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Predicting and Controlling Bubble Clogging in Bioreactor for Bone Tissue Engineering

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A common problem in small scale bioreactors like those used for tissue engineering is the clogging of microchannels by gas bubbles. In case of clogging, the flow distribution inside the bioreactor changes and can not guarantee the adequate transport of nutrients and efficient removal of catabolites. Bubbles may (i) enter with the flow during the priming phase, when the reactor is first filled with the culturing medium, or may (ii) form locally during operations, because of gas desorption from scaffold, intense cellular metabolic activity or degassing .
In this work, we develop and use an analytical model to identify the conditions (bioreactor region, flow rate, limiting bubble size) for which bubbles may adhere stably to the scaffold, potentially leading to bubble clogging. Based on the flow and shear stress distribution calculated by numerical simulation, the model indicates that clogging may occur in the region around the scaffold and along scaffold channels. Operative conditions under which clogging can be avoided are identified.

1. Configuration under Study

A sketch of the bio-reactor studied in this work is shown in Figure 1(a). The flow enters from the bottom side through a cylindrical pipe (feeding pipe, 4 mm diameter) and then is feeded to the the square bioreactor main chamber through four distributing pipes (1 mm diameter) and a conical join (distributing cone). The scaffold is held fixed inside the main chamber by a central cylindrical hollow pipe which fits onto a cylindrical support. The scaffold is made of square fibers arranged in a 5 x 5 x 5 structure with an inter fiber distance which is 1.25 times the fiber dimension (see Figure 1 (b)). A free volume is available around the scaffold (1 mm thick). The flow rate is 1 cm^3/min which corresponds to an inlet velocity equal to v_{inlet} = 1.326 mm/s . The average velocity increases up to v_{distr} = 5.3 mm/s inside the distributing pipes and then decreases to $v_{scaffold}$ = 0.24 mm/s inside the main volume of the bio-reactor and to v_{around} = 0.15 mm/s around the scaffold.
In this geometry, the local accumulation of bubbles may lead to channel clogging in three critical regions: (1) the scaffold channels, (2) the gap between scaffold and wall of bioreactor and (3) the inlet of scaffold channels.

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The interaction of a single bubble with the fluid and with the wall controls bubble behavior: if the 'affinity' with the wall is strong enough, bubbles initially suspended in the fluid may move toward the wall and attach, while bubbles initially attached to the wall may stay attached for long times, even in the presence of shear flow. If the interaction with the fluid is strong enough, bubbles initially attached to the wall can detach and move into the fluid bulk, while bubbles suspended in the fluid can be dragged away with the flow.

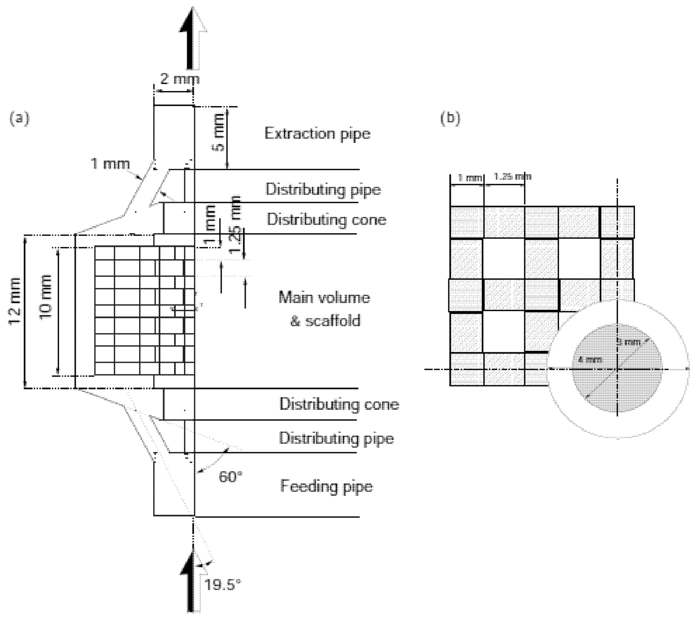

Figure 1: Sketch of (a) bioreactor geometry and (b) scaffold arrangement.

Predicting the behavior of bubbles in microchannels is crucial for the safe design of the bioreactor which should work properly even in the presence of gas bubbles.
The main parameters controlling bubble behavior are (i) bubble dimension, (ii) distance from the wall and (iii) affinity between the bubble and the solid surface. Based on these parameters, mathematical relationship describing the different forces arising in bubble/fluid interaction and bubble/wall interaction can be derived and used to predict bubble behavior for different geometries and flow conditions. The final aim of this work is to identify geometrical/operating conditions for which bubbles can be carried away with the flow, to control/minimize the risk of clogging of the bioreactor.

2. Methodology

We will consider the case of bubbles of different size initially attached to the wall and examine the forces acting on them in three "reference" rectangular channel configurations; if H (height) and W (width) are channel dimensions, we may have (1) small size bubble (i.e. bubble smaller than any geometrical dimension of channel); (2)

medium size bubble (i.e.bubble larger than one channel dimension, H); (3) large size bubble (i.e. bubble larger than both channel dimensions, generating a discontinuity between the fluid before and after it). Depending on the specific bubble/channel configurations, different forces are important and should be evaluated to predict bubble behavior: retentive and adhesive forces may keep the bubble fixed in a specific region of the bioreactor, while the external shear and buoyancy forces may promote bubble detachment.

2.1 Forces acting on bubbles

The forces acting on a bubble adhering to a surface are sketched in Figure 2.

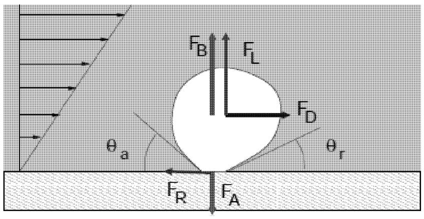

Figure 2: Sketch of the forces acting on a bubble: Net Buoyancy force (F_B), Lift force (F_L), Drag force (F_D), Adhesion force (F_A) and Retentive force (F_R).

The body force, F_B, is the net effect of gravity and buoyancy:

$$F_B = (\rho_l - \rho_g) V_B g \tag{1}$$

where ρ_l and ρ_g are the fluid and bubble density, V_B is the bubble volume and g is the gravity vector; the retentive force, F_R, i.e. the along the wall component of the surface force, is given by (Extrand and Gent, 1990):

$$F_R = \frac{4}{\pi} R_c \sigma_{gl} (\cos\theta_r - \cos\theta_a) \tag{2}$$

where R_c is the contact radius and θ_a and θ_r are the contact angles for the liquid fronts advancing and receding For a bubble in still flow, $\theta_a = \theta_r = \theta_e$, where θ_e is the static contact angle. When a bubble is exposed to an external shear flow, the bubble deforms to find a new static equilibrium between surface forces and shear. The variation of θ_a and θ_r as a function of shear and gas/liquid/solid properties has been modeled by Cox (1986) based on three dimensionless parameters (Basu et al., 1996): (1) the capillary number, $Ca = \mu_l (U_l - U_b)/\sigma_{gl}$, i.e the ratio between the shear force and the surface force, where μ_l is the viscosity of the shearing fluid U_l and U_b are the velocity of the shearing fluid and the droplet and σ_{gl} is the surface tension between the droplet and the shearing fluid; (2) the viscosity ratio, $\lambda = \mu_g/\mu_l$; (3) the scale ratio, $\varepsilon = s/r$ where s is a microscopic slip length and r is a macroscopic length scale.

Advancing and receding contact angles can be calculated solving two integral Equations (see Basu et al., 1996 and Blackmore et al., 2001 for details) if $Ca \ll 1$.

The adhesive force, F_A, i.e. the normal to the wall component of the surface force, is given by (Basu et al., 1996):

$$F_A = \pi R_c \sigma_{gl} \left[\sin\theta_a - \left(\frac{\cos\theta_r - \cos\theta_a}{\theta_r - \theta_a} \right) \right] \tag{3}$$

The lift force, F_L, due to the difference of velocity of the shearing fluid between the top and bottom of the bubble (Saffman, 1965), is given by:

$$F_L = 6.4\mu_l (U_l - U_b) \left(\frac{d_b}{2} \right)^2 \gamma^{1/2} \left(\frac{\mu_l}{\rho_l} \right)^{-1/2} \tag{4}$$

where $\gamma = \tau_w/\mu_l$ is the shear rate at the solid wall and d_b is the "equivalent" bubble diameter; the drag force, F_D, due to the difference in velocity between the bubble and the fluid, is given by:

$$F_D = 1.7 \cdot 3\pi\mu_l d_b (U_f - U_b) \tag{5}$$

To avoid bubble accumulation, we should achieve two target states for the bubble: (1) bubble sliding along the surface ($F_D \geq F_R$); and (2) bubble detaching from the wall ($F_L + F_B \geq F_A$). Equations (1)-(5) can be used to identify: (1) the minimum value of fluid velocity/shear at the wall necessary to make the bubble slide or the minimum size of bubbles sliding along the wall for a given flow condition; (2) the minimum size of bubbles for which detachment may be promoted by buoyancy effect.

When the bubble is large enough to touch the lower and the upper wall of the channel, the only way to avoid local accumulation of bubbles is to have the bubble sliding along the channel ($F_D \geq F_R$).

3. Results

Bubbles of air in water across channels made of PMMA have been considered. Flow conditions are summarized by the following dimensionless parameters: Bo∼0.1; Ca∼10^{-6}; Re∼10. Bo is Bond number, i.e. the ratio between net gravitational force and surface tension force and Re is Reynolds number, i.e. the ratio between inertial and viscous forces. In our test conditions, (1) the shape of the bubble can be considered spherical, (2) the deformation imposed by shear is such that surface tension is controlling, and the shape of the bubble can be approximated by spherical caps, and (3) the flow is laminar.

Figure 3 shows the variation in bubble shape. The geometrical deformation of the bubble is independent of the flow rate. For bubble diameter less than 1.25 mm, the variation of bubble height and contact radius are linear with bubble size. When the bubble becomes large enough to touch the second wall, a sudden reduction of the contact radius is observed first, followed by a (slightly less than) linear increase of this parameter with bubble diameter. At this stage, the height of the bubble is already fixed by the height of the channel.

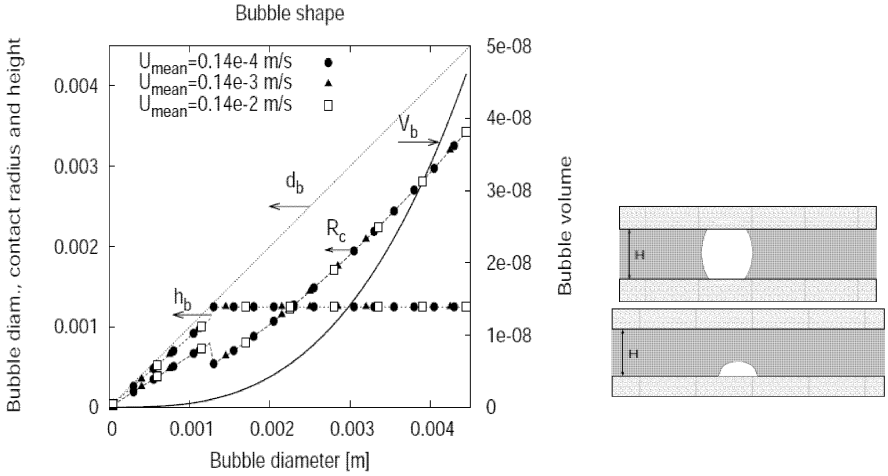

Figure 3: Variation of bubble shape as a function of bubble dimension: transition from one surface to two surface contact condition; bubble height, h_b, and contact radius, R_c.

Figure 4 shows the change in drag force and retentive force acting on the bubble as a function of bubble size. For small size bubbles ($d_b < 1.25$ mm) the drag force is slightly larger than the retentive force and the bubble, attached to one surface only, is able to slide along the wall. When the bubble size exceeds the channel height, the retentive force almost doubles because of the contact with the second wall. The bubble remains attached to the wall if the size is less than a critical value. Above this value, the drag becomes again large enough to overcome the retentive force, and the bubble can slide along the channel again. The larger the force, the larger will be the sliding velocity relative to the fluid velocity.

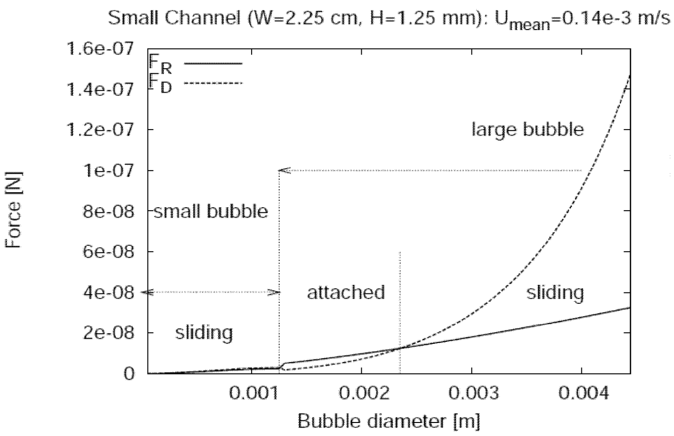

Figure 3: Variation of horizontal force acting on bubbles as a function of bubble size: drag, F_D, and retentive force, F_R.

4. Conclusions

The fluid dynamic behavior of bubbles inside the bioreactor/scaffold system is controlled by a balance among surface forces (surface tension/adhesion to wall), body forces (buoyancy and gravity) and forces generated by the interaction between the bubble and the fluid (drag, lift). For a given channel geometry, the value of these forces depends on surface properties, bubble size and fluid flow. The net force normal to the wall and parallel to the wall determines if a bubble initially attached to the solid surface will remain attached, will be able to slide along the surface or may be able to detach from the surface.

Calculations have been made to predict the behavior of bubbles of different size considering a simplified geometry (plane channel) which may be considered representative of specific regions inside the bio-reactor.

Results indicate that, for the reference flow conditions calculated for the scaffold (U_{mean} = 0.14 mm/s) small size bubbles (d_b < 1 mm) attached to any solid wall do not detach from the wall but may slide along the surface (fluid drag is larger than adhesion forces); medium size bubbles (d_b > 1 mm) which are large enough to touch two walls of the channel remain attached to the wall if d_b < 2.3 mm ; they are able to slide along the channel if d_b >2.3 mm.

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