Thermal fluid models of a hydrogel delivery system for pancreatic cancer treatment

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THERMAL FLUID MODELS OF A HYDROGEL DELIVERY SYSTEM FOR PANCREATIC CANCER TREATMENT

by

Nesrine Bouhrira

A Thesis

Submitted to the Department of Mechanical Engineering College of Engineering
In partial fulfillment of the requirement For the degree of
Master of Science in Mechanical Engineering at Rowan University
May 1, 2017

Thesis Chair: Thomas Lad Merrill
Dedications

To my father, my mother and all my family. To all the people who helped me to achieve my goals.
Acknowledgments

This work would not have been possible without the help of Dr. Thomas Lad Merrill who have been supportive of my career goals and who worked actively to provide me with the time to achieve those goals. I am grateful to all of those with whom I have had the pleasure to work during this project.

I would like to thank the rest of my thesis committee: Dr Jennifer Vernengo and Dr. Anil Attaluri for their insightful comments and encouragement.

I thank my fellow labmates for the stimulating discussions, for the sleepless nights we were working together before deadlines. Also, I thank my friends at Rowan University.

Last but not the least, I would like to thank my family especially my parents who are the ultimate role models. I would also like to thank my Sister for supporting me spiritually throughout writing this thesis and my life in general.
Abstract

Nesrine Bouhrira
THERMAL FLUID MODELS OF A HYDROGEL DELIVERY SYSTEM FOR PANCREATIC CANCER TREATMENT
2016-2017
Thomas Lad Merrill
Master of Science in Mechanical Engineering

Pancreatic cancer is one of the most devastating cancers with low survival rates. This disease is difficult to detect due to the pancreas’s location deep within the body. Therefore, diagnoses are often made in the later stages, making treatment options more limited and difficult. It has been hypothesized that direct injection into the tumor would enhance drug effectiveness. Therefore, we examined the use of endoscopic ultrasound (EUS) combined with a fine needle injection to deliver a drug-eluding thermosensitive hydrogel directly into the tumor. Unfortunately, normal body temperatures surrounding the EUS can warm the hydrogel drug combination beyond its phase transition temperature before its final destination inside the tumor. A modified version of FocalCool’s technology CoolGuide™ catheter, now called the CoolGuide™ sheath, will be used to provide temperature control along the injection pathway, ensuring that the hydrogel remains below its phase transition temperature LCST. The objective of this work is to build and explore thermal fluid models of a temperature controlled device using a finite volume conjugate heat transfer approach. Using experimental results for validation we intend to demonstrate that the sheath has the ability to control and deliver 30% hydrogel (Pluronic F127) below its LCST under body temperature conditions.
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Chapter 1

Literature Review

1.1. Background

1.1.1 Pancreatic cancer overview. Pancreatic cancer is one of the most devastating cancers. This disease, in which malignant tumors form in the organ responsible for creating digestive enzymes, is currently the fourth leading cause of cancer death in the United States and is predicted to become the second by 2020 [1]. It has a five year relative survival rate of just 4%. An estimated 73% of patients will die in the first year of diagnosis [2]. The number of patients with pancreatic cancer will increase more than 2-fold and the number of death will increase 2.4-fold by the year 2030 [3]. The most common risk factors for developing pancreatic cancer are family history of the disease, age, smoking, obesity and long-standing diabetes.

1.1.2 Stages of pancreatic cancer. Pancreatic cancer has a very low survival rate. Of all adults with pancreatic cancer, 19% live for 1 year after they are diagnosed, only about 4% has a five year survival rate [4]. The outcome of pancreatic cancer depends on how advanced the cancer is when it is diagnosed. In other words, it depends on the stage of the pancreatic cancer. There are 4 stages of pancreatic cancer [5].

Stage 1: In this stage, the cancer is completely inside the pancreas and has not spread to the lymph nodes. It is divided into two parts:
-Stage 1A: The cancer is completely inside the pancreas with a tumor size smaller than 2cm. No cancer in the lymph nodes or other areas of the body.

-Stage 1B: Here there is no cancer in the nodes or other areas but the tumor size is bigger than 2cm.

Stage 2: This stage also has two parts:

-Stage 2A: The cancer has started to grow into surrounding tissues but no cancer is in the nearby blood vessels or lymph nodes.

-Stage 2B: The cancer can be any size and may have grown into the tissues surrounding the pancreas and may also be localized in the nearby lymph nodes.
Stage 2B: The tumor has grown into the surrounding tissues and the nearby lymph nodes. [6]

Stage 3: In this stage the cancer is designated as locally advanced pancreatic cancer (LAPC), it is growing outside the pancreas, into the nearby large blood vessels. However, it has not spread to other areas of the body.

Stage 4: The cancer has spread to other areas of the body such as the liver or lungs. It is also called metastatic cancer.

1.1.3 Treatment of pancreatic cancer. The location of the pancreas deep inside the body makes the tumor hard to find and diagnose in its early stages. Patients usually have no symptoms until the cancer has already spread to other organs [7]
Treatment of pancreatic cancer depends on the stage of the tumor. Chemotherapy is a common option for treating locally advanced pancreatic cancer (LAPC). Most patients are treated with Gemcitabine. Surgery is often necessary for tumor removal, however, surgical tissue removal is only a viable option for about 20% of patients.

1.1.4 Endoscopic Ultrasound. Accurately diagnosing pancreatic cancer patients is very important to select the optimal treatment for their disease. One approach that holds promise is the use of endoscopic ultrasound (EUS) combined with a fine needle injection. The EUS simultaneously provides primary diagnostic and staging information[8]. Early in its development, the EUS demonstrated its superiority over other endoscopic imaging modalities[9]. Over the last 20 years, EUS has gone from an imaging modality to an interventional procedure. The use of an endoscopic ultrasound (EUS) combined with a fine needle injection was examined to deliver drugs directly into the tumor. Some of the work with EUS-guided FNI included botulinum toxin injection for patients with pancreatic pain from pancreatic malignancy[8]. These applications demonstrated the feasibility and safety of EUS-guided FNI. This technique was extended to the application of delivering antitumor agents.

1.1.5 EUS-Guided antitumor injection. An EUS-guided injection of allogenic mixed lymphocyte culture (Cytoimplant) in patients with LAPC was reported in 2000[8]. In this study, doses of cytoimplant cells were delivered slowly and steadily into pancreatic tumor for eight patients by a single EUS-guided FNI. Patients received different number of cells. This study demonstrated that injection of antitumor agents in lesions was feasible
and safe. A final evaluation was made at 24 months to follow up with the tumor regression. Two patients had a partial response and one patient had a minor response. The overall median survival was 13.2 months.

A second phase I/II trial involving EUS-guided injection of ONYX-015, were performed in 2003 by Hecht et al [10], this study included 21 patients over an 8-week period. Patients received up to 10 injections consisting of 1 mL of virus depending on the tumor size. In a second testing, a combination therapy was investigated by adding Prophylactic antibiotics to the initial drug.

The first study without the combination therapy showed that no patients had a tumor response at day 35. After combination, two patients had partial regressions and two had minor regressions, six had stable disease and the remaining 11 patients had progressive disease. The overall median survival was 7.5 months.

Most recently (2005), a multicenter phase I clinical trial of a novel gene transfer therapy (TNFerade) was completed against unresectable, LAPC. The drug was delivered by an EUS-guided FNI. The treatment involved Thirty-seven Patients who received intratumoral injections of TNFerade during 5 weeks. 73% of patients in the EUS group had tumor stabilization, with 13 % having a >50% reduction in tumor size at 3 months. However the Localized intratumoral (IT) injection of a liquid drug is limited by lesion characteristics causing unsafe drug leakage into surrounding tissues (Fig.2). Thermosensitive hydrogels may overcome this challenge by presenting an alternative to
direct liquid drug injection since they can undergo a phase transition presenting a drug reservoir for sustained drug release over a period of time.

Figure 2. Up-close section to pancreas lesion [37]. Effectively treating LAPC is challenging because lesions are hypovascular, have a high interstitial pressure, and have a dense extracellular matrix. The lesion characteristics limit systemic drug effectiveness.

1.1.6 Hydrogels overview. For over fifty years hydrogels have been used in numerous biomedical applications such as manufacturing contact lenses, hygiene products, tissue engineering scaffolds, drug delivery systems and wound dressings. The main advantage of these hydrogels is that they have potential biomedical uses; they are stable under varying pH and temperature. In the 1980s, hydrogels were modified for
other applications and they are currently present in other advanced applications, such as drug delivery systems [11].

1.1.7 Hydrogels as a drug delivery system. The thermosensitive hydrogels are polymers that can undergo a transition to a semisolid depot into the tumor tissue under variation of temperature [12]. A hydrogel consists of a network of polymer chains that are either covalently bounded, ionically bounded or linked through intermolecular force (Fig. 3). They are swollen networks possessing a hydrophilic character allowing them to swell and form gels in contact with water and under certain stimuli[13] such as temperature, solvent quality, pH, elastic field, etc [14].

*Figure 3.* Schematic of hydrogel structure with hydrophilic polymer chains connected through crosslink points or crosslinking polymers [15]. $M_c$ designates the number average molecular weight between two adjacent crosslinks and $\xi$ represents the distance between consecutive crosslinking points.
For biomedical applications such as drug delivery system, thermosensitive hydrogels are widely used as the temperature at which they form gels are adjustable[14]. They may be injected in liquid form, stiffening inside the body due to the change in temperature[13].

When a thermosensitive hydrogel reacts with water in the right temperature, the hydrophobic parts of the polymer will attract each other and create micelles which are lipid molecules that arrange themselves in a spherical form in aqueous solutions. The micelles will aggregate and bind water, therefore forming a gel. The formation of the gel depends on the structure of the molecules and its mass. A typical thermosensitive hydrogel is a poloxamer (PEO-PPO-PEO), it consists of 2 monomers, PEO (poly(ethylene oxide)) and PPO (poly(phenylene oxide)). PEO is a hydrophilic monomer, whereas PPO is a hydrophobic monomer [16].

Figure 4. Schematic illustration of the micellar phases formed by the Pluronics (hydrogel) with increasing temperature [17]. From left to right, the temperature is increasing. The formation of a micelle is a response to the amphipathic nature of fatty acids, meaning that they contain both hydrophilic regions (polar head groups) as well as hydrophobic regions (the long hydrophobic chain).
One of the common hydrogels used is the Pluronic F127. This hydrogel contains molecules that can self-assemble into micelles in aqueous solutions above critical micelle concentrations. The critical micelle concentration decreases with increasing temperature. As temperature increases, micelles appear and lead to gel form, thus F127 has the ability to undergo sol-gel phase transition by the change of environmental temperature. Pluronic F-127 presents an attractive drug encapsulating device since it has unique thermoreversible characteristics such as the dynamic viscosity. Fig. 5 shows the complex viscosity variation of the Pluronic F127 as a function of temperature as well as the storage $G'$ and the loss Modulus $G''$. These tests were conducted at a constant shear rate. The complex viscosity, $\eta^*$ is characterized by the frequency-dependent viscosity function determined during forced harmonic oscillation of shear stress [18].
Figure 5. Mechanical behavior of hydrogel F127 investigating storage, loss modulus, and complex viscosity as a function of the temperature.

Encapsulating a common can drug like Gemcitabine in a thermally reversible hydrogel allows the drug to be injected as a liquid, transitioning into a gel inside the tumor at body temperature (Fig.6). As a result, a hydrogel-drug combination creates a drug reservoir, enabling sustained and effective drug release.
An injectable thermosensitive hydrogel was developed by Chen et al [13]. This delivery system has the ability to undergo sol-gel phase transition under body temperature conditions. In their study, they introduced the Hexamethylene diisocyanate (HDI) into Pluronic-F127 as a chain extender to improve its mechanical stability. Results showed that the HDI-PF127/HA nanocomposite hydrogel can be solidified at temperatures near the body temperature condition, 37°C. The study showed that the release of anticancer drug DOX from HDI-PF127/HA composite hydrogel was a zero order profile and sustained drug release for over 28 days[13]. Fig.7 shows an example of drug release behavior from a hydrogel.
Figure 7. Example of drug release from a hydrogel showing the degradation and diffusion of the hydrogel. The circular red parts present the drug being diffused from the swollen hydrogel represented by the black lines.

1.1.8 Integrated use of hydrogels with EUS. The use of endoscopic ultrasound (EUS) combined with a fine needle injection to deliver a drug-eluding hydrogel directly into the tumor has been examined. Fig. 8 shows a picture of an endoscopic ultrasound and a fine needle injector (EUS-FNI).
Matthes et al [20] invented a new technique to provide a minimally invasive local treatment option for unresectable pancreatic tumors. In this study Oncogel (ReGel/paclitaxel) was examined. The ReGel, is a thermosensitive biodegradable triblock copolymer combination of poly(lactide-co-glycolide)-polyethylene glycol-poly(lactide-co-glycolide)[20]. The Oncogel was injected under EUS-guidance, with a 22-gauge needle into the tail of pancreas. This study included Eight Yorkshire breed pigs. Experiments showed that the EUS-guided injection of OncoGel provided a high and sustain localized concentration of paclitaxel into the pig pancreas (Fig.9). The procedure has shown its ability to perform safely and without complications for the animals however, some limitations of the EUS-FNI delivery techniques were noticed. The high pumping
pressure needed to push the gel down the FNI shaft, caused the gel to leak around fittings which were not designed for high pressure. This was a result of the sol-to-gel phase transition that occurred within the FNI needle. The hydrogel-drug combination was warmed to a temperature that exceeded the lower critical solution temperature (LCST).

Figure 9. Image of the pancreatic tail split longitudinally showing the OncoGel depot [20].

1.1.9 Hydrogel delivery challenges. Unfortunately, normal body temperatures surrounding the EUS can warm the hydrogel drug combination beyond its phase transition temperature or lower critical solution temperature (LCST) before its final destination inside the tumor. This transition leads to sharp viscosity increases and injection pathway plugging, requiring unrealistic delivery pressures [20]. To address this problem, a modified version of FocalCool’s technology CoolGuide™ catheter, now called the
CoolGuide™ sheath, will be used to provide temperature control along the needle injection pathway, ensuring that the hydrogel remains below its LCST through most of its pathway. The CoolGuide™ sheath is made of Pebax® and includes three lumens (Fig.10), a central circular lumen for hydrogel flow as well as wing-shaped lumens for the coolant. The coolant pathway has a slot at the distal end to allow the closed-loop circulation of coolant.

![Diagram of CoolGuide sheath]

*Figure 10.* Schematic of the CoolGuide sheath. This figure shows: a central lumen for hydrogel flow (1), an inlet coolant flow (2), an outlet coolant lumen (3) which carries the coolant from distal tip to the coolant exit, and a slot (4) to allow for coolant turnaround.

In pre-clinical testing CoolGuide™ technology has already shown that it has the potential to save heart tissue using localized rapid therapeutic hypothermia after heart attacks[21]. Recently the original CoolGuide™ was tested inside a mock Endoscopic Ultrasound system controlling gel temperatures precisely to ensure that the hydrogel
temperature is maintained below the LCST. Figure 11 shows the mock Endoscopic Ultrasound configuration: a temperature controlled multi-lumen sheath with the standard EUS-FNI needle.

*Figure 11. Schematic of the mock EUS system (gray) and CoolGuide™ (blue). The mock EUS was created with a braided metal tube partially surrounded with a helical tube heat exchanger to maintain body-temperature boundary conditions. A cooling console provides cooling to the system.*

1.2. Problem Statement

To our knowledge there are no published models that predict delivery temperature and pressure using thermosensitive hydrogels. The goal of this thesis work is to develop a thermal fluid model for hydrogel delivery system using the CoolGuide™ technology inside the EUS. Using experimental results for validation, we intend to demonstrate that the CoolGuide™ technology has the capability to successfully deliver drug-laden hydrogel
into pancreatic tumors. In addition, we intend to enhance the original CoolGuide™ design so that it improves temperature control performance for this new application. Research and development work will include three thermal fluid models:

Model 1: A finite volume conjugate heat transfer model of the original design of the CoolGuide™ catheter that is validated with pre-existing experimental work inside a mock cardiovascular system.

Model 2: A finite volume conjugate heat transfer model of the original CoolGuide™ used without a standard fine needle injection (FNI) needle and validated with our mock EUS test loop.

Model 3: A finite volume conjugate heat transfer model of the original CoolGuide™ used with a standard fine needle injection (FNI) needle and validated with our mock EUS test loop.

Model 4: A finite volume conjugate heat transfer model that refines the original CoolGuide sheath in terms of improved temperature control capability.

![Figure 12. 3D model of the distal end of an EUS system showing the CoolGuide™ cooling sheath and the fine needle injection needle (FNI). In a clinical setting the FNI is injected into the pancreatic tumor. Our new thermal fluids models were experimentally validated.](image)
1.3. Thesis Organization

The rest of the thesis is structured as follows. The mathematical equations are outlined in Chapter 2 to better define flow in straight tubes with constant and variable material properties. More focus will be given to non-Newtonian fluids. These details are important to develop the thermal fluid models.

In Chapter 3, we develop CFD models to investigate the cooling performances of a temperature controlled sheath (CoolGuide). We first studied the CoolGuide catheter inside a mock cardiovascular system, then a modified version of the catheter now called CoolGuide sheath was used to demonstrate its ability to deliver thermosensitive hydrogels under body temperature conditions. These models are validated with experimental work. Chapter 4 gives an insight about the different CoolGuide sheath optimized models to enhance its performances for the pancreatic cancer application. Features such as, hydrogel circulation lumen and coolant lumens were optimized for better cooling. Therefore, lower delivery temperatures were achieved.

Finally, a restatement of the results and Future work recommended are presented in Chapter 5.
Chapter 2

Physics Foundation

This chapter will discuss the background needed to understand how the computational models are solved. There is a need to describe the governing equations that are required for a solution. This includes studying laminar flow in straight tubes with both constant and variable properties. This work will set the stage for in-depth fluid models such as non-Newtonian fluids and the characteristics of the shear thinning behavior of thermosensitive hydrogels.

2.1. Steady Isothermal Flow in a Straight Tube

In this section, we will introduce the basic steps to solve an isothermal flow inside a simple pipe with constant material properties. A set of steps are necessary to solve a CFD model.

- Defining the geometry (length, diameter…)
- Defining the governing equations necessary for the model.
- Setting the boundary conditions and initial conditions in order to solve the governing equations.
- Setting the material properties.
- Solving the model with the appropriate CFD approach.
- Validation of the model
2.1.1 **Geometry.** Fig. 13 shows a 3D model of a simple pipe with a diameter D and length L. The flow is one directional, will enter the pipe from the inlet and leave from the outlet.

![Figure 13](image)

*Figure 13.* 3-D schematic of a straight tube of length L and diameter D. Flow is steady and fully developed, meaning the fluid velocity profile is parabolic in the tube and does not change over the length of the tube.

2.1.2 **Governing equations.** In this study we will consider the motion of fluids and we will treat them as continuum. The three primary unknowns that can be obtained by solving these equations are: velocity, pressure, and temperature. The flow is assumed to be governed by the laminar Navier-Stokes equations, mass conservation and energy conservation, which may be written in differential form as:

2.1.2.1. **Conservation of mass.** The conservation of mass equation can be established using the Eq. (2.1).

\[ \nabla \cdot \mathbf{V} = 0 \quad (2.1) \]
2.1.2.2. Conservation of momentum. Equations for the conservation of momentum for a fluid are known as the Navier-Stokes equations which are written in three-dimensional Cartesian coordinates Eq. (2.2):

\[
\rho \left( \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) = - \frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \tag{2.2}
\]

\[
\rho \left( \frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) = - \frac{\partial p}{\partial y} + \mu \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \n\]

\[
\rho \left( \frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) = - \frac{\partial p}{\partial z} + \mu \left( \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) \n\]

The equation can also be written in its more general form as shown in Eq. (2.3):

\[
\rho \left( \frac{\partial \vec{V}}{\partial t} + \vec{V} \cdot \nabla \vec{V} \right) = -\nabla p + \mu \nabla^2 \vec{V}, \tag{2.3}
\]

where \( \rho \) is the fluid density (kg/m\(^3\)), \( \vec{V} \) is the fluid velocity vector (m/s), \( p \) is the fluid pressure (Pa), \( \mu \) is the dynamic viscosity (Pa-s).

2.1.3 Boundary conditions. To solve the governing Eqs (1), (2) and (3) , boundary conditions are required. The isothermal model consists of a primary domain for the fluid flowing through the tube. (Fig.14) provides a description of these boundary conditions for a 3-D model.
2.1.4 Material properties. For any CFD model, material properties are needed. They define the properties of parts which impact the physics of a simulation. For an isothermal model, the material properties necessary are the density of the fluid and the dynamic viscosity.

2.1.5 Model validation. The validation is an indispensable step to build confidence in modeling. This step could be achieved with experimental work, published work and analytical or empirical solutions. One of the equations for validating a flow through a simple pipe is the pressure drop equation. Eq. (2.4) shows the pressure drop equation for a developing flow through a pipe:
\[ \Delta P = f_{DWD} \frac{L}{D} \rho \frac{V_{avg}^2}{2}, \quad (2.4) \]

where \( \rho \) is the fluid density \((\text{kg/m}^3)\), \( f_{DWD} \) is the friction factor for the developing flow; It represents the weighted average of fully developed flow and developing flow \([22]\), \( L \) is the length of the catheter in \((\text{m})\), \( D \) is the diameter of the catheter \((\text{m})\) and \( V_{avg} \) is the velocity at the inlet \((\text{m/s})\).

The average velocity at the inlet of the tube was calculated by setting a constant flow rate with a fixed cross-sectional area using Eq.(2.5):

\[ Q = V_{avg} A, \quad (2.5) \]

where \( Q \) is volumetric flow rate \((\text{m}^3/\text{s})\), \( A \) the cross-sectional area in \((\text{m}^2)\), and \( V_{avg} \) is the inlet velocity in \((\text{m/s})\).

2.2 Non-Isothermal Flow With Variable Properties in Simple Tubes

2.2.1 Geometry. We consider the same pipe of diameter \( D \) and length \( L \). The flow is one directional, will enter the pipe from the inlet and leave from the outlet. The pipe is heated with a constant wall temperature \((T_s)\).

2.2.2 Governing equation. The same equations (Eq.2.1 and 2.2) are applied to the non-isothermal flow except that there is and additional equation that needs to be addressed which is the conservation of energy.
2.2.2.1. Conservation of Energy. The energy equation can be written in many different ways, but in our case the problem is 3-dimensional, steady state and there is no heat generation. The final expression is given by Eq. (2.6):

$$\rho C_p\left[\frac{\partial u T}{\partial x} + \frac{\partial v T}{\partial y} + \frac{\partial w T}{\partial z}\right] = \left[\frac{\partial}{\partial x}\left(k \frac{\partial T}{\partial x}\right) + \frac{\partial}{\partial y}\left(k \frac{\partial T}{\partial y}\right) + \frac{\partial}{\partial z}\left(k \frac{\partial T}{\partial z}\right)\right],$$

(2.6)

where $T$ is the absolute temperature (K), $k$ is the thermal conductivity (W/m-C), $\rho$ is the density and $C_p$ is the specific heat (J/kg-K).

2.2.3 Boundary conditions. Fig. 15 shows the boundary conditions applied to the heated pipe. The flow will penetrate the pipe with a constant temperature and flow rate. The outer wall is exposed to constant temperature $T_s$.

*Figure 15. Boundary conditions for the simple pipe model. The inlet boundary condition is set to a mass flow inlet condition and temperature. The outlet is set to a pressure outlet. The outer wall is exposed to constant temperature and the no slip condition is activated.*
2.2.4 Newtonian fluids. For an incompressible Newtonian fluid in laminar flow, the resulting shear stress is equal to the product of the shear rate and the viscosity of the fluid medium. The model for Newtonian fluid contained between parallel plates is described by Eq.(2.7). The fluid is subject to shear by the application of a force in the x-direction (Fig.16).

\[
\frac{F}{A} = \tau_{yx} = \mu \left( -\frac{\partial v_x}{\partial y} \right) = \mu \gamma_{yx}
\]  

where, \( F \) is the force applied in the x direction, \( A \) is the surface area and \( \mu \) is the dynamic viscosity. The Newtonian viscosity is by definition independent of shear rate or shear stress and depends only on the material and its temperature and pressure. The plot of shear stress against shear rate for a Newtonian fluid is called rheogram and is a straight line of slope, \( \mu \) and passing through the origin.

*Figure 16.* Schematic representation of unidirectional shearing flow. This represents a thin layer of fluid contained between two parallel plates a distance \( dy \) apart. The fluid is subject to shear by the application of a force \( F \).[23]
2.2.5 Non-Newtonian fluid viscosity behavior. A non-Newtonian fluid has a non-linear flow curve. The ratio of shear stress and shear rate is not constant at a given temperature and pressure but depends on flow conditions such as flow geometry, shear rate, etc.

Such materials may be grouped into three general classes: (1) time independent or generalized Newtonian fluids for which the rate of shear at any point is determined by only the value of the shear stress at that point and instant, (2) time-dependent fluids which are more complex where the relation between shear stress and shear rate depends on the duration of shearing and, (3) visco-elastic fluids exhibiting both characteristics of ideal fluids and elastic solids. Fig.16 shows a graph describing the time-independent flow behavior.

![Diagram of shear stress vs. shear rate for different types of fluids](image)

*Figure 17. Types of time-independent flow behavior.* Three types of fluid behaviors are distinguished, (1) Newtonian fluids are characterized by a constant shear rate, (2) time dependent fluids where the relation between shear stress and shear rate depends on the duration of shearing, and (3) visco-elastic fluids exhibiting both characteristics of ideal fluids and elastic solids [23].
The flow behavior of this class of materials may be described by a constitutive relation of the form:

\[ \gamma_{yx} = f(\tau_{yx}) \]  

(2.8)

These fluids may be further subdivided into three types: shear thinning, shear thickening and viscoplastic. This thesis will focus on the shear thinning fluid behavior.

**2.2.5.1. Shear thinning or pseudoplastic fluids.** This fluid is characterized by an apparent viscosity which decreases with an increase of shear rate. Apparent viscosity which is sometimes denoted \( \eta \), is the shear stress applied to a fluid divided by the shear rate. For a Newtonian fluid, the apparent viscosity is constant, and equal to the Newtonian viscosity of the fluid, but for non-Newtonian fluids, the apparent viscosity depends on the shear rate. Both at very high and very low shear rates, most shear thinning polymer solutions exhibit Newtonian behavior. There are three different models that characterize a shear thinning fluid, 1) the power law model, 2) the Carreau-Yasuda model and, 3) the cross model. They are providing a shear dependent viscosity equation.

**2.2.5.1.1. Power law models.** The simplest model to describe a shear-rate dependent viscosity behavior is the power law. The relation between shear stress and shear rate is analyzed with different rheological models: Ostwald-de Waele, Herschel-Bulkley, Bingham, and Casson [24]

\[ \tau = k\gamma^n \]  

(2.9)
\[ \tau = \tau_0 + k\dot{\gamma}^n \]  

(2.10)

\[ \tau = \tau_0 + \eta \dot{\gamma}^n \]  

(2.11)

\[ \tau^{0.5} = \tau_0^{0.5} + \eta^{0.5} + \dot{\gamma}^{0.5} \]  

(2.12)

where, \( \tau \) is the shear stress (Pa), \( \dot{\gamma} \) is the shear rate (1/s), \( \eta \) is the viscosity (Pa-s), \( \tau_0 \) is the yield stress (Pa) associated with the critical stress applied for determining the start of hydrogel flow, \( k \) is the consistency index (Pa-s) related to the hydrogel viscosity, \( n \) is the flow behavior index (Dimensionless)

2.2.5.1.2. The Power Law - WLF viscosity model. This is the model chosen in our work. The simplest model to describe a shear-rate and temperature dependent viscosity behavior is the power law relationship that also takes into account an explicit temperature adjustment \( a_T \).[24]

\[ \mu(\dot{\gamma}) = a_T k \dot{\gamma}^{n-1} \]  

(2.13)

where, \( k \) is the consistency factor, \( n \) is the power law exponent, and \( a_T \) is the temperature shift factor. The value of the power law exponent \( n \) determines the class of the fluid:

- \( n = 1 \) Newtonian fluid
- \( n > 1 \) Shear-thickening (dilatant) fluid
- \( n < 1 \) Shear-thinning (pseudo-plastic) fluid.
The explicit temperature dependency parameter $a_T$ is approximated by the Arrhenius and Williams-Landel-Ferry (WLF) equation[25]. The WLF equation has been used widely to describe the temperature dependence of the viscosity and relaxation time in polymeric systems [25]. The empirical equation is given by Eq. (2.13):

$$\log a_T = \frac{-C_1(T-T_0)}{C_2 + (T-T_0)}$$  \hspace{1cm} (2.13)

where, $a_T$ is the temperature shift factor, $T_0$ is the reference temperature to which the curves (viscosity vs (T-To))[25] are generated by shifting the dynamic mechanical test data at other temperatures, and $C_1$ and $C_2$ are material coefficients determined by fitting the test data of the shift factor. For many polymers, $C_1$ and $C_2$ are estimated to 17.4 and 51.6 respectively [26].

2.2.5.1.3. The Carreau viscosity model. Although this model was not used in our research, it is used to account for the significant deviations from the power law model at very high and very low shear rates[23]. It is expressed by Eq (2.14):

$$\frac{\mu - \mu_\infty}{\mu - \mu_0} = (1 + (\lambda \gamma')^2)^{\frac{n-1}{2}}$$  \hspace{1cm} (2.14)

where, $\mu$ is the apparent viscosity(Pa-s), $\mu_\infty$ is the dynamic viscosity at infinite shear rate(Pa-s), $\mu_0$ is the dynamic viscosity at zero shear rate(Pa-s), $\gamma'$ is the shear rate($s^{-1}$), and $\lambda$ is the relaxation time constant (s).
2.2.5.1.4. The Cross viscosity model. Once again, even though this model was not used, it is appropriate to use the Ellis model when the derivations from the power-law model are significant only at low shear rates.

\[ \mu = \mu_\infty + \frac{\mu - \mu_\infty}{(1 + (k\dot{\gamma}))^n} \]  

(2.15)

where, \( \mu \) is the apparent viscosity (Pa-s), \( \mu_\infty \) is the dynamic viscosity at infinite shear rate (Pa-s), \( \mu_0 \) is the dynamic viscosity at zero shear rate (Pa-s), \( \dot{\gamma} \) is the shear rate (s\(^{-1}\)), \( k \) is the consistency factor, and \( n \) is the power law exponent.

2.2.6 Other material properties. Other temperature dependent properties, such as \( c_p \), \( \rho \), and thermal conductivity, can be approximated by using a polynomial function of the form:

\[ M = a_0 + a_1 T + a_2 T^2 + a_3 T^3 + a_4 T^4 + a_5 T^5 + \ldots + a_n T^n \]  

(2.17)

where \( M \) is the material property of the hydrogel and water, \( T \) is the temperature of the fluid in (C), \( a_i \) (i=0,1,2,3,4,5,..n) are coefficients determined by a polynomial of the material property.

2.3. Finite Volume Method – STAR-CCM+

This section introduces the Finite Volume Method (FVM) for the solution of partial differential equations. These methods are widely used due to their robustness and computational advantage such as solving complex problems such as turbulent models and other complex geometries that we cannot validate experimentally.
2.3.1 Finite volume method. The finite volume method (FVM) is utilized as a discretization technique for partial differential equations. The integral conservation law is enforced for small control volumes defined by the computational mesh. The objective is to obtain linear algebraic equations with the total number of unknowns in each equation system. Transforms the mathematical model into a system of algebraic equations. This means discretizing the governing equations in space and time. The resulting linear equations are then solved with an algebraic multigrid solver.

2.3.2 Geometry and mesh. Consider a domain subdivided into a finite number of control volumes. The pattern created by the lines setting the boundaries of the control volumes is called the computational grid or mesh. Fig. 18 shows an example of a control volume. A node is referred to P, and the neighbors are designated E for east, W for west, N for north, and S for south.

![Diagram of a control volume](image)

*Figure 18.* Example of a typical control volume[27]. The nodes are designated by P, N, E and S and are located at the center of the control volume.
2.3.3 **Mathematics.** Integral form of conservation law: The partial differential equation is valid at all points in the domain. The domain is subdivided into small number of control volumes $dv$ and the conservative form is derived for a finite volume $dv$ bounded by a surface $ds$. The non-linear governing equations are solved iteratively one after the other for the solution variables such as $u$, $v$, $w$ and $p$.

When the appropriate constitutive relations are introduced into the conservation equations a closed set of equations is obtained. All conservation equations can be written in terms of a generic transport equation. By integrating the generic transport equation over a control volume $dV$ and applying Gauss's divergence theorem.

2.3.4 **Tool to apply the FVM.** All the models were developed based on the finite volume method (FVM) using the commercial software STAR-CCM+ (11.02). STAR-CCM+ uses discretization methods to convert the continuous system of equations to a set of discrete algebraic equations, which can be solved using numerical techniques.
Chapter 3

Thermal Fluid Models

This chapter will discuss the computational methods used to solve the different thermal fluid models outlined. First a breakdown of the model will be presented to emphasize the difference between the different thermal fluid models then, a description of each model will be conducted separately with the different steps to solve the CFD model.

3.1 Modeling Objectives

The goal of this thesis work is to design a hydrogel delivery system. We intend to develop thermal fluid models of the CoolGuide™ technology inside the EUS system. Using experimental results for validation, we intend to demonstrate that the CoolGuide™ catheter has the capability to control hydrogel temperature along the injection pathway.

The thermal fluid model will be created using a finite volume conjugate heat transfer approach. Using experimental results for validation we demonstrate that the sheath has the ability to reduce blood analog delivered temperatures, 2) control distilled water temperatures, and 3) help deliver drug encapsulated hydrogel into pancreatic lesions below its LCST. This section provides a description of the models developed in this study.

Model 1 studied a CoolGuide catheter that was used to cool blood analog while circulating through the aorta.

Model 1 was used as a validation process of the CoolGuide catheter.

Model 2 studied the CoolGuide sheath inside the mock EUS system without needle.
Model 3 studied a thermal fluid model of the hydrogel delivery system using the EUS and the FNI-Needle. The geometry included the CoolGuide sheath, the FNI needle and the EUS system.

Model 4 is an optimized model of the CoolGuide sheath that will be shared in Chapter 4.

3.2. Models

3.2.1 CoolGuide design overview. Previous use with a mock cardiovascular system: Heart disease continues to be the leading cause of death in the United States [28]. One of the common heart disease is a heart attack. A heart attack occurs when the blood flow to a part of the heart is blocked by a blood clot. If this clot cuts off the blood flow below the ischemic threshold, the part of the heart muscle supplied by that artery begins to die. Heart specific cooling devices may provide local, rapid cooling that might save tissue at risk. A cooling catheter CoolGuide™ (Fig.19) was designed and tested by FocalCool, LLC to provide access to the heart and provide protection by rapidly cooling localized tissue [21].
Figure 19. CoolGuide™ catheter design. The catheter consists of an inlet coolant lumen (1), an outlet coolant lumen (2), central lumen for blood analog flow (3) and a slot (4) which allows for coolant turnaround.[21].

Figure 20. Schematic of the heart showing the CoolGuide™ distal tip inserted into the right coronary artery[21].
3.2.1.1. New use with EUS and hydrogel delivery. A modified version of the CoolGuide™ catheter now called CoolGuide™ sheath will be used in conjunction with an FNI-Needle and an Endoscopic ultrasound system to help deliver thermosensitive hydrogels into pancreatic lesions. Fig. 21 shows a Solidworks rendered model of the EUS system with the CoolGuide™ sheath.

![Solidworks rendered model of the EUS system. This includes the endoscope, the FNI-Needle and the CoolGuide™ sheath.](image)

**Figure 21.** Solidworks rendered model of the EUS system. This includes the endoscope, the FNI-Needle and the CoolGuide™ sheath.

3.2.2 CoolGuide validation with the mock cardiovascular system.

3.2.2.1 Materials and methods. To explore the CoolGuide™ catheter cooling performances we (1) developed a mock cardiovascular system that simulates the conditions inside the carotid artery. (2) Developed a thermal fluid models using a finite volume method to predict blood analog delivered temperatures that we validated with experiments.
3.2.2.1 Experimental setup. Fig.22 shows the mock cardiovascular system. This system was built and tested by Merrill et al.[21]. The CoolGuide™ catheter was placed inside a glass aorta. The system included two circuits. A circuit for blood analog (38% glycerol and 62% distilled water) which was pumped at a flow rate of 3.5 L/min through the glass aorta (1), a circuit for the same flowing fluid but pumped through the internal Lumen of the CoolGuide™ catheter at different flow rates (2), and (3) a path for the coolant flow presented with the dashed lines to cool the blood analog.

![Schematic of the mock cardiovascular system](image)

*Figure 22. Schematic of the mock cardiovascular system. The CoolGuide™ catheter is placed inside a glass aorta. This device is labeled catheter. The two dashed lines present the inlet and outlet for the coolant flow.[23].*

3.2.2.1.2 Mathematical statement. Fig.23 shows a 3D model of the CoolGuide™ with the braiding. This includes a circular lumen for blood analog flow as well as a wing-
shaped lumen for the coolant. The coolant side turns at the end to allow for outflow. An outer braid is added to the CoolGuide™ catheter to add stiffness to the model [21]. Based on previous experimental work the length and diameter of the different lumens were imposed to achieve the goal of heart cooling[21].(Table 1).

![Figure 23. 3D model of the CoolGuide™ catheter. This figure shows: a central lumen for blood analog flow (1), an inlet coolant lumen (2), an outlet coolant lumen (3) which carries the coolant from distal tip to the coolant exit and a slot (4) which allows for coolant turnaround.]

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Dimension(cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoolGuide catheter Length</td>
<td>110.0</td>
</tr>
<tr>
<td>CoolGuide catheter inside the aorta</td>
<td>85.0</td>
</tr>
<tr>
<td>CoolGuide catheter Outer diameter</td>
<td>0.267</td>
</tr>
<tr>
<td>CoolGuide catheter Inner diameter</td>
<td>0.157</td>
</tr>
<tr>
<td>Coolant lumen hydraulic diameter</td>
<td>0.0458</td>
</tr>
</tbody>
</table>
a. Governing equations

In this study we will consider the motion of fluids and we will treat them as continuum. The three primary unknowns that can be obtained by solving these equations are: velocity, pressure, and temperature. The equations governing the blood analog flow are the mass conservation, the laminar Navier-Stokes, and energy conservation equations.

b. Boundary conditions

Apart from the geometry, it was necessary to describe the boundary conditions in order to be able to solve the governing equations. The numerical analysis is a direct comparison to experimental results. Therefore, the boundary conditions were fixed in a manner suitable to reproduce the experimental conditions.

The model consists of two primary domains, the fluid domain for blood analog flow, and distilled water flow as well as a solid domain for the catheter (Teflon core + Braid). The body core temperature remains constant due to the blood perfusion (38.4°C). Since the blood aorta flow is able to transfer heat to the catheter wall by convection, a convective boundary condition was applied to that wall. A value of 286.8 $\text{W/m}^2\text{-k}$ was chosen based on Eq. (3.19):

$$
\text{Nu} = \frac{h \times (D_1 - D_o)}{k},
$$

where, $h$ is the heat transfer coefficient ($\text{W/m}^2\text{-K}$), $k$ is the thermal conductivity of blood.
analog (W/m-K), and $D_i$ is the aorta average inner diameter (m) and $D_o$ is the catheter outer diameter (m). $Nu$, is the Nusselt number of a concentric annulus and equal to 10.44 assuming concentric annulus[22].

For all simulations, the coolant flow rate and temperature, the catheter thermal and flow wall boundary condition and the blood analog inlet temperature were kept constant, however the blood analog flow rates were varied from 18.3 ml/min to 76.7 ml/min to explore its impact on the catheter performances. Fig.24 depicts the boundary conditions used for the catheter model. Variable mass flow rates were chosen for inlets to keep consistent with previous experimental work[21].

- 0.85 m of the CoolGuide™ is inside of the aorta blood and exposed to blood side convection ($h_{aorta}$).
- All CoolGuide™ walls apply the no slip condition, which constrains the velocity to zero along it.
- The blood analog is pumped at variable mass flow rates and constant temperature.
- The coolant is pumped at constant mass flow rate and temperature.
- The outlet boundary condition is set to a zero pressure outlet for both the blood analog and coolant. Table 2 summarizes all the boundary conditions used for the model.
Figure 24. Boundary conditions for the CoolGuide™ model at the inlet. The inlet boundary conditions for both coolant and blood analog are set to a mass flow inlet condition. The outlets for the blood and coolant sides were set as pressure outlets. The wall, has a no-slip condition that will constrain the velocity to zero along it.

Table 2

Boundary conditions assigned for the different domains of the CoolGuide™ catheter.

<table>
<thead>
<tr>
<th>Boundary</th>
<th>Boundary Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood analog inlet [1]</td>
<td>Mass Flow Rate</td>
<td>18.3 ml/min – 76.7 ml/min</td>
</tr>
<tr>
<td>Blood analog inlet temperature [1]</td>
<td>Temperature</td>
<td>38.4 °C</td>
</tr>
<tr>
<td>Blood analog exit [output]</td>
<td>Pressure Outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Coolant inlet [2]</td>
<td>Mass Flow Rate</td>
<td>45 ml/min</td>
</tr>
<tr>
<td>Coolant inlet Temperature [2]</td>
<td>Temperature</td>
<td>4 °C</td>
</tr>
<tr>
<td>Coolant exit [3]</td>
<td>Pressure Outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Catheter outer wall (Inside aorta) [4]</td>
<td>Convection</td>
<td>h=286.8 W/m²-K</td>
</tr>
</tbody>
</table>
c. Material properties

The material properties that were assigned to both fluid and solid domains are listed in Table 3. This includes, the blood analog, distilled water, the CoolGuide™ catheter and the outer braiding. The blood analog is a 38% by volume Glycerol (Appendix A). The braiding is a mixture of stainless steel and Pebax and its thermal properties were determined based on the Maxwell derivation for thermal conductivity of composites [29] (See Appendix B).

Table 3

*Material Properties for the different domains: fluids and solids [5] [6]*

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (kg/m³)</th>
<th>Dynamic viscosity (Pa-s)</th>
<th>Specific heat (J/kg-K)</th>
<th>Thermal conductivity (W/m-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled water</td>
<td>999.6</td>
<td>0.001236</td>
<td>4186</td>
<td>0.59</td>
</tr>
<tr>
<td>Blood analog</td>
<td>1102</td>
<td>μ(T)=10.31exp(-0.035T)</td>
<td>3560</td>
<td>0.477</td>
</tr>
<tr>
<td>Catheter core extrusion</td>
<td>2160</td>
<td>-</td>
<td>1125</td>
<td>0.25</td>
</tr>
<tr>
<td>Braid(Pebax+stainless steel composite)</td>
<td>2500</td>
<td>-</td>
<td>910</td>
<td>0.34</td>
</tr>
</tbody>
</table>

d. Solution Strategy

A Xi MTower™ 2P64 computer with 3.7 GHz speed, 32GB RAM and 8 cores processor was used for all simulations. The governing equations were solved with the software
STAR-CCM+ version 11.04 based on the finite volume method. The numerical computation was considered to be converged when the residuals of all variables were less than $1 \times 10^{-4}$. More modeling details are seen in Table 4.

Table 4

*Modeling details with STAR-CCM+

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time stepping</td>
<td>Steady state</td>
</tr>
<tr>
<td>Tolerance</td>
<td>0.15</td>
</tr>
<tr>
<td>Solver</td>
<td>Segregated flow/Segregated fluid temperature</td>
</tr>
<tr>
<td>Flow</td>
<td>Laminar flow</td>
</tr>
<tr>
<td>Dimension</td>
<td>3 Dimensional</td>
</tr>
</tbody>
</table>

**e. Under relaxation factors**

The under relaxation factors are set by default to 0.9 and 0.99 for fluid and solid solvers respectively. If the convergence behavior is acceptable, the under relaxation factors for both solid and fluid might be increased to help with convergence speed. In our case, were increased to 0.99 and 0.999 for the fluid and solid energy solvers respectively so that we increase the convergence rate. The solver solves the equations related to mass, momentum and energy. For each case, the values of the variables that the solver is trying to solve get closer after each iteration until convergence. Making the under relaxation
factor closer to 1, will make the solution more stable like shown in eq. (3.20):

\[ X_{k+1} = \text{Urf} \cdot X_{\text{cal}} + (1-\text{Urf}) \cdot X_k, \quad (3.20) \]

where, \( X_k \) is the variable at iteration \( k \), \( X_{k+1} \) is the variable at the iteration \( k+1 \) and \( \text{Urf} \) is the under relaxation factor.

3.2.2.2 Results.

3.2.2.2.1 Isothermal model. To reduce the computational time, isothermal models were conducted to determine the pressure drops for the coolant and blood analog sides. In each case, instead of modeling the whole catheter, the fluid region was extracted and modeled apart. In each case the blood analog and coolant flow rates were varied, and the pressure drop was determined.

a. Mesh for the blood analog side

A trimmer mesh was used to generate the volume mesh for the blood analog side, and additional prism layers were defined along the wall boundary to ensure that the near wall effects are adequately resolved as well as generalized cylinders at the wall.

A mesh independence study was performed to minimize the discretization error over the computational domain. The test was done by solving an isothermal steady flow simulation and predicting the blood analog side pressure drop for a variety of mesh sizes. The model was considered to be mesh independent when the pressure drop over the entire domain did not significantly change with an increase in the number of mesh elements.
Mesh convergence was achieved with a total number of cells of 21,113,624 like shown in Fig.25.

*Figure 25.* Plot of Pressure Drop versus number of cells for the model. At approximately 21 million elements the model becomes mesh independent.

Fig.26 and 27 show the final volume mesh generated for the internal lumen and a close up section of the same mesh to emphasize the different types of mesh utilized.
Figure 26. Final mesh generated for the internal circular lumen of the CoolGuide™ containing approximately 21 million elements. A surface remesher and a Trimmer mesh were used in addition to generalized cylinders to form the volume mesh.

Figure 27. A close-up section of the mesh showing the trimer mesher, the generalized cylinders and the prism layers along the wall boundary.
b. Mesh for the Coolant Side

In this case a trimmer mesh was also used, and additional prism layers were defined along the wall boundary. The coolant lumens were extracted from the catheter geometry and modeled apart.

The same test was done for mesh convergence for the coolant side. The model was considered to be mesh independent when the pressure drop over the entire domain did not significantly change with an increase in the number of mesh elements. The final mesh generated includes 40,930,076. (Fig.28)

![Coolant Pressure Drop vs Number of Cells](image)

**Figure 28.** Plot of the coolant side pressure drop versus the number of cells. At approximately 41 million elements the model was considered to be mesh independent.
Fig. 29 and 30 show respectively, the final volume mesh generated for the model and a close up section of that same mesh.

**Figure 29.** Final mesh generated for the coolant lumens of the CoolGuide™. The coolant lumens were extracted from the catheter, modeled and meshed separately. The model includes approximately 40 million elements.

**Figure 30.** A close-up section of the mesh showing the trimmer mesher and the prism layers at the wall. Three prism layers generated at the wall boundary, were enough to ensure that the near wall effects are adequately resolved.

c. Model Validation
c.i. Pressure drop prediction for the blood analog side
Modeling results were verified through comparison with empirical solutions using Eq. (3.21). Fluid flow was validated by measuring the blood analog side pressure drop for the different mass flow rates. Results from the two different approaches are listed in Table 5 and plotted in Fig.31.

\[
\Delta P = f_{DWD} \frac{L}{D} \cdot \rho \frac{V_{avg}^2}{2},
\]  

(3.21)

where \( \rho \) is the fluid density in (kg/m\(^3\)), \( f_{DWD} \) is the friction factor for the developing flow and is different from the friction factor of a fully developed flow [22], \( L \) is the length of the catheter in (m), \( D \) is the diameter of the catheter in (m) and \( V_{avg} \) is the velocity at the inlet in (m/s).

The average velocity at the inlet of the tube was calculated by setting a constant flow rate with a fixed cross-sectional area using Eq. (3.22):

\[
Q = V_{avg} A,
\]  

(3.22)

where \( Q \) is volumetric flow rate (m\(^3\)/s), \( A \) the cross-sectional area in (m\(^2\)), and \( V_{avg} \) is the inlet velocity (m/s).
Table 5

Comparison between the empirical and numerical solution of the different pressure drop for different flow rates.

<table>
<thead>
<tr>
<th>Flow rate (ml/min)</th>
<th>Empirical pressure drop (kPa)</th>
<th>Numerical pressure drop (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>2.974</td>
<td>3.086</td>
</tr>
<tr>
<td>18.3</td>
<td>5.459</td>
<td>5.510</td>
</tr>
<tr>
<td>26.7</td>
<td>7.972</td>
<td>8.120</td>
</tr>
<tr>
<td>35.0</td>
<td>10.456</td>
<td>10.550</td>
</tr>
<tr>
<td>43.3</td>
<td>12.955</td>
<td>12.836</td>
</tr>
<tr>
<td>51.7</td>
<td>15.485</td>
<td>15.512</td>
</tr>
</tbody>
</table>

The pressure drop between the entrance and the exit of the blood analog lumen were determined at different flow rates. These results show that the numerical solution is in good agreement with the empirical solution.
Figure 31. Comparison between the numerical and empirical pressure drops for different flow rates of the blood analog. The numerical solution matched the empirical solution well.

c.ii. Pressure drop prediction for the coolant side

Results for the pressure drop for the coolant side were given by the Eq.(3.23): [21]

\[ \Delta P = \left[ f \frac{L}{D_h} \rho \frac{V_{avg}^2}{2} \right]_{\text{inlet to tip}} + \left[ f \frac{L}{D_h} \rho \frac{V_{avg}^2}{2} \right]_{\text{tip to outlet}} + \left[ \sum_{i=1}^{n} k_i \rho \frac{V_i^2}{2} \right]_{\text{minor losses}} \]  

(3.23)

where, \( f \) is the friction factor, \( L \) is the length of the coolant pathway (m), \( D_h \) is the hydraulic diameter of the coolant lumen (m), \( V_{avg} \) is the fluid average velocity (m/s) and \( k_i \) are the coolant minor losses coefficients.
Results from Star-CCM+ were compared to the empirical solution and experimental results (Fig. 32). Fig. 32 shows that the numerical solution is in good agreement with the experimental work. The average error between the numerical solution and experimental work was about 10.5%. Some differences in the predicted values could be attributed to several factors; (1) the coolant side has a complicated shape so there is nonlinear dependence on the hydraulic diameter and, (2) during experimental work the catheter wall got deformed during circulation of coolant which was not accounted for in the numerical model.

Table 6

*Pressure drop prediction for the coolant side for different mass flow rates*

<table>
<thead>
<tr>
<th>Flow rate (ml/min)</th>
<th>Numerical pressure drop (kPa)</th>
<th>Numerical pressure drop (Psig)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>172.500</td>
<td>25.01</td>
</tr>
<tr>
<td>20.0</td>
<td>355.806</td>
<td>51.60</td>
</tr>
<tr>
<td>25.0</td>
<td>449.512</td>
<td>65.19</td>
</tr>
<tr>
<td>30.0</td>
<td>544.637</td>
<td>78.99</td>
</tr>
<tr>
<td>45.0</td>
<td>767.623</td>
<td>111.00</td>
</tr>
</tbody>
</table>
Figure 32. Experimental data compared to the empirical and numerical predictions for the CoolGuide™ coolant pressure-flow behavior. The bars present the standard deviation for coolant flow and pressure.

3.2.2.2 Non-isothermal model. In this case, we intend to demonstrate the catheter’s ability to reduce blood analog delivered temperatures for a range of flow rates. The catheter was partially exposed to ambient temperature, the rest of the model was inserted inside the aorta blood (Fig.3). The non-isothermal model will include additional boundary conditions such as temperatures and heat transfer coefficient (Table 2).

a. Mesh

For a conjugate heat transfer problem where there is variation of temperature within a solid and fluid, the mesh type is different. To properly solve the model, we generated a polyhedral mesh and additional prism layers were activated on the fluid side of the fluid-solid interface. The interfaces were added to ensure continuity between the different
continuums. The solid part had no prism layers however, we activated the embedded thin mesher to provide more suitable cells inside the solids. Having 3 layers of cells defining the solid thickness is important to resolve the temperature gradients in the solid.

Before solving the model, a mesh independence study was performed to minimize the discretization error over the computational domain. Using the average exit temperature, mesh convergence was achieved with a total number of cells of approximately 24 million cells as shown in Fig. 33. Fig. 34 and 35 show respectively the final mesh generated and a close up section of the same mesh.

![Plot of the blood exit temperature versus number of cells for the CoolGuide™ model. At approximately 24,009,582 elements the model becomes mesh independent.](image)

*Figure 33. Plot of the blood exit temperature versus number of cells for the CoolGuide™ model. At approximately 24,009,582 elements the model becomes mesh independent.*
Figure 34. Final mesh generated for the Catheter containing approximately 24 million elements. A surface remesher was generated as the surface mesh and a polyhedral mesh formed the volume mesh. The white and orange colors define the inlets and outlets respectively.

Figure 35. A close up section of the mesh showing the polyhedral cells and the prism layers at the fluid-solid interface as well as the 3 layers of embedded thin mesher on the solid region to properly solve the temperature gradient.
3.2.2.2.1. Model validation.

a. Exit temperature prediction for the blood analog

An accuracy check was conducted to validate the CoolGuide™ catheter model. Fig. 36 shows the delivered temperatures results compared to published data. The results seen in this figure show the effect of the blood analog flow rate on the average exit temperature. When the flow rate increases the delivered temperature increases as well. The numerical model predicted the delivered temperatures within 2 °C for flow rates lower than 43.3 ml/min and 1 °C for the rest of the tested flow rates (Table 7). The numerical results matched reasonably well with the experimental work.

Table 7

Exit temperatures determined with CCM+.

<table>
<thead>
<tr>
<th>Flow rate (ml/min)</th>
<th>Numerical Distal Tip Exit temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.3</td>
<td>21.10</td>
</tr>
<tr>
<td>26.7</td>
<td>22.22</td>
</tr>
<tr>
<td>35.0</td>
<td>23.48</td>
</tr>
<tr>
<td>43.3</td>
<td>24.72</td>
</tr>
<tr>
<td>51.7</td>
<td>25.85</td>
</tr>
<tr>
<td>60.0</td>
<td>26.88</td>
</tr>
<tr>
<td>68.8</td>
<td>27.60</td>
</tr>
<tr>
<td>76.7</td>
<td>28.20</td>
</tr>
</tbody>
</table>
Figure 36. Experimental data compared to EES and Numerical model predictions with varying flow rates and given the same inputs. For flow rates higher than 43.3 ml/min, all computational values are within 2°C of the experimental data. The error bars describe to standard deviation for three data sets.

b. CoolGuide™ catheter cooling capacity

From the predicted temperatures and flow data of the blood analog, the cooling capacity was calculated using Eq. (3.24):

\[ Q_B = \dot{m}_B \cdot C_{p,B} (T_c - T_{del}), \]  

(3.24)

where \( Q_B \) is the heat capacity of the blood analog (W), \( \dot{m}_B \) is the mass flow rate of the blood analog in kg/s, \( T_c \) is the core temperature (°C), \( T_{del} \) is the temperature at the catheter distal tip or delivered temperature (°C) (Table 7) and \( C_{p,B} \) is the specific heat
capacity of the blood analog J/kg-C (Table 3).

The blood analog flow rate ranged from 18.3 ml/min to 76.6 ml/min and Fig.37 shows the corresponding cooling capacity compared to published data[21]. Even though the numerical solution was in good agreement with the present data for flow rates higher than 51.7 ml/min, the required minimum cooling capacity of 20 W was achieved for all flow rates[21].

The average error of the cooling capacity between the numerical solution and the experimental data was about 7%. This new finite volume method was more accurate than the empirical solution determined with EES which predicted the cooling capacity within approximately, 11% from experimental work. This was expected since the heat transfer correlations used for the EES model are often within ±15% accurate [30].
Figure 37. CoolGuide™ cooling capacity comparison between experimental work, numerical solution and EES model. The error bars indicate the sample standard deviation for three different testing.

c. Plot of the temperature and dynamic viscosity as a function of the length for a flow rate of 60 ml/min

Fig. 38 shows the temperature and viscosity profiles of the blood analog as a function of the catheter length. The flow rate of 60 ml/min was randomly chosen to explore the blood analog behavior at various longitudinal positions from the inlet to the exit (1.1m) with 0.1m increment. At every position, the blood analog temperature and viscosity were determined based on the surface average method. The surface average of a scalar quantity \( \phi \) inside STAR-CCM+ is computed on a surface as:

\[
\text{Surface average} = \frac{1}{a} \int \Phi \, da = \frac{\sum_f \Phi_f A_f}{\sum_f A_f},
\]  

(3.25)
where, $\Phi_f$ is the face value of the selected scalar and $A_f$ is the face area.

When the temperature of the blood analog decreased from 38.4°C to 26.88°C from the inlet to the outlet respectively, the dynamic viscosity increased and matched its associated temperature at each position along the catheter. The dynamic viscosity of the blood analog is clearly dependent on the temperature.

![Figure 38](image.png)

*Figure 38.* Plot of the blood analog temperature and dynamic viscosity as a function of the CoolGuide™ catheter length. The blood analog enters at a constant temperature (38.4°C), then gets cooled as it exits the catheter. The dynamic viscosity however, increases.

Because the model has different boundary conditions (partly exposed to ambient temperature and partly to the aorta blood) and the coolant side has a turnaround at the distal
tip of the catheter, the temperature and viscosity behaviors are not uniform along the catheter length. From the inlet to approximately 0.1m, the temperature of the blood analog decreases drastically from 38.4 °C to 31.52° C. This drastic change is due to the heat exchanged between the blood analog inside the central lumen, the ambient temperature and the coolant. In this region, the catheter is still outside the aorta blood so the heat is transferred from the blood analog inside the central lumen (38.4 °C) to the coolant (4° C) and ambient temperature. Therefore the blood analog will cool down fast.

From 0.1 m to 1 m the temperature of the blood analog decreases from 31.52 ° C to 26.38° C. Here the catheter is exposed to the aorta blood; the central lumen as well as the coolant lumens are gaining more heat, this is why the blood analog takes longer time to cool down. At 1 m, the temperature rises slightly until it exists the catheter. In fact at that position the coolant temperature is not uniform due to the coolant turnaround. Fig.39 shows the coolant temperature distribution at the turnaround. The coolant temperature at location 2 is higher than the one at location 1.
Figure 39. Temperature distribution close to the blood analog exit. The temperature distribution at the turnaround shows 1) Coolant before the turnaround and 2) Coolant temperature after the turnaround.

d. Temperature distribution along the coolant pathway

Fig. 40 and 41 show a plot of the coolant temperature as a function of the coolant pathway. The blood flow rate was kept the same as earlier in the study (60 ml/min) with a coolant flow rate of 45 ml/min. The temperature behavior of the coolant at various longitudinal positions was explored based on the surface average method. The coolant pathway length is twice as long as the catheter length (2.2 m) since the coolant side has a turnaround which carries the coolant from the catheter distal tip to the coolant exit (Fig.1). Unlike the blood flow, the coolant temperature increases from the catheter inlet to the exit since the coolant will gain heat from both the aorta blood and the blood analog circulating inside the central lumen. From the catheter inlet to the distal tip, the temperature of the coolant increases from approximately 4° C to 21.08 °C, here the coolant lumen is
exchanging the maximum heat with the blood aorta and the blood analog inside the central lumen. The temperature of the coolant at the distill tip was found to be different at location 1 and 2 (Fig. 39), which explains why the coolant temperature at 1.1 m (Fig. 40) is equal to 21.08 °C and the temperature at the second pathway is equal to 20.68.

At a distance of 0.85 m (Fig. 41) the coolant temperature slightly decreases due to the change in boundary conditions. In fact, that position presents a distance of 0.25 m from the inlet of the catheter. That portion of the catheter is outside the aorta blood and exposed to environment conditions. Since the environment conditions are colder than the aorta blood, the coolant temperature will slightly decrease.

Figure 40. Plot of the coolant temperature from the coolant inlet to the distal tip.
Figure 41. Plot of the coolant temperature from the distal tip to the coolant exit. The coolant side has a slot at the distal tip of the catheter to allow it to turnaround. This makes the coolant pathway twice as long as the catheter.

3.2.3. CoolGuide temperature control of hydrogel without FNI-Needle.

3.2.3.1 Material and methods. To explore the CoolGuide™ sheath delivery capabilities we (1) developed a mock Endoscopic Ultrasound system that mimics the hydrogel delivery under body temperature conditions (without the needle),(2) Developed thermal fluid models using a finite volume method to predict water and hydrogel delivered temperatures that we validated with experiments.

3.2.3.1.1 Experimental setup. Mock EUS system: An in vitro experimental set-up was built to control and record hydrogel temperatures along the injection pathway (Fig.42). A temperature controlled sheath called CoolGuide™ was inserted into the EUS working channel to the proximal end. The EUS working channel was made of 3/8” ID stainless steel tubing and exposed partly to ambient conditions and partly to body
temperature. Body temperature was maintained at 37.5°C ± 0.5°C conditions and created using a heated reservoir and 3/32” ID Tygon wrapped tubing around the last 65cm EUS working channel.

A syringe pump was used to inject through the central lumen of the CoolGuide™ sheath 1) Distilled water and 2) hydrogel (30% Pluronic F-127). Both fluids were injected at variable flow rates ranging from 1-5 ml/min. The cooling console was used to deliver chilled distilled water through the coolant lumens.

Figure 42. Schematic of the test setup without the FNI-Needle. From left to right 1) a syringe pump for injecting hydrogel or water through the CoolGuide™ sheath 2) A cooling console used provide coolant to the CoolGuide sheath 3) A heated reservoir used to simulate body temperature conditions and 4) An EUS working channel made of stainless steel tubing exposed partly to ambient conditions and partly to body temperature. Temperature, pressure, and flowrate are labeled with T,P, and F respectively.
Seven Probes were used in the experimental work to measure the different fluids, ambient and body temperatures. One of the most challenging measurement was the fluid temperature exiting the sheath. Due to the CoolGuide sheath geometry (Fig.43), the top and bottom wall are surrounded by different temperatures which will lead to the non-uniformity of the temperature inside the central lumen causing limitation of the exact exit temperature measurement.

The use of mixers at the exit would have helped the tested fluid to mix properly to allow for an accurate measurement. However, there are definitely challenges to implementing this technique. Given the low flow rates of the water and hydrogel circulating through the CoolGuide sheath, this may lead to elevation of the temperature exiting the sheath before reaching the probe causing inaccurate temperature measurement.

To investigate the effect of the probe orientation within the exit area, the probe was placed in three different locations inside the fitting: 1) close to the bottom wall, 2) close to the top wall (in contact with coolant lumens) and 3) on the centerline (Fig.44). For the three different cases the exit temperatures were collected for three data sets and with water as the flowing fluid since it is easier than hydrogel to deal with.

Fig.43 shows a SolidWorks sketch for the three different probe locations. The probe was inserted inside the fitting, and each time a picture of the fitting with the probe was imported into SolidWorks. The tip of the probe was then localized to determine its approximate position with respect to the center.
Figure 43. 2D sketch of the CoolGuide™ sheath showing the location of the probes.
Figure 44. SolidWorks 2D sketches showing the location of the probe for the three different cases: 1) centerline, 2) top wall and 3) bottom wall. A picture of the Y-fitting with the thermocouple location was imported into Solidworks, then a 2D sketch was drawn.

e. Testing protocol

A consistent testing method was maintained for both distilled water and hydrogel. The testing began when a set of initial conditions was met (Table 8). The test fluid was then pumped (distilled water or hyrdogel) and the test data was recorded.
Table 8

*Initial conditions for the testing setup*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Acceptable Value for Test Start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>37.5°C +/- 0.5°C</td>
</tr>
<tr>
<td>Coolant to CoolGuide RTD Temperature</td>
<td>&lt; 5.0°C</td>
</tr>
<tr>
<td>Coolant to CoolGuide Flow Rate</td>
<td>&gt; 35 ml/min</td>
</tr>
<tr>
<td>Room Temperature</td>
<td>23.5°C +/- 3.0°C</td>
</tr>
</tbody>
</table>

3.2.3.1.2 *Mathematical model.* Our mathematical model was created to predict the fluid delivered temperatures when injected under body temperature conditions inside a mock endoscopic ultrasound and without the FNI-Needle.

a. Geometry

Fig.45 shows a 3D model of the distal end of the mock EUS system including the CoolGuide™ sheath, the EUS and the fine needle injector (FNI). The CoolGuide™ is 1.5m long sheath and provides cooling to avoid hydrogel warming beyond its phase transition temperature or lower critical solution temperature (LCST) before its final destination inside the lesion. This study involves internal flow of 30% Pluronic F127 hydrogel inside the CoolGuide™ sheath without the needle injector.
Figure 45. 3D model of the distal end of the mock EUS system showing the CoolGuide™ cooling sheath, the fine needle injection needle (FNI) and the air gap between the mock EUS and the CoolGuide™.

For the purpose of modeling, we considered a triple lumen CoolGuide sheath positioned inside a mock EUS system and surrounded by non-moving air. The air gap was assumed to be a solid part given the thermal conductivity of air. This assumption is valid due to the non-motion of the air and will decrease computational time. The braided stainless steel mock EUS has an embedded layer of plastic (PVC). Fig.46 shows the mock EUS system and a close up section outlining the different layers surrounding the CoolGuide sheath.
Figure 46. Schematic of the mock EUS system This figure shows a CoolGuide sheath (1), a Mock EUS (2), an embedded layer of plastic (PVC) (3) and an air region surrounding the CoolGuide sheath (4). The system is 1.53 m long including a 1.2m of mock EUS. The different layers in the 3D model derive from the existing device used in the experimental work.

Table 9

*Dimensions of the CoolGuide™ sheath*

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Dimension(cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoolGuide™ sheath Length</td>
<td>153.0</td>
</tr>
<tr>
<td>EUS “Body Temperature” Warming Loop</td>
<td>65.0</td>
</tr>
<tr>
<td>EUS length</td>
<td>125.0</td>
</tr>
<tr>
<td>CoolGuide™ sheath Outer diameter</td>
<td>0.267</td>
</tr>
<tr>
<td>CoolGuide™ sheath Inner diameter</td>
<td>0.157</td>
</tr>
<tr>
<td>Coolant lumen hydraulic diameter</td>
<td>0.046</td>
</tr>
</tbody>
</table>
b. Governing Equations

Similar to Model 1, the flow is assumed to be governed by the laminar Navier-Stokes equations, mass conservation, and energy conservation outlined in section (2.1.2).

c. Boundary and Initial Conditions

The model consists of different domains, the fluid domains for hydrogel, and distilled water flow, as well as the solid domains for the CoolGuide sheath, the air and the mock EUS. The thermal boundary condition between the solid and fluid is a conjugate heat transfer. The continuity is ensured at the fluid-solid interface, which means that the energy equations are coupled for the two domains to allow for heat transfer between them.

Description of the boundary conditions is provided below (Fig.47 and Table.10):

- 0.650 m of the mock EUS (Outer layer surrounding the CoolGuide™ will be held at a constant temperature equal to the temperature of the body (37.5°C).
- All CoolGuide™ walls apply the no slip condition, which constrains the velocity to zero along it.
- The hydrogel and water will be injected at variable mass flow rates and constant temperature inside the center lumen.
- The coolant (distilled water) will be injected at constant mass flow rate and Temperature.
- A pressure outlet was assigned to the hydrogel and coolant outlets
- The CoolGuide sheath outside the body and the mock EUS was exposed to natural convection.
The natural convection heat transfer coefficient was determined based on the following equation:

\[ \text{Nu} = \frac{h D}{k}, \quad (3.26) \]

where, \( h \) is the natural convection heat transfer coefficient (W/m\(^2\)-k), \( k \) is the thermal conductivity of air (W/m-C), \( D \) is the CoolGuide diameter (m) and \( \text{Nu} \), is the Nusselt number.

The natural convection heat transfer coefficient was determined based on Van Der Hegge Zijnen method [31] The Nusselt number is determined as a function of Grashof and Prandtl numbers as follows:

\[ \text{Nu} = 0.35 + 0.25 (\text{Gr Pr})^{1/8} + 0.45 (\text{Gr Pr})^{1/4}, \quad (3.27) \]

where, the Grashof number is a dimensionless number which approximates the ratio of buoyancy to viscous forces acting on a fluid. It is expressed using Eq. (3.28):

\[ \text{Gr} = \frac{g \beta (T_s - T_0) D^3}{\nu^2}, \quad (3.28) \]

where, \( g \) is the acceleration due to earth’s gravity, \( \beta \) is the coefficient of thermal expansion, \( T_s \) is the surface temperature (K) \( T_0 \) is the bulk temperature (K). \( D \) is the cylinder diameter (m), \( \nu \) is the kinematic viscosity (m\(^2\)/s ). Prandtl number is determined based on Eq. (3.29) as follows:
Figure 47. Schematic of the Mock EUS system with the boundary conditions. This includes hydrogel and coolant inlet temperatures and mass flow rates as well as the wall boundary conditions.
### Table 10

*Boundary conditions imposed on the CoolGuide™ model*

<table>
<thead>
<tr>
<th>Boundary</th>
<th>Boundary Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water/hydrogel inlet [1]</td>
<td>Mass Flow Rate</td>
<td>1ml/min – 6ml/min</td>
</tr>
<tr>
<td>Water/hydrogel inlet temperature</td>
<td>Temperature</td>
<td>1ml/min – 6ml/min</td>
</tr>
<tr>
<td>[1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water/hydrogel exit [output]</td>
<td>Pressure outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Coolant inlet Temperature [2]</td>
<td>Temperature</td>
<td>5-7 °C</td>
</tr>
<tr>
<td>Coolant exit [3]</td>
<td>Pressure outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Outer wall (Inside body) [4]</td>
<td>Temperature</td>
<td>37.5°C</td>
</tr>
<tr>
<td>Outer wall (Outside body) [4]</td>
<td>Temperature</td>
<td>30°C</td>
</tr>
<tr>
<td>CoolGuide sheath outer wall</td>
<td>Convection</td>
<td>6 W/m²-k</td>
</tr>
<tr>
<td>Thermal exit boundary condition</td>
<td>Constant heat flux</td>
<td>-</td>
</tr>
</tbody>
</table>

**d. Material Properties**

Two different fluids were tested and modeled: 1) distilled water and 2) 30% Pluronic F127 Hydrogel. Since there is a gap in knowledge about the Pluronic F127 hydrogel material properties, the thermal conductivity, specific heat and density of the hydrogel were assumed to be the same as water. Considerable uncertainty exists in those property values, so that the accuracy of the computed results may be affected to some extent by errors in those values.
The dynamic viscosity of the hydrogel however was the only known property which is dependent on the temperature and the shear rate of the fluid. The material properties that were assigned to both fluids were a function of temperature. The solid domains however include, 1) the CoolGuide™ sheath which is made of Pebax with a thermal conductivity of 0.29 W/m-C, 2) the Endoscopic Ultrasound made of stainless steel and, 3) the plastic part.

Table 11

*Materials properties of the different fluids and solids used in the 3D model.*

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (kg/m³)</th>
<th>Dynamic viscosity (Pa-s)</th>
<th>Specific heat (J/kg-K)</th>
<th>Thermal conductivity (W/m-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled Water</td>
<td>999.6</td>
<td>Variable</td>
<td>4186</td>
<td>Variable</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>1000</td>
<td>Variable</td>
<td>4186</td>
<td>Variable</td>
</tr>
<tr>
<td>Catheter(Pebax)</td>
<td>2160</td>
<td>-</td>
<td>1125</td>
<td>0.29</td>
</tr>
<tr>
<td>EUS (Stainless Steel)</td>
<td>2500</td>
<td>-</td>
<td>910</td>
<td>15.06</td>
</tr>
<tr>
<td>Plastic(PVC)</td>
<td>1400</td>
<td>-</td>
<td>840 - 1170</td>
<td>0.19</td>
</tr>
<tr>
<td>Air</td>
<td>1.225</td>
<td>-</td>
<td>1000</td>
<td>0.02633</td>
</tr>
</tbody>
</table>

e. Modeling details

All simulations were run on an ‘HPC cluster’ of high performance computing of Rowan University. The models were run on 5 nodes (23 processor per node) with a total number
of processors of 162. The cluster reduced our Computational time from 8 hours to approximately 2 hours compared to local computers.

The governing equations were solved using the computational fluid dynamics software STAR-CCM+ based on the finite volume method. Convergence criteria included residuals of continuity, velocity, and energy as well as the average fluid exit temperature. The numerical computation was considered to be converged when the residual errors of all variables were less than $1 \times 10^{-4}$.

f. Solvers

The segregated fluid temperature model was chosen. It solves the total energy equation with temperature as the solved variable. Enthalpy is then computed from temperature according to the equation of state. The Segregated solid energy was activated for the solid regions: The energy solver here controls the solution update for the segregated fluid energy model. Table 12 summarizes the modeling details used for the simulations.

Table 12

*Modeling details with STAR-CCM+

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time stepping</td>
<td>Steady-state state</td>
</tr>
<tr>
<td>Tolerance</td>
<td>0.15</td>
</tr>
<tr>
<td>Solver</td>
<td>Segregated flow/Segregated fluid temperature</td>
</tr>
<tr>
<td>Flow</td>
<td>Laminar flow</td>
</tr>
<tr>
<td>Dimension</td>
<td>3-Dimensional</td>
</tr>
</tbody>
</table>
g. Mesh study

A mesh independence study was performed by solving a steady flow simulation and predicting the water exit temperature for a variety of mesh sizes. The model was considered to be mesh independent when the average exit temperature over the entire domain did not significantly change with an increase in the number of mesh elements.

For the conjugate heat transfer problem, we generated a polyhedral mesh and additional prism layers were activated on the fluid side of the fluid-solid interface. The solid part had no prism. Fig. 48 shows the final mesh, approximately 19.8 million cells. Fig. 49 shows a close up section of the CoolGuide sheath mesh.

Figure 48. Final mesh for the mock EUS system including approximately 19.8 million cells. The volume mesh was generated using polyhedral cells.
Model Validation with water

The delivery system was first validated with distilled water. Distilled water testing can be performed more rapidly, and without drastic changes in viscosity, compared to hydrogel. The aim of this work is to demonstrate the CoolGuide™ sheath ability to control distilled water temperatures for a range of flow rates. The flow rates were varied from 1ml/min to 6 ml/min with 1ml increment. Through these tests we can gauge the system’s ability to maintain the temperature of the delivered fluid below body temperature and hydrogel transition temperature.

The numerical model was validated with experimental data performed inside a mock EUS system. The water exit temperature was first collected using a probe placed at three different locations (Fig.44). The aim of this study was to determine the impact of probe
location on the final results. Therefore, numerical solution was compared to present data collected with the appropriate probe location.

i. Effect of the probe location on the water exit temperature

Fig. 50 shows the water exit temperature for the three different probe locations. Three flow rates were tested: 2, 4, and 6ml/min. The centerline and bottom wall probes measured almost the same exit temperatures, however the top wall probe measured lower temperatures as expected due to its contact with the coolant lumens (Fig.44), where the temperature tend to be lower than the one measured at the centerline or the bottom wall.

Since the centerline and bottom wall probes gave almost the same results, we decided to use the centerline probe. All experimental work therefore was done using the centerline probe. The numerical solution then, was compared to those data.
Figure 50. Experimental data for the three different probe locations. The water flow rate varied from ml/min to 6ml/min. The error bars describes the standard deviation for three different data sets.

j. Validation of the numerical solution with experimental results for the distilled water

An accuracy check was conducted to validate the CoolGuide™ sheath model with water as the tested fluid. The inlet temperature was not constant for the different tests due to the low flow rates which cause the water temperature to warm up quickly from the injection location to the probe. These inlet temperatures were used as the inputs for our models.

The results of the first set of experiments compared to numerical solution using water as the flowing fluid are shown in Fig. 51. The temperatures were measured using the centerline probe. The numerical model predicted the delivered temperatures within an average of 0.5 °C for all tested flow rates. The average error between numerical solution and experimental results therefore, was about 4%.
Due to the low flow rates, no significant change was recorded in the water outlet temperature even though the flow rate was six times greater. Higher coolant flow rates provide colder temperatures and high heat transfer coefficients. Since the dominant thermal resistance is on the inside of the sheath, changing internal flow rates does not impact performance significantly.

Figure 51. Water experimental data compared to numerical solution prediction with varying flow rates and given the same inputs. The error bars represent the sample standard deviation for three data sets.

k. Cross sectional views of the distilled water temperature and dynamic viscosity at the exit of CoolGuide sheath

Cross sectional views of the sheath model (Fig.52) show the temperature and dynamic viscosity distributions at the exit of the sheath. The flowing fluid in this case is water, and
was injected at 2ml/min. The choice of this flow rate was arbitrary and aims to explore the behavior of the water around the CoolGuide™ sheath.

![Figure 52. Temperature and dynamic viscosity distribution of the water at the exit. The flow rate is 2ml/min.](image)

1. Water temperature along sheath

Fig. 53 shows the water temperature profile as a function of the CoolGuide™ sheath length for a flow rate of 2 ml/min. These plots explore the water behavior inside the central lumen and at various longitudinal positions from the inlet to the exit (1.53m) with 0.2m increment. At every position, the water temperature was determined based on the surface average method.
From the inlet of the sheath to the outlet, the water temperature increased from 4.85°C to 11.44 °C steadily. Even though the temperature was increasing, the CoolGuide™ sheath was able to limit the warming that took place.

*Figure 53.* Plot of the water temperature as a function of the CoolGuide™ sheath length for a 2 ml/min flow rate. The water enters at a constant temperature (5.85°C) and leaves at 9.59°C.
m. Model Validation with Hydrogel (30% Pluronic F127)

m.i. Determination of the power law equation for 30% Pluronic F127

Rheology models are grouped under the categories; (1) empirical, (2) theoretical, and (3) structural. Empirical models such as the power law model are deducted from experimental data.[24].

The hydrogel viscosity is dependent on the temperature and shear rate. In order to gain further understanding on the behavior of the 30 % Pluronic F127 a rheological study was first conducted. The primary task of mathematical modeling applied rheology is to predict the rheological properties of 30% hydrogel F127. From the work of Abdel-Hamid et al(2006) the power law model was the best fit for pluronic compared to the Bingham and Casson model.

m.ii. Rheometry

Rheological measurements of pluronic F127 (30% by volume) were performed on a strain-controlled rheometer. An oscillating geometer (parallel plate, 20 mm diameter) with the Peltier thermal stage serving as the lower surface, was used to run flow sweeps on the F127 hydrogel. Fig. 54 shows the experimental setup. For each test 0.5 ml of test solution was in contact with the lower plate and the upper geometer was lowered to contact the solution. The temperature dependence of rheological properties was studied at a range of 4C to 30 C. The shear rate was varied at a constant temperature each time.

From the rheometer, we obtained the relationship between the viscosity and the shear rate
for the 30% hydrogel at each temperature. The flow profiles were investigated by fitting the Power Law model to the rheological data. Fig. 55 shows the variation of the viscosity as a function of the shear rate for different temperatures. The viscosity decreases with an increase in shear rate which proves that Pluronic F127 is a shear thinning polymer [23].

*Figure 5.4. Actual picture of the Rheometer setup used for the rheology analysis. An oscillating geometry (parallel plate, 20 mm diameter) was used to run flow sweeps on the F127 hydrogel.*
To find the power law index (n) and the consistency factor (K), both sides of Eq.(2.12) were changed into the logarithmic of shear rate Eq.(3.30) to get a linear plot (Fig.56). The power law model describes the data of shear thinning fluid [32].

\[
\log (\mu) = (n-1) \log (\dot{\gamma}) + \log (k) \tag{3.30}
\]

Table 13 summarizes the power law index (n) and the consistency index (k) for the two different temperatures. Those values were used in the 3D model. The viscosity was modeled using the power law model.

Figure 55. Viscosity versus shear rate plot at different temperatures. The temperature of the hydrogel varies from 4 C to 30C. The LCST is 14 C.
Figure 56. Logarithmic plot of the viscosity versus shear rate at different temperatures. The temperature of the hydrogel varies from 4°C to 30°C. The LCST is 14°C.

Table 13

Rheological properties of 30% Pluronic F127

<table>
<thead>
<tr>
<th>30% Pluronic F127</th>
<th>n</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 8°C</td>
<td>0.54</td>
<td>2.29</td>
</tr>
<tr>
<td>At 20°C</td>
<td>0.2</td>
<td>3.39</td>
</tr>
</tbody>
</table>

From the distilled water model and testing, the ability of the CoolGuide™ sheath to control fluid temperatures while delivery under body temperature conditions was demonstrated. In this section, we intend to investigate the CoolGuide™ sheath ability to deliver Pluronic F-127 hydrogel below its LCST (14°C for 30% hydrogels).
m.iii. Validation of the numerical solution with experimental results

A comparison plot of the hydrogel exit temperature between present data and the numerical solution is shown in Fig.57. The coolant and hydrogel inlet temperatures were variable for each test, which explains the large offsets between the three tests.

A good match exists between the numerical solution and the experimental work with an average error of 2% between the two approaches. The delivered temperatures were found to be below the LCST (14 °C).

![Graph showing hydrogel exit temperatures as a function of flow rates](image)

*Figure 57.30% Pluronic F-127 hydrogel exit temperatures as a function of the flow rates. Experimental data are compared to numerical solution given the same inputs. The error bars represent the sample standard deviation for three different data sets.*
Fig. 58 shows how the hydrogel temperature increases as a function of the CoolGuide sheath length for a flow rate of 2 ml/min. Like explained in the water case, the sheath showed its ability to control hydrogel temperatures while delivery under body temperature conditions.

Figure 58. 30% Pluronic F-127 hydrogel temperature distribution as a function of the CoolGuide sheath length for a flow rate of 2ml/min. The CoolGuide sheath was able to control the hydrogel temperature and maintain it below the LCST. The LCST of the 30% Pluronic.
m.v. Comparison between the CoolGuide sheath and a standard sheath in terms of delivery capabilities

Two sheath configurations were explored 1) A standard circular sheath and 2) The CoolGuide™ sheath. The aim of this study is to show that the temperature controlled sheath has the ability to deliver hydrogel under body temperature conditions and keep it in liquid form along the injection pathway.

Given the same inputs as the CoolGuide™ sheath, modeling results of the standard sheath showed that hydrogel delivered temperature exceeded the LCST (14°C). For a flow rate of 2ml/min, hydrogel delivered temperature was about 27°C with an average viscosity of 3010 Pa-s. The pressure recorded with numerical solution to deliver hydrogel through the sheath exceeded the limit provided with the syringe pump. Fig. 59 shows the temperature and viscosity distributions of the hydrogel through the CoolGuide™ and the standard sheath.
3.2.4. CoolGuide temperature control with an FNI-Needle aspirator.

3.2.4.1 Material and methods. To explore the hydrogel delivery capabilities we (1) developed a mock Endoscopic Ultrasound system that mimics the hydrogel delivery under body temperature conditions using an FNI-Needle, and (2) developed thermal fluid models using a finite volume method to predict water and hydrogel delivered temperatures that we validated with experiments.

Figure 59. Temperature and viscosity distributions along the two different sheath configurations. The CoolGuide sheath delivered hydrogel at a temperature of 9.53 C and 9.5 PSIG while the delivery temperature with the standard sheath was about 27C.
3.2.4.1.1 Experimental setup. Mock EUS system. An in vitro experimental set-up was built to control and record hydrogel temperatures along the injection pathway (Fig.60). The temperature controlled sheath (CoolGuide™) was inserted into the EUS working channel to the proximal end to provide temperature control along the injection pathway. A needle was placed inside the whole assembly and was kept in contact with the CooGuide sheath. A 3 cm portion of the needle was sticking out of the mock EUS and the CoolGuide to mimic the injection procedure inside the body.

A syringe pump was used to inject through the central lumen of the CoolGuide™ sheath 1) Distilled water at variable flow rates and 2) hydrogel (30% by volume Pluronic F-127). The cooling console was used to deliver chilled distilled water through the coolant lumens.

Figure 60. Schematic of the test setup without the FNI-Needle. The mock tissue was created to ensure body temperature conditions surrounding the 3 cm needle out the EUS.
a. Mock tissue creation

A temperature controlled mock tissue was created to mimic body temperature environment to the 3 cm needle outside of the Mock EUS system. The tissue was created using a 3 cm Aluminum part, and drilled in the center to allow for the needle insertion (Fig.61). The hole was 0.049”, which is slightly bigger than the needle outer diameter. Any gap between the needle and the mock tissue was sealed using conductive paste (Halnziye HY710 20g Tube Syringe Silver Thermal Paste). The body temperature environment was created using a New Era heater (New Era Pump System Inc, USA) where the primary heating pad was wrapped around the Aluminum part (Fig. 62).

*Figure 61.* Top and side views of the mock tissue created using Aluminum part of 3cm length. The part was drilled with a 0.049” drill bit to allow for the needle insertion.
Figure 62. Primary heating pad and the heating pad connector. The primary red heating pad is wrapped around the Aluminum part and a temperature set point of $37^\circ$ C was adjusted to create the body temperature conditions around it.

3.2.4.1.2 Mathematical model. Our mathematical model was created to predict the fluid delivered temperatures when injected under body temperature conditions inside a mock endoscopic ultrasound and the FNI-Needle.

a. Geometry

Fig. 63 shows the geometry of the delivery system with the FNI-Needle. This geometry is similar to model 2 except that we added the FNI-Needle to the system.
Figure 63. Schematic of the mock EUS system This figure shows a CoolGuide sheath (1), a Mock EUS (2), an embedded layer of plastic (PVC) (3) and an air region surrounding the CoolGuide sheath (4). The system is 1.53 m long including a 1.2m of mock EUS.

To accurately predict delivered temperature, two different needle positions were modeled, 1) fully eccentric, and 2) needle touching the coolant lumens (Fig.64). Modeling revealed which needle orientation will better match the experiments.
Figure 64. Needle orientations within the CoolGuide sheath. Two configurations were studied (a) needle touching the CoolGuide bottom wall and, (b) needle touching the coolant wall. The second configuration (b) was the closest to experimental set-up.

Table 14

*Dimensions of the CoolGuide™ sheath*

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Dimension(cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoolGuide™ sheath Length</td>
<td>153.0</td>
</tr>
<tr>
<td>Needle length</td>
<td>65.0</td>
</tr>
<tr>
<td>EUS “Body Temperature” Warming Loop</td>
<td>173.0</td>
</tr>
<tr>
<td>EUS length</td>
<td>125.0</td>
</tr>
<tr>
<td>CoolGuide™ sheath Outer diameter</td>
<td>0.267</td>
</tr>
<tr>
<td>CoolGuide™ sheath Inner diameter</td>
<td>0.157</td>
</tr>
<tr>
<td>Coolant lumen hydraulic diameter</td>
<td>0.0458</td>
</tr>
</tbody>
</table>

b. Governing equations

Similarly, to Model 1 and 2, the flow is assumed to be governed by the laminar Navier-Stokes equations, mass conservation and energy conservation.
c. Boundary and initial conditions

The boundary conditions were fixed in a manner suitable to reproduce the experimental conditions. The model consists of two domains, the fluid domains for hydrogel, and distilled water flow, as well as the solid domains for the CoolGuide sheath, the air, the needle and the mock EUS. The thermal boundary condition between the solid and fluid is a conjugate heat transfer. The continuity was ensured at the fluid-solid and solid-solid interfaces. Description of the boundary conditions is provided below (Fig.65 and Table.15):

- 0.650 m of the mock EUS (Outer layer surrounding the CoolGuide™ will be held at a constant temperature equal to the temperature of the body (37.5°C).
- All CoolGuide™ walls apply the no slip condition, which constrains the velocity to zero along it.
- The hydrogel and water will be injected at variable mass flow rates and constant temperature inside the center lumen.
- The coolant (distilled water) will be injected at constant mass flow rate and Temperature.
- A pressure outlet was assigned to the hydrogel and coolant outlets
- The CoolGuide sheath and the needle outside the EUS and the body were insulated.
- The 3 cm needle was surrounded by body temperature.
Figure 65. Schematic of the Mock EUS system with the boundary conditions. This includes hydrogel and coolant inlet temperatures and mass flow rates as well as the wall boundary conditions applied to the needle, the CoolGuide sheath and the mock EUS.
Table 15

*Boundary conditions imposed on the CoolGuide™ model*

<table>
<thead>
<tr>
<th>Boundary</th>
<th>Boundary Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water/hydrogel inlet</td>
<td>Mass Flow Rate</td>
<td>1ml/min - 5ml/min</td>
</tr>
<tr>
<td>Water/hydrogel inlet temperature</td>
<td>Temperature</td>
<td>1ml/min - 5ml/min</td>
</tr>
<tr>
<td>Water/hydrogel exit [output]</td>
<td>Pressure outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Coolant inlet</td>
<td>Mass Flow Rate</td>
<td>40-45 ml/min</td>
</tr>
<tr>
<td>Coolant inlet temperature</td>
<td>Temperature</td>
<td>5-7 °C</td>
</tr>
<tr>
<td>Coolant exit</td>
<td>Pressure outlet</td>
<td>0 [Pa]</td>
</tr>
<tr>
<td>Outer wall (Inside body)</td>
<td>Temperature</td>
<td>37.5°C</td>
</tr>
<tr>
<td>Outer wall (Outside body)</td>
<td>Temperature</td>
<td>30°C</td>
</tr>
<tr>
<td>Outer wall of the needle</td>
<td>Insulated</td>
<td>0 W/m²</td>
</tr>
<tr>
<td>CoolGuide sheath outer wall</td>
<td>Insulated</td>
<td>0 W/m²</td>
</tr>
<tr>
<td>Outer wall of the 3 cm needle (outside of the EUS)</td>
<td>Temperature</td>
<td>37°C</td>
</tr>
</tbody>
</table>

d. Material properties

Two different fluids were tested and modeled: 1) distilled water and 2) Pluronic F-127 Hydrogel.

The solid domains include, 1) the CoolGuide™ sheath which is made of Pebax with a thermal conductivity of 0.29 W/m·C, 2) the Endoscopic Ultrasound made of stainless steel,
3) the needle made of Nitinol and, 3) the plastic part made of PVC. Table 16 lists the different materials used in the models.

Table 16

*Materials properties of the different fluids and solids used in the 3D model.*

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (kg/m³)</th>
<th>Dynamic viscosity (Pa·s)</th>
<th>Specific heat (J/kg·K)</th>
<th>Thermal conductivity (W/m·C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled Water</td>
<td>999.6</td>
<td>Variable¹</td>
<td>4186</td>
<td>Variable²</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>1000</td>
<td>Variable³</td>
<td>4186</td>
<td>Variable²</td>
</tr>
<tr>
<td>Sheath (Pebax)</td>
<td>2160</td>
<td>-</td>
<td>1125</td>
<td>0.29</td>
</tr>
<tr>
<td>EUS (Stainless Steel)</td>
<td>7500</td>
<td>-</td>
<td>910</td>
<td>15.06</td>
</tr>
<tr>
<td>Plastic (PVC)</td>
<td>1400</td>
<td>-</td>
<td>840 - 1170</td>
<td>0.19</td>
</tr>
<tr>
<td>Air</td>
<td>1.225</td>
<td>-</td>
<td>1000</td>
<td>0.02633</td>
</tr>
<tr>
<td>Needle (Nitinol)</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
</tr>
</tbody>
</table>

(1) Function found in appendix C  
(2) Function found in appendix D  
(3) Function found in Eq.2.12

e. Mesh study

For the conjugate heat transfer problem, we generated a polyhedral mesh and additional prism layers were activated on the fluid side of the fluid-solid interface. The solid part had
no prism layers. Fig. 66 shows the final mesh generated (19.8 cells). Fig. 67 shows a close up section of the Mock EUS system mesh.

**Figure 66.** Final mesh for the mock EUS system including 52018295 cells. The volume mesh was generated using polyhedral cells

**Figure 67.** A close-up section of the mesh generated for the mock EUS system. The volume mesh was generated using Polyhedral cells and 4 prism layers were added to the fluid-solid interface to resolve the boundary layer.
3.2.4.2 Model validation. Validation without the mock tissue: The delivery system was first validated without the mock tissue. The 3cm needle out of the mock EUS was only exposed to ambient conditions for simplification.

The aim of this work is to demonstrate the CoolGuide™ sheath ability to control distilled water temperatures for a range of flow rates. The flow rates were varied from 1ml/min to 5 ml/min with 1ml increment. Through these tests we can gauge the system’s ability to maintain the temperature of the delivered fluid below body temperature and hydrogel transition temperature.

An accuracy check was performed to validate the mock EUS system with water as the tested fluid. We chose water for simplicity reasons. Two needle orientations were modeled (Fig.64) to investigate the impact of its orientation on the delivered temperature.

Numerical models were validated with experiments. Fig. 68 shows the water delivered temperatures as a function of the flow rates. The temperature behavior showed that all model predictions for configuration (a) were within 2 % of experimental data. However configuration (b) was approximately 30 % off from the actual data.

Results showed that configuration ‘a’ is closer to experiments. This was expected because the needle was not fully eccentric inside the CoolGuide sheath but most of the time touching the coolant wall.
Figure 68. Water delivered temperature as function of the delivery length using FNI-Needle. The numerical solution using the two different configurations was compared to experimental results. Configuration (b) delivered lower temperature compared to Configuration (a).

There is a 5 C difference in the temperature prediction with the two different configurations. This is due to the orientation of the needle inside the CoolGuide sheath. For configuration (a), the needle is in contact with the bottom of the sheath which is touching the warm wall of the EUS (37 C). This causes the needle to be situated in the region of the air that is exposed to warmer temperatures. For configuration (b), the needle is exposed to the surface adjacent to the coolant lumen. Therefore, the final results will be...
depending on the needle location within the CoolGuide. Fig. 69 and 70 show how the cooling of the fluid circulating inside the needle differs for the two cases.

**Figure 69.** Water temperature distribution at a cross section of the EUS system using the two different needle orientation inside the CoolGuide sheath (from left to right, Configuration “a” and “b”). The placement of the needle towards the coolant lumens (Configuration

**Figure 70.** Water temperature distribution at the exit showing the difference between the two needle locations inside the CoolGuide sheath. Placing the needle against the solid surface adjacent to the external warm regions leads to higher temperatures at the exit.
a. Validation with the mock tissue

ai. Water delivered temperature

The Mock EUS system was validated with a mock tissue surrounding the needle. Configuration.2 of the needle was used in our modeling since it is the closest to the experimental results. Fig. 71 shows the delivered temperatures as a function of the water flow rate. Numerical solution was compared to experimental work and a reasonable match between the two approaches was noticed. Some errors could be attributed to experimental work limitations such as maintaining the mock tissue at body temperature. The standard deviation for the flow rates 2ml/min and 3ml/min were approximately twice the other standard deviations due to some experimental errors caused by the mock tissue temperature which was hard to maintain at body temperature condition. This leads the exit temperature to drop for some cases.
Figure 71. Water exit temperature as a function of the flow rate. Results are a comparison between numerical solution and experimental work. Error bars present the standard deviation between three data sets.

a.ii. Water delivery pressure

Water delivery pressure was validated with experiments. Fig. 72 shows a comparison plot between the numerical solution and the experimental work. The average error between the numerical solution and experimental work was about 10.5%. Some differences in the predicted values could be attributed to some uncertainties about the actual inner diameter of the needle. There is a strong relationship between the diameter and the pressure drop and any difference could affect the final results. For this reason, two different inner diameters were modeled. The ID of 0.92 mm gave more accurate results compared to experimental work.
Figure 72. Pressure variation as a function of the water flow rate. The experimental data were compared to three numerical solutions: 1) EES model, 2) CCM+ prediction with an inner diameter of 0.88mm, and 3) CCM+ prediction with an inner diameter of 0.92mm.

a.iii. Temperature distribution along the injection pathway

As soon as the hydrogel exits the temperature controlled region (location 1) shown in Fig. 73 and enters the 3cm needle it warms up and exits the needle at almost body temperature (Location 4). Fig. 74 shows the temperature distribution along the 3 cm needle out of the mock EUS system and at the four different locations (Fig.73). This region is heated with body temperature, and since the flow is very slow, the fluid delivered warms up quickly as soon as it exits the controlled region. The exit temperature at the exit of the mock EUS (location 1) is 13.1°C for a flow rate of 3ml/min, however it exits the needle at almost body temperature.
Figure 73. Schematic showing the four studied locations along the 3cm heated needle.

Figure 74. Water Temperature distribution along the 3cm portion of the needle. The temperature distribution was plot at locations 1, 2, 3 and 4.
Modeling results showed that the CoolGuide sheath was able to control water temperature along the portion of the needle inside it. Fig. 75 shows the temperature profile of the water along the 3cm needle. As soon as it exits the temperature controlled region the water temperature hits body temperature.

**Figure 75.** Hydrogel temperature distribution along the 3 cm needle for the flow rates of 2 ml/min and 4ml/min. The hydrogel temperature rises until it reaches almost body temperature as soon as it leaves the temperature controlled region.

a.iv. Validation with 30% Pluronic F127 hydrogel

Fig. 76 shows the hydrogel exit temperatures as a function of the flow rates. As the flow rate increases, the exit temperature decreases but still higher than 30 °C. The numerical model predicted the delivered temperatures within an average of 0.9 °C for all flow rates tested. The average error between numerical solution and experimental results was about
3%. These differences are due to some measurement uncertainty related to the different probes used in the experimental setup especially the probe measuring the exit temperature.

Figure 76. Hydrogel Delivered temperature as a function of the flow rate. This plot is a comparison between the numerical solution and experimental data.

Fig. 77 shows the delivery pressure for the different flow rates. Experiments and modeling showed that the hydrogel is injectable under body temperature conditions with reasonable pressures that are below the syringe pump pressure limit (100 psig).
Data and modeling results showed that thermosensitive hydrogel was injectable through the delivery system. Modeling and experiments showed that the hydrogel was leaving the tip of the needle at almost body temperature (gel form), however modeling results showed that the hydrogel at the exit of the temperature controlled zone was in liquid form at a temperature of 13.1 °C. The hydrogel was heated quickly at the 3cm needle due to the low flow rates and the high conductivity of the needle. Without a temperature controlled sheath the hydrogel pumping through the needle would be impossible. Fig.78 shows the temperature distribution without the temperature controlled sheath.

*Figure 77. 30% Pluronic hydrogel delivery pressure at different flow rates. This shows a comparison plot between numerical solution and experiments.*
Figure 78. Hydrogel delivery temperatures and viscosity distribution without the temperature controlled sheath. The hydrogel delivery pressure required is unrealistic (3000 Pa-s) and the hydrogel delivery temperature is close to body temperature.
Chapter 4

Hydrogel Temperature Control Refinement

The objective of this chapter is to enhance the hydrogel delivery system capabilities. We aim to optimize the original CoolGuide™ sheath design to achieve better cooling by improving the temperature control and reducing the delivered temperatures.

4.1. Thermal Fluid Model Assessment

In this study, thermal fluid models were developed, explored and compared to experimental data to investigate the CoolGuide™ sheath ability to control and deliver lower temperatures fluids for medical treatment. The study showed that the CoolGuide™ has the ability to, 1) control fluid temperatures as they were injected under body temperature conditions, and 2) reduce delivered temperatures.

Even though the work established a confident framework for possible pancreatic cancer treatment, it has some limitations. The original CoolGuide™ catheter was designed for heart cooling application, thus it should be optimized to improve temperature control performances.

4.2. Device Design Refinement

4.2.1 Refinement goals. The goal was to allow a boarder range of possible designs for the CoolGuide™ sheath to deliver hydrogel deeper inside the body. Features such as the coolant lumen cross sectional area and the central lumen will be refined to
improve temperature control capabilities. We seek to deliver thermosensitive hydrogels under the LCST and keep it liquid along the injection pathway.

In chapter 3, it has been demonstrated that the needle location within the CoolGuide™ strongly impacts the delivered temperatures. The closer the needle to the coolant walls, the cooler the exit temperature will be. Therefore we decided to explore CoolGuide™ designs that will allow the needle to be touching the coolant walls or completely surrounded by them.

**4.2.2 Refinement protocol.** The CoolGuide™ sheath was redesigned to allow for lower hydrogel delivered temperatures. Unfortunately the 3cm part of the needle could not be controlled because it has to stick inside the tumor to allow for the drug injection.

For refinement, features of the CoolGuide sheath will be modified to help improve temperature control along the injection pathway. To achieve that, we will change the coolant lumens geometry to allow for a better cooling. By modeling the new design of the sheath we will investigate the impact of the coolant lumens on the hydrogel delivery through the delivery system. A concentric design (Fig.78) was explored, here the coolant lumens are surrounding the central lumen from all sides to allow for better cooling.

The inner lumen diameter was also optimized for the eccentric model to reduce the air gap between it and the needle. This will allow for a better cooling of the hydrogel.
a. Geometry

Fig. 79 shows the geometries of the two different designs used for optimization purpose. The two sheath designs were modeled separately inside the EUS system. Model A represents the concentric design, here the coolant lumens were refined. Model A is the same as the original model except that the central inner lumen was refined, the ID was reduced by 40%.

Model A
Model B

Figure 79. Two different CoolGuide designs emphasizing the refined features. Model A shows the concentric design. Model B shows the optimized eccentric design.
b. Governing equations

The same governing equations as model 3 were used in this model. This includes the Navier-Stokes equations (Eq. 2.1), the conservation of mass (Eq. 2.2) and the conservation of energy (Eq. 2.6).

c. Boundary conditions

Boundary conditions from Model 3 were used for the optimized models (Table 15).

d. Mesh

A mesh study was conducted on both optimized models (concentric and eccentric). The final mesh generated for both models was polyhedral mesh with prism layers. Model A includes the concentric sheath and has 27 million cells, model B includes the eccentric sheath and has 25 million cells.

*Figure 80.* Mesh generated for the two different models. Model A includes the concentric sheath and has 26925529 cells, model B includes the eccentric sheath and has 25477979 cells.
e. Material properties

Same material properties as the original design were used for both optimized models (Table 16).

4.3. Optimization Outcomes

4.3.1 Temperature profile at the exit of the sheath. Fig. 81 shows the hydrogel exit temperatures at Location 1 (Fig. 71). The plots are a comparison between the two optimized models and the original CoolGuide™ design. The two optimized models reduced the delivered temperature and improved the cooling capabilities. The optimized eccentric design reduced the average exit temperature by 54% while the concentric design reduced the exit temperature by 37%. This difference in performance is due to the difference in the two geometries. The concentric design allows for a larger area of the central lumen thus, the hydrogel to be cooled.
Figure 81. Comparison plot between the three different sheath designs in terms of needle temperature at the exit of the sheath.

a. Temperature distribution along the 3 cm needle (Comparison between original design and the optimized eccentric

Fig.82 shows the temperature variation along the 3 cm needle for the two different design configurations. Although the hydrogel exits at the same temperature with the two different designs, the Eccentric optimized model showed its ability to deliver lower temperatures along the 3 cm needle.
Figure 82. Hydrogel temperature distribution along the 3cm needle length for a hydrogel flow rate of 2 ml/min. The plot is a comparison between the original design and the optimized eccentric design.

4.3.2 Delivery pressure. Fig. 83 shows the delivery pressure comparison plot between the two optimized models and the original CoolGuide™ design. The two optimized models reduced the delivery pressure. The optimized eccentric design reduced the average delivery pressure by 60 % while the concentric design reduced the average delivery pressure by 24 % relative to the original design.
Figure 83. Pressure drop variation with hydrogel flow rates. The plot is a comparison between three different sheath configurations. Design optimization lowered delivery pressure.

a. Temperature distribution at the exit

To explore the different designs cooling capabilities, cross sectional plots of the temperature distribution at the exit location were displayed. Fig. 84 shows the temperature distribution at the exit along the CoolGuide, needle, hydrogel and air regions for the three different designs. This figure aims to emphasize the heat transfer process between the coolant lumens and the hydrogel inside the central lumen. Model B reduced the average exit temperature by 54% while Model C reduced the exit temperature by 37%.
Figure 84. Hydrogel temperature distribution along a cross sectional area at the sheath exit showing the three different sheath designs. The optimized models have shown a lower temperature distribution across the sheath and the needle compared to the original design.
Chapter 5

Conclusion and Future Work

This chapter provides a summary of the work conducted in this thesis and the challenges faced. We will also discuss the limitations of the models and suggest recommendation for future work for improvement.

5.1. Re-Statements

In this work, the hydrogel delivery under body temperature conditions was challenging due to its thermosensitive properties that leads to a sharp increase in viscosity. A temperature controlled sheath was used along the injection pathway to help keep the hydrogel below its phase transition temperature (LCST).

We developed thermal fluid models to investigate the cooling performances of the temperature controlled sheath that helps deliver thermosensitve hydrogels using an EUS system and an FNI-Needle under body temperature conditions. All models were validated with in-vitro testings.

The first model used a finite volume method to investigate the cooling performances of a CoolGuide catheter to deliver blood analog at lower temperatures than body temperature to save heart tissue. This model was validated with experiments inside a mock cardiovascular system. Blood analog was the working fluid with a temperature dependent viscosity. The study showed that the catheter delivered temperatures within 1°C for high flow rates and 2.5°C for low flow rates compared to experimental work. Even though there
are some errors between the different results, the cooling capacity of 20 W was exceeded for a flow rate greater than 25ml/min which is in good agreement with published data. The exit temperatures and cooling capacity are dependent on the blood analog mass flow rate.

In the second model, a modified version of the CoolGuide catheter now called CoolGuide sheath was used with an EUS system without an FNI-Needle to help deliver thermosensitive hydrogels under body temperature conditions. For validation, two fluids were used 1) water and, 2) Pluronic F127 hydrogel (30% by volume). Distilled water was first injected into the system to show the ability of the CoolGuide sheath to control the tested fluid temperatures. The water was modeled as a Newtonian fluid with a temperature dependent viscosity. However, the hydrogel was modeled as a shear and temperature dependent fluid using the Power-Law-WLF model with consideration of a temperature shift factor. This equation correlates the hydrogel viscosity to the shear and temperature dependency. The flow rates were varied from 1ml/min to 5 ml/min with 1ml increment. Results showed that the CoolGuide sheath has the ability to control fluid temperature and deliver the fluid below its LCST.

The third model, was validated using the same in vitro set-up as the second model with the addition of an FNI-Needle. The FNI-Needle was placed inside the CoolGuide sheath and hydrogel was injected through it.

The numerical model predicted the delivered temperatures within an average of 0.9 °C for all flow rates tested. The average error between numerical solution and experimental results was about 3%.
In model 4, we provided possible CoolGuide sheath design refinements to improve delivery outcomes. Two different sheath designs were explored. Both designs showed their ability to reduce delivered temperatures for the different flow rates compared to the actual design and improve temperature control.

5.2. Limitations of the Work

Each of the models described in this thesis have some limitations. Model 1, utilized the blood analog as a Newtonian fluid with a temperature dependent viscosity.

For model 2 and 3, an obvious limitation was related to the hydrogel thermal fluid properties: density, thermal conductivity, specific heat, and dynamic viscosity. In this study the hydrogel viscosity was modeled using the power law model with the temperature shift factor. The coefficients C1 and C2 were assumed to be constant and derived from the literature. The other properties of the hydrogel were assumed to be equal to water.

Another limitation was related to the fidelity to estimate fluid exit temperature because there is a potential for large offsets between actual exit temperature and that reported by a probe located in the exit as described in Chapter 3. The use of mixers at the exit would have helped the tested fluid to mix properly to allow for an accurate measurement. However, there are definitely challenges to implementing this technique. Given the flow rates of the water and hydrogel passing through the CoolGuide sheath, this may lead to elevation of the temperature exiting the sheath before reaching the probe causing inaccurate temperature measurement.
5.3. Future Work

This work demonstrated the efficacy, feasibility, and safety of using a temperature controlled device to successfully deliver hydrogels.

Future work will include the use of a real endoscope in the experimental to accurately mimic the real EUS application. The approach of exit temperature measurement should be improved for more accurate results. The thermal fluid model should take into consideration that the coefficients $C_1$ and $C_2$ of the temperature shift factor are determined based on a rheology study of the Pluronic F-127. The exact values based on experimental work will improve modeling outcomes.

Model 4, was only a CFD prediction. Even though these models showed the ability of the refined CoolGuide™ designs to reduce hydrogel delivered temperatures for a range of flow rates, experimental work is needed to validate these models and build confidence for future applications.

Another issue that needs to be addressed is the temperature surrounding the 3 cm needle. Insulation could be provided at that portion of the needle to prevent hydrogel transitioning. The Insulon® device (Fig. 83) could present a thermal barrier to limit the heat exchange at the 3cm needle, which will help achieve lower delivered temperatures. This device works fine even for components surrounded by extremely high or low temperatures from -321 to 2000 F.
Figure 85. Insulative ideas for the 3 cm needle to prevent hydrogel transitioning [33]. The thermal barrier helps prevent heat exchange with the body temperature environment.

Other hydrogel types and concentrations could be explored in future studies. In fact, Pluronic F127 has been shown to have poor mechanical stabilities and cannot sustain drug release over a long period of time at body temperature. This work sets the stage for the study of the diffusion of the drugs from hydrogels within the pancreatic cancer lesions.
**References**


[17] “Schematic illustration of the micellar phases formed by the Pluronic.” [Online]. Available: https://www.google.com/search?q=Schematic+illustration+of+the+micellar+phases+formed+by+the+Pluronic+(hydrogel)+with+increasing+temperature&biw=2133&bih=1021&source=lnms&tbm=isch&sa=X&ved=0ahUKEwj80sTDpe7MAhXFXh4KHeHCsUQ_AUIBigB&dpr=0.9#imgrc=zOOEpgGCGF1Q. [Accessed: 01-Jan-2016].


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Appendix A

Equation of the Viscosity as a Function of Temperature for the Glycerol Mixture (38% by volume)

\[
\mu (T)=10.31\exp(-0.035T) \tag{31}
\]

where, \(\mu\) is the dynamic viscosity of the Glycerol mixture (cp), and \(T\) is the temperature (°C)[34]
Appendix B

Maxwell Derivation for Thermal Conductivity Composite [35]

\[
\frac{k_{\text{eff}}}{k_0} = \frac{3\phi}{k_1 + 2k_0 - \phi},
\]

(32)

where,

\(k_{\text{eff}}\) effective thermal conductivity (W/m.K)

\(k_1\) thermal conductivity of embedded material (W/m.K)

\(k_0\) thermal conductivity of continuous phase (W/m.K)

\(f\) : volume fraction of embedded material
Appendix C

Water Viscosity

Table 17

*Water viscosity as a function of temperature*

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<th>Temperature (C)</th>
<th>Viscosity(Pa-s)</th>
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<tr>
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</table>
Appendix D

Thermal Properties of Water

Figure 86. Thermal properties of water [36]