**Numerical simulation and theoretical study of O2 transport through a tri-layer hollow fiber BAL**

**Abstract**

A mathematically model has been developed to describe the behavior of a three-layer hollow fiber membrane bioreactor applicable as bio artificial liver (BAL). The model has provided the oxygen concentration profile in each of the three layers; 1) extracapillary space nutrient where the oxygen molecules transfer, 2) membrane (cell layer), the most important layer, where oxygen molecules transfer and consume, and 3) blood plasma layer where oxygen molecules transfer again. The equations solved with finite element method in MATLAB. The results have been validated by experimental data and compared with the results of other model. The model predicted that oxygen concentration consumption in plasma with different flow rates in range of 1.7 to 27 ml/min varied about 12 to 41%, in agreement with experimental data and the error of this work was about to 2.7% and also showed that oxygen mass transfer decreased with blood plasma flow rate. From results of this modeling, it is revealed that oxygen transport in bioartificial liver at the beginning of the system is very larger than the end of it. It is concluded that three-layer hollow fiber has been described very well with this assumption, and this work could help plant in better design and economy purpose.

**Keywords**

Bioartificial liver; Hollow fiber; Oxygen consumption; Plasma; Tri-layer modeling

**1. Introduction**

 Some types of membrane bioreactors have been applied for liver failure such as liver assist devices (LADs). Advances of bioartificial liver assist devices (BLADs) have been improving in last two decades to support patients with severe liver failure (SLF) during natural liver retrieval, or till an orthotropic liver replacement ([1-4](#_ENREF_1)).

some study cases exist in support of the bioartificial liver (BAL) and hollow fiber and their application in vivo limb such as in liver failure ([5-7](#_ENREF_5)).

Various types of BAL are divided into hollow fiber and porous matrix systems ([8](#_ENREF_8), [9](#_ENREF_9)); which hollow fiber systems could be included various types such as BLAD (amphioxus cell technologies) ([10](#_ENREF_10)).

The challenges of oxygen concentration in the BLAD layer have been discussed and because of vitally requirement of oxygen it is also ongoing . Various modeling for oxygen concentration have been reported ([11-13](#_ENREF_11)); some considered the oxygen partial pressure with respect to angle of hollow fiber ([14](#_ENREF_14)), some led to oxygen partial pressure just in lumen layer with respect to radial and axial directions of the hollow fiber ([15-17](#_ENREF_15)), and the others calculated oxygen partial pressure in different input feed ratio in lumen site ([10](#_ENREF_10)). Curcio et al. derived a model for the oxygen concentration with different extra capillary feeds ([18](#_ENREF_18)). Many models have considered oxygen partial pressure concentration distribution in the hollow fiber in lumen side, just with respect to either diffusive mass transfer or convective mass transfer. In this work, oxygen concentration within all the three layers of hollow fiber has been tried to be predicted regarding both diffusive and convective mass transfer. The calculated results have been then compared with not only experimental data, but also the results of other previous models. This tri-layer modeling studies the oxygen concentration within BAL and investigates on simultaneously mass transfer in the three layer.

**2. Theory and model**

There are many basic forms of hollow fiber bioreactor (HFB) designed and discussed in the literature ([16](#_ENREF_16), [19-28](#_ENREF_19)). In order to model the BALs, a significant method based on the immovability of the cells in the internal or external areas of the porous hollow fibers is applied. This arrangement allows oxygen and nutrients to be reserved to cells using a liquid flow diverse from the blood stream or plasma flow. The nutrient flows adjacent to the membrane surface, where the cells and cells layer are set, while blood flows on the other side of the membrane. The stream pattern can be similar flow (cocurrent) or contrary flow (countercurrent), but typically, the similar plan reported ([27](#_ENREF_27)).

The module is a number of hollow fibers packed in a cylindrical casing. The basic consideration in the modeling of this work is to predict the oxygen concentration profile in the three layers. However, to calculate the oxygen transfer rates in the layers would be vital. Both the axial and radial directions of the hollow fiber have been considered for oxygen concentration in different plasma rate to find the crucial zone in the membrane for cell livability.

Considerations of this model are:

Nutrients stream is just in the outer side of the fibers; i.e., nutrient cannot be in plasma or membrane layer. Cells are immovable on exterior of the fibers. Blood flows within the lumen; blood plasma stream cannot be in membrane or nutrient layer.

In order to have the maximum contact, cocurrent pattern of nutrient and plasma streams was considered ([27](#_ENREF_27)). So that the maximum oxygen transfer could be achieved.

At all sections, transported oxygen from the nutrient side into the cells has been considered to occur as follows: (i) Oxygen transfer through the outer flowing film, (ii) oxygen diffusion and oxygen consumption take place simultaneously in cell layers, (iii) oxygen transfers through the membrane, and (iv) oxygen transfers in the blood plasma inside the tube.

Assumptions of the steady state model of this study are as follow: There is no change in mass flow rate in axial direction. ([14](#_ENREF_14)). Since oxygen concentration has negligible changes in radius direction, the nutrient stream could be assumed to follow as a plug flow pattern. A semi permeable membrane is used as BAL ([7](#_ENREF_7), [14](#_ENREF_14), [29](#_ENREF_29)). Due to the immovability of the cells, oxygen just diffuses in the radial direction through the cells layer ([27](#_ENREF_27)). The flow of blood plasma in the lumen side of the membrane is laminar. Therefore, oxygen concentration changes in both radial and axial directions in the lumen side. However, the convective term of radial mass transfer within the lumen is negligible, so does the diffusive term in the axial direction. When Newton's law is uses to a fluid, the motion equation that acquired is:

(Density × acceleration = divergence of shear stresses - gradient of pressure)

Viscosity is constant. Stress depends on normal and shear strain rates and the pressure applied on it. Also a shear thinning fluid. So as it revealed, blood plasma presumed to be a Newtonian fluid ([30-32](#_ENREF_30)). In addition, because of natural and undeniable role of hemoglobin in oxygen transport in blood, and essential presence of that in blood stream, in this study, influence of hemoglobin in oxygen transport in this work has been eliminated. In this work, all modeling done with MATLAB 2013a.

**2.1. Modeling**

Three zones of the model of this study, shown in Figure 1, are including: I) Intra lumen volume, the zone where plasma stream flows (0 < r < ri), II) Cells layer (ri <r < re), and III) Extra fiber chamber, the zone where nutrient flows (re < r < R) .

Fig. 1. Schematic of tri-layer bioartificial hollow fiber of this study. I: extra capillary space nutrient, II: membrane (cell layer), and III: blood plasma layer.

***Extra fiber volume mass balance***

Volume mass balance for extra fiber stream could be written as a dimensionless equation as follow:

$\frac{d\overline{C}\_{e}}{d\overline{z}}=\frac{1}{Pe\_{e}}.\left(\overline{C}\_{e}-\frac{C\left(r\_{e}\right)}{C\_{e}^{0}}\right) (1) $

Where $Pe\_{e}$ is extrafiber Peclet’s number ($=Re\_{e}∙Sc\_{e}=\frac{Q\_{e}}{2.K\_{e}.π.r\_{e}.N\_{f}.L}$), $\overline{C}\_{e}= \frac{C\_{e}}{C\_{e}^{0}} $and$\overline{z}= \frac{z}{L}$. In these dimensionless parameters, Ce is the outer oxygen bulk concentration and C(re) is the oxygen concentration adjacent to the outer cell layer, assumed to be constant; Qe is the extracapillary space (ECS) volumetric rate of flow, Ke the oxygen mass transfer coefficient and Nf is the fiber numbers. re is radius of external membrane layer, L is the module length, z is the the axial and r is the radial coordinates and C0e is the oxygen concentration of input nutrient stream to module. Additionally, Reynolds number is a dimensionless number for flow and its type. For this differential equation, the boundary condition is $\overline{C}\_{e}(0) = 1 at \overline{z}= 0 $.

***Membrane (cells layer) mass balance***

In this section, the axial mass transfer could be neglected. Due to the zero order of the reaction ([27](#_ENREF_27)), the mass balance is rewritten as:

$\frac{1}{\overline{r}}\frac{∂}{∂\overline{r}}\left( \frac{∂\overline{C}\_{m}}{∂\overline{r}} \right)=φ^{2} (2)$

where $φ^{2}$ is the cellular Thiele’s module ( a module for making the equations dimensionless and more understandable) ($=\frac{q\_{max}.r\_{i}^{2}.ρ\_{cells}}{D\_{eff}.C\_{e}^{0}}$), $\overline{C}\_{m}= \frac{C}{C\_{e}^{o}} , \overline{r}= \frac{r}{r\_{i}} $ and $\overline{C}\_{p}= \frac{C\_{p}}{C\_{p}^{0}}$. Here, $ρ\_{cells}=\frac{n}{π.\left(r\_{e}^{2}-r\_{i}^{2}\right).L.N\_{f}}$, C(r) is the oxygen concentration in cell layer, Deff is the oxygen effective diffusivity in membrane (cell layer), qmax is the maximum oxygen consumption rate per cell, n is the number of cells that exist in the membrane, $C\_{p}^{0}$ is oxygen concentration of internal plasma to bioreactor, re is the radius of the external membrane layer and ri is the radius of internal membrane layer and L is the length of hollow fiber.

The boundary conditions:

$$\overline{C}\_{m}= \frac{C\_{p}\left(r\_{i}\right)}{C\_{e}^{o}} at \overline{r}=1$$

 $D\_{eff}. \frac{∂\overline{C}}{∂\overline{r}}=K\_{e}\left(\frac{C\_{e}(z)}{C\_{e}^{o}}-\overline{C}\_{m}\right) at \overline{r}\_{e}=1 $

where, $,\overline{r}\_{e}= \frac{r}{r\_{e}}$, $C\_{e}\left(z\right)$ is assuming mean of $C\_{e}$ in nutrient and $C\_{p}\left(r\_{i}\right)$ is mean of $C\_{p}$ (concentration of oxygen in lumen) in $r=r\_{i}$.

***Inside of lumen mass balance***

The convective term of mass transfer in the radial direction and the diffusive term in the axial direction could be neglected in the lumen. Until the lumen fluid follows laminar flow pattern, the velocity profile is parabolic with a maximum axial velocity of the two times of the average velocity:

$u\_{z}\left(r\right)= 2.\frac{Q\_{p}}{π.N\_{f}.r\_{i}^{2}}.\left(1-\left(\frac{r\_{i}}{r}\right)^{2}\right) (3)$

where $Q\_{p} $is the plasma blood volumetric flowrate through the all fibers.

Oxygenmass balance inside the lumen is:

$$u\_{z}\left(r\right).C\_{p}\left(r,z\right).dS\_{b}|\_{z}+ J.dS\_{l}|\_{r+dr}=u\_{z}\left(r\right).C\_{p}\left(r,z\right).dS\_{b}|\_{z+dz}+ J.dS\_{l}|\_{r} (4) $$

where *J* is the term of diffusion, d*Sb* is the area of base surface and d*Sl* is the area of lateral surface of the hollow fiber.

Applying fick’s equations for J and equation 3, the mass balance could be rewritten as:

$ \left(1-\overline{r}\right). \frac{d\overline{C}\_{p}}{d\overline{z}}=\frac{1}{Pe\_{i}}\frac{1}{\overline{r}}\frac{∂}{∂\overline{r}}\left( \frac{∂\overline{C}\_{p}}{∂\overline{r}} \right) (5) $

where $Pe\_{i}$ is inner transmembrane of Peclet’s number ($=2.\frac{Q\_{p}}{D\_{p}.π.N\_{f}.L}$); *Dp* is oxygen diffusivity in lumen.

Boundary conditions:

$$D\_{p}\left(\frac{∂\overline{C}\_{p}}{∂\overline{r}}\right)=0 at \overline{r}=\overline{z}=0 $$

$$D\_{p}∙C\_{p}^{o}\left(\frac{∂\overline{C}\_{p}}{∂\overline{r}}\right)= D\_{eff}∙C\_{e}^{o}\left(\frac{∂\overline{C}\_{m}}{∂\overline{r}}\right) at \overline{r}=1 $$

$$\overline{C}\_{p}= 1 at \overline{z}=0 $$

where $C\_{p}^{o}$is the oxygenconcentration of internal plasma in the bioreactor.

The quantities of the model parameters, have been extracted from the literature ([29](#_ENREF_29), [30](#_ENREF_30), [33-36](#_ENREF_33)), are tabulated in Table 1.

Table. 1. All quantities of the model parameters for this simulation.

**3. Results and Discussion**

**3.1 ECS modeling results**

Fig. 2 displays the oxygen concentration in ECS versus length of HFB in different *Pee*s. As seen in the figure, the oxygen concentration reduces gradually and exponentially in the axial direction, in agreement with Equation 1 (which called exponential reduces equation). The slope of oxygen concentration got sharper with *Pee* and the cause is the Qe term in Equation 1. the result can be explained with experimental data and artificial liver and BAL function ([17](#_ENREF_17)) because of mass transfer (convective term). The results of this work have shown that the oxygen consumption rate in ECS changes between 0- 13% . Comparing to P. Sullivan et al. and Jason E. Gordon et al. work. where, the results of their work show that the oxygen consumption rate in ECS changes between 0- 15 % . These results show the consistent of these modeling results with the other modeling in ECS consumption; however, the difference is because of assumption or conditions of the models. The results of modeling that have been compared with the results of P. Sullivan et al. and Jason E. Gordon et al. work are based on experimental results and modeled with experimental data([30](#_ENREF_30)).

Fig. 2. Dimensionless O2 concentration alterations in the axis direction in ECS .Qp=1.7,7,17,27 ml/min(Qe=0.25Qp),Ke = 1.62 × 10-6,Nf = 1900.

**3.2 Membrane (cell layer) modeling results**

Fig. 3 displays the oxygen concentration through the membrane (cells layer). As seen, the oxygen consumption rate is about 12%. It could be due to the thickness and immovability of cells, however, other factors like the characteristics of the membrane and the order of the reaction could play an important role ([27](#_ENREF_27), [37](#_ENREF_37), [38](#_ENREF_38)). In Fig. 3. the oxygen consumption rate (slope) around the radius of internal membrane layer is very greater than around the radius of external membrane layer and it is because of membrane type , plasma flow and oxygen diffusion in radius direction in lumen ([31](#_ENREF_31), [37](#_ENREF_37), [39](#_ENREF_39)). Adjacent to the radius of external membrane layer, slope approach to zero, and it shows that the oxygen exchange in this area is too low. It could be due to the rate of consumption in ECS. In the other works ([17](#_ENREF_17), [29](#_ENREF_29), [40](#_ENREF_40)), the change of oxygen concentration is very comparable with the result of this work(14%) with small difference and it is stemming from the round of error (ROF) of MATLAB or the Finite Elements Method which aforementioned equations have been solved by this method in MATLAB. It also could be caused by difference in cell density ([34](#_ENREF_34)).

Fig. 3. dimensionless O2 concentration alternations in the radius direction in membrane (cell layer), qmax= 2.5 × 10-18 mol/(cell.s), ρcell = 1.3 × 108 cell/ ml

**3.3 Lumen results and comparison**

Fig. 4 is an oxygen concentration figure in four different volumetric flowrates of plasma blood (Qp) in the lumen. The following results are inferred from this figure:

1. Oxygen concentration reduces in lumen axially because of mass transfer (convective term). And it reduces radially because of mass transfer (diffusive term), both of them are caused by lack of oxygen concentration in membrane and concentration difference between membrane and plasma flow in lumen ([27](#_ENREF_27), [37](#_ENREF_37)). It seems, the concentration changes at $\overbar{r}$ = 0 because of plasma flowrate and convective mass transfer. in the other hand, seems that changes of concentration are negligible at $\overbar{z}$ = 0 and it is because of negligible effect of convective term compare to diffusive term (Equation 5) besides, the oxygen influences radially which causes the oxygen concentration behavior in this figure.
2. Another important thing that has been concluded is the plasma flowrate that plays an important role in distribution of oxygen concentration in hollow fiber. When Qp changes, some differences are appeared. When Qp increases, the slope of concentration curve is smoother than lower Qp and it can be explained mathematically and experimentally. the mathematical reason exist in the differential equation, as seen in the Equation 5, according to the right side of the equation ,the transfer of oxygen decreases by increase of Qp and consumption rate in length and radius of hollow fiber is less than the lower flow rate. The other reason is that in lower flow rate the oxygen molecules have more time to transfer within cells layer. Now these results are compared with the results of other researches. In a work of chen et al. ([30](#_ENREF_30)) oxygen concentration decreases in axial direction of hollow fiber, though the changes are a little greater than this modeling, which could be stemmed from modeling simplification or number of fibers used in module. In another modeling ([29](#_ENREF_29)) the changes of oxygen concentration are alike this model with a little difference and the difference could be because of number of fiber or loses of pressure in the input or output of hollow fiber([30](#_ENREF_30)). In another works ([17](#_ENREF_17), [40](#_ENREF_40)) the consumption of oxygen in lumen changes 15- 45% with these plasma flow rates and in the presented modeling it changes 12-41%. These results show that the modeling results have a good compatibility to another works the presence difference is because of different inner oxygen concentration and a little different between oxygen diffusivity in lumen.in the other hand, another cause could be the difference between the radius of hollow fiber in the modeling and experimental results.

Fig. 4. dimensionless contour for O2 concentration change in different radius and different Qp with length

In fig. 5. experimental data ([30](#_ENREF_30)) and modeling data at $\overbar{z}$ = 1 and Qp =0 .0025 cm3/min have been compared. As seen, the modeling and experimental data are almost close to each other which error is very small (about to 2.7%). Fiber numbers or the membrane materials could be the Cause of this deviation (from equation number 5 and Pei). In the other hand the membrane material is able to change the distribution of oxygen consumption in radius dimension. ([30](#_ENREF_30)).

Fig. 5. dimensionless comparison of experimental data at Qp = 0.00251 and end of the hollow fiber and modeling results at Qp = 0.0025 and end of the hollow fiber.

**4. Conclusions**

The model for a tri-layer hollow fiber bioreactor just described and studied. In this work, there was a little deviation from experimental results, but the model presented good results in compare with experimental results. In the axial direction, these deviations were so low and well-done assumption about convective flow in axial direction was contemplated. In the radial direction, the diffusion term must be considered, because diffusive term plays vital role in mass transfer between plasma and membrane. This work also described if inner plasma flow rate gets bigger the changes in oxygen concentration will get lower. Finally, it concluded that three-layer hollow fiber has been described very well with this assumption, and this work could help plant in better design and economy purpose.

**Abbreviations**

LAD liver assists devices

BLAD bioartificial liver assists devices

SLF severe liver failure

BAL bioartificial liver

HFB hollow fiber bioreactor

ECS extracapillary space

ROF round of error

**Nomenclature**

*parameters*

ri Internal radius

re Internal radius + membrane thickness

R Overall radius

$\overline{C}\_{e}$ Extrafiber dimensionless bulk oxygen concentration

$\overline{z}$ dimensionless axial length

$Pe\_{e}$ extrafiber Peclet’s number

$C\left(r\_{e}\right)$ outer cell layer concentration

$C\_{e}^{0}$ oxygen concentration of input nutrient stream to module

$Q\_{e}$ extracapillary space (ECS) volumetric rate of flow

$K\_{e}$ oxygen mass transfer coefficient

п Pi number

$N\_{f}$ fiber numbers

$L$ module length

$C\_{e}$ Extrafiber bulk oxygen concentration

$\overline{C}\_{m}$ oxygen concentration in cell layer

$\overline{r}$ dimensionless radius

$q\_{max}$ the maximum oxygen consumption rate per cell

$D\_{eff}$ oxygen effective diffusivity in membrane (cell layer)

$n$ number of cells

$z$ axial length

r radius

$\overline{C}\_{p}$ dimensionless concentration of oxygen in lumen

$C\_{p}$ concentration of oxygen in lumen

$C^{0}\_{p}$ oxygen concentration in the internal plasma to bioreactor

$C\_{p}\left(r\_{i}\right)$ mean of concentration of oxygen in lumen

$u\_{z}\left(r\right)$ average axial velocity

$Q\_{p}$ plasma blood volumetric flowrate through the all fibers

$dS\_{b}$ area of base surface of the hollow fiber

d*Sl* area of lateral surface of the hollow fiber

$J$ term of diffusion

$Pe\_{i}$ Inner transmembrane number of peclet

$D\_{p}$ oxygen diffusivity in lumen

*Greek symbols*

ρcell cells density

ϕ the module of cellular Thiele’s

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**Figure captions:**

Fig. 1. Schematic of tri-layer bioartificial hollow fiber of this study. I: extracapillary space nutrient, II: membrane (cell layer), and III: blood plasma layer.Fig. 2. Transects of hollow fiber element and the velocity element of the lumen

Fig. 2. Dimensionless O2 concentration alterations in the axis direction in ECS .Qp=1.7,7,17,27 ml/min(Qe=0.25Qp),Ke = 1.62 × 10-6,Nf = 1900.

Fig. 3. Dimensionless O2 concentration alternations in the radius direction in membrane (cell layer), qmax= 2.5 × 10-18 mol/(cell.s), ρcell = 1.3 × 108 cell/ ml

Fig. 4. Dimensionless contour for O2 concentration change in different radius and different Qp with length

Fig. 5. Dimensionless comparison of experimental data at Qp = .00251 and end of the hollow fiber and modeling results at Qp = .0025 and end of the hollow fiber.

Table. 1. All quantities of the model parameters for this simulation.

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters | Unit | Value | Ref |
| C0p | mol/m3 | 4.6 | [Hilal-Alnaqbi, 2014] |
| C0e | mol/m3 | 10.8 | [Hilal-Alnaqbi, 2014] |
| Qp | cm3/min | 1.7, 7,17,27 | [Hilal-Alnaqbi, 2014] |
| Qe | cm3/min | 0.25 Qp | [Hilal-Alnaqbi, 2014] |
| ri | cm | 0.0165 | [Hilal-Alnaqbi, 2014] |
| re | cm | .015 | [Hilal-Alnaqbi, 2014] |
| R | cm | .0735 | [Hilal-Alnaqbi, 2014] |
| L | cm | 11.5 | [Hilal-Alnaqbi, 2014] |
| Nf | - | 1900 | [Hilal-Alnaqbi, 2014] |
| qmax | mol/(cell.s)  | 2.5×10-18 | [Wagner, 2011] |
| ρcell | cells/mL | 1.3×108 | [Smith, 1996] |
| Dp | cm2/s | 3 × 10-5 | [Chen, 2009;Nishikawa, 2008] |
| Deff | cm2/s | 0.6Dp | [Chen, 2009;Nishikawa, 2008] |
| Ke | cm/min | 1.62 × 10-2 | [Tribe, 1995] |