HEAT TRANSFER ANALYSIS FOR A PERFUSION BIOREACTOR

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Abstract. *Biofabrication of tissue and organs can provide an emergent solution for the lack of organs for transplant. One of the challenges to produce a functional 3D tissue is the mass transfer dependent only by diffusion, since the engineered tissue do not have its own circulatory system. In this project we present an alternative for an artificial circulatory system using needles that will nourish the tissue and maintain the temperature of 37°C. The objective is to estimate the number of needles using, as parameter of analysis, the heat transfer between the tissue and the flow of the needles.*

Keywords*: Bioreactor, CFD, Biofabrication, Bioprinting, Heat Transfer.*

1. INTRODUCTION

The number of patients in waiting lists is far more superior than the number of donors, the Organ Procurement and Transplantation Networks (OPTN) Web site offers a wealth of information about transplantation, in 2017 in United States, the waiting list of organs for transplant reached 115,398 patients and the total of transplants performed was 34,769, only 30% of the patients. Bioprinting of tissues and organs is a process of biofabrication that can offer a new advantageous form to solve this problem.

Bioprinting of tissues and organs could be defined as a computer-aided, layer-by-layer, additive biofabrication of functional 3D tissue and organs constructs based on a digital model using tissues spheroids as self-assembling building blocks (Mironov *et al.*, 2008). Tissue spheroids are spherical structures that can be composed by hydrogel and cells. After the process of bioprinting the construct that leaves the process is a diffuse mass of hydrogel and cells, not a fully operational organ. Therefore, must be maturating, a process that occurs in the bioreactor.

One approach for a bioreactor is a device in which biological and biochemical process develop under closely monitored and tightly controlled environmental and operating conditions (e.g. pH, temperature, pressure, nutrient supply and waste removal) (Martin *et al*., 2004). In the bioreactor, during the process of maturation, the tissue spheroids will fuse, the ability of fusion of the hydrogel helps the cells to get in contact to each other, and form the tissue, posteriorly the hydrogel will degrade as the tissue becomes ready to be implanted in the patient.

The very concept of tissue engineering is the interdisciplinary area between engineering and life science (Langer *et al.*, 1993). Therefore, the use of Information Technology (IT) is a great allied to biofabrication, assisting the development of all the equipment for the process like the bioprinter, the bioreactor, the experiments and so on.

Another approach of IT in the development of bioprinting processes is the computational simulations, that are very useful to predicting certain conditions and exclude others non-interesting, preventing large amount of trial and error expensive experiments in laboratories. Even if the models are too simple if compared to the real experiment, it is a practical way to try different theories.

The engineered tissues do not have their own blood system, the cells are only nourished by diffusion (Tabesh *et al.*, 2009; Kannan *et al.*, 2005), and in high vascularized organs (liver, kidney, lungs, spleen, heart, pancreas, or thyroid), the formation of new blood vessels becomes essential for a tissue to grow beyond the diffusion limit (Richards *et al.*, 2017; Santos *et al.*, 2010). Because of the dependence of the diffusion, which is too slow and only reaches a limited distance between each cell to realize the mass transfer, the size of the organ is limited, this dependence can be considered one of the greatest challenges to create 3D organs structures (Pörtner *et al.*, 2005). This project proposes the use of porous needles to nourish the cells in the center of the organ working as an artificial blood system until the tissue develops its own. The objective is to estimate the number of needles required to maintain the temperature of the tissue at 37°C, generally considered as the average center temperature of the body (Guyton and Hall, 2006).

The original model of the tissue is a structure formed by spheres (tissue spheroids) representing the bioprinted tissue. In order to reduce the total count of mesh elements in the model, the structure of the tissue was substituted by a cylindrical porous solid. The tissue produces a metabolism, a quantity of energy per volume of tissue, that will increase the temperature of the system. The idea is to find the greater diameter of the tissue that a needle can refrigerate keeping its temperature at 37°C while the tissue produces a metabolism.

2. METHODOLOGY

The geometry of study is a set of two cylinders, one for the needle and the other for the tissue. The needles have diameter of 0.47mm and pores with 0.04mm of diameter. For the tissue the diameter varies to determine the maximum value that the needle can maintain at 37°C and the length is fixed in 50mm, Fig. (1) shows the model with details, the geometry of the needle was built at the software Rhinoceros 5.0® and the tissue at the software Ansys/Design Modeler 18.2®.

Through the needle passes a flux of blood at 36°C that will irrigate the tissue that produces a quantity of energy per volume representing the metabolism. The properties of the blood are demonstrated in Tab. (1), the values of density, specific heat capacity and thermal conductivity were used according to Werner *et al.* (1988) and the viscosity according to Chatziprodromou *et al.* (2007). The properties of the tissue are according to Werner *et al*. (1988) in Tab (2).

According to Guyton and Hall (2006), the average temperature of the human body is between 36.5 and 37°C, although it can reach 40°C under intense exercise. Because of that, the maximum acceptable temperature of the bioprinted tissue was set to 37°C. The tissue produces an amount of energy, the metabolism, that will increase its temperature, because of that, the temperature of nutrition fluid was set to 36°C, therefore the temperature of the tissue will be kept at the average temperature of the human body. In this project, there was no consideration other than the flow of the needles to help the tissue to maintain it temperature in 37°C.

Table 1. Properties of the blood

Density [kg/m^3]	Viscosity [Pa.s]	Specific Heat Capacity [J/kgK]	Thermal Conductivity [W/m.K]
1059	0.0035	3850	0.47

Table 2. Properties of the tissue

Density [kg/m^3]	Metabolism [W/m^3]	Specific Heat Capacity [J/kgK]	Thermal Conductivity [W/m.K]
1080	24128	3550	0.47

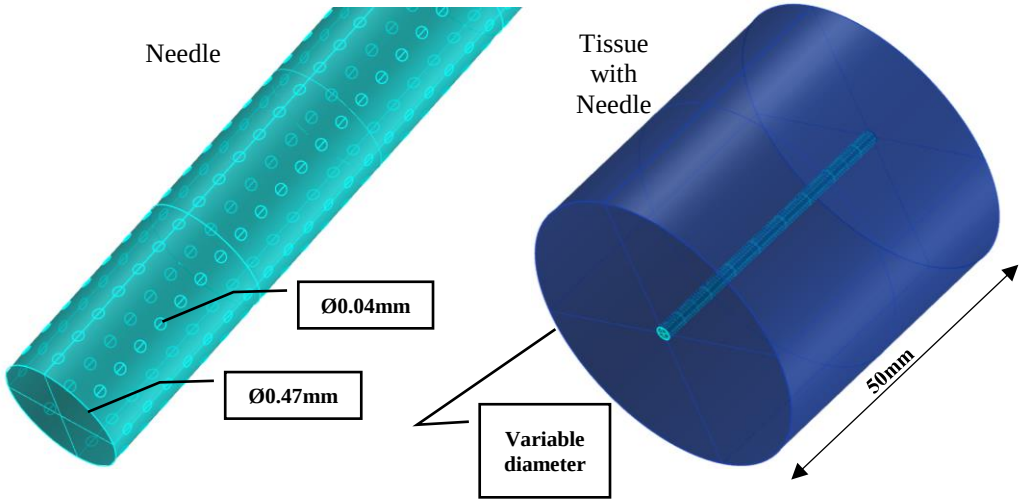

Figure 1. Geometry of the model

According to Guyton and Hall (2006) the same volume of blood must flow for each segment of the circulatory system and the velocity of the blood flow is inversely proportional of the total cross-sectional area of each type of vase. The cross-sectional area of the aorta is 250mm^2 and the velocity of the blood through it is 330mm/s. The total cross-sectional area of the capillaries (the summation of the cross-sectional area of all the capillaries of the body) is 250000mm^2, a thousand times greater than the aorta, therefore, the velocity through them is 1/1000 the velocity of the aorta, that is, 0.3mm/s. Therefore, the velocity of the needle should be calculated based on the cross-section area of all the needles but, estimate the number of needles is the aim of this work.

Because the relation with the cross-section area cannot be used, another approximation was proposed, using a proportional relation between the diameter and the velocity of the aorta and the capillaries (Eq. (2) and Eq. (3)). The

diameter of the aorta was calculated from the area of the circle given a value of 17.84mm (Eq. (1)). The chosen value of the diameter of the capillary was 0.005mm, selected between 0.004-0.009mm (Guyton and Hall, 2006).

$$d_{aorta} = \sqrt{\frac{250*4}{\pi}} = 17.84[mm] \quad (1)$$

$$v_{capillary} = \frac{0.005*330}{17.8} = 0.093\left[\frac{mm}{s}\right] \quad (2)$$

$$v_{aorta} = \frac{17.8*0.3}{0.005} = 1068\left[\frac{mm}{s}\right] \quad (3)$$

For the calculation of the aorta velocity, the value is three times greater than the real one, and for the capillary, the value is 1/3 of what supposed to be. Although it is not a perfectly approximation, it is a good calculation for a first model. Therefore, to estimate the flow velocity of the needle was used a relation in which the velocity is directly proportional to the diameter showed in Eq. (4) where d_{needle} is the diameter of the needle, $v_{capillary}$ is the velocity in the capillary and $d_{capillary}$ is the diameter of the capillary. The calculated value for the velocity of the inlet is 30mm/s, and the temperature of the flow was set to 36°C. The inlet and outlet of the system are demonstrated in Fig. (2).

$$v_{inlet} = \frac{d_{needle}*v_{capillary}}{d_{capillary}} = \frac{0.47*0.3}{0.005} = 28.2\left[\frac{mm}{s}\right] \quad (4)$$

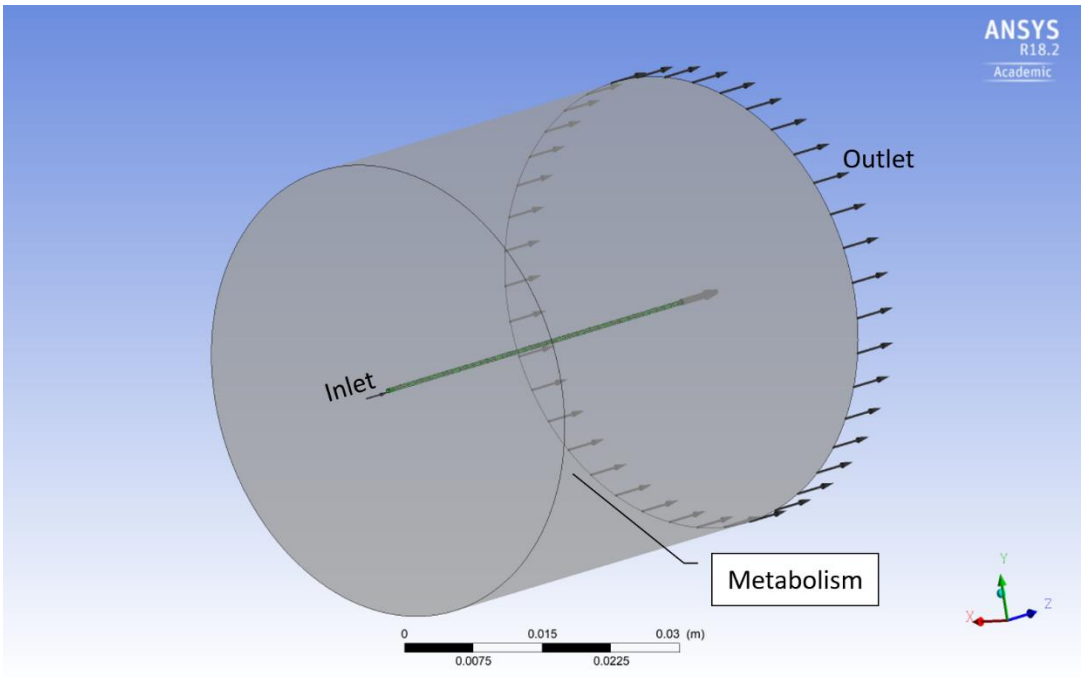

Figure 2. Boundary conditions

For the optimization, the diameter of the tissue varies until the temperature of the side of the tissue stabilize at 37ºC. In order to estimate the initial interval for the cylinder diameter, the value of the upper limit was defined using data from previous simulations which concludes that one needle is not enough to refrigerate a tissue of 10mm in diameter, since the value of the temperature on its outer surface extrapolate 37°C. Since there was not any reference for the lower limit, it was arbitrarily defined as 1mm of diameter.

To calculate the number of needles (n) needed to nourish the tissue (Eq. (7)), it was used the ratio between the volume of the entire tissue (V_T), calculated in Eq. (5), by the volume of the maximum diameter found (V_{sample}), calculated in Eq. (6).

$$V_T = \frac{\pi d_T^2}{4} * L \quad (5)$$

$$V_{\text{sample}} = \frac{\pi d_{sample}^2}{4} * L \quad (6)$$

$$n = \frac{V_{\text{T}}}{V_{\text{sample}}} \quad (7)$$

At Eq. (5), the variable d_{T} is the diameter of the entire tissue, and at Eq. (6), d_{sample} is the diameter found in the analysis. The variable 'L' in both equations is the length of the tissue, equal to 50mm. Equation 7 is the total number of needles needed for each dimeter of sample.

In that case, the structure of the tissue is simplified as a cylindrical volume, therefore Eq. (7) can be simplified as the ratio between the diameter of the entire tissue in the second power and the diameter of the sample in the second power (Eq. (8)).

$$n = \frac{d_T^2}{d_{sample}^2} \quad (8)$$

3. RESULTS

Considering the first interval of diameter, 1-10mm, ten samples were generated, but the criterion of 37°C was extrapolated at 2mm where the temperature reached 38.99°C as showed in Tab. (1).

Table1. Results for the first interval

Diameter [mm]	Temperature [°C]
1.45	36.71
2.35	38.99
3.25	39.08

A new interval of 1mm-2mm was set and the value of temperature extrapolated the maximum of 37°C with a diameter of 1.5875mm, showed in Tab. (2).

Table 2. Results for the second interval

Diameter [mm]	Temperature [°C]
1.4775	36.76
1.5325	36.86
1.5875	37.01

The precision of this diameter is important, since the objective is to estimate the minimum number of needles to maintain the tissue temperature in an optimum value of 37°C, with that in mind, a new interval of diameter of 1.5325-1.5875mm was tested to find a value really close to the maximum of temperature, Tab. (3). This simulation found a maximum value for the diameter of 1.581mm.

Table 3. Results for the final simulation

Diameter [mm]	Temperature [°C]
1.533	36.86
1.539	36.87
1.545	36.89
1.551	36.91
1.557	36.92
1.563	36.94
1.569	36.94
1.575	36.96
1.581	36.98
1.587	37.01

Using the value of 1.581mm (found in the simulation), for a tissue represented by a cylindrical structure with 50mm of diameter and 50mm length, the number of needles calculated from Equation 8 is 1001 needles.

$$n = \frac{50^2}{1.581^2} = 1000.17 \approx 1001\ needles$$

4. CONCLUSIONS

This work shows a preliminary estimation of the number of needles to nourish a bioprinted tissue based on the heat transfer between the tissue and the needle flow. Other parameters must be considered to discusses heat transfer in the bioreactor like other controls of the bioreactor that can help to maintain the optimal temperature of the organ, the tissue control mechanisms of themselves. Those other parameters will decrease the dependency of the tissue in the needle flow to maintain it temperature, so the number of 1001 needles can suffer an alteration.

There are other functions of the needle that must be considered before the determination of the optimal value of needles to nourish a tissue like the geometry and the distribution of those needles, which must be optimized to improve the efficient of transport of nutrients and oxygen between the needle and the tissue and help eliminate the metabolites of the cells. That is why this value of 1001 needles may decrease or increase according to the variation of those other parameters.

This first estimation helps to determine future studies introducing new parameters and different conditions. It is important to emphasize that different tissues need specific conditions, thus different bioreactors that will determinate different types of studies.

It is also important to evaluate the consequences in case of failure or damage of one or more needles in the system, and the solution to repartee the lack of fluid in those regions.

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