Title
Optical Coherence Tomography–Guided Robotic System for Automated Retinal Microsurgery

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ABSTRACT OF THE DISSERTATION

Optical Coherence Tomography–Guided Robotic System
for Automated Retinal Microsurgery

by

Matthew Gerber
Doctor of Philosophy in Mechanical Engineering
University of California, Los Angeles, 2019
Professor Tsu-Chin Tsao, Chair

Retinal vein occlusion is one of the most common disease-related causes of vision loss. It occurs when a blood clot or other obstruction occludes a retinal vein inside the eye. While treatment options exist, there is no cure. One potential remedy is retinal vein cannulation, a surgical procedure where the occluded vein is cannulated and infused with an anticoagulant to dissolve the obstruction. However, due to the physiological limitations of human surgeons—including hand tremor and limited resolution of depth perception—retinal vein cannulation remains only a theoretical practice.

This work presents a robotic system capable of performing automated retinal vein cannulation on custom retinal vein phantoms. The system is integrated with an optical coherence tomography probe to provide depth information in the form of visual imagery. Through the automation of critical procedural steps, the developed system reduces the challenges of vein access and infusion to a simple guidance problem with only a single degree of freedom.

The developed system was evaluated through a set of trials and shown to be capable of performing retinal vein cannulation with minimal surgical complications. The developed technology is expected to lead to improvements in other vitreoretinal surgical procedures which are difficult or infeasible to perform with traditional techniques.
The dissertation of Matthew Gerber is approved.

Dennis W Hong

Jean-Pierre Hubschman

Jacob Rosen

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University of California, Los Angeles

2019
“You will never amount to anything.”

My 8th-grade English teacher, Mr. Thery, said this to me in Junior High School.

I hope my success proves him wrong.
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CHAPTER 1

Introduction

Robotic systems have found widespread use across many surgical applications due to their increased precision, higher maneuverability, and improved visualization over traditional surgical techniques. For example, the da Vinci Surgical System (Intuitive Surgical, Inc.) is the most prevalent robotic system in the world having been used to perform more than 1.5 million surgical procedures in the fields of gynecology, urology, and general surgery [Int17]. In comparison, the adoption of robotic systems into intraocular surgical practice has been limited. This low degree of acceptance can be attributed to the unique advantages of intraocular surgery which may lessen the beneficial impacts of using a robotic system. These benefits include the minimally invasive nature of intraocular procedures, the unobstructed and high-magnification views of the surgical field, and the high maneuverability and large range of motion of manually controlled surgical instruments.

Despite these advantages, intraocular surgery remains challenging for surgeons to perform. Physical control of the surgical tool must be accomplished with exceptionally high accuracy and precision in a tiny workspace. The scale of these manipulations is so small that intrinsic physiological hand tremor becomes a substantial concern. In result, the ability to accurately target a specific anatomical site or hold the surgical tool stationary for prolonged durations is difficult or impossible. Also, humans have limited resolution when it comes to depth perception [HHH17]. This limited resolution is insufficient to accurately sense the distance between the surgical tool and the retina during vitreoretinal surgical procedures.

For these reasons, robotic systems offer a promising solution to the aforementioned human limitations because a robotic system can facilitate precise, tremor-free motion and offer
increased depth resolution through a variety of integrated imaging modalities such as digital microscopy and optical coherence tomography (OCT). By improving resolution and accuracy of depth-sensing capabilities, such unified systems would naturally increase both the safety and efficacy of surgical procedures. Additional benefits of robotic surgery in ophthalmology include collaborative capabilities for specific procedures (partially to fully automated) and the integration of augmented feedback.

1.1 Main Contributions

This work develops an automated robotic system for the purpose of performing retinal vein cannulation—a surgical procedure which remains theoretical in practice due to its technically challenging nature. While other research groups have demonstrated successful retinal vein cannulation with in vivo pig eyes and on live human patients (Section [3]), the current work aims to supersede the existing work by automating critical steps of retinal vein cannulation and providing augmented vision guidance through an integrated OCT system. These advances promise improved safety and efficiency through enabling high-resolution depth-sensing capability and reducing the complexity of vein access to simple guidance of a single degree of freedom for the surgeon.

The main contributions of this work are:

1. Accurate ($\leq 20$ $\mu$m) targeting of a vein cannulation site in the presence of large ($300–400$ $\mu$m) positional uncertainties

2. Provision of fast (10 Hz), augmented visual feedback of micropipette depth via OCT during the critical vein cannulation step

3. Simplification of vein access to guidance of a single degree of freedom and a single-decision problem for the surgeon

These contributions were validated by performing automated retinal vein cannulation on 30 custom retinal vein phantoms.
This dissertation is organized as follows. Chapter 2 introduces the problem statement and provides the clinical motivation. Chapter 3 provides a review of existing intraocular robotic systems. Chapter 4 describes the robotic system and the OCT system used in this work. Chapter 5 describes the custom retinal vein phantom. Chapter 6 forms the bulk of the work and describes the technical approach to performing automated retinal vein cannulation on the custom retinal vein phantoms. Chapter 7 shows the experimental validation results. Finally, Chapter 8 concludes and discusses areas of future work.
CHAPTER 2

Problem Statement and Clinical Motivation

The human eye is the second most complex organ in the human body after the brain. Like any organ, it is susceptible to disease and impairment. One such impairment is retinal vein occlusion (RVO), which affects approximately 2% of the population of the United States \[LCL11\]. RVO occurs when a blood clot or other obstruction occludes a retinal vein inside the eye. In a healthy individual, these veins carry blood away from the retina, but in the case of RVO, the vein is occluded and the blood flow is diminished or stopped. RVO can cause vision loss through macular edema, glaucoma, and vitreous hemorrhage. In macular edema, blood leaking onto the macula causes swelling resulting in blurring or loss of vision. In glaucoma, RVO can cause pain and a dangerous increase in intraocular pressure. In vitreous hemorrhage (Figure 2.1), RVO causes the affected vein to leak blood into the vitreous and may result in retinal detachment. However, despite the high prevalence rate of RVO, there is currently no cure. Common treatments address only the symptoms and involve steroid injections or focal laser therapy.

One potential cure for RVO is retinal vein cannulation (RVC). In this technique, a micropipette is used to infuse an anticoagulant into the affected vein to dissolve the obstruction (Figure 2.2 \[HZ15\]). The anticoagulant must be infused over a prolonged duration (≥ 10 min) and therefore, the micropipette must be held stationary inside the vein for the entire infusion period. However, retinal vein diameters are approximately 120–200 µm (Table 5.2) while human hand tremor is approximately 200–350 µm (Figure 2.3 \[RRK97\]). Therefore, RVC is challenging for a surgeon to perform and remains only a theoretical practice. However, the motion stability and precise positioning requirements of RVC are not prohibitive to a robotic system and research in this area has increased in the past decade (Section 3).
In addition to physical limitations due to hand tremor, surgeons also suffer from limited resolution of depth perception [H17]. Specifically, the human ability to accurately ascertain the distance between the tip of a surgical tool and intraocular tissue is limited. It is common practice for surgeons to rely on indirect visual cues such as cast shadows or color change, which are insufficient indications of exact depth measurements. This deficiency
further complicates RVC. The research groups that have used a robotic system to perform RVC on *in vivo* models (Section 3) all reported difficulty in correctly assessing successful cannulation due to limits in visualization.

Finally, like most vitreoretinal surgical procedures, RVC is expected to be a complex, stressful guidance problem. The surgeon would be required to safely guide the micropipette through the eye while avoiding collateral damage, approach the vein, adjust the lateral positioning of the micropipette while controlling depth and infusion—all while maintaining a stable pivot point about the surgical incision in the sclera. In addition, the introduction of a robotic system into the surgical workflow to overcome these challenges may actually *increase* the surgeon’s cognitive load due to the system’s unfamiliarity.

It is the goal of this work to develop a robotic system that can guarantee successful vein access while reducing the cognitive load on the surgeon during RVC.
CHAPTER 3

Existing Intraocular Robotic Systems

3.1 Surgical Robotic Systems in Ophthalmology

Intraocular robotic surgical systems have been applied in both anterior and posterior segment surgery. This review focuses on active research projects that have been used to perform retinal vein cannulation (RVC). One method to categorize the range of intraocular robotic surgical systems is according to the degree of human vs. robotic control (Figure 3.1).

1) In traditional surgery, a surgeon controls the surgical tool(s) and uses an optical microscope as visual feedback.

2) In a robot-assisted tool, the surgical tool itself is modified to be a miniature robotic system. The surgeon controls this tool to perform a hands-on surgical procedure while the robotic tool offers tremor cancellation, depth-locking capabilities, and other features.

3) In teleoperated robotic surgery, the surgeon controls a robotic system through joysticks and uses an optical microscope or digital heads-up display as visual feedback. The joystick motion is mapped to robotic motion and therefore advantages such as haptic feedback, tremor filtering, and motion scaling can be implemented.

4) In a cooperative robotic system, the surgeon holds and controls the surgical tool simultaneously with the robotic system and uses a microscope and optical coherence tomography (OCT) as visual feedback. The surgeon maintains manual control over the motion of the surgical tool while the robotic system provides assistive compensation for hand tremor and allows for prolonged immobilization of the surgical tool.
5) Finally, in an automated system, the robotic system is integrated with the microscope and OCT system to provide feedback and guidance to the motion commands of the robotic system, which holds and operates the surgical tool(s). Specific procedures or steps of a procedure are automatically performed by the robotic system while the surgeon supervises through the provided visual feedback. Override commands are commonly offered.

A representational example of a robot-assisted tool, Figure [3.1(b)], is the MICRON (Figure [3.2]), a hand-held manipulator developed in 2010 through a collaboration between the Robotics Institute at Carnegie Mellon University and Johns Hopkins University [MBT11]. The MICRON incorporates a Gough-Stewart platform that constrains the remote center of motion near the tool tip. The tool demonstrated trajectory-following errors of $\leq 20 \mu m$ and a 90% reduction in hand tremor [YMR14]. Most recently, the researchers demonstrated the ability to detect the puncture of a stretched vinyl membrane by integrating a force-sensing needle into the tool [GCG17]. In addition, the group also demonstrated an automated position-holding feature that allowed the tool tip to be held stationary for longer periods of time with significantly reduced tool-tip motion after venipuncture. However, this system still relies on human guidance during vein access and cannulation. Furthermore, the system provides no additional visual feedback beyond the standard surgical microscope.

A representational example of a teleoperated robotic system, Figure [3.1(c)], is the Preceyes Surgical System (Figure [3.3]). This system was developed at the Eindhoven University of Technology in the Netherlands and is currently undergoing clinical testing through Preceyes B.V., a spin-off company of the university. The robotic system is comprised of an input joystick held by the surgeon and a robotic system which controls the surgical instrument and performs the physical manipulation of intraocular tissue. By moving the input joystick, the surgeon can guide the motion of the tool through the incision and throughout the intraocular workspace.

The design of the Preceyes is based on a parallelogram linkage common to many surgical robotic systems. This design offers a mechanical remote center of motion and improved
Figure 3.1: Varying degrees of human and robot control in intraocular surgical setups.

tool-tip positional precision over serial linkages. The authors report a tool-tip positional resolution of 10 µm and initially demonstrated the capabilities of the system by creating venous occlusions in live, anesthetized pigs [SSM16].
In 2018, the Preceyes Surgical System was used to conduct a clinical trial to compare robot-assisted surgery with traditionally performed surgery [EXM18]. In this study, a set of trials was performed in patients requiring sub-retinal injection, a procedure with very similar requirements and constraints as RVC. Three patients were placed under local anesthesia and the robot assisted in the delivery of 0.025–0.10 ml of anticoagulant into the sub-retinal space. Indicative of the safety of the robotic system, the robot-assisted procedures resulted in fewer overall inadvertent retinal touches and micro-hemorrhages across all trials. However, the system relies on a standard surgical microscope as visual feedback and likewise suffers from limited resolution of depth perception.

In 2013, the Department of Robotics and Embedded Systems at the Technical University of Munich introduced RAM!S (Figure 3.4), a hybrid parallel–serial mechanism that includes piezoelectric motors for actuation [NEN13]. Kinematically, the mechanism consists of two joints coupled in parallel, one prismatic joint, and one optional revolute joint to collectively enable six degrees of freedom of tool motion. The researchers claimed the advantages of
this mechanism included higher stiffness and increased precision over more common serial mechanism designs. RAM!S is also physically compact (94±28×33.5×18.5 mm) and designed to secure to the head of a patient to mitigate the effects of patient motion. Additional cited metrics include a tool-tip positional precision of 5 µm, a total weight of 306 g, and a tool-tip workspace of 28 × 28 × 28 mm.

The same team developed a virtual-fixture control method and experimentally evaluated its use on an *ex vivo* pig eye. These virtual fixtures included the virtual constraint and autonomous adjustment of the remote center of motion. Additional work used the RAM!S device to develop teleoperated capabilities. Using a controller that featured force feedback, a control scheme for the positional error was implemented. The resulting system allowed the surgeon to perform precise and comfortable manipulation.

In their latest work, the performance of the software-constrained remote center of motion was evaluated through a series of experiments using a tissue model and *ex vivo* pig eyes.
Figure 3.4: The RAM!S system from the Technical University of Munich.

[ZYM19]. The remote center of motion was demonstrated to operate with an accuracy of within 1 mm. Furthermore, the researchers used the system to track the depth of the needle during insertion into models, supplementing the microscopic imagery by also displaying OCT-generated volume scans of the needle. The researchers claimed that with the help of their system, surgeons could focus more on making decisions during sub-retinal injection and less on dexterous control of the tool.

Finally, a representational example of a cooperative robotic system, Figure 3.1(d), is the system from the Catholic University of Leuven (Figure 3.5). In 2014, the researchers presented a cooperative robotic system complete with motion scaling, tremor compensation, and scaled force feedback [GVS14]. The system was designed to offer increased stability and precision to the surgeon by reducing the magnitude of hand-generated tremor and facilitating the ability to maintain a fixed position for prolonged durations. The device consists of a
parallel arm mechanism with a mechanical remote center of motion.

Notably, this system was used to perform RVC on *in vivo* pig eyes [WGS17]. Complete success was defined as a stable intravenous position of the needle tip for more than three minutes, and was confirmed in 15 out of 18 eyes. Following this initial success, the same group reported on the clinical evaluation of their system in the world’s first, in-human, robot-assisted RVC [GSS18]. In this study, four patients with retinal vein occlusion were treated at the University Hospital of Leuven in the context of a phase I clinical trial. The trial involved infusing an anticoagulant into a retinal vein with an infusion duration of up to 10 minutes. The successful results demonstrated the possibility of performing RVC with the aid of robotic technology. Like the Preceyes group, the researchers reported the primary challenge as limited visualization of the retinal veins and inability to guarantee successful cannulation.


3.2 OCT-Guided Surgical Robotic Systems

In the realm of automated OCT-guided robotic intraocular systems—Figure 3.1(e)—little work has been done. In one series of studies, researchers used a forward-imaging OCT probe alongside a teleoperated robotic system to evaluate the efficacy of robot-assisted trajectory following with OCT guidance [YSJ16, JS13, YSS15, YSJ13]. The OCT probe was integrated with a surgical tool and mounted on a Stewart platform with seven degrees of freedom. The Stewart platform was controlled by a surgeon through a joystick and the remote center of motion was enforced via software control. The OCT-integrated tool allowed for constant feedback of tool depth and was evaluated with simulated membrane peeling.

Various studies have investigated the efficacy of OCT-guided cooperative robots in which the surgeon controls the robot with their hand, rather than with a haptic device [SPG13, CHC15, BHI09, SGK12, YBW13]. These systems used OCT integrated into the surgical tools themselves to provide closed-loop feedback for locking of tool depth and reduction of hand tremor. One such group controlled the axial positioning of the tool through actuation of high-speed piezoelectric motors driven by an OCT system [SPG13, SGK12]. The OCT system was used as a distance sensor and the researchers used automated edge detection to determine tool-to-surface distance and the magnitude of hand tremor. This data was used as feedback to drive the piezoelectric motors for automatic motion compensation. Another group used a real-time surface-detection algorithm on a layered retinal phantom to perform depth locking of the tool [CHC15]. Using spatially shifted A-scans, the position error of the tip was determined and then fed into a Kalman filter to drive the piezoelectric motors in the handheld device.

These studies focused on handheld or cooperative robotic systems and incorporated only limited OCT-generated information to guide a specific step of a procedure. The underlying difficulty is in the image processing of low signal-to-noise data acquired by the OCT probe. In all reported literature, the robotic system does not make decisions beyond low-level depth-locking or trajectory-tracking objectives.
CHAPTER 4

OCT-Integrated Robotic Surgical System

Figure 4.1: Model of the robotic system (outlined components) with OCT system and retinal vein phantom.

The robotic system developed in this work is shown in Figure 4.1. At the core of the
system is the Intraocular Robotic Interventional Surgical System (IRISS), which controls the motion of the micropipette and is discussed in detail in Section 4.1. Also of importance are the OCT system with integrated camera (Section 4.2), the glass micropipette (Section 4.3), and the custom retinal vein phantom (Chapter 5).

The system architecture is outlined in Figure 4.2. An air tank is connected to the vitrectomy machine, which controls the infusion through the micropipette by regulating the air pressure. The vitrectomy machine is sent pressure commands by a custom control box which interfaces with a National Instruments PXI real-time target. The real-time target also sends digital commands to the power amplifiers to control all system actuators (XYZ stage, IRISS joints, and OCT probe z-position) and runs at a sampling rate of 1 kHz. A laser source provides the signal for the OCT probe to acquire data. The IRISS computer interfaces with the PXI and is connected to the OCT computer via an Ethernet router. The IRISS computer is dedicated to operating the IRISS while the OCT computer is used to acquire OCT data and run the software developed in this work.

Figure 4.2: Overview of system architecture.
4.1 Intraocular Robotic Interventional Surgical System (IRISS)

The Intraocular Robotic Interventional Surgical System (IRISS) was designed for performing a suite of common procedures for cataract and vitreoretinal surgery \cite{WTH10, RWT13, WGP18a}. The system has been used to demonstrate complete, teleoperated lens extraction \cite{WGP18a} as well as partially automated lens removal on \textit{ex vivo} pig eyes \cite{WGP18b, CGF19}.

4.1.1 Mechanical Design

The mechanical design of the IRISS includes two independently controllable arms, each with two mounted surgical tools. For the study presented here, only a single arm with a single tool holder was required and used (Figure 4.3). The surgical tool (a micropipette) is secured to a tool holder mounted on a carriage that rides along a circular track (HepcoMotion 180° double-edge ring slide) to enable rotation about \( \hat{Y}_I \) by \( \theta_2 \). This circular track is anchored at one end to a joint residing in the base of the robot and rotates about \( \hat{Z}_I \) by \( \theta_1 \). These two serial elements are aligned such that their rotational axes are orthogonal and intersect at a kinematically determined remote center of motion (RCM), or “pivot point,” such that—regardless of commanded joint angles—the micropipette is constrained to pass through the RCM. This design is ideal for performing minimally invasive surgical procedures (such as those required by intraocular surgery) because this kinematic constraint limits the motion of the surgical tool to a single point at the incision.

The rotational shaft of \( \theta_1 \) is cantilevered off a mounting stage through a pair of bearing blocks. To reduce backlash and improve accuracy, the actuator for \( \theta_1 \) was chosen to be a harmonic drive “zero backlash” motor (RH-11D-3001 DC motor with E100 encoder). The tool carriage is mounted to the circular track through three, v-groove bearings (HepcoMotion PRT2). The inner bearing has its axis of rotation mounted on a cam, which ensures the three-point-wheel system is constrained perpendicular to the v-groove of the track. The carriage is actuated by a brushed DC motor (Maxon Motor A-max 22; GP 22-A planetary gearhead; MR Type M encoder) attached to an outer bearing.
Figure 4.3: Schematic of the IRISS with coordinate frame definition and kinematic variables highlighted. All axes of rotation and translation are defined coincident with the RCM. The orientation shown is with $\theta_1 = \theta_2 = 0$ and $d_3 = 0$.

The micropipette holder translates parallel to its centerline axis along a linear slide (Igus drylin NK-02-17). The $d_3$ translational motion is actuated by a brushed DC motor (Maxon Motor RE 13; GP-13-A planetary gearhead; MR Type-S encoder). The sliding mechanism exhibits a translational range of 85 mm: 25 mm beyond the RCM point (“into” the eye) and 60 mm in the retracted direction (“away” from the eye). The output torque of the $d_3$ motor is converted to linear force via a nylon rack-and-pinion mechanism secured to the side of the slider. The initial positions of all three joints are calibrated with use of photo-interrupter sensors (Honeywell HOA7720) which are used to provide a reliable homed position.

To allow three-dimensional translation of the RCM, the robotic system is mounted on a set of three stages fixed orthogonal to each other. The stages are composed of three roller
guide stages (Part No. B11-80A, Saruga Seiki) coupled together with a mounting bracket (Part No. A47-6, Saruga Seiki) to allow Z-axis travel. The translational motion of the stage is actuated by three brushed DC electric motors (Part No. Z812, ThorLabs), each with a range of ±12.5 mm from their centered positions. An advantageous feature of this configuration is the mechanical decoupling between robotic motions about the RCM (namely $\theta_1$, $\theta_2$, and $d_3$) and the XYZ translational motion of the RCM itself with respect to the robotic base frame. This allows the RCM to be aligned to the surgical incision of an eye and to do so independently from actuation of the joint angles.

4.1.2 Manipulator Kinematics

The IRISS possesses two rotational degrees of freedom ($\theta_1$ and $\theta_2$) and one translational degree of freedom ($d_3$) with all three joint axes intersecting at a single point to establish the RCM. The forward kinematic map $T(q)$ of the IRISS can be written as

$$T(q) = \begin{bmatrix} c_2 & 0 & s_2 & s_2d_3 \\ s_1s_2 & c_1 & -s_1c_2 & -s_1c_2d_3 \\ -c_1s_2 & s_1 & c_1c_2 & c_1c_2d_3 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

or

$$T(q) = \begin{bmatrix} R(q) & t(q) \\ 0 & 1 \end{bmatrix}, \quad q := \begin{bmatrix} \theta_1 \\ \theta_2 \\ d_3 \end{bmatrix}$$

where $c_i := \cos(\theta_i)$, $s_i := \sin(\theta_i)$, and joint angles are defined as in Figure 4.3.

Given a desired point $p^* := [p_x \ p_y \ p_z]^T$ within the robotic workspace, the inverse kinematics are given by

$$d_3 = \|p^*\|$$

$$\theta_2 = \text{atan2}(s_2, c_2), \quad s_2 = \frac{\sqrt{p_x^2 + p_y^2}}{d_3}, \quad c_2 = -\frac{p_z}{d_3}$$

$$\theta_1 = \text{atan2}(s_1, c_1), \quad s_1 = \frac{p_y}{s_2d_3}, \quad c_1 = \frac{p_x}{s_2d_3}$$
where $\text{atan2} \left( \cdot, \cdot \right)$ is the arctangent function with two arguments and $\| \cdot \|$ is the standard Euclidean norm.

The IRISS is actuated by brushed DC electric motors which are driven by current-type drive electronics. The position of each joint is measured by rotational optical encoders, with the manufacturer-reported resolutions shown in Table 4.1. Servo-level feedback control is based on the reference signals of the controller and the encoder outputs of the joints.

Table 4.1: Resolutions of Joint Motion

<table>
<thead>
<tr>
<th>Joint</th>
<th>Counts/Revolution</th>
<th>Gear Ratio</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>4000</td>
<td>100:1</td>
<td>0.90 mdeg/count</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>2048</td>
<td>588:1</td>
<td>0.30 mdeg/count</td>
</tr>
<tr>
<td>$d_3$</td>
<td>1024</td>
<td>60:1</td>
<td>1.26 $\mu$m/count</td>
</tr>
</tbody>
</table>

4.1.3 System Evaluation and Performance

In this section, the RCM performance and accuracy of the IRISS are reported. In addition, the description of RCM calculation is important for fine-tuning the orientation of the micropipette during automated procedures (Section 6.5).

4.1.3.1 RCM Theory

The ideal RCM of the IRISS is the point in space, $p_{\text{RCM}}$, that the centerline of the micropipette is constrained to pass through regardless of the pose in the workspace. However, due to errors in misalignment and assembly, this condition is never satisfied in practice for any robotic system. Therefore, the definition of the RCM is revised as follows. Given $n$ poses of a micropipette, the RCM is defined as

$$p_{\text{RCM}} := \arg \min_{p} J(d_1, \ldots, d_n) \quad (4.6)$$
where $d_i$ is the Euclidean distance from $p \in \mathbb{R}^3$ to the centerline of the micropipette in pose $i$ and $J$ is a cost function chosen from an appropriate physical meaning (Figure 4.4).

![Figure 4.4: Schematic of the RCM definition.](image)

The purpose of a kinematically determined RCM is to limit stress in the tissue at the surgical incision. For this reason, an appropriate choice for $J$ is the maximum Euclidean distance from $p$ to each pose centerline. This can be written in terms of the $\infty$-norm as

$$J_{\infty}(d_1, \ldots, d_n) := \| (\|d_1\|, \ldots, \|d_n\|)^T \|_\infty$$

$$= \max_i \|d_i\|$$

(4.7)

(4.8)

The minimization of Equation 4.8 can be formulated as a second-order cone problem in which $p_{RCM}$ minimizes $J_{\infty}(d_1, \ldots, d_n)$. Physically, $p_{RCM}$ minimizes the maximum stress applied to the tissue at the surgical incision during operation.

Although the $\infty$-norm solution is physically meaningful, its computation is costly because it involves solving a convex program. Despite its less apparent physical meaning, the 2-norm is more convenient for its computational simplicity. For $n$ poses, the cost function associated with the 2-norm is the sum of the squares of the Euclidean distance between $p$ and each centerline

$$J_2(d_1, \ldots, d_n) := \|d_1\|^2 + \ldots + \|d_n\|^2$$

(4.9)

The 2-norm solution minimizes the variance of the sum of the squares of the normal Euclidean distance from the RCM to the centerline. While the physical meaning is not apparent, it is a useful metric of the RCM performance. For the purpose of evaluating the performance of the IRISS, both metrics were calculated (Table 4.2).
Table 4.2: RCM Performance Metrics

<table>
<thead>
<tr>
<th>Norm</th>
<th>Mean</th>
<th>RMS</th>
<th>Maximum</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_2$</td>
<td>0.729</td>
<td>0.835</td>
<td>1.86</td>
<td>0.414</td>
</tr>
<tr>
<td>$J_\infty$</td>
<td>0.917</td>
<td>0.975</td>
<td>1.64</td>
<td>0.338</td>
</tr>
</tbody>
</table>

* All values in units of mm

4.1.3.2 Evaluation of RCM

The overall approach to measure the RCM location and evaluate its “performance” is outlined next. First, the OCT system (Section 4.2) is used to acquire $n$ volume scans of $n$ different tool poses. The tool location in each volume scan is identified and used to determine the three-dimensional centerline pose in the OCT frame of reference (Section 6.5).

Having determined the tool centerline in all $n$ poses, the RCM is computed from the procedure described in Section 4.1.3.1. “Performance metrics” of the RCM are computed as statistical measures of the values of $d_i$ (the Euclidean distance from the calculated $p_{RCM}$ to the centerline of the surgical tool for each tool pose $i$). These results are reported in Table 4.2 calculated with the $J_\infty$ (Equation 4.7) and $J_2$ (Equation 4.9) cost functions.

As expected, $J_\infty$ minimizes the maximum distance from the centerlines to $p_{RCM}$, while $J_2$ minimizes the root mean square (RMS) of the distance from the centerlines to $p_{RCM}$. For $p_{RCM}$ calculated with the $\infty$-norm, the maximum stress in the tissue at the incision point is reduced; for $p_{RCM}$ calculated with the 2-norm, the average stress in the tissue at the incision point over the range of motion is reduced. Therefore, the choice of cost function depends on what is of more importance for a surgical procedure: reducing the magnitude of the largest stress experienced at the incision point or minimizing the average stress at the incision point over the duration of surgery.
4.1.3.3 Precision, Accuracy, and Mechanical Performance

To evaluate the tool-tip positional accuracy of the IRISS, the three-dimensional location of the micropipette was measured using the OCT system (Section 6.5). The IRISS was commanded to move the micropipette to various points in its workspace. In each pose, the tip location was determined by the OCT system and converted to physical units based on the known calibrated relationship. This analysis produces two sets of points: the tool-tip location as calculated from the forward kinematics (the commanded position) and the tool-tip location as measured by the OCT system. The difference between these points is a measure of the accuracy of the device and has an RMS of 0.205 mm.

To judge the precision of the IRISS, a similar procedure was used. The IRISS was commanded to move the tip to two points in its workspace, a distance 0.345 mm apart, where the trajectory required actuation of all three joints. Thus, two groups of tip position were obtained: OCT-measured tip positions when the tool was commanded to touch point A (at $\theta_1 = 15^\circ$, $\theta_2 = 15^\circ$, and $d_3 = 2.55$ mm), and OCT-measured tip positions when the tool was commanded to touch point B (at $\theta_1 = 5^\circ$, $\theta_2 = -5^\circ$, and $d_3 = 2.10$ mm). The distance between the centroid location of each group and each tip location was calculated. The relevant statistical measures ($n = 29$) are shown in Table 4.3 and provide a measure of the precision of the IRISS.

<table>
<thead>
<tr>
<th>Point</th>
<th>RMS</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30.5</td>
<td>50.8</td>
</tr>
<tr>
<td>B</td>
<td>34.6</td>
<td>53.0</td>
</tr>
</tbody>
</table>

* All values in units of $\mu$m

Finally, a series of quantitative performance metrics were measured to characterize the IRISS (Table 4.4). Backlash was measured as the difference between initial and final position of $d_3$ after the joint was commanded to move from a starting position to an intermediary
position and back to its starting position. Stiction was measured as the average distance that $d_3$ “jumped” when the joint was commanded to move in its smallest possible increments ($1.29 \, \mu m/count$).

### Table 4.4: Performance Metrics of the IRISS Joints

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$ max. joint limit</td>
<td>+1.57</td>
<td>–</td>
<td>rad</td>
</tr>
<tr>
<td>$\theta_1$ min. joint limit</td>
<td>-0.200</td>
<td>–</td>
<td>rad</td>
</tr>
<tr>
<td>$\theta_1$ max. joint velocity</td>
<td>0.572</td>
<td>$3.63 \times 10^{-3}$</td>
<td>rad/s</td>
</tr>
<tr>
<td>$\theta_2$ max. joint limit</td>
<td>+0.700</td>
<td>–</td>
<td>rad</td>
</tr>
<tr>
<td>$\theta_2$ min. joint limit</td>
<td>-0.700</td>
<td>–</td>
<td>rad</td>
</tr>
<tr>
<td>$\theta_2$ max. joint velocity</td>
<td>1.10</td>
<td>0.0348</td>
<td>rad/s</td>
</tr>
<tr>
<td>$d_3$ max. joint limit</td>
<td>+25.0</td>
<td>–</td>
<td>mm</td>
</tr>
<tr>
<td>$d_3$ min. joint limit</td>
<td>-60.0</td>
<td>–</td>
<td>mm</td>
</tr>
<tr>
<td>$d_3$ max. joint velocity</td>
<td>131</td>
<td>2.95</td>
<td>mm/s</td>
</tr>
<tr>
<td>$d_3$ backlash</td>
<td>70.0</td>
<td>22.0</td>
<td>(\mu m)</td>
</tr>
<tr>
<td>$d_3$ stiction</td>
<td>4.20</td>
<td>1.90</td>
<td>(\mu m)</td>
</tr>
<tr>
<td>$d_3$ resolution</td>
<td>1.29</td>
<td>0.751</td>
<td>(\mu m)</td>
</tr>
</tbody>
</table>

Of particular relevance are the values of $d_3$ backlash ($70.0 \pm 22.0 \, \mu m$) and resolution ($1.29 \pm 0.75 \, \mu m$). These values are important during the cannulation step of the developed procedure, as they determine the ability to repeatability reverse direction (in the case of backlash) and the smallest possible incremental motion (in the case of resolution).

### 4.2 Optical Coherence Tomography (OCT) System

Optical coherence tomography (OCT) is an imaging technique that uses low-coherence, near-infrared light to capture high-resolution images of an optical scattering media such as bio-
logical tissue (Figure 4.5 [rev]). An OCT imaging system can capture one-dimensional depth images (A-scans), two-dimensional cross-sectional images (B-scans), and three-dimensional volumetric images (volume scans). The generated images are within micron-level resolution and millimeters of imaging depth. OCT imaging modalities have found widespread use in medical imaging due to their nondestructive, noninvasive method of sensing, making them suitable to imaging in vivo biological tissue. The light generated by the OCT laser source is directed at a target material, which backscatters it as it passes through layers of material. This reflected light is compared to a stable reference signal to generate the OCT images. In this way, OCT is the optical analog to ultrasound but with less imaging depth and much higher resolution (Figure 4.6 [tho]). For correctly assessing successful cannulation by overcoming limits in visualization, OCT technology is superior to standard microscope-based visualization due to its ability to provide accurate depth information.

Figure 4.5: Schematic of human eye with an example of an OCT-acquired B-scan.

A commercially available spectral-domain OCT imaging system (Telesto II, Model No. 1060LR, Thorlabs) was integrated with the IRISS (Figure 4.7a). The OCT system operates
Figure 4.6: Range of imagining technologies including OCT.

with a broadband super-luminescent diode with a central wavelength of 1060 nm, axial resolution of 9.18 µm, and imaging depth of 9.4 mm (Figure 4.7b). The objective lens (Model No. LSM04BB, Thorlabs) offers a focal length of 54 mm, a lateral resolution of 25 µm, and a 10 × 10 mm field of view. Integrated into the OCT probe, and calibrated with respect to it, is a full-color camera with resolution 640 × 480 px.

The OCT system is mounted to an XY stage with 25 mm of translational range and a resolution of approximately 10 µm. The probe is also equipped with a z-direction actuator for approximately 40 mm of vertical motion and a resolution of approximately 1 µm. These augmentations allow for translating the scanning volume (Figure 4.7b) with respect to the custom retinal vein phantom and the IRISS.
4.3 Anticoagulant-delivery System System for Vein Infusion

A custom tool and anticoagulant-delivery system was created for this work (Figure 4.8). The anticoagulant-delivery system has three components: (1) a glass micropipette for piercing the retinal vein phantom and cannulating the vein (Section 4.3.1), (2) a fluid reservoir for storing the anticoagulant analog (Section 4.3.2), and (3) a standard vitrectomy machine for controlling infusion pressure (Section 4.3.3).

4.3.1 Glass Micropipette

Because RVC is not currently performed in practice, no surgical instrument is commercially available. However, one candidate is a 38 Ga (∅100 µm) blunt-tipped cannula (Figure 4.9). The blunt-tipped cannula is designed for use by a human surgeon; namely, the flexible plastic tip deforms upon contact with a surface, thereby providing visual information to assist the
Figure 4.8: (a) Glass micropipette secured in holder. (b) Fluid reservoir with anticoagulant analog. (c) Vitrectomy machine for controlling infusion pressure. Note: Labeled numbers are points of connection.

surgeon in ascertaining tool depth. However, the flexibility of the tip is undesirable in a robotic system whose motion guidance would be complicated by its dynamic behavior.

Figure 4.9: Photograph of a typical 38 Ga blunt-tipped cannula.

Figure 4.10: Photograph of glass micropipette with tip shown in the enlarged view.

Instead of the flexible, blunt-tipped cannula, a thick-walled, beveled, glass micropipette (Catalog No. B100-58-80, Clunbury Scientific LLC) with 80 µm tip was used (Figure 4.10).
These micropipettes are manually beveled with a diamond grinding wheel for a predictable tip shape that facilitates puncturing of material. However, the glass micropipette cannot be used without modification: its size and material render it physically fragile and its outer diameter ($\varnothing 1.0\, \text{mm}$) does not securely mate to any standard syringe or tubing. To overcome these issues, the glass micropipette is embedded inside a custom stainless steel hypodermic needle tube (Catalog No. 316H17TW, MicroGroup) and secured with two-part epoxy (Catalog No. GPMR6049, GreatPlanes).

Note, a portion of the glass micropipette (the “tool tip”) remains unprotected by the stainless steal tube, as is necessary for vein access. However, the glass tool tip is physically fragile—small amounts of lateral force (such as those enacted by a paper-towel graze) are sufficient to fracture the tip. Destruction of the tip requires fabrication of a new tool, replacement of the broken tool in the tool holder, recalibration of the new tool’s physical alignment, fresh derivation of tool registration, and calculation of offsets in the image-processing algorithms. Therefore, a manual safety check is incorporated into the automated procedure during the critical insertion step to guarantee the safety of the micropipette.

Furthermore, due to the small internal diameter of the micropipette (estimated $\leq \varnothing 30\, \mu\text{m}$), the tip is easily clogged by particulate matter such as dried food coloring. Various attempted methods to unclog occluded micropipettes proved unsuccessful and risked irreparable damage. Instead, the micropipette is flushed with dry, medical-grade air after every session to ensure no particulate matter remains in the tip.

The micropipette is aligned such that its centerline passes through the RCM using a custom adjustment mechanism. The adjustment mechanism houses three fine-thread adjusters (Part No. F2D5ES8, ThorLabs) with thread pitch 0.20 mm housed in phosphor bronze bushings (Part No. F2D5ESN1P, ThorLabs). The orientation of the three adjusters allows for fine-tuning the rotational position of the micropipette about $\hat{Z}_I$ and fine-tuning the linear translation of the micropipette along $\hat{Y}_I$ (Figure 4.3). Tygon microbore tubing ($\varnothing 2.29\, \text{mm}$) press-fits onto the end of the stainless steel tube and connects to the fluid reservoir via a standard Luer-lock connection.
The alignment process is required only once and its results are used for all subsequent trials. First, the tool is aligned approximately “by eye” by adjusting the three fine-thread adjusters. A custom, automated script is run where the tool is commanded from $\theta_2 = -15^\circ$ to $\theta_2 = 15^\circ$ in increments of $1^\circ$. In each pose, the camera image is acquired and the micropipette manually fitted with a centerline. A script is run to calculate the RCM (Section 4.1.3.1) and the angular and linear offsets necessary to correct the position and orientation of the micropipette. Using the known pitch of the adjustment screws, these offsets were manually implemented and the automated image-capture and RCM-calculation scripts run again. This process is repeated until the calculated error is within the camera resolution ($\leq 25 \, \mu\text{m}$).

To align $\theta_1$, a similar procedure is used. The micropipette was commanded from $\theta_1 = -10^\circ$ to $\theta_1 = 50^\circ$ in increments of $1^\circ$. In each pose, the OCT acquires a B-scan through the approximate tool centerline and the resulting image is manually fitted with a centerline. A script is run to calculate the RCM (Section 4.1.3.1) as well as the linear offset necessary to correct the orientation of the micropipette. To implement this offset, stainless steel shim stock (thickness $25 \, \mu\text{m}$) was added in subsequent layers between the adjustment mechanism and the base of the tool holder. The process was repeated to confirm the calculated error is within $25 \, \mu\text{m}$.

Finally, it is important to note that all accumulated error from this series of mechanical alignments is incorporated into the registration error and will be addressed in Section 6.5.2.

4.3.2 Fluid Reservoir

The micropipette is connected via tubing to a port of a custom designed and fabricated fluid reservoir (Figure 4.8b). A second port of the reservoir connects to a 20 mL syringe to facilitate refilling. Another port is permanently sealed while the fourth port connects to the viscous fluid control (VFC) line of the vitrectomy machine. When commanded, the vitrectomy machine increases the air pressure inside the fluid reservoir via its VFC output line, which presses down on the stored fluid and forces it in the micropipette. While not strictly necessary, the fluid reservoir is practically useful as it eliminates the need for an
onboard syringe, facilitates easy refills, and guarantees a sufficient supply of anticoagulant analog for every trial.

### 4.3.3 Infusion of Anticoagulant Analog

A vitrectomy machine (Model No. 800CS, Alcon), referred to as the “Accurus,” was incorporated into the system setup (Figure 4.8c). The Accurus is equipped with a VFC line for proportional, pressure-actuated infusion of viscous fluids. Standard VFC operation requires the surgeon to hold the surgical tool while depressing a foot pedal to control the fluid pressure of the infusion. However, for the purpose of automated control, the Accurus was reverse-engineered to ascertain the communication protocol with the foot pedal. In the case of VFC operation, the relationship between output pressure and input commands is

\[
p_{\text{out}} = \begin{cases} 
0 & \text{for } f \in [0, f_t], \\
\frac{(f - f_t) \cdot p_{\text{max}}}{f_{\text{max}} - f_t} & \text{for } f \in (f_t, f_{\text{max}}] 
\end{cases} 
\]  (4.10)

where \( p_{\text{out}} \in \mathbb{R} \) is the output pressure in psi, \( p_{\text{max}} \) is the maximum output pressure of the Accurus (80 psi), \( f \in \mathbb{Z} \) is the accumulated number of 5 V pulses sent to the Accurus as a command signal, \( f_t \in \mathbb{Z} \) is the threshold number of 5 V pulses to transition from no pressure output to initiation of infusion, and \( f_{\text{max}} \in \mathbb{Z} \) is the maximum number of 5 V pulses allowed by Accurus before the system throws a maximum-pressure error. The 16-pin Fischer connector was replicated and connects to the National Instruments PXI through a custom electronics box which reproduces the analog and digital signals expected by the Accurus. In this way, the control software controls the VFC output of the Accurus, which in turn controls the infusion pressure in the micropipette.
Performing retinal vein cannulation (RVC) on live human patients would require approval by the federal Food and Drug Administration of an extensively validated system. However, the novelty of automated, OCT-guided, robotic-controlled RVC necessitates the use of a retinal vein phantom as a substitute for an \textit{in vivo} human eye.

### 5.1 Biological Eye Models

Biological eye models can be classified as (1) \textit{in vivo} animal models, (2) \textit{ex vivo} animal models, and (3) non-animal biological models (Table 5.1).

Common \textit{in vivo} animal models include those of pigs, rabbits, and goats. These models require approval from an ethics committee for the humane treatment of animals, which is likely unattainable for the purposes of development and testing. Even with approval, the system must be operated in a vivarium, a practical inconvenience that makes these models unsuitable for development and preliminary testing.

\textit{Ex vivo} animal models include cadaver (human), cow, and pig eyes. Cadaver eyes were deemed unsuitable for testing due to expense (approximately $1,500 per eye) and their special handling considerations. \textit{Ex vivo} cow eyes were tested for physical realism and appearance under OCT. As expected, the main issue limiting their use was their unrealistically large size, although the visual clarity and diameter of the retinal veins (approximately $\varnothing290 \, \mu m$) offers an easy cannulation target.

While \textit{ex vivo} pig eyes represent one of the best analogs to human eyes due to their
physical accuracy and are relatively inexpensive (approximately $5 per eye), they suffer from several known deficiencies. First, the mean vein diameter in porcine retinas is approximately two times greater than values reported for human retinal veins \([\text{BSH11]}\). Second, the quality of the pig eyes depends on the time of slaughter and the expediency of the shipping method; for example, corneal edema, clouding, and dehydration are common. Likewise, because it is an \textit{ex vivo} model, the longer the eye is out of refrigeration, the more quickly the eye degrades, thereby placing a time constraint on their use. Third, while individually inexpensive, shipping and transportation costs are \textit{not} (approximately $100 per box) and quickly accumulate into a major expense. Finally, the Thorlabs OCT system was designed for anterior segment surgical procedures (specifically lens extraction) and cannot image posterior enough in the eye to visualize the retinal surface. Removal of the cornea, lens, and vitreous overcomes this deficiency but at the expense of structural rigidity of the eye. This results in an unrealistic model that is difficult to work with.

Available non-animal biological models are limited. A group at John Hopkins University incubated a chicken egg for 12 days then opened the shell to cannulate blood vessels using their hand-held MICRON system \([\text{GPI18]}\). However, the vessel diameters ranged from 199–916 \(\mu\text{m}\) and were mostly too large to present a realistic model. In addition, biological variables such as tissue degradation and the incubation period place restrictive constraints on development and testing because the incubated eggs must be used when ready.

<table>
<thead>
<tr>
<th>Model</th>
<th>Physical Accuracy</th>
<th>Expense ($)</th>
<th>Setup Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{In vivo} Human</td>
<td>–</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>\textit{In vivo} Pig, Rabbit, and Goat</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>\textit{Ex vivo} Human</td>
<td><strong>High</strong></td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>\textit{Ex vivo} Cow</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>\textit{In vivo} Pig</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Partially incubated chicken egg</td>
<td>Low</td>
<td><strong>Low</strong></td>
<td>Medium</td>
</tr>
</tbody>
</table>
A few companies sell commercially available artificial eye models including SimulEye, Bioniko Models, and eyecre GmbH. However, no company currently markets an eye phantom for performing retinal vein cannulation. Discussion with two companies (SimulEye and Bioniko Models) reveals that work on retinal vein phantoms is in progress but is not expected to be completed in the near future.

5.2 Artificial Retinal Vein Phantoms

Several artificial retinal vein phantoms have been developed by other research groups for a variety of purposes and are presented here.

Figure 5.1: An artificial retinal vein phantom developed in the literature: painted human hair on a yellow background.

In [BML13], the authors presented a simple retinal vein phantom (Figure 5.1) in which a curved vein was created from a piece of human hair painted red. This “vein” was taped to a yellow paper background that was glued to the inside of a table tennis ball (⌀42 mm). This model was used for surgeon-guided, tool-tip positional tracking. The main deficiency of this model was the inability to cannulate, as the hair is a solid tube.

In [NIY10], the authors fabricated various-diameter microchannels from polydimethyl siloxane (PDMS) with circular cross sections. A photoresist pattern was fabricated atop a silicon substrate, consisting of the retinal vein pattern and a pattern for alignment. The
Figure 5.2: An artificial retinal vein phantom developed in the literature: circular channels fabricated from PDMS.

segments were separately cured in PDMS, plasma treated, and then aligned using surface tension before heating to secure the two halves together (Figure 5.2). This process created retinal vein phantoms with circular cross sections. The main deficiency of this method was its complexity and time requirements: several steps required 30 minutes to complete and there were 21 steps in total.

Figure 5.3: An artificial retinal vein phantom developed in the literature: rectangular channels fabricated from PDMS.

In [THI15], a retinal vein phantom was made using a PDMS microfluidics method. The retinal vein phantoms were either 60 \( \mu \text{m} \) or 90 \( \mu \text{m} \) rectangular microchannels (Figure 5.3). The channels were fabricated using PDMS, but the process was much simpler than the one
presented in [NIY10]. The process includes using a negative photoresist spin-coated onto a silicon wafer then exposing the wafer to ultraviolet light through a photomask with a microchannel pattern. After baking and rinsing in isopropyl alcohol, PDMS was poured onto the wafer and cured. After plasma treatment, a PDMS sheet was placed atop the microchannels and bonded together. While this process created microchannels of various cross-sectional widths, and was much simpler than the method presented in [NIY10], the main deficiency was that it resulted in rectangular cross sections, which are non-representational of actual retinal veins.

Figure 5.4: An artificial retinal vein phantom developed in the literature: rectangular channels created from a spin-coating method.

Finally, another group of researchers validated their robotic manipulator on a multi-channel retinal model [GWS13]. Details of the model’s fabrication are lacking. However, it was created with a heat-curable flexible polymer cured in a mold and spin-coated to seal the top of the model (Figure 5.4). A unique feature of this model was that when fluid was successfully infused into a channel, it flowed to a drainage port in the center of the model. This model only allowed vein access from the sides of the rectangular channels (ranging from 80–500 µm) and is therefore unrealistic.
5.3 Developed Eye Model

All existing eye models and retinal vein phantoms were deemed unsuitable for development and testing of the proposed robotic system due to unmitigated practical concerns or deficiencies in accuracy and physical realism. Therefore, a new fabrication technique was created. The design requirements were:

1. Realistic (both in physical dimension and appearance under OCT)
2. Feasible (in-house fabrication possible)
3. Simple (minimal fabrication steps and time requirement)
4. Repeatable (minimal variation between models)
5. Reusable (non-degradable and physically robust)

The requirement of physical realism includes accurately reproducing the diameter of a human retinal vein. A range of diameters was found in the literature (Table 5.2) and chosen to be 120–200 µm based on surgeon feedback. If the system is able to cannulate the lower bound (Ø120 µm), then the system is expected to also be capable of cannulating vein phantoms with larger diameter (Ø200 µm).

Table 5.2: Diameters of Retinal Veins Reported in the Literature

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>137.69</td>
<td>13.84</td>
<td>[GSL13]</td>
</tr>
<tr>
<td>214.0</td>
<td>22.2</td>
<td>[WIK06]</td>
</tr>
<tr>
<td>119.6</td>
<td>29.9</td>
<td>[OSS15]</td>
</tr>
</tbody>
</table>

* All values in units of µm

The thickness of a retina varies: it is thinnest at the foveal floor (100–200 µm) and thickest at the foveal rim (230–320 µm) [TSW09]. Outside the fovea, the retina thins until
it vanishes at the equator. It is assumed that RVC would be performed near the optic disc where the retinal thickness is approximately 300 µm and this value was chosen for the model thickness (Figure 5.5). The surface area of the model was chosen to be approximately 200 mm², comparable to the visible area of a human retina when imaged through a surgical microscope.

![Figure 5.5: Schematic of the custom retinal vein phantom with relevant dimensions.](image)

The model requirements for OCT-guided surgical procedures are unique in that the model must appear visually realistic under OCT. This requirement is in addition to the requirements of visual realism in the camera view and physical realism during performance of a surgical procedure. Several materials were investigated to find one that satisfied these unique requirements (Table 5.3). Of these, silicone was chosen due to cost and material properties. The constituent components of the silicone substrate were mixed by volume in a 1:1 ratio. Approximately three drops of yellow liquid dye (Catalog No. B07JHG578Q, Limino US) were added for every 10 mL of volume.

Excluding an overnight cure time, fabrication of the models required approximately 20 minutes to perform and involved six steps (Figure 5.6), as follows:

1. The aluminum mold is cleaned by hand with acetone and isopropyl alcohol.

2. A stainless steel wire (Ø100–200 µm) is inserted into the mold and fixed in place with spring clamps.
Table 5.3: Materials for Retinal Substrate

<table>
<thead>
<tr>
<th>Material</th>
<th>Realistic?</th>
<th>Robust?</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Gelatin</td>
<td>No¹</td>
<td>No²</td>
<td>Kraft Foods Group (Northfield, IL)</td>
</tr>
<tr>
<td>PDMS (Sylpot 184)</td>
<td>No</td>
<td>Yes</td>
<td>Dow Corning Toray (Tokyo, Japan)</td>
</tr>
<tr>
<td>Silicone (Ecoflex 0030)</td>
<td>Yes</td>
<td>Yes</td>
<td>Smooth-On (Easton, PA)</td>
</tr>
</tbody>
</table>

¹High reflectance in OCT view; ²Physical degradation and collapse of vein within 2–3 days

3. The constituent components of the silicone substrate are mixed and poured into the mold. The substrate is allowed to rest for 5–10 min to release air bubbles. A top cover is secured to the mold and it is allowed to cure overnight at room temperature.

4. The wire is removed from the mold, creating a void space.

5. The model is removed from the mold.

6. The vein is manually filled from the side with blood analog using a flexible-tip cannula.

Note: Cured air pockets result in a model that is physically unrealistic (there are no bubbles in an actual retina) and their presence would degrade OCT image quality (refraction differences between air pockets and the silicone substrate would cause dimensional mismatch). The mold used and the final retinal vein phantom are shown in Figure 5.7.

For the blood analog, various combinations of available liquids were tested to find a ratio that was visually realistic in both the camera and OCT views. Ultimately, a combination of distilled water and red liquid dye was used in a 10:1 ratio by volume. It was found that balanced salt solution (NDC 0065-0800-94, Alcon) and Kenalog (NDC 0003-0293-05, Bristol-Myers Squibb) would clog the tip of the micropipette and were therefore avoided. The blood analog was manually injected into the model vein from the side using a 38 Ga (⌀100 µm) plastic-tip cannula (Model No. 3233, MedOne Surgical Inc.) under an optical microscope.

For comparison, the developed model is shown alongside all models reported in the literature (Table 5.4). “Physical realism” refers to the vein being physically realistic in both
Figure 5.6: Illustration of the fabrication process for the retinal vein phantoms. Note: dimensions are not to scale and have been exaggerated purely for illustrative clarity.

Figure 5.7: (a) Photograph of the mold for fabrication of the retinal vein phantoms. (b) Photograph of a complete retinal vein phantom.

diameter and shape; “complexity” refers to time requirement and number of fabrication steps; and “optical realism” refers to the model being optically realistic under both OCT and microscope (a function of material properties).
<table>
<thead>
<tr>
<th>Model</th>
<th>Physical Realism</th>
<th>Complexity</th>
<th>Optical Realism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painted Hair [BML13]</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>PDMS Circular [NIY10]</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>PDMS Square [THI15]</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Multi-Channel [GWS13]</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Developed Model</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
CHAPTER 6

Technical Approach to Automated RVC

This chapter describes the technical approach of using the IRISS and optical coherence tomography (OCT) system to achieve automated retinal vein cannulation (RVC) on the custom retinal vein phantoms.

The automated RVC procedure is composed of eight steps (Figure 6.1):

1. **Pipette Registration**: The micropipette is used to register the OCT frame into the IRISS frame such that any point in the OCT frame can be known in the IRISS frame (and vice versa).

2. **Eye Modeling**: The retinal vein phantom is scanned by the OCT and this data modeled such that the dimensions and geometry of the retinal vein phantom are known.

Figure 6.1: Flowchart of the automated RVC procedure.
The user is asked to select a specific cannulation site in the camera view of the retinal surface.

3. **Trajectory Generation**: Two trajectories are generated: (1) a trajectory for the XYZ stage of the robotic system to result in the remote center of motion becoming coincident with the surgical incision and (2) a trajectory to safely guide the micropipette through the incision into the eye to a near-vein location.

4. **Proximate Placement**: The system follows the trajectory generated in Step 3 and moves the micropipette to the near-vein location. Camera and real-time OCT scans track the micropipette and provide feedback to the user.

5. **Fine-Tune Orientation**: Volume scans are acquired of the tool near the vein and corrective joint commands are generated to accurately align the micropipette to the cannulation point selected in Step 2. Following this step, cannulation is simply a matter of guiding the micropipette forwards.

6. **Vein Cannulation**: The user increments the micropipette into the vein while being guided by augmented OCT feedback. A suite of automated functions are provided.

7. **Infusion**: The system confirms vein access through visual feedback and then infuses the vein with the anticoagulant analog at desired pressure and for a desired duration.

8. **Tool Retraction**: The micropipette is retracted from the eye and the surgery is considered complete.

This chapter details the steps enumerated above.

### 6.1 Step 1: Pipette Registration

To initialize a trial, the XYZ stage, the IRISS, and the OCT z-direction are automatically homed using their integrated homing sensors. The robotic workspace of the IRISS is a cone with apex at the RCM and is able to translate ±6 mm in $\hat{X}_I$, $\hat{Y}_I$, and $\hat{Z}_I$. The scanning
workspace of the OCT is $10 \times 10 \times 9.4$ mm but can be vertically translated (along $\hat{Z}_O$) approximately 40 mm and manually translated in $\hat{X}_O$ and $\hat{Y}_O$ by approximately ±12.5 mm. By centering the XYZ stage and positioning the micropipette such that its tip is at the RCM ($d_3 = 0$), the OCT XY stage can be moved such that the micropipette tip is in the center of the camera frame. From this position, the OCT is translated in $\hat{Y}_O$ by approximately 10 mm. This offset ensures that the tool-tip will be approximately centered during cannulation for ideal visualization. This initial alignment requires approximately three minutes of manual effort and is only required once (the alignment can be used for all subsequent trials). The coordinate frame definitions and dimensions between the integrated camera and the OCT scanning volume are shown in Figure 6.2.

Figure 6.2: (a) Coordinate frames between the camera’s visual field and the OCT scanning range. (b) Maximum range of the OCT scanning volume.

Once the stages are aligned, the model can be placed within the workspace of the IRISS and scanning range of the OCT system. Its exact positioning is irrelevant: any position roughly beneath the OCT scanning frame is sufficient provided the vein is visible in the camera view. At this point, the system is ready for automated performance. The surgeon presses a “start” button in the graphical user interface (GUI) to begin a trial.
In this step, the micropipette is registered within the OCT frame, $\mathcal{F}_O$. The purpose of performing this registration is to enable placement of the tool within $\mathcal{F}_O$ by relating the internal coordinate frame of the robotic system, $\mathcal{F}_I$, to the coordinate frame of the OCT. Two methods to accomplish this registration have been developed by the author. The first method relies on Procrustes superimposition and requires the acquisition and processing of approximately 15 high-sensitivity volume scans of different tool poses [WGP18a, WGP18b]. This method is time-consuming (each scan requires 35 s for acquisition and approximately 20 s for processing) and was deemed too inconvenient for development and testing of the present system. Instead, a faster—but less accurate—method was created, as described next.

The micropipette is commanded to $\theta_1 = \theta_2 = 0$ and $d_3 = 8$ mm such that it is within the OCT scanning volume, specifically within the top 3 mm (for optimal scan quality), and a volume scan is acquired. In each B-scan of the volume scan, the model surface is detected and used to eliminate all model data in the scan, leaving only the micropipette data. The tool appears as either a high-intensity crescent in the case of the steel part of the tool or a circular cross section in the case of the glass micropipette. In either case, the B-scan is converted to

![Micropipette Tip Data](image-url)
binary data based on a custom algorithm and these points converted to physical dimensions using the known OCT calibration parameters. Using the known dimensions of the tool, all acquired data not near the micropipette tip are eliminated and the remaining points are fit with a three-dimensional line. This line is defined as the tool centerline, $O_t$. The intersection of $O_t$ with the B-scan that represents the transition from B-scans with micropipette data to those without is defined as the tool-tip location, $O_p$. Figure 6.3 illustrates the detection of the micropipette tip and centerline.

In addition to $O_t$ and $O_p$, the tool centerline and tip position in $F_I$ are also calculated from forward kinematics. The transformation from $F_O$ to $F_I$ is assumed to be linear and composed of a rotation, translation, and uniform scaling:

$$
\overset{I}{T}_O = \begin{bmatrix}
\overset{I}{R}_O & \overset{I}{t}_O \\
0 & 1
\end{bmatrix}
$$

(6.1)

where $\overset{I}{T}_O \in \mathbb{R}^{4 \times 4}$ is the homogeneous transformation matrix from $F_O$ to $F_I$, $\overset{I}{R}_O \in \mathbb{R}^{3 \times 3}$ is the rotation matrix from $F_O$ to $F_I$, and $\overset{I}{t}_O \in \mathbb{R}^3$ is the translation vector from $F_O$ to $F_I$. The rotation matrix is calculated as the rotational difference from $O_t$ to the tool centerline calculated from forward kinematics. Applying this rotation to the OCT data of micropipette
Figure 6.5: OCT data of micropipette transformed into the IRISS frame using the derived coordinate transformation.

points results in Figure 6.4. That is:

\[
\mathbf{i}p_t = \mathbf{i}R_O \cdot \mathbf{o}p_t \tag{6.2}
\]
\[
\mathbf{i}t_t = \mathbf{i}R_O \cdot \mathbf{i}t_t \tag{6.3}
\]

The translation vector is then calculated by comparing \(\mathbf{i}p_t\) to the tool-tip position from forward kinematics. Unity scaling is assumed since the underlying dimensions are equivalent. The resulting rotation matrix and translation vector are assembled into \(\mathbf{i}T_O\) (Equation 6.1).

The inverse transformation, \(\mathbf{o}T_I = (\mathbf{i}T_O)^{-1}\), represents the coordinate transformation from \(\mathcal{F}_I\) to \(\mathcal{F}_O\). With \(\mathbf{i}T_O\) and \(\mathbf{o}T_I\) known, any point in \(\mathcal{F}_O\) can be converted to a point in \(\mathcal{F}_I\) (and vice versa). To confirm the derived coordinate transformation is valid, the OCT data of micropipette points is transformed into \(\mathcal{F}_I\) (Figure 6.5). Because these points approximately represent the micropipette position from forward kinematics (\(\theta_1 = \theta_2 = 0\) and \(d_3 = 8\) mm), we have confidence \(\mathbf{i}T_O\) is valid.
In the example shown, the calculated transformation matrix was

\[
^I T_O = \begin{bmatrix}
-0.9998 & 0.0210 & -0.0000 & 5.2074 \\
0.0210 & 0.9998 & -0.0016 & -0.3518 \\
-0.0000 & -0.0016 & -1.0000 & 2.6490 \\
0 & 0 & 0 & 1.0000
\end{bmatrix}
\] (6.4)

The value of \( d_3 \) from forward kinematics was 8 mm; the calculated tip distance from the OCT scan was 8.17 mm.

While this method is fast (\( \leq 1 \) minute) compared to the Procrustes superimposition method [WGP18a, WGP18b], it suffers from significant error. To quantify the registration error, the IRISS was commanded to touch a series of \( n = 20 \) randomly generated points within its workspace. At each point, a volume scan was acquired, \( ^O p_t \) was determined as previously described, and the derived coordinate transformation was used to transform \( ^O p_t \) to \( ^I p_t \). Ideally, all values of \( ^I p_t \) would perfectly overlap the tool-tip positions calculated from forward kinematics. In reality, error exists between each pair of points, calculated as the three-dimensional interpoint Euclidean distance. The statistical measures of the errors for a typical derivation of the coordinate transformation are shown in Table 6.1. The pipette registration represents the largest source of error of the entire process and will be accounted for in Step 5.

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Maximum</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>190.0</td>
<td>77.1</td>
<td>340.6</td>
<td>20</td>
</tr>
</tbody>
</table>

* All values except \( n \) in units of \( \mu m \)

### 6.2 Step 2: Eye Modeling

At the beginning of this step, the system displays the camera image of the retinal surface to the user. The user is asked to specify a desired cannulation site via mouse click. The
selected point in the camera frame, \( C_p_s \), is scaled to physical dimensions and transformed to the OCT scan frame, \( F_S \), using the manufacturer-provided calibration parameters:

\[
S_p_s = S R_C (C_p_s \circ s) + S t_C, \quad s = \begin{bmatrix} s_x \\ s_y \end{bmatrix}
\] (6.5)

where \( S_p_s \in \mathbb{R}^2 \) is the coordinate of the clicked point in \( F_S \); \( S R_C \in \mathbb{R}^{2 \times 2} \) is the rotation from \( F_C \) to \( F_S \); the notation \( \circ \) represents the standard Hadamard product; \( s_x \) and \( s_y \) are the constant camera-scaling factors; and \( S t_C \in \mathbb{R}^2 \) is the translational vector from \( F_C \) to \( F_S \).

The resulting point, \( S_p_s \), is then scaled to pixels in \( F_O \) as

\[
O_p_C = S_p_s \circ r, \quad r = \begin{bmatrix} r_x \\ r_y \end{bmatrix}
\] (6.6)

where \( O_p_C \in \mathbb{R}^2 \) is the selected cannulation point in \( F_O \) and \( r_x \) and \( r_y \) are the manufacturer-provided scaling factors \( r_x = r_y = 40 \) px/mm. If the resulting value is outside the range of the acquired volume scan, it is coerced to within the limits.

![Camera View Example B-Scan Regions of Interest](image.png)

Figure 6.6: Processing single B-scan to isolate vein center.

The system then acquires a volume scan of the retinal vein phantom. From the volume scan, a region of interest (ROI) approximately \( 1 \times 2 \) mm in size and centered around \( O_p_C \) is chosen. In each B-scan, the system segments the top surface of the model from the data and uses the constant model thickness (300 µm) to generate a region in which to search for
the vein cross section (Figure 6.6). A Gaussian blur is added to the ROI and each image is summed with its nearest neighbors. The center of the vein is determined as the center of the ellipsoidal region of minimum intensity in the resulting image. These three-dimensional points are then fit with a smoothed curve under the assumption that the radius of curvature of the vein is large around $O_p$ (Figure 6.7). Clinically, this is a safe assumption, as cannulation is expected to be performed near the optic disc where retinal veins are straighter and branch less.

![Vein Model](image)

Figure 6.7: Vein and cannulation site as modeled from OCT data.

A human user cannot be guaranteed to select a point on a pixel image absolutely accurately. Experimentally evaluated error of targeting a specific point in the displayed image was $16.2 \pm 14.9 \, \mu m$ with maximum $63.8 \, \mu m$ ($n = 100$) in $\hat{X}_C$ and $14.4 \pm 13.3 \, \mu m$ with maximum $42.9 \, \mu m$ ($n = 100$) in $\hat{Y}_C$. Therefore, the point chosen by the user is used only as an initial estimate. Instead, the true cannulation point, $p_C \in \mathbb{R}^3$, is chosen as the point on the smoothed line that is closest (in a Euclidean-distance sense) to the selected site. Surgically, a small ($\leq 100 \, \mu m$) deviation from a desired position along the vein may be irrelevant, but for the automated process, it is important to ensure $p_C$ is actually within the vein. Therefore, this step is added to reduce the possibility that an inaccurate mouse click by the user would generate a physically inaccessible cannulation point.
6.3 Step 3: Trajectory Generation

Using the retinal vein phantom generated in Step 2, the system automatically determines two trajectories (Figure 6.8):

1. The three translational motions of the XYZ stage necessary to result in the robotic pivot point, \( p_{RCM} \), becoming coincident with the surgical incision, \( p_{SI} \)

2. A trajectory in joint coordinates to safely guide the tool tip from \( p_{SI} \) to a near-vein point, \( p_i \)

![Figure 6.8: Automatically generated trajectory from OCT data and retinal vein phantom.](image)

Implementation of the first step is technically trivial: the XYZ stage is simply commanded to move the required distance. The error associated with translating the XYZ stage is
a function of the physical actuation and control (Table 6.2). Despite being technically trivial, this movement is surgically relevant because the RCM quality is directly related to physical stress in the scleral incision. Excess stress can cause vitreous leakage, result in scleral hemorrhage, or diminish the self-healing properties of the tissue.

<table>
<thead>
<tr>
<th>Direction</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Maximum</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{X}_I$</td>
<td>5.4</td>
<td>4.1</td>
<td>15.8</td>
<td>106</td>
</tr>
<tr>
<td>$\hat{Y}_I$</td>
<td>5.1</td>
<td>3.3</td>
<td>12.9</td>
<td>106</td>
</tr>
<tr>
<td>$\hat{Z}_I$</td>
<td>4.1</td>
<td>2.6</td>
<td>9.9</td>
<td>106</td>
</tr>
</tbody>
</table>

* All values except $n$ in units of $\mu$m

### 6.4 Step 4: Proximate Placement

The goal of the second portion of the trajectory of Step 3 is to insert the micropipette past $p_{SI}$ into the eye such that the micropipette tip becomes coincident with the near-vein point, $p_i$ (Figure 6.9). This trajectory, $t_i^*$, is a function of three joint variables: $\theta_1$, $\theta_2$, and $d_3$.

If the micropipette was simply commanded to move from $p_{SI}$ to $p_C$, it is unlikely to achieve accurate targeting due to the accumulation of errors from registration and the XYZ stage motion. Instead, $p_i$ is defined such that, even in the worst-case performance (maximum error), the micropipette is guaranteed not to collide with the retinal surface. The near-vein point $p_i$ is defined a distance $\lambda$ from the retinal surface and on $t_i^*$ (Figure 6.10).

The bounds of the accumulated maximum error can be visualized as a sphere centered on $p_i$. The radius of this sphere, $r_e$, is the maximum measured magnitude of error from all sources contributing to positional error of the micropipette tip:

$$r_e = r_r + r_s \approx 356.4 \mu m$$ (6.7)

where $r_r$ is the maximum error due to registration and $r_s$ is the maximum error due to stage
Figure 6.9: Schematic of planned trajectory. (a) Side view of the virtual eye and vein phantom. (b) Top view of the vein phantom.

Figure 6.10: Calculation of the maximum error range.

From geometrical considerations:

$$\lambda \geq \frac{r_e + b}{\cos(\pi/6)} \approx 412 \, \mu m$$  \hspace{1cm} (6.8)$$

where $b = 100$ is the sum of half the smallest vein diameter ($\Phi 120 \, \mu m$) plus the distance from the model top to the vein top (40 $\mu m$). The value of $b$ is added due to geometrical
considerations. From Equation 6.8, any value of $\lambda > 412 \mu m$ is expected to guarantee that the micropipette does not collide with the retinal surface during its approach to $p_i$, despite the presence of significant uncertainties. With $p_i$ defined, the tool is commanded to insert through $p_{SI}$ and access $p_i$.

6.5 Step 5: Fine-Tune Orientation

At the conclusion of Step 4, the micropipette tip $p_t$ is unlikely to have accurately achieved $p_i$ due to accumulation of error. Instead, the goal has been to locate $p_C$ and safely guide the tool to $p_i$ (a distance $\lambda$ from $p_C$) in the presence of significant error. This accumulated error will now be accounted for.

At the beginning of this step, the configuration of the tool is expected to be similar to that shown in Figure 6.11. Namely:

1. The tool tip, $p_t$, is not coincident with $p_i$. Therefore, $t_t^*$ cannot be relied upon to achieve cannulation. Relatedly, the actual tool centerline $t_t$ does not point at $p_C$. Therefore, simply incrementing the $d_3$ joint is not expected to result in successful cannulation.

2. Both $p_t$ and $p_C$ are guaranteed to be within the scanning range of an OCT B-scan, allowing all future steps to simultaneously image both points.

3. The tool centerline is angularly displaced by an error $\delta_\theta$ and linearly displaced by an error $d_e$ from $p_C$. It is the goal of Step 4 to reduce these errors.

The iterative approach to fine-tune the orientation of the micropipette is illustrated in Figure 6.12. First, an OCT volume scan of the micropipette is acquired. Via image processing, $t_t$ is determined and used to calculate $d_e$, the Euclidean distance between $p_C$ and $t_t$:

$$d_e \equiv \| h - (h \cdot \hat{n}) \hat{n} \|$$

(6.9)
Figure 6.11: Micropipette position and orientation at the initiation of Step 5.

Figure 6.12: Algorithm to fine-tune the orientation of the micropipette in Step 5.
where \( h \equiv \mathbf{a}_t - \mathbf{p}_C, \mathbf{a}_t \in \mathbb{R}^3 \) is any point on \( t_t \), and \( \mathbf{\hat{n}} \) is the unit vector in the direction of \( t_t \). If \( d_e < d_t \), then the tool centerline is considered to accurately intersect \( \mathbf{p}_C \) and the step is finished. From geometric considerations \( d_t = 20 \mu m \).

If \( d_e > d_t \), the system uses the expected location of \( \mathbf{p}_{RCM} \) to calculate \( \theta_1^* \) and \( \theta_2^* \), the joint motions expected to cancel \( d_e \). Note, at this stage, \( \mathbf{p}_{RCM} \) suffers from error and is simply an initial guess. The IRISS is then commanded to move by \( \theta_1^* \) and \( \theta_2^* \). For actuation of \( \theta_1 \) and \( \theta_2 \), angular resolution of the actuators corresponds to a tool-tip arc-displacement resolution calculated from geometry (Table 6.3).

<table>
<thead>
<tr>
<th></th>
<th>( \theta_1 )</th>
<th>( \theta_2 )</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular Resolution</td>
<td>0.90</td>
<td>0.30</td>
<td>mdeg/count</td>
</tr>
<tr>
<td>Tool-tip Displacement Resolution</td>
<td>0.29</td>
<td>0.10</td>
<td>( \mu m )</td>
</tr>
</tbody>
</table>

For the second pose, the algorithm repeats with one significant difference: in this iteration, the system determines \( \mathbf{p}_{RCM} \) using the method from Section 4.1.3.1. This results in a more accurate estimate of \( \mathbf{p}_{RCM} \) and likewise more accurate values for \( \theta_1^* \) and \( \theta_2^* \). The IRISS then commands the first two joint angles to attempt a cancellation of \( d_e \) and the algorithm repeats again. If additional iterations are required, then three or more known centerlines are used to calculated \( \mathbf{p}_{RCM} \). Once \( d_e \leq d_t \), Step 5 is considered complete: the micropipette accurately “points at” \( \mathbf{p}_C \) such that the user only has to increment \( d_3 \) to access the vein and achieve cannulation.

### 6.5.1 Image Processing for Micropipette Centerline Detection

This section describes the image-processing algorithm to detect the micropipette centerline. No error is associated with the definition of \( \mathbf{p}_C \); it is simply a point defined in \( \mathcal{F}_O \). The background noise of OCT data acquisition using the Thorlabs system is shown in Table 6.4.

At the beginning of this step, \( \mathbf{p}_t \) is near \( \mathbf{p}_C \) and approximately a distance \( \lambda \) from the
Table 6.4: Baseline Noise of OCT Data (B-scans)

<table>
<thead>
<tr>
<th>Direction</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Maximum</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \hat{X}_O )</td>
<td>0.61</td>
<td>0.42</td>
<td>1.84</td>
<td>70</td>
</tr>
<tr>
<td>( \hat{Z}_O )</td>
<td>3.38</td>
<td>2.55</td>
<td>12.40</td>
<td>70</td>
</tr>
</tbody>
</table>

* All values except \( n \) are in units of µm

retinal surface. The OCT probe is translated upwards such that the retinal surface is in the bottom 2 mm of the scan range. This configuration maximizes the amount of the micropipette that can be imaged by the OCT while maintaining view of the surface of the retinal vein phantom.

A volume scan is acquired and each B-scan processed. The retinal surface is segmented by fitting a line (Figure 6.13a) to peaks in intensity in the bottom region of the scan. This line is used to define a region of interest, which is motion blurred in \( \hat{Z}_O \) to produce Figure 6.13(b). By averaging the intensity values of the region of interest in \( \hat{Z}_O \), and applying a smoothing filter to these data, the global minimum points can be discerned. These points are down-sampled based on their near-neighbor gradients to isolate only the points assumed to be within the tool shadow. The average \( x \) value of these points is assumed to be the shadow center, while the width of the shadow is calculated and used as a measure of shadow width. This process is repeated for all 400 B-scans in the volume scan.

To guarantee all found shadow center points are within the shadow, the points which do not have a corresponding shadow-width value within an expected range (1.50–1.65 mm) are rejected. The remaining points are used to determine the edge of the stainless steel portion of the tool, \( p_S \) (Figure 6.14a). The value of \( p_S \) corresponds to a B-scan number; in this example, \( p_S = 120 \). The remaining shadow-center points are then processed to eliminate outliers and fit with a line (Figure 6.14b). This line is the shadow centerline.

Finally, all data beneath the retinal surface is summed to produce an image of the micropipette, as shown in Figure 6.14c. During the offline calibration procedure, the shadow
Figure 6.13: Example of processing a B-scan for shadow detection. (a) B-scan data. (b) Region of interest. (c) Data processing.

centerline is overlaid atop this image. It is then adjusted by a constant angular and linear offset to conform to the centerline of the “tool tip” (the glass portion of the micropipette). This adjustment is necessary because the centerline of the shadow (cast by the stainless-steel portion of the tool only) cannot be guaranteed to be colinear with the centerline of the glass tip due to errors in manufacture. It is only necessary to calculate these offsets once and they remain consistent over the operational life of a micropipette. The resulting centerline, $t_\ell$, is used to align the tool (Section 6.5.2) as well as compile a useful B-scan for determining error in $\theta_1$, next.

Using the volume scan acquired for this process, the detected micropipette centerline is used to compile a custom B-scan of the micropipette as follows. Noting that a fully horizontal
Figure 6.14: Method to detect tool centerline. (a) Data for edge detection of stainless steel portion of micropipette. (b) Line fit. (c) Found centerline overlaid atop micropipette.

B-scan would fail to capture portions of the tool, the detected micropipette centerline is instead used as the B-scan center, thereby guaranteeing that the B-scan is colinear with the tool. However, due to misalignments or miscalculations, it is possible this single B-scan does not fully encompass all of the micropipette tool tip. To avoid this outcome, several custom B-scans, defined as planes parallel to the first, are also found and summed into a single 400 × 1024 px intensity dataset (Figure 6.15a). Note, even in the produced image, data of the glass tip is insufficient for standard image-processing algorithms. Furthermore, once the micropipette enters the retina, it may be impossible to localize $p_t$.

For these reasons, the stainless steel portion of the tool is used as an easy-to-detect fiducial and related to the actual tool tip and tool centerline by angular and linear offsets. It is known that steel has a high reflectivity in OCT data and this characteristic is exploited here. The steel portion is found and fit with a line (Figure 6.15b) and the edge of the steel part is also found. The line and edge point are sufficiently invariant to tool motion and are
used to define constant offsets for the true centerline and the tool tip (Figure 6.15). It is only necessary to calculate these offsets once and they remain consistent over the operational life of a micropipette.

Figure 6.15: Determination of micropipette centerline and tip position. (a) Custom B-scan. (b) Steel portion of tool with line fit. (c) Overlaid tool centerline and tip.

The image-processing algorithm outputs the $\theta_1$ tool centerline (from the side view) and the $\theta_2$ centerline (from the top view). These are calculated for every iteration of the fine-tuning process (Section 6.5.2).
6.5.2 Iterative Fine-Tuning Process

Figure 6.16 illustrates an example of the iterative process to align $\mathbf{t}$ to $\mathbf{p}_C$. In this example, four micropipette poses (three iterations) were required. The driving metric behind the algorithm is to minimize $d_e$ (Equation 6.9) by commanding $\theta_1$ and $\theta_2$ to move the tool centerline increasingly closer to $\mathbf{p}_C$ (Figure 6.17). A constant threshold, $d_t = 20 \mu m$, is set for $d_e$. Once $d_e < d_t$, the iteration is considered complete and the system progresses to the next step.

In Pose 1, Figure 6.16(a), the tool centerline is detected and $d_e$ is calculated as 392 $\mu m$. A guess must be made regarding the location of the RCM based on the forward kinematics of the IRISS. This guess results in $\theta_1^* = 2.46^\circ$ and $\theta_2^* = 1.24^\circ$. The IRISS is commanded to move the joint angles by these amounts.

In Pose 2, Figure 6.16(b), the $\theta_1$ motion has resulted in the tool centerline approaching $\mathbf{p}_C$, but the $\theta_2$ motion overshot $\mathbf{p}_C$ and resulted in larger absolute error (Figure 6.17). Regardless, a second OCT volume scan is acquired and the tool centerline is re-found. The system now has two centerlines available: the previous centerline from Pose 1 and the current centerline from Pose 2. Therefore, an improved estimate of $\mathbf{p}_{RCM}$ can be calculated (Section 4.1.3.1). Using this updated RCM position results in $\theta_1^* = 1.77^\circ$ and $\theta_2^* = -1.69^\circ$. The IRISS is commanded to move the joint angles by these amounts.

In Pose 3, Figure 6.16(c), the motion of both $\theta_1$ and $\theta_2$ has resulted in a reduction of $d_e$, as desired. However, $d_e < d_t$, and therefore the joints are commanded to move once more to result in Pose 4, Figure 6.16(d). In this pose, $d_e = 0.256 \mu m$ and the algorithm is considered complete. As expected, $\theta_1^* = -0.0132^\circ$ and $\theta_2^* = 0.0142^\circ$ are small.

6.6 Step 6: Vein Cannulation

At the initiation of Step 6, control is relinquished to the user. The vein-access problem has been reduced to a single degree of freedom such that the user only has to increment $d_3$ to access the vein.
The user guides the micropipette forward in constant $10\,\mu m$ increments while being provided with top-down camera feedback as well as a pair of OCT B-scans. One B-scan images along the centerline of the micropipette, while the second intersects the tip and is
Once $p_t$ pierces the retinal phantom surface, the OCT is unable to clearly image a visual difference between the silicone of the model and the glass of the micropipette. Therefore, a marker is overlaid atop the OCT B-scan at $p_t$ and tracks the micropipette as it passes through the retinal phantom into the vein (Figure 6.19). This overlay is determined from image processing (Section 6.5.1) and then updated based on the $d_3$ joint encoder feedback. In addition, a point is overlaid atop the OCT B-scans to indicate $p_C$. These overlays allow the user to track the progress of the micropipette even when it is invisible inside the retina.

Once the micropipette pierces the vein, $p_t$ becomes visible again. If the user is confident cannulation was successful, an automated “full infusion procedure” can be executed. However, if there is any doubt, the user can instead choose to execute an automated “test injection procedure.” The test injection procedure executes as follows:

1. The micropipette tip is flickered in $\theta_1$ and $\theta_2$ by $\pm 0.1^\circ$, corresponding to approximately
15 µm of tip displacement at a rate of 100 Hz.

2. The vein is infused at low pressure (5 psi) in a quick burst (500 ms).

3. The camera image is captured and automatically processed to detect color change (red to green) in the vein.

First, the micropipette flicker has been shown to facilitate piercing of the vein in the event the silicone substrate has not parted under the piercing motion of the micropipette. Note, the necessity of the micropipette flicker is a deficiency of the model material and not the system. However, this functionality may be beneficial when performing RVC on biological models to facilitate cannulation or prevent double-piercing. Second, the test injection procedure involves infusing a quick (500 ms) burst of anticoagulant analog at low pressure (5 psi). This pressure is sufficiently low that—in the event the vein is not cannulated—no reflux or sub-retinal bled formation will occur. However, if the vein is cannulated, then the test
injection will successfully infuse the vein. In this event, the color change is detected by the system (Figure 6.20), which automatically executes the full infusion procedure, next.

### 6.7 Step 7: Infusion

With the vein successfully cannulated (either by user guidance or by automated confirmation by the system), the vein is infused at the desired pressure (25 psi) and for the full duration (5 s), as directed by the user. For practical considerations, a duration of 5 s was selected for the present tests. Once the final duration has been reached, the infusion pressure is set to 0
Figure 6.20: Automated camera-based detection of successful test injection.

Figure 6.21: External camera view of successful infusion.

and the step is considered complete.
6.8 Step 8: Tool Retraction

Finally, the tool is automatically retracted from the retinal vein phantom and virtual eye model. The extraction trajectory is purely a function of $d_3$ with $\theta_1$ and $\theta_2$ held constant at their previous values. The micropipette retracts approximately 3 mm from $p_{SI}$, at which point all joints and the XYZ stage are commanded to their homed positions. Final data is recorded and the system reverts to standby mode. At this point the surgical trial is considered complete.
CHAPTER 7

Experimental Validation

To evaluate the developed system on its ability to perform retinal vein cannulation (RVC), the system was used to cannulate and infuse \( n = 30 \) retinal vein phantoms. For these trials, three vein sizes were chosen: 120 \( \mu \text{m} \), 160 \( \mu \text{m} \), and 200 \( \mu \text{m} \). These three sizes represent the full range of \textit{in vivo} human retinal vein diameters reported in the literature (Table 5.2). The author assumed the role of the user and the trials were performed over the course of one week. The developed software (Figure 7.1) was used to perform cannulation and infusion in all trials as discussed in Chapter 6. For surgical validation, it was sufficient to demonstrate the ability to cannulate a retinal vein and infuse it with a liquid. The effectiveness of anticoagulants and their ability to dissolve clots are widely studied and accepted—therefore, it was unnecessary to demonstrate clot dissolution in this evaluation.

7.1 Surgical Evaluations

The metrics by which the performance was evaluated were:

1. \textit{Total Trial Time}: Measured from beginning to end of a trial. This corresponds to the amount of time the micropipette would spend inside the eye.

2. \textit{Time to Achieve Cannulation}: Measured as the time elapsed between the end of Step 5 and the initiation of Step 7. This is the amount of time the user spent moving the micropipette before achieving cannulation.

3. \textit{Number of Test Injections}: Counted as the number of test injections before vein cannulation was confirmed.
4. **Surgical Complications**: This metric includes reflux of anticoagulant analog onto the retinal phantom surface and sub-retinal bleb formation.

5. **Infusion Success**: Did the anticoagulant analog fill the vein and exit the model? Assessed through visual inspection.

The total time to achieve cannulation was recorded by the system as the time from when the system relinquishes control to the user at the initiation of Step 6 to the time when the user requests the system begin full infusion at the end of Step 6. In other words, it is a measure of how long the user spends guiding the micropipette before cannulation is confirmed. The durations were analyzed after completion of all trials (Figure 7.2). The average time was 10:01 minutes. The minimum amount of time was 7:25 minutes, which occurred in the ∅200 µm retinal vein phantom; the maximum amount of time was 15:23 minutes, which occurred in the ∅120 µm retinal vein phantom. In general, the ∅200 µm retinal vein phantom required less time to cannulate than the larger sizes, as expected due
to the increased ease of confirming cannulation in larger veins.

![Time to Confirm Cannulation](image)

**Figure 7.2:** Time to achieve cannulation in all trials.

The number of executed test injections before successful cannulation was achieved was recorded by the system and analyzed after the completion of all trials (Table 7.1). The minimum number of test injections (zero) occurred for the larger veins (Ø160 and Ø200 µm). Here, “zero” test injections implies the user was confident the vein was cannulated and chose to skip the test injection in favor of proceeding to full infusion. On the other hand, the maximum number of test injections was nine, occurring with the Ø120 µm vein. Post-trial analysis revealed this large number of test injections was necessary because the retinal vein was located above an air gap in the sclera (a defect of the phantom) and therefore was more flexible and resistant to piercing than in other trials. In general, the smaller the vein, the larger the mean number of test injections before successful cannulation was confirmed. This makes sense, as with decreasing vein diameter, the amount of useful visual data in the OCT B-scan decreases. Note, for unsuccessful test injections (the vein is not cannulated), no visible complications occur (Figure 7.3a). This allows the user to modify the tool depth and re-attempt cannulation.

Two surgical complications were defined and their occurrence recorded: reflux and sub-retinal bleb formation. In reflux, the micropipette tip was too anterior and infusion at full pressure caused all or a portion of the anticoagulant analog to leak (reflux) onto the retinal
Table 7.1: Number of Test Infusions before Successful Cannulation

<table>
<thead>
<tr>
<th>Vein Diameter</th>
<th>Minimum</th>
<th>Mean</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ø120 µm</td>
<td>1</td>
<td>3.2</td>
<td>9</td>
</tr>
<tr>
<td>Ø160 µm</td>
<td>0</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>Ø200 µm</td>
<td>0</td>
<td>0.5</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 7.3: (a) Unsuccessful test injection (vein is not cannulated). (b) Reflux of anticoagulant analog into the vitreous. (c) Sub-retinal bleb formation.

phantom surface (Figure 7.3b). In surgical practice, this would be considered unsatisfactory due to the large cost associated with anticoagulants ($6400 per 100 mg vial in 2014 [KBD17]). In sub-retinal bleb formation, the micropipette tip was too posterior and infusion at full pressure caused all or a portion of the anticoagulant analog to form a bleb in the sub-retinal space (Figure 7.3c). In the context of RVC, sub-retinal injection would be considered unsatisfactory due to the surgical complications associated with unintentionally injecting an anticoagulant beneath the retina.

Both reflux and sub-retinal bleb formation were recorded by post-trial analysis of the acquired camera images (Table 7.2). Reflux was more common, occurring in one trial with a Ø120 µm vein and in a second trial with a Ø160 µm vein. Sub-retinal bleb formation was recorded only once, in the Ø120 µm vein. None of the trials with the Ø200 µm vein suffered from either surgical complication. These results suggest that the smaller the vein diameter, the more likely that surgical complications will result.
Finally, for infusion success, all \( n = 30 \) trials were deemed successful, as the anticoagulant analog filled the vein and exited the model. This is confirmed by analysis of the video recorded during each trial.

### 7.2 Engineering Evaluations

A series of engineering performance metrics were recorded:

1. **Total OCT Acquisition Time for Volume Scans**: Measured as the scan time for all volume scans acquired during a trial.

2. **Total Time Spent Moving OCT Z-Stage**: Measured as the program runtime between command send and motion settle of the OCT z-position.

3. **Number of Iterations for Tool Alignment**: The number of iterations the system required before the tool was considered aligned.

The total trial was also recorded by the system (Figure 7.4).

The total OCT acquisition time for volume scans was 210.7 ± 51.6 s (minimum: 175 s; maximum: 386 s). The minimum number of scans is five: one for modeling the retinal vein, one for the initial micropipette-centerline detection, one for a second micropipette-centerline detection, one for a third micropipette-centerline detection, and a final scan for micropipette-tip detection to create the OCT overlay. With an approximate acquisition time
of 35 s, this results in the 175 s recorded in the cases where the micropipette was aligned in only three iterations. However, this total increases by 35 s for every additional iteration of the fine-tuning orientation.

The total time spent translating the OCT Z-stage was 70.6 ± 16.8 s (minimum: 46 s; maximum: 102 s). The variance is small as expected because the probe translated distance is a function of the model height, which is consistent between trials. However, large deviations were a result of the system not being fully homed in-between trials.

![Figure 7.4: Total time divided into four sources.](image)

The number of alignment iterations was 4 ± 1.46 (minimum: 3; maximum: 9). These required 178.5 ± 65.0 s (minimum: 130 s; maximum: 404.7 s) to execute. The large deviation is the result of OCT-generated noise and signal loss in the acquired volume scans which negatively affected the performance of the image-processing algorithm to detect the micropipette centerline. With poor-quality data input, a non-repeatable centerline will skew
the calculated joint-angle correction and result in several additional iterations before the error magnitude was reduced. The minimum number required was three, requiring approximately 130 to execute: 105 s to acquire the volume scans, 30 s to run the image-processing algorithm.

For the additional system time (Figure 7.4), these values are approximately equivalent between all trials: 152.0 ± 10.0 s (minimum: 128.0 s; maximum: 181.3 s). They are purely a function of the system algorithm and incorporate such processes as moving the XYZ stage, saving data, and transitioning between steps, which are not a function of the model or user performance.
CHAPTER 8

Conclusions and Future Work

This work presented a robotic system capable of performing automated retinal vein cannulation on custom retinal vein phantoms. The developed system reduces the complex, stressful problem of retinal vein access to guidance of a single translational motion for the surgeon by automating critical steps of the process. These automated steps include: (1) safe guidance of the micropipette to a near-vein position, (2) provision of augmented optical coherence tomography and camera feedback during the critical cannulation step, (3) automated confirmation of successful vein cannulation, (4) maintenance of a stationary position during prolonged infusion, and (5) safe guidance of the micropipette out of the eye following successful cannulation. The system was evaluated through a series of 30 trials and shown to be capable of performing retinal vein cannulation with minimal surgical complication. It is expected that the developed technology can lead to improvements in other intraocular surgical procedures including sub-retinal injection.

Future work includes transitioning to ex vivo and in vivo pig eye models, extending the system to include the ability to automatically perform sub-retinal injection, and developing an automated procedure for segmentation and tracking of the vein during cannulation. In addition, incorporation of a piezo actuator for the translational motion of the micropipette could facilitate additional piercing techniques such as a high-frequency, low-amplitude vibration or an automated piercing procedure. Enabling rotation of the glass micropipette may also facilitate vein piercing, as the beveled tip could “carve” a hole into the tissue. Finally, improvements to the retinal vein phantom include the addition of retinal layers, identifying a less-rigid material, and improving the overall visual appearance by shaping it into a circular depression.
REFERENCES


