along any bifurcation can be correlated by applying unsteady Bernoulli equation with head loss given by:

$$P_b - P_e = \Delta P_i + \frac{1}{2} \rho (v_e^2 - v_i^2) + \gamma (z_e - z_i) + \rho \int_{S_i}^{S_e} \frac{dv_i}{dt} ds + \gamma h_i \quad (1)$$

where the first term on right hand side of the equation (1) represents the pressure jump across the bubble interface, the second term represents the steady inertial forces, the third term the gravitational effects, the fourth term the unsteady inertial forces, and the last term represents the viscous losses. The subscripts i , e , and b denote the bifurcation channel the bubble nose is in, reservoir surface, and bubble respectively. Also, v represents the bubble

nose velocity; P is pressure; h is head loss due to viscous effects in the tubes; and $\gamma = \rho g$, is the liquid-specific weight.

As a bubble nose propagates through a channel, the length of that channel occupied by water, l_f decreases in time. This rate of decrease, v_i , can be evaluated as

$$v_i = -\frac{dl_i}{dt} \quad (2)$$

where t is time. Additionally, the unsteady flow imposed on the bubble as it propagates through the bifurcations results in a rate change in time of the velocity of the bubble nose. This acceleration (a_i) can be calculated as

$$a_i = \frac{dv_i}{dt} \quad (3)$$

The pressure jump across the interface of each bubble nose and the fluid, $P_i = P_i - P_b$, can be approximated by the expression determined by (Bretherton 1961), given that the bubble can be considered semi-infinite and under small Ca , as follows:

$$P_i = \frac{2\sigma}{d_i} \left(1 + 3.58 \left(\frac{3\mu}{\sigma} v_i \right)^{\frac{2}{3}} \right) \quad (4)$$

where σ is the surface tension between the gas and the bubble; and μ is the viscosity of the fluid.

The gravitational effect (γZ_i) due to the elevation differences of a bubble nose can be determined through geometry. For a bubble nose in the upper primary daughter tube (L_2):

$$\gamma z_2 = \gamma \sin\left(\frac{\varphi}{2}\right) \sin(\theta) (L_2 - l_2) \quad (5)$$

where φ is the angle between bifurcating channels, θ is the roll angle measured along an axis extending through the center of the parent tube (L_0) and L_2 is the total length of the upper primary daughter tube. The unsteady inertial forces are calculated by integrating the mass and acceleration of the fluid between the bubble nose and the reservoir. Assuming that the fluid is incompressible and fluid velocities in the second generation tube are identical before the bubble reaches that tube, this yields

$$\rho \int_{S_1}^{S_e} a_i ds = \rho \sum_{j=1}^n l_j \frac{A_n}{A_1} \frac{dv_j}{dt} \quad (6)$$

where n is the number of different channels the fluid passes through before reaching the reservoir and A_j is the cross-sectional area of the tube.

The viscous losses, h_f , are determined based on the head loss experienced as the fluid flows through a tube. Considering the fluid between the bubble nose and the reservoir for each daughter tube travels through several varying diameters of tubing, and neglecting minor

losses due to the fittings used and bending in the tubing, the head loss can be estimated by the following equation:

$$h_i = \frac{32\mu}{\rho g} \sum_{j=1}^n \frac{l_j}{d_j^2} v_i \quad (7)$$

where d is the diameter of the tube. An equation relating the position of a bubble nose to the bubble pressure and exit pressure can then be constructed for each bifurcation where a bubble nose exists, such that

$$P_b - P_e = \Delta P_i + \frac{1}{2}\rho(v_e^2 - v_i^2) + \gamma(z_e - z_i) + \rho \sum_{j=1}^n l_j \frac{dv_j}{dt} + \gamma \frac{32\mu}{\rho g} \sum_{j=1}^n \frac{l_j}{d_j^2} v_i \quad (8)$$

A reference bubble nose is used to eliminate the P_e , v_e , and z_e terms, as the reservoir pressure is unknown, by setting the equations for each of the other bubble nose positions equal to the reference bubble and consolidating terms. This leaves the number of unknowns one larger than the number of equations; however, imposing conservation of mass on the entire system allows for a balanced system of equations. Mass conservation requires the sum of the flows in each daughter tube to equal the total flow, such that

$$\sum_{i=1}^m \frac{\pi d_i^2}{4} v_i = Q \quad (9)$$

where m is the total number of different channels the bubble has bifurcated into.

To better compare the relative importance of gravitational and flow parameters, as measured by Bo , Ca , and Wm , the following scales were used to non-dimensionalize the governing equations

$$P = \frac{2\sigma}{D_p} \widehat{P}, z = D_p \widehat{z}, l = D_p \widehat{l}, t = \frac{1}{\omega} \widehat{t}, v = D_p \omega \widehat{v}, a = D_p \omega^2 \widehat{a}, d = D_p \widehat{d}, \text{ and } Q = D_p^3 \omega \widehat{Q}$$

Substituting these parameters into equations 8 and 9, choosing one channel as a reference point (ref) for comparing bubble noses in other channels, and relating velocities and accelerations in downstream channels to the velocity and acceleration in the channel occupied by the bubble nose through the relation,

$$A_1 v_1 = A_2 v_2 \quad (10)$$

which results from mass conservation for the incompressible liquid within the channel, yields the following system of non-dimensional equations that can be used, along with non-dimensional forms of equations 2 and 3, to solve for the position ($\widehat{l}$), velocity ($\widehat{v}$), and acceleration ($\widehat{a}$) of each bubble nose in its respective bifurcation channel

$$\begin{aligned}
& \sum_{i=1}^{m-1} 3.58 \frac{D_p}{\widehat{d}_{ref}} (3Ca) \frac{2}{3} \left[\widehat{v}_2^{\frac{2}{3}} - \frac{\widehat{d}_{ref}}{\widehat{d}_i} \widehat{v}_{11}^{\frac{2}{3}} \right] + \frac{Ca\alpha^2}{4} [\widehat{v}_{ref}^2 - \widehat{v}_i^2] \\
& - \frac{Bo}{2} \sin(\theta) \sin(39) [2\widehat{l}_i - \widehat{l}_{ref}] + \frac{Ca\alpha^2}{2} \left[\widehat{l}_{ref} \widehat{a}_{ref} - \widehat{l}_i \widehat{a}_i \right] + L \frac{\widehat{d}_{ref}^2}{\widehat{d}_i^2} [\widehat{a}_{ref}] \\
& + Y \left[\frac{\widehat{d}_{ref}^2}{\widehat{d}_T^2} \widehat{a}_{ref} - \frac{\widehat{d}_b^2}{\widehat{d}_T^2} \widehat{a}_i \right] - 16Ca \left[\frac{1}{\widehat{d}_{ref}^2} \widehat{l}_{ref} \widehat{v}_{ref} - \frac{1}{\widehat{d}_i^2} \widehat{l}_i \widehat{v}_i \right] + L \frac{\widehat{d}_{ref}^2}{2\widehat{d}_b^4} [\widehat{v}_{ref}] \\
& + \widehat{Y} \left[\frac{\widehat{d}_{ref}^2}{2\widehat{d}_T^4} \widehat{v}_{ref} - \frac{\widehat{d}_i^2}{\widehat{d}_T^4} \widehat{v}_i \right] = 0
\end{aligned} \tag{11}$$

while the non-dimensional conservation of mass equation yields

$$\widehat{v}_{ref} + \sum_{i=1}^{m-1} \frac{\widehat{d}_i^2}{\widehat{d}_{ref}^2} \widehat{v}_i = \frac{4}{\pi \widehat{d}_{ref}^2} \widehat{Q} \tag{12}$$

The equations can be solved knowing the input parameters for the flow rate. Flow rates used in the theoretical model were taken directly from experimental data. A curve fit to the experimental flow data was obtained using piecewise cubic interpolation. Figure 5 shows the experimental data for one of the trials (open circles) along with the fitted function ($Q(t)$) used in the theoretical model. Additionally, a Fourier analysis was performed to determine the angular frequency (ω) of each flow waveform. The inverse of this value serves as the time scale in the theoretical model.

With knowledge of the bifurcation geometry and bubble nose position n at each time step, stop conditions are imposed in the code to pause when a bubble nose reaches a bifurcation, at which point the system of equations is modified to represent the updated channels occupied by a bubble nose. A final stop condition is also imposed based on the experimental time required for the bubble to split in two, at which point the assumption of uniform pressure within the bubble no longer holds. An IDA solver (Hindmarsh et al. 2005) utilizing variable-step-size backward differentiation formulas was used to compute the solution to the system of equations in Comsol (Boston, MA).

3 Results

Splitting ratios (V_b/V_t) at the first bifurcation for each roll angle and for experimental constant flow, experimental pulsatile flow, and theoretical pulsatile flow are shown in Figure 6 for frequencies of 80 BPM (a), 105 BPM (b), and 130 BPM (c). Predictions were obtained from the theoretical model for conditions corresponding to the experimental set-up over a broad range of vessel diameters ($0.025 - 0.0001$ m), flow rates ($8 \cdot 10^{-5} \text{ m}^3/\text{s} - 3 \cdot 10^{-13} \text{ m}^3/\text{s}$), and pulsilities ($1 - 0$). The data show that there is no significant difference between the splitting ratios during pulsatile flow rates when compared to constant flow. For all cases, the maximum deviation in splitting ratio from the constant flow case was seen to be a modest +

–3%. Greater roll angle values caused a higher fraction of bubble volume to enter the upper half of the bifurcation (V_1) as a result of increasing buoyancy effects independent of whether the flow was pulsatile or constant.

Figure 7 shows a plot of the steady and pulsatile flow experimental V_1 splitting ratios (V_1/V_0) vs. roll angle. This is an indication of the volume fraction of the bubble that lodged in the lower daughter tube of the first bifurcation. For pulsatile and constant flow, bubbles did not become lodged in bifurcation 1 until reaching a roll angle of 45 degrees. Also at 45 degrees, pulsatile flow rates of 80 BPM and 130 BPM showed greater bubble volume lodged in daughter tube 1 (L_1) when compared to 105 BPM and constant flow at that roll angle. This is an example of how pulsatility can cause bubbles to lodge earlier (further upstream) within a bifurcation compared to constant flow.

In Figure 8, steady and pulsatile flow experimental V_3 splitting ratios (V_3/V_0) are plotted vs. roll angle. At greater roll angles, less bubble volume (V_3) is lodged in daughter tube three (L_3) due to increasing buoyancy effects. Pulsatile flow consistently shows a greater bubble volume to lodge in L_3 when compared to constant flow. Differences in pulsatile flow frequencies did not result in any significant differences in V_3 values except for constant flow at a roll angle of 0 degrees and 105 BPM at a roll angle of 45 degrees.

Figure 9 depicts steady and pulsatile flow experimental V_4 splitting ratios (V_4/V_0) vs. roll angle. This data shows an increased amount of instability when comparing pulsatile flow rate values to constant flow rate values. At 15 and 45 degrees, pulsatile flows of 105 BPM and 130 BPM showed a decreased bubble volume to be lodged in L_4 compared to constant flow. At a frequency of 80 BPM, greater bubble volumes were observed lodged in L_4 when compared to other pulsatile frequencies at 15, 30, and 45 degrees.

In addition to the theoretical splitting ratio results shown in Figure 6, theoretical results related to the dynamics of bubble splitting for $\omega = 105$ BPM and $\theta = 45^\circ$ are shown in Figures 10–11. In each of the graphs, t_1 is the time at which the bubble bifurcates into the L_3 and L_4 channels, t_2 is the time at which the bubble bifurcates into the L_5 and L_6 channels, and t_3 is the time at which the bubble splits into two bubbles. Figure 10 shows the position, l , of each of the bubble noses in each daughter with respect to time. The position, l , is measured along the tube centerline relative to the point where L_0 bifurcates into L_1 and L_2 , as shown in Figure 4. As the bubble enters the first bifurcation (tube segments L_1 and L_2), the bubble starts to split, and the length in segment L_1 is denoted by l_1 and the length in segment L_2 by l_2 . The bubble travels further into the bifurcating network and when the bubble nose in tube segment 2 reaches the second bifurcation (junction of tube segments L_2 , L_5 , and L_6), it starts to split. The position of the bubble nose in tube segment L_6 is denoted by l_{11} and the position of the bubble nose in tube segment L_5 is denoted by l_{12} . Although the bubble is in the process of splitting as the nose divides and enters the daughter branches of subsequent bifurcations, the bubble remains a single bubble until the rear meniscus of the bubble reaches the first bifurcation and splits. The time at which this occurs is denoted by t_3 in Figures 10 and 11. The position of the bubble noses in channels L_5 and L_6 are seen to begin to level off near the end of the simulation time.

Figure 11 shows the respective velocity of each bubble nose with respect to time. The subscripts on the velocities, correspond to the same subscripts on bubble position in Figure 10, e.g. the velocity of the bubble nose whose position is denoted by l_{21} is denoted by v_{21} . As the bubble bifurcates further into the daughter channels, channels L_5 and L_6 are both seen to experience negative velocities, indicating movement of the bubble nose back towards the intersection of the L_0 , L_1 , and L_2 channels.

A plot of splitting ratio vs. bubble length is shown for several values of roll angle for a frequency of 105 BPM in Figure 12. The dimensionless bubble length that is shown is the dimensional length of the initial bubble in the parent tube, prior to entering the first bifurcation, scaled by parent tube diameter. The splitting ratio is lower for higher roll angles, and is lower for longer bubbles (provided the roll angle is non-zero). The curves are generally non-linear with a series of steeper segments between relatively flatter segments.

4 Discussion

The theoretical model provides a simplified form of the experimental model, but its predicted outcomes are accurate when the two are compared. Both the theoretical and experimental results demonstrate that splitting ratio has a strong dependence on roll angle due to buoyancy effects (Figure 6). As roll angle increases, the splitting ratio decreases, showing that more bubble volume goes into the top branches of the bifurcation. The theoretical and experimental models are in close agreement over the range of experimental values tested. Flow pulsatility has a relatively small effect on the splitting ratio. Although unsteady flow effects are often neglected in the smallest vessels of the microcirculation, the $O(1)$ Womersley number values in the larger vessels of the microcirculation and in the experiments here suggest that the effects of unsteady flow would contribute to the bubble splitting behavior. However, the small capillary number in the current experiments indicates that surface tension dominates the viscous effects. Apparently the strength of surface tension is also sufficient to overwhelm the effects of flow pulsatility on bubble splitting.

The effect of pulsatile flow is evident in the dependence of splitting ratio on bubble length. The “steps” in splitting ratio seen in Figure 12 are due to the pulsatility of the flow. As the bubble length is increased, the time during the pulsatile cycle at which the rear meniscus reaches the bifurcation, resulting in the actual splitting of the bubble, changes. This behavior corresponds to the oscillations in bubble nose position and velocity that are evident in Figures 10 and 11. The bubble nose position changes non-linearly with time, as seen in Figure 10, and the bubble length affects at which time the bubble splits. We have previously observed the general trend that increasing bubble length decreases the splitting ratio for steady flow in a single bifurcation with at a roll angle of 15° , and the current findings now show that the dependence is non-linear when the flow is pulsatile.

Observations of bubble lodging behavior at the bifurcations during the experimental trials were also of interest to clinical applications. Bubble lodging is an important phenomenon for air embolism and gas embolotherapy. The general trend of the experimental and theoretical models showed that pulsatility may not be an important determinant of splitting ratio. However, at 105 BPM and 130 BPM at a roll angle of 45 degrees, there was a significant

difference in splitting compared to constant flow. Less bubble volume was lodged in L_4 during these pulsatile trials. This suggests that there may be specific situations when frequency does have an effect on splitting and bubble lodging. To understand this behavior, consider that flow rate ranges from 0.06-0.30 ml/min during pulsatile flow. At lower flow velocities, bubbles have more of an opportunity to lodge due to (1) an increased likelihood of contact with the wall, and (2) once contact occurs a higher surface tension forces opposing the pressure force moving the bubble. Initially the long bubbles are separated from the tube wall by a thin layer of liquid. As the bubble slows down, the film of water between the bubble and channel wall rapidly becomes thinner. This film thickness is known to scale $\sim Ca^{2/3}$ for $Ca \ll 1$ (Bretherton 1961). The capillary number decreases quickly as velocity decreases, allowing the air inside the bubble to come in direct contact with the wall of the channel. This occurs at a higher cycle-averaged Ca than the Ca for contact in the steady flow case. Subsequently, the bubble lodges before it would if the flow was constant.

Retrograde flow of bubbles has been observed in constant flow experiments (Calderon, Fowlkes et al. 2005). This reversal comes as a result of flow competing with gravity. At higher roll angles, gravity and buoyancy have more of an effect. Retrograde bubble flow was not seen in the experiments in the present study, suggesting that pulsatility and the accompanying bubble lodging may be a significant factors preventing retrograde flow. A small amount of retrograde flow was predicted by the theoretical model for roll angles of 30, 45 and 60 degrees, as indicated by the negative velocities between times of 2 and 3 seconds in Figure 11. However, the reversal was brief, lasting 1/10 of a pulse cycle. It is possible that this reversal did occur experimentally, but went unseen because of the small time interval. It is also important to note that once bubbles became lodged, they tended remain lodged, shunting to the upper channels. The theoretical model did not specifically consider lodging. The observed lodging behavior suggests that gas embolotherapy and air embolism have the ability to occlude blood flow in vasculature with pulsatile flow, which is consistent with in vivo demonstrations of flow occlusion by microbubbles. While bubble lodging is of interest for the gas embolotherapy application, it is less likely to occur within the flow parameters typically selected for microfluidic applications where bubble lodging is typically undesired.

In this study, bubbles were long enough to span the parent, first, and second-generation daughter tubes, as is expected to be the case in gas embolotherapy and air embolism. This results in an increased surface tension force opposing the bubble motion compared to the scenario in which the bubble only extends through a single bifurcation. The 22% decrease in diameter of each successive daughter tube increased the effects of surface tension and pressure difference across the bubble. The small radius of curvature of the front meniscus made the bubble more likely to lodge and remain lodged instead of reversing motion as observed in the previous single bifurcation experiments (Calderon, Heo et al. 2006).

The ability to predict bubble splitting provides information regarding a scenario that has typically been avoided in bubble logic applications, which have focused on the binary outcome of the bubble going entirely down a single branch of a bifurcation. This information can be either used to design channels that will only have the binary bifurcation transport or to use the bubble splitting behavior in the logic algorithm. Additionally, the unsteady flows considered here can encode additional information into the bubble dynamics, compared to

steady flow, because the resulting bubble conformation depends on the unsteadiness of the flow. The theoretical model can then be used to decode this information. Recent advances in valves and pumping in microfluidic devices (Eddington and Beebe 2004; Gu, Zhu et al. 2004; Studer, Hang et al. 2004; Squires and Quake 2005; Melin and Quake 2007; Brett, Zhao et al. 2011; Prettyman and Eddington 2011), could allow generation of complicated unsteady flows within bubble logic devices.

The theoretical model presented here has the advantage of low computational cost compared to computational approaches to modeling single or two-phase flow in microfluidics channels (Powell, Savage et al. 2002; Pozrikidis 2003; Ye and Bull 2004; Bull, Hunt et al. 2005; Pozrikidis 2005; Ye and Bull 2006). More expensive two- and three-dimensional models (Ye and Bull 2004; Ye and Bull 2006; Eshpuniyani, Fowlkes et al. 2008; Calderon, Eshpuniyani et al. 2010) do provide additional information about velocity and stress fields near the bubble and the bifurcation, but the bubble length and splitting behavior is well approximated by the model presented here. Additionally the model is easily adaptable to consider various geometries and additional bifurcations.

The theoretical model is powerful because it can simulate situations that can be impractical to test on the bench top and can be applied to large bifurcating networks, potentially including patient specific models, with relatively low computational expense. Although the theoretical model results agree closely with the experimental results, there are some limitations inherent in a one-dimensional model. The flow details and corresponding viscous losses within the actual bifurcation are neglected in the one-dimensional model, although the viscous losses within the straight vessel segments are considered. Although the channels used in this study are hundreds of μm in diameter, the relevant dimensionless parameters (Reynolds, capillary, Womersley, and Bond numbers) are in ranges that are typical of microfluidic flows (Whitesides, Ostuni et al. 2001; Huh, Tung et al. 2002; Calderon, Heo et al. 2006; Nieuwstadt, Seda et al. 2011), including those in smaller channels. While the model assumes laminar flow, it does not assume Stokes flow or place restrictions on the Womersley number. The assumption of small capillary number appears in the stress jump at the bubble interface, but a more general relationship could be used to extend the model to higher capillary numbers. Future work related to gas embolotherapy should also incorporate the bubble lodging phenomena into the theoretical model by including the situation in which slow bubble speed leads to rupture of the liquid film separating the bubble from the wall and interaction of adsorbed species on the bubble surface with the endothelium. It should be noted that the constant pressure outlet boundary conditions for the theoretical model, while applicable for the small vessels and microfluidics circuits considered here, are not applicable for larger vessels, such as large arteries. For larger vessels and larger flow rates, time dependent pressure boundary conditions exist due to the compliance of the vasculature that must be accounted for.

5 Conclusions

In conclusion, roll angle is an important contributor to bubble splitting ratio at each bifurcation within the bifurcating network. The one-dimensional theoretical model provided close agreement with the experiments and represents a platform that may be extended to

consider two-phase flow in a range of biomedical microdevices and to consider more complicated and realistic vascular networks. The ability to accurately predict the bubble dynamics in unsteady flow within a bifurcating network suggests the potential for bubbles in microfluidics devices to encode information in both steady and unsteady aspects of their dynamics. The experimental and theoretical models of bubble transport in large arterioles both demonstrate that increasing buoyancy effects through higher roll angle cause more bubble volume to be shunted into the upper bifurcation. When compared to corresponding constant flow, pulsatile flow was shown to produce insignificant changes to the overall splitting ratio of the bubble despite the $O(1)$ Womersley numbers, suggesting that bubble splitting through the vasculature could be modeled adequately with a more modest constant flow model. However, bubble lodging was affected by the flow pulsatility, and the effects of pulsatile flow were evident in the dependence of splitting ratio of bubble length. The ability of bubbles to remain lodged after reaching a steady state in the bifurcations is promising for the effectiveness of gas embolotherapy to occlude blood flow to tumors, and indicates the importance of understanding where lodging will occur in air embolism.

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Figure 1. Schematic (top) and photograph (bottom) of the experimental setup. Pulsatile flow from the syringe is generated by the linear actuator. The exit of the bifurcating channel network is connected to a constant pressure reservoir.

Figure 2.

Bifurcation schematic (left) and photograph (right). The parent tube of the bifurcating channel is labeled L_0 . The first generation daughter tubes are denoted by L_1 and L_2 . The second generation daughter tubes are denoted by L_3 - L_6 . The angle between daughter tubes at each bifurcation is 78° . L_0 has a length of 5.0 cm and a diameter of 1mm. L_1 and L_2 are 0.5cm long with a diameter of $780\ \mu\text{m}$. The second generation daughter tubes have a length of 5 cm and a diameter of $608\ \mu\text{m}$. The bifurcating network is planar. The roll angle is the angle the plane of the bifurcation makes with the horizontal, where the parent tube is maintained in a horizontal configuration.

Figure 3. Capillary numbers used at each roll angle. The pulsatile test measurements were taken under a similar average capillary number value as the constant flow tests ($5.71 \cdot 10^{-5}$ and $5.47 \cdot 10^{-5}$ respectively).

Figure 4.

Schematic of bubble splitting process. The bubble is shown in blue. (A) At time $t = 0$, the bubble nose reaches the first bifurcation and the bubble begins to split. (B) At time t_1 , the bubble in the upper first daughter tube segment L_1 reaches the second bifurcation. (C) At time t_2 , the bubble in first generation daughter tube segment L_2 reaches the second bifurcation. (D) At time t_3 the rear meniscus of the bubble reaches the first bifurcation and splits, yielding two separate bubbles that extend through the daughter tubes, one in the upper part and one in the lower part of the network.

Figure 5. Comparison of experimental flow rate data collected and the curve fitted flow rate function used in the theoretical model.

Figure 6.

Splitting ratio vs. roll angle. Note that splitting ratio is the ratio of the volume of the air bubble in the bottom half of the bifurcation (V_b) / volume of the air bubble in the top half of the bifurcation (V_t) versus roll angle. This is an indicator of the evenness of splitting at the first bifurcation. Each pulsatile frequency was compared against a constant flow rate with an equivalent average capillary number. Measures of bubble volume were taken after all bubble splitting had occurred and the bubbles had completely passed the second bifurcation.

Figure 7.

The ratio of the volume of air bubble lodged in the lowest (relative to floor) of the first-generation daughter tubes (V_1) / initial air bubble volume before splitting (V_0) vs. roll angle. A value of zero represents no bubble lodging in V_1 . Measures of bubble volume were taken after the bubble had either traveled beyond the second bifurcations or had become permanently lodged in the first-generation daughter tube. Each pulsatile frequency was compared against a constant flow rate with an equivalent average capillary number (except at 60 degrees).

Figure 8.

The ratio of the volume of air bubble lodged in the lowest (relative to floor) of the second-generation daughter tubes (V_3) / initial air bubble volume before splitting (V_0) vs. roll angle. Measures of bubble volume were taken after the bubble had either traveled beyond the second bifurcations or had become permanently lodged in the second-generation daughter tube. Each pulsatile frequency was compared against a constant flow rate with an equivalent average capillary number (except at 60 degrees).

Figure 9.

The ratio of the volume of air bubble lodged in the second lowest (relative to floor) of the second-generation daughter tubes (V_4) / initial air bubble volume before splitting (V_0). Measures of bubble volume were taken after the bubble had either traveled beyond the second bifurcations or had become permanently lodged in the second-generation daughter tube. Each pulsatile frequency was compared against a constant flow rate with an equivalent average capillary number (except at 60 degrees).

Figure 10.

Theoretical model results for bubble nose position vs. t , for $\omega = 105$ BPM and $\theta = 45^\circ$. The t_1 and t_2 values are times at which a bubble nose splits into two new daughter tubes. The t_3 value is the time at which the rear of the bubble splits into the L_1 and L_2 daughter tubes. The y-axis zero point is at the intersection of the L_0 , L_1 , and L_2 channels.

Figure 11.

Theoretical model results for bubble nose velocity at $\omega = 105$ BPM and $\theta = 45^\circ$. The t_1 and t_2 values are times at which a bubble nose splits into two new daughter tubes. The t_3 value is the time at which the rear of the bubble splits into the L_1 and L_2 daughter tubes. Velocities less than zero represent a reversal of direction of the bubble nose in the direction of the intersection of the L_0 , L_1 , and L_2 channels.

Figure 12.
Theoretical prediction of splitting ratio vs. bubble length for several values of roll angle.