A multi-scale computational model for micro-vascular oxygen transfer applied to radiotherapy

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Academic Year 2018-2019
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Abstract
INTRODUCTION

The circulatory system is the set of organs and vessels responsible for the transport of blood in the tissues in order to provide nutrients and remove waste products. Micro-vascular vessels are typically classified as arterioles, capillaries, and venules. In particular, the gas and nutrient exchanges take place at the capillary level, where the vessels have the diameter similar to the red blood cells (RBCs) one. In this work, firstly, the commonly used model to compute the transport and exchange of oxygen in the capillary network, the Krogh’s model, has been described. Krogh’s model sees the capillaries as concentric cylinders adjacent to each other (Figure 1.2).

In particular, the system of equations and the assumptions at the base of the Krogh’s model have been discussed to highlight the its limits. The Krogh’s model has been considered as the starting point to develop a more complex oxygen transport model. Indeed, a finite element model has been developed to describe the oxygen distribution in the micro-vascular environment, in particular, the model computes the transport and exchange of oxygen between the capillary network and the interstitium. This aim has been achieved thanks to a numerical solver able to simulate the exchanges between a vascular network and surrounding tissue. The numeric resolver, implemented in C++ using the finite element library open-source GetFEM++ 5.0, and has been implemented from the work previously developed by Notaro at the Laboratory of Modelling and Calculation Scientific - MOX. In the mathematical and numerical model, the reduction technique has been used to model capillaries as 1D channels within the 3D interstitial domain and it is at the base of the solver.
Starting from the results obtained from the resolution of the fluid dynamic and the transport of erythrocytes \cite{38}, in the present work, the oxygen transport model has been taken up and modified suitably to make it more representative of the biological environment described by non-linear constitutive models, such as Michaelis-Menten kinetics in the tissue and Hill model for the RBCs saturation.

The Michaelis-Menten formula describes the non-linear consumption rate of a certain solute, in this case, the oxygen, by a substrate, the interstitium. On the other side, Hill equation describes the saturation of the RBCs in function on the oxygen content in the capillaries. The RBCs play a fundamental role in the oxygen supply to the tissues, thanks to the haemoglobin, a macro-molecule which can bind to oxygen and to release it when necessary. By Hill’s equation, we introduce the concept of oxyhemoglobin in the model.

This last step would have been impossible without the implementation of the hematocrit transport model \cite{37,38}, which is of fundamental importance for the correct description of blood movement in the capillaries not only under physiological conditions but also under pathological conditions. Furthermore, this model takes into account various biological phenomena, such as Fåhræus–Lindqvist effect and Zweifach-Fung effect.

The 3D1D oxygen transport, described in this work, has an interesting application to the radiotherapy. It can be combined to the commonly used radiobiological model, the Linear-Quadratic (LQ) model, to predict the distribution of the fraction of cells surviving to ionizing radiation, knowing the distribution of oxygen partial pressure, \( pO_2 \).

The 3D1D model is versatile in the computation of physiological parameters, such as velocity, hydrostatic pressure and partial pressure of oxygen in the capillaries and the interstitium. Moreover, the results, obtained by the combination of LQ and 3D1D models, proved to be interesting in clinical relevance.
MATERIAL AND METHODS

The Krogh’s model

The Krogh’s model is based on a generic advection-diffusion-reaction equation for the tissue domain and on an flow rate oxygen balance in the bloodstream for an infinitesimal section of the capillary, $dz$:

$$\frac{\partial C}{\partial t} = D \nabla \cdot (\nabla C) - \nabla (u \ C) + P(C) - V(C)$$  \hspace{1cm} (1)

$$\pi R_i^2 u_z C - \pi R_i^2 u_z (C + \frac{\partial C}{\partial z} dz) = \pi (R_o^2 - R_i^2) dz V$$  \hspace{1cm} (2)

where $C=C(r,z,\vartheta)$ is the free oxygen concentration as function of the position, D is the diffusion coefficient in the tissue, $u=u(r,z,\vartheta)$ is the velocity field, $P(C)$ and $V(C)$ are, respectively, volumetric oxygen source and oxygen consumption terms, functions of the concentration.

The oxygen concentration profile has been computed through the tissue and along the capillary’s axis, applying the following assumptions:

1. Steady-state condition;

2. Negligible axial diffusion in the tissue and the advection contribution is not considered in the tissue;

3. Homogeneous oxygen consumption rate, $V(C)$, neglecting the source term, $P(C)$;

4. The $\vartheta$ coordinate is not involved, due to the symmetrical structure of the capillary;

and the following boundary conditions:

$$BC1 : if \quad r = R_i \quad C = C_0(z)$$

$$BC2 : if \quad r = R_o \quad - D \frac{\partial C}{\partial r} = 0$$
So, the system of equations (15) and (16) is reduced as below:

\[ 0 = \frac{D}{r} \left[ \frac{1}{r} \left( r \frac{\partial C}{\partial r} \right) \right] - V \quad (3) \]

\[ C(z) = C_0 - \left( \frac{R_o^2}{R_i^2} - 1 \right) \frac{V}{u_z} z \quad (4) \]

Imposing the boundary concentration and merging (17) and (18), the Krogh’s model for the free oxygen concentration profile in the tissue is obtained as below:

\[ C(r, z) = C_0 + \frac{V R_o^2}{4 D} \left[ \left( \frac{r}{R_o} \right)^2 - \left( \frac{r}{R_i} \right)^2 \right] - 2 \ln \left( \frac{r}{R_i} \right) - \left( \frac{R_o^2}{R_i^2} - 1 \right) \frac{V}{u_z} z; \quad (5) \]

The equation (19) presents some criticalities, such as the presence of the dissolved oxygen phase alone, the linear consumption rate in the interstitium and the absence of the solute and fluid exchange between the two domains by diffusive, hydrostatic and oncotic gradients.

The 3D1D Oxygen Transport Model

In this work, the oxygen transport model is based on a previous computational model which solves the fluid dynamic problem as a combination of Darcy and Poiseuille equations, and hematocrit transport problem ([37], [38]). Oxygen transport and consumption are modelled in a domain, a subspace of \( \mathbb{R}^3 \), called \( \Omega \subset \mathbb{R}^3 \), that consists of two regions: tissue, \( \Omega_t \), and vessel (plasma and RBCs), \( \Omega_v \). The capillary has been reduced to its centerline, \( \Lambda \), imposing particular assumptions ([34]) that are able to consider the capillary as a 1D object immersed in a 3D structure, namely the interstitium considered as a porous medium.

In the blood, the oxygen flows both free and haemoglobin-bound, so for the mass balance the total oxygen concentration must be considered as sum of two contributes. The oxygen transport model is based on the following assumptions:

- Oxyhemoglobin cannot diffuse. The oxygen is able to bound to the haemoglobin,
Hb, a macromolecule made of four binding sites for oxygen, called heme groups. The reaction between oxygen and haemoglobin leads to oxyhemoglobin formation. It is not able to diffuse along the radial direction, through the capillary membrane.

- **Negligible dynamic diffusion of oxygen from RBCs.** We neglect the dynamics of oxygen release by erythrocytes into the bloodstream and oxygen capture by red blood cells. These reactions are considered instantaneous. We consider the concentration of oxygen as a unique quantity made up of the sum of the contributions of free and bound-haemoglobin.

At the base of the oxygen transport model there are two partial differential equations: one is for the free oxygen concentration in the 3D tissue domain and the other is for the total oxygen concentration, which is the sum of free, $C_v$, and bound-haemoglobin, $C_{HbO_2}$, oxygen concentration, in the 1D network domain. The transport of free oxygen in the tissue is modelled by the following equation:

$$\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t \, C_t) + M \, C_t = J_{O_2} \quad \text{on } \Omega_t. \quad (6)$$

where $D_t$ is the oxygen diffusive coefficient in the interstitium, expressed as $m^2/s$, $u_t$ is the velocity of the fluid in the interstitium, known thanks to the solution of the fluid dynamic problem, $M$ is the oxygen consumption rate. The rate $M$ is expressed as $ml_{O_2}/cm^3/s$ and it is assumed constant as first approximation. Instead, the transport equation in a vessel can be derived starting with the mass balance along a linear and cylindrical capillary, estimating the difference of flow rate between inlet and outlet. We report the general 3D transport equation for total oxygen concentration, $C_{tot}$:

$$\nabla \cdot [(\pi R^2 \, D_v \nabla (C_{tot})) - \pi R^2 \, (u_v \, C_{tot})] + M \, C_{tot} = -J_{O_2} \quad (7)$$

where $C_{tot} = C_v + C_{HbO_2}$.

The last term, $J_{O_2}$, in both equations (20) and (21), represents the exchange term modelled according to Kedem-Katchalsky equation (25) in presence of a semi-permeable...
membrane:

\[
\begin{align*}
J_{\text{diff}} &= 2\pi R P_l (C_v - C_t); \\
J_{\text{adv}} &= 2\pi R \left( \frac{C_v + C_t}{2} \right) L_p (1 - \sigma_{\text{oxy}}) (\Delta P - \sigma \Delta \pi); \\
J_{O_2} &= J_{\text{diff}} + J_{\text{adv}};
\end{align*}
\]

where \(P_l\) is the permeability, defined as diffusivity over the width of the capillary membrane; \(L_p\) is the hydraulic conductivity of the capillary walls in \((m ml_O_2)/ml_B/mmHg\); \(\sigma\) is a pure number and represents the reflection coefficient of the capillary membrane to proteins in the blood flow, instead \(\sigma_{\text{oxy}}\) is the reflection coefficient relative to oxygen molecule.

The previous equations (20) and (21) have been modified by introducing the Michaelis-Menten formula, modelling the non-linear tissue consumption rate, and of Hill equation, computing the oxyhaemoglobin concentration, respectively.

\[
M(C_{O_2}) = \frac{V_{\text{max}} C_{O_2}}{C_{O_2} + \alpha_t P_{m_{50}}}
\]

where \(V_{\text{max}}\) is the maximum consumption rate of oxygen in biological tissue calculated in \(ml_O_2/cm^3/s\), \(P_{m_{50}}\) is the oxygen partial pressure at half consumption rate, also known as Michaelis-Menten constant, which acts as a threshold for oxygen partial pressure.

\[
C_{\text{HbO}_2} = N \ H_t \ MCHC \ S(C_{O_2}) = N \ H_t \ MCHC \ \frac{C_{\text{O}_2}^T}{C_{\text{O}_2}^T + (\alpha_{pl} P_{s_{50}})^\gamma};
\]

where \(N\) is the Hüfner factor, or bound coefficient, \(H_t\) is the hematocrit in the blood flow, the MCHC (Mean Corpuscular Hematocrit Concentration) is a clinical parameter, which represents the amount of haemoglobin in each RBC, \(P_{s_{50}}\) is the oxygen partial pressure at haemoglobin half-saturation and \(\gamma\) is the Hill exponent.
By substituting the equations (22) and (23) into the equations (20) and (21), the non-linear 3D1D oxygen transport model is obtained:

\[
\begin{align*}
\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t C_t) + V_{\text{max}} \frac{C_t}{C_t + K_M} &= \frac{2}{\pi R} \left[ P_t (C_v - C_t) + \frac{C_v + C_t}{2} L_p \left( 1 - \sigma_{\text{oxy}} \right) \left( \Delta P - \sigma \Delta \pi \right) \right]; \quad \text{on } \Omega_t \\
\pi R^2 D_v \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial (u_v C_v)}{\partial s} - \pi R^2 \frac{\partial}{\partial s} (u_v k_1 H_t \frac{C_t^\gamma}{C_t^{\gamma} + k_2}) &= -2\pi R \left[ P_t (C_v - C_t) + \frac{C_v + C_t}{2} L_p \left( 1 - \sigma_{\text{oxy}} \right) \left( \Delta P - \sigma \Delta \pi \right) \right]; \quad \text{on } \Omega_v
\end{align*}
\]

where

\[
\begin{align*}
k_1 &= N MCHC; \\
k_2 &= (\alpha_{\text{pl}} P_{\text{50}})^\gamma
\end{align*}
\]

with the following boundary conditions:

\[
\begin{align*}
C_v &= C_{\text{in}} \quad \text{on } \partial \Lambda_{\text{IN}} \\
-\frac{D_v}{d} \frac{\partial C_v}{\partial s} &= 0 \quad \text{on } \partial \Lambda_{\text{OUT}} \\
-\frac{D_t}{d} \nabla C_t \cdot n &= 0 \quad \text{on } \partial \Omega
\end{align*}
\]

where at the vessel inlet boundary, \( \partial \Lambda_{\text{IN}} \), a Dirichlet condition has been set and at the vessel outlet boundary, \( \partial \Lambda_{\text{OUT}} \), and at the tissue domain faces, \( \partial \Omega \), a Neumann condition has been set. However, the introduction of the Michaelis-Menten and Hill equations have made the oxygen transport problem to be non-linear, indeed both constitutive models are described by a sigmoidal function. To obtain an appropriate formulation, therefore, it was necessary to use a fix-point iterative method.

The Radiobiological Model

The most commonly used radiobiological model is the Linear-Quadratic (LQ) model. The LQ model takes into account the energy type transferred to the tissue, the cell
type and the irradiation dose:

\[
S_f(D) = e^{(-\alpha D - \beta D^2)}; \tag{12}
\]

The model (4.1) represents the survival fraction, \( S_f \), of cells that survive an applied dose of radiation, \( D \). The \( \alpha \), \( [Gy^{-1}] \), and \( \beta \), \( [Gy^{-2}] \), parameters are two general radiosensitivity parameters. In this work, according to the works Wenzl et al [48, 49], the LQ model has been modified, in particular, the \( \alpha \) and \( \beta \) coefficients are re-written as linear function on the Linear Energy Transfer (LET) (3) and as non-linear function of oxygen partial pressure of the tissue, \( pO_2 \):

\[
\alpha(pO_2, LET) = \frac{(a_1 + a_2 \, LET) \cdot pO_2 + (a_3 + a_4 \, LET) \cdot K}{pO_2 + K}; \tag{13}
\]

\[
\sqrt{\beta(pO_2)} = \frac{b_1 \, pO_2 + b_3 \, K}{pO_2 + K}; \tag{14}
\]

where the \( a_1, a_2, a_3, a_4, b_1 \) and \( b_2 \) are constant coefficients, obtained by fitting of experimental surviving fraction curve and \( K \) is the oxygen concentration at which the relative radiosensitivity equals half of its maximum.

The LQ model has been used to compute the distribution of surviving fraction of cells in both healthy and tumoural tissue.

**RESULTS**

Following the definition of the non-linear oxygen transport model, firstly, some tests have been performed on simple geometries such as single branch case, a bifurcation case and an anastomosis case, to discuss the distribution of free oxygen concentration and the oxyhaemoglobin concentration in the capillaries.

Concerning the distribution of oxyhaemoglobin concentration, it has been observed that jumps at the junction due to the direct proportionality with respect to the hematocrit, as reported in equation (23). The distribution of hematocrit with respect to the capillaries radius (Zweifach-Fung effect) affects, also, the distribution of oxyhaemoglobin
concentration. For instance, in the bifurcation test case (Figure 5):

![Figure 2: Charts of oxyhemoglobin with a variation in radius. The oxyhemoglobin jumps at the junction and the jump is proportional to the hematocrit.](image)

**Figure 2:** Charts of oxyhemoglobin with a variation in radius. The oxyhemoglobin jumps at the junction and the jump is proportional to the hematocrit.

Then, the focus of the following simulations has become the oxygen partial pressure distribution and its effect on the surviving fraction of cells. Indeed, several Voronoi artificial networks with different capillary density have been obtained by a MATLAB tool, previously developed ([37]). Particular parameters have been set to simulate healthy and tumoral tissue properties since they are characterized by relevant physicochemical differences. The goal is to obtain the oxygen partial distribution in the interstitium, by solving the 3D1D oxygen transport model, to apply the LQ model and observe how the distribution of oxygen impacts on the surviving fraction of the cells. Several networks with an increasing number of capillaries have been taken into account to change
the oxygenation level in the tissue, obtaining $pO_2$ result consistent with the literature ([9], [19]). For each chosen case, the LQ model has been applied (Figure 6).

**Figure 3:** The a) panel represents the oxygen partial pressure distribution, instead the b) panel represents the surviving fraction, $S_f$, distribution. The results are reported for each network, from V2 (top) to V36 (bottom), for both healthy (first column) and tumoural (second column) tissue, respectively for each panel.
We noticed an homogeneous oxygen content distribution for healthy tissue cases and an heterogeneous oxygen content distribution for tumoural tissue cases in panel a) of [6]. Indeed, the oxygen affects the radiosensitivity of the tissue. The higher the oxygen content, the higher will be the effect the ionizing radiation. We notice, in the panel b), a low number of surviving fraction for an healthy and well-oxygenated tissue tissue (see V18 case) and an high number of $S_f$ for a tumoural tissue, due to different oxygen content. The $S_f$ is useful to compute clinical parameters, such as Oxygen Enhancement Ratio (OER) and Tumoural Control Probability (TCP), which can aid clinical decision-making.

**CONCLUSIONS**

The proposed mathematical model proved to be extremely versatile, to be able to simulate physiological and pathological conditions by setting accurately the input parameters. The 3D1D model takes into account many biological phenomena, well described by non-linear constitutive equations. The iterative method has been helpful in the solution of the transport problem. The results reported are consistent with the literature. In particular, the 3D representation of the results gave an original view of the surviving fraction, confirming radiobiological phenomena, such as the reduced killing effect of radiation on low-oxygenated biological or tumoural tissues.

Moreover, the 3D1D model is suitable for interesting future developments, such as treatments simulations by changing the ionizing radiation source (carbon ions or protons) or implementation of radiotherapy with fractionation.
Sommario
INTRODUZIONE

Il sistema circolatorio è l’insieme degli organi e dei vasi responsabili del trasporto del sangue nei tessuti per fornire sostanze nutritive e rimuovere i prodotti di scarto. I vasi microvascolari sono tipicamente classificati come arteriole, capillari e venule. In particolare, gli scambi di gas e di nutrienti avvengono a livello capillare, dove i vasi hanno un diametro simile a quello dei globuli rossi (RBCs). In questo lavoro, in primo luogo, è stato descritto il modello comunemente usato per calcolare il trasporto e lo scambio di ossigeno nella rete capillare, il modello di Krogh.

Il modello di Krogh vede i capillari come cilindri concentrici adiacenti l’uno all’altro (Figura 1.2).

In particolare, il sistema di equazioni e le assunzioni alla base del modello di Krogh sono stati discusse per evidenziarne i limiti. Il modello di Krogh è stato considerato come il punto di partenza per sviluppare un modello di trasporto dell’ossigeno più complesso.

Infatti, è stato sviluppato un modello agli elementi finiti per descrivere la distribuzione dell’ossigeno nell’ambiente microvascolare, in particolare, il modello calcola il trasporto e lo scambio di ossigeno tra la rete capillare e l’interstizio. Questo obiettivo è stato raggiunto grazie ad un solutore numerico in grado di simulare gli scambi tra una rete vascolare e il tessuto circostante. Il risolutore numerico, implementato in C++ utilizzando la libreria ad elementi finiti open-source GetFEM++, è stato implementato dal lavoro precedentemente sviluppato da Notaro [34] presso il Laboratorio di Modellazione e Calcolo Scientifico - MOX. Nel modello matematico e numerico, la tecnica di riduzione è stata utilizzata per modellare i capillari come canali 1D all’interno del
dominio interstiziale 3D ed è alla base del solutore. Partendo dai risultati ottenuti dalla risoluzione della fluidodinamica e dal trasporto degli eritrociti (38), nel presente lavoro, il modello di trasporto dell’ossigeno è stato ripreso e modificato opportunamente per renderlo più rappresentativo dell’ambiente biologico descritto dai modelli costitutivi non lineari, come la cinetica di Michaelis-Menten nel tessuto e il modello di Hill per la saturazione dei RBCs. La formula di Michaelis-Menten descrive il tasso di consumo non lineare di un determinato soluto, in questo caso l’ossigeno, da un substrato, l’interstizio. Dall’altro lato, l’equazione di Hill descrive la saturazione dei RBCs in funzione del contenuto di ossigeno nei capillari. I RBC svolgono un ruolo fondamentale nell’apporto di ossigeno ai tessuti, grazie all’emoglobina, una macromolecola in grado di legarsi all’ossigeno e di rilasciarlo quando necessario. Con l’equazione di Hill, introduciamo il concetto di ossiemoglobina nel modello. Quest’ultimo passo sarebbe stato impossibile senza l’implementazione del modello di trasporto dell’ematocrito (37, 38), che è di fondamentale importanza per la corretta descrizione del movimento del sangue nei capillari non solo in condizioni fisiologiche ma anche in condizioni patologiche. Inoltre, questo modello tiene conto di vari fenomeni biologici, come l’effetto Fåhræus-Lindqvist e l’effetto Zweifach-Fung. Il trasporto di ossigeno 3D1D, descritto in questo lavoro, ha un’interessante applicazione alla radioterapia. Può essere combinato al modello radiobiologico comunemente usato, il modello lineare-quadratico (LQ), per prevedere la distribuzione della frazione di cellule che sopravvive alle radiazioni ionizzanti, conoscendo la distribuzione della pressione parziale dell’ossigeno, \( pO_2 \).

Il modello 3D1D è versatile nel calcolo dei parametri fisiologici, come la velocità, la pressione idrostatica e la pressione parziale dell’ossigeno nei capillari e nell’interstizio. Inoltre, i risultati, ottenuti dalla combinazione dei modelli LQ e 3D1D, si sono dimostrati interessanti per la rilevanza clinica.
MATERIALI E METODI

Il modello di Krogh

Il modello di Krogh si basa su un’equazione generica di convezione-diffusione-reazione per il dominio del tessuto e su un equilibrio di flusso di ossigeno nel flusso sanguigno per una sezione infinitesimale del capillare, $dz$:

$$\frac{\partial C}{\partial t} = D \nabla \cdot (\nabla C) - \nabla (u C) + P(C) - V(C) \quad (15)$$

$$\pi R_i^2 u_z C - \pi R_i^2 u_z (C + \frac{\partial C}{\partial z} dz) = \pi (R_o^2 - R_i^2) dz V \quad (16)$$

dove $C = C(r,z,\vartheta)$ è la concentrazione di ossigeno libero in funzione della posizione, $D$ è il coefficiente di diffusione nel tessuto, $u = u(r,z,\vartheta)$ è il campo di velocità, $P(C)$ e $V(C)$ sono, rispettivamente, i termini di sorgente volumetrica di ossigeno e di consumo di ossigeno, funzioni della concentrazione. Il profilo di concentrazione dell’ossigeno è stato calcolato per il tessuto e lungo l’asse capillare, applicando le seguenti ipotesi:

1. Condizione stazionaria;

2. La diffusione assiale è trascurabile nel tessuto e il contributo convettivo non sono considerati nel tessuto;

3. Tasso di consumo omogeneo di ossigeno, $V(C)$, trascurando il termine fonte, $P(C)$;

4. La coordinata $\vartheta$ non è coinvolta, data la struttura simmetrica del capillare;

e le seguenti condizioni al contorno:

$$BC1 : if \quad r = R_i \quad C = C_0(z)$$

$$BC2 : if \quad r = R_o \quad - D \frac{\partial C}{\partial r} = 0$$
Quindi, il sistema di equazioni (15) e (16) è ridotto come segue:

\[ 0 = \frac{D}{r} \left( \frac{1}{\partial r} \left( r \frac{\partial C}{\partial r} \right) \right) - V \] (17)

\[ C(z) = C_0 - \left( \frac{R_o^2}{R_i^2} - 1 \right) \frac{V \ z}{u_z} \] (18)

Imponendo le condizioni al contorno e unendo (17) e (18), il modello di Krogh per il profilo di concentrazione di ossigeno libero nel tessuto si ottiene come segue:

\[ C(r, z) = C_0 + \frac{V R^2}{4 D} \left[ (r^2 - \frac{R_i^2}{R_o^2}) - 2 \ln \left( \frac{r}{R_i} \right) \right] - \left( \frac{R_o^2}{R_i^2} - 1 \right) \frac{V \ z}{u_z} ; \] (19)

L’equazione (19) presenta alcune criticità, come la presenza della sola fase di ossigeno dischelto, il tasso di consumo lineare nell’interstizio e l’assenza dello scambio di soluto e fluido tra i due domini per gradienti diffusivi, idrostatici e oncotici.

Il modello 3D1D di trasporto di ossigeno

In questo lavoro, il modello di trasporto dell’ossigeno è basato su un precedente modello computazionale che risolve il problema fluidodinamico come combinazione delle equazioni di Darcy e Poiseuille, e il problema del trasporto dell’ematocrito ([37, 38]). Il trasporto e il consumo di ossigeno sono modellati in un dominio, un sottospazio di \( \mathbb{R}^3 \), chiamato \( \Omega \subset \mathbb{R}^3 \), che consiste di due regioni: tessuto, \( \Omega_t \), e vaso (plasma e RBCs), \( \Omega_v \). Il capillare è stato ridotto alla sua "centerline", \( \Lambda \), imponendo particolari ipotesi ([34]) che sono in grado di considerare il capillare come un oggetto 1D immerso in una struttura 3D, ossia l’interstizio, considerato come un mezzo poroso. Nel sangue, l’ossigeno fluisce sia libero che legato all’emoglobina, quindi per il bilancio di massa si deve considerare l’ossigeno totale come la somma di due contributi. Il modello di trasporto dell’ossigeno si basa sui seguenti presupposti:

- L’ossiemoglobina non può diffondere. L’ossigeno è in grado di legarsi all’emoglobina, \( Hb \), una macromolecola composta da quattro siti di legame per l’ossigeno, chiamati gruppi eme. La reazione tra ossigeno ed emoglobina porta alla forma-
zione di ossiemoglobina. Non è in grado di diffondere lungo la direzione radiale, attraverso la membrana capillare.

- Dinamica di diffusione dell’ossigeno dai RBCs trascurabile. Si trascura la dinamica del rilascio di ossigeno da parte degli eritrociti nel flusso sanguigno e la cattura dell’ossigeno da parte dei globuli rossi. Queste reazioni sono considerate istantanee. Consideriamo la concentrazione di ossigeno come una quantità unica costituita dalla somma dei contributi di emoglobina libera e legata all’emoglobina.

Alla base del modello di trasporto dell’ossigeno ci sono due equazioni differenziali alle derivate parziali: una è per la concentrazione di ossigeno libero nel dominio dei tessuti 3D e l’altra è per la concentrazione totale di ossigeno, che è la somma di free, $C_v$, e legata all’emoglobina $C_{HbO_2}$, nel dominio della rete 1D. Il trasporto di ossigeno libero nel tessuto è modellato secondo la seguente equazione:

$$\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t C_t) + M \, C_t = J_{O_2} \quad \text{on } \Omega_t. \quad (20)$$

dove $D_t$ è il coefficiente diffusivo dell’ossigeno nell’interstizio, espresso come $m^2/s$, $u_t$ è la velocità del fluido nell’interstizio, nota grazie alla soluzione del problema fluidodinamico; $M$ è il tasso di consumo di ossigeno. Il tasso $M$ è espresso come $ml_{O_2}/cm^3/s$ ed è assunto costante, in prima approssimazione. Invece, l’equazione di trasporto in un vaso può essere derivata partendo dal bilancio di massa lungo un capillare lineare e cilindrico, stimando la differenza di portata tra ingresso e uscita. Riportiamo l’equazione generale del trasporto in 3D per la concentrazione totale di ossigeno, $C_{tot}$:

$$\nabla \cdot [(\pi R^2 \, D_v \nabla (C_{tot})) - \pi R^2 \, (u_v \, C_{tot})] + M \, C_{tot} = -J_{O_2} \quad (21)$$

dove $C_{tot} = C_v + C_{HbO_2}$.

L’ultimo termine, $J_{O_2}$, in entrambe le equazioni (20) e (21), rappresenta il termine di scambio modellato secondo l’equazione di Kedem-Katchalsky (25) in presenza di una
membrana semipermeabile:

\[
\begin{align*}
J_{diff} &= 2\pi R \left( C_v - C_t \right) P;
J_{adv} &= 2\pi R \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) \left( \Delta P - \sigma \Delta \pi \right);
J_{O_2} &= J_{diff} + J_{adv};
\end{align*}
\]

dove \( P_L \) è la permeabilità, definita come diffusività sulla larghezza della membrana capillare; \( L_P \) è la conducibilità idraulica delle pareti capillari in \((m \cdot ml_{O_2})/ml_B/mmHg\); \( \sigma \) è un numero puro e rappresenta il coefficiente di riflessione della membrana capillare alle proteine nel flusso sanguigno, invece \( \sigma_{oxy} \) è il coefficiente di riflessione relativo alla molecola di ossigeno. Le precedenti equazioni (20) e (21) sono state modificate introducendo la formula di Michaelis-Menten, che modella il tasso di consumo non lineare dei tessuti, e dell’equazione di Hill, che calcola la concentrazione di ossiemoglobina, rispettivamente.

\[
M(C_{O_2}) = V_{max} \frac{C_{O_2}}{C_{O_2} + \alpha_t P_{m50}}
\]  
(22)

dove \( V_{max} \) è il tasso di consumo massimo di ossigeno nel tessuto biologico calcolato in \( ml_{O_2}/cm^3/s \); \( P_{m50} \) è la pressione parziale di ossigeno a metà del tasso di consumo, nota anche come costante di Michaelis-Menten, che agisce come soglia per la pressione parziale di ossigeno.

\[
C_{HbO_2} = N H_t MCHC S(C_{O_2}) = N H_t MCHC \frac{C^\gamma_{O_2}}{C^\gamma_{O_2} + (\alpha_{pl} P_{s50})^\gamma};
\]
(23)

dove \( N \) è il fattore Hifner, o coefficiente legato, \( H_t \) è l’ematocrito nel flusso sanguigno, l’MCHC (Mean Corpuscular Hematocrit Concentration) è un parametro clinico, che rappresenta la quantità di emoglobina in ogni RBC, \( P_{s50} \) è la pressione parziale di ossigeno a metà saturazione dell’emoglobina e \( \gamma \) è l’esponente Hill.
Sostituendo le equazioni (22) e (23) nelle equazioni (20) e (21), si ottiene il modello non lineare di trasporto di ossigeno 3D1D:

\[
\begin{cases}
\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t C_t) + V_{max} \frac{C_t}{C_t + K_M} = \\
2\pi R \left[ P_l (C_v - C_t) + \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) (\Delta P - \sigma \Delta \pi) \right]; \quad \text{on } \Omega_t \\
\pi R^2 D_v \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial (u_v C_v)}{\partial s} - \pi R^2 H_t \left( \frac{C_{O_2}}{C_{O_2}^\gamma} k_2 \right) = \\
-2\pi R \left[ P_l (C_v - C_t) + \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) (\Delta P - \sigma \Delta \pi) \right]; \quad \text{on } \Omega_v
\end{cases}
\]  

(24)

dove

\[
\begin{cases}
k_1 = N MCHC; \\
k_2 = (\alpha pl P_{50})^\gamma
\end{cases}
\]

con le seguenti condizioni al contorno:

\[
C_v = C_{in} \quad \text{on } \partial \Lambda_{IN} \\
- \frac{D_v}{d U} \frac{\partial C_v}{\partial s} = 0 \quad \text{on } \partial \Lambda_{OUT} \\
- \frac{D_t}{d U} \nabla C_t \cdot n = 0 \quad \text{on } \partial \Omega
\]

(25)

dove al confine di ingresso del vaso, \( \partial \Lambda_{IN} \), è stata impostata una condizione di Dirichlet e al confine di uscita del vaso, \( \partial \Lambda_{OUT} \), e alle facce del dominio dei tessuti, \( \partial \Omega \), è stata impostata una condizione di Neumann. Tuttavia, l’introduzione delle equazioni di Michaelis-Menten e Hill hanno reso il problema del trasporto dell’ossigeno non lineare, infatti entrambi i modelli costitutivi sono descritti da una funzione sigmoidale. Per ottenere una formulazione appropriata, quindi, è stato necessario utilizzare un metodo iterativo a punto fisso.

Il modello radiobiologico

Il modello radiobiologico più comunemente usato è il modello Lineare-Quadratico (LQ). Il modello LQ tiene conto del tipo di energia trasferita al tessuto, del tipo di cellula e
della dose di irradiazione:

\[ S_f(D) = e^{(-\alpha D - \beta D^2)}; \]  

Il modello (4.1) rappresenta la frazione di cellule sopravvissute, \( S_f \), ad una dose di radiazioni, \( D \). I parametri, \( [Gy^{-1}] \), e \( \beta, [Gy^{-2}] \), sono due parametri generali di radiosensibilità. In questo lavoro, secondo i lavori Wenzl et al [48, 49], il modello LQ è stato modificato, in particolare, i coefficienti \( \alpha \) e \( \beta \) sono riscritti come funzione lineare sul trasferimento di energia lineare (LET) (3) e come funzione non lineare della pressione parziale di ossigeno del tessuto, \( pO_2 \):

\[ \alpha(pO_2, LET) = \left( a_1 + a_2 \cdot LET \right) \cdot pO_2 + \left( a_3 + a_4 \cdot LET \right) \cdot K; \]  

\[ \sqrt{\beta(pO_2)} = \frac{b_1 \cdot pO_2 + b_3 \cdot K}{pO_2 + K}; \]

dove \( a_1, a_2, a_3, a_4, b_1 \) e \( b_2 \) sono coefficienti costanti, ottenuti con l’adattamento della curva sperimentale delle frazioni di sopravvivenza e \( K \) è la concentrazione di ossigeno alla quale la radiosensibilità relativa è pari alla metà del suo massimo. Il modello LQ è stato utilizzato per calcolare la distribuzione della frazione superstite delle cellule sia nel tessuto sano che in quello tumorale.

**RISULTATI**

In seguito alla definizione del modello non lineare di trasporto dell’ossigeno, in primo luogo, sono stati effettuati alcuni test su geometrie semplici come il caso di un singolo ramo, un caso di biforcazione e un caso di anastomosi, per discutere la distribuzione della concentrazione di ossigeno libero e la concentrazione di ossiemoglobina nei capillari. Per quanto riguarda la distribuzione della concentrazione di ossiemoglobina, è stato osservato che assume valori differenti alla giunzione, a causa della proporzionalità diretta rispetto all’ematocrito, come riportato nell’equazione (23). La distribuzione dell’ematocrito rispetto al raggio capillare (effetto Zweifach-Fung) influenza anche sulla distribuzione della concentrazione di ossiemoglobina. Ad esempio, nel caso del test di biforcazione (Figura 5):
Figura 5: Grafico di ossiemoglobina con una variazione di raggio. L’ossiemoglobina salta alla giunzione e il salto è proporzionale all’ematocrito.

Poi, il fulcro delle seguenti simulazioni è diventato la distribuzione parziale della pressione dell’ossigeno e il suo effetto sulla frazione di cellule sopravvissuta. Infatti, diverse reti artificiali Voronoi con diversa densità capillare sono state ottenute tramite uno strumento MATLAB, precedentemente sviluppato ([37]). Particolari parametri sono stati impostati per simulare le proprietà dei tessuti sani e tumorali in quanto sono caratterizzati da rilevanti differenze fisico-chimiche. L’obiettivo è quello di ottenere la distribuzione parziale dell’ossigeno nell’interstizio, risolvendo il modello di trasporto dell’ossigeno 3D1D, di applicare il modello LQ e di osservare come la distribuzione dell’ossigeno influisca sulla frazione superstite delle cellule. Sono state prese in considerazione diverse reti con un numero crescente di capillari per modificare il livello
di ossigenazione nel tessuto, ottenendo un risultato di $pO_2$ coerente con la letteratura ([9][19]). Per ogni caso scelto, è stato applicato il modello LQ (Figura 6).

**Figura 6:** Il pannello a) rappresenta la distribuzione parziale della pressione dell’ossigeno, mentre il pannello b) rappresenta la frazione superstite, $S_f$, distribuzione. I risultati sono riportati per ogni rete, da V2 (top) a V36 (bottom), sia per il tessuto sano (prima colonna) che per quello tumorale (seconda colonna), rispettivamente per ogni pannello.
Abbiamo notato una distribuzione omogenea del contenuto di ossigeno per i casi di tessuto sano e una distribuzione eterogenea del contenuto di ossigeno per i casi di tessuto tumorale nel pannello a) di Figura 6. L’ossigeno influisce sulla radiosensibilità del tessuto: più alto è il contenuto di ossigeno, più alto è l’effetto della radiazione ionizzante. Notiamo, nel pannello b), un basso valore di $S_f$ per il tessuto sano e ben ossigenato (vedi caso V18) e un alto valore di $S_f$ per il tessuto tumorale, a causa del diverso contenuto di ossigeno. Il $S_f$ è utile per calcolare i parametri clinici, come l’Oxygen Enhancement Ratio (OER) e il Tumoural Control Probability (TCP), che possono aiutare il processo decisionale clinico.

**CONCLUSIONI**

Il modello matematico proposto si è dimostrato estremamente versatile, in grado di simulare condizioni fisiologiche e patologiche impostando accuratamente i parametri di input. Il modello 3D1D tiene conto di molti fenomeni biologici, ben descritti da equazioni costitutive non lineari. Il metodo iterativo è stato utile per la soluzione del problema del trasporto. I risultati riportati sono coerenti con la letteratura. In particolare, la rappresentazione 3D dei risultati ha dato una visione originale della frazione sopravvissuta, confermando fenomeni radiobiologici, come il ridotto effetto di uccisione delle radiazioni su tessuti biologici o tumorali a bassa ossigenazione. Inoltre, il modello 3D1D è adatto per interessanti sviluppi futuri, come simulare trattamenti con la modifica della sorgente di radiazioni ionizzanti (ioni carbonio o protoni) o l’implementazione della radioterapia con frazionamento.
Chapter 1

Introduction to micro-vascular oxygen transport and the Krogh’s model

1.1 The micro-vascular environment

The circulatory system is the set of organs and vessels responsible for the transport of blood in the tissues in order to provide nutrients and remove waste products, allowing maintaining optimal cellular functioning conditions. The vessels within the circulatory system are very heterogeneous and have structures and different functions. In the systemic circulation (Figure 1.1), blood pumped from the left heart enters the systemic arteries, vases equipped with a resistant and elastic wall that allows the transport of blood at high pressure. Downstream of the arteries are the arterioles, small-calibre vessels that act as flow regulation systems into the capillaries. At the distal end of the capillaries, the blood enters the venules flows into the veins and returns to the right side of the heart.

Even if morphology and functionality of the micro-vascular environment are highly tissue-dependent, it is typically described listing three main components: microvessels,
Micro-vascular vessels are typically classified as arterioles, capillaries, and venules. Arterioles and venules are characterized by a branching structure, and they are connected to the bigger vasculature. They have a diameter in the range of tens of µm, and their role is mainly convective transport of blood within tissues. Arterioles are also directly involved in flow regulation, being subject to vascular tone alterations due to metabolic signals, myogenic response and shear stress. The capillaries instead tend to form a more 'network-like' structure. Their diameter approaches the dimension of red blood cells (RBC) - that is 8µm. In addition, the leakiness of their wall (both in terms of fluids and solutes) allows the delivery of nutrients and the withdrawal of waste products from tissues.

The second main component of the micro-vascular environment is the lymphatic capillaries. They are the first vessels of the lymphatic system, which is responsible for returning fluids from the interstitium to blood, significantly contributing to fluid bal-
ance. Also, it is involved in immune system response.

Lastly, the interstitium has been described in physiology textbooks as the space between cells, accounting for one-sixth of the total body volume. It is composed of both fluid, therefore named interstitial fluid (ISF), and solid structure, the extra-cellular matrix (ECM). The composition of such a structure is greatly tissue-dependent, and it affects mechanical properties, cell-cell signalling, and movement of fluid flow through the interstitium. However, as a general description, collagen (which composes more than two-thirds of ECM proteins in many soft tissues) and proteoglycans are the most common component of ECM. In this space is the transport of the substances that are exchanged between blood and interstitial fluid and between interstitial fluid and cells: the water inside it moves by a pressure gradient, while the solutes, like the oxygen, move by diffusion, namely pushed by the concentration gradient, or by convection, namely driven by the motion of the fluid. A mathematical model for the transport and exchange of oxygen between the capillary network and the interstitium can provide useful data, especially at the clinical level, regarding the oxygenation of the tissue, whether healthy or pathological, to be able to take targeted action.
1.2 The Krogh’s model

August Krogh, professor of zoophysiology at University of Copenhagen, focused his own studies about the micro circulation of solutes and nutrients at capillary level and the gas exchanges at alveolar-pulmonary level. He proposed a model, which earns him the Nobel prize in 1920, which is able to describe, in first approximation, the perfusion of dissolved oxygen from capillaries into the surrounding tissue and the transport along the axis of the capillary ([28]). The Krogh’s model approximates the capillary bed as a set of concentric cylinders, adjacent and equidistant from each other, in which the solute, in this case the oxygen, can flow in two directions: the axial direction, identified by $s$ coordinate, and the radial direction, $r$ coordinate. Each capillary has a length, $L$, an inner radius $R_i$ and a outer radius $R_o$, as shown in Figure 1.2.

![Figure 1.2: Geometry of a capillary proposed by Krogh.](image)

The oxygen concentration profile has been computed through the tissue and along the capillary’s axis, applying the following assumptions:

1. Steady-state condition;

2. Negligible axial diffusion in the tissue and the advection contribution is not considered in the tissue;

3. Homogeneous oxygen consumption rate, $V(C)$, neglecting the source term, $P(C)$;

4. the $\theta$ coordinate is not involved, due to the symmetrical structure;

So, the Krogh’s model consists of two steps:
Step 1. Transport by convection along the capillary axis;

Step 2. Transport by diffusion and reaction effect in the surrounding tissue;

1.2.1 Transport in the surrounding tissue

The Krogh’s model is based on a generic advection-diffusion-reaction equation:

\[
\frac{\partial C}{\partial t} = D \nabla \cdot ( \nabla C ) - \nabla ( u \, C ) + P( C ) - V( C )
\]  

(1.1)

where \( C = C(r, z, \theta) \) is the concentration as function of the position, \( D \) is the diffusion coefficient in the tissue, \( u = u(r, z, \theta) \) is the velocity field, \( P(C) \) and \( V(C) \) are, respectively, volumetric oxygen source and oxygen consumption terms, functions on the concentration.

Re-writing the nabla operator in cylindrical coordinates and having the previous assumptions from 1 to 4, the equation (1.1) becomes:

\[
0 = \frac{D}{r} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C}{\partial r} \right) \right] - V
\]

(1.2)

with the following boundary conditions:

\[
\begin{align*}
BC1 & : \text{if } r = R_i \quad C = C_0(z) \\
BC2 & : \text{if } r = R_o \quad -D \frac{\partial C}{\partial r} = 0
\end{align*}
\]

where the first condition is a Dirichlet condition which impose \( C_0 \) as the concentration at the capillary wall and the second one is a Neumann condition, namely at the outer capillary wall.

So, the equation (1.2) has the general integral:

\[
\frac{C(r, z)}{C_0(z)} = 1 + \frac{VR_o^2}{4C_0D} \left[ (\frac{r^2}{R_o^2} - \frac{R_i^2}{R_o^2}) - 2 \ln(\frac{r}{R_i}) \right];
\]

(1.3)
Chapter 1: Introduction to micro-vascular oxygen transport and the Krogh’s model

The equation (1.3) shows that the concentration in the tissue has a non-linear profile, with respect to the \( r \) coordinate. The consumption rate, \( V \), has been set to be constant by Krogh.

### 1.2.2 Transport along the axis capillary

The model overlooks the oxygen concentration gradient along the \( z \)-axis of the capillary that is created in the bloodstream for effect of the consumption of \( O_2 \) in the tissue. The oxygen balance in the bloodstream of the capillary can be taken into account by estimating the mass flow rate incoming in an infinitesimal section of the capillary, \( dz \),

\[
\pi R_i^2 u_z C - \pi R_i^2 u_z (C + \frac{\partial C}{\partial z} dz) = \pi (R_o^2 - R_i^2) dz V
\]

Namely:

\[
\{ \text{Mass inflow term} \} - \{ \text{Mass outflow term} \} = \{ \text{Consumption term in the capillary thickness} \}
\]

The \( z \)-component of the velocity field, \( u_z \), has been considered as constant. The equation (1.4) can be re-written as:

\[
\frac{\partial C}{\partial z} = -(\frac{R_o^2}{R_i^2} - 1) \frac{V}{u_z} \tag{1.5}
\]

Imposing the initial boundary concentration, \( C_0 \), the concentration decays along the \( z \)-coordinate in a linear way:

\[
C(z) = C_0 - (\frac{R_o^2}{R_i^2} - 1) \frac{V}{u_z} z \tag{1.6}
\]

Finally, by union (1.3) and (1.6), the oxygen concentration profile in the tissue is obtained as below:

\[
C(r, z) = C_0 + \frac{V R_o^2}{4 D} \left[ (\frac{r^2}{R_o^2} - \frac{R_i^2}{R_o^2}) - 2 \ln(\frac{r}{R_i}) \right] - \left( \frac{R_o^2}{R_i^2} - 1 \right) \frac{V}{u_z} z; \tag{1.7}
\]
For instance, if we set the parameters, similar to physiological ones, to solve the equation \((1.7)\), as reported in Table \(1.1\), we will obtain the result, reported in term of oxygen partial pressure, \(P_{O_2}\), as in the Figure \(1.3\).

### Table 1.1: Set of parameters to solve the Krogh’s model.

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>DEFINITION</th>
<th>UNIT</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(L)</td>
<td>Capillary length</td>
<td>(\mu m)</td>
<td>200</td>
</tr>
<tr>
<td>(R_i)</td>
<td>Inner radius</td>
<td>(\mu m)</td>
<td>3</td>
</tr>
<tr>
<td>(R_o)</td>
<td>Outer radius</td>
<td>(\mu m)</td>
<td>30</td>
</tr>
<tr>
<td>(D)</td>
<td>Diffusion coefficient in the tissue</td>
<td>(m^2/s)</td>
<td>(2 \cdot 10^{-9})</td>
</tr>
<tr>
<td>(V)</td>
<td>Consumption rate in the tissue</td>
<td>(ml_{O_2}/cm^3/s)</td>
<td>5</td>
</tr>
<tr>
<td>(u_z)</td>
<td>Z-component of the velocity field</td>
<td>(mm/s)</td>
<td>1.6</td>
</tr>
<tr>
<td>(C_0)</td>
<td>Initial oxygen concentration</td>
<td>(ml_{O_2}/ml_B)</td>
<td>(3 \cdot 10^{-3})</td>
</tr>
</tbody>
</table>

**Figure 1.3**: Radial and axial oxygen decay according to Krogh’s model, \((1.7)\), with the set of parameters in Table \(1.1\).

As shown until now, the Krogh’s model is a good starting point, even if its strong assumptions, to define a more general micro circulation model, introducing terms which allows to consider realistic phenomena, e.g., presence of red blood cells (RBCs), oxygen consumption rate depending as a function of the partial pressure of oxygen in the tissue, considering the effect of both diffusion and advection term.
Chapter 1: Introduction to micro-vascular oxygen transport and the Krogh's model
Chapter 2

A computational model for oxygen transfer in micro circulation

Mathematical modelling is a well accepted tool of investigation in micro circulation, because it complements experimental investigation by facilitating the formulation of hypotheses to be tested against real data. Mathematical models for micro circulation have evolved over the last three decades (at least), with the attempt to advance the state of art from phenomenological models to predictive ones. More precisely, the importance of nonlinear blood rheology depending on hematocrit the role of the microvascular morphology and of the extravascular pressure gradient and the importance of oxygen transport, being an essential molecule to survivability of the cells is well accepted. The development of mathematical and computational models able to address the complexity of these phenomena is still a vivid area of research. This may be due to the intrinsic difficulty to solve the micro circulation problem, because it involves differential and nonlinear governing equations defined on networks of complex shape. The objective of this work is to derive a model of oxygen transport in the micro circulation and its interaction with the interstitial volume. As mentioned before, the model does also include non-linear oxygen-dependent terms in both environment of the biological system: vessels and interstitium. The resulting mathematical problem consists
of coupled partial differential equations (PDEs) on manifolds with heterogeneous dimensionality. Namely, it couples a flow and transport problem in one-dimension (1D) with a porous media flow problem in three-dimensions (3D).

### 2.1 The 3D-1D Multi-scale Mathematical Model

The following transport model is based on a previous computational model which solves the fluid dynamic problem as a combination of Darcy and Poiseuille equations, and hematocrit transport problem ([37, 38]). This chapter focuses on the introduction of the oxygen transport model in the micro-vascular bed in presence of red blood cells, namely considering that the oxygen will be transported in two different phases, free, $C$, and hemoglobin-bound, $C_{HbO_2}$, whose sum is the total oxygen in the microvasculature, called $C_{tot}$. Oxygen transport and consumption was modeled in a domain, a subspace of $\mathbb{R}^3$, called $\Omega \subset \mathbb{R}^3$, that consists of two regions: tissue, $\Omega_t$, and vessel (plasma and RBCs), $\Omega_v$. The capillary has been reduced to its centerline, $\Lambda$, imposing particular assumptions ([34]) that are able to consider the capillary as a 1D object immersed in a 3D structure.

The problem has been written in terms of the free oxygen concentration, $C = C(x, t)$, function of the position $x$ and time, using subscript $t$ and $v$ to identify $\Omega_t$ and $\Omega_v$, respectively; other quantities as oxygen partial pressure or oxyhemoglobin concentration has been derived from free oxygen concentration as explained below.

From now on, free concentration will be expressed in term of $ml_{O_2}/ml_{Blood}$ for the vessel and in terms of $ml_{O_2}/cm^3$ for the tissue.

Based on the previous works, we made the following assumptions assumptions to write the starting equation of the model:

- **Steady state condition**. this assumption is reasonable and widely used in computational models of the microvasculature. Thus, any possible transient phenomena is neglected.
Chapter 2: A computational model for oxygen transfer in micro circulation

- Body forces. any body force (i.e. gravity, inertia) is neglected.

The transport of free oxygen in the tissue is modelled by the following equation:

\[ \nabla \cdot \left( D_t \nabla (C_t) \right) - \nabla \cdot (u_t C_t) + M \; C_t = J_{O_2} \quad \text{on } \Omega_t. \quad (2.1) \]

The different components acting on the oxygen, in the equation (2.1) are: \( D_t \), the oxygen diffusive coefficient in the interstitium, expressed as \( m^2/s \); \( u_t \), the velocity of the fluid in the interstitium, known thanks to the solution of the fluid dynamic problem; \( M \), the oxygen consumption rate. The rate \( M \) is expressed as \( ml_O_2/cm^3/s \) is assumed constant as first approximation, even if it does change in a non-linear way with the oxygen partial pressure, \( pO_2 \), which changes with the distance from the capillary.

The last term, \( J_{O_2} \), represents the sum of the filtration contributions of diffusive mass flow, \( J_{diff} \) and convective mass flow, \( J_{adv} \), according to Kedem-Katchalsky equation (25) in presence of a semi-permeable membrane:

\[
\begin{align*}
J_{diff} &= 2\pi R \; P_l (C_v - C_t); \\
J_{adv} &= 2\pi R \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) (\Delta P - \sigma \Delta \pi); \\
J_{O_2} &= J_{diff} + J_{adv};
\end{align*}
\]

where \( P_l \) is the permeability, defined as diffusivity over the width of the capillary membrane; \( L_p \) is the hydraulic conductivity of the capillary walls in \( (m/ml_{O_2})/ml_B/mmHg \); \( \sigma \) is, a pure number and represents the reflection coefficient of the capillary membrane to proteins in the blood flow, instead \( \sigma_{oxy} \) is the a reflection coefficient relative to oxygen molecule.

On the other hand, the free oxygen diffuses through the capillary membrane and it is transported by the blood flow. The transport equation in a vessel can be derived starting with the mass balance along a linear and cylindrical capillary, estimating the difference of flow rate between inlet and outlet. In the blood, the oxygen flows both free and hemoglobin-bound, so for the mass balance it necessary to consider the total oxygen as sum of two contributes. The oxygen transport model is based on the
Figure 2.1: Mass balance in a single vessel. The mass flow rate is calculated as $\pi R^2 u_v C_{\text{tot}}$ and the mass flow exchanged between vessel and interstitium is computed by the Kedem-Katchalsky equation following assumptions:

- Oxyhemoglobin cannot diffuse. The oxygen is able to bound to the hemoglobin, Hb, a macro molecule made of four binding sites for oxygen, called heme groups. The reaction between oxygen and hemoglobin leads to oxyhemoglobin formation. It is not able diffuse along radial direction, through the capillary membrane. Moreover, it is also reasonable assuming that the hemoglobin cannot diffuse along radial direction;

- Negligible dynamic diffusion of oxygen from RBCs. We neglect the dynamics of oxygen release by erythrocytes into the bloodstream and oxygen capture by red blood cells. These reactions are considered instantaneous. We consider the concentration of oxygen as a unique quantity made up of the sum of the contributions of free and bound-hemoglobin.

We report the general 3D transport equation for total oxygen concentration, $C_{\text{tot}}$:

$$
\nabla \cdot \left[ (\pi R^2 D_v \nabla (C_{\text{tot}})) - \pi R^2 (u_v C_{\text{tot}}) \right] + M C_{\text{tot}} = -J_{O_2} \quad (2.2)
$$

where $C_{\text{tot}} = C_v + C_{\text{HbO}_2}$.

According to previously discussed assumptions and to the mass balance, shown in Figure 2.1, the equation (2.2) is reduced to the following equation along the axis coordinate, $s$:

$$
\frac{\partial}{\partial s} \left( \pi R^2 D_v \frac{\partial C_v}{\partial s} - \pi R^2 u_v C_{\text{tot}} \right) = -J_{O_2}
$$
In particular, the radii are modelled to be constant along the capillaries’ axis. So, expanding the derivative, the vessel equation in its dimensional form is:

\[ \pi R^2 D_v \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial(u_v C_{tot})}{\partial s} = -J_{O_2} \]  \hspace{1cm} (2.3)

The considerations just discussed about the transport of oxygen in vessels and through interstitium bring the following system of equations:

\[
\begin{aligned}
\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t C_t) + M C_t = J_{O_2}; & \quad \text{on } \Omega_t \\
\pi R^2 D_v \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial(u_v C_v)}{\partial s} - \pi R^2 \frac{\partial(u_v C_{HbO_2})}{\partial s} = -J_{O_2} & \quad \text{on } \Omega_v \\
J_{O_2} = 2\pi R [P_t(C_v - C_t) + \left(\frac{C_v + C_t}{2}\right)L_p (1 - \sigma_{oxy}) (\Delta P - \sigma \Delta \pi)]; & \quad \text{on } \Omega_v
\end{aligned}
\]  \hspace{1cm} (2.4)

This system will be modified in order to specify the transport model to oxygen taking account constitutive models that describe physiological phenomena.

### 2.1.1 Improvements to the transport model: non-linear terms

In this section, the central point of the work is presented, where particular constitutive equations are combined with the model [2.4] to compute the physiological and pathological behaviour of the oxygen transport in microvasculature. Here, different phenomena are taken into account.

**Michaelis-Menten formula.** Which takes into account the kinetics of oxygen consumption. It describes the oxygen partial pressure-dependent behaviour of the biological tissue:

\[ M(pO_2) = V_{max} \frac{pO_2}{pO_2 + P_{m50}} \]  \hspace{1cm} (2.5)

where $V_{max}$ is the maximum consumption rate of oxygen in biological tissue calculated in $mlO_2/cm^3/s$, $P_{m50}$ is the oxygen partial pressure at half consumption rate, also known as Michaelis-Menten constant, which acts as a threshold for oxygen partial pressure.
For instance, if the partial pressure is less than the $P_{m50}$ value, the tissue is hypoxic. The model have been written in terms of free oxygen concentration. So, we have to rewrite the formula (2.5) in terms of free oxygen concentration. We need a relationship that can describe the partial pressure of a gas as a function of its concentration. The Henry’s equation is helpful:

$$C = \alpha P$$ (2.6)

which relates the concentration of a gas, $C$, in a solution with its partial pressure, $P$, by a coefficient $\alpha$, the solubility of that gas which depends on the temperature, $T$ [°C]. For sake of simplicity, we set a human body average temperature at 37°C. That relationship has been substitute in (2.5), in order to express the Michaelis-Menten formula in term of free oxygen concentration, our variable of interest:

$$M(C_{O_2}) = V_{max} \frac{C_{O_2}}{C_{O_2} + \alpha_t P_{m50}}$$ (2.7)

where $\alpha_t$ is the oxygen solubility in the interstitium and the product $\alpha_t P_{m50}$ is called Michaelis-Menten constant, $K_M$. The Figure 2.2 shows the Michaelis-Menten curve as function of concentration normalized for the maximum consumption rate, $V_{max}$. The curve increases monotonically and approaches $V_{max}$ asymptotically. Physiological values of the coefficients in equation (2.7) are reported in Table 2.1.

<table>
<thead>
<tr>
<th>SYMBOLS</th>
<th>DEFINITIONS</th>
<th>VALUES</th>
<th>UNITS</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{max}$</td>
<td>Maximum oxygen consumption rate</td>
<td>$6.17 \cdot 10^{-5}$</td>
<td>$mlO_2/cm^3/s$</td>
<td>[17]</td>
</tr>
<tr>
<td>$\alpha_t$</td>
<td>Interstitium oxygen solubility</td>
<td>$3.89 \cdot 10^{-5}$</td>
<td>$mlO_2/cm^3/mmHg$</td>
<td>[30]</td>
</tr>
<tr>
<td>$P_{m50}$</td>
<td>$pO_2$ at half consumption rate</td>
<td>1.0</td>
<td>$mmHg$</td>
<td>[18, 30, 47]</td>
</tr>
</tbody>
</table>
Previously the total concentration in blood flow, $C_{tot}$, has been introduced as sum of free oxygen, $C_v$ and oxyhemoglobin, $C_{HbO_2}$. The oxyhemoglobin concentration can be re-written as follow:

\[ C_{HbO_2} = C_{Hb} \cdot S(pO_2) \]

namely the product of $C_{Hb}$, the concentrations of hemoglobin inside the blood flow, and $S(pO_2)$, their saturation of RBCs.

- **Hemoglobin concentration.** We model the presence of red blood cells and their capability to transport oxygen thanks to the hemoglobin and its heme groups. The amount of heme groups which the oxygen is able to bound with is given by:

\[ C_{Hb} = N \cdot [Hb]; \quad (2.8) \]
where \([Hb]\) is the concentration of hemoglobin per unit of volume, \(N\) is the Hülner factor, or bound coefficient, defined as amount of oxygen per unite of haemoglobin, \(ml_{O_2}/g_{Hb}\), therefore representing the oxygen binding capacity of human haemoglobin.

The \([Hb]\) can be defined as:

\[
[Hb] = H \cdot MCHC
\]  

(2.9)

where \(H\) is the hematocrit in the blood flow, the MCHC (Mean Corpuscular Hematocrit Concentration) is a clinical parameter, which represents the amount of haemoglobin in each RBC, expressed in \(g_{Hb}/ml_{RBC}\).

The maximum amount of haemoglobin-bound oxygen in blood can be estimated, combining (2.8) and (2.9), as:

\[
C_{Hb} = N \cdot H_t \cdot MCHC; \tag{2.10}
\]

- **Saturation of RBCs.** This is a percentage that represents the number of bonding sites occupied, i.e. how much oxygen is bound compared to how much can be bound. It is a function of the partial pressure of oxygen. That behaviour is well described by the Hill equation:

\[
S(pO_2) = \frac{pO_2^\gamma}{pO_2^\gamma + P_{s50}^\gamma}
\]  

(2.11)

which well fit the dissociation curve of haemoglobin.

The (2.11) has been used to describe the equilibrium curve between \(pO_2\) and \(S\), where \(P_{s50}\) is the oxygen partial pressure at hemoglobin half-saturation and \(\gamma\) is the Hill exponent.

The \(P_{s50}\) depends on:

- Temperature (°C);
- pH inside RBCs (Bohr effect);
Chapter 2: A computational model for oxygen transfer in micro circulation

Figure 2.3: Hill curve at physiological values for $P_{s50}$ and $\gamma$, used in out model

- $CO_2$ partial pressure (Haldane effect);
- 2,3-Bisphosphoglyceric acid concentration (or 2,3-DPG), a protein which reduce the affinity of the hemoglobin to oxygen;

Each term affects the slope and the position of the curve \cite{12, 46}. We took physiological values for $P_{s50}$ and $\gamma$ suitable for haematic flow, as reported in Table 2.2 in order to well fit data for normal human blood. In that way, we assume that temperature, pH, partial pressure of carbon dioxide and 2,3-Bisphosphoglyceric acid concentration constant. For sake of clarity, we report here some cases where the Hill curve changes its slope and its position with temperature, pH and Hill exponent, $\gamma$. To estimate the oxygen partial pressure at half-saturation, we applied an empirical equation from Kelman’s model \cite{12}:

$$P_{s50} = 26.8 \cdot 10^{(0.4 \cdot (7.24-pH)+0.06 \cdot log\left(\frac{P_{CO_2}}{40}\right)+0.024 \cdot (T-37))}$$ \hspace{1cm} (2.12)

We took in consideration two un-physiological cases and we compared them with the physiological case (red curve), as shown below in Figure 2.4.

A multi-scale computational model for micro-vascular oxygen transfer applied to radiotherapy 17
Chapter 2: A computational model for oxygen transfer in micro circulation

Figure 2.4: At the top left corner, the panel shows the how the saturation curve changes its position when the temperature increases, maintaining constant pH and $\gamma$; at the top right corner, instead, the curve changes position when the pH increases form 6.92 (a more acid environment) to 7.56 (a more basic environment); the last panel at bottom, shows how the curve changes its slope with respect $\gamma$ (\[6\]), at the same pH and temperature.

As done before, we apply the Henry’s equation, $C = \alpha \ P$ (\[2.6\]), to (2.11):

$$S(C_{O_2}) = \frac{C_{O_2}^{\gamma}}{C_{O_2}^{\gamma} + (\alpha_{pl} \ P_{50})^{\gamma}}$$

(2.13)

The oxyhemoglobin concentration is obtained combining the (2.10) and (2.13):

$$C_{HbO_2} = N \ H_t \ MCHC \ \frac{C_{O_2}^{\gamma}}{C_{O_2}^{\gamma} + (\alpha_{pl} \ P_{50})^{\gamma}};$$

(2.14)

The (2.14) describes how the concentration of bound-hemoglobin oxygen is linearly proportional to hematocrit, which in turn is function on the position, and is non-linearly proportional to free oxygen concentration.
The parameters in (2.14) are summarised in the Table 2.2.

<table>
<thead>
<tr>
<th>SYMBOLS</th>
<th>DEFINITIONS</th>
<th>VALUES</th>
<th>UNITS</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>Bound coefficient (or H&quot;ufner factor)</td>
<td>1.36</td>
<td>$ml_{O_2}/g_{Hb}$</td>
<td>[17]</td>
</tr>
<tr>
<td>$MCHC$</td>
<td>Mean Corpuscolar Hemoglobin Concentrations</td>
<td>0.34</td>
<td>$g_{Hb}/ml_{RBC}$</td>
<td>[17]</td>
</tr>
<tr>
<td>$\alpha_{pl}$</td>
<td>Plasma oxygen solubility</td>
<td>$2.82 \cdot 10^{-5}$</td>
<td>$ml_{O_2}/ml_{B}/mmHg$</td>
<td>[30]</td>
</tr>
<tr>
<td>$P_{ss50}$</td>
<td>$pO_2$ at half saturations</td>
<td>27</td>
<td>mmHg</td>
<td>[32, 47]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Hill constant</td>
<td>2.64</td>
<td>-</td>
<td>[30, 17]</td>
</tr>
<tr>
<td>$T$</td>
<td>Temperature</td>
<td>37</td>
<td>°C</td>
<td>-</td>
</tr>
<tr>
<td>$pH_{RBC}$</td>
<td>pH in RBCs</td>
<td>7.24</td>
<td>-</td>
<td>[12]</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>Partial pressure of carbon dioxide</td>
<td>40</td>
<td>mmHg</td>
<td>[12]</td>
</tr>
<tr>
<td>$[2,3-DPG]$</td>
<td>Concentration of 2,3-Bisphosphoglyceric acid</td>
<td>4.65</td>
<td>mM</td>
<td>[12]</td>
</tr>
</tbody>
</table>

Now, if we replace the constant reaction term with (2.7) and the $C_{HbO_2}$ with the equation (2.14) in the coupled system of equations (2.4), the whole non-linear oxygen transport model is obtained in its dimensional form, as follows:

$$
\begin{align*}
\nabla \cdot (D_t \nabla (C_t)) - \nabla \cdot (u_t \ C_t) + V_{max} \frac{C_t}{C_t + K_M} = \\
2\pi R \left[ P_t (C_v - C_t) + \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) (\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_t \\
\pi R^2 D_v \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial (u_v \ C_v)}{\partial s} - \pi R^2 \frac{\partial}{\partial s} \left( u_v \ k_1 \ H_t \ \frac{C_v^\gamma}{C_v^\gamma + k_2} \right) = \\
-2\pi R \left[ P_t (C_v - C_t) + \left( \frac{C_v + C_t}{2} \right) L_p \left( 1 - \sigma_{oxy} \right) (\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_v
\end{align*}
$$

(2.15)
For sake of simplicity and clarity the following coefficients are called:

\[
\begin{aligned}
  k_1 &= N MCHC; \\
  k_2 &= (\alpha_{pl} P_{s_{so}})^\gamma;
\end{aligned}
\]

### 2.1.2 Boundary conditions

To ensure the uniqueness of the solution, the system of equations needs boundary conditions. These are established by physiological hypotheses, can be read in the literature, or from available data. Different types of boundary conditions are available: the Dirichlet condition (or first type), which imposes a value on the boundary solution; the Neumann condition (or second type), which imposes a value on the derivative of the boundary solution; and the Robin condition (or third type), which is a linear combination of the previous boundary conditions. Speaking of the vascular domain, we decided to apply:

\[
C_v = C_{in} \quad \text{on } \partial \Lambda_{IN}
\]

\[
- \frac{D_v}{dU} \frac{\partial C_v}{\partial s} = 0 \quad \text{on } \partial \Lambda_{OUT}
\]

Those conditions are Dirichlet condition, at the vessel inlet boundary, \( \partial \Lambda_{IN} \), and Neumann condition, at the vessel outlet boundary, \( \partial \Lambda_{OUT} \), respectively. The Dirichlet’s condition dictates the initial concentration of free oxygen within the arterial blood, while Neumann’s condition dictates that oxygen can flow out of the system.

At the boundary of the volume \( \Omega \), we have flow of oxygenated interstitial fluid (IF); the quantity of oxygen exchanged with the exterior depends on the oxygen concentration itself. We model this condition with a Robin condition:

\[
- \frac{D_t}{dU} \nabla C_t \cdot \mathbf{n} = \beta_t (C_t - c_{0,t}) \quad \text{on } \partial \Omega
\]

That means, the oxygenated IF on the boundary is proportional to a \( \beta \) coefficient, called
boundary conductivity, and to the concentration gradient between the tissue oxygen concentration, $C_t$, on the boundary of our domain and an oxygen concentration, $c_{0,t}$, set a priori, which simulate the presence of adjacent oxygenated tissue domain.

**Remark** We set the previous boundary conditions to describe the physical conditions that we need to close the problem; nevertheless, in the model we developed a more general framework for boundary conditions, considering all the different cases. Therefore, from now on we will consider those general boundary conditions:

$$C_v = C_{in} \quad \text{on } \partial \Lambda_{IN}$$

$$-\frac{D_v}{d U} \frac{\partial C_v}{\partial s} = \beta_v (C_v - c_{0,v}) \quad \text{on } \partial \Lambda_{OUT} \quad (2.16)$$

$$-\frac{D_t}{d U} \nabla C_t \cdot n = \beta_t (C_t - c_{0,t}) \quad \text{on } \partial \Omega$$

### 2.1.3 Dimension analysis

In this section, we will express our model in dimensionless form. Let us rewrite the problem (2.15) in order to make it not dependent on units and to highlight the relative relevance of the physical phenomena or mechanisms governing the perfusion, transport and oxygen consumption in a biological environment. Let us identify the characteristic dimensions of our model: (i) the average spacing between capillary vessels $d$, (ii) the average velocity in the capillary bed $U$, (iii) the average pressure in the interstitial space $P$ and (iv) the characteristic concentration of free oxygen $C$. The chosen characteristic parameters are report in the Table 2.3. The characteristic concentration $C$ was taken as the free oxygen concentration of arterial blood at the entrance of a capillary with $pO_2$ at 100 mmHg, considering an average solubility of plasma oxygen at 37 °C, equal to $3 \cdot 10^{-5} \text{ mlO}_2/\text{mlB/mmHg}$. 
Table 2.3: Characteristic parameters taken into account dimension analysis.

<table>
<thead>
<tr>
<th>SYMBOLS</th>
<th>DEFINITIONS</th>
<th>VALUES</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>characteristic length</td>
<td>$5 \cdot 10^{-4}$</td>
<td>m</td>
</tr>
<tr>
<td>U</td>
<td>characteristic velocity</td>
<td>$1 \cdot 10^{-3}$</td>
<td>m/s</td>
</tr>
<tr>
<td>P</td>
<td>characteristic pressure</td>
<td>133.32</td>
<td>Pa</td>
</tr>
<tr>
<td>C</td>
<td>characteristic concentrations</td>
<td>$3 \cdot 10^{-3}$</td>
<td>$ml_{O_2}/ml_B$</td>
</tr>
</tbody>
</table>

Consequently, the dimensional groups of coefficient became:

- $R^* = \frac{R}{d}$ non-dimensional radius;
- $D_t^* = \frac{D_t}{dU}$ dimensionless diffusive coefficient for tissue;
- $D_v^* = \frac{D_v}{dU}$ dimensionless diffusive coefficient for vessels;
- $M_0 = \frac{V_{max}}{U} \frac{d}{C}$ oxygen consumption rate;
- $P_t^* = \frac{P_t}{U}$ permeability of the capillary membrane;
- $L^*_p = \frac{L_p}{U}$ hydraulic conductivity of the capillary membrane;

For simplicity of notation, we used the same symbols notation in the model for the dimensionless variables such as velocity ($u_t$ and $u_v$), pressure ($P$) and concentration ($C$). After replacing the dimensionless variables into the model, we obtain:

\[
\begin{align*}
\nabla \cdot (D_t^* \nabla C_t) - \nabla \cdot u_t \ C_t - u_t \cdot \nabla C_t + \frac{M_0}{C_t + K_M/C} & \ C_t = \\
2\pi R^* \left[P_t^*(C_v - C_t) + \left(\frac{C_v + C_t}{2}\right)L_p^* (1 - \sigma_{oxy}) \ P (\Delta P - \sigma \Delta \pi)\right] & \text{ on } \Omega_t \\
\pi R^* D_v^* \frac{\partial^2 C_v}{\partial s^2} - \pi R^* \frac{2}{\partial s} \left(\frac{u_v \ C_v}{C_v^*} + k_1 H_1 \ C_v^*/(C_v^* + k_2)\right) & = \\
-2\pi R^* \left[P_t^*(C_v - C_t) + \left(\frac{C_v + C_t}{2}\right)L_p^* (1 - \sigma_{oxy}) \ P (\Delta P - \sigma \Delta \pi)\right] & \text{ on } \Omega_v
\end{align*}
\]

(2.17)
2.1.4 Treatment of non-linear terms

The model (2.17) presents two relevant non-linear terms: Michaelis-Menten formula (2.7) and oxyhemoglobin concentration as function on saturation of RBCs (2.14). The multi-scale coupled model, as written until now, namely equation (2.15), is presented as a non-linear system of partial differential equations. In the presence of non-linear terms, iterative methods are useful to solve the numerical problem. They work by comparing the solution at iteration $k$ with the solution at previous iteration $k - 1$, until an error, we called $\epsilon$, is small enough to be minor than a threshold, $\epsilon_{\text{max}}$. We decide to apply a fixed point method in order to linearize the system of equations by evaluating the reaction term in the tissue and the oxyhemoglobin concentration in the capillary, at the previous iteration. Consequently, we will need an initial concentration guess for starting iteration. We report a flow chart, in Figure 2.5, to summarize the steps of fixed point method, we followed to solve the model iteratively.

![Flow chart](image)

**Figure 2.5**: Flow chart followed to solve the non-linear oxygen transport problem in a iterative way

Let us call $k$ the current iteration and $k - 1$ the previous iteration. The fixed point
algorithm for equation (2.17) is:

\[
\nabla \cdot (D_t \nabla C_t^{(k)}) - \nabla \cdot u_t C_t^{(k)} - \nabla C_t^{(k)} + \frac{V_{\text{max}}}{C_t^{(k-1)} + K_M} C_t^{(k)} = \\
2\pi R \left[ P_l(C_v^{(k)} - C_t^{(k)}) + \left( \frac{C_v^{(k)} + C_t^{(k)}}{2} \right) L_p (1 - \sigma_\text{oxy}) (\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_t
\]

\[
\pi R^2 \frac{\partial^2 C_v^{(k)}}{\partial s^2} - \pi R^2 \frac{\partial C_v^{(k)}}{\partial s} \frac{\partial u_v^{(k-1)}}{\partial s} C_v^{(k)} - \pi R^2 \Psi^{(k-1)} \frac{\partial C_v^{(k)}}{\partial s} u_v^{(k-1)} - \pi R^2 \frac{\partial C_v^{(k)}}{\partial s} \frac{\partial C_v^{(k)}}{\partial s} u_v^{(k)} = \\
-2\pi R \left[ P_l(C_v^{(k)} - C_t^{(k)}) + \left( \frac{C_v^{(k)} + C_t^{(k)}}{2} \right) L_p (1 - \sigma_\text{oxy}) (\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_v
\]

(2.18)

The new coefficient, \( \Psi \), is the oxyhemoglobin concentration at the previous iteration, in its dimensionless form:

\[
\Psi^{(k-1)} = \frac{k_1}{C} H_t \frac{C_{O_2}^{(k-1)^{\text{eq}}}}{C_{O_2}^{(k-1)^{\text{eq}}}} + k_2/C
\]

(2.19)

Such formulation of the oxyhemoglobin term highlights the effect of the transport of free oxygen with respect to the bound-hemoglobin oxygen. By a mathematical point of view, the blood velocity can be re-written as follows:

\[
u_u^{(k)} = u_v (1 + \Psi^{(k)});
\]

(2.20)

Taking into consideration (2.19) and (2.20) in (2.18), the linearized system of equations is:

\[
\nabla \cdot (D_t^{*} \nabla C_t^{(k)}) - \nabla \cdot u_t C_t^{(k)} - \nabla C_t^{(k)} + \frac{M_0}{C_t^{(k-1)} + K_M/C} C_t^{(k)} = \\
2\pi R^{*} \left[ P_l^{*}(C_v^{(k)} - C_t^{(k)}) + \left( \frac{C_v^{(k)} + C_t^{(k)}}{2} \right) L_p^{*} (1 - \sigma_\text{oxy}) P(\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_t
\]

\[
\pi R^{*2} \frac{\partial^2 C_v^{(k)}}{\partial s^2} - \pi R^{*2} \frac{\partial C_v^{(k)}}{\partial s} \frac{\partial u_v^{(k-1)}}{\partial s} C_v^{(k)} - \pi R^{*2} \Psi^{(k-1)} \frac{\partial C_v^{(k)}}{\partial s} u_v^{(k-1)} = \\
-2\pi R^{*} \left[ P_l^{*}(C_v^{(k)} - C_t^{(k)}) + \left( \frac{C_v^{(k)} + C_t^{(k)}}{2} \right) L_p^{*} (1 - \sigma_\text{oxy}) P(\Delta P - \sigma \Delta \pi) \right]; \text{ on } \Omega_v
\]

(2.21)
2.2 Weak formulation of 3D-1D problem

The presented model (2.17) does not have an explicit analytical solution, so to compute the approximate solution application of the finite element method is required. Before proceeding with the discretization we have written the variational form of the system.

2.2.1 Weak formulation of the tissue problem

Let us consider the problem in its dimensionless form (2.17); we proceed by integrating each term of the equation over its respective domain, \( \Omega \), and then by multiplying by a sufficient smooth function, \( q_t \), called test function. The test space for the concentration in \( \Omega \) is:

\[
Q_t := H^1_{0,\partial\Omega} (\Omega)
\]

Writing the weak formulation of the problem:

\[
\int_{\Omega} D^* \nabla \cdot (\nabla C_t^{(k)}) \ q_t \ d\Omega - \int_{\Omega} \nabla \cdot u_t C_t^{(k)} \ q_t \ d\Omega - \int_{\Omega} u_t \nabla C_t^{(k)} \ q_t \ d\Omega + \int_{\Omega} \frac{M_0}{C_t^{(k-1)} + K_M/C} C_t^{(k)} \ q_t \ d\Omega = \]

\[
= \int_{\partial\Omega} 2\pi R^* [P^* + \frac{L^*_p}{2} (1 - \sigma_{oxy}) \ P (P_v - P_l - \sigma \Delta \pi)] \ C_v^{(k)} \cdot q_t \ d\partial\Omega +
\]

\[- \int_{\partial\Omega} 2\pi R^* [P^* - \frac{L^*_p}{2} (1 - \sigma_{oxy}) \ P (P_v - P_l - \sigma \Delta \pi)] \ C_t^{(k)} \cdot q_t \ d\partial\Omega
\]

Before proceeding, we apply the Green formula to the diffusion term:

\[
\int_{\Omega} D_t^* \nabla \cdot (\nabla C_t) \ q_t \ d\Omega = \int_{\partial\Omega} D_t^* \nabla C_t \cdot \mathbf{n} \ q_t \ d\partial\Omega - \int_{\Omega} D_t^* \nabla C_t \cdot \nabla q_t \ d\Omega \quad (2.22)
\]
2.2.2 Weak formulation of the vessel problem

As done for the tissue in Section 2.2.1, let us integrate the vessel problem over $\Omega_v$ and multiply it by a smooth function, $q_v$. Now the test space for $\Lambda$ is:

$$Q_v := H^1_{0,\partial\Lambda, N}(\Lambda)$$

Now, the weak formulation of the problem can be written as follows below:

$$\int_{\Lambda} \pi R^* 2 D^*_v \frac{\partial^2 C_v^{(k)}}{\partial s^2} q_v \, d\Lambda - \int_{\Lambda} \pi R^* 2 \frac{\partial u_v^*}{\partial s} C_v^{(k)} q_v \, d\Lambda - \int_{\Lambda} \pi R^* 2 u_v^* \frac{\partial C_v^{(k)}}{\partial s} q_v \, d\Lambda =$$

$$= - \int_{\Lambda} 2\pi R^* [P^* - \frac{L_p}{2} (1 - \sigma_{oxy})] P (P_v - P_t - \sigma \Delta \pi) C_v^{(k)} q_v \, d\Lambda +$$

$$+ \int_{\Lambda} 2\pi R^* [P^* - \frac{L_p}{2} (1 - \sigma_{oxy})] P (P_v - P_t - \sigma \Delta \pi) C_t^{(k)} q_v \, d\Lambda$$

Before proceeding with the integration by parts, the diffusive term should be split at each junctions, in order to express the integral over the whole network as sum of many integrals over the single branches:

$$\int_{\Lambda} \pi R^* 2 D^*_v \frac{\partial^2 C_v^{(k)}}{\partial s^2} q_v \, d\Lambda = \sum_{i=1}^{N} \int_{\Lambda_i} \pi R_i^* 2 D^*_v \frac{\partial^2 C_v^{(k)}}{\partial s^2} q_v \, d\Lambda_i$$

where $N$ is the number of branches. Now we can proceed integrating by parts:

$$\sum_{i=1}^{N} \int_{\Lambda_i} \pi R_i^* 2 D^*_v \frac{\partial^2 C_v^{(k)}}{\partial s^2} q_v \, d\Lambda_i = - \int_{\Lambda} \pi R^* 2 D^*_v \frac{\partial C_v^{(k)}}{\partial s} \frac{\partial q_v}{\partial s} \, d\Lambda + \sum_{i=1}^{N} \pi R_i^* 2 \left[ D^*_v \frac{\partial C_v^{(k)}}{\partial s} q_v \right]_{\Lambda_i^-}^{\Lambda_i^+};$$

where $\Lambda_i^-$ and $\Lambda_i^+$ represent the input and output extremes of $i$-th branch, $\Lambda_i$ according to the orientation of $\lambda_i$.

So, writing the diffusive term in its integrated form, the transport equation in the vessel is:

$$\int_{\Lambda} -\pi R^* 2 D^*_v \frac{\partial C_v^{(k)}}{\partial s} \frac{\partial q_v}{\partial s} \, d\Lambda_i - \int_{\Lambda} \pi R^* 2 \frac{\partial u_v^*}{\partial s} C_v^{(k)} q_v \, d\Lambda - \int_{\Lambda} \pi R^* 2 u_v^* \frac{\partial C_v^{(k)}}{\partial s} q_v \, d\Lambda =$$
\[
= - \int_{\Lambda} 2\pi R^* \left[ P^* + \frac{L_p^*}{2} (1 - \sigma_{\text{oxy}}) \right] P(P_v - P_t - \sigma \Delta \pi) C^{(k)} q_v \, d\Lambda \\
+ \int_{\Lambda} 2\pi R^* \left[ P^*_t - \frac{L_p^*}{2} (1 - \sigma_{\text{oxy}}) \right] P(P_v - P_t - \sigma \Delta \pi) C^{(k)} q_v \, d\Lambda \\
- \sum_{i=1}^{N} \pi R^2_i \left[ D_v \frac{\partial C_v^{(k)}}{\partial s} q_v \right]_{\Lambda^+_i} \Lambda^-_i;
\]

2.2.3 Mathematical model of vascular junctions and mass conservation

We assume that the free oxygen concentration is continuous at the junction, but the oxyhemoglobin concentration depends on haematocrit and velocities which may jump at junctions. We have to deal with the mass conservation at the junctions:

\[
\Phi = \pi R^2 u_v C_{v\text{tot}} - \pi R^2 D_v \frac{\partial C_v}{\partial s}
\]

where \(\Phi\) is the total mass flow rate along a capillary, expressed by the difference of convective mass flow rate and diffusive mass flow rate. We recall that the total oxygen concentration is defined by \(C_{\text{tot}} = C_v + C_{HbO_2}\).

Mass conservation at junctions can be expressed as,

\[
\Phi_0 = \Phi_1 + \Phi_2 \tag{2.24}
\]

being \(\Phi_{i=0,1,2}\) the flow through each branch. We will demonstrate is that the condition \(2.24\) is expressed "naturally", namely the continuity equation is preserved by already previous validated balances.

We assume that the free oxygen concentration is continuous at the junctions, so we can write, for an hypothetical bifurcation:

\[
C_{v_0} = C_{v_1} = C_{v_2}
\]
where the subscript 0 means the inlet and 1 and 2 subscripts are the outlets of the capillary. Previous works ensures that the fluid flow rate and the RBCs flow rate, in the capillaries, are preserved:

\[ \pi R_0^2 u_{v0} = \pi R_1^2 u_{v1} + \pi R_2^2 u_{v2}; \]

\[ \pi R_0^2 u_{v0} H_0 = \pi R_1^2 u_{v1} H_1 + \pi R_2^2 u_{v2} H_2 \]

Now, we have all the necessary mass balance equations to verify the balance of total oxygen concentration at the junctions. So, firstly, we can multiply the flow rate conservation by the free oxygen concentration, that we supposed to be continuous at the junctions:

\[ \pi R_0^2 u_{v0} C_{v0} = \pi R_1^2 u_{v1} C_{v1} + \pi R_2^2 u_{v2} C_{v2}; \] (2.25)

Secondly, we can multiply the RBCs flow rate conservation by the saturation equation, (2.13), we will call it \( S(C_v) \):

\[ \pi R_0^2 u_{v0} H_0 \ S(C_{v0}) = \pi R_1^2 u_{v1} H_1 \ S(C_{v1}) + \pi R_2^2 u_{v2} H_2 \ S(C_{v2}) \] (2.26)

We can re-write the (2.26) in terms of oxyhemoglobin concentration, \( \Psi \), by the equation (2.14):

\[ \pi R_0^2 u_{v0} \Psi_0 = \pi R_1^2 u_{v1} \Psi_1 + \pi R_2^2 u_{v2} \Psi_2 \] (2.27)

Thirdly, we sum the (2.25) and the (2.27) and we apply the definition of total oxygen concentration:

\[ \pi R_0^2 u_{v0} C_{v_{tot0}} = \pi R_1^2 u_{v1} C_{v_{tot1}} + \pi R_2^2 u_{v2} C_{v_{tot2}}; \] (2.28)

With the equation (2.28), we have just demonstrate the conservation of total oxygen concentration by combining mass balance equations previously validated.
Combining (2.28) with (2.23), we obtain that:

\[-D_v \frac{\partial C_v}{\partial s} = -D_v \frac{\partial C_{v1}}{\partial s} - D_v \frac{\partial C_{v2}}{\partial s}\]

The last equation ensures that the residual terms of the Green’s formula in the weak formulation, namely the second term of equation (2.23), are identically null at the junction. In conclusion, the solely condition to be enforced is the conservation of the free oxygen concentration: \(C_{v0} = C_{v1} = C_{v2}\). Thanks to this condition, the left terms of (2.23) related to internal junctions comes out. The only surviving terms are those related to end points on the domain boundary, that are used to enforce boundary conditions for the network problem.

Therefore, the whole weak formulation of the oxygen transport problem results to be:

\[
\begin{aligned}
(D_t^* \nabla C_t^{(k)} \cdot \nabla q_v + (u_t \cdot \nabla C_t^{(k)}, q_v)_\Omega + (\nabla \cdot u_t C_t^{(k)}, q_v)_\Omega - (\frac{M_0}{C_t^{(k-1)}} + \frac{K_M}{C} C_t^{(k)}, q_v)_\Omega \\
+ (2\pi R^* P_t^* + \frac{L_p^*}{2} (1 - \sigma_{oxy}) P(P_v - P_t - \sigma\Delta\pi)) C_t^{(k)}, q_v)_\Omega \\
- (2\pi R^* P_t^* - \frac{L_p^*}{2} (1 - \sigma_{oxy}) P(P_v - P_t - \sigma\Delta\pi)) C_t^{(k)}, q_v)_\Omega \\
= (D_t^* \nabla C_t^{(k)} \cdot n, q_v)_{\partial\Omega_{INT}}; \quad \forall q_v \in Q_t
\end{aligned}
\]

\[
\begin{aligned}
\left(\pi R^* D_v^* \frac{\partial C_v^{(k)}}{\partial s}, q_v\right)_\Lambda + (\pi R^* u_v^* \frac{\partial C_v^{(k)}}{\partial s}, q_v)_\Lambda + (\pi R^* \frac{\partial u_v^*}{\partial s} C_v^{(k)}, q_v)_\Lambda \\
- (2\pi R^* P_t^* + \frac{L_p^*}{2} (1 - \sigma_{oxy}) P(P_v - P_t - \sigma\Delta\pi)) C_t^{(k)}, q_v)_\Lambda \\
+ (2\pi R^* P_t^* - \frac{L_p^*}{2} (1 - \sigma_{oxy}) P(P_v - P_t - \sigma\Delta\pi)) C_t^{(k)}, q_v)_\Lambda \\
= [\pi R^* D_v^* \frac{\partial C_v^{(k)}}{\partial s} q_v]_{\partial\Omega_{OUT}} - [\pi R^* D_v^* \frac{\partial C_v^{(k)}}{\partial s} q_v]_{\partial\Omega_{IN}}; \quad \forall q_v \in Q_v
\end{aligned}
\]

Where the notation \((\cdot, \cdot)_s\) represents the inner product over the domain \(*\).
2.3 Numerical approximation

We cannot calculate the exact solution of the problem, but we can estimate an approximated solution thanks to the Galerkin’s method. It allows us to pass from a problem defined on a continuous setting to a discretized one, where the variables are defined as linear combinations of elements of the discrete approximation space. Let us introduce that method step by step, firstly, by discussing about the discretization of $\Omega$ and $\Lambda$ and then by showing the algebraic formulation of the weak and discrete problem.

2.3.1 Discretization of tissue and vessel problems

The discretization of problem is achieved by means of the finite element method. One of the main advantages of our formulation is that the partitions of $\Omega$ and $\Lambda$ are completely independent. For this reason we address the two approximations separately. We denote with $T$ an admissible family of partitions of $\bar{\Omega}$ into tetrahedrons $K$:

$$\bar{\Omega} = \bigcup_{K \in T^h} K,$$

that satisfies the usual conditions of a conforming triangulation of $\Omega$. Here, $h$ denotes the mesh characteristic size, i.e. $h = \max_{K \in T^h} h_K$, being $h_K$ the diameter of simplex $K$. Moreover, we are implicitly assuming that $\Omega$ is a polygonal domain. The solutions of the weak problem are approximated using continuous piecewise-polynomial finite elements for the concentration, in particular we have:

$$Y^h_k := \{ f_h \in C^0(\Omega), \ f_h|_K \in P_k(K) \quad \forall K \in T^h \},$$

for every integer $k \geq 0$, where $P_k$ indicates the standard space of polynomials of degree $\leq k$ in the variables $\mathbf{x} = (x_1, \ldots, x_d)$.

Concerning the capillary network, we adopt the same approach used at the continuous level, namely we split the network branches in separate sub-domains. Furthermore,
each branch $\Lambda_i$ is approximated by a piecewise linear 1D line, denoted with $\Lambda^h_i$. More precisely the latter is a partition of the $i$-th network branch made by a sufficiently large number of segments, named $S \subset \Lambda^h_i$. In this way, we obtain the following discrete domain:

$$\Lambda^h = \bigcup_{i=1}^{N} \Lambda^h_i.$$ 

The solution of (2.29) over a given branch $\Lambda^h_i$ is approximated using continuous piecewise-polynomial finite element spaces for concentration. We will use the following families of finite element spaces for pressure and velocity, respectively:

$$X^h_k (\Lambda) := \{ g^h \in C^0(\bar{\Lambda}), g^h|_S \in P^k(S) \quad \forall S \in \Lambda^h \},$$

for every integer $k \geq 0$. The discrete formulation arising from (2.29) is easily obtained by projecting the equations on the discrete spaces

$$Q^h_t = Y^h_k(\Omega) \quad \text{and} \quad Q^h_v = X^h_k(\Lambda)$$

for $k \geq 0$ and adding the subscript $h$ to each variable ($c^t_h$ and $c^v_h$).

Now, we need to re-write the concentration in (2.29) as a discrete variable, the mesh characteristic variable size $h$ has to be written explicitly. So the weak and discretized
formulation of \([2.4]\) results to be:

\[
\begin{align*}
&D^*_t \nabla C^{h(k)}_t, \quad \nabla q_t)_{\Omega} + (u \cdot \nabla C^{h(k)}_t, \quad q_t)_{\Omega} + (\nabla \cdot u C^{h(k)}_t, \quad q_t)_{\Omega} - \left( \frac{M_0}{C_t^{(k-1)} + K_M/C} \right) C^{h(k)}_t, \quad q_t)_{\Omega} \\
&+ (2\pi R^* [P^*_l + \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_v, \quad q_t)_{\Omega} \\
&- (2\pi R^* [P^*_l - \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_t, \quad q_t)_{\Omega} \\
&= (D^*_t \nabla C^{h(k)}_t \cdot \n), \quad q_t)_{\partial \Omega_{MIX}}; \quad \forall q^h_t \in Q^h_t \\
&- (2\pi R^* [P^*_l + \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_v, \quad q_v)_{\Lambda} \\
&- (2\pi R^* [P^*_l - \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_t, \quad q_v)_{\Lambda} \\
&+ (2\pi R^* [P^*_l - \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_t, \quad q_v)_{\Lambda} \\
&\left[ \frac{\pi R^* [P^*_l + \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_v, \quad q_v)_{\partial \Lambda_{OUT}} - \frac{\pi R^* [P^*_l - \frac{1}{2}(1 - \sigma_{oxy}) \Pi \Pi (P_v - P_t - \sigma \Delta \pi)] C^{h(k)}_t, \quad q_v)_{\partial \Lambda_{INT}} \right]; \quad \forall q^h_v \in Q^h_v \\
\end{align*}
\]

(2.30)

2.4 Algebraic formulation

In order to proceed estimating an approximated solution of the problem, let us intro-
duce the algebraic formulation of the complete problem. It is worth nothing that the
problem has been linearized, so the algebraic formulation has been obtained by using
the fix-point method: we will highlight the step \(k\) of the iterative method when showing
the linear combination of the elements of the discrete domains.

Starting form the discrete problem, in order to study the algebraic formulation it needs
to:

1. defined the number of degrees of freedom (DOFs) of the discrete domains \(Q^h_t\) and
\(Q^h_v\):
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\[ N^h_t = \text{dim}(Q^h_t) \quad \text{and} \quad N^h_v = \text{dim}(Q^h_v); \]

2. introduce the finite elements basis function, \( \varphi \), of the discrete domains:

\[ \{ \varphi^i_t \}_{i=1}^{N^h_t} \text{ for } Q^h_t \quad \text{and} \quad \{ \varphi^j_v \}_{j=1}^{N^h_v} \text{ for } Q^h_v; \]

each basis function is defined point-wise for each degree of freedom of the corresponding discrete domain;

3. finally, the linear combination of finite elements can be written using those basis functions:

\[ C^h_t(x) = \sum_{i=1}^{N^h_t} c^h_{t,i}(k) \varphi^i_t(x), \quad \forall x \in Q^h_t \]
\[ C^h_v(s) = \sum_{j=1}^{N^h_v} c^h_{v,j}(k) \varphi^j_v(s), \quad \forall s \in Q^h_v \]

Substituting the linear combination in the weak discrete problem (2.30) and exploiting the linearity of the inner product, it is possible to achieve the following linear system of partial differential equations for each iterative step:

\[
\begin{bmatrix}
D_t + A_t + R_t + B_{tt} & B_{tv} \\
B_{vt} & D_v + A_v + B_{vv}
\end{bmatrix}
\begin{bmatrix}
C^h_t(k) \\
C^h_v(k)
\end{bmatrix} =
\begin{bmatrix}
F_t \\
F_v
\end{bmatrix} \quad (2.31)
\]

The (2.31) is in the form of \( MU = F \), where \( M \) is the monolithic (linear) matrix, \( U \) is the unknowns vector and \( F \) is the vector of known terms.
Submatrices and subvectors in (2.31) are defined as follows:

\[
[D_i]_{ij} := (D_t^i \varphi_i^j, \varphi_i^j)_{\Omega} + (\beta_t \varphi_i^j, \varphi_i^j)_{\partial \Omega_{MIX}}, \quad D_t \in \mathbb{R}^{N^h \times N^h},
\]

\[
[A_t]_{ij} := (u_t^h \cdot \nabla \varphi_i^j, \varphi_i^j)_{\Omega} + (\nabla \cdot u_t^h \varphi_i^j, \varphi_i^j)_{\Omega}, \quad A_t \in \mathbb{R}^{N^h \times N^h},
\]

\[
[R_i]_{ij} := \left( \frac{M_0}{C_t^{h(k-1)}} + \frac{K_M}{C} \right) \varphi_i^j, \varphi_i^j)_{\Omega}, \quad R_t \in \mathbb{R}^{N^h \times N^h},
\]

\[
[D_v]_{ij} := (\pi R^2 D_v^* \frac{\partial \varphi_v^j}{\partial S}, \frac{\partial \varphi_v^j}{\partial S})_{\Omega}, \quad D_v \in \mathbb{R}^{N^v \times N^v},
\]

\[
[A_v]_{ij} := (\pi R^2 u_v^h(k-1) \frac{\partial \varphi_v^j}{\partial S}, \varphi_v^j)_{\Omega} + (\pi R^2 \frac{\partial u_v^h(k-1)}{\partial S} - \varphi_v^j, \varphi_v^j)_{\Omega} + (\pi R^2 \beta_v \varphi_v^j, \varphi_v^j)_{\partial \Omega_{OUT}}, \quad A_v \in \mathbb{R}^{N^v \times N^v},
\]

\[
[B_{tt}]_{ij} := -(2\pi R^2 [P_t^* + \frac{L^*}{2} (1 - \sigma_{oxy}) P (P_v - P_t - \sigma \Delta \pi)] \varphi_i^j, \varphi_i^j)_{\Omega}, \quad B_{tt} \in \mathbb{R}^{N^h \times N^h},
\]

\[
[B_{tv}]_{ij} := + (2\pi R^2 [P_t^* + \frac{L^*}{2} (1 - \sigma_{oxy}) P (P_v - P_t - \sigma \Delta \pi)] \varphi_i^j, \varphi_v^i)_{\Omega}, \quad B_{tv} \in \mathbb{R}^{N^h \times N^v},
\]

\[
[B_{vv}]_{ij} := -(2\pi R^2 [P_t^* + \frac{L^*}{2} (1 - \sigma_{oxy}) P (P_v - P_t - \sigma \Delta \pi)] \varphi_v^j, \varphi_v^i)_{\Omega}, \quad B_{vv} \in \mathbb{R}^{N^v \times N^v},
\]

\[
[B_{vt}]_{ij} := + (2\pi R^2 [P_t^* + \frac{L^*}{2} (1 - \sigma_{oxy}) P (P_v - P_t - \sigma \Delta \pi)] \varphi_v^j, \varphi_i^j)_{\Omega}, \quad B_{vt} \in \mathbb{R}^{N^v \times N^h},
\]

\[
[F_t]_{i} := - (\beta_t c_{0,t} \varphi_i^j)_{\partial \Omega_{MIX}}, \quad F_t \in \mathbb{R}^{N^h},
\]

\[
[F_v]_{i} := - (\pi R^2 \beta_v c_{0,v} \varphi_v^i)_{\partial \Omega_{OUT}}, \quad F_v \in \mathbb{R}^{N^v},
\]

Where \(u_v^*\) is:

\[
u_v^{(k-1)} = u_v \left( 1 + \frac{k_1}{C} H_t \frac{C_v^{(k-1)^{\gamma-1}}}{C_v^{(k-1)^\gamma} + k_2/C} \right)
\]

Riccardo ROSATI
The aim of this chapter is to present the results of various simulations of the model we presented in Chapter 2. In particular, we tested different cases on some geometries, from the simplest, the single branch geometry, to the most complex one, the capillary network. The chapter is divided into four sections, one for each tested geometry: single branch, bifurcation, anastomosis and Voronoi capillary network.

The first geometry is a single capillary. In this case, we compare our model’s results to Krogh’s model, which has been discussed in Chapter 1. In the bifurcation section, the model’s results have been used to complete the vascular problem description by adding the transport of free and haemoglobin-bound oxygen concentration highlighting the effect due to the heterogeneity of RBCs-mediated transport. Then, anastomosis has been tested on a physiological case. Finally, we have analyzed the results of the Voronoi capillary network, which is a randomly generated artificial network. The equations reported in this chapter are in non-dimensional form, noting the presence of “∗” near each coefficient. The set of parameters used for the following simulations are reported in Table 3.3. Although the model is able to resolve the model with general boundary conditions such as those reported in Chapter 2, in the next tests we have used as parameters the values reported in the Table 3.2.
Table 3.1: Physiological parameters used for all the numerical tests (unless differently specified).

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>PARAMETER</th>
<th>UNIT</th>
<th>VALUE</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>characteristic length of the domain</td>
<td>m</td>
<td>$5 \times 10^{-4}$</td>
<td>[38]</td>
</tr>
<tr>
<td>$R$</td>
<td>average radius</td>
<td>m</td>
<td>$4 \times 10^{-6}$</td>
<td>[38]</td>
</tr>
<tr>
<td>$K$</td>
<td>tissue hydraulic conductivity</td>
<td>m$^2$</td>
<td>$1 \times 10^{-18}$</td>
<td>[29, 38]</td>
</tr>
<tr>
<td>$\mu_t$</td>
<td>interstitial fluid viscosity</td>
<td>cP</td>
<td>1.2</td>
<td>[38]</td>
</tr>
<tr>
<td>$\mu_v$</td>
<td>blood viscosity</td>
<td>cP</td>
<td>9.33</td>
<td></td>
</tr>
<tr>
<td>$L_p$</td>
<td>wall hydraulic conductivity</td>
<td>m$^2$ s kg$^{-1}$</td>
<td>$10^{-12}$</td>
<td>[29, 38]</td>
</tr>
<tr>
<td>$\delta \pi$</td>
<td>oncotic pressure gradient</td>
<td>mmHg</td>
<td>25</td>
<td>[38]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>reflection coefficient</td>
<td></td>
<td>0.95</td>
<td>[38]</td>
</tr>
<tr>
<td>$\sigma_{oxy}$</td>
<td>oxygen reflection coefficient</td>
<td></td>
<td>0.1</td>
<td>[29]</td>
</tr>
<tr>
<td>$P_l$</td>
<td>permeability coefficient</td>
<td>m/s</td>
<td>$3.5 \times 10^{-5}$</td>
<td>[10, 29]</td>
</tr>
<tr>
<td>$D_v$</td>
<td>diffusivity coefficient in vessels</td>
<td>m$^2$/s</td>
<td>$2.18 \times 10^{-9}$</td>
<td>[30]</td>
</tr>
<tr>
<td>$D_t$</td>
<td>diffusivity coefficient in tissue</td>
<td>m$^2$/s</td>
<td>$2.41 \times 10^{-9}$</td>
<td>[30]</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>oxygen consumption rate in tissue</td>
<td>ml$O_2$/cm$^3$/s</td>
<td>$6.17 \times 10^{-5}$</td>
<td>[47]</td>
</tr>
</tbody>
</table>

Table 3.2: Boundary values used for all the numerical tests (unless differently specified).

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>DEFINITION</th>
<th>UNIT</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{vin}$</td>
<td>Vessel inlet oxygen concentration</td>
<td>ml$O_2$/ml$B$</td>
<td>$3 \times 10^{-3}$</td>
</tr>
<tr>
<td>$\beta_v$</td>
<td>Boundary vessel conductivity on $\partial \Omega_{OUT}$</td>
<td>m$^2$ s/kg</td>
<td>0.0</td>
</tr>
<tr>
<td>$\beta_t$</td>
<td>Boundary tissue conductivity on $\partial \Omega_{OUT}$</td>
<td>m$^2$ s/kg</td>
<td>0.0</td>
</tr>
</tbody>
</table>

3.1 Single branch test case

In this test, we compare Krogh’s model (1.7) and oxygen transport model, namely (2.15). Krogh’s model didn’t take into account the presence of cells in the hematic flow, indeed it just considered the concentration profile of dissolved oxygen. Therefore, for each case the oxygen transport model, has been quite simplified to be able to solve a similar problem to Krogh’s one as will be shown in the following sections.

We organized this section in three tests:
Chapter 3: Results

Test 1 - Comparison of tissue concentration We have set a constant oxygen concentration along the vessel by considering a high blood velocity, namely a great pressure gradient between the inlet and the outlet of the vessel. Doing so, we want to simulate the Krogh’s conditions within the tissue neglecting the axial variation of the concentration, namely considering the r dependence of $C_t$. This test aims to compare the oxygen concentration curves in the tissue domain with respect the Krogh’s model, changing the permeability of the capillary wall;

Test 2 - Transport Model and Krogh’s Model Setting physiological conditions, both for parameters and boundary conditions, we want to analyse common points and differences between Krogh’s problem and oxygen transport one;

Test 3 - Varying the exchange term in Krogh’s model We focused this test on the capillary domain. As discussed previously in Chapter 1, the Krogh’s model shows a constant exchange from capillary to surrounding tissue, equals to $\pi(R_{out}^2 - R_{in}^2) V_{max}$. That term is not dependent on the oxygen concentration, both $C_v$ and $C_t$. So, we decided to change that term imposing a concentration-dependent diffusive exchange flux, as in our model, following the Fick’s law.

Numerical discretization. The numerical discretization is performed with linear finite elements (FE). The three-dimensional domain consists of 1728 DOFs (11 elements per cube side). The one-dimensional domain consists of 41 DOFs (40 linear elements). The method of resolution used is the factorization method, superLU, implemented by using GetFem++ 5.0 libraries.

Remark We notice that for each simulations on the single branch geometry, we do not take into account the erythrocytes and the non-linear terms in order to the model be similar to Krogh’s one.
### 3.1.1 Test 1 - Comparison of tissue concentration

Parameters of the model have been set for this test as shown in Table 3.3.

**Table 3.3: Parameters used to solve Krogh’s model.**

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>PARAMETER</th>
<th>UNIT</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d$</td>
<td>length of the vessel</td>
<td>m</td>
<td>$5 \times 10^{-4}$</td>
</tr>
<tr>
<td>$u_v$</td>
<td>axial velocity</td>
<td>m/s</td>
<td>0.2</td>
</tr>
<tr>
<td>$R_{in}$</td>
<td>inner radius</td>
<td>m</td>
<td>$4 \times 10^{-6}$</td>
</tr>
<tr>
<td>$R$</td>
<td>ratio between outer and inner radius</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>$D_t$</td>
<td>diffusivity coefficient in tissue</td>
<td>[m$^2$/s]</td>
<td>$2.41 \times 10^{-9}$</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>oxygen consumption rate in tissue</td>
<td>mlO$_2$/cm$^3$/s</td>
<td>$6.17 \times 10^{-5}$</td>
</tr>
<tr>
<td>$C_{v_{in}}$</td>
<td>Vessel inlet oxygen concentration</td>
<td>mlO$_2$/ml$_B$</td>
<td>$3 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

To achieve flow conditions similar to the ones assumed by the Krogh’s model, we set $L_p = 0$ to uncouple the fluid dynamic problem and neglect the fluid filtration, expressed by Starling equation.

We decided to take different order of magnitudes for permeability, $P_l$, as reported in Table 3.4, to study the importance of the diffusive flux on the model.

**Table 3.4: Set of permeability for comparison tissue simulations.**

<table>
<thead>
<tr>
<th>$P_l$ [m/s]</th>
<th>Physio</th>
<th>x10</th>
<th>x100</th>
<th>x200</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3.5 \times 10^{-5}$</td>
<td>$3.5 \times 10^{-4}$</td>
<td>$3.5 \times 10^{-3}$</td>
<td>$7.0 \times 10^{-3}$</td>
<td></td>
</tr>
</tbody>
</table>

In order to have a tissue velocity close or equals to 0, as Krogh’s model wants, we imposed a Dirichlet condition equal to 0 for all the faces of the tissue domain in the fluid dynamic problem. On the other hand, we imposed a Neumann condition to all the faces of the tissue domain in the transport problem, so the oxygen is able to leave the system because of transport. On the vessel domain, we have set a Dirichlet condition equals to $C_{v_{in}}$ at the inlet of the vessel and a Neumann condition at the outlet.
So, our model is presented as follows:

\[
\begin{align*}
D_t \nabla \cdot (\nabla C_t) + V_{max} &= 2\pi R^* [P^*_l (C_v - C_t)]; \\
\pi R^2 D_v^* \frac{\partial^2 C_v}{\partial s^2} - \pi R^2 \frac{\partial}{\partial s} (u_v C_v) &= -2\pi R^* [P^*_l (C_v - C_t)];
\end{align*}
\]

Here, the oxygen consumption rate as been imposed constant to $V_{max}$ according to Krogh’s model.

\[\text{Figure 3.1: Oxygen distribution tissue domains, obtained solving the changed model (3.1). The free oxygen difference between inlet and outlet of the capillary has been considered negligible.}\]
The results of the comparison between the analytical solution of the Krogh’s model to the simplified oxygen transport model has been reported in the figures below:

![Oxygen vessel concentration comparison](image)

**Figure 3.2:** Free oxygen concentration comparison. The upper panel shows the free oxygen concentration in the vessel comparison between Krogh’s model (red curve) and the simplified model (3.1) at various permeability coefficient. The lower panel shows the evolution of tissue oxygen concentration along the perpendicular direction starting from the middle-point of the vessel, at various permeability coefficient.

The top panel of Figure 3.2 shows, clearly, the Krogh’s oxygen curve and the free
oxygen concentration overlapping, but the bottom panel shows that the tissue oxygen concentration curves of the Krogh’s model and ours are very different. This behaviour is due to the diffusive exchange term, $J_{\text{diff}}$, modelled in the oxygen transport model, but absent in the Krogh’s model. Krogh imposed an equilibrium condition on the concentration at the capillary wall between vessel and tissue concentration, $C_v$ and $C_t$ respectively. More precisely, it sets no concentration gradient and so, no diffusive flux. That means the initial value of oxygen tissue concentration is the oxygen concentration at a certain point of the vessel. This is an assumption that does not take into consideration some biological factors as the biological structure of the capillary wall, assumed as a porous membrane.

Instead, increasing the permeability of some order of magnitude, the vessel oxygen concentration curves become more and more different with respect to Krogh solution, reaching lower values, and the tissue oxygen concentration becomes closer to the Krogh’s concentration curve, reaching higher value. An increase of permeability coefficient allows freeing oxygen in the vessel to leave the capillary in an easier way and to perfuse the tissue, making the interstitium more oxygenated.

### 3.1.2 Test 2 - Transport Model and Krogh’s Model

Here, we analyzed, by comparison, the oxygen transport model and the Krogh’s model, setting the same physiological parameters. The aim of this kind of test was to identify the most significant differences and common points.

The chosen parameters have been the same as reported in Table 3.3, instead, the boundary conditions have been chosen following the Krogh’s model, that is Dirichlet condition at the inlet, set to $C_{v_{\text{in}}}$, and a Neumann condition at the outlet of the vessel. The fluid dynamic problem has been solved imposing a pressure gradient of 3.5 mmHg between the inlet and outlet of the vessel, in particular $P_{\text{in}}$ set to 32 mmHg and $P_{\text{out}}$ set to 28.5 mmHg to reproduce conditions specified in [37]. The 3D representation of the results of the model with physiological parameters is reported in the following figure.
Figure 3.3: Distribution of free oxygen partial pressure inside the intestitium ($pO_2$) and along the capillary ($pO_2_v$), with physiological parameters.

Figure 3.4: Concentration comparison between Krogh’s model (red crossed curve) and our model at various permeability coefficient, in vessel domain.

In Figure 3.4, free oxygen concentration curves are reported for different permeability coefficient values. That chart shows a series of an important difference between our model and Krogh’s one. First of all, the Krogh’s oxygen curve has a linear evolution, instead, the oxygen transport shows a non-linear behaviour, that is because Krogh defined the oxygen transport in the vessel as an axial flow rate balance between inlet
and outlet of the vessel in presence of a constant oxygen consumption:

\[ \pi R^2 u_v (C_v - (C_v + \frac{\partial C_v}{\partial s} ds)) = \pi (R_o^2 - R_i^2) ds V_{max} \]

The Krogh’s model exchanges what is consumed, whereas, in the 2.15 model, we have a diffusive exchange term independent of consumption, \( V_{max} \). The difference in oxygen curves is due to a different definition of the exchange terms.

The most remarkable difference in Figure 3.4 is the absence of a diffusive effect, which characterizes the biological structures. The main force that transports the oxygen, according to Krogh’s theory, is a convective force proportional to the velocity. That assumption, in addition to lack of exchange terms, gives to vessel oxygen transport a linear behaviour.

Moreover, decreasing the permeability, setting physiological parameters, the solution is closer to Krogh’s one. This happens because an infinitesimal permeability coefficient could make the free oxygen evolution in the vessel closer to the Krogh solution.

### 3.1.3 Test 3 - Changing the exchange term in Krogh’s model

We decided to change the Krogh’s model in order to analyse what happens to the oxygen concentration curve in the vessel if the constant exchange term had changed into a concentration-dependent term, more similar to our model. Moreover, parameters and boundary conditions have been changed to simplify the model setting \( C_t = 0 \) for all the tissue DOFs, namely high tissue diffusivity and a Dirichlet condition set to 0 for all the faces in the transport problem. This test shows how the Krogh’s model is characterised by strong assumptions, they do not allow to describe the dynamic of perfusion of biological tissue in a realistic way, even if the model remains the most used model as starting point to study oxygen transport. The new system of equations for Krogh’s model, in cylindrical coordinates, is reduced to a single equation, as shown below:

\[ \pi R^2 u_v \frac{\partial C_v}{\partial s} = 2\pi R P_l C_v \]  

(3.2)
Chapter 3: Results

Our interest is the oxygen transport along the axis of the vessel, so we computed the analytical solution of (3.2) by MATLAB tool, MuPad:

\[ C_v(s) = 0.003 \ e^{-87500 \ s} \] (3.3)

The comparison between (3.3) and our model is reported in the Figure 3.5.

There is a relevant evolution exchange with respect to what has been found in Figure 3.4. Now, the Krogh’s curve assumes a non-linear behaviour, closer to the oxygen model’s results due to the addition of diffusive exchange term, \( J_{diff} \), as done in our model. However, the curves do not overlap, a difference remains between the two cases taken into consideration: that gap is due to the not modelled diffusive contribution. If this phenomenon was added to Krogh’s model, the red curve would have moved closer to the model curve, thanks to the contribution of diffusion.
3.2 Bifurcation test case

The geometrical model consists of a Y-shaped bifurcation, where all branches have the same length. The radii of the daughter branches are calculated on the basis of the Murray’s law:

\[ R_{in0}^3 = R_{out1}^3 + R_{out2}^3, \]

where index (0) denotes the parent vessel and (1), (2) are the daughter channels. We tested (2.4) over the bifurcation and we focused on the vessel domain and analyzed the behaviour of free and bound-haemoglobin oxygen at a variation of radius of the capillary. That kind of geometry allows us to study how the amount of RBCs is subdivided among daughter capillaries, namely the Fåhræus–Lindqvist (F-L) effect, in particular how the hematocrit changes, being a function of radius, and so the oxyhemoglobin, namely (2.14).

Parameters and Boundary conditions. The characteristic parameters have been set according to [38], to Table 2.1 and to Table 2.2 in particular we imposed \( L_p = 0 \), in order to not allow the filtration of the fluid. We imposed a non-zero permeability coefficient, \( P_l \), allowing concentration exchange form capillary to the interstitium. We set the boundary conditions for the fluid dynamic problem and hematocrit transport: an inlet pressure of 32 \( \text{mmHg} \) and an inlet hematocrit value at 0.45, then, at the outlet we set an outlet pressure of 28.5 \( \text{mmHg} \). We set a Neumann condition for all the tissue faces and the outlet of the vessel, instead, we imposed a Dirichlet condition set to \( C_{vin} \).
at the inlet.

**Numerical Discretization.** The numerical discretization is performed with linear finite elements (FE). The three-dimensional domain consists of 1728 DOFs (11 elements per cube side). The one-dimensional domain consists of 61 DOFs (20 linear elements per segment, which are 3). The method of resolution used is the factorization method, *superLU*, implemented by using *GetFem++ 5.0* libraries. The total computational time to resolve the whole 3d1d problem is 485 seconds (s), divided as follows: 18 s for fluid dynamics problem, 463 s hematocrit transport problem and 4 oxygen transport problem.

We reported velocity, hematocrit, free and bound-haemoglobin oxygen concentration distribution in capillaries and, then, their sum, namely the total oxygen concentration, along capillary’s axis with a variation of daughter capillary’s radii of ±5% and ±10% with respect to the parent branch radius (Table 3.5). More precisely, we increased the

<table>
<thead>
<tr>
<th>Branch</th>
<th>reference</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R [µm]</td>
<td>4.000</td>
<td>3.170</td>
<td>3.170</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branch</td>
<td>4.000</td>
<td>3.330</td>
<td>3.020</td>
<td>4.000</td>
<td>3.490</td>
<td>2.860</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.5:** Set of radii for bifurcation simulations.

radius of the upper branch ($R_1$) of 5% and, then, 10%, and we decreased the radius of the lower branch ($R_2$) of the same amount.

In the Figure 3.7 are reported the results of fluid dynamic simulations on bifurcation as also shown in [37]. The first row shows how the haematocrit distribution is affected by the change in radius of the daughter branches. The haematocrit variations are also amplified concerning the magnitude of the perturbation. More precisely, because of the Zweifach-Fung (Z-F) effect, red blood cells hardly flow into the daughter branch with a smaller radius. For this reason, hematocrit is lower in the branches where the radius has been decreased than in the ones where it was increased. The second row, instead, shows the variation of fluid velocity, along the capillaries axis, of a Poiseuille’s
Figure 3.7: Haematocrit distribution (first row) and fluid velocities (second row) for each branch with a variation in radius, as see in Table 3.5, from left to right.

\[
\Delta P = \frac{8 \mu L}{\pi R^4} Q, \quad \text{with } Q = u_v A
\]

The velocity is a continuous quantity along the branch, but it assumes different values from branch to another, due to the effect of changing radius. In particular, the variation in radius affects the flow rates, \( Q \). In the analysis of flow rates for increasing radii, we see that the +5\% and +10\% variation of the radius significantly affects the distribution of flow rate downstream to the bifurcation, because resistance to flow is highly sensitive to the channel diameter at these small scales. The same discussion can be developed for decreasing radii cases. The results confirm the data found by [38]. For what concerns the oxygen transport simulations, the results are reported in Figure 3.8.

The free oxygen concentration is a continuous quantity, in fact, at the junction, the mass balance is maintained. The \( C_v \) changes in a non-linear way with respect progressing along the bifurcation, as shown by the charts in Figure 3.8. The effect of the radius is less significant in the first and second panel, from left, but in the third, the 10\% variation in both daughter branches brings to a more evident variation at the downstream of the bifurcation. Indeed, with the increasing of the radius, the curves
Figure 3.8: Free oxygen concentration, $C_v$, in a 3D representation and its value along the capillaries with a variation in radius of daughter branches. The red curve is the concentration in bifurcation inlet, the blue curve is the upper branch and the green curve is the lower branch.
begin to distance themselves from the values of the first panel. For example, taking into account the lower branch, the oxygen tends to diffuse more easily due to a decreasing in velocity. This behaviour can be studied analyzing the Peclèt number, defined as:

$$P_e = \frac{u_v \cdot h}{D_v},$$

(3.4)

where $u_v$ is the axial velocity, $D_v$ is the radial diffusive coefficient and $h$ is the length travelled by the fluid. Keeping constant $D_v$ and $h$ (e.g., in a uniform discretization in space) and decreasing the velocity, it brings to a linear decreasing in Peclèt number, that means the fluid becomes slower and, so, the diffusion is more relevant than the advection.

![Figure 3.9: Bound-hemoglobin, or oxyhemoglobin, (top panels) and total oxygen concentration (bottom panels) 3D representation.](image)

In the Figure 3.9 we reported the variation along branches of oxyhemoglobin, $C_{HbO_2}$, and the total oxygen concentration, called by us $C_{tot}$. The 3D representations show how the oxyhemoglobin jumps from branch to another, due to the linear dependence of the hematocrit, which can be discontinuous at junctions. Moreover, the oxyhemoglobin has a non-linear behaviour along the capillary’s axis as the free oxygen concentration. It is worth noting that the oxyhemoglobin concentration is higher than the free oxygen
concentration of two orders of magnitude, due to the presence of the RBCs: they allow to carry a significant amount of oxygen along with micro circulation, up to 97% of the total of oxygen concentration ([27]), and to release it when necessary. Indeed, we reach a similar value taking the ratio between oxyhemoglobin concentration and total oxygen concentration. For instance, taking the maximum value of both concentrations by Figure 3.9 ($CHbO_2$ equals to 0.22 $mlO_2/ml_B$ and $C_{tot}$ equals to 0.23 $mlO_2/ml_B$) and taking their ratio, we obtain a value around of 96%. So the total oxygen concentration behaves as the oxyhemoglobin, as confirmed by Figure 3.9. Follow, we report the chart of oxyhemoglobin in bifurcation along the tissue length: In the Figure 3.10, we notice that the oxyhemoglobin concentration jumps at the junction and it is continuous along
each capillary. The jumping effect is due to the different distribution of hematocrit in daughter capillaries (F-L effect).

### 3.3 Anastomosis test case

The anastomosis is a biological situation where two branches join together (Figure 3.11).

![Figure 3.11: Anastomosis geometry and flow directions](image)

We decided to simulate the coupled fluid dynamic problem, namely setting $L_p \neq 0$, and the oxygen transport problem with non-linearities, both (2.7) and (2.14). As done before, the radii have been estimated by Murray’s law:

$$R_{in0}^3 + R_{in1}^3 = R_{out2}^3,$$

where $R_{in0} = 4 \mu m$, $R_{in1} = 5 \mu m$ and $R_{out2} = 6 \mu m$.

**Parameters and Boundary Conditions.** The parameters are the ones reported in Table 3.3. We set $C_{vin}$ as Dirichlet conditions at the inlet of the vessels and Neumann condition at the outlet of the anastomosis; we imposed a Neumann condition for all the faces of the tissue domains. We decided to simulate a particular case where the haematocrit is set at a different values at the inlets of the anastomosis, namely $H_0 = 0.35$ (lower branch) and $H_1 = 0.45$ (upper branch), at the same inlet pressure, set to 32 mmHg. As for bifurcation, the outlet pressure has been set to 28.5 mmHg.
Numerical Discretization. The numerical discretization is performed with linear finite elements (FE). The three-dimensional domain consists of 1728 DOFs (11 elements per cube side). The one-dimensional domain consists of 61 DOFs (20 linear elements per segment, which are 3). The method of resolution used is the factorization method, superLU, implemented by using GetFem++ 5.0 libraries. The total computational time to resolve the whole 3d1d problem is 481 seconds (s), divided as follows: 14 s for fluid dynamics problem, 463 s hematocrit transport problem and 4 oxygen transport problem.

Firstly, we report the result of fluid dynamic problem and haematocrit transport in Figure 3.12. As discussed in Section 3.2, the change in radius affects the flow rate and so the velocity. Then, we report the free oxygen concentration along the anastomosis and the distribution in the tissue domain. The Figure 3.13 shows a particular free oxygen concentration behaviour for the lower branch. As observed before, the hematocrit is set to a different amount at the inlets, the fluid moves with different velocity, and so the Péclet number changes. More precisely, the lower branch has a lower Péclet number, due to the lower flow rate. Near the junction, the concentration in the lower branch features a U-shaped profile. Having different velocities, the free oxygen concentration, in inlet branches, exchange a different amount of oxygen with the interstitium (Figure 3.14). Near the junction, the curves join together due to a concentration balance condition.
Figure 3.13: 3D and 2D representation of free oxygen concentration. The blue curve is the upper branch, the green curve is the lower branch and the red curve is the outlet branch.

Figure 3.14: Central section of the tissue showing the change in oxygen concentration in the tissue.

There, we reported the oxyhemoglobin concentration and the total oxygen concentration. We expect that, as discussed for bifurcation, the total oxygen concentration is "guided" by the evolution of the free oxygen in the vessels. Indeed, as shown in Figure 3.15, the inlet curves have similar shape to the evolution of free oxygen concentration in Figure 3.13.

3.3.1 Changing the diffusive coefficient

We decided to simulate another case where the diffusive coefficient in the vessels, $D_v$, has been set to a higher order of magnitude, namely at $2.18 \cdot 10^{-5} m^2/s$, in order to increase the oxygen exchanged by the lower branch, maintaining constant the per-
Figure 3.15: 3D and 2D representation of oxyhemoglobin and total oxygen concentration. The evolution of the curve are very similar due to the presence of the cells, which bind a relevant amount of oxygen. The curves jump from branch to another, due to the dependence on hematocrit of the oxyhemoglobin (see equation (2.14)).

meability of the capillary’s wall. We compared the results of the following test with the previous $C_v$ and $C_t$ results, reported in Figure 3.13 and 3.14, to see, if present, a relevant variation in 3D and 2D representations. That kind of change in parameters affects the diffusive effect but in particular the diffusive flux (by Fick’s law). The fluid dynamics results, in Figure 3.12, do not change. We are not changing any geometrical parameter nor boundary conditions. The Figure 3.16 shows a significant change in free oxygen concentration the in capillaries. Also this time, the explanation is to be found in the Péclet number. This test explain, clearly, the importance of that number: being velocity and length, $h$, (see equation (3.48)) equal to the physiological case, increasing the $D_v$ of five order of magnitude, brings to a remarkable reduction in Péclet number. It is known that a low Péclet number means that the diffusion has a more relevant role in the mass transport than the advection one. Indeed, the top right panel of $C_v$ shows that the concentration is nearly constant to the inlet value, $C_{vin}$, namely the
Figure 3.16: Comparison between free oxygen concentration with different values of $D_v$ [$2.18 \cdot 10^{-9}$ (physiological); $2.18 \cdot 10^{-6}$; $2.18 \cdot 10^{-5}$] $m^2/s$. The upper row shows the 3D representations of the tests with physiological $D_v$ (left) and $D_v$ set to $2.18 \cdot 10^{-5}$ (right).

Concentration in the capillary is distributed around the input value.
Figure 3.17: Comparison of tissue concentration at various diffusive coefficient: \( D_v = 2.18 \cdot 10^{-9} \text{ m}^2/\text{s} \) in the panel a) and \( D_v = 2.18 \cdot 10^{-5} \text{ m}^2/\text{s} \) in the panel b).

Analyzing the intestitium, in Figure 3.17, there is a high concentration of free oxygen near the junction: the increased \( D_v \) has brought to quite uniform distribution of free oxygen in the vessels, that has brought to an increase in the gap between \( C_v \) and \( C_t \):

\[
J_{\text{diff}} = 2\pi R \left[ P_1 (C_v - C_t) \right].
\]

So the diffusive exchange flux has increased accordingly, for each branch.
3.4 Voronoi network test case

Finally, the final step is the Voronoi capillary 3D network simulation made of more than one set of non-trivial one-dimensional manifold (\( \Lambda \) domain) immersed in a three-dimensional unitary cube (\( \Omega \) domain). The Voronoi network represents the most complex and inhomogeneous case examined which manages to capture the heterogeneities of micro circulation.

3.4.1 Low density capillary network

We took into consideration a geometry made of two network capillaries made of 28 vessels (low capillary density case), characterised by many bifurcations and anatomises. The geometry has been obtained by a previously developed MATLAB tool, which can generate artificial 3D random networks ([37, 38]) with the correct radii ratio between parent vessel and daughter vessels, following Murray’s law. Defining capillary density is crucial to simulate a configuration similar to biological tissue. The capillary density changes by body district; moreover it has more than one definition, it can be estimated as count of perfused capillaries per \( \text{mm}^2 \) ([17]), as the ratio between flowing blood vessels in the selected region and the occupied area by the vessels. (e.g. in eye district, the capillary density, in healthy people is 55\%\pm3.2\%) ([31, 36, 51]) or as lateral surface of the capillaries over tissue volume ([27, 52]). However, it is worth recalling that we are analysing a geometry characterised by a low capillary density. In the next chapter, we will also analyse networks with different densities. Here, we show the low-density capillary network to describe some phenomena in a geometry that still has a reduced number of vessels.

**Parameters and Boundary Conditions.** To each chosen inlet of the network has been imposed an initial concentration condition equals to \( C_{\text{vin}} \), a fluid pressure set to 32 mmHg and a haematocrit value of 0.45; instead, to each outlet has been imposed a Neumann condition on transport problem and fluid pressure of 28.5 mmHg. The
physiological parameters are reported in Table 3.3.

**Numerical Discretization.** The numerical discretization is performed with linear finite elements (FE). The three-dimensional domain consists of 1728 DOFs (11 elements per cube side). The one-dimensional domain consists of 560 DOFs (20 linear elements per segment, which are 28). The method of resolution used is the factorization method, *superLU*, implemented by using *GetFem++ 5.0* libraries. The total computational time to resolve the whole 3d1d problem is 704 seconds (s), divided as follows: 19 s for fluid dynamics problem, 631 s hematocrit transport problem and 54 oxygen transport problem.

Firstly, we report the fluid dynamic results, in particular haematocrit and axial velocities, as done for the previous simulations. Secondly, we report the free oxygen concentration in the vessels and the distribution of oxygen in the cube of tissue. Thirdly, we report the oxyhemoglobin concentration and the total concentration of oxygen, in particular, we will show a section of the cube highlighting the distribution of oxygen inside the cube.

From Figure 3.18 one is able to identify the high level of heterogeneity of the microcirculation. Each branch has a different value of hematocrit and velocity, indeed both change with respect the radius (F-L effect, Z-F effect and Poiseuille’s flow). At each junction the balance of hematocrit and flow rate is verified.

![Figure 3.18: Haematocrit distribution and fluid velocity for a simple Voronoi network.](image)
Chapter 3: Results

Instead, the free oxygen concentration, reported in Figure 3.19 changes along the capillary’s axis of the network. In the network the free oxygen concentration passes from high values, equals to \(C_v\), which corresponds to an arterial blood (according to Henry’s law (2.6), \(pO_2 = 100 \text{ mmHg}\)), to a values that bring the oxygen partial pressure to be under venous blood ones (\(pO_2 = 40 \text{ mmHg}\)). There are areas of the sample tissue not well perfused by the capillary network. Such areas are not able to receive the correct amount of oxygen to survive, justifying the risk of hypoxic conditions ([9], [19]) for an irregular configuration of the microvessels.

In fact, as shown in Figure 3.20, the RBCs presence bring a remarkable contribute to

---

**Figure 3.19:** Evolution of free oxygen concentration along the axis of the capillaries of the network. Both scale concentration and partial pressure, obtained by Henry’s law, are presented.

**Figure 3.20:** Oxyhemoglobin concentration (right panel) and total concentration (left panel) in the capillary network.

the amount of oxygen. The RBCs bound the oxygen to hemoglobin, a huge quantity
of oxygen with respect the free one, and they bring it to the target tissue. Even the lowest value reached by the oxyhemoglobin concentration is higher than the maximum value of free oxygen concentration, that leads to highlight the significant role conduct by the RBCs.

Figure 3.21: Oxygen tissue distribution and total concentration of oxygen. It can be analyzed how the oxygen is exchanged from capillary to tissue and how it is consumed by the tissue.

The distribution of oxygen inside the interstitium close to each branch represents an interesting point of discussion (Figure 3.21).

The free oxygen exchanged by the vessels is quickly consumed near the branch. The consumption in the tissue is modelled as the Michaelis-Menten non-linear formula (2).

The number of capillaries, 28 in Figure 3.21, does not meet the oxygen requirement by the tissue, leading to evident hypoxic areas. The oxygen partial pressure in the tissue \( pO_2 \) reaches low values for biological tissue. Despite all, the mechanism at the basis of oxygen perfuses the tissue is well captured by the simulation.
In this last chapter we will introduce therapies for the treatment of cancer, with a special focus on the role of radiotherapy. The pros and cons of radiotherapy and its side effects on patients are discussed. We analyze the particular clinical parameters that are able to quantify the effect of radiotherapy (e.g. the Surviving Fraction (Sf), the Alpha/Beta ratio, the Probability of Tumor Control (TCP) and the Probability of Normal Tissue Complication (NTCP)). Then, applying the well-known Linear-Quadratic model (LQ), we introduce how the multi-scale transport model, introduced in chapter 2, is able to simulate the irradiation of a generic tissue (e.g. oxygenated or hypoxic) by an ionizing source. We show the model results on Voronoi capillary networks with a different capillary density. Then, we discuss the possibility to study what happens inside the hypoxic region of a tumour (low capillary density geometry) or the well-perfused region (high capillary density), and we compare the scenario of healthy tissue and tumour tissue.
4.1 The biology of a solid tumor

In his work [50], the pathologist Rupert Allan Willis gave, in 1935, the definition of neoplastic tissue, recognised internationally: "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimulus which evoked the change”.

Cancer is a disease of the cells due to accumulating mutations in genes due to random errors during DNA replication. The origin of these mutations can be of genetic origin (hereditary, in particular), lifestyle (e.g. smoking, alcohol, bad nutrition or excessive exposure to ultraviolet rays) or environmental factors (e.g. physical, infectious or chemical factors). Tumour cells need oxygen to survive in the host organism and their high capability to reproduce themselves harms healthy tissues or whole organs by compression (mechanical damage) or by general dysfunction. The tumour tissue has a multi-layer structure: the outer one is characterized by a well-perfused layer, and going to the core the tissue oxygen becomes lower and lower. Middle layers are hypoxic, where the $pO_2$ reaches critical values, which are proposed to be 8–10 mmHg ([9]). Instead, the core is characterized by necrotic cells. The Figure 4.1 is a good representation of the multi-layer structure:

![Figure 4.1: Tumour multi-layer structure and oxygen profile from the outer layer to the inner one, adapted from [15].](image)
Even if tumours could present a higher level of oxygenation than 10 \( \text{mmHg} \), \( pO_2 \) value is always lower in the tumour than in the respective normal tissue, according to definition of hypoxia reported by Carreau et al. \([9]\). The values of \( pO_2 \) are very heterogeneous, they change by body district, for instance, studying the skin oxygenation \([19]\), the oxygen partial pressure changes from approximately 8.0 ± 3.2 mmHg in the superficial region of the skin (5–10 \( \mu \text{m} \)) to approximately 35.2 ± 8.0 mmHg just above the sub-papillary plexus (100–120 \( \mu \text{m} \)).

Today, there are many strategies to treat cancer, indeed each tumour has a different way manifesting itself, different tissue type and healing times. Medicine has various tools to treat cancer, for instance, surgery, chemotherapy, immunotherapy \([35]\), radiotherapy or a combination of them. In particular, radiotherapy is used over 50% of patients with cancer \([1, 14]\). It is a therapy which uses ionizing radiation, such as X-rays. Radiations are directed against the tumour mass in a series of daily fractions \([1]\) and they damage in particular the cancer cells that are no longer able to proliferate in this way: the tumour treated in this way is no longer able to grow and is progressively reduced. That procedure is called External Beam Radiotherapy (EBRT), namely, the ionizing source is external to the body.

It has become well established that the response of cells to ionizing radiation is strongly dependent upon the oxygenation condition \([22, 39, 44]\). In particular, a significantly lower cell death rate is observed after exposure to ionizing radiation in the presence of a reduced concentration of oxygen in the cells, e.g. in hypoxic conditions \([23]\). As shown in Figure 4.1, solid tumours can contain oxygen-deficient regions, thus increasing their radioresistance and potentially leading to treatment failure.

Moreover, some healthy cells close to the diseased area can be affected by radiation, e.g due to their well-oxygenated condition. So, even the healthy tissue could be damaged, leading to toxicity, to early and late side effects (e.g. chronic inflammation as tissue fibrosis) and various biological dysfunctions, according to the age and the diseased area \([13]\).

Knowledge of the mechanisms leads to a more rational approach for controlling radiotherapy toxicity, which may result in improved symptom control and quality of life for patients. Indeed, even if radiotherapy is a common treatment for tumour aimed at
damaging and killing cancer cells, the mechanism of these phenomena are not completely understood.

### 4.2 Mathematical modelling and parameters of clinical relevance

The mathematical modelling plays a fundamental role in the clinical applications: it is able to simulate or predict the behaviour of the particular tissue regions, under ionizing radiation, with different degree of vascularization. For instance, the V2 network could represent the boundary between necrotic and hypoxic tumour regions, or the V18 or V36 (introduced in the following sections) network could represent the normoxic tumour region, characterized by a high number of capillaries. We are able to do this procedure because the multi-scale model is not tissue-specific, so it can simulate different scenarios (e.g. healthy tissue and tumoural tissue) through a careful selection of parameters. We will report results about oxygen distribution in the tissue by changing the degree of vascularization, namely the number of capillaries inside the tissue domain.

We report the following figure to clarify the potential of mathematical modelling:

![Figure 4.2: Representation of the model results in different regions of a hypothetical tumour. The cube called V2 is the low-capillary density network. The cube called V18 is the oxygenated condition.](image)

Radiobiological models can only aid clinical decision-making if their input parameters
are reasonably accurate. In what follows, we will present the common radiobiological model and clinical parameters. Moreover, we will show the results obtained by modelling healthy and tumoral tissue and applying the most common radiobiological model for both tissue type.

### 4.2.1 Linear-Quadratic model

The literature provides various models to estimate the biological response ionizing radiation ([4, 5, 26, 40]), but the most commonly used is the Linear-Quadratic (LQ) model. The LQ model takes into account the energy type transferred to the tissue, the cell type and the irradiation dose.

The LQ model is in widespread used in both experimental and clinical radiobiology and generally works well in reproducing experimental results both in vitro and in vivo [45]. The LQ model is written as:

\[
S_f(D) = e^{(-\alpha D - \beta D^2)}; \quad (4.1)
\]

The model (4.1) represents the survival fraction, \( S_f \), of cells that survive an applied dose of radiation, \( D \). The \( \alpha, [Gy^{-1}] \), and \( \beta, [Gy^{-2}] \), parameters are two general radiosensitivity parameters, representing intrinsic radiosensitivity proportional to the absorbed dose and the repair capability of a specified tissue proportional to the dose squared.

In particular, in this work we decided to modify the (4.1) according to the works Wenzl et al [48, 49], where the \( \alpha \) and \( \beta \) coefficients are re-written by using the Alper-Howard-Flanders model ([2]), as linear function on the Linear Energy Transfer (LET) ([3]) and as non-linear function on oxygen partial pressure of the tissue, \( pO_2 \):

\[
\alpha(pO_2, LET) = \frac{(a_1 + a_2 \text{LET}) \cdot pO_2 + (a_3 + a_4 \text{LET}) \cdot K}{pO_2 + K}; \quad (4.2)
\]

\[
\sqrt{\beta(pO_2)} = \frac{b_1}{pO_2 + K} \cdot \frac{pO_2 + b_3 K}{pO_2 + K}; \quad (4.3)
\]
where, the $a_1, a_2, a_3, a_4, b_1$ and $b_2$ are constant coefficients, obtained by fitting of experimental surviving fraction curve. We report the values used by Wenzl et al, in the Table 4.1. The LET is the energy transferred by a ionizing radiation to a material, it is measured in $keV/\mu m$. The LET value can be different from radiation to another. For instance, if we consider the X-rays, we talk about of radiations at low-LET, or the fast neutron beams are radiations at high-LET ([49]). The $K$ term represents the oxygen concentration at which the relative radiosensitivity equals half of its maximum, it can assume values between 2.5 and 3 $mmHg$ ([43]).

The modified LQ model, obtained substituting the equation (4.2) and (4.3) into the equation (4.1), is the following:

$$S_f(D, pO_2, LET) = e^{(-\alpha(pO_2,LET)D-\beta(pO_2,LET)D^2)}; \quad (4.4)$$

Finally, the presented Linear-Quadratic model (4.4) takes account of many factors: oxygen partial pressure distribution, type of irradiated tissue and ionizing radiation type. Clinically, the LQ model is mainly used to estimate equivalent radiotherapy schedules, but increasingly also to predict Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). The LQ parameters $\alpha$, $\beta$ and, in particular their

**Table 4.1:** List of constant coefficients used in the modified LQ model according to [48]. The LET has been chosen according to an application of X-rays (low-LET ionizing radiation).

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>UNIT</th>
<th>VALUE</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>$Gy^{-1}$</td>
<td>0.22</td>
<td>[48]</td>
</tr>
<tr>
<td>$a_2$</td>
<td>$\mu m/(Gy \ keV)$</td>
<td>0.0024</td>
<td>[48]</td>
</tr>
<tr>
<td>$a_3$</td>
<td>$Gy^{-1}$</td>
<td>0.05</td>
<td>[48]</td>
</tr>
<tr>
<td>$a_4$</td>
<td>$\mu m/(Gy \ keV)$</td>
<td>0.0031</td>
<td>[48]</td>
</tr>
<tr>
<td>$b_1$</td>
<td>$Gy^{-1}$</td>
<td>0.4</td>
<td>[48]</td>
</tr>
<tr>
<td>$b_2$</td>
<td>$Gy^{-1}$</td>
<td>0.015</td>
<td>[48]</td>
</tr>
<tr>
<td>LET</td>
<td>$keV/\mu m$</td>
<td>2.0</td>
<td>[48, 49]</td>
</tr>
<tr>
<td>$K$</td>
<td>$mmHg$</td>
<td>2.5</td>
<td>[48]</td>
</tr>
</tbody>
</table>
ratio, $\alpha/\beta$ are pivotal for a reliable estimate of radiation response. The literature shows several values of $\alpha$ and $\beta$ both for normal and tumoural tissues. We summarize some of the radiosensitivity parameters values reported by the literature, in Appendix A.

4.2.2 Oxygen Enhancement Ratio (OER)

The Oxygen Enhancement Ratio is a clinical parameter which quantifies the "oxygen effect" ([21]), namely the radiosensitivity of a biological tissue depending on the presence of oxygen, in particular, the greater the oxygen concentration, the greater the effect of radiation and therefore the damage to the tissue (healthy or sick). It is defined as a comparison between two cases of oxygenated tissue (aerobic, $P_a$, and hypoxic, $P_h$) to which the same type of radiation is applied, but with different dosage, to obtain the same surviving fraction, $S_f$:

$$OER = \left. \frac{D(P_h)}{D(P_a)} \right|_{S_f=\text{const}}$$

The behavior of the OER with dose per fraction depends primarily on the ratios of the LQ parameters $\alpha$ and $\beta$ under hypoxic and aerobic conditions, which themselves depend on LET, $pO_2$ and the cell or tissue type. To estimate the OER, as we will show in the following section, we used the following equation according to [49]:

$$OER(D, \alpha_a, \alpha_h, \beta_a, \beta_h) = \frac{2D \beta_a}{\sqrt{\alpha_a^2 + 4\beta_a(\alpha_h D + \beta_h D^2) - \alpha_a}};$$

where the D is the dose applied on the RBCs and $\alpha_a$, $\beta_a$, $\alpha_h$ and $\beta_h$ are the radiosensitivity parameters for aerobic tissue and hypoxic tissue, respectively.
4.2.3 Tumor Control Probability (TCP) and Normal Tissue Complications Probability (NTCP)

Radiotherapy treatment plan evaluation relies on an estimation of the TCP and NTCP arising from a given dose distribution. Radio-biological models and biological variables become in tools of making decisions in planning treatments to patients for radioncol- ogist and medical physicist. The aim is to predict custom treatment that shows a high TCP and minor NTCP, to kill tumoural cells without excessively damaging the surrounding healthy tissue.

Classically, the TCP has been used as a tool in radiotherapy to measure the probability that the goal of the treatment - tumour eradication by the elimination of all clonogenic cells - will be achieved. The TCP can be computed by the following sigmoidal expression (24):

\[ TCP(D) = e^{-N S_f(D)}; \]  

where \( N \) is the initial number of clonogens cells, in particular tumorogenic ones, and \( S_f \) is the surviving fraction. The exponent of equation (4.7) represents the number of cells survived to irradiation. The NTCP is used, instead, to measure the probability that the healthy tissues, surrounding the tumour site, have complications following the radiotherapy. The NTCP is not tissue-specific, it depends on many clinical parameters like age, gender, prescribed total dose, tumour location.

4.3 Connecting radiobiological and the 3D1D models

In this section, we illustrate the application of the 3D1D multi-scale model to the radiobiological LQ model taking into account healthy and tumoral tissue. We show the results obtained by numerical Voronoi simulations of several capillary networks, characterized by an increasing vascularization, on healthy and tumoral tissue. We applied the model to a low-density capillary network, made of 2 networks (we will call V2) and
to a high-density capillary one, made of 18 networks (we will call V18), taking into account also intermediate cases, V8 and V13.

Since healthy and tumour tissue properties are characterized by relevant physicochemical differences, to compare the fluid dynamics in the capillary networks and, most importantly, the surviving fraction distribution, $S_f(D)$, we changed parameters: (i) oxygen consumption in tissue, $V_{\text{max}}$, (ii) osmotic reflection coefficient, $\sigma$, (iii) hydraulic conductivity of the interstitium, $k$, and of the vessels wall, $L_p$, ([8, 41, 47]) and (iv) degree of vascularization, by computing the surface area of network per unit of tissue volume, $S/V$, to simulate the microvasculature of tumour.

Indeed, the growth of a tumour dramatically impacts the structural and dynamical properties of blood vessels, inducing changes in, for instance, their morphology, blood flow, oxygen distribution and pH. Tumour vessels exhibit typical behaviour, such as an altered geometry characterized by overlapping, being disorganized and having tortuous vases. This altered geometry results in dramatic differences in the blood flow and up to 50 % of vessels being non-functional ([41]). The micro circulation is completely different from tumour vasculature which often presents large gaps (range from 100 nm to 1 $\mu$m) in the vessel walls, inducing the capillary wall to be leaky, favouring intravasation of cancer cells and extravasation of nanoparticles. Moreover, the biochemistry of tumour endothelium is profoundly different from that of healthy vasculature.

We selected the parameters which assume a different value in tumour microvasculature, with respect to the physiological ones. We report the parameters used in tumour simulations in Table 4.2. So, in addition to the previous capillary networks, we decide to simulate a tumoural tissue characterized by a hyper-vascularized network. As reported in the Table 4.2, the $S/V$ parameter is varying, indeed it results to be twice, three or four times the normal one. In Figure 4.3, we report the $S/V$ parameter with various tumour size, from the work [52].
Table 4.2: Parameters used to simulate microfluidics of a tumour.

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>UNIT</th>
<th>VALUE</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>$m^2/(Pa\ s)$</td>
<td>$6.4 \cdot 10^{-15}$</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Tumour</td>
<td>$30 \cdot 10^{-15}$</td>
<td>[41]</td>
</tr>
<tr>
<td>$L_p$</td>
<td>$m/(Pa\ s)$</td>
<td>$1 \cdot 10^{-12}$</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Tumour</td>
<td>$21 \cdot 10^{-12}$</td>
<td>[41]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Normal</td>
<td>$0.95$</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Tumour</td>
<td>$0.82$</td>
<td>[41, 42]</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>Normal</td>
<td>$6.17 \cdot 10^{-5}$</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Tumour</td>
<td>$2.47 \cdot 10^{-4}$</td>
<td>[37]</td>
</tr>
<tr>
<td>$S/V$</td>
<td>$cm^{-1}$</td>
<td>$70$</td>
<td>[7, 41]</td>
</tr>
<tr>
<td></td>
<td>Tumour</td>
<td>$120 - 260$</td>
<td>[7, 41, 42, 52]</td>
</tr>
</tbody>
</table>

Figure 4.3: Surface area over the volume tissue.

We chose as hyper-vascularized network, the one made of 36 capillary network (twice the V18 network and we will call it V36). We computed the $S/V$ parameter, for each network, in the Table 4.3.

Setting the parameters for tumoural vasculature, as reported in Table 4.2, we allow
the passage of more fluid flow through the capillary membrane ($L_p$), we increased the fluid velocity inside the porous medium by increasing hydraulic conductivity ($k$), we reduced the capability of the endothelium to prevent passage to bigger particles ($\sigma$) and we imposed a tissue able to consume more oxygen than the normal values ($V_{max}$).

Table 4.3: Surface area per unit of tissue volume ($S/V$) for each networks.

<table>
<thead>
<tr>
<th></th>
<th>V2</th>
<th>V8</th>
<th>V13</th>
<th>V18</th>
<th>V36</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S/V$ [m$^{-1}$]</td>
<td>1019</td>
<td>3272</td>
<td>5260</td>
<td>7090</td>
<td>14416</td>
</tr>
</tbody>
</table>
4.3.1 Effect of $\alpha$ and $\beta$ on surviving fraction

The $\alpha$ and $\beta$ parameters define the kind of response, more precisely the radiosensitivity, of an irradiated tissue (healthy or tumoural). Indeed, a tissue can be more radioresistant or more radiosensitive to radiation in function on $\alpha$ and $\beta$ values. We show the variability of the $\alpha$ and $\beta$, in the Table 4.4 and Table 4.5, where we report the minimum, the median, the maximum values and the first and third quartile:

Table 4.4: Variability of $\alpha$ and $\beta$ values for healthy tissue.

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$ [Gy$^{-1}$]</th>
<th>$\beta$ [Gy$^{-2}$]</th>
<th>$\alpha/\beta$ [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>0.43</td>
<td>0.05</td>
<td>8.6</td>
</tr>
<tr>
<td>1$^{st}$ Quart</td>
<td>0.5125</td>
<td>0.0575</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.565</td>
<td>0.06</td>
<td>9.417</td>
</tr>
<tr>
<td>3$^{rd}$ Quart</td>
<td>0.6975</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>1.02</td>
<td>0.156</td>
<td>6.538</td>
</tr>
</tbody>
</table>

Table 4.5: Variability of $\alpha$ and $\beta$ values for tumoural tissue.

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$ [Gy$^{-1}$]</th>
<th>$\beta$ [Gy$^{-2}$]</th>
<th>$\alpha/\beta$ [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>0.014</td>
<td>0.002</td>
<td>7</td>
</tr>
<tr>
<td>1$^{st}$ Quart</td>
<td>0.1</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.1777</td>
<td>0.04548</td>
<td>3.9</td>
</tr>
<tr>
<td>3$^{rd}$ Quart</td>
<td>0.29044</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>0.88075</td>
<td>0.1271</td>
<td>6.92</td>
</tr>
</tbody>
</table>

We applied the Linear-Quadratic model (4.1), without the oxygen effect, taking into account the minimum, median and maximum values of $\alpha$ and $\beta$ in order to highlight the effect of those parameters on surviving fraction curves for healthy and tumoural tissue, by changing the radiation dose. Figure 4.4 shows a significant radioresistant behaviour of the tumour tissue compared to the $S_f$ of healthy tissue.
Figure 4.4: Comparison of surviving fractions in function on the radiation dosage, \( D \), by considering minimum, median and maximum \( \alpha \) and \( \beta \) values for healthy (continuous curve) and tumoural (dashed curves) tissue.

In particular, for the same radiation dosage, high values of \( \alpha \) and \( \beta \) lead to an increase in radiosensitivity of the tissue, in fact the blue curves have a major slope, vice versa low values of \( \alpha \) and \( \beta \) lead to an increase in radioresistance.
4.3.2 The $pO_2$ effect

We have calculated the distribution of partial oxygen pressure in healthy and tumour tissue and vessels, for each network (V2, V8, V13, V18 and V36).

**Parameters and Boundary Conditions.** In the model (2.15), we imposed physiological parameters as reported in the Table 3.3, for the healthy tissue simulations; we modelled tumour tissue setting the parameters according to Table 4.2. For both healthy and tumoural case, we set the boundary conditions for oxygen transport problem: Dirichlet condition to each inlet of the vessels equals to $C_{v_{in}}$ and Neumann condition to each outlet of the vessels and each face of the tissue domain. Then, we applied the oxygen-dependent LQ model, namely the equation (4.1), where $\alpha$ and $\beta$ are function on $pO_2$, namely the equations (4.2) and (4.3), respectively. The goal is to calculate the distribution of $S_f$ for a single dose of 2 Gy, to analyze the effect of oxygen. Moreover, in the equations (4.2) and (4.3), the coefficients $a_1$ and $b_1$ (they are the coefficients that most influence the variation of $\alpha$ and $\beta$ at equal $pO_2$) have been modified to set $\alpha$ and $\beta$, both for healthy and tumour case, equal to the median values, reported in the Table 4.4 and Table 4.5.

**Numerical Discretization.** The numerical discretization is performed with linear finite elements (FE). The three-dimensional domain consists of 1728 DOFs (11 elements per cube side) for each chosen network (20 elements per segment). In the Table 4.6, we report the number of DOFs and the number of capillaries for each network and the total computational time of the whole 3D1D problem, namely fluid dynamic problem, hematocrit transport problem and oxygen transport problem (the tests have been performed on a machine with 8 GB of RAM). To solve the linear system ((2.31)), the factorization method, superLU, has been implemented by using GetFem++ 5.0 libraries. We believe that the 3D mesh is adequate for the developed tests, naturally, the model gives the possibility to proceed with a mesh thickening. As further developments, a mesh sensitivity analysis will be carried out, duplicating or tripling the DOFs of the 3D mesh, to see if the characteristic quantities, such as pressure and speed,
change significantly as the mesh varies.

**Results.** We report the colour map for $pO_2$ and for $S_f$ distribution in the Figure 4.5.

![Figure 4.5: The a) panel represents the oxygen partial pressure distribution, instead the b) panel represents the surviving fraction, $S_f$, distribution. The results are reported for each network, from V2 (top) to V36 (bottom), for both healthy (first column) and tumoural (second column) tissue, respectively for each panel.](image-url)
The first column in the a panel in Figure 4.5 shows an homogeneous distribution of $pO_2$ in healthy case. We see an increase in oxygen content due to an increase in the degree of vascularization. For instance, the scenario at the bottom of the first column, the V18 network, shows an oxygen content in the tissue which is consistent with respect the literature ([19]); also, the oxygen partial pressure range in the vessels goes from $100 \text{ mmHg}$ (the imposed arterial condition at the inlet) to an outlet value of $75 \text{ mmHg}$: these values are reasonable for $pO_{2v}$, since the tissue domain is a cube with $500 \mu\text{m}$ side. Instead, the change in parameters has caused a relevant variation both in the interstitium and in the network, bringing the biological tissue to a remarkable modification in oxygen distribution in the second column: it shows a heterogeneous distribution of $pO_2$ in tumoural case. In particular, regions at low oxygen content are highlighted, for instance, looking at V13 and V18 scenarios, where the regions near the capillaries have a high oxygen content than the distant regions (near the boundary).

We can summarize the effects of a tumoural condition on interstitium of biological tissue as lack of homogeneous oxygenation (e.g. presence of localized hypoxic areas) due to excessive oxygen demand.

The panel b in Figure 4.5 shows the effect of the oxygen on the surviving fraction, $S_f$, with the same level of radiation dosage. As we said before, the first column is the healthy case: in the V2 network, the oxygen is not so well distributed, indeed the $S_f$ is high in the regions close to the capillaries, where the oxygen content is high, vice versa, the $S_f$ is low at the distant regions, where the tissue results to be more hypoxic.

Looking at the well-oxygenated cases (V8, V13 and V18), the distribution of surviving fraction is homogeneous, but it results to be low (equals to 0.25), that means the X-rays radiation has killed a $3/4$ of the total amount of healthy cells, due to the high oxygen content in the tissue.

On the other hand, the heterogeneity of the oxygen content in the tissue is reflected on the $S_f$ for tumoural networks: in V2, V8 and V13, the surviving fraction is high near the capillaries, and it is low away from capillaries. Instead, the oxygen effect is less evident in V18 and V36 due to the small gradients of $pO_{2v}$.
4.3.3 Dose and pO2 combined effect

We report the $S_f$ data, dependent on $pO_2$, for each network of the healthy and tumoural case, by changing the radiation dosage (D). We recall that the chosen $\alpha$ and $\beta$ values are the median ones reported in Table 4.4 and Table 4.5. The goal is to show the variability of the surviving fraction due to the oxygen effect for different dose in Figure 4.6 and Figure 4.7.

![Figure 4.6: Variability of surviving fraction in healthy tissue. In each panel, the boxplots of surviving fraction are reported for each radiation dose. The red curve is the surviving fraction computed for the oxygen partial pressure median value.](image-url)

Figure 4.6: Variability of surviving fraction in healthy tissue. In each panel, the boxplots of surviving fraction are reported for each radiation dose. The red curve is the surviving fraction computed for the oxygen partial pressure median value.
In the Figure 4.6, we notice a relevant variability of $S_f$ in the V2 network panel, due to the heterogeneous oxygen distribution in the tissue. For the other panels, the spatial heterogeneity of $S_f$ is no longer significant: from the V8 network panel, $S_f$ is quite homogeneous.

![Graphs showing variability of surviving fraction in tumoural tissue](image)

**Figure 4.7:** Variability of surviving fraction in tumoural tissue. In each panel, the boxplots of the surviving fraction are reported for each radiation dose. The red curve is the surviving fraction computed for the oxygen partial pressure median value.

In Figure 4.7, the heterogeneous effect of the oxygen in the tissue is evident even in the V18 network panel. For instance, in the V13 network panel, there are regions which are oxygenated in a different manner: there are resistant regions (low oxygen content) and radiosensitive regions, namely, they are well-oxygenated. Instead, in the V36 network panel, the oxygen is homogeneously distributed in space (seeing the Figure 4.5), and so the $S_f$.

The next step is the TCP computing for each tumoural network, applying the oxygen 3D1D model to the modified LQ model ((4.4)), for different radiation dosage. As
reported in the literature ([24, 43]), the total TCP has been estimated by the product of local TCP for each node in the tissue domain:

\[
TCP(D) = \prod_{i=1}^{M} TCP_i(D); \quad (4.8)
\]

where \( M \) is the number of elements in tissue domain. So, the equation (4.8) can be re-written as:

\[
TCP(D) = \prod_{i=1}^{M} e^{(-N \sum_i S_f_i(D))} = e^{(-N \int V_t S_f(D) dV_t)}; \quad (4.9)
\]

where \( S_f(D) \) is the surviving fraction at a given dose, \( D \), \( V_t \) is the tumoural volume and \( N \) is the number of clonogenic cells (tumoural cells) in the tumour per unit of non-dimensional volume, set to be 375, according to a total number of clonogenic cells in a tumour of \( 10^6 \) ([5]). So, applying the equation (4.9), we report the TCP curves for each tumoural network in the figure below:

Figure 4.8: Tumour Control Probability curves computed for each tumoural network as function on the oxygen content in the tissue. The TCP cyan curve has been computed without the oxygen effect, by imposing the median \( \alpha \) and \( \beta \) values (see Table 4.5).
The Figure 4.8 shows the effect of oxygen in the probability to eradicate a tumour: since the $\alpha$ and $\beta$ values have been set as median values, the cyan curve is the nominal situation, that means the network curves move from left (nominal situation) to right in function on the oxygen content in the tissue. In particular, the shifting of a curve will be more evident for low-oxygen content tissue due to the poor vascularization (see V2 or V8 tumoural network): the lower the vascularization, the lower the oxygen content, the higher the radioresistance of the tissue and therefore the lower the probability of tumour removal.

We report the numerical TCP values for a single dose of 5, 10, 15 and 20 Gy, in Table 4.7.

<table>
<thead>
<tr>
<th></th>
<th>5 Gy</th>
<th>10 Gy</th>
<th>15 Gy</th>
<th>20 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V8</td>
<td>0</td>
<td>0</td>
<td>0.0017</td>
<td>0.04</td>
</tr>
<tr>
<td>V13</td>
<td>0</td>
<td>0.22</td>
<td>0.73</td>
<td>0.87</td>
</tr>
<tr>
<td>V18</td>
<td>0</td>
<td>0.61</td>
<td>0.99</td>
<td>0.9998</td>
</tr>
<tr>
<td>V36</td>
<td>0</td>
<td>0.77</td>
<td>0.995</td>
<td>1</td>
</tr>
<tr>
<td>NO OXY</td>
<td>0</td>
<td>0.789</td>
<td>0.999</td>
<td>1</td>
</tr>
</tbody>
</table>
We report the $\alpha$, $\beta$, $\alpha/\beta$ and $S_f$ results with respect $pO_2t$, data considering a radiation dose of 2 Gy, for healthy case in Figure 4.9 and Figure 4.10, respectively.

**Figure 4.9:** Evolution of $\alpha$ (left panel), $\beta$ (middle panel) and $\alpha/\beta$ (right panel) with respect the $pO_2t$ in healthy tissue.

**Figure 4.10:** Surviving Fraction curve (yellow curve) for a single dose of 2 Gy on the oxygen partial pressure and $S_f$ distribution for V2 and V18 networks.

The Figure 4.10 confirms that a hypoxic tissue has a relevant resistance to radiation.
(which could decrease the efficiency of the treatment), but an oxygenated tissue, such as healthy biological tissue, is more sensitive to radiation. The $S_f$ results for tumoural tissue are reported in the Figure 4.11 and Figure 4.12.

**Figure 4.11:** Evolution of $\alpha$ (left panel), $\beta$ (middle panel) and $\alpha/\beta$ (right panel) with respect to $pO_2$ in tumoural tissue.

**Figure 4.12:** Surviving fraction curve (yellow curve) for a single dose of 2 Gy on the oxygen partial pressure and $S_f$ distribution for V2, V18 and V36 networks.
In the Figures 4.9 and 4.11, we notice the variation of $\alpha$ and $\beta$ in function on the $pO_2$. By the equations (4.2) and (4.3), for $pO_2 << K$, $\alpha$ and $\beta$ assume a quasi-linear behaviour, instead for $pO_2 >> K$ they assume a non-linear behaviour. Given a tissue characterized by a level of oxygenation, dependent on its degree of vascularization, the Figure 4.10 and Figure 4.12 show that region of the $S_f$ curve we are simulating.

So far, in this section we have shown the variability of surviving fraction with respect the dose, taking into account the heterogeneity of the $pO_2$ on healthy and tumoral tissue, the resulting change in TCP, as function on the $S_f$, and the variability of $\alpha$, $\beta$ and $\alpha/\beta$ on the $pO_2$. We can quantify the oxygen effect by computing the Oxygen Enhancement Ratio (OER) for the dose, $D$. We took the V2 and V36 tumoural network and applied the equation (4.6). The objective is to quantify the radiosensitivity of an aerobic (well-oxygenated) and hypoxic tissue in comparison subjected to a radiation dose to have the same surviving fraction. Indeed, in the OER formula, there are both sensitivity parameters for aerobic ($\alpha_a$ and $\beta_a$) and hypoxic ($\alpha_h$ and $\beta_h$). Firstly, we defined an aerobic condition, a priori, setting an oxygen partial pressure of 60 mmHg (plateau region of the surviving fraction) to compute $\alpha_a$ and $\beta_a$ as constant; then, we computed the OER as function on the $pO_2$ as shown by the equation below:

$$OER(D, \alpha_a, \alpha_h, \beta_a, \beta_h, pO_2) = \frac{2D\beta_a}{\sqrt{\alpha_a^2 + 4\beta_a(\alpha_h(pO_2, LET)D + \beta_h(pO_2, LET)D^2)} - \alpha_a};$$

(4.10)

We report the variability of the OER due to the heterogeneous spatial distribution of oxygen content in tumoural tissue for V2 and V36 network: Figure 4.13 shows, in the case of network V2, a significant variation of OER due to heterogeneous oxygenation; instead, the variation of OER in V36 is less predominant, being an oxygenated tissue. In particular, OER values can be interpreted as the radiation dose required to treat hypoxic tissues to obtain the same surviving fraction in an aerobic tissue. In particular, the dose required for an hypoxic tissue is equal to OER times the radiation dose applied to an aerobic tissue. For example, looking at the tumour network V36 at 9 Gy, the radiation dose applied to a hypoxic tissue should be about twice the radiation dose applied to a well-oxygenated tissue. We expected the high OER values because being
the tumor tissue with V2 network characterized by a high degree of hypoxia, the radiation dose on hypoxic tissue (and therefore very radioresistant tissue) must be very high, almost 3-4 times the dose applied on an oxygenated tissue to kill the same number of interstitial cells. The trend of the OER is consistent with the literature for a tumorogenic cell lines ([49]).

### 4.3.4 Effect of radiosensitivity

In the previous sections, we set $\alpha$ and $\beta$ as median (MED) values, like those reported in Table 4.4 and Table 4.5. Now, we will show the results on the variability of the surviving fraction and TCP by changing tissue type, also taking into account the minimum (MIN) and maximum (MAX) values of Table 4.4 and Table 4.5. For the healthy case, the V2 and V18 networks were considered and, for the tumor case, the V2 and V36 networks. We report the distribution of the surviving fraction, setting a

---

**Figure 4.13:** Boxplots of OER variability for a range of radiation dosage.
single radiation dose of 2 Gy, for all 3 cases of $\alpha$ and $\beta$, both for healthy and tumour tissue, in the following Figure 4.14 and Figure 4.15:

**Figure 4.14:** Distribution of $S_f$ in healthy tissue, by changing degree of vascularization and radiosensitivity parameters (see 4.4).

**Figure 4.15:** Distribution of $S_f$ in tumoural tissue, by changing degree of vascularization and radiosensitivity parameters (see 4.5).
In the Figure 4.14 and Figure 4.15, the variation on the tissue radiosensitivity shows radioresistance when $\alpha$ and $\beta$ values are low, and, vice versa, radiosensitivity when $\alpha$ and $\beta$ are high, with the same dose.

Then, we have analyzed how the $S_f$ changes with the dose. For sake of simplicity, we considered the V2 and V36 tumoural network, to estimate also the effect of $\alpha$ and $\beta$ variation on the TCP. Figure 4.16 shows an interesting combined effect between oxygen and tissue radiosensitivity. The first row of Figure 4.16 is the case of the V2 network: we notice a not so relevant shift of the $S_f$ curve changing $\alpha$ and $\beta$, but we notice a significant variability of the $S_f$ due to oxygen, which changes heterogeneously in space. In the second row of Figure 4.16 we notice a different behaviour for the V36 network: since the tissue is characterized by a homogeneous oxygen distribution and can be considered well-oxygenated, given the high number of capillaries, the variation of radiosensitivity leads to an evident shift of the $S_f$ curve, so the tissue becomes more radiosensitive. Therefore, a tissue with a vascularization similar to V2 case, which is characterized by a high degree of hypoxia and an important heterogeneous spatial distribution of the oxygen content, is not affected by a variation of the tissue type; instead, a tissue with a vascularization similar to V36 case, which is homogeneously...

Figure 4.16: Boxplots and $S_f$ curve for V2 and V36 networks by changing tissue radiosensitivity.
well-oxygenated, shows a change in its radiosensitivity. We report the TCP curves for each case reported.

In the Figure 4.17, the TCP curves show, under another point of view, the combined effect between oxygen and tissue radiosensitivity: for a well-oxygenated and averagely radiosensitive tissue, a few Gy (3 Gy for the dashed blue curve and 8 Gy for the dashed green curve) is enough to obtain a high probability to eradicate the tumour; for a hypoxic and radioresistant or just highly radioresistant tissue, you need to reach a range of 70-90 Gy to increase slightly the TCP.

**Figure 4.17:** Effect of radiosensitivity change on TCP calculation.
In the present work, a finite element model has been developed to describe the oxygen distribution in the micro-vascular environment. The model is based on non-linear constituent models (Michaelis-Menten kinetics and Hill’s model for saturation). It enables the application of the LQ model to study the distribution of cell survival, a function of partial oxygen pressure, at a particular case of homogeneous radiation dose.

The objectives of the thesis are:

1. The analysis of the distribution of the oxygen partial pressure both in the tissue domain and in the capillary network, starting with the resolution of the coupled partial differential equations for the transport of oxygen concentration, using a finite element method;

2. Knowing the distribution of $pO_2$, the study of the biological tissues response to given radiation dosage through the Linear-Quadratic radiobiological model and the calculation of clinical parameters, such as OER and TCP.

This aim has been achieved thanks to a numerical solver able to simulate the exchanges between a vascular network and surrounding tissue. The numeric resolver, implemented in C++ using the finite element library open-source GetFEM++ 5.0,
and has been implemented from the work previously developed by Notaro [34] at the Laboratory of Modelling and Calculation Scientific - MOX. In the mathematical and numerical model, the reduction technique has been used to model capillaries as 1D channels within the 3D interstitial domain and it is at the base of the solver. Starting from the results obtained from the resolution of the fluid dynamic and the transport of erythrocytes ([38]), in the present work, the oxygen transport model has been taken up and modified suitably to make it more representative of the biological phenomenon described by non-linear constitutive models, such as Michaelis-Menten kinetics in the tissue and Hill’s model for the RBCs saturation.

The non-linear models have been implemented in the code and solved through a fixed point iterative method, to obtain a linear system solvable with the solver at our disposal. The introduction of Michaelis-Menten kinetics has allowed the computation of the non-linear consumption rate in the tissue as a function of the oxygen partial pressure, which changes with respect space; while, Hill’s model allowed the introduction of the concept of oxyhaemoglobin, under a biological point of view, a molecule obtained from the oxygen link with the 4 heme groups of the macro-molecule haemoglobin inside the RBCs. Oxyhemoglobin can bind about 97% of oxygen present in the blood fluid and release it from the body districts where it is required.

In its absence, free (or dissolved) oxygen alone would not be sufficient for the correct oxygenation of each body district. This last step would have been impossible without the implementation of the hematocrit transport model, which is of fundamental importance for the correct description of blood movement in the capillaries not only in physiological conditions but also in pathological conditions. Furthermore, this model takes into account various biological phenomena, such as Fähraeus–Lindqvist effect and Zweifach-Fung effect effects. The model proposed here and the corresponding resolver implemented proved to be extremely versatile. Although the mathematical model is not tissue-specific, partial oxygen pressure values consistent with the literature have been obtained ([9, 19]). These results were crucial for the application of the LQ model, in particular modified according to Wenzl et al. ([48, 49]). Through the correct application of the LQ model and an accurate choice of radiosensitivity parameters (α and β), it was possible to obtain the distribution in the tissue of
the surviving fraction, $S_f$, i.e. the fraction of cells that survive to an ionizing radiation dose. This work also shows how the $S_f$ depends on space: it will have a more or less homogeneous distribution depending on the oxygenation of the tissue. In particular, in cases of heterogeneous oxygenation, it was possible to confirm, at a mathematical modelling level, that regions with low oxygen content (hypoxic) are characterized by high values in $S_f$. In other terms, hypoxia makes the tissue more resistant to radiation. This was also possible thanks to the generation of more or less complex 3D artificial vascular networks tool. Indeed, in this work, healthy and tumoral tissues have been simulated with a different degree of the vasculature. From the clinical point of view, knowing which areas have a lower or higher oxygen content, allows a therapy with more targeted and local radiation treatments. Moreover, with the distribution of $S_f$ at our disposal it was possible to calculate clinical parameters, such as OER and TCP, used today for making decisions in planning treatments.

Below, there are several future developments to the 3D1D and LQ model coupling:

**Treatment simulations.** The results reported in this work refer to a single dose of X-ray (fixed LET) homogeneously distributed in the tissue. Radiotherapy treatments may use different types of radiation, such as carbon ions or protons, with different energy release. Moreover, the dose release is a function of the tissue position; therefore, in the model, the LET should be taken into account depending on the chosen radiation, for instance for both carbon ions and protons the LET is not constant, and dose should depend on the tissue position.

**Fractionation simulation.** Fractionation is a clinical radiotherapy schedule aimed at reaching the maximum of TCP by minimizing the healthy tissue complications. This is based on the damage of the most oxygenated layer of the tumour, leading to tumoral tissue re-oxygenation. Such an increased level of oxygen would improve the damage to cancer cells. Anyway, two further steps are required to model this scenario. The first one is the possible changes in tissue response to multiple irradiations. The second one is the repair mechanisms of the cells. Indeed, sub-lethal radiation damages may be repaired by cells before the new
treatment fraction.

Network modifications. The micro-vascular environment is affected by radiations. This may lead to the increase of vascular wall permeability, or edema formation and other phenomena. Such modifications are important when analyzing multiple irradiation on the same tissue.
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[38] L. Possenti, S. di Gregorio, F.M. Gerosa, G. Raimondi, G. Casagrande, M.L. Costantino, and P. Zunino. A computational model for microcirculation including fahraeus-lindqvist


## The $\alpha$ and $\beta$ parameters

### A.1 The $\alpha$ and $\beta$ parameters for tumoural cell lines.

<table>
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<tr>
<th>Cell Lines</th>
<th>Hystology</th>
<th>$\alpha [Gy^{-1}]$</th>
<th>$\beta [Gy^{-2}]$</th>
<th>$\alpha/\beta [Gy]$</th>
<th>Ref.</th>
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</table>

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### A.2 The α and β parameters for healthy cell lines.

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