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# Computational and experimental investigations of the mechanisms used by coaxial fluids to fabricate hollow hydrogel fibers

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ABSTRACT

Biological three-dimensional printing is a promising field of research, and offers potential for overcoming the main technological barriers to the fabrication of three-dimensional vascularized tissues and organs. One of the major methods to fabricate vascular-like networks that can support perfusion of nutrients and oxygen is the printing of hollow hydrogel fibers. In the present work, we investigate the effects of operating conditions on the dimensions of hollow hydrogel fibers and the interaction mechanism of coaxial fluids. The continuity equation and momentum equation integrated with the reaction–diffusion model established by Kim et al. [1] are used to establish a mathematical model of the fabrication of hollow fibers from coaxial fluids. The volume of fluid model by the computational fluid dynamics software package FLUENT 6.3.26 is applied to quantitatively simulate the flow pattern details. A stable liquid/liquid jetting co-laminar flow in the coaxial nozzle is obtained. In order to verify the validity of the simulation model, a coaxial nozzle is used to fabricate hollow hydrogel fibers under various flow rates. The results from simulations and experiments are consistent with each other.


## 1. Introduction

Significant advances have been made in the field of tissue engineering in the past decade, and investigators in this field have aimed to produce biological substitutes for tissue and organ regeneration [2]. But the lack of vascularization remains the main technological barrier in fabricating tissue-engineered constructs. Vascularization is needed to supply oxygen and nutrients to living tissues and organs as well as to remove wastes from them, and the vascularized network should display strong perfusion and significant mechanical strength and elasticity [3]. The importance of producing functional vasculatures for in vivo implants has also been demonstrated for various tissues and organs such as bone, skin, muscles, nerve pathways, and bladders [4–10]. Therefore, realizing vascularization has been a critical process in biofabrication.

Various methods have been attempted to enhance the fabrication of vascular networks within constructs engineered for tissue and organ regeneration [11–18]. Much recent research has been aimed at using biomaterials combined with microfabrication to realize the pre-vascularization of tissue-engineered constructs. But many hydrogel-based scaffolds lack microchannels and cell-sized pores, and such microchannels and micropores are highly desirable since they supply the cells with oxygen and nutrients and remove waste products [19]. Tubular constructs with microchannels, however, can effectively connect to the host vasculature in tissues and organs [20,21]. Thus, cell-laden fibers containing microchannels and micropores have become promising applications in the field of tissue engineering.

The application of coaxial microfluidic channels to the production of hollow hydrogel fibers offers a method to realize a three-dimensional vascularized construction. Zhang et al. [3,22] investigated the manufacturability of printable coaxial microfluidic channels, and a pressure-assisted solid freeform fabrication platform combining with such channels was developed with a coaxial needle dispenser unit, and was used to print hollow hydrogel fibers. Onoe et al. [23] fabricated meter-long core–shell Ca–alginate microfibers encapsulating extracellular matrices (ECMs) proteins and differentiated cells by using a microfluidic device with double-coaxial laminar flow. Oh et al. [24] employed a microfluidic coaxial flow-focusing system to generate cell adhesive chitosan microtubes of controlled sizes. Overall, producing hollow hydrogel fibers by using coaxial microfluidics has become an ideal method to achieve vascularization [25]. Microtube dimensions can be influenced by various factors, such as the flow rates and viscosities of two solutions that are used in the microfluidics

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**Nomenclature**

$C_0$ Concentration of Ca ions at the inner surface of the hollow fibers
$D_e$ Effective coefficient of Ca ion in the gelled layer
$N$ Transferred moles of Ca ions
$p$ Composition of sodium alginate in the solution
$q$ Moles of Ca ions required for complete gelation based on the weight of sodium alginate
$r_c$ Radial distance from the inner surface of the gelled layer to the center of a bead
$R_s$ Radius of a spherical bead at time (s)
$R_0$ Initial radius of a spherical bead
t Gelling time
$W$ Weight of sodium alginate

device. While hollow fibers have been widely studied experimentally, a theory or mechanism that explains how they function remains elusive.

Many researchers have been focused on the flow pattern in microfluidic multiphase flows, with dripping and jetting being the two main flow patterns. Kashid et al. [26] used the method proposed by Hickox et al. [27] and the Orr–Sommerfeld equation to study core-annular flows. Ghosh et al. [28] studied the core-annular downflow of water and highly viscous oil using computational fluid dynamics (CFD), in particular using the Euler–Euler based volume of fluid (VOF) technique for two-phase modeling. Gañán-Calvo et al. [29] studied the focusing of the flow of liquids and gases in electrosprays. The momentum and Bernoulli equations were used to establish a theoretical model of jet diameter and droplet size. However, these researchers mainly focused on analyzing the fundamental fluid dynamics, rather than the reaction–diffusion process.

In the current work, a coaxial fluid dynamic model combined with the reaction–diffusion model of Kim was established to numerically study the effects of operating conditions on the coaxial liquid annular flow occurring in the process of fabricating hollow hydrogel fibers. In addition, CFD simulations were performed using the VOF model in FLUENT 6.3.26 to simulate the flow details numerically. Different flow patterns could be obtained by changing the parameters in the CFD software. In order to validate the numerical model, the coaxial nozzle was used to produce hollow hydrogel fibers under different flow rates. Finally, the experimental, numerical and theoretical results were compared.

## 2. Model development

Crosslinked alginate is composed of blocks of β-D-mannuronic acid residues (M), blocks of α-L-guluronic acid residues (G), and blocks with alternating M and G residues [30]. Hydrogel was formed by the binding of divalent calcium ions in a $CaCl_2$ solution with the carboxylic groups on the G-blocks when the $CaCl_2$ solution was used as the crosslinker. Specifically, when the $CaCl_2$ and alginate solutions contacted each other, the calcium ions diffused into the alginate volume and the Ca–alginate hydrogel formed. Since the size of the metallic cation is smaller than that of the polymer molecules, it is mainly the cation that diffuses between the alginate chains [31]. Ionic crosslinking, however, inhibits convection between the two solutions, making it hard for the $CaCl_2$ to mix with the crosslinked alginate, and the concentration of alginate cannot be changed.

In fact, the crosslinking mechanism between the $CaCl_2$ solution and the alginate contains the interaction of coaxial fluids and the diffusion of the crosslinker. It is not only the interaction of coaxial fluids that can affect the dimensions of the hollow fibers, but the diffusion process can also have a significant effect on the gelation of a polymer. Many researchers have found that hydrogels shrink during the gelation process [1,32,33]. To explain this shrinkage, first note that the gel in our work is formed quickly at the boundary between these two liquid layers. The interior surface of the hydrogel has been observed to act like a belt that progressively tightens the forming gel tube and resists the diffusion of calcium within this tube. But over a period of time, calcium ions diffuse into the shell portion and form a complete Ca–alginate hydrogel. For hollow fibers, due to the tightening of the inner surface and the diffusion of calcium ions, the boundary of the Ca–alginate gel moves toward the shell part from the surface, while calcium ions penetrate the porous gelled layer. Thus, shrinkage of the shell occurs.

Based on this coaxial fluid flow and diffusion process, a mathematical model was established as follows. As shown in Fig. 1, a cylindrical coordinate system was established with the flow direction as the $x$ axis and the radial direction of the tube as the $r$ axis. First, a model based on the two immiscible fluids is given. Under these conditions, the equations for incompressible Newtonian fluids include the continuity Eq. (1) and momentum Eq. (2) [34]:

$$\nabla \times V = 0 \tag{1}$$

$$\frac{\partial V}{\partial t} + V \times \nabla V = -\frac{1}{\rho}\nabla p + f + \nu \nabla^2 V \tag{2}$$

where $V$ is a velocity vector, $p$ is pressure, $\nu$ is constant kinematic viscosity, $\rho$ is fluid density, and $f$ is the body force vector.

The following differential equations proposed by Lan et al. [35,36] were applied for the analysis of core-annular flows:

$$f = \mu_c\left[\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}u_c}{\mathrm{d}r}\right)\right]$$

$$f = \mu_d\left[\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}u_d}{\mathrm{d}r}\right)\right]$$

These two equations correspond to the continuous phase (represented by the crosslinked alginate) and dispersed phase (represented by the crosslinker).

Boundary conditions were specified in cylindrical coordinates.

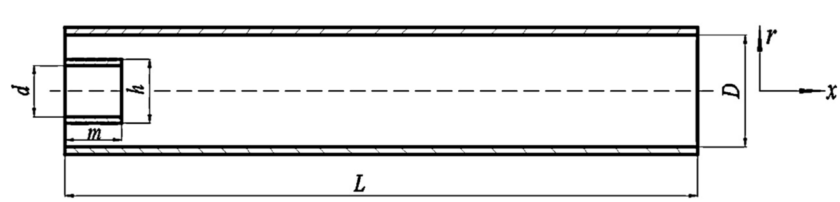


**Fig. 1.** Schematic of experimental system and geometry applied in the simulations: $L = 18$ mm, $D = 1.3$ mm, $d = 0.51$ mm, $h = 0.8$ mm, $m = 0.5$ mm.