Simulation of Perfusion Flow Dynamics for Contrast Enhanced Imaging

By:

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ABSTRACT

Dynamic Contrast Enhanced Computed Tomography is an imaging tool that aids in evaluating functional characteristics in different stages of disease assessment: diagnostic, treatment effectiveness and monitoring. At the present time, following all the technological advances, there remains no universally validated method of quantitative, non-invasive, perfusion imaging. In order to address this challenge, certain quality assurance flow phantoms have been developed. This work presents the first step in the prospective framework of phantom simulations with the goal of enhancing the understanding of contrast agent kinetics. Existing knowledge about a two-compartmental fluid exchange phantom was used to validate the constructed computational fluid dynamics (CFD) simulation model. The sensitivity of various parameters, both in the geometric and computational domains, was determined. Finally, the model was employed to evaluate current perfusion parameter estimation models. This provides the groundwork for future phantom developments within the framework.
ACKNOWLEDGEMENTS

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<th>Definition</th>
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<tr>
<td>AIF</td>
<td>Arterial Input Function</td>
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<td>BL</td>
<td>Boundary Layer</td>
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<td>CA</td>
<td>Contrast Agent</td>
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<tr>
<td>CE</td>
<td>Contrast Enhanced</td>
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<td>CFD</td>
<td>Computational Fluid Dynamics</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
</tr>
<tr>
<td>DOE</td>
<td>Design of Experiments</td>
</tr>
<tr>
<td>DOF</td>
<td>Degrees of Freedom</td>
</tr>
<tr>
<td>EES</td>
<td>Extravascular Extracellular Space</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
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<tr>
<td>ID</td>
<td>Inner diameter</td>
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<tr>
<td>IRF</td>
<td>Impulse Residue Function</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTT</td>
<td>mean transit time</td>
</tr>
<tr>
<td>OD</td>
<td>Outer diameter</td>
</tr>
<tr>
<td>PCE</td>
<td>Perfusion Contrast Enhanced</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PMH</td>
<td>Princess Margaret Hospital</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
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<tr>
<td>TAC</td>
<td>Time Attenuation Curve</td>
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<td>US</td>
<td>Ultrasound</td>
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1. INTRODUCTION
The Canadian Cancer Society estimated that there will be 186,400 new cases of cancer of which 75,700 will result in death within Canada in 2012 [1]. Approximately 40% of women and 45% of men will develop cancer during their lifetime and 1 in 4 Canadians will die from cancer. With such high occurrences of cancer, it is critical to expand our knowledge of the field.

There is a vast amount of research underway to understand the causes of the disease, improve diagnostic methods as well as to develop more effective therapeutics. Knowledge of generic and patient specific tumour physiology and vascularity has significantly increased with recent medical advances in diagnostic and imaging tools. Angiogenesis is a fundamental step in tumour growth.

Tumour angiogenic tissue features include: increased vascular density, disorganization of vascular anatomy, variability in vessel size and increased permeability of the endothelium [2]. New antiangiogenic therapies have shown therapeutic efficacy in a preclinical setting. Conventional therapeutic intervention response assessment is based mainly on tumour sizing such as the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. The efficacy of these new antiangiogenic agents is not always reflected in changes in size due to their cytostatic properties [3,4,5,6], thus emphasizing the need to measure local tumour perfusion and permeability. The ability to measure and quantify functional characteristics may help to improve early detection, guide therapeutics and monitor treatment efficacy.

Dynamic Contrast Enhanced (DCE) Computed Tomography (CT) is one of many tools used which provides health care professionals with the information required to make appropriate treatments decisions while remaining minimally invasive. DCE-CT combines two medical specialties: anatomy, to visualize anatomical features, and physiology, to determine functional characteristics over time. Contrast agents are used to enhance the visualization of anatomical features as well as to observe the movement of a bolus in the time domain. After intravenous (IV) injection of a Contrast Agent (CA), the agent is circulated through the body’s vascular network. Within the tissues, the CA flows from the intravascular network into the extravascular space which is captured by time-sequenced images.

DCE methods, currently in clinical trial stages, seek to characterize the vascular/intra-tumor transport as a metric of disease and quantify its response to therapy. Various pharmacokinetic models have been developed in the literature to estimate perfusion parameters for diffusible tracers based on the contrast enhancement measured with DCE-CT along with other imaging modalities [7,8]. Perfusion
measurements obtained include: perfusion (ie: blood flow), permeability, blood volume and mean transit time (MTT). The models currently available seek to provide quantitative insight. Despite their relative success, the models lack validation [9,10] and thus many resort to the use of semi-quantitative measures directly taken from time-attenuation curves such as peak enhancement, uptake slope and area under the curve (AUC) [11]. These semi-quantitative techniques are much simpler; however, they are not easily related to physiological events. Confusion and misinterpretation of the measures derived from the pharmacokinetic model is also problematic [12].

Research and development into validation methods for the assessment of kinetic models has become an area of interest within the oncology community [13,9,6,7,8]. Newer, more accurate, methods of perfusion measurement using diffusible tracers are being sought out. This can be approached in many different ways: validation of the current kinetic models or development of a new method. This project seeks to provide a tool that can be used to further investigate current kinetic models and gain insight into transport phenomena with the hopes of obtaining a clearer vision of non-invasive quantification of physiological changes.

1.1. RESEARCH OBJECTIVES

It is hypothesized that the accuracy of kinetic modeling of DCE-CT measurements can be assessed using the combination of a flow phantom and CFD software. This project is the first component in a prospective framework for computational phantom simulations in order to investigate the accuracy of existing tracer kinetic models.

This project employs Computational Fluid Dynamics (CFD) modeling techniques to replicate the flow phantom (described in Section 2.2) available at Princess Margaret Hospital (PMH), built in Dr. Coolens’ lab, to expand our knowledge of two compartmental exchange and contrast pharmacokinetics. This phantom is ideal for the purposes of this project as the geometry is known accurately and the CFD computations can be directly compared and validated against known experimental measures.

The flow phantom (described in Section 2.2) was designed to produce different CT enhancement curves by adjusting model inputs such as valve position, flow rate and contrast injection time. This provides the flexibility to produce contrast uptake curves corresponding to various vascular networks characterized by features such as peak enhancement, uptake slope and washout slope and mean transit time. In addition, short as well as long injection pulses can be implemented in this system.
The impact of variables specific to the flow phantom and the CFD software COMSOL Multiphysics will be investigated. This will provide the structure required for future phantom replication, validation and investigation using CFD modeling tools. The existing flow phantom will be the stepping stone of the development of this desired framework.

The development of this platform will represent a significant contribution to the area of functional imaging. Not only will this have a direct impact on the area of CT imaging, but it may be implemented across imaging modalities (e.g., MRI). On another hand, it opens the door for the potential modeling of solid tumour by utilizing microscopy data in a CFD environment. More advanced perfusion imaging could lead to more sophisticated treatment planning and improved response assessment guidelines such as those of RECIST which are mainly based on size at the current time.

In order to achieve this initial framework, the following specific research objectives will be addressed:

1) Can CFD modeling tool COMSOL Multiphysics accurately reproduce the two compartment exchange phantom geometry and experiments?
   a. CFD software parameters optimized for phantom geometry and flow rates
   b. CFD model validated using a set of the characteristic time-attenuation curves (TACs) generated experimentally. The set of TACs were drawn from the existing database of flow phantom experiments.

2) What are the implications of changing various parameters in the flow phantom and in COMSOL Multiphysics?
   a. Evaluation of the sensitivity of certain variables on the characteristic TACs. A list of parameters is shown in the Figure 3.

3) What additional information can be obtained from this CFD model about fluid exchange and contrast kinetics?
   a. Comparison of quantitative perfusion estimates using various models with analogous physics (CFD) based parameters.
2. BACKGROUND

2.1. PERFUSION IMAGING

DCE-CT imaging measures x-ray attenuation of anatomical features as well as the movement of a contrast agent (CA) bolus profile in time. During an imaging series, there are a number of factors influencing the time-attenuation or time-concentration curves. Some of these parameters are: [14]

1) Imaging parameters: overall length of time of image series, number and frequency of images, number and thickness of CT slices and x-ray exposure factors

2) Injection parameters: agent type, concentration, volume and rate of injection of contrast medium

Perfusion imaging (or PCE-CT) is the use of these time sequenced DCE-CT images in further analysis to estimate kinetic parameters. The parameters are optimized to generate the best fit to the imaged tissue enhancement curve. From this point forward, DCE-CT will refer to the raw time sequenced images while PCE-CT (or perfusion imaging) will be used when further analysis to obtain perfusion parameters is performed on the images.

Two other major functional imaging techniques are MRI and PET. Historically, MRI was the preferred method of perfusion measurement [15] because of its inherently larger field of view (FOV). For perfusion quantification, the non-linear relationship between blood contrast concentration (typically gadolinium) and MR signal intensity makes it difficult to estimate the absolute contrast concentration in tissues [16,14,17,18]. Another common method of functional characterization is PET nuclear imaging. A positron emitting tracer molecule (eg: isotope) is chosen to give insight about the tissue metabolic activity and the compound uptake. This technique is normally used alongside CT but can also be performed with MRI. Capability of quantifying perfusion directly in CT without the adjunct PET techniques would provide both a time and money savings for hospitals [6]. Availability of PET is also limited [17].

The biggest advantage of DCE-CT is the linear relationship between the concentration of contrast media and CT measurements and therefore TACs [6]. This means that any measures derived from concentration can be considered absolute. CT also has the highest spatial resolution of all imaging modalities [17,13]. The major detriment of CT imaging is the induced radiation exposure.
No single imaging modality is ideal for all circumstances [17] but for the above mentioned reasons, perfusion CT has been a recent area of interest in oncology for the quantification and validation of perfusion measurements. The algorithms and methods used in order to determine these perfusion parameters are overviewed herein.

2.1.1. Contrast Agents
DCE-CT uses a contrast agent to both enhance soft tissue contrast and determine perfusion of tissue. The various types of contrast agents available are: non-specific, targeted and smart [15]. Non-specific contrast agents lack specificity and only provide information about surrogate markers. Targeted contrast agents have high specificity for the target and are designed to bind to specific markers. This is accomplished by altering the ligands on the compounds. Smart contrast agents have high specificity for the target and undergo some form of change due to the interaction with the target.

At the moment, clinically used contrast agents are nonspecific agents and thus only provide information about the surrogate markers (or indirect marker) of the tumour physiology.

There is a wide range of contrast agents available. Their use depends on the imaging modality and the desired image output. A typical agent used for x-ray (including CT) is iodine and gadolinium for MRI.

Iodinated compounds are the most common intravenously administered agent. It enhances blood vessel and organ visualization and is considered “generally safe”. Iodinated agents have been used for decades. Their properties include high contrast density and low toxicity. Iodinated agents are available with a variety of side chains. The different combinations of side chains alter the physiochemical and biological characteristics [19].

Gadolinium is used mainly in MR imaging due to its physical structure where it has a 3+ oxidation state and 7 unpaired electrons. Under a magnetic field, the presence of gadolinium alters the relaxation times of the tissues thus enhancing contrast. Gadolinium is administered as a chelated agent and is generally regarded as safe.

Most contrast agents are considered “generally safe” and the imaging and use of contrast agent comes down to a cost-benefit analysis where the benefit of imaging outweighs the potential risk of an adverse events.
2.1.2. DCE Curves and Kinetic Analysis Models
Pharmacokinetics is the study of the action (distribution, metabolism and elimination) of a substance in the body. Contrary to previous beliefs, recent studies show that the differences in contrast agents have a significant impact on the pharmacokinetics, and therefore TACs. Lack of information about pharmacokinetics of contrast agents can be attributed to the sampling methods currently used (i.e. blood samples) as well as the lack of understanding of transport processes. Information about contrast agents and bolus dispersion in the body is limited to qualitative dependencies such as heart rate, vessel geometry and circulatory parameters [20]. The transport mechanisms and equations that describe the contrast agent movement on the microscopic scale are unknown.

Methods have been described in the literature to quantify a range of physiological parameters with the aim of indicating the functional status of tissues, referred to as perfusion parameters. These compartment and kinetic based modeling techniques have been developed to quantify perfusion parameters on a macroscopic scale. These methods do not account for agent specific properties such as solubility, viscosity, oncotic pressure, electric charge, protein binding and hydrophobicity [21].

Perfusion related measurements seek to quantify and provide insight on tumour angiogenesis. The relationship between physiological parameters and those derived from DCE-CT is very complex. Perfusion is a clinical indicator that aims to determine the flow in a given tissue region in relation to its volume (or mass). Other perfusion parameters seek to quantify the contrast agent transport phenomenon with the use of rate transfer constants. Miles et al [7] recently suggested new terminology for all related perfusion parameters to be used in both future publications and in clinical practice to ensure proper interpretation of results reported. The physiological phenomenon that perfusion imaging seeks to quantify are [7]:

1) Regional tumour blood flow: blood flow per unit volume or mass of tissue
   a. Sometimes referred to as perfusion
2) Regional tumour blood volume: fraction of tissue that consist of flowing blood
   a. Sometimes referred to as relative blood volume (rBV)
3) Mean transit time (MTT): average time for contrast material to traverse the tissue vasculature
4) Blood flow extraction product: reflecting the unidirectional rate of transfer of contrast material from intravascular to extravascular space
5) Permeability surface area product: reflecting the diffusion of contrast material across the capillary endothelium and the surface area of the endothelium
Other semi-quantitative parameters can readily be obtained straight from the time-attenuation curves:

1) Peak enhancement
2) Area under the time-attenuation curve (AUC)
3) Maximum slope

All analysis methods utilize time-attenuation curves (TACs). These are obtained by measuring the change in CT number, or Hounsfield Unit (HU), over time for an ROI. TACs are also referred to as contrast enhancement curves and uptake curves. The CT number is defined in Equation 1 where \( K \) is the scaling factor (typically 1000), \( \mu_p \) is the mean attenuation coefficient of a pixel and \( \mu_w \) is the attenuation coefficient of water.

\[
CT\ Number = K \frac{\mu_p - \mu_w}{\mu_w}
\]

A sample of the idealistic time attenuation curve is shown in Figure 1. The first peak is due to the first passage of the contrast agent and the second smaller peak is due to recirculation of the contrast material. Complete mixing between the blood and contrast agent occurs after approximately four complete circulation cycles [19].

Blomley and Dawson [21] reported that time attenuation curves are dependent on the following four factors:

1. Rate of contrast medium transfer to extracellular fluid (ECF)
2. Osmality driven transit of water between ECF and plasma
3. Heart and pulmonary circulation
4. Distribution of transit times for contrast medium in circulation and recirculation
There are a few methods that have been proposed for the calculation of perfusion parameters such as compartmental modeling and deconvolutions. This section only provides an overview of each method and is by no means a comprehensive review.

Single compartment models are used for first pass studies. This consists of a single inflow and single outflow configuration. Perfusion is calculated based on the maximum slope of the tissue TAC and is normalized to a factor of the arterial input function (AIF) (ie: arterial TAC) \([6]\) such as peak enhancement. It is known that the steepest slope method systematically underestimates tissue perfusion especially when the flow network has multiple outputs or when contrast escapes before time of maximum slope is reached \([22]\) \([23]\).

A two compartment pharmacokinetic model (sometimes called Tofts model) adds a small amount of complexity by considering two spaces where the contrast agent passes from the blood plasma through the vascular endothelium and into the tissue space. The contrast is assumed to remain in the plasma and extracellular extravascular spaces \([17]\). The generalized kinetic model used is shown in \textbf{Equation 2}.

\[
\frac{dC_t}{dt} = K^{\text{trans}} \left(C_p - C_t/v_e\right) = K^{\text{trans}} C_p - K_{ep} C_t
\]

In convolution notation:

\[
C_t(t) = K^{\text{trans}} \exp \left(\frac{-K^{\text{trans}}}{v_e} \cdot t\right) \otimes C_p(t)
\]

Where \(C_t\) is the tracer concentration in tissue, \(C_p\) is the tracer concentration in plasma, \(K^{\text{trans}}\) is the rate of flux of contrast agent into the extracellular extravascular space, \(v_e\) is the volume of the extracellular extravascular space and \(K_{ep}\) is the rate constant for the back flux from the extracellular extravascular space to the vasculature. Note that the symbol \(\otimes\) denotes a convolution. Unfortunately, this model cannot be used for certain anatomical features such as the liver, in which the blood flow circulation is more complex. The Tofts model is only applicable to poorly vascularized tissues (small blood volume) \([24]\). This method can produce erroneously higher \(K^{\text{trans}}\) values for tissues where the vascular fraction is high such as a tumour \([14]\). In attempt to increase the range of applicability, the modified Tofts model was developed.
The modified Tofts model (Equation 4), an extension of the two compartment model, enables the calculation of fractional plasma volume, $v_p$. This increases the applicability range to include that of highly perfused tissues or high blood flows.

$$C_t(t) = v_pC_p(t) + K_{\text{trans}} \exp \left( -\frac{K_{\text{trans}}}{v_e} \cdot t \right) \otimes C_p(t)$$

If the leakage is small then the rate of contrast leakage is diffusion dependent whereas if it is large then it will be dependent on the flow rate or permeability. Therefore $K_{\text{trans}}$ reflects both permeability and diffusion and the two impacts cannot be separated.

Both Tofts and modified Tofts model assume well mixed independent compartments where the contrast agent exchange can be expressed as an effective permeability, combining the effects of permeability and diffusion. A limitation of these methods is that very high resolution is required, both temporal and spatial, as continuous contrast enhancement curves are required to perform the deconvolution and produce accurate solutions. Due to very high sensitivity to noise in deconvolution analysis, there is often more than one solution, even with the clearest images. These models allow calculation of perfusion type parameters for weakly vascularized (Tofts and modified Tofts) and highly perfused tissues (modified Tofts) [24].

The last model commonly used is the Adiabatic Tissue Homogeneity (ATH) model which is based on the contributions from Johnson and Wilson [25] and St Lawrence and Lee [26]. This model was not used in further analysis and is omitted from this review.

Validation of perfusion parameters using all modeling methods has been difficult. There is currently a huge array of data acquisition protocols and variable processing methods for Perfusion Contrast Enhanced CT (PCE-CT) that leads to confusion in this field. Accuracy and sensitivity of perfusion measurements in various body networks is still lacking. Angiogenic vasculature has a very complex geometry, increasing difficulty in phantom replication. Inability to reproduce this setting has led to unknown accuracy of the estimated perfusion measurements. Most studies in this field simply show correlations between perfusion measurements and tumour vascularity, providing only a qualitative assessment of kinetic models. An absolute assessment of the perfusion parameters values is required.

Time-attenuation curves are a function of many parameters such as cardiac output and central blood volume, which vary between patients and even between study periods. It is therefore concluded that changes in quantitative parameters could indeed be due to changes in tumour vascularity, but
alterations to cardiovascular function could also be factor [23]. There also exist variations in hematocrit between the blood in arteries and that in tissue [23]. Another limitation of the current methods is that they attempt to describe a microscopic process of diffusion and permeability using macroscopic kinetic models which contain inherent errors and assumptions. Caution must be used when interpreting perfusion type parameters.

For all of the above mentioned reasons, the interpretation of TACs still remains semi-quantitative as they lack validation. Moving forward with the above limitation in mind, there exists a need for quantitative perfusion type parameters. This can be achieved in one of two ways: improving and building upon the current modeling methods (potentially validating current models) or by developing a new innovative analysis technique.

A dynamic flow imaging phantom, to be referred to as the flow phantom, was developed at PMH with the hopes of validating the perfusion parameters and providing a quality assurance tool for imaging technologies. Phantom simulations provide an easy approach to understanding the movement of contrast in a controlled environment, putting aside the in-vivo microscopic effects. This flow phantom is described in detail in Section 2.2.

2.2. DYNAMIC FLOW PHANTOM
Availability of volumetric DCE-CT has led to re-evaluation of the methods in which the perfusion parameters are obtained. Lack of existence of quality assurance tools, within the physiological flow range, to ensure accuracy of the measurements, led to attempts to create models that replicate perfusion kinetics.

The flow phantom was designed in Dr. Coolens’ group [27] to create a quality assurance tool that can be used across imaging modalities. It was built with the intent of standardizing and validating quantitative measures obtained from DCE-CT and perfusion imaging as well as increasing knowledge about contrast kinetics. The flow phantom was designed to:

1) Produce a range of characteristic TACs (Range)
   - Perfusion varies significantly between various parts of the body and thus the ability to replicate these flow rates is critical.
2) Produce reproducible and predictable TACs (Reproducibility and robustness)
   - Reproducibility between consecutive experiments and between imaging devices
3) Typical Arterial Input Function (AIF) shaped input TACs
- **AIFs** represent the arterial input to a tissue subset. As previously mentioned this input function is required in many perfusion models.

The phantom consists of an external cylinder and a distribution tube with perforations to create a two-compartment model exchange (*Figure 2*). Fluid enters at the “Phantom Input” (bright green), passes through the “Distribution tube” and exits the system at either the “Cylinder Output” (turquoise) or the “Distribution Tube Output” (red). The major phantom measurements are summarized in Table 1. The pump and injection characteristics can be set as desired. The flow ratio, defined as the ratio of cylinder outflow rate to inlet flow rate, can be adjusted using valves located on each outlet.

![Figure 2: Flow Phantom Images A) Cross Section As Imaged in CT, B) 3D Reconstruction in AMIRA [27]](image)

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Property</th>
<th>Size/Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylinder</td>
<td>Length</td>
<td>10cm</td>
</tr>
<tr>
<td></td>
<td>Diameter</td>
<td>5cm</td>
</tr>
<tr>
<td></td>
<td>Outlet diameter (x2) (on each end of the cylinder)</td>
<td>¼” ID</td>
</tr>
<tr>
<td>Distribution tube</td>
<td>Length</td>
<td>100cm</td>
</tr>
<tr>
<td></td>
<td>Tubing diameter</td>
<td>⅛” ID</td>
</tr>
<tr>
<td></td>
<td>Inlet and outlet connector diameter</td>
<td>¼” ID</td>
</tr>
<tr>
<td>Perforations</td>
<td>Drilled diameter</td>
<td>1.2mm</td>
</tr>
<tr>
<td></td>
<td>Effective diameter (outer bend/inner bend)</td>
<td>0.7mm/0.5mm</td>
</tr>
<tr>
<td></td>
<td>Spacing</td>
<td>Equally spaced along 100cm</td>
</tr>
</tbody>
</table>

Experiments with the phantom were performed using a blood mimicking fluid (mixture of glycerol and water) and contrast agent such as Visipaque (iodixanol). The phantom and its prediction model compute the input and output TACs based on a given set of parameters (pump flow rate, injection pump flow rate, injection contrast concentration and valve positions). The prediction model can also be
used in reverse: feeding it the desired TACs and letting it compute the control parameters to be used in the experiment.

The phantom was able to produce a wide range of physiologically relevant TACs. It was noted experimentally that the contrast “was not perfectly homogeneous within the cylinder which leads to variability in the rate in which it is expelled” [27]. This created discrepancies between prediction model and the experimental curves.

Minimal differences were observed between experiments within as well as across devices such as CT scanners. This demonstrated the potential utility of the phantom in quality assurance protocols across imaging modalities. More details can be found in Driscoll et al [27].

The flow phantom, a two-compartment exchange system, is a great tool to be used alongside CFD. The series of experiments performed at the hospital and the known geometry can be utilized to validate the CFD models, and provide a basis for further investigation of perfusion dependencies such as flow rates and injection characteristics.
3. TRANSPORT PHENOMENON – THEORY AND EQUATIONS

The transport phenomenon theory and equations utilized in all aspects of this project and implemented in the CFD software are outlined here-in. Two major aspects are covered: momentum and mass conservation. The equations described in this section are referenced throughout this report.

3.1. FLUID FLOW: MOMENTUM CONSERVATION

Flow in a channel or pipe can be characterized by the dimensionless number called the Reynolds number. The Reynolds number is the ratio of inertial forces to viscous forces (Equation 5). Laminar flow occurs when a fluid flows in parallel layers with no disruptions between layers. This occurs at low velocities where fluids do not experience lateral mixing. In a straight pipe, a flow holding a Reynolds number less than 2100 is considered laminar and yields a parabolic flow profile. Turbulent flow is a more chaotic flow with variations in pressure and higher velocity creating eddies and vortices. Flow described by a Reynolds number of above 4000 is considered turbulent. The region between laminar and turbulent is called the transition zone.

\[ Re = \frac{Inertial \ Forces}{Viscous \ Forces} = \frac{\rho u^2}{\mu L} = \frac{\rho u L}{\mu} \]  

Where \( Re \) is the Reynolds number [dimensionless], \( \rho \) is the fluid density [kg/m\(^3\)], \( \mu \) is the fluid dynamic viscosity [kg-s/m], \( u \) is the fluid velocity [m/s] and \( L \) is the characteristic length [m].

If the inlet flow to the geometry is pulsatile, a second dimensionless number called the Womersley number describes the added complexity in the fluid mechanics behavior. This parameter represents the ratio of the transient and oscillatory inertial force to the shear force (or pulsatile flow frequency to viscous effects) (Equation 6). When the Womersley number is relatively small (<1), the frequency of pulsation is sufficiently low that a parabolic velocity profile (in a straight pipe) can develop during each cycle. When the number is relatively large (10+), the fluid exhibits a plug-flow-like profile.

\[ \alpha = r \left( \frac{W}{v} \right)^{1/2} \]

Where \( \alpha \) is the Womersley number [dimensionless], \( r \) is the pipe radius [m], \( w \) is the angular frequency of the oscillations or pulsation [rad/s] and \( v \) is the kinematic viscosity [m\(^2\)/s].

Flow in a helical type pipe is characterized by yet another dimensionless parameter called the Dean number. The Dean number is equal to the ratio of the square root of the product of the inertia and
centrifugal forces to viscous forces (Equation 7). Dean vortices are counter-rotating cells in the transverse direction. The critical Reynolds number, the number at which the flow exits the laminar region, in a straight pipe is around 2100 but in a curved pipe it is much larger, by a factor of two or more [28]. An in-depth discussion of Dean flow is found in Section 3.1.1.

\[
De = Re \left( \frac{r}{R} \right)^{1/2}
\]

Where \( De \) is the Dean number [dimensionless], \( Re \) is the Reynolds number [dimensionless], \( r \) is the radius of pipe [m] and \( R \) is the radius of curvature (cylinder diameter) [m].

The above dimensionless numbers seek to describe different types of flow. All equations require geometric measures such as diameter but most importantly, they depend on the velocity in the pipe. The velocity can be determined using Navier-Stokes equation. This version of the continuity equation is derived from basic conservation principles where mass, momentum and energy are all conserved. The Navier Stokes equation for an incompressible fluid is shown is Equation 8. The unsteady acceleration plus the convective acceleration (left hand side) equal the sum of viscous stress, pressure force and gravitational force (right hand side).

\[
\rho \frac{du}{dt} + \rho u \nabla u = \nu \nabla^2 u + \nabla P + \rho g
\]

Where \( \rho \) is the density [kg/m³], \( \nu \) is the viscosity [kg-s/m], \( u \) is the velocity [m/s], \( P \) is the pressure [Pa], \( g \) is the gravitational constant [kg/m-s²] and \( t \) is the time [s]

3.1.1. Dean Flow Theory

The flow phantom used in all aspects of this project exhibits Dean flow as the distribution tube coiled inside the cylinder creates a helix. This section describes the impact of helical geometries on flow patterns.

Dean vortices are counter-rotating cells in the transverse direction. Their characteristics depend on the fluid dynamics and geometry of the entity in question. The Dean number is equal to the ratio of the square root of the product of the inertia and centrifugal forces to viscous forces [28] (Equation 7). It is essentially a measure of the magnitude of secondary flow as they are induced by centrifugal forces and their interaction with viscous forces. The ratio of pipe radius to curvature radius seeks to quantify the balance of the inertia, viscous and centrifugal forces due to geometric factors. For low Dean numbers,
the axial velocity remains near the center and there is one pair of symmetrical vortices in secondary flow. As the Dean number increases, the maximum axial velocity shifts to the outer bend and appears “bean shaped”.

The three effects of curvature and torsion found in helical geometries are [29]:

1. Form counter-rotating cells of the secondary flow
2. Push the maximum axial velocity to the outer bend
3. Push the two cells in the secondary flow to the outer bend

Helical geometries are described using two measures: the curvature radius and the pitch. The pitch refers to the distance between two consecutive helical rotations. The system curvature (Equation 9) and torsion (Equation 10) are often reported as descriptors of the geometry.

\[ K = \frac{R}{R^2 + (p/2\pi)^2} \]  
\[ T = \frac{p/2\pi}{R^2 + (p/2\pi)^2} \]

Where \( K \) is the curvature [m], \( T \) is the torsion [m], \( R \) is the curvature radius [m], \( r \) is the pipe radius [m] and \( p \) is the helical pitch [m].

As previously mentioned, the critical Reynolds number (number at which the flow regime switches from laminar to transition) is different than that of a straight pipe network. The equation to approximate the critical Reynolds number is shown (Equation 11):

\[ Re_c = 2.10^4 \left( \frac{d}{1 + \left( \frac{p}{D\pi} \right)^2} \right)^{0.32} \]

Where \( D \) is the curvature diameter [m], \( d \) is the pipe diameter [m] and \( p \) is the helical pitch [m].

**3.1.2. Dean Flow Literature**

There is a range of literature covering various:

a) Cross-sectional geometries (circular, elliptical, square, rectangular, triangular...)

b) Pipe paths (toroidal, spiral, helical...)

c) Flow regimes (laminar, mixed, turbulent...)

d) Approaches (experimental, analytical, numerical...)
The results obtained from a small subset of the literature are presented here. Table 2 summarizes the geometry, mesh and flow regimes investigated in the three articles found utilizing numerical approaches. All three models listed assumed incompressibility and used the fluid properties of water.

<table>
<thead>
<tr>
<th>Author / Date</th>
<th>Geometry</th>
<th>Software</th>
<th>Flow Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moll et al (2007) [31]</td>
<td>1) Circular: a) Diameter: 0.2-2mm 2) Helical path a) Diameter: 0.36-110mm b) Pitch: 0-200mm</td>
<td>FIDAP 788x360 (nodes per section x length, eight node brick elements)</td>
<td>Re: 10-3000  De: 0.4-730</td>
</tr>
</tbody>
</table>

In terms of best software settings, all papers concluded that the most accurate solutions were generated when a complete mesh was generated where no symmetry planes were used. As for physical phenomenon observed, authors noted that flow remained within the laminar range even when the Reynolds number exceeded 2100. This confirms the hypothesis that the critical Reynolds number with Dean type flows are higher and can be described using Equation 11. As expected, an increased flow rate (higher Reynolds number) created a larger increase in local shear stress as compared to a straight pipe [31]. As curvature increases, axial flow spread out and the maximum velocity moved closer to the external wall resulting in less homogenous wall shear stress [31]. Two authors [30] [31] noticed that the principal flow was not significantly affected by torsion and thus for a constant Dean number, the velocity profile was the same regardless of pitch.

The third author [32] investigated a much higher range of Reynolds and Dean numbers. It was observed that above a certain Reynolds number (depends on curvature and torsion), the bean shaped contour began to extend at both top and bottom ends. The distortion is thought to be attributed to the twisting vortices in the central plane which attempt to counter balance the centrifugal force. This behavior disappeared as the flow reaches the transition flow regime.
3.1.3. Dean Flow with Pulsatile Flow Literature

The combination of helical geometries and pulsatile flow creates fairly complex fluid mechanics behaviour. A study [33] used laser doppler velocimetry to measure the velocity at discrete positions along a single helical rotation. A pulsatile flow generator composed of 1) steady flow and 2) oscillatory flow was use (described in Equation 12).

\[ W = W_m + W_o \sin \theta \]

Where \( W \) is the axial velocity averaged over cross section \([\text{m}^3/\text{s}]\), \( W_m \) is the steady flow component \([\text{m}^3/\text{s}]\), \( W_o \) is the oscillatory flow component \([\text{m}^3/\text{s}]\) and \( \Theta \) is the phase angle (wt=angular frequency x time).

Sumida et al [33] showed a reversal of flow for higher frequency factor at the minimum phase angle of 270 deg. The second phenomenon observed was that an increase in the curve radius over pipe radius ratio resulted in flow development being achieved at a smaller turn angle but at a longer distance (length). Lastly, an increase in Dean number resulted in intensified centrifugal force, making secondary flow more appreciable, as expected. More details can be found in Sumida et al [33].

3.1.4. Flow Profiles in Perforated Pipe Networks

The tubing used in the flow phantom contains a series of perforations. In perforated pipes, variations in fluid pressure arise from 1) pressure loss due to the friction with the surface of the pipe in the direction of flow, and 2) the momentum of the main fluid produces a rise in the pressure because the main fluid stream is decelerated due to the continuous loss of fluid from the holes. The friction and momentum work in opposing directions and thus the flow distribution out of each perforation is a function of the balance of these two forces [34,35]

Perforated pipes are often used in industry for chemical vapour deposition, ventilation systems, pressurized heavy water reactors emergency shutdown systems and spargers (bubble column reactor). A literature search was performed to find articles that experimentally or numerically investigated the flow profile in perforated pipes. Unfortunately, all literature found were restricted to closed-ended pipes. No literature was found for perforated open-ended pipes using an incompressible fluid. Therefore no literature could be used as either a baseline or comparison point for the flow profiles predicted in COMSOL Multiphysics. Only generic conclusions about the fluid discharge profile dependencies from the literature could be applied to this project. These dependencies include: flow
velocity, pipe diameter, discharge coefficients, perforation area/size, perforation distribution (spacing), excess pressure across perforation and length of pipe [34,35,36,37]. CFD provides the advantage that, with proper boundary conditions and mesh, prediction of both pressure and flow distributions can be generated for any given geometry without knowledge of friction coefficients in pipe and orifice discharge coefficients [35].

3.1.5. Pressure Loss in Pipe Networks
Pressure losses in non-perforated pipes are well documented in literature. Correlations describing the pressure differential in both straight and helical pipes are reported herein. While this topic may not be directly applicable to the flow phantom geometry which contains perforations, it can provide a baseline for evaluation of simulation computations. Most importantly, they help to assess the quality of the mesh.

The pressure loss in a straight pipe is very well documented and can be calculated using one of two methods. The first is the Hagen-Poiseuille equation which predicts the pressure drop in a long cylindrical straight pipe with constant diameter for laminar incompressible flows.

\[
\Delta P = \frac{8\mu LQ}{\pi R^4} = \frac{128\mu LQ}{\pi D^4}
\]

Where \(\Delta P\) is the pressure loss [Pa], \(\mu\) is the fluid viscosity [kg s/m], \(L\) is the pipe length [m], \(Q\) is the fluid flow rate \([m^3/s]\) and \(R\) is the pipe radius (=D/2) [m].

The second method uses friction factors. For laminar flow, two types of friction factors can be used: Darcy (Equation 14) or Fanning (Equation 15). The Darcy friction factor is equal to four times that of the Fanning. The pressure loss using the Fanning friction factor can be estimated with Equation 16.

\[
f_d = \frac{64}{\text{Re}}
\]

\[
f_f = \frac{16}{\text{Re}}
\]

\[
\Delta P = \frac{2f_f L v^2 \rho}{D}
\]

Where \(f_d\) is the Darcy friction factor, \(f_f\) is the Fanning friction factor, \(\text{Re}\) is the Reynolds number [dimensionless], \(\rho\) is the fluid density \([m^3/s]\), \(v\) is fluid average velocity \([m/s]\), \(L\) is the length of the pipe \([m]\) and \(D\) is the pipe diameter \([m]\).
The flow phenomenon in a helical pipe is much more complex than in a straight pipe. Therefore the pressure required to drive a desired flow in a helical pipe will be higher than its equivalent straight pipe (same diameter and length). A vast amount of literature aiming to predict the pressure loss in helical and curved pipe can be found. They cover a range of fluid (ex: air, water, two-phase), flow types (ex: laminar, turbulent) and geometry (ex: helical, spiral, toroidal). Table 3 summarizes the equations applicable to the flow phantom, ie: one phase liquid solution with laminar flow.

**Table 3: Pressure Loss Correlations for Helical Pipes** [38] [39] [40]

<table>
<thead>
<tr>
<th>Author</th>
<th>Correlation</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| Ito (1959) Cited by Naphon et al [38] and Ali [39] | \[
\frac{f_c}{f_s} = \frac{21.5\, De}{[1.56 + \log De]^{2.73}} \]
Laminar, \(13.5 < De < 2000\) |
\begin{align*}
\frac{f_c}{f_s} &= \frac{32}{Re} \\
\frac{f_c}{f_s} &= 5.22\left(\sqrt{Re(D/d)}\right)^{-0.6} \\
\frac{f_c}{f_s} &= 1.8\left(\sqrt{Re(D/d)}\right)^{-0.5}
\end{align*}
\] 0.0097 < \(d/D\) < 0.125, \(Re\sqrt{d/D} < 30\), 30 < \(Re\sqrt{d/D}\) < 300, 300 < \(Re\sqrt{d/D}\) < \(Re_{crit}\) |
| Mishra and Gupta (1979) Cited by Mishra and Gupta [40], Naphon et al [38] and Ali [39] | \[
\frac{f_c}{f_s} = 1 + 0.033\left[\log He\right]^{4} \\
He = Re\left[\frac{d/D}{1 + (p/\pi D)^{2}}\right]^{1/2}
\] Laminar, \(1 < He < 3000\), 2.89E-3 < \(d/D\) < 0.155, 0 < \(p/D\) < 254 |
\begin{align*}
fcRe &= \left[16 + \left(0.378De\lambda\frac{1}{3} + 12.1\right)De\lambda\frac{1}{3}Y^{2}\right] \\
\frac{d}{D} &= \left[1 + \left(0.0908 + 0.0233\lambda\frac{1}{2}\right)De^{\frac{1}{2}} - 0.132\lambda + 0.37\lambda - 0.2\right] \\
\lambda &= \left[\frac{p/\pi}{(D/2)^{2} + (p/\pi D)^{2}}\right]^{1/2} \\
\eta &= \left[\frac{p/\pi}{(D/2)^{2} + (p/\pi D)^{2}}\right], \gamma = \eta / \lambda De^{\frac{1}{2}}
\end{align*}
\] |
\frac{f_c}{f_s} = 0.556 + 0.0969\sqrt{De}
\] Laminar |
\begin{align*}
EuG &= 21.88Re^{-0.9} \\
EuG &= 5.25Re^{-2/3} \\
EuG &= \frac{dp}{2pD^2} \frac{d^{2}G}{L_c}
\end{align*}
\] \(Re < 500\) (low laminar), \(500 < Re < 6300\) (laminar) |

Friction factors reported in Table 3 are Fanning friction factors except for Ito which uses the Darcy factor. Variables in Table 3 are defined as follows: \(f_c\) is the friction factor for coil, \(f_s\) is the friction factor for a straight pipe, \(He\) is the helical number, \(Re\) is the Reynolds number, \(De\) is the Dean number, \(Eu\) is Euler’s number, \(G\) is the geometric number, \(d\) is the tube diameter, \(D\) is the coil diameter and \(p\) is the pitch.

Upon evaluation of the correlations for a given set of geometry and experimental settings, it was proven that they all yield different pressure losses. As no single correlation has been widely accepted among the community, no single correlation is deemed most accurate. While they are not
representative of the flow phantom, the correlations in both straight and helical geometries can be used to assess the quality of the mesh when the boundary conditions are changed to a single inflow, single outflow (ie: no holes).

3.2. FLUID FLOW: POROUS MEDIUM

A modified version of the Navier-Stokes equation can be used to describe flow in a porous medium. Starting with the simplest version of flow in a porous medium, complexity is added in a stepwise fashion.

A porous medium is defined as a material consisting of a solid matrix with voids spaces which allow fluid to pass. The porous medium is also characterized using its permeability. Permeability is a measure of the ability of porous material to transmit fluids or allow fluid to pass through it. This can be quantified using Darcy’s Law (Equation 17 and 18). The equation assumes that the porous and fluid media are homogenized into a single medium. The equation allows estimation of the fluid flow in the porous medium when the pressure gradient is the major driving force. This form of the equation implies a linear proportionality between the flow and pressure difference and is valid for low porosity, low permeability and slow flow.

\[ u = \frac{K \Delta P}{\mu \Delta x} \]  

17

Or in vector differential form:

\[ \frac{\mu}{K} u = -\nabla P \]  

18

Where \( v \) is the velocity through the medium [m/s], \( k \) is the permeability of the medium [m\(^2\)], \( \mu \) is the dynamic viscosity of the fluid [Pa s], \( \Delta P \) is the applied pressure differential [Pa], \( \Delta x \) is the porous bed thickness [m] and \( \varepsilon \) is the bed porosity [dimensionless] (value from 0 to 1).

Additional forms of Darcy’s law can be implemented depending on the flow conditions of the system. The first is the Darcy-Brinkman equation (Equation 19, in vector differential form) which is used when the boundaries of the porous medium need to be accounted for. This form is used if there is boundary where transition between slow flow in porous media (Darcy’s law) and fast flow in a channel (Navier-Stokes) exists. The Brinkman equation extends Darcy’s equation to include a term that accounts for viscous transport.
\[ \frac{\mu}{K} u = -\nabla P + \mu \nabla^2 u \]

A final variation on Darcy’s law is the Brinkman-Forchheimer-Darcy equation which is a generalized equation for flow transport in porous medium. This form should be used when inertia cannot be neglected as it considered additional effects such as drag. It can account for additional effects and complications such as boundary conditions, drag and other convective effects. The generic form used in COMSOL Multiphysics accounting for all the above mentioned forces is shown here in vector differential form (Equation 20).

\[ \frac{\rho}{\varepsilon} \left( u \cdot \nabla \right) \frac{\mu}{\varepsilon} = \nabla \cdot \left[ -P + \frac{\mu}{\varepsilon} \nabla^2 u \right] - \frac{2\mu}{3\varepsilon} (\nabla u) - \left( \frac{\mu}{K} + \beta|u| + Q_{BR} \right) u + F \]

Where \( \varepsilon \) is the porosity (0 to 1), \( \beta \) is the Forchheimer drag [kg/m\(^4\)], \( F \) is the volume force [N/m\(^3\)] and \( Q_{BR} \) is the source term [kg/m\(^3\)s].

### 3.3. INDICATOR MOVEMENT: MASS CONSERVATION

Now that the equations for the flow phenomena have been described, the contrast or indicator movement can be investigated. It is well known that for any given geometry, the concentration time curve is dependent on the manner of injection (speed and rate) and the transit time (pipe length, diameter and flow rate).

A study [41] looked at the dispersion of a single instantaneous injection of red dye (1% Amaranth) solution in straight and curved circular cross-sectional pipe as well as steady and pulsatile flows (Reynolds number of 102-3690). The dye concentration was measured using a photomultiplier. It was observed experimentally that bends gave rise to secondary flows as predicted by Dean’s theory. These secondary motions resulted in indicator delay of first onset, steeper rise and higher peak concentration values as compared to the straight pipe. These were greatest around a Reynolds number of 1000 with decreasing importance/impact on either side (smaller and larger). The next experiment investigated the effects of pulsatile flow on both straight and bent pipes. No significant changes were observed between the steady inflow and pulsatile inflow for the flow rates below a Reynolds number of 1000. For Reynolds number above this 1000 threshold, the indicator was eliminated more quickly than that of the steady flow. All above conclusions were observed experimentally. See Caro et al [41] for more detailed information and graphical representation of the results.
The above conclusions were observed experimentally. In the flow phantom geometry, transport phenomena equations must be used in order to determine the movement of an indicator in the flow network. Two methods are commonly used to describe the motion of indicators and contrast agents.

The first utilizes the diffusion convection equation. This attempts to capture the overall effect rather than the movement of each particle. This type of equation is typically implemented where the inlet concentration and a characteristic diffusion coefficient are defined. More information on diffusion coefficients is found in Section 3.3.1.

\[ \frac{\partial c}{\partial t} + \nabla \cdot (- D \nabla c) + u \cdot \nabla c = R \]  

Where \(c\) is the concentration [mol/m\(^3\)], \(D\) is the diffusion coefficient [m\(^2\)/s], \(u\) is the velocity [m/s] and \(t\) is time [s].

In order to determine the significance of the diffusion and convection components, the Peclet number can be calculated. When the Peclet number is large, convection dominates the transport of the indicator particles and diffusion is negligible.

\[ Pe = \frac{Lu}{D} \]  

Where \(L\) is the characteristics length [m], \(u\) is the fluid velocity [m/s] and \(D\) is the diffusion coefficient [m\(^2\)/s].

While the diffusion convection equation seeks to describe the overall effect of particle movement, a second method sometimes referred to as particle tracing (or tracking) attempts to predict the movement of each particle. This characteristic equation depends on the following three variables: particle mass, particle density, particle diameter. The position of these particles at the inlet or release site is defined based on a) mesh (in CFD software) or b) density function (proportional to velocity).

\[ \frac{d}{dt}(m_p v_p) = F_D + F_g \]  

Where \(F_D\) is the drag force [N], \(F_g\) is the gravitational force [N], \(m_p\) is the particle mass [kg] and \(v_p\) is the particle velocity [m/s].
Where \( v \) is the fluid velocity [m/s], \( \eta \) is the fluid viscosity [Pa s], \( \rho_p \) is the particle density \([m^3/s]\) and \( d_p \) is the particle diameter [m]

\[
F_D = m_p F_a (v - v_p) = m_p \left( \frac{18 \eta}{\rho_p d_p^2} \right) (v - v_p)
\]

Where \( g \) is the gravitational acceleration \([m/s^2]\) and \( \rho \) is the fluid density \([m^3/s]\)

### 3.3.1. Diffusion Coefficient

Diffusion of a particle or molecule within a bulk fluid depends on: a) temperature, b) pressure, c) effective diffusivity, and d) species (solute/solvent pair).

There are two types of diffusion that occur simultaneously. The first is translational diffusion which maintains and restores equilibrium of statistical distribution of particles position in space. The second is the rotational diffusion which maintains the equilibrium of statistical distribution of overall orientation of particles. It is important to differentiate the two as both are reported among the literature. While this section presents the equations to calculate both diffusion coefficients, only the translational diffusion is considered in this project.

The translational diffusion portion can be described using the Stokes-Einstein equation (Equation 26). The diffusion coefficient is inversely proportional to the friction coefficient or the hydrodynamic radius. The hydrodynamic radius is defined as the radius of a hard sphere that diffuses at the same rate as the molecule of interest. This includes the behaviour due to hydration and shape. The Stokes hydrodynamic radius is smaller than the effective radius (rotational radius).

\[
D = \frac{k_B T}{f} = \frac{k_B T}{6 \pi \eta R_h}
\]

Where \( D \) is the translational diffusion coefficient \([m^2/s]\), \( k_B \) is the Boltzmann’s constant = 1.38065E-23 \([m^2 kg/s^2 K]\), \( R_h \) is the hydrodynamic radius of particle [m], \( T \) is the temperature [K] and \( \eta \) is the fluid viscosity [Pas].

The rotational diffusion, \( D_r \), can be determined using a very similar equation, Equation 27.
\[ D_r = \frac{k_B T}{8\pi\eta r^3} \]

The radius of the particle, \( r \), is related to its molecular weight as shown in Equation 28.

\[ MW = N\rho V = N\rho \frac{4}{3}\pi r^3 \]

Where \( N \) is Avogadro’s number=6.022x10^{23} [molecules/mol], \( MW \) is the molecular weight [g/mol], \( \rho \) is the density of particle [kg/m^3] and \( V \) is the volume of particle [m^3].

3.3.2. Contrast Particle Properties

A literature review was performed in order to find the particle properties required for both these methods; diffusion-convection (overall effect) and particle tracking (specific movement of particles). Two agents readily available at PMH were investigated, Iodixanol (Visipaque) which is commonly used in CT imaging and Gadopentetate dimeglumine (Magnevist) used in MRI.

### Table 4: Visipaque Particle Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Source</th>
<th>Value and Method Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Diameter</td>
<td>Sontum et al [42]</td>
<td>Hydrodynamic diameter=1.4nm Determined using dynamic light scattering</td>
</tr>
<tr>
<td></td>
<td>Schwuchow et al [43]</td>
<td>Molecular diameter for short and longest axes=1.3-2.1nm Method by which this was determined was not mentioned</td>
</tr>
<tr>
<td></td>
<td>Andersen et al [44]</td>
<td>Cross-sectional diameter =1.5nm Value reported comes from personal communication with Nycomed Imaging</td>
</tr>
<tr>
<td></td>
<td>Andersen et al [45]</td>
<td>Maximal extension of molecule varies from 1.6nm to 1.8nm Value reported comes from personal communication with Nycomed Imaging</td>
</tr>
<tr>
<td>Diffusion Coefficient</td>
<td>Nair [46]</td>
<td>Diffusion coefficient = 2.5E-10 m^2/s</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td></td>
<td>1550g/mol (Iodixanol)</td>
</tr>
<tr>
<td>Solution Concentrations</td>
<td></td>
<td>270mg Iodine/mL (550mg iodixanol/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>320 mg Iodine/mL (652mg iodixanol/mL)</td>
</tr>
<tr>
<td>Solution Density and Viscosity</td>
<td></td>
<td>270 at 20degC 1.314g/mL and 12.7cP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>320 at 20degC 1.369g/mL and 26.6cP</td>
</tr>
</tbody>
</table>

### Table 5: Gadopentetate Dimeglumine Particle Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Source</th>
<th>Value and Method Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Diameter</td>
<td>Otopalik et al [47]</td>
<td>Molecular diameter=0.82nm Value reported comes from personal communication</td>
</tr>
<tr>
<td></td>
<td>de Lussanet et al [48]</td>
<td>Molecular diameter &lt;1nm</td>
</tr>
<tr>
<td>Diffusion Coefficient</td>
<td>Kim et al [49]</td>
<td>Diffusion coefficient in water =3.8E-10m^2/s</td>
</tr>
<tr>
<td></td>
<td>Gordon et al [50]</td>
<td>Diffusion coefficient= 3.8E-10m^2/s Based on interpolation between sucrose (MW=434.2Da) and ribonuclease (MW=13683Da) using 5.3E-10 and 1.19E-10 m^2/s (utilizing the 1/3 power of molecular weight)</td>
</tr>
<tr>
<td></td>
<td>Gordon et al [50]</td>
<td>Diffusion coefficient =2.7E-10m^2/s Based on the Wilke-Chang empirical correlation (assuming specific volume of 0.77mL/g)</td>
</tr>
<tr>
<td></td>
<td>Gordon et al [50]</td>
<td>Diffusion coefficient in 10% PVA-C solution =2.6E-10m^2/s +/- 0.3 Mean value obtained from experimental measured using MRI</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td></td>
<td>938g/mol (Gd-DTPA)</td>
</tr>
<tr>
<td>Solution Concentrations</td>
<td></td>
<td>469.01 mg gadopentetate dimeglumine/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>461.01mg Gd-DPTA/mL at 20degC 1.195g/mL and 4.9cP</td>
</tr>
</tbody>
</table>
4. ROADMAP

The flow phantom developed in Dr. Coolen’s lab [27] was designed and constructed to quantitatively validate dynamic flow imaging based on two-compartmental exchange which is widely used in clinical perfusion applications. This phantom was used in all aspects of this thesis project.

Figure 3 shows a flow chart illustrating the various steps in this CFD phantom investigation. The first step lists the CFD software settings that require optimization. The second, listing the experimental parameters used to ensure that the CFD models are representative of the real system and experiments. Satisfactory COMSOL Multiphysics settings along with proper flow phantom variables are required in order to obtain this ultimate simulation validation. Finally, the third step shows the variables used in the sensitivity analysis. The very last step, excluded from the figure, is an evaluation of perfusion measures. The methods and materials utilized in each of these four sections are described herein.

<table>
<thead>
<tr>
<th>CFD Set-up</th>
<th>CFD Model Validation</th>
<th>Parameter Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Type of mesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mesh Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Number of boundary layers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Direct or iterative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Governing equations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Boundary conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration profiles obtained from DCE curves for three ROIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Phantom inlet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Distribution tube outlet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cylinder outlet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Perforation size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Curvature and pitch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fluid properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Injection concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow rates and ratios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pump flow rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Flow ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Injection rate and length</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 3: OUTLINE OF FRAMEWORK STEPS

The methodology, results and discussion are divided into four modular chapters, each building upon the previous sections:

a. Software optimization
b. Validation of CFD simulation
c. Parameter investigation (sensitivity analysis)
d. Evaluation of perfusion measures
5. MULTIPHYSICS SOFTWARE SETTINGS OPTIMIZATION

As with any project utilizing CFD software, a series of preliminary investigations must be performed before proceeding with the intended model. This chapter focuses mainly on determining the appropriate CFD set-up or software implementation. This refers to first the translation of a defined problem into a CFD simulation environment and second the optimization of various CFD software features. These optimizations must be performed before proceeding to the more complex workings of the flow phantom.

5.1. METHODS

The simulation software COMSOL Multiphysics was used in order to obtain solutions to the geometric networks of interest. This software package was chosen for its integration of all steps required in modeling: geometry creation, meshing, physics implementation, solving and visualization of results. It can also be used on both Windows operated PCs as well Linux clusters.

5.1.1. Geometry, Governing Equations and Material

Common features in each optimization performed include the geometry, the governing equations and the fluid properties (ie: material).

5.1.1.1. Geometry

COMSOL Multiphysics offers a built-in tool to import both geometry and meshes from other compatible software (eg: SolidWorks, AutoCAD, AMIRA). The segmentation performed in AMIRA using the CT images were not detailed enough and created very rough surfaces. These rough surfaces are less than ideal for meshing and would also not provide an accurate representation of the smoothness of the PVC tubing used. The segmentation quality is a factor of both the image resolution and the software used. Some meshing softwares are capable of smoothing out rough surfaces. However, at the current time, there are very few programs compatible with COMSOL Multiphics. Due to the geometry complexities generated, the flow phantom images segmented from the obtained CT images were not used. Rather, the geometry was recreated based on the dimensions provided (Table 1). Features that describe a helical geometry such as pitch (distance between two consecutive loops of a helix) and curvature radius were approximated based on the known flow phantom dimensions. The value of curvature radius was determined to be 2.18cm as the cylinder had an internal diameter of 2.5cm and the tubing thickness of ¼”. The pitch was backwards calculated as 0.7cm based on the distance between the inlet and outlet locations on the cylinder (~6cm) and the length of tubing (100cm). The pitch was then confirmed through visual comparison of the CT images and the CFD geometry.
Two models were created with the help of the graphical user interface built into COMSOL Multiphysics. The first model represented the complete flow phantom geometry, shown in Figure 4.

Where finer meshes were required, a smaller subset of the geometry was adopted, called “simplified geometry” (Figure 5). These high quality meshes require extensive computational power, rendering the complete geometry unfeasible. The geometry used for each optimization is noted in its respective section.
5.1.1.2. Governing Equations
The incompressible Navier-Stokes equation (Equation 8) was used to determine the flow profile in the geometries of interest. These computed velocities were in turn used to critically assess a variety of software settings. The boundary conditions applied to the Navier-Stokes equation are described in each optimization section.

5.1.1.3. Material
The properties of water at 20 degrees Celsius were used for this portion of the project. Take note that this is not the fluid used in the real experiments. The flow phantom was designed for use with “blood mimicking fluid” which is a mixture of water and glycerol. As no contrast curves or even perforations were simulated and no assessment was performed on the fit of the simulation to experiments, the exact fluid properties were not deemed critical in this step. Rather, this set of optimizations sought to create a starting point and determine the required steps to ensure proper software settings. In turn, this knowledge can be used in future investigations under the framework.

5.1.1.4. Experimental Data Set
A sample set of experimental settings were obtained in order to perform this initial optimization. The only variables of interest in this portion of the project were the flow rates and thus all concentration related parameters were neglected. Table 6 illustrates the limited amount of information known about flow type parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q pump</td>
<td>Pump flow rate (steady rate)</td>
<td>3.5</td>
<td>mL/s</td>
</tr>
<tr>
<td>Q inject</td>
<td>Injection flow rate (combined with pump flow rate during injection)</td>
<td>1.0</td>
<td>mL/s</td>
</tr>
<tr>
<td>Flow ratio</td>
<td>Ratio of flow leaving cylinder versus that coming into the phantom</td>
<td>0.58</td>
<td>mL/s / mL/s</td>
</tr>
</tbody>
</table>

The flow ratio is a parameter was estimated by measuring the volume or mass expelled at each outlet collection bin.

5.1.2. Software Optimization
Three major components of the software set-up were optimized based on flow profile features for a given geometry. The solver, the boundary conditions and the mesh were each analyzed independently.
5.1.2.1. **Equation Solvers**

COMSOL Multiphysics utilizes a Finite Element Method (FEM) to solve the set of differential equations for the model. The points or nodes for which it solves are determined by the mesh generated. Within the FEM there are two ways to solve the set of equations: direct or iterative (Table 7).

<table>
<thead>
<tr>
<th>Solver Type</th>
<th>Solver Abbreviation</th>
<th>Solver Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iterative</strong></td>
<td>GMRES</td>
<td>Generalized Minimum RESidual</td>
</tr>
<tr>
<td></td>
<td>FGMRES</td>
<td>Flexible Generalized Minimum RESidual</td>
</tr>
<tr>
<td></td>
<td>Conjugate Gradients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BICGStab</td>
<td>BiConjugate Gradient Stabilized</td>
</tr>
<tr>
<td><strong>Direct</strong></td>
<td>PARDISO</td>
<td>Parallel Sparse Direct Linear Solver</td>
</tr>
<tr>
<td></td>
<td>SPOOLES</td>
<td>SParse Object Oriented Linear Equations Solver</td>
</tr>
<tr>
<td></td>
<td>MUMPS</td>
<td>Multifrontal Massively Parallel Sparse</td>
</tr>
</tbody>
</table>

Direct methods attempt to solve a problem using a finite sequence of operations also known as Gaussian Elimination or LU factorization. As long as the problem is set up properly (i.e., equations and boundary conditions), the direct method always obtains a solution. In the absence of rounding errors, direct methods provide an exact solution; in turn it is deemed a very robust deterministic approach. It is well known that the direct solvers can often provide convergence for difficult or complex models. The trade-off is the computational time and computer memory requirements. These simulations require an enormous amount of RAM and virtual memory.

In comparison, the iterative solvers use an initial guess to generate successive approximations to a solution. Each iteration performed helps to improve the approximation of the solution. These solvers typically require very high quality meshes. The solution obtained is considered less robust as different solution can be obtained by running the exact same model twice. On the other hand, the iterative solvers require much less computer power and memory.

The optimal solver would ideally 1) minimize computation time, 2) minimize memory requirements, and 3) obtain an accurate solution.

The simplified flow phantom model consisting of a single helix with no perforation was used for this portion of the investigation. The inlet flow rate was defined on one end of the tubing as per Table 6. The other end was defined as an open boundary with an arbitrary pressure of zero. Non-slip conditions were set on the tubing walls. The impact of the solver on both the velocity profile and computational
times was investigated to determine the most appropriate solvers for the given geometry and sample experimental settings.

5.1.2.2. Boundary Conditions

Boundary conditions “are statements describing how the process relates to its surroundings” [51]. This refers to the interaction between various parts of the model geometry as well how it interacts with the surrounding environment which is not included or solved for in the simulation itself. Boundary conditions must be chosen carefully as they can have a substantial impact on the solution produced.

The pressure values in the flow phantom system are unknown. The only momentum related variables measured are the flow rates; the remainder can be considered a “black-box”. Based on this limited information, the best type of boundary conditions had to be determined.

There exist two methods of setting up the boundary conditions for this geometry with the limited information. In both cases, the inlet laminar flow rate was defined. In the first method, a parametric sweep on the pressure at the hole/cylinder interface was carried out to obtain the desired flow ratio. A parametric sweep computes the solution to a series of input parameters. For this first method, the distribution tube outlet was defined as an arbitrary pressure of zero Pascals. The second method prescribed the flow rate at the distribution tube outlet and set an arbitrary zero pressure at the hole/cylinder boundaries. Setting pressures on boundaries forces the software to determine all other pressures required to meet the boundary conditions relative to the one defined.

Both of these methods of setting up the boundary conditions were explored and the flow profiles compared. The flow rates were defined as per Table 6. This analysis was performed on the complete flow phantom geometry with perforations. The solutions were obtained using the PARDISO solver.

5.1.2.3. Mesh Settings

The total number of elements in the mesh should not have an impact on the solution and thus the mesh is refined until the solution no longer changes. Two major types of elements were varied in the generated free mesh: the mean size of the bulk elements and the number of boundary layers. In a 3D model, the boundary layers are represented by hexahedral elements and bulk elements by tetrahedrals. Due to the complexity of the geometry, the free tetrahedral mesh type was the only one investigated.

The number of elements in any given cross-section was optimized using a series of geometric models. Flow profiles were computed for a range of mesh settings and compared in order to determine the
most adequate mesh. The pressure and velocity profiles were investigated independently and their optimal mesh conclusions compared.

The pressure loss exploration considered both a straight piece of tubing (10cm in length with ¼” ID) as well as the complete flow phantom. The numerical pressure losses for a series of meshes in both geometries were compared with those obtained using published pressure loss correlations (refer back to Section 3.1.5 for equations). The minimum number of elements (i.e., threshold) that can adequately describe the pressure loss was determined.

The velocity profile examination utilized the simplified geometry with no perforations and an even smaller subset of the geometry, 1% of a helical rotation. Smaller geometric entities allowed much finer meshes to be investigated while keeping the computation power and times down. Both inlet and outlet values are reported as parabolic laminar flow is observed at the entrance and Dean flow at the outlet (after encountering curvature). Both of these flow profiles are of interest in the flow phantom as the inlet will have a parabolic laminar profile from the straight tubing before the phantom entrance and Dean flow should be observed along the tubing after the fluid encounters a series of bends.

The boundary conditions applied depend on the geometry used. Regardless of the geometry, no perforations were included in this subset of simulations. In the simplified geometry, the inlet flow rate was defined on one end of the tubing as per Table 6. The other end of the tubing was defined as an open boundary.

Unfortunately, the same boundary conditions could not be used in the mini geometry. Instead, periodic boundary conditions were utilized. This type of boundary condition equates the solution on one boundary to that of another (inlet is equal to outlet). In turn, this is able to show the steady state Dean flow for a very small geometric subset. A drawback from using this type of boundary condition is that a flow rate cannot be set. The solution is computed based on the pressure differential between the two boundaries. Thus, a parametric sweep was performed at intervals of 0.1 Pascal. Regression analysis between the two closest points revealed the pressure differential capable to yielding the desired flow rate as per Table 6.
5.2. RESULTS AND ANALYSIS

5.2.1. Equation Solvers

A free tetrahedral mesh containing 6 boundary layers was generated containing approximately 186 triangular and 192 quadrilateral elements per cross-section. The mesh contained a total of 1,090,796 elements. A 12GB computer was used to solve the same set-up using all four iterative solvers.

Table 8 summarizes the time required for the iterative solvers to obtain a solution. No solution was found using the conjugate gradients and BiCGStab methods. The solutions obtained for both the GMRES and FGMRES solvers were identical. However, the FGMRES solver took much less time to find the solution and fewer iterations were required.

<table>
<thead>
<tr>
<th>Solver Name</th>
<th>Solver Type</th>
<th>Time to Solve</th>
<th>Iterations Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMRES</td>
<td>Iterative</td>
<td>51mins</td>
<td>13</td>
</tr>
<tr>
<td>FGMRES</td>
<td>Iterative</td>
<td>39mins</td>
<td>9</td>
</tr>
<tr>
<td>Conjugate Gradients</td>
<td>Iterative</td>
<td>Failed to find solution</td>
<td>Failed to find solution</td>
</tr>
<tr>
<td>BiCGStab</td>
<td>Iterative</td>
<td>Failed to find solution</td>
<td>Failed to find solution</td>
</tr>
</tbody>
</table>

Unfortunately the same mesh could not be used with the direct solvers due to computational power (RAM) requirements. Therefore, the mesh was made coarser in order to reduce computation time and memory requirements. Instead, a free tetrahedral mesh containing approximately 70 triangular and 96 quadrilateral elements per cross-section was generated. The mesh contained a total of 186,896 elements. A 12GB computer was used to solve this set-up using all three direct solvers.

Only two direct solvers were able to yield a solution for the described geometry and mesh. The SPOOLES direct solver required too much memory for the computer used. The solution obtained for both MUMPS and PARDISO solvers were identical.

<table>
<thead>
<tr>
<th>Solver Name</th>
<th>Solver Type</th>
<th>Time to Solve</th>
<th>Iterations Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUMPS</td>
<td>Direct</td>
<td>16 mins</td>
<td>8</td>
</tr>
<tr>
<td>PARDISO</td>
<td>Direct</td>
<td>12 mins</td>
<td>8</td>
</tr>
<tr>
<td>SPOOLES</td>
<td>Direct</td>
<td>Computer crash due to high memory requirements</td>
<td></td>
</tr>
</tbody>
</table>

It would appear that the two best solvers for a single processor computer are the PARDISO for direct and FGMRES for iterative. As direct solvers are known to be more robust and easier to use in complex geometries, PARDISO will be the solver of choice for simulations.
5.2.1. Limitations
Uncertainty exists in the times reported to solve the model. While the simulations were left running, the computer was still used to perform other tasks. Due to high memory requirements for these simulations, it is possible that other running processes may have interfered with the simulation. Therefore the shorter solution times obtained for the FGMRES and PARDISO solvers could be attributed to the absence of other running processes that were present when the other two solvers were used.

5.2.2. Boundary Conditions
A free tetrahedral mesh was generated for the complete flow phantom geometry with no boundary layers. The resulting mesh contained a total of 372,092 elements where there were approximately 40 and 14 elements on inlet/outlet and perforation boundaries respectively. This set of investigations was performed to compare the two boundary condition set-ups and not necessarily the accuracy of the obtained solution.

The results obtained for both methods are essentially identical. Therefore either method can be used in subsequent analyses. However, method 2, where the inflow and outflow to the distribution tube are defined, is much less time intensive as only a single simulation is required. Therefore, the best method of replicating how the simulation environment relates to its environment is to set the inflow and outflow to the distribution tube. The pressure at the perforation boundaries can then arbitrarily be set to zero and all other pressures calculated in relation to that. This method cuts down on time consuming parametric sweeps.

5.2.3. Mesh Settings: Pressure Losses
5.2.3.1. Pressure Loss in Straight Pipe Segment
Figure 6 shows that the numerical pressure calculations diverge considerably as the number of elements decreases. It appears that the convergence with the baseline correlation value is based on the combined number of elements rather than the discrete size of the bulk elements or the number of boundary layers (BL). The figure indicates that approximately 350 elements are required to obtain an adequate pressure loss in straight tubing of equivalent diameter to the distribution tube.
5.2.3.2. Pressure Loss in Helical Pipe Segment

The pressure losses for 1m length of helical tubing of ¼” ID estimated using pressure loss correlations found in literature (see Section 3.1.5) are shown in Table 10.

<table>
<thead>
<tr>
<th>Correlation Used by Author</th>
<th>Pressure Loss Estimate (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasson (1955)</td>
<td>9472</td>
</tr>
<tr>
<td>Ito (1959)</td>
<td>9258</td>
</tr>
<tr>
<td>Srinivasan et al (1968)</td>
<td>9766</td>
</tr>
<tr>
<td>Mishra and Gupta (1979)</td>
<td>9935</td>
</tr>
<tr>
<td>Ali (2001)</td>
<td>10612</td>
</tr>
</tbody>
</table>

The pressure difference between the distribution tube inlet and outlet were evaluated for three mesh settings to provide a crude comparison to correlations. Table 11 shows that the percent difference between the pressure loss for the mesh containing 160 triangular and 144 quadrilateral elements (10901 Pa) and each of the correlations ranged from 1.3 (Ali) to 8.1% (Ito).

<table>
<thead>
<tr>
<th># Elements (Triangular/Quadrilateral)</th>
<th>Pressure Loss (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64/96</td>
<td>10906</td>
</tr>
<tr>
<td>130/144</td>
<td>10806</td>
</tr>
<tr>
<td>160/144</td>
<td>10901</td>
</tr>
</tbody>
</table>
5.2.4. Mesh Settings: Velocity Profiles

5.2.4.1. Simplified Geometry

Figure 7A shows that the maximum inlet velocity changes significantly with mesh size and number of boundary layers. These differences are much smaller when 10 boundary layers are implemented. The maximum outlet velocity appears to change a lot across bulk mesh size but remains relatively stable among identical numbers of boundary layers, except at 4 boundary layers. More details regarding meshing features are found in Appendix C. Note that the values reported were evaluated just before and after the helical portion in the simplified geometry (Figure 5) and are referred to as inlet and outlet for this section only. The curvature and pitch effects begin at this defined inlet and therefore the flow is not purely parabolic.

![Graph A: Impact of number of boundary layers and bulk mesh size on maximum velocity inlet](image)

![Graph B: Impact of number of boundary layers and bulk mesh size on maximum velocity outlet](image)

**FIGURE 7: IMPACT OF NUMBER OF BOUNDARY LAYERS AND BULK MESH SIZE ON MAXIMUM VELOCITY INLET (A) AND OUTLET (B)**

In determining the optimal mesh, the observations at both maximum inlet and outlet velocities are taken into account. The optimal mesh is determined based on 1) the observed (visually) thickness of the boundary layers, 2) the expected Dean type flow profile (bean shape) and 3) the observed velocities...
(magnitude and difference). Based on these criteria, the extremely fine calibration with 6 boundary layers (186 triangular and 192 quadrilateral elements per cross-section) proves to contain the smallest number of elements while maintaining a fairly accurate solution. Percent differences of 0.41% in maximal inlet velocity and 0.55% in maximal outlet velocity are obtained when compared with the solution obtained using 8 boundary layers.

5.2.4.2. Mini Geometry

The geometry, 1% of a helical loop, was meshed using free tetrahedral elements of varying sizes. Table 12 shows the settings used and the resulting maximum velocity in any given cross-section. The changes in pressure differential, even if small, also reflect the impact of the mesh quality. The percent differences between two trials of increasing number of elements remain under 5 percent.

<table>
<thead>
<tr>
<th>Trial #</th>
<th># Elements on Surface</th>
<th>Maximum Velocity (m/s)</th>
<th>Pressure Differential (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>392</td>
<td>0.7464</td>
<td>7.37</td>
</tr>
<tr>
<td>2</td>
<td>392/352</td>
<td>0.7160</td>
<td>5.33</td>
</tr>
<tr>
<td>3</td>
<td>848</td>
<td>0.7740</td>
<td>6.15</td>
</tr>
<tr>
<td>4</td>
<td>1558</td>
<td>0.7529</td>
<td>5.67</td>
</tr>
<tr>
<td>5</td>
<td>1558/672</td>
<td>0.7424</td>
<td>5.43</td>
</tr>
<tr>
<td>5</td>
<td>4046</td>
<td>0.7419</td>
<td>5.4</td>
</tr>
</tbody>
</table>

5.2.4.3. Mesh Settings Interpretation

There is no single widely accepted single ‘truth’ for helical flow networks. Two approaches were used in attempt to determine the optimal mesh settings: 1) the overall pressure loss and 2) the velocity contour in a cross-section were investigated.

In a straight pipe, there exists a threshold were the total number of mesh elements allows convergence with the known pressure loss as determined using the Hagen-Poiseuille relationship. This occurs at approximately 350 elements. The type of element used, whether free tetrahedral or boundary layer hexahedral, did not appear to impact the solution.

As for a helical geometry, the simulated pressure loss in the complete flow phantom geometry was shown to be within 1.3 (Ali) and 8.1 (Ito) percent difference of the pressure losses evaluated using equations found in literature. Unfortunately, no real optimization for the pressure profile could be performed on the helical geometry as there is no well accepted pressure loss estimation method for helixes.

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Taking another approach and looking at the velocity contours instead, the single helix investigation concluded that a mesh containing 186 triangular and 192 quadrilateral elements created a good balance between number of mesh elements and solution accuracy. The maximum velocity at the outlet for this mesh is 0.7227m/s. In contrast, the 1% of a helical rotation investigation containing the highest number of elements, 4046 triangular elements and no boundary layers, resulted in a maximum velocity of 0.7424m/s. Only 1.34% difference was observed in the maximum velocity (Figure 8) for this increase of 3668 elements (Figure 9). While the exact velocity contours differ slightly at the two ends of the “bean” shape, these changes are minimal. This confirms the adequacy of the optimal mesh settings determined in the single helix investigation.

![Velocity Profiles](image1)

**FIGURE 8: VELOCITY PROFILES USING MESHES CONTAINING A) 4046 TRIANGULAR ELEMENTS, B) 186 TRIANGULAR AND 192 QUADRILATERAL ELEMENTS PER CROSS-SECTION**

![Meshes](image2)

**FIGURE 9: MESHES CONTAINING A) 4046 TRIANGULAR ELEMENTS, B) 186 TRIANGULAR AND 192 QUADRILATERAL ELEMENTS PER CROSS-SECTION**

While approximately 375 elements per cross-section were shown to produce adequate pressure losses and velocity profiles for the flow rate of 3.5mL/s, it is recommended that the pressure differential be evaluated in each simulation. In reality, higher flow rates lead to larger velocity gradients and thus smaller element sizes may be required.
5.3. CONCLUSION

This chapter presented the optimization results for three distinct software components: the solver, the mesh and the boundary conditions. These investigations must be performed before proceeding to the intended simulations and the interpretation of their results. This step ensures that the results produced accurately represent the system (mesh and solver) and how it is related to its surroundings (boundary conditions).

Direct solvers are well known for their ability to provide robust solutions. Therefore, only direct solvers should be used in subsequent investigations. The PARDISO solver showed the best balance between computational power, computational time and solution accuracy. The MUMPS solver did not increase the computational time dramatically and can therefore be considered as a viable alternative if problems are encountered with the PARDISO solver.

The very limited information known about the flow phantom includes the inlet flow rate and the two outlet flow rates. The best method of applying the boundary conditions given the flow phantom geometry was to set the inlet flow rate (laminar) and the distribution tube outlet flow rate. The perforation/cylinder boundary can then be set to an arbitrary pressure where all other pressures in the system are calculated relative to it. This method requires minimal computational time and is very straightforward.

Finally, the mesh was optimized based on two factors: the flow and pressure profiles. The velocity profile mesh analysis performed on a single helix showed that approximately 186 triangular and 192 quadrilateral elements are required. However, the conclusion drawn for the pressure loss in straight tubing was approximately 350 elements. It was therefore concluded that a mesh containing approximately 375 elements per cross-section (highest of the two) was optimal.

Pressure and velocity are not independent of each other; rather they are related as set out in the Navier-Stokes equation. As this series of optimizations was only performed on one set of characteristic flow rates, the quickest way of assessing the mesh quality in subsequent simulations (eg: different flow characteristics) is to evaluate the pressure differential across the non-perforated version of the geometry. This pressure can then be compared against correlations found in literature (Section 3.1.5).
6. VALIDATION OF CFD MODEL

Before proceeding with any CFD investigations using the created simulation model (geometry, equations and boundary conditions), it was deemed necessary to ensure adequate fit of the simulation with known experimental results. This is referred to as the validation of the CFD model. In turn, this ensures that the CFD model and its settings adequately represent the system in a real experimental setting.

This validation was performed using a series of data sets ranging in properties. Extrapolation beyond those data sets can be judged reasonable if proper convergence is obtained for the finite number of experimental settings. In that light, this portion of the project ensures confidence in computations performed at the discrete experimental settings as well as beyond those specific experiments (covered in the next chapter).

6.1. METHODS

6.1.1. Data Set Characteristics

Five data sets were drawn from the existing database of previously carried out flow phantom experiments to validate the results produced by models created in COMSOL Multiphysics. The data sets were chosen to ensure that a wide range of characteristics were investigated such as flow rates and concentrations. The characteristics of the five data sets are summarized in Table 13. Note that the injection flow rate is not included in the pump flow rate. For example, data set 1 would have a steady pump flow rate of 3.5mL/s throughout the experiment. However, during the injection, the total inflow rate would be of 4.5mL/s.
For the first two data sets, the geometry set-up 1 was used and thus the concentration curves were obtained right before and after the flow phantom. For the latter three, the geometry set-up 2 was utilized which contains 4m of tubing between the injection port and the imaging region followed by another 0.5m tubing before entering the flow phantom itself. The same 0.5m before imaging was also present on both outlets. Therefore, the geometry created in the simulation software was modified to incorporate 0.5m of ¼” ID tubing before and after the coiled portion shown in Figure 4.

Note that due to the increased geometric scope and short injection length for data sets 3, 4 & 5, only the pump flow rates were used to obtain numerical solution. Contrast onset delay is observed due to the length of tubing used between the injection port and the imaging site. By the time the contrast reached the imaging section, the injection was completed and the flow had returned to its minimum flow (ie: pump flow).

Derived system characteristics or measures for each data set are summarized in Table 13. This includes parameters previously defined in the background such as the Reynolds number (Equation 5), the Dean number (Equation 7) and the Peclet number (Equation 22). Peclet numbers were estimated using the diffusion coefficient for Visipaque, 2.5E-10 m²/s (Section 3.3.2). Derived properties are listed for both minimum (pump flow) and maximum (pump flow + injection flow) where applicable. Expected pressure losses are expressed as a range where the lowest and highest values obtained for all correlations are reported (see Table 3 for equations).
Careful consideration must be made in the methods in simulations for the way in which the concentration curves were acquired in CT. The TACs for the ROIs were extracted for each data set as follows:

1) Volume averaged over a few centimeters just outside the phantom
2) Finite area averaged over a few slices (to reduce noise) right at the inlet and outlet locations
3) 4) and 5) Volume averaged over a few centimeters approximately 0.5m past the phantom

The simulated concentration profiles (over time) were compared to that of the experimental set-up. A sample set of TACs for data set 1 are shown in Figure 10.

![Figure 10: Contrast Enhancement Curve for Described Experimental Settings](image)

The experimental results were obtained in the form of CT numbers or Hounsfield Units (HU). The conversion between CT number and iodine concentration is performed using a contrast calibration.
Calibrations were obtained using the NEMA IEC Body Phantom filled with blood mimicking fluid. For data set 1, contrast concentrations of 0, 5, 10, 25 and 50 mgI/mL were used to generate the calibration factor of 20.8 HU/(mgI/mL). The phantom was imaged and segmented to obtain the enhancement or CT number for each tube (corresponding to a different contrast concentration). Additional figures of the phantom and contrast calibration for the data set are shown in Appendix A.

6.1.2. Derivation of Cylinder Concentration
The simulation software only includes the distribution tube and thus the cylinder concentration had to be derived post-simulation. The normal convective flux at each perforation boundary was evaluated along with their flow rate at 0.05s intervals. The data tables were imported into MS Excel and a compartment analysis was performed in order to obtain the cylinder concentration. The cylinder is assumed to be well-mixed, no spatial variations.

6.1.3. Measures of Goodness of Fit
The following parameters, in order of importance, were evaluated to determine existence, or lack, of goodness of fit between experimental results and simulation outputs. Note that the last measure, the release slope, is not a factor used clinically and is of lowest priority.

1) Area Under the Curve (AUC) 4) Visual inspection
2) Peak Value 5) Maximum Release Slope
3) Maximum Uptake Slope

The parameters were evaluated for all three ROIs in each data set. Percent differences were used in order to determine adequacy of the fit between the simulated and experimental results. The distribution tube inlet concentration curves are expected to be identical as the experimental profiles were used to set the concentration at the inlet boundary for the diffusion-convection equation. The cylinder is the ROI of most importance as this has been shown to be representative of tissue TACs [27] in terms of peak enhancement, AUC, uptake and washout slopes.

The temporal resolutions of the simulations are very high and much more precise than the imaging temporal resolution. Therefore, the resolution of the simulations concentration curves were downsized to match that of their corresponding experiment.

As previously noted, the last three data sets were obtained using a much larger geometry sub-set (0.5m of tubing before and after the flow phantom chamber). It was therefore reasonable for the errors to be
larger. Due to the doubling of the piping network, the distribution tube outlet concentration profile was neglected and focus was placed mainly on the cylinder curve features.

6.1.4. Geometry, Governing Equations, Material and Mesh

6.1.4.1. Geometry
The complete flow phantom geometry, previously shown in Figure 4, was used in an attempt to replicate the results produced in the flow phantom experiments.

6.1.4.2. Governing Equations
The Navier-Stokes equation (Equation 8) and the diffusion/convection equation (Equation 21) were used to generate the TACs. The boundary conditions applied to the geometry for the Navier-Stokes equation were:

a) Distribution tube inlet set to desired flow rate
b) Distribution tube output set to desired flow rate (based on flow ratio)
c) Pressure at perforation/cylinder boundary arbitrarily set to zero.

The boundary conditions applied to the diffusion/convection equations were:

a) Distribution tube inlet set to concentration profile obtained experimentally
b) Distribution tube output and perforation/cylinder boundary set as outlets where species are transported out of the model by fluid flow (convection is dominant and diffusion is ignored)

6.1.4.3. Mesh Settings
The optimal number of elements for a given distribution tube cross-section was determined in the previous chapter. The optimal mesh of 375 elements per cross-section could not be used in the complete flow phantom geometry due to the number of elements produced. Several million elements were generated for geometry set-up 1 and even more for geometry set-up 2. Instead, a mesh containing approximately 70 and 40 elements per distribution tube cross-section and perforation cross-section, respectively, was generated. This allows for quick simulation times and minimal computational power requirements (RAM). While this is dramatically less than optimal, the determining factor was the fit of the simulation with the experimental concentration curves. This will be discussed further in the results portion.
6.1.4.4. Material Properties
The glycerol water mixture properties were used in this validation stage. Method 6 [52] described in Appendix B (Table 33) was used as it allowed the estimation of the viscosity and density over a continuous spectrum of mixtures.

6.2. RESULTS AND ANALYSIS

6.2.1. Flow Ratio Consistency Validation
The CFD software requires boundary conditions to be set for all time-points. The flow ratios provided with each data set were estimated based on the total mass release in each compartment. While this might be representative of the overall average flow ratio, it was important to determine the validity of the assumption that the flow ratio is maintained before, during and after injection as the boundary conditions applied are based on these values. The transient flow behaviour is very hard to determine using standard flow meters. A single experimental set-up was used (ie: valve remained untouched) to determine the flow ratio for a given set of flows. The flow rates used were representative of data sets 1 & 2. These are the two sets where both flow rates were required in the TAC computation.

Table 15 shows no significant changes in the flow ratio for all four experimental flow rates.

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Pre/Post Injection</th>
<th>Distribution Tube Inlet Flow Rate (mL/s)</th>
<th>Cylinder Outlet Flow Rate (mL/s)</th>
<th>Distribution Tube Outlet Flow Rate (mL/s)</th>
<th>Flow Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre</td>
<td>3.5</td>
<td>1.84</td>
<td>1.82</td>
<td>0.502</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>4.5</td>
<td>2.34</td>
<td>2.33</td>
<td>0.501</td>
</tr>
<tr>
<td>2</td>
<td>Pre</td>
<td>5</td>
<td>2.6</td>
<td>2.61</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>5.5</td>
<td>2.81</td>
<td>2.86</td>
<td>0.495</td>
</tr>
</tbody>
</table>

6.2.2. Goodness of Fit Evaluation
All five validation data sets were used to assess the fit of the simulation software set-up (eg: geometry, mesh). Table 16 reports the percent differences between the experimental and simulated results. All three regions of interest and all four measures of fit are shown in Figure 11.
### TABLE 16: SUMMARY OF GOODNESS OF FIT PARAMETERS FOR ALL DATA SETS (IN PERCENT DIFFERENCE)

<table>
<thead>
<tr>
<th>Data Set #</th>
<th>Peak Value Inlet</th>
<th>Peak Value Outlet</th>
<th>Peak Value Cylinder</th>
<th>AUC Inlet</th>
<th>AUC Outlet</th>
<th>AUC Cylinder</th>
<th>Maximum Uptake Slope Inlet</th>
<th>Maximum Uptake Slope Outlet</th>
<th>Maximum Uptake Slope Cylinder</th>
<th>Maximum Release Slope Inlet</th>
<th>Maximum Release Slope Outlet</th>
<th>Maximum Release Slope Cylinder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.11</td>
<td>0.96</td>
<td>4.28</td>
<td>0.09</td>
<td>0.44</td>
<td>8.65</td>
<td>0.60</td>
<td>1.86</td>
<td>8.59</td>
<td>3.86</td>
<td>6.57</td>
<td>7.13</td>
</tr>
<tr>
<td>2</td>
<td>0.38</td>
<td>1.66</td>
<td>2.74</td>
<td>1.32</td>
<td>0.84</td>
<td>0.33</td>
<td>1.51</td>
<td>2.12</td>
<td>3.62</td>
<td>5.35</td>
<td>3.80</td>
<td>9.89</td>
</tr>
<tr>
<td>3</td>
<td>0.16</td>
<td>11.46</td>
<td>8.29</td>
<td>0.48</td>
<td>3.50</td>
<td>9.18</td>
<td>1.43</td>
<td>6.56</td>
<td>17.39</td>
<td>0.24</td>
<td>28.97</td>
<td>9.80</td>
</tr>
<tr>
<td>4</td>
<td>0.66</td>
<td>4.51</td>
<td>5.10</td>
<td>0.51</td>
<td>3.62</td>
<td>3.48</td>
<td>1.03</td>
<td>1.93</td>
<td>9.00</td>
<td>1.56</td>
<td>12.52</td>
<td>5.83</td>
</tr>
<tr>
<td>5</td>
<td>0.27</td>
<td>1.72</td>
<td>9.46</td>
<td>7.04</td>
<td>5.73</td>
<td>8.57</td>
<td>0.50</td>
<td>1.25</td>
<td>8.20</td>
<td>2.88</td>
<td>0.35</td>
<td>9.74</td>
</tr>
<tr>
<td>Mean Value</td>
<td>0.26</td>
<td>2.70</td>
<td>5.42</td>
<td>0.73</td>
<td>1.93</td>
<td>3.78</td>
<td>0.92</td>
<td>2.29</td>
<td>8.32</td>
<td>1.86</td>
<td>5.02</td>
<td>8.30</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.22</td>
<td>4.35</td>
<td>2.81</td>
<td>2.92</td>
<td>2.19</td>
<td>3.94</td>
<td>0.46</td>
<td>2.16</td>
<td>4.99</td>
<td>1.98</td>
<td>11.28</td>
<td>1.88</td>
</tr>
</tbody>
</table>

---

**Data Set 1**

**Data Set 2**

**Data Set 3**

---

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Upon qualitative (visual) inspection of all the curves, data sets 1, 2, 4 and 5 appear to match the experimental results relatively well. Data set 3 shows the most deviation from experimental results in both cylinder and tube outlet profiles. Note that this is also the data set with the lowest flow rate, 3mL/s. At this flow rate, it is hypothesized that the well mixed cylinder assumption does not hold. This would explain the higher uptake slope for the cylinder in the simulated output versus experimental. On another hand, data set 3 contained additional tubing, therefore potentially increasing the existence of inaccuracies. As the AUC remains within 10% difference, the mass division among the two compartments remains within reason.

6.2.3. Limitations and Assumptions
While the above discussed the most likely explanation for obvious discrepancies observed in data set 3, the following is a comprehensive list of the assumptions made in the simulation software. The validity of each is discussed herein.
1) **Incompressible fluid (constant density and viscosity):**
   - It is a good assumption as the simulations utilized a water glycerol liquid mixture.

2) **Convection based movement:** The contrast agent molecules entering the phantom are assumed to distribute themselves in the flow phantom via convection.
   - Based on the calculations for the Peclet number at various radius and flow rates, this would seem to be an adequate assumption.

3) **Flow ratio measured is accurate:** The flow ratio estimated experimentally is assumed to be accurate.
   - The flow meters used to measure the flow at both outlet locations fluctuate a lot throughout the experiment and thus the flow ratio is more of estimation. Therefore there is some error in this measure. This is one of the parameters addressed in the next section of this project *(Section 7.2.4)*

4) **Mixture properties:** Addition of the contrast agent has no impact on the fluid mixture properties which are assumed those of the water-glycerol mixture.
   - This holds true if a) the injection rate is small in proportion to the bulk fluid flow rate b) the contrast properties are similar to the bulk fluid. As shown in **Table 17** while the density may be similar, the viscosities differ significantly. The validity of this assumption is therefore unknown at this point in time. This is another parameter to be investigated in the next portion of this thesis project *(Section 7.2.1)*.

   **TABLE 17: SUMMARY OF FLUID PROPERTIES OF CONTRAST AGENTS AND WATER GLYCEROL MIXTURES**

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (g/cm³)</th>
<th>Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visipaque (270mgI/mL) at 20degC</td>
<td>1.303</td>
<td>12.7</td>
</tr>
<tr>
<td>Visipaque (320mgI/mL) at 20degC</td>
<td>1.356</td>
<td>26.6</td>
</tr>
<tr>
<td>Magnevist (461.01mg Gd-DPTA/mL) at 20 degC</td>
<td>1.195</td>
<td>4.9</td>
</tr>
<tr>
<td>Water Glycerol Mixture (15% by vol)</td>
<td>1.046</td>
<td>1.646</td>
</tr>
<tr>
<td>Water Glycerol Mixture (40% by vol)</td>
<td>4.0</td>
<td>1.118</td>
</tr>
</tbody>
</table>

5) **Concentrations provided are exact and true:** The values obtained for concentration at the three locations of interest are assumed to be exact and true.
   - The concentrations curves have proven reliability and reproducibility.

6) **Well-mixed inlet concentration:** The entire inlet surface area is assumed to be at the given concentration determined experimentally (back-calculated from the enhancement).
   - The concentrations profiles provided are the average concentrations over a cross section (or volume depending on the data set). The fluid velocity near the wall is near zero and thus the contrast agent would take longer to reach this location as compared to the center line which
moves significantly faster. This is assumed to be a source of error. However, there is no feasible correction method for this.

7) **Well-mixed cylinder:** The contrast molecules entering the cylinder are assumed to spread instantaneously to create a well-mixed fluid with no spatial variations in concentration.
   - For high flow rates, this is likely true as the movement of a lot of fluid would create good mixing conditions. However, for low flow rates this may not hold. This exact assumption was proven questionable for data set 3. This lack of mixing can be observed experimentally on the DCE-CT images where spatial variation exists within the cylinder.

8) **Mass and flow conservation:** All of the flow entering the flow phantom exit through either the cylinder or the distribution tube outlet.
   - Experimentally, the flow measurements taken for the outlets do not match exactly the inlet flow rate. It can also be seen visually that some of the iodinated contrast agent leaks into the basin where the flow phantom is held. The leakage is very small in portion and therefore mass conservation is a reasonable assumption.

In addition to the above limitations, the mesh utilized to solve all models in this validation portion is under optimal (as mentioned in **Section 6.1.4.3**). While this does raise a concern about the potential accuracy of the simulation, the five data sets were shown to be accurately represented by the created CFD model and its accompanying settings. However, finer details about the transport phenomenon may not be assessed utilizing these settings.

### 6.3. CONCLUSION

Five data sets were pulled from the existing experiment database in order to validate the simulated results. Deviations are observed in the distribution tube outlet features, however these are not considered critical. Discrepancies are most likely due to the presence of potentially flow modifying features on the tubing line. The non-conformity or lack of fit in the cylinder concentration curve for data set 3 is attributed to the underlying assumptions of a well-mixed cylinder. This assumption may not hold at low flow rates. The increased geometric scope for data set 3-5 also contributed to the observed errors. Keeping in mind the limitations that exist, the system still shows satisfactory fit with the experimental results over the large range of experimental settings.
7. PARAMETER SENSITIVITY ANALYSIS

With the knowledge that the designed CFD simulation set-up shows adequate fit for discrete data sets, it is assumed that all simulation results are representative of the real system. This chapter discusses the investigation of the impact/sensitivity of yet unexplored parameters on the time attenuation curves (cylinder concentration curves). In turn, this provides insight into the importance of various factors within a two compartmental exchange system, which is often used in perfusion kinetic modeling. It is well known that there are many factors that can impact the flow and concentration profiles. A number of these were investigated herein.

1) Flow rate 
2) Curvature radius 
3) Pitch 
4) Tubing diameter 
5) Tubing length 
6) Number of holes 
7) Diameter of holes 
8) Hole spacing and location

7.1. METHODS

7.1.1. Geometry and Governing Equations

The complete flow phantom geometry was once again used in this sensitivity analysis (Figure 4), unless otherwise noted. The 1m ¼” ID tubing with 10 equally spaced holes of 0.5mm diameter was coiled inside a cylinder of 5cm in diameter resulting in an approximate pitch of 0.7cm and curvature radius of 2.18cm.

The Navier-Stokes equation (Equation 8) and the diffusion/convection equation (Equation 21) were used to generate the concentration-time curves. Once again, the cylinder concentration curves were obtained post-simulation in MS Excel. These calculations assume that the contrast agent is well-mixed and that no spatial variations in contrast concentration are present.

The types of boundary conditions implemented were the same for all investigations. The exact values prescribed at the boundaries are listed in each respective section. For the Navier-Stokes equation:

a) Distribution tube inlet set to desired flow rate
b) Distribution tube output set to desired flow rate (based on flow ratio)
c) Pressure at perforation/cylinder boundary arbitrarily set to zero.
The boundary conditions applied for the diffusion/convection equation were:

a) Distribution tube inlet set to a given concentration profile (e.g., experimental)

b) Distribution tube output and perforation/cylinder boundary set as outlets where species are transported out of the model by fluid flow (convection is dominant and diffusion is ignored)

7.1.2. Sensitivity Analysis

The five data sets used in the validation were utilized as baselines for this sensitivity analysis. In turn this allowed the inlet concentration curves determined experimentally to be utilized rather than generating these from scratch. Six properties were investigated in this sensitivity analysis: fluid properties, curvature radius, pitch, diameter of perforations, flow ratio and injection characteristics.

The fluid used experimentally (40% v/v for data set 1 and 15% v/v for all others) is mixed by the user and therefore small variations may be present. In addition, this helps to determine the impact of fluctuations in fluid properties which occur in the body. Glycerol concentrations of 5, 15, 25, 35, 55 and 75% v/v and their associated density and viscosity (Table 18) were implemented in the simulation software. The CFD model was solved using these properties for the prescribed flow rate and flow ratio of data sets 1 and 2. The inlet concentration profiles from the experimental data set were applied to the inlet boundary.

<table>
<thead>
<tr>
<th>Concentration (glycerol % vol)</th>
<th>Concentration (glycerol % mass)</th>
<th>Density (kg/m³)</th>
<th>Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.2</td>
<td>1014</td>
<td>1.173</td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>1046</td>
<td>1.642</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>1076</td>
<td>2.398</td>
</tr>
<tr>
<td>35</td>
<td>40</td>
<td>1104</td>
<td>3.693</td>
</tr>
<tr>
<td>55</td>
<td>60</td>
<td>1157</td>
<td>10.946</td>
</tr>
<tr>
<td>75</td>
<td>78.5</td>
<td>1206</td>
<td>51.952</td>
</tr>
</tbody>
</table>

The curvature radius and pitch thus far were approximated as 2.18cm and 0.7cm respectively. Variations in curvature and pitch along the length of the cylinder are most likely present in the experimental set-up. It was therefore important to determine the sensitivity of the simulation to such factors. The theoretical pressure losses for data set 1 were computed along with the cylinder concentration profiles for two pitch and curvature radius combinations: 0.7cm and 2.18cm and 1cm and 2.5cm.

The impact of the perforation sizes on the flow profiles were quantified in a 2D axisymmetric model and the 3D flow phantom geometry using flow rates from data set 1 (steady pump flow rate of 3.5mL/s
and peak flow rate of 4.5mL/s during injection). The cylinder concentration profiles were not analyzed here.

The flow ratio between the cylinder outlet and the distribution tube inlet for all five data sets were estimated experimentally based on the total mass of the fluid accumulated in each discard tank. As there is an inherent error in this measurement, it was deemed important to quantify the changes in the cylinder concentration curves for small variations in flow ratios. Data set 1 with a given flow ratio of 0.58 was used and the flow ratio was varied at 0.02 intervals between 0.56 and 0.62.

The last portion of this sensitivity analysis, i.e.: the injection characteristics, was of most clinical relevance. With the goal of quantifying the impacts of injection lengths and pump flow rates, the experimental inlet concentration profiles could not be used as boundary conditions. Therefore, a 2D axisymmetric model of a ¼” ID pipe of 1m in length was used to generate the inlet concentration profile for use in the 3D complete flow phantom geometry. Set properties included: flow ratio of 0.5, injection concentration of 135mgI/mL and injection rate of 1mL/s. Concentration profiles were generated for injection lengths of 10 and 20 seconds as well as pump flow rates of 3, 4, 5, 6 and 7mL/s.

The impacts of all of these properties on cylinder concentration curves were quantified using the four goodness-of-fit parameters used in the validation stage: peak concentration, AUC, uptake slope and release slope. In most sensitivity analyses, the percent differences between solutions are reported for each feature.

### 7.2. RESULTS AND ANALYSIS

#### 7.2.1. Fluid Properties

The first and second data sets show some differences in cylinder concentration curve features amongst different glycerol concentrations (Table 19). The differences were deemed very small in comparison to the magnitude of change applied to the density and viscosity (Table 18).

<table>
<thead>
<tr>
<th>Data Set Number</th>
<th>Concentrations Compared</th>
<th>% Difference in Peak Concentration</th>
<th>% Difference in Uptake Slope</th>
<th>% Difference in Release Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% and 55%</td>
<td>3.5</td>
<td>4.3</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>5% and 55%</td>
<td>3.2</td>
<td>3.6</td>
<td>7.2</td>
</tr>
<tr>
<td>2</td>
<td>5% and 75%</td>
<td>4.2</td>
<td>5.3</td>
<td>12.6</td>
</tr>
</tbody>
</table>

While changes in fluid properties did not yield any significant changes in cylinder concentrations curves, note that the inlet concentration curve determined experimentally was still imposed at the distribution
tube inlet regardless of fluid property changes. Upon completion of a 2D axisymmetric simulation using 1m of ¼"ID tubing, this was shown to be an appropriate assumption.

Note that the flow ratio from the original data set was used for all glycerol concentration as the impacts of valves were neglected. The valves pressurize the two outlets and in part contribute to the flow ratio value obtained by restricting the flow. In reality, if the valves were maintained throughout each fluid change, the flow ratio would most likely differ significantly. However, the goal of this investigation was simply to show that, given flow rates and flow ratios obtained experimentally, the exact properties of the blood mimicking fluid did not have a significant impact on the concentration curves.

7.2.2. Pitch and Curvature Radius

7.2.2.1. Theoretical
As shown in Figure 12 (evaluated for an equivalent non-perforated geometric version to the flow phantom) some of the empirical correlations used to estimate the pressure loss (refer to Table 3 for equations) do not take into account the pitch of the helix. However, all correlations show pressure variations with curvature. Only two correlations truly describe a helical geometry: Mishra and Ali.

Removing all correlations that do not take into account both pitch and curvature radius, a change from 7mm to 11mm in pitch resulted in a total decrease of 376 and 1045 Pa in total pressure loss for the system, according to Ali and Mishra respectively. A change from 2.5cm to 2.02cm in curvature radius resulted in an increase of 188 and 479 Pa in total pressure differential for the system, according to Ali and Mishra respectively. Mishra predicts much more dramatic changes in pressure due to both factors. These changes in pressure impact the velocity profiles (recall the Navier-Stokes equation) which could in turn be reflected on the concentration profiles.
7.2.2.2. Simulated
Features that describe a helical geometry such as pitch (distance between two consecutive loops of a helix) and curvature radius were approximated based on the known flow phantom dimensions. The value of curvature radius was determined to be 2.18 cm and the pitch 0.7 cm. While both parameters have shown significant impact on the pressure loss in a non-perforated version of the flow phantom (Section 7.2.2.1), its impact on a perforated pipe is unknown.

This sensitivity analysis shows that small changes in cylinder concentration curves are observed for various sets of pitch and curvature radius. The two combinations of 1) pitch of 1 cm and curvature radius of 2.5 cm and 2) pitch of 0.7 cm and curvature radius of 2.18 cm, result in a small difference in peak concentration as shown for the first data set in Figure 13. This difference in turn affects all three other fit parameters: AUC, uptake slope and release slope. This change is reflected as a 4% difference in peak concentration, 3.4% in AUC, 0% in uptake slope and 5.6% in release slope. No impact on the uptake slope is noted as only the steepest portion of the curve is used to estimate this slope, rather than the entire uptake curve. For this data set, the uptake slope would be estimated using between times 10-15 s.

![Figure 13: Impact of Pitch and Curvature Settings on Cylinder Concentration-Time Curves](image)

In order to confirm these observations, the second data set was used as input boundary conditions. This data set contains different flow and contrast injection characteristics leading to a peak cylinder enhancement of 3.2 mgI/mL as compared 7.5 mgI/mL for the second data set. For this data set, 1.4% difference in peak concentration, 0% in uptake slope and 1.1% in release slope were shown.

While the differences in cylinder concentration curves could be due to the pitch and curvature radius, it is hypothesized that it could also be due to the inexact placement of the perforation on the tubing
cross-section. The perforations could not be placed perfectly centered on the tubing and thus small variations in their placement are observed between the two geometries utilized. These variations were present due to the problems “decomposing” the geometry, an internal step in the software COMSOL Multiphysics. Therefore, the perforations were shifted, as little as possible from true center, until the geometry could be successfully created.

Other limitations and assumptions in this analysis are:

1) The pitch is assumed constant for simulation purposes but realistically, the pitch may not constant throughout the cylinder length. While this was neglected from this analysis, this is a factor that could be investigated further using micro-CT imaging to obtain exact measurements.
2) The flow ratio was assumed to remain the same regardless of geometric changes. In a real experimental setting, the ratio could potentially change as the pressure profile inside the distribution tube has been changes. Unfortunately, the impacts of valves which pressurize the outlet were neglected.

### 7.2.3. Perforation Size

The rate of fluid loss in each perforation at a flow rate of 3.5mL/s is shown in Figure 14. With large diameters, fluid re-enters the distribution tube in the last few holes. For the given flow rate, a threshold where minimal flow re-enters the distribution tube is observed at a diameter of approximately 0.4mm. At diameters smaller than this, fluid only escapes the distribution tube and nothing re-enters it.

![Flow Rate](image)

**FIGURE 14**: FLOW RATE EITHER LEAVING OR ENTERING EACH PERFORATION ALONG THE LENGTH OF A STRAIGHT TUBE FOR A GIVEN STEADY INLET FLOW RATE OF 3.5ML/S
The two dimensional axisymmetric model indicates that large perforation diameters cause a reversal in the direction of flow due to the pressure differential present. In turn, this causes fluid to re-enters the distribution tube in the latter holes. There exists a perforation diameter where fluid escapes the distribution throughout its length, for a given flow and flow ratio. Some of the limitations of the two dimensional models are:

1) Cannot simulate the effects of curvature and torsion.
   a. The 2D model shows that identical pressures at both top and bottom walls. In a curved pipe, there exists a pressure difference between the inner and outer walls of the tubing.
   b. Dean vortices cannot be observed in 2D axisymmetric model.

2) Cannot simulate the true perforations geometry.
   a. In two dimensions, the cylinder and hole are assumed to extend infinitely in the third dimension.

Regardless of these limitations, the two dimensional model did provide some insight into the effect of perforation size on flow distribution. To ensure a similar phenomenon was observed in the three dimensional model, the flow profiles for a few perforations sizes were also evaluated. A similar phenomena was observed in the three dimensional geometry (complete 3D flow phantom geometry shown in Figure 4) as well as over a range of flow rates.

7.2.4. Output Flow Ratio
In the experimental set-up, the valves on the flow phantom outlets determine the amount of fluid that escapes in each compartment and the ratio is estimated based on flow meter measurements. As measurement error exists, this sensitive analysis was required to assess the amount of potential error induced due to un-exact measurements of flow ratio. The cylinder concentration curves showed changes in all four measures. Table 20, Table 21, Table 22 and Table 23 show the percent differences observed between two flow ratios.
For a given change in flow ratio of 0.02 (anywhere along the 0.56 to 0.62 spectrum), percent changes in the order of 2-3% are observed for the peak enhancement, AUC and uptake slopes. On the other hand, 5-6% differences are shown for release slope. Therefore, small changes in the experimentally estimated flow ratios could account some error in the goodness of fit measures. In turn, this could account for some of the deviations observed in the validation portion of this project.

### 7.2.5. Injection Characteristics

Figure 15 shows the changes observed in the cylinder concentration curve for two injection lengths for a wide range of pump flow rates, all else remaining constant (injection rate of 1mL/s and injection concentration of 135mg/mL). Upon graphical inspection, there exists a small contrast onset delay for smaller flow rates, as expected. For a given injection length, similar peak concentrations are attained. However, major differences in release slope exist.
To better assess the degree of change among the concentration curves, the percent differences were evaluated 1) across injection length for a given pump flow rate and 2) across pump flow rate increments of 1mL/s. Table 24 percent differences indicates that for a doubling of injection length, all three parameter (the peak enhancement, AUC and release slope) result in approximately 60% difference. However, the uptake slope remains unchanged.

Table 25 confirms that peak enhancement changes minimally, <2.28% difference for a 1mL/s increase, with pump flow rate, as observed in Figure 15. The table shows a trend of approximately 11% differences in AUC for any given 1mL/s pump flow rate change throughout the range of 3mL/s to 7mL/s. The uptake slope for the flow rate of 3mL/s reveals great differences as compared to all other flow rates. This is represented by percent differences of less than 5.19% between 4&5, 5&6 and 6&7 mL/s but of 16.22% between 3&4 mL/s. As shown in Figure 15, the pump flow rate has greatest impact on the release.

Table 24: Percent difference across injection lengths of 10 and 20 s for a given pump flow rate

<table>
<thead>
<tr>
<th>Pump Flow Rate (mL/s)</th>
<th>Peak Enhancement</th>
<th>AUC</th>
<th>Release Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>63.78</td>
<td>63.46</td>
<td>61.65</td>
</tr>
<tr>
<td>4</td>
<td>62.60</td>
<td>63.64</td>
<td>63.58</td>
</tr>
<tr>
<td>5</td>
<td>61.51</td>
<td>63.81</td>
<td>57.52</td>
</tr>
<tr>
<td>6</td>
<td>60.38</td>
<td>64.13</td>
<td>62.87</td>
</tr>
<tr>
<td>7</td>
<td>59.20</td>
<td>64.38</td>
<td>59.87</td>
</tr>
</tbody>
</table>

Table 25 confirms that peak enhancement changes minimally, <2.28% difference for a 1mL/s increase, with pump flow rate, as observed in Figure 15. The table shows a trend of approximately 11% differences in AUC for any given 1mL/s pump flow rate change throughout the range of 3mL/s to 7mL/s. The uptake slope for the flow rate of 3mL/s reveals great differences as compared to all other flow rates. This is represented by percent differences of less than 5.19% between 4&5, 5&6 and 6&7 mL/s but of 16.22% between 3&4 mL/s. As shown in Figure 15, the pump flow rate has greatest impact on the release.
### TABLE 25: PERCENT DIFFERENCE ACROSS PUMP FLOW RATE INCREMENTS OF 1ML/S FOR GIVEN INJECTION LENGTHS

<table>
<thead>
<tr>
<th>Pump Flow Rates Compared (mL/s)</th>
<th>Injection Length(s)</th>
<th>Peak Enhancement (%)</th>
<th>AUC (%)</th>
<th>Uptake Slope (%)</th>
<th>Release Slope (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 and 4</td>
<td>10</td>
<td>0.40</td>
<td>11.71</td>
<td>16.22</td>
<td>31.57</td>
</tr>
<tr>
<td>3 and 4</td>
<td>20</td>
<td>1.71</td>
<td>11.51</td>
<td>16.22</td>
<td>33.65</td>
</tr>
<tr>
<td>4 and 5</td>
<td>10</td>
<td>0.81</td>
<td>11.96</td>
<td>0.57</td>
<td>21.48</td>
</tr>
<tr>
<td>4 and 5</td>
<td>20</td>
<td>2.01</td>
<td>11.77</td>
<td>0.57</td>
<td>14.86</td>
</tr>
<tr>
<td>5 and 6</td>
<td>10</td>
<td>1.03</td>
<td>11.63</td>
<td>5.19</td>
<td>15.38</td>
</tr>
<tr>
<td>5 and 6</td>
<td>20</td>
<td>2.28</td>
<td>11.28</td>
<td>5.19</td>
<td>21.22</td>
</tr>
<tr>
<td>6 and 7</td>
<td>10</td>
<td>0.96</td>
<td>10.89</td>
<td>2.20</td>
<td>16.02</td>
</tr>
<tr>
<td>6 and 7</td>
<td>20</td>
<td>2.26</td>
<td>10.61</td>
<td>2.20</td>
<td>12.73</td>
</tr>
<tr>
<td>3 and 7</td>
<td>10</td>
<td>3.21</td>
<td>45.44</td>
<td>18.62</td>
<td>80.12</td>
</tr>
<tr>
<td>3 and 7</td>
<td>20</td>
<td>8.26</td>
<td>44.46</td>
<td>18.62</td>
<td>78.46</td>
</tr>
</tbody>
</table>

### 7.3. CONCLUSION

A variety of flow-related parameters were investigated and their impacts on cylinder TACs quantified. The fluid properties, pitch, curvature radius, perforation rise and output flow ratio were simulated to 1) ensure that the prescribed values during the simulation validation were adequate and 2) determine dependencies of cylinder concentration curves. In addition, the impact of injection characteristics such as injection length was assessed. This chapter does not present a comprehensive review of all parameters but does demonstrate the ease of performing sensitivity analyses in CFD software.
8. INVESTIGATION OF PERFUSION MEASURES

As described in Section 2.1.2, many methods of estimating perfusion parameters are found in literature and some are available in commercial software. Literature has attempted to show changes in angiogenesis via perfusion imaging surrogate markers derived using the described models. All models are derived based on very different theoretical relationships and simplifying assumptions. Within each modeling technique, different inputs are required such as the AIF and the location of the ROI (pixel or entire tissue). Every chosen input influences the value and meaning of the derived variables. The perfusion variables have shown dependence on acquisition protocols [53]. Due to the complexity of the human body, many human physiological processes take place which cannot be accounted for using these models [13]. To date, there remains no accepted validated surrogate endpoint for routine clinical practice [54].

This chapter takes a different direction with the aim of demonstrating the relationship between these theoretical models and physics based approach (solved for using CFD software). Two perfusion modeling methods were critically assessed in this project. The first was the slope-peak method based on Fick’s principle and the second was the modified Tofts model. The methods employed to evaluate each model are different as they each seek to quantify very different parameters. This section outlines the simulation models and related settings used to evaluate variables analogous to those defined in each respective model.

8.1. METHODS

Definition based equations for two models, Fick’s principle and modified Tofts, and their related parameters were used for an initial attempt to validate the existing kinetic models for perfusion parameter estimation.

Five data sets containing a wide range of flow rates and injection characteristics were drawn from the pre-existing phantom experiment database. These five data sets are the same as those used in all other portions of this project. Only four of those could be evaluated using the DCE Tool (ie: modified Tofts) because of data corruption during the analysis process for data set 1, therefore limiting the number of points used in this comparison.

8.1.1. Fick’s Principle (Slope-Peak Method)

Fick’s law is one of the most simplistic methods used to estimate the regional tumour blood flow. It does not require any complex computations of model. The regional tumour blood flow is determined
using the ratio between the uptake slope of the tissue enhancement curve and the peak arterial enhancement (in mL/mL min). From here-on in, it will be referred to as the slope-peak value.

$$\text{Slope - Peak - Value}\left[\frac{\text{mL}}{\text{mL.min}}\right] = \frac{\text{SlopeTissueContrastUptake Curve}\left[\frac{\text{mgI}}{\text{mL.s}}\right]}{\text{PeakArterialEnhancement}\left[\frac{\text{mgI}}{\text{mL}}\right]} \cdot 60[\text{s/min}]$$

This equation is derived based on Fick’s principle which shows the relationship between concentrations of arterial, venous and tissue curves. The mass of contrast agent in the tissue, M, is equal to the difference between the total inflow and outflow of the contrast agent.

$$M(t) = F \int_0^t C_a(t) dt - F \int_0^t C_v(t) dt$$

Assuming that time, t, is less than the minimum traversal time, the injected medium will remain within the tissue (no venous outflow). Thus,

$$M(t) = F \int_0^t C_a(t) dt$$

Converting this equation into differential form and rearranging,

$$\frac{dM(t)}{dt} = \frac{dC_t(t)}{dt}$$

Knowing that the mass of contrast agent can also be expressed as the product of its concentration and volume and that the volume is constant,

$$\frac{dC_t(t)}{dt} = \frac{F}{V}$$

Now relating the definition of regional tumour blood flow back to the flow phantom system, all dimensions are known and thus this ratio can also be calculated based on its known experimental settings. The flow phantom can be seen as a vascular network where the inlet is the arterial input, the distribution tube output is the vein and the cylinder is the tissue of interest. Therefore, Equation 34 could be used to calculate the true regional tumour flow.
\[
DefinitionBasedValue\left[\frac{mL}{mL\cdot min}\right] = \frac{CylinderFlowRate\left[\frac{mL}{s}\right]}{CylinderVolume\left[mL\right]} \cdot 60[\text{s/min}]
\]

The slope-peak values and the definition based values were evaluated and compared for all five data sets. The following section outlines the simulation software setting used in order to obtain the characteristic TACS from which the slope-peak values are derived.

### 8.1.1.1. Simulation Set-Up

The geometry generated in COMSOL Multiphysics was the same as that described in the previous investigations (Figure 4). The 1m ¼” ID tubing contained 10 equally spaced holes of 0.5mm diameter. The tubing was coiled inside a cylinder of 5cm in diameter resulting in a pitch of 0.7cm and curvature radius of 2.18cm.

The Navier-Stokes equation (Equation 8) and the diffusion/convection equation (Equation 21) were used to generate the TACs. Once again, the cylinder concentration curve was obtained post-simulation in MS Excel. These calculations assume that the contrast agent is well-mixed and that no spatial variations in contrast concentration are present.

The boundary conditions for the Navier Stokes Equation were:

a) Distribution tube inlet set to desired flow rate
b) Distribution tube output set to desired flow rate (based on flow ratio)
c) Pressure at perforation/cylinder boundary arbitrarily set to zero.

The boundary conditions applied to the diffusion/convection equations were:

a) Distribution tube inlet set to concentration profile obtained experimentally
b) Distribution tube output and perforation/cylinder boundary set as outlets where species are transported out of the model by fluid flow (convection is dominant and diffusion is ignored)

### 8.1.2. Modified Tofts Model

Beginning with the general two compartment model where flow can only enter and escape the system via the plasma.
The rate of accumulation of contrast particle inside the EES is equal to the fluxes in and out of the EES:

\[ v_e \frac{dC_e}{dt} = PS \cdot C_p - PS \cdot C_e \]  

35

\( V_e = \) volume of extravascular extracellular space per unit volume of tissue [unitless]

\( PS = \) permeability surface area product [1/min]

\( C_e = \) EES concentration [mg/mL]

\( C_p = \) plasma concentration [mg/mL]

Assuming that the arterial concentration is equal to that of the plasma:

\[ v_e \frac{dC_e}{dt} = PS \cdot C_a - PS \cdot C_e \]  

36

In convolution notation:

\[ C_t(t) = \frac{PS}{v_e} \exp\left(\frac{-PS}{v_e} \cdot t\right) \otimes C_a(t) \]  

37

Assuming that the total concentration is equal to \( C = v_p C_p + v_e C_e \) and changing the variable \( PS \) to \( K_{\text{trans}} \):

\[ C_t(t) = v_p C_a(t) + K_{\text{trans}} \exp\left(\frac{-K_{\text{trans}}}{v_e} \cdot t\right) \otimes C_a(t) \]  

38

\( K_{\text{trans}} = \) volume transfer constant between blood plasma and EES [1/min]

The above equation described the modified Tofts model, an extension of the two compartment model, which is a three parameter model measuring: fractional plasma volume \( (v_p) \), fractional EES volume \( (v_e) \) and the volume transfer constant between blood plasma and EES \( (K_{\text{trans}}) \). The rate constant between EES and blood plasma is calculated using the ratio of \( K_{\text{trans}} \) to \( v_e \). This version of the two compartment model...
exchange does not allow the measurement of plasma flow and assumes that the plasma concentration profile is equal to the arterial concentration curve (AIF).

In order to provide a comparison between the three modified Tofts parameters and their true physical meaning, a definition based counterpart was sought out. The definition of each parameter was translated into a concrete equation. The two parameters used in this comparison are Ktrans and Kep. The first is Ktrans which represents the volume transfer constant between plasma and EES [1/min] and the second is Kep which is the rate constant between EES and blood plasma [1/min].

Ktrans reflects the permeability limitations and diffusional transfer from the vessel into the tissue compartment. The very large Peclet number previously calculated for each data set (refer back to Table 14) indicates that the diffusion component is negligible and therefore Ktrans should be reflecting mainly the effect of permeability.

Kep reflects the rate at which the agent is eliminated from the tissue. The flow configuration defined in the modified Tofts model (Figure 16) differs significantly from that of the flow phantom (one inlet and two outlets) and therefore an analogous variable to Kep was found. In the flow phantom, the contrast is eliminated from the system via the cylinder outlet. As no fluid comes back into the distribution tube, the only route of elimination for the “tissue” is this precise outlet. Therefore, Kep values are compared to the ratio of cylinder outlet flow rate to cylinder volume, as indicated by the units.

Volume and flow rates have already been well defined experimentally for five data sets and thus the only remaining unsolved variable was the permeability which is reflected in the Ktrans parameter. In order to determine this permeability factor, the simulation software was once again used and the software settings summarized in the next section.

8.1.2.1. Simulation Set-Up
For this model comparison, the perforated tubing was converted into one continuous permeable membrane of set thickness. Two thicknesses, 1mm and 0.5mm, were used in order to ensure that the chosen value did not influence the results produced. Concentration curves for the discrete perforations were compared to those of the continuous permeable membrane to ensure that no significant deviations were observed.

The Darcy-Brinkman equation (Equation 19) and the diffusion/convection equation (Equation 21) were used to generate the TACs. Once again, the cylinder concentration curve was obtained post-simulation in MS Excel. These calculations assume that the contrast agent is well-mixed and that no spatial variations in concentration are present.
The boundary conditions for the geometry containing a permeable membrane (Darcy-Brinkman equation) were set-up as follows:

a) Distribution tube inlet set to desired flow rate
b) Distribution tube outlet arbitrarily set to pressure of zero
c) Perforation/cylinder interface arbitrarily set to pressure of zero

This type of boundary set-up allowed the permeability to be iterated in order to obtain the desired flow rates at each outlet location.

The boundary conditions applied to the diffusion/convection equations were:

a) Distribution tube inlet set to concentration profile obtained experimentally
b) Distribution tube output and membrane/cylinder boundary set as outlets where species are transported out of the model by fluid flow (convection is dominant and diffusion is ignored)

**8.2. RESULTS AND ANALYSIS**

**8.2.1. Fick’s Principle (Slope-Peak Method)**

The slope-peak value (Equation 29) was calculated for all five data sets used in the validation portion of this thesis project (refer to Section 6.1.1 for the characteristics of each data set). This ratio aims to estimate the regional tissue flow in relation to its volume. Based on this definition, it would imply that this slope-peak value should be equal to the ratio between the tissue (ie: cylinder) flow rate and volume (Equation 34). As illustrated in Table 26, the values of the slope-peak value differ significantly in magnitude from the definition based value.

<table>
<thead>
<tr>
<th>Data Set Number</th>
<th>Slope-Peak Value (mL/mL min)</th>
<th>Definition Based Value (using flow rates before and during injection if applicable) (mL/mL min)</th>
<th>Mixed Concentration (mg/mL or μM Gd-DTPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8214</td>
<td>0.7675/0.9868</td>
<td>33.33</td>
</tr>
<tr>
<td>2</td>
<td>0.7761</td>
<td>0.9452/1.0398</td>
<td>12.27</td>
</tr>
<tr>
<td>3</td>
<td>0.4977</td>
<td>0.6250</td>
<td>50.00</td>
</tr>
<tr>
<td>4</td>
<td>0.8212</td>
<td>1.0360</td>
<td>50.00</td>
</tr>
<tr>
<td>5</td>
<td>1.2073</td>
<td>1.5937</td>
<td>50.00</td>
</tr>
</tbody>
</table>

A problem arises when comparing perfusion measurements for experiments of varying bolus injection features. Two data sets, 1 and 4, yielded the same slope-peak value despite the existence of a different cylinder flow rate (refer values in Table 27). This clearly indicates that the bolus properties play a major...
factor in the slope-peak parameter estimation and absolute perfusion values can only be compared if the bolus characteristics are identical.

**TABLE 27: SUMMARY OF SLOPE-PEAK VALUE ESTIMATION ALONGSIDE INJECTION FEATURES AND CYLINDER FLOWS**

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Slope-Peak Value (mL/mL min)</th>
<th>Mixed Concentration (mg/mL or µM Gd-DTPA)</th>
<th>Injection Flow (mL/s)</th>
<th>Injection Length (s)</th>
<th>Cylinder Flow Rate (at minimum) (mL/s)</th>
<th>Cylinder Flow Rate (at maximum) (mL/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8214</td>
<td>33.33</td>
<td>1</td>
<td>20</td>
<td>2.03</td>
<td>2.61</td>
</tr>
<tr>
<td>4</td>
<td>0.8212</td>
<td>50.00</td>
<td>1.6</td>
<td>10</td>
<td>2.74</td>
<td>2.74</td>
</tr>
</tbody>
</table>

For the latter three data sets, the mixed injection concentration (after the injection is mixed with the pump flow), rate and length are all identical. The only change for these three data sets is the inlet flow rate (ie: pump flow rate). For these data sets, a linear correlation ($R^2$ of 0.9987) exists between the slope-peak value and the definition based value.

While the absolute values of the slope-peak and definition based values are very different, the ratio between two evaluations of identical mixed concentrations does indeed appear to reflect the change in flow rate to the cylinder. **Table 28** shows the ratios for both variables for the following data set combinations 3-4, 4-5 and 3-5. The ratio between two measurements or data sets appears to show good convergence.

**TABLE 28: RATIOS ACROSS THREE DATA SETS FOR SLOPE-PEAK VALUE AND CYLINDER FLOW RATE**

<table>
<thead>
<tr>
<th>Data Sets Used to Compute Ratio (i, i+1)</th>
<th>Ratio of Slope-Peak Value (i+1)/(i)</th>
<th>Ratio of Definition Based Value (i+1)/(i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4</td>
<td>1.65</td>
<td>1.66</td>
</tr>
<tr>
<td>4,5</td>
<td>1.47</td>
<td>1.54</td>
</tr>
<tr>
<td>3,5</td>
<td>2.43</td>
<td>2.55</td>
</tr>
</tbody>
</table>

It can therefore be concluded that in the absence of bolus injection differences, the slope-peak value measurement could potentially capture the magnitude of change of flow in the tissue. Absence of bolus injection differences refers to the mixed injection concentration (injection mixed with bulk fluid), injection rate (flow) and length, not the total dosage.

Taking a different view of these results, it can be seen that the flow ratio determined experimentally is analogous to the leakiness of the vessel/tissue interface. Therefore an increase in the flow ratio should be reflected in parameters assessing leakiness or permeability. We know experimentally that an increase in this flow ratio results in increased peak cylinder enhancement and uptake slope. Data set 1 concentration curves were obtained using COMSOL Multiphysics where the only variable changed was the flow ratio (**Table 29**). For identical inflow and bolus conditions, the slope-peak value showed great
correlation ($R^2 0.9999$) to increased tissue flow thereby confirming that this ratio reflects the leakiness (ie: flow rate into tissue compartment) and the bolus dependency.

<table>
<thead>
<tr>
<th>Data Set #</th>
<th>Flow Ratio</th>
<th>Slope-Peak Value (mL/mL min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.56</td>
<td>0.783</td>
</tr>
<tr>
<td>1b</td>
<td>0.58</td>
<td>0.807</td>
</tr>
<tr>
<td>1c</td>
<td>0.6</td>
<td>0.832</td>
</tr>
<tr>
<td>1d</td>
<td>0.62</td>
<td>0.855</td>
</tr>
</tbody>
</table>

8.2.1.1. Interpretation and Comparison

The values obtained for the regional tissue flow using Fick’s principle proved to be systematically lower than its definition based counter pair. Literature has reported that the slope-peak value underestimates the regional blood flow when contrast in fact escapes the system before peak tissue concentration is reached [23] [55]. In the flow phantom set-up, there is indeed contrast leaving the system which accounts for this lower than expected value. The “no outflow” condition is reflected by the mean residence time of the contrast agent in the intravascular space.

According to literature, the slope-peak method depends on the bolus volume, rate of injection [56] and patient cardiac output [57]. Similar observations were noted in this investigation regarding dependency on bolus properties. Furthermore, in the previous investigation (Section 7.2.5) it was noted that for a given injection rate, the pump flow rate (ie: cardiac output) created changes in peak enhancement, uptake slope, release slope and AUC. An increase in pump flow rate resulted in a decrease in peak enhancement, faster uptake and washout. This demonstrates the dependency of the derived measures on the cardiac output.

Further analysis of Fick’s principle showed that the magnitude (or exact value) of a slope-peak value could not provide insight into the regional tissue flow. However, if the mixed concentration (injection plus steady pump flow) remains identical, then successive DCE-CT evaluations could be compared and indeed reflect differences in regional tissue (ie: cylinder) flow. Injection protocols are set within a hospital setting, thereby eliminating one factor of variation in the mixed concentration. The second factor, the steady pump flow which is analogous to the patient blood flow rate, can vary between imaging periods. The patient’s cardiac output is a function of heart rate, stroke volume and blood pressure. Both of these have been shown to change throughout a 24 hours period [58,59]. Changes are likely to be observed even if the patient is able to reach and maintain a “resting phase” during DCE-CT.

In conclusion, this method is the simplest of all found in the literature as it requires very little information: slope of tissue enhancement curve and peak arterial enhancement. If there was a simple
way to remove the contrast bolus differences, in other words, a normalization method, then this ratio could prove to be very useful in clinical practice.

8.2.2. Modified Tofts Model

8.2.2.1. Permeability Estimation (Simulation)

As previously described (Section 8.1.2.1), the boundary conditions used were modified for this permeability study. As the permeability is considered an input to the system of equations, it had to be iterated upon. The permeability estimates were modified up to three significant digits to offer the best fit to the two measured outlet flows. In addition, the average fluid flow velocity in the permeable membrane was extracted from the simulation software (shown in Table 30). Note that two membrane thicknesses were investigated for data sets 3, 4 and 5.

<table>
<thead>
<tr>
<th>Data Set #</th>
<th>Inlet Flow Rate (mL/s)</th>
<th>Permeability Layer Thickness (m)</th>
<th>Permeability Estimate (m²)</th>
<th>Velocity in Membrane (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>1.00E-03</td>
<td>2.89E-13</td>
<td>1.53E-04</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1.00E-03</td>
<td>2.49E-13</td>
<td>1.96E-04</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1.00E-03</td>
<td>1.59E-13</td>
<td>1.87E-04</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1.00E-03</td>
<td>1.48E-13</td>
<td>2.06E-04</td>
</tr>
<tr>
<td>5</td>
<td>7.5</td>
<td>1.00E-03</td>
<td>1.25E-13</td>
<td>1.25E-04</td>
</tr>
</tbody>
</table>

As expected this shows great variation in the permeability parameter across membrane thicknesses. A ratio that could eliminate the effect of the thickness was required in order to compare the simulated results to those of the modified Tofts model. Recall that the simplest method of estimating permeability in porous mediums is using Darcy’s law (Equation 17). This equation was rearranged to remove the effect of thickness by taking the product of the velocity, v [m/s], and membrane thickness, Δx [m], relative to the permeability, K [m²]. This ratio with units of inverse time will be referred to as “Ratio of Membrane Normalized Permeability”.

Evaluation of this new ratio shows that it can eliminate the effect of the chosen membrane thickness (Table 31).
TABLE 31: RATIO OF AVERAGE VELOCITY IN MEMBRANE TO THICKNESS NORMALIZED PERMEABILITY FOR DATA SETS 3, 4 AND 5

<table>
<thead>
<tr>
<th>Data Set #</th>
<th>Membrane Layer Thickness (m)</th>
<th>Ratio of Membrane Normalized Permeability (1/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5.00E-04</td>
<td>4.50E+05</td>
</tr>
<tr>
<td>3</td>
<td>1.00E-03</td>
<td>4.46E+05</td>
</tr>
<tr>
<td>4</td>
<td>5.00E-04</td>
<td>1.04E+06</td>
</tr>
<tr>
<td>4</td>
<td>1.00E-03</td>
<td>1.03E+06</td>
</tr>
<tr>
<td>5</td>
<td>5.00E-04</td>
<td>2.06E+06</td>
</tr>
<tr>
<td>5</td>
<td>1.00E-03</td>
<td>2.02E+06</td>
</tr>
</tbody>
</table>

Graphical comparison of the cylinder concentration curves for discrete perforations and two membrane thicknesses (Figure 17) shows that thinner membranes result in earlier contrast onset and slightly higher peak concentrations. The early contrast onset is expected as the fluid does not have to travel as far to reach the cylinder due to reduced membrane thickness.

![Graphical comparison of the cylinder concentration curves](image)

FIGURE 17: COMPARISON OF CYLINDER CONCENTRATION CURVES OBTAINED USING DISCRETE PERFORATIONS AND PERMEABLE MEMBRANES (1MM AND 0.5MM).

LEFT: DATA SET 3, MIDDLE: DATA SET 4, RIGHT: DATA SET 5

Recall that the discrete perforation curves have been compared to experimental results and found to adequately represent the real system. Therefore the small variations observed in the concentration curves in Figure 17 are most likely negligible. It can therefore be concluded that the discrete perforations could indeed accurately represent the physiological process of perfusion and transport through a permeable membrane. On another hand, this also demonstrates that the permeable membrane could be used in the CFD environment to represent the flow phantom geometry, in turn simplifying the geometric complexities and potential problems encountered with a perforated helix.
8.2.2.2. Model Parameter Estimation (CT Images)
The modified Tofts perfusion model parameters were obtained upon analysis of the CT images using the DCE Tool (shown in Table 32). Unfortunately, no parameters estimation could be generated for data set 1 due to data corruption during the analysis process.

<table>
<thead>
<tr>
<th>Data Set #</th>
<th>Ktrans (mL/g/min)</th>
<th>Kep (1/min)</th>
<th>Vb (mL/g)</th>
<th>Mean Square Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.550</td>
<td>0.854</td>
<td>6.12E-03</td>
<td>7.97</td>
</tr>
<tr>
<td>3</td>
<td>0.462</td>
<td>0.462</td>
<td>1.00E-05</td>
<td>5.76</td>
</tr>
<tr>
<td>4</td>
<td>0.710</td>
<td>0.825</td>
<td>9.44E-03</td>
<td>2.49</td>
</tr>
<tr>
<td>5</td>
<td>1.254</td>
<td>1.411</td>
<td>1.00E-05</td>
<td>6.18</td>
</tr>
</tbody>
</table>

8.2.2.3. Comparison of Experimental and Model Estimates
The rate of transfer into the tissue compartment shows good linear relationship for data sets 3, 4 and 5 ($R^2$ of 0.9959) (Figure 18: Left). However, data set 2 seems to be an outlier. As for the rate of elimination from the tissue compartment, all four data sets evaluated showed good linear correlation ($R^2$ of 0.9835) between the kinetic model parameter and the definition based value (Figure 18: Right).

The values obtained for the Ktrans do not solely represent what is truly defined as permeability but rather showed good correlation with a membrane normalized permeability ratio (for data sets 3, 4 and 5).
There is no evident explanation for the deviation observed for data set 2 in the Ktrans comparison but the higher mean squared error could indicate inadequate fit of the modified Tofts parameters with the experimental data (refer back to Table 32). There is also potential error induced by the assumed hematocrit value of 0.6. As the flow phantom utilizes blood mimicking fluid, a value has to be assumed to move forward with the modified Tofts analysis. Alternatively it could indicate that Ktrans in fact takes into account other feature such as those of the bolus (reflected in the IRF). The true reasons for this deviation are even more uncertain as the Kep showed good correlation with its definition based value. It would be valuable to perform an analysis on a range of injection characteristics (length, concentration and rate) to rule this out.

In contrast, the Kep values obtained for all four data sets (2, 3, 4 and 5) demonstrated good correlation. All data sets used in this investigation represent highly perfused tissues due to their high flow ratios (ranging between 0.5 and 0.6). Fortunately for this study, the assumptions made when deriving the modified Tofts equation, ensure applicability for poorly and highly perfused tissues. Analysis of data sets containing weakly perfused cylinder should be performed for completeness. The amount of deviation in the modified Tofts parameters for intermediately perfused cylinder would also be a great asset.

Analysis over a larger data set would be required to determine the sensitivity and dependencies of the modified Tofts model. Unfortunately, commercially available kinetic modelling software requires CT images. There would be great value in the development of a method of importing the simulated results from COMSOL Multiphysics into the analysis software. This would greatly reduce the burden of performing physical experiments and would allow a larger range of variables to be investigated using simulation software. It would also allow finer changes in parameters.

8.3. CONCLUSION

On overarching goal of this project was determine if additional information about two compartment exchange models could be obtained using the CFD modeling tool COMSOL Multiphysics. Some insight about both contrast kinetics and fluid flow in this flow system were gained through the sensitivity analysis presented in the previous chapter. While knowledge of TAC dependencies is important to the perfusion imaging field, quantitative assessment of the existing kinetic models is much needed.

This chapter compared quantitative perfusion parameters using Fick’s principle and modified Tofts model with analogous physics (CFD) based parameters. Limitations of Fick’s principle, as discussed in literature, were reaffirmed using the CFD model. Its dependency on bolus features and characteristics
proved to be problematic in assessing the regional perfusion. The modified Tofts model provided inconclusive results. Great fit was observed for data sets 3 to 5, however, data set 2 Ktrans was an outlier. The good fit over the three data sets demonstrates that Ktrans indeed reflects what it was intended to, permeability limitations for highly perfused systems. On the other hand, no obvious reasons for this outlier could be noted and therefore further investigation is recommended. In addition, all of the data sets utilized had flow ratios in the 0.5 to 0.6 range, therefore further limiting the perfusion range investigated to that of highly perfused tissues. The generation of weakly and intermediately perfused cylinders would be of great value to ensure applicability of the kinetic models over a range of potential physiological conditions.

On a different note, it was noted that the permeable membrane gave rise to similar cylinder concentration curves as those with the 10 discrete perforations. This proves that the flow phantom containing discrete perforations may indeed adequately represent the physiological event of perfusion through a permeable membrane. It also indicates that further analysis could be performed with a permeable membrane to avoid software errors in geometry and mesh creation.
9. DISCUSSION

This project proposed the use of CFD software in a framework of phantom simulations. These offer the flexibility to investigate a range of flow networks and characteristics thus producing a wide range of TACs. The various sections of this project have demonstrated that CFD can be a great asset when used alongside experimental phantoms.

The first part of this framework used experimental data sets in order to validate the simulated results in COMSOL Multiphysics. Inlet concentrations were applied to the simulation software and the cylinder concentration curves compared. While small discrepancies were observed, the overall fit of the simulation model was deemed appropriate. Therefore, any investigations beyond the discrete data sets were assumed to be accurate.

The sensitivity of numerous parameters impacting flow and concentration profiles was investigated. The impact of (i) density and viscosity, (ii) pitch and curvature radius, (iii) perforation size, (iv) flow ratio and, (v) injection length and pump flow rate were characterized. The simulated results were able to quantify the impacts of these variables on the tissue (ie: cylinder) concentration curves, as desired.

The accuracy of two perfusion kinetic models, Fick’s principle and modified Tofts, were assessed using both CT images and the CFD models built. Neither perfusion estimation model was able to capture the true transport phenomenon present in the flow phantom and the variations in human physiology. Fick’s law’s slope-peak values were systematically lower; however, they showed good correlation with flow ratio when bolus characteristics (ie: mixed concentration) remained constant. Modified Tofts model showed good correlation with a physics definition based counterpart for three data sets (3, 4 and 5). Data set 2 was an outlier with no apparent explanation. All data sets used in these investigations were considered analogous to highly perfused tissues and thus further investigations are required.

Two phantoms have been described in literature for use in DCE MRI quantification. The first group created a micro-fabricated phantom to represent a capillary network [60]. Flow profiles were quantified using the simulation software COMSOL Multiphysics and the concentration curves were generated in both experiments and simulation software. The paper provided a comparison between simulated and experimental perfusion parameters such as mean transit time, CBV and regional tissue perfusion. Differences between estimated and true measurements were present and potential sources of error are suggested. No future work was proposed for its use in further validation of the available kinetic models. The second paper [61] presents the design of two hollow fiber phantoms, a single fiber and a set of 75 fibers. Preliminary DCE experiments demonstrated the potential use of the phantoms in...
development, testing and validation of DCE quantification. While no comparison with kinetic models has been made at this point in time, it is suggested in future work.

This project, a subset of a prospective framework, is the first to propose the combined use of CFD and phantoms for evaluation of existing kinetic models. A CFD based approach can help to determine the sensitivity of various measures derived from kinetic models. In a simulation environment, a sensitivity analysis over a large range of parameters can be performed to determine the dependencies. This is something that can be both resource and time intensive to perform experimentally. It can open the door to an endless number of parameter permutations such as those of contrast agents. In addition, the physics based approach of CFD can help to reveal the relationship between the true underlying physiological phenomenon and the derived measures.

The ideal pharmacokinetic model would permit analysis of perfusion type parameters over a wide range of characteristics to account for variations amongst the population. The parameters derived, whatever they may be (eg: flow rate, permeability, washout rate), should be surrogate markers for the underlying physiological phenomenon and allow differentiation between healthy and pathological tissue. It would also produce minimal variability for a given individual to allow proper comparison between subsequent evaluations. Furthermore, sensitivity of quantitative measurements is important to be able to separate the physiological events of interest and assess variability between subsequent evaluations. In addition, it is also critical to understand the relationship between the measurements and the physiological process. There is often lack of understanding of the meaning of existing compartmental model parameters in relation to true hemodynamic parameters.
10. CONTRIBUTIONS AND FUTURE WORK

The framework of phantom simulations was begun by first providing the steps required to replicate experimental set-ups with simulation software. The contrast uptake curves generated by the CFD software were validated against a series of experiments. Second, the impacts of flow profile dependencies on tissue TACs were quantified. Variables investigated included: fluid properties, geometric properties (pitch, curvature radius, and perforation size), flow ratios (reflecting leakiness) and injection characteristics (length and pump flow rate). Lastly, CT images were analyzed using pharmacokinetic models described in literature (Fick’s principle and modified Tofts). The values obtained to describe the regional tissue flow and effective permeability (permeability and diffusion) were compared to their definition counterparts using the information from the CFD software. The CFD models (geometry set-up 1 and 2) built were able to provide accurate representation of the true transport phenomenon given the numerous assumptions. Further, the models were proven to be a great asset in sensitivity analysis and assessment of pharmacokinetic models used to quantify perfusion parameters.

With these contributions in mind, there are many potential paths that can be explored. The very first would be to determine if there is an equivalent and simpler model/geometry that could be created in CFD software that would produce the same TACs. Ideally it would require fewer number of elements (meshing) therefore cutting down geometry decomposition error in the software as well as reducing memory requirements and computational times. This would make CFD more readily accessible as no high power computers would be required. It is suggested that first a straight (ie: non helical) pipe be investigated followed by the use of a permeable membrane rather than discrete perforations. Both of these suggestions would decrease the number of problems encountered in the geometry and mesh creation in COMSOL Multiphysics. In addition, the use of a permeable membrane would be ideal as this would be more physiologically accurate than the discrete perforations. The contrast uptake curves from discrete perforations and permeable membranes have been proven to be very similar in this project (Section 8.2.2.1).

Downsizing or scaling of the current geometry would also prove to be a great asset as it could simulate more realistic diameters and flow rates which are present in flow networks in the body.

On another hand, more complexity could be added to the current model to gain insight into more microscopic processes. This could include the addition of the Fahraeus-Lindqvist effect which states that the hematocrit, and thus viscosity of blood, changes with radial position in capillary sized tubes.
The mixing phenomenon between the bulk fluid and the contrast agent could also be incorporated. This could help determine the impact of contrast specific properties such as viscosity and density.

This project presents a first step in a framework of phantom simulation. For a complete breakdown of interactions or sensitivities, design of experiments (DOE) would be ideal. This method can simultaneously determine the individual and interaction effects of identified variables. This method helps to minimize the number of experiments performed while ensuring that adequate data is obtained for accurate interaction estimations.

On another hand, the sensitivity analysis performed in the CFD software could help to determine the most critical parameters. In turn, these can be further investigated in an experimental setting and concentration curves obtained using DCE-CT. This could help reduce the number of parameters investigated experimentally therefore reducing the resources and time required to run the experiments.

Looking back at the bigger picture, the overall goal was to gain insight into contrast pharmacokinetics. This dissertation is the beginning of a phantom simulation framework. The development of dynamic flow phantoms with different structures and flow networks will increase the range of TACs that could be reproduced using physics based principles such as those applied in CFD.

With the completion of the framework, covering range of physiological flow networks, a strategy for the use of CFD modeling to inform simpler clinical models would be greatest importance. It is not necessarily suggested that CFD models be implemented on a clinical level, but rather that the knowledge acquired be translated to a more accessible means. It could be envisioned that a database, containing all the relevant information and knowledge gained from the framework, could guide clinicians to more accurate approximations of perfusion type parameters. The database would contain information on perfusion parameters computed over a range of flow rates and injection characteristics for a variety of flow networks describing different regions of the body. The simulation results can be tabulated and a graphical user interface utilized to provide ease of access and quick extraction of required information from a database.
11. REFERENCES


12. APPENDIX

A CALIBRATION PHANTOM

B FLUID MIXTURE PROPERTIES

The physical properties of a binary mixture cannot be estimated based on a simple linear equation. Rather they are calculated using empirical correlations, readily found in literature. The two main physical properties of interest for a fluid dynamic analysis are density and viscosity. Dynamic viscosity is a measure of the resistance of a fluid to deformation due to shear stress or tensile stress. Kinematic viscosity describes the ratio of inertial force to viscous force as shown in Equation 39, where \( \nu \) is the kinematic viscosity \([\text{m}^2/\text{s}]\), \( \mu \) is the dynamic viscosity \([\text{kg/ms}]\) and \( \rho \) is the density \([\text{kg/m}^3]\).
Correlations to estimate dynamic and kinetic viscosity of a glycerol-water mixture were found upon completion of a literature search. These correlations and their limitations are listed in Table 33.

### Table 33: Summary of Literature Equations Found to Calculate Glycerol-Water Mixture Viscosity (Dynamic or Kinematic)

<table>
<thead>
<tr>
<th>Method Number</th>
<th>Equations</th>
<th>Comments and Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Chen 1987</td>
<td>( \nu = \exp \left[ 4.5490 - 0.12309T + 9.1129 \times 10^{-4}T^2 \right] )</td>
<td>Valid for temperature range of (-16.5 \text{deg} C ) to (90 \text{deg} C ) [62]</td>
</tr>
<tr>
<td>2) Stengel et al 1982</td>
<td>( \nu = \exp \left[ -4.7562 \times 10^{-6}T^3 + 1.3296 \times 10^{-8}T^4 \right] )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \nu ) = kinematic viscosity [cm(^2)/s] ( T ) = temperature [deg C]</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \mu = A_1 \exp \left[ A_2(T)^{-1} + A_3(T) + A_4(T)^{-1} \right] )</td>
<td>Coefficients are only solved for discrete concentration of 40, 50, 60, 70, 80, 90, 99, 100 wt % of glycerol. Interpolation required for other concentrations [52] Maximum and average relative errors are greatly reduced for those discrete concentrations previous correlations [62]</td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \ln(\nu / \nu_w) / \ln(\nu / \nu_g) = C_m \left[ 1 + (1 - C_m)(B_1 + B_2 C_m + B_3 C_m^2) \right] )</td>
<td>Coefficients are only solved for five discrete temperatures (10, 20, 30, 40 and 50 deg C). Interpolation required for other concentrations [52]</td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \nu = 1 + 0.125C_{mol} \exp \left( \frac{C_{mol}^{0.29}}{2.291[(T + 273.1)/273.1]^3 - 1} \right) )</td>
<td>No unknown coefficients. Not accurate for high glycerol concentrations [52]</td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \nu_w = 0.09607 \times 10^{-6} \exp \left( \frac{2.9}{(T + 273.1)/273.1} \right) )</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \nu = \frac{\mu}{\rho} ) ( \rho = \text{density} )</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \mu = \mu_w \exp(A \alpha) ) ( A = \ln(\mu_w / \mu_g) )</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \alpha = \ln(\mu / \mu_g) / \ln(\mu_w / \mu_g) = 1 - C_m + \frac{abC_m(1 - C_m)}{aC_m + b(1 - C_m)} )</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( a = 0.705 - 0.0017T ) ( b = (4.9 + 0.036T)a^{2.5} )</td>
<td></td>
</tr>
<tr>
<td>2) Chen and Pearstein 1987</td>
<td>( \mu_w = 1.790 \exp \left( \frac{(-1230 - T)T}{36100 + 360T} \right) )</td>
<td>Applies to concentration ranges from 0 to 100 and temperature range of 0degC to 100degC. Able to reproduce 95% of measured viscosities from three databases with less than 5% deviation [52]</td>
</tr>
</tbody>
</table>

\[ v = \frac{\mu}{\rho} \]
\[ \mu_g = 12100 \exp\left( \frac{-1233 + T}{9900 + 70T} \right) \]

\( \mu \) = dynamic viscosity of mixture [cP]  
\( \mu_g \) = dynamic viscosity of glycerol [cP]  
\( \mu_w \) = dynamic viscosity of water [cP]  
T=temperature [degC]  
A, a, b=coefficients  
A=weighting factor

<table>
<thead>
<tr>
<th>Method 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Gonzalez 2011</td>
</tr>
<tr>
<td>2) Gonzalez 2011</td>
</tr>
</tbody>
</table>

\[ \eta = \eta^o \exp\left( (28.75 - \ln \eta^o) \left( \frac{T_g}{T} \right)^\alpha \right) \]

\[ \eta^o = 6.3 \times 10^{-4}, T_g = 177K, \alpha = 3.2 \]

T=temperature [K]  
T=glass temperature [k]

As shown above, some literature reports kinematic viscosity while others use dynamic viscosity. The two viscosities are related by a single factor, the density. Equations 40, 41 and 42 describe how to calculate the density of the water-glycerol mixture. These equations are based on a series of assumptions such as the negligible chemical species interactions between the two components. The equation is technically inexact but the error induced is very small (+/-0.8%) [52].

\[ \rho = \rho_g C_m + \rho_w (1-C_m) \]  \hspace{1cm} 40

\[ \rho_g = 1277 - 0.654T \]  \hspace{1cm} 41

\[ \rho_w = 1000 \left( 1 - \left| \frac{T - 41.7}{622} \right| \right) \]  \hspace{1cm} 42

Where \( \rho \) is the mixture density [kg/m³], \( \rho_g \) is the glycerol density [kg/m³], \( \rho_w \) is the water density [kg/m³], T is the temperature [deg C] and C_m is the mass concentration [%w/w].

The temperature range of interest for flow phantom is from room temperature to that of the human body. Thus very high and low temperatures are not of interest here. A method valid over the full spectrum of glycerol concentrations (0 to 100) was sought out. With both these considerations, method 5 by Cheng described in Table 33 was deemed the best for simulation purposes.
C MESHING DETAILS

C.1. Meshes Optimization – Velocity Profiles Portion

Table 34 contains the details about a selection of the meshes used in the velocity profile based mesh optimization (Section 5.2.4.1) applied to the simplified geometry (Figure 5).

<table>
<thead>
<tr>
<th>Bulk Mesh Predefined Size</th>
<th>Number of Boundary Layers</th>
<th>Total Number of Elements</th>
<th># of Elements per Cross-Section (Triangular/Quadrilateral)</th>
<th>Approximate # of Elements per Diameter (1/4”ID) (Triangular/Quadrilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine</td>
<td>4</td>
<td>86081</td>
<td>40/48</td>
<td>7/8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>121841</td>
<td>40/96</td>
<td>7/16</td>
</tr>
<tr>
<td>Finer</td>
<td>4</td>
<td>153502</td>
<td>70/64</td>
<td>10/8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>181054</td>
<td>70/96</td>
<td>10/12</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>208606</td>
<td>70/128</td>
<td>10/16</td>
</tr>
<tr>
<td>Extra Fine</td>
<td>4</td>
<td>344938</td>
<td>126/96</td>
<td>13/8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>391082</td>
<td>126/144</td>
<td>13/12</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>437226</td>
<td>126/192</td>
<td>13/16</td>
</tr>
<tr>
<td>Extremely Fine</td>
<td>4</td>
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<td>186/123</td>
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