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QUANTIFYING AND MODELLING THE FLUID TRANSPORT THROUGH POLYLACTIC ACID SCAFFOLDS

Margo Steuperaert[1], Charlotte Debbaut[1], Peter Dubruel[2], Sandra Van Vlierberghe[2], Jasper Van Hoorick[2], Wim Ceelen[3] and Patrick Segers[1]
[1] IBiTech – bioMMeda, Department of Electronics and Information Systems, iMinds Medical IT Department, Ghent University. Campus Heymans, Blok B, De Pintelaan 185, B-9000 Gent, Belgium, {Margo.Steuperaert, Charlotte.Debbaut, Patrick.Segers}@Ugent.be
[2] Department of Organic Chemistry, Polymer Chemistry and Biomaterials Research Group, Ghent University, Krijgslaan 281, S4 Bis, Ghent 9000, Belgium, {Peter.Dubruel, Sandra.VanVlierberghe, Jasper.VanHoorick}@Ugent.be
[3] Department of Surgery, University Hospital Ghent, De Pintelaan 185, B-9000 Ghent, Belgium, Wim.Ceelen@Ugent.be

SUMMARY

Tissue permeability is a key parameter when examining the drug transport in tumors during intraperitoneal chemotherapy. As part of our research on understanding the determinants of the therapy, this study aims to develop scaffolds that mimic the tissue permeability of tumors and to study their corresponding fluid flow characteristics. In order to do so, a framework is presented in which a virtual 3-dimensional scaffold is created, a virtual permeability test is performed on this scaffold by means of computational fluid dynamics simulations as well as an experimental validation of the findings.

Key words: *polylactic acid scaffolds, permeability, computational fluid dynamics*

1. INTRODUCTION

Peritoneal carcinomatosis is characterized by a widespread growth of tumor nodules in the peritoneal cavity. The intraperitoneal (IP) administration of chemotherapy is an alternative treatment to conventional intravenous chemotherapy, allowing for higher intratumor concentrations of the cytotoxic agent compared to intravenous administration [1]. Although this therapy appears promising, the poor drug penetration (only a few millimeters) in tumor nodules limits its actual application. In previous work [2], we showed that tissue permeability plays an important role in governing the drug transport in the tissue during IP chemotherapy.

As part of our research on understanding the determinants of IP chemotherapy, we are developing controlled environments in which tumor cells can be seeded and cultured in order to eventually test the therapeutic effects of different cytotoxic drugs. An important aspect of this work is to mimick of tumor tissue by developing scaffolds (as a support matrix for cell culture) of which the permeability characteristics can be predicted based on its printing parameters. The aim of this study is to assess the feasibility of designing and creating 3D printed scaffolds with a priori determined permeability characteristics. We therefore present a three-step framework including (i) the creation of 3-dimensional scaffolds, (ii) an experimental permeability test of the scaffold and (iii) a computational analysis of the scaffold permeability.

2. MATERIALS AND METHODS

2.1 3-dimensional scaffold fabrication

Polylactic acid (PLA) scaffolds were printed using an Ultimaker 1 device (Ultimaker, Geldermalsen, the Netherlands) and a transparent PLA filament (Velleman, Gavere, Belgium). The instructions for printing were written in G-code using Microsoft Excell and Visual Basic for Applications (VBA). The target filament thickness was 400µm with an interfilament distance of 500 µm Scaffolds were printed in a solid slab of approximately 5 by 5 cm and a height of 6 mm with a lay-down pattern of 0/90°. Three scaffolds were force-cut from the slab in a cylindrical shape with a 1 cm diameter. An Axiotech microscope (Zeiss, Oberkochen, Germany) was used to measure and verify the scaffold dimensions, i.e. the pore and strut size in both x, y and z directions (Fig. 1).

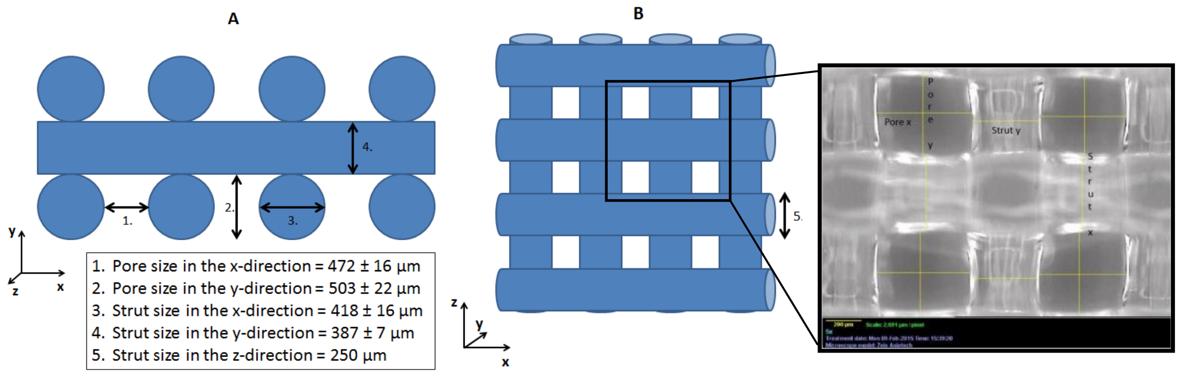

Figure 1: Schematic representation of the scaffold geometry: (a) side view of 3 layers of struts in the xy plane and the corresponding dimensions; (b) view in the zx plane and example of a microscopic image of the scaffold pores and struts.

2.2 Experimental permeability test setup

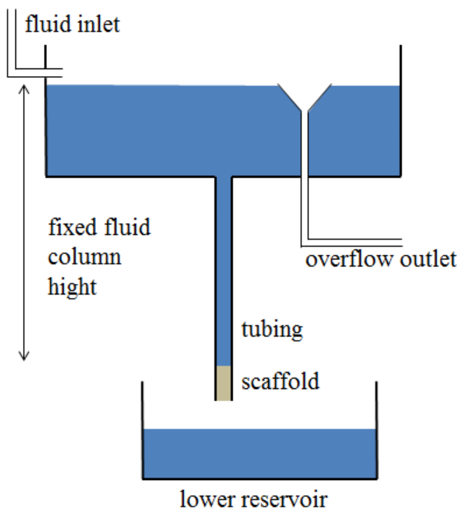

Figure 2: Schematic representation of the experimental permeability setup

To measure the permeability of the scaffolds experimentally, a gravity-based setup was constructed consisting of a fluid reservoir supplying the flow, a tubing holding the scaffold in place, and a second reservoir in which the fluid that has passed through the scaffold is collected (Fig. 2). The fluid head over the scaffold is kept at a constant height of 20 cmH_2O (equaling 1960 Pa) by means of an overflow outlet and a pump. Given that the height of the water column on the scaffold is fixed and that there is free outflow at the outlet of the scaffold, the pressure drop over the scaffold (ΔP [Pa]) can be calculated using the equation for hydrostatic pressure due to the fluid column on top of the scaffold (with ρ the density [kg/m³], g the gravitational acceleration [N/kg], h the height[m]).

$$\Delta P = \rho . g . h \quad \text{(Eq. 1)}$$

The lower reservoir will collect the fluid that has passed through the scaffold. The flow through the scaffold (Q [m³/s]) can be calculated by dividing the volume of fluid that is collected in this reservoir by the duration of the experiment. Knowing that the Darcy equation describes the relation between the pressure drop in and flow through a porous material, the Darcy permeability k [m²] can be calculated as follows for a cylindrical scaffold with length l [m], area A [m²] and μ the dynamic viscosity [Pa.s]:

$$k = -\frac{Q . l . \mu}{A . \Delta P} \quad \text{(Eq. 2)}$$

The three scaffold samples that were force-cut from the slab, were placed in the experimental setup. The mantle surface of the scaffolds was sealed with Teflon™ tape (Egeda, Herentals, Belgium) to ensure that all fluid passed through the scaffold and that there was no leakage between the mantle surface and inner wall of the tubing. Each scaffold was tested 3 times and the duration of each experiment was 5 minutes. Every 30 seconds, the volume of fluid was measured and the average flow during the experiment was then used to calculate the corresponding permeability (Eq. 2).

2.3 Computational analysis of scaffold permeability

A virtual 3-dimensional scaffold model was created in pyFormex (http://www.pyFormex.org) with an in-house developed parametrical Python code using the same scaffold dimensions as defined in section 2.1 (see also Fig. 1). The scaffold volume was subsequently subtracted from a cuboid volume to retain the fluid domain in the scaffold. Furthermore, inflow and outflow volumes were added to facilitate flow calculations and convergence near the multiple in- and outlets (Fig. 3). Subsequently, a volume mesh of the simulation geometry was created in ICEM (ANSYS inc, Canonsburg/PA, USA) with a seed size of 0.05.

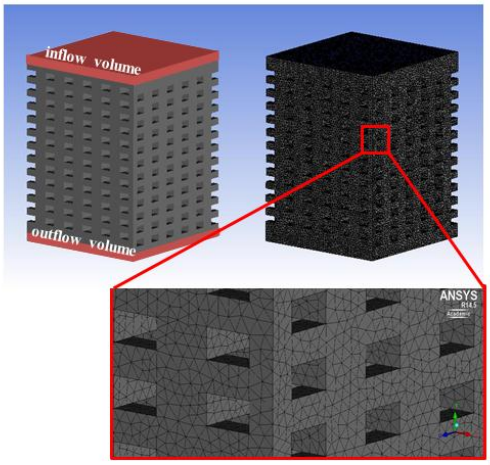

Figure 3: Left: The fluid zone of the cuboid scaffold model including the inflow and outflow volumes. Right: Volume mesh of the fluid zone

Because the fluid domain counts a high number of cells and the simulation geometry is of a repetitive nature, a feasibility study was performed earlier aiming at reducing the computational requirements to solve the problem. Several strategies were undertaken (changing the shape of the domain from a cylinder to a cuboid, reducing the x, y, z dimensions, …) and it was found that the most efficient way to reduce the computational requirements without compromising accuracy was by cropping the domain of the scaffold along the axis perpendicular to the pressure head and by using a cuboid scaffold macro-geometry. As such, final CFD simulations were performed on a cuboid volume with dimensions 5 x 5 x 6 mm^3 and resulting in a mesh of $1,5 \cdot 10^6$ tetrahedral elements.

Using the resulting volume mesh, a computational fluid dynamics (CFD) model was created in Fluent (ANSYS inc, Canonsburg/PA, USA). A pressure boundary condition was applied at both the in- (1960 Pa) and outlet surface (0 Pa). The pressure conditions were chosen such that they matched the experimental boundary conditions. The working fluid was set to water. Similar to the experimental setup, the scaffold permeability was calculated based on Darcy's law using the outlet flow (Eq. 2).

3 RESULTS

3.1 Experimental data

The measured permeabilities are listed in Table 1. Values of $7.27 \pm 0.10 \cdot 10^{-10}$, $6.89 \pm 0.05 \cdot 10^{-10}$ and $7.70 \pm 0.14 \cdot 10^{-10}$ m^2 were found for the three scaffolds. The overall average was $7.29 \pm 0.36 \cdot 10^{-10}$ m^2.

Scaffold	Measurement 1	Measurement 2	Measurement 3	Average	Standard Deviation
1	$7.17 \cdot 10^{-10}$	$7.26 \cdot 10^{-10}$	$7.36 \cdot 10^{-10}$	$7.27 \cdot 10^{-10}$	$9.59 \cdot 10^{-12}$
2	$6.87 \cdot 10^{-10}$	$6.86 \cdot 10^{-10}$	$6.95 \cdot 10^{-10}$	$6.89 \cdot 10^{-10}$	$4.82 \cdot 10^{-12}$
3	$7.66 \cdot 10^{-10}$	$7.86 \cdot 10^{-10}$	$7.58 \cdot 10^{-10}$	$7.70 \cdot 10^{-10}$	$1.44 \cdot 10^{-11}$

Table 1: Summary of the experimental permeabilities of the three PLA scaffolds

3.2 Computational analysis of scaffold permeability and comparison with experimental data

In figure 4 the pressure and velocity profiles across a yz-plane in the center of the scaffold can be seen. The range of pressures is from -3 to 1930 Pa and the range of the velocities is from 0 to 1.8

m/s. The total outflow over the outlet of the scaffold equaled 6.4 $\cdot 10^{-6}$ m^3/s resulting in a theoretical permeability permeability of $7.85 \cdot 10^{-10}$ m^2.

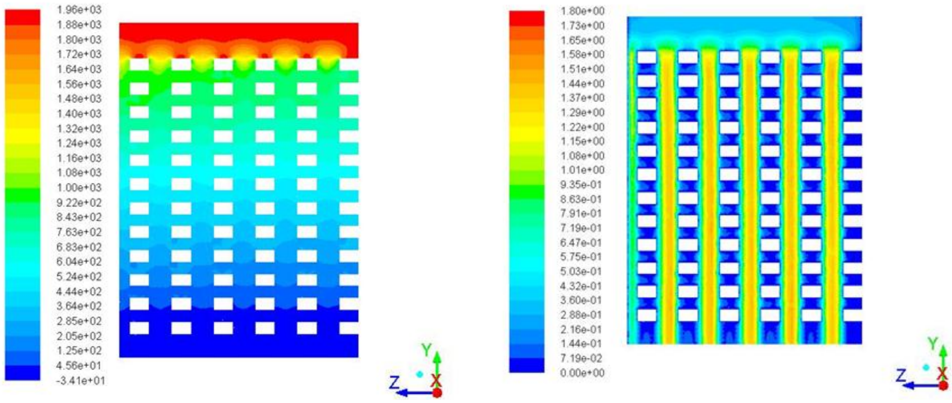

Figure 4: Left panel: Representation of pressure distribution (Pa) across a yz-plane in the center of the scaffold. Right panel: Representation of the velocity magnitude contours (m/s) across a yz-plane in the center of the scaffold.

Upon comparison of the experimental and virtual permeability values, it was found that, even though the values were in the same order of magnitude, virtual permeability was slightly overestimating the experimental values by 7.4, 12.2 and 1.9 % for scaffold 1, 2 and 3, respectively. This could be due to the approximations of the theoretical geometry in our CFD model (i.e. the usage of rectangular struts, the same height for all struts, perfectly aligned struts etc.). Future work will therefore include obtaining micro-CT images of the scaffolds before and after experimental permeability testing. These data will allow developing CFD models based on realistic scaffold geometries in order to assess the importance of actual versus theoretical scaffold dimensions.

4 CONCLUSION

In this work, a three-step framework is presented for developing scaffolds (as a support matrix for cell culture) of which the permeability characteristics can be predicted based on its printing parameters. The experimental and computed permeabilities are in the same order of magnitude, but virtual permeabilities underestimated the experimental permeabilities by 2 to 12%.

A next step will be to make the switch to more deformable gelatin scaffolds [3] or hybrid PLA scaffolds with collagen embedded in the pores to better mimic human tissue.

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