Assistive Device for Efficient Intravitreal Injections

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ABSTRACT: Intravitreal therapy is the most common treatment for many chronic ophthalmic diseases, such as age-related macular degeneration. Due to the increasing worldwide demand for intravitreal injections, there exists a need to render this medical procedure more time- and cost-efficient while increasing patient safety. The authors propose a medical assistive device that injects medication intravitreally. Compared to the manual intravitreal injection procedure, an automated device has the potential to increase safety for patients, decrease procedure times, allow for integrated data storage and documentation, and reduce costs for medical staff and expensive operating rooms. This work demonstrates the development of an assistive injection system that is coarsely positioned over the patient’s head by the human operator, followed by automatic fine positioning and intravitreal injection through the pars plana. Several safety features, such as continuous eye tracking and iris recognition, have been implemented. The functioning system is demonstrated through ex vivo experiments with porcine eyes.


INTRODUCTION
Since the approval of the first intravitreally applied drugs for the treatment of age-related macular degeneration (AMD), intravitreal injections have become one of the most frequently performed surgical procedures in ophthalmology, with more than 4 million injections worldwide in 2014. The demand for intravitreal therapy (IVT) of various drugs, including mostly vascular endothelial growth factor (VEGF) inhibitors, evolved dramatically during the past decade. The demand for IVT to treat the chronic diseases AMD and diabetic maculopathy/retinopathy is especially high and will increase in the foreseeable future due to increasing prevalence of diabetes mellitus and age demographics, especially in industrialized countries. To cope with the increasing demand for IVTs, we propose an assistive device capable of performing intravitreal injections into the vitreous cavity of the eye. The system allows for precise and safe injections but is still controlled and monitored by the treating physician.

Intravitreal Therapy
Pharmaceutical companies discovered IVTs as a new area of investment and development. For the first time, ophthalmic drugs achieve more than $1 billion in U.S. revenue. Even more intravitreal drugs for an expanding spectrum of ophthalmic diseases are likely
to be introduced to the market in the near future, thus severely raising the number of IVTs and the related health care costs. The access to IVT will further increase with the beginning of the expiration of the patent of the popular approved anti-VEGF drug ranibizumab (Lucentis; Genentech, South San Francisco, CA) in 2017. This may open the market for generics. In addition, the off-label use of other VEGF inhibitors, such as bevacizumab (Avastin; Genentech, South San Francisco, CA) and ziv-afibercept (Zaltrap; Sanofi Genzyme, Bridgewater, NJ) — both approved for cancer treatment — is common in some countries (eg, the United States), despite serious issues of compounding. However, the cost of off-label drugs is up to 10-times lower than that of approved agents.8 With decreasing drug cost, a larger population will gain access to treatment.

There is increasing pressure on reducing the compensation for intravitreal injection, mostly performed by doctors.9 Physicians and hospitals are struggling to manage an increasing workload while obtaining reduced reimbursement. This situation calls for a radical change in the way ophthalmologists deliver IVTs. A challenge arises as the IVT needs to remain under the control of physicians, but costs are to be minimized. Thus, the time the physician spends performing IVTs has to be significantly reduced while maintaining or even increasing safety and precision of the IVT for patient safety. In this context, the system we propose allows for automated, remotely controlled intravitreal injection and fulfills a large number of requirements.

**Related Robotics**

Perhaps the most well-known example of a surgical robot is the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) that was designed for general laparoscopic surgery and gained U.S. Food and

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**Figure 1.** The system overview summarizes the system's functions, such as the general automated injection, the local sterile environment, a communication system, and the user interface.
Drug Administration approval in 2000. This master-slave surgical system consists of three arms for surgical tools and one arm with a camera that provides stereoscopic 3-D vision for the surgeon. Currently, it is being used for many medical procedures in the fields of urology and gynecology. Other medical devices that do not comprise of the more traditional robotic manipulation systems are based on eg, magnetic actuation, or radiotherapy. Respective examples are the EPOCH system (Stereotaxis, St. Louis, MO) and the Aeon Phocus (Aeon Scientific, Zürich, Switzerland) that provide catheter steering by magnetic guidance and the CyberKnife (Accuray, Sunnyvale, CA) that delivers radiotherapy.

The first automated laser-assisted surgery was reported in the 1980s to reshape the eye’s cornea in order to improve visual acuity. In general, robotic assistance is of particular interest for ophthalmic interventions as the required manipulation dexterity and force perception lies below human capabilities. To overcome these limitations, various robotic platforms have been proposed as assistive tools for ophthalmic surgery. Examples are active support systems that filter human hand-tremor (Micron) or systems that provide cooperative manipulation of surgical tools (Steady-Hand). Teleoperated systems, such as the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA), the Preceyes Surgical System (Preceyes, Eindhoven, the Netherlands), or a parallel robot for vitreoretinal surgery translate the surgeon’s hand motion to the scaled motion of tethered surgical instruments. Although such tethered systems leave an incision with protruding surgical tools during intravitreal operation, untethered devices exist that can be inserted with minimal invasiveness in the eye and guided without any physical connection to the outside world. The OctoMag (ETH Zurich, Zürich, Switzerland) is such a system and can guide an untethered magnetic microrobot in the vitreous humor of the eye.

Although all mentioned systems provide capabilities for direct medical interventions (eg, surgery), more recently, an increasing interest has been observed in the system development for more specific procedures. One example is a medical device that enables automated intravenous injections for drawing blood or delivering fluids. Currently, two devices have been designed for such automated venipuncture, namely Veebot (Veebot LLC, Mountain View, CA) and VenousPro (VascuLogic LLC, Piscataway, NJ). Both systems use real-time imaging and robotic techniques for improved needle-based procedures and aim for complete automation. One reason for the development of such system is the frequency these procedures are carried out. Venipuncture is one of the most routinely performed invasive procedures and, depending on regulations, performed by physicians or other nursing staff.

**Robot-Assisted Injection Procedure**

Here we propose an automated system that assists ophthalmologists during the administration of intravitreal injections with high positioning accuracy, repeatability, and several integrated safety features.
The proposed system consists of two modules and is suspended from a passive arm with lockable joints. The positioning module allows for computer assisted placement of the injection module. The injection module is suspended from the positioning module and is responsible for orienting a prefilled syringe with an attached injection needle to a preselected location on the sclera and inject medication into the vitreous cavity of the eye.

**System Requirements**

The assistive system for automated intravitreal injections was designed according to several requirements concerning patient and physician safety, cost and time efficiency, and usability of the system as summarized in the Table. To ensure safety of the system, it must be sterilizable and the precision of the injection must be high, with position accuracy of the needle of less than 100 µm and orientation accuracy less than 1°. The patient and eye must be correctly identified and the pupil of the treated eye must be tracked at all times, such that the injection procedure can be stopped in case of patient motion. To prevent eye motion, the system should include a stable fixation of the patient’s direction of gaze. The position control of the system should be based on anatomic landmarks of the patient to account for anatomical differences among patients. To prevent multiple injections into the same location, which might cause thinning of the sclera, a history of previous injections and their locations should be saved for each patient. In order to render the assistive device attractive to the market, time and cost efficiency of the injection procedure must be provided by reducing the time spent by the physician to a maximum of 1 minute per injection. Thus, the system should allow for automated documentation of the procedure and the possibility to inject different drugs into the patient’s eye. Also, the system should be remotely controlled, such that one physician can supervise several patients at the same time. To ensure easy handling and usability of the system, it must allow for quick positioning over

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<th>Requirements</th>
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<td>Safety</td>
<td>Reduction of bacterial contamination and sterilizability; better position accuracy &lt; 100 µm; orientation accuracy &lt; 1°; safety automated recognition of patient and eye; eye tracking at &gt; 15 Hz; stable fixation of the patient’s direction of gaze; control based on anatomic landmarks; possibility to save injection history</td>
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<tr>
<td>Cost/Time Efficiency</td>
<td>Remotely controlled system; possibility to inject several different drugs; automated documentation of procedure</td>
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<tr>
<td>Usability</td>
<td>Lightweight (&lt; 5 kg); audio-visual communication between patient and doctor; located in an operating room or defined injection room</td>
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**Figure 3.** A computer vision algorithm allows for continuous pupil tracking during the injection process. The pupil and its center are tracked from different sides to determine the eye’s orientation in 3-D: (A) top view, (B) side view.
the patient’s face by a nurse, constraining size and weight. In order to account for guidelines concerning location of the intravitreal injection procedure,9 the injection system must fit into an operating room or a designated injection room. Audiovisual communication between patient and doctor should be included to increase patient acceptance.

System Outline
The proposed system for intravitreal injections and its multiple functions are outlined in Figure 1. According to the requirements, the system consists of a wall- or ceiling-mounted dome that can easily be positioned over the patient’s face by a human operator (ie, a nurse), using only one hand. The shape of the dome allows for the establishment of a local sterile environment utilizing laminar airflow. The hemispherically shaped casing covers all essential parts for the injection procedure, such as the mechatronic system, which moves a needle with high precision to the selected injection site on the sclera. For patient convenience, an audiovisual communications system is added, which consists of a camera system, a screen, a speaker, and a microphone. To allow for several medications to be injected into the eye, external drug reservoirs are attached. Alternatively, a prefilled syringe23 can be directly clipped into a fitted holder for injection. For physician convenience, the system features an intuitive user interface that allows for remote control of the injection procedure. Prior to injection, the camera identifies the patient through an iris scan. In order to increase time efficiency, the system automatically documents and saves the patient’s injection history in a database.

Preparation of the Procedure
Prior to the intravitreal injection procedure, the patient is prepared by a nurse according to the standard of care. The nurse gives local topical anesthetics, spreads the eyelids using a speculum, and disinfects the eye. The nurse then manually positions the system coarsely over the patient’s head by moving the passive arm into position and locking the joints. The system is illustrated hanging over a patient’s head in Figure 2. Visual information provided by a vision system during the injection process allows for automated fine adjustment of the system over the treated eye.

Iris Recognition
The human iris offers a unique, stable pattern, which has been shown to be suitable for person and eye identification.24 Thus, automated iris recognition of the patient’s iris has been implemented into the system for safety. In daily practice, human error may lead to injections into the wrong eye (eg, left instead of right), or the wrong patient (eg, two patients with the same or a similar name). If the wrong medication or a different dose of the drug is injected, treatment of the eye’s disease may not be optimal. Thus, we implemented an iris scan that is executed after initialization of the injection procedure. The algorithm compares the iris to previously stored patient images.

Figure 4. The safe region for intravitreal injection spans between ± 80° from the horizontal on the temporal side of the eye with a radial distance of 3.5 mm to 4 mm from the limbus.
in a database. The injection process is started only if the iris is recognized as the right patient and eye.

The iris recognition algorithm initially acquires an image of the eye under near infrared illumination, thereby reducing specular reflections and revealing the complex features of the iris pattern. Subsequently, the pupil and iris are detected utilizing the intensity gradient at the boundaries of the latter. The iris is isolated from the image and converted into a rectangular form by applying a coordinate transformation. Specular reflections in the iris are filtered by thresholding the image and can be ignored during further analysis. Convoluting the unwrapped iris with a Gabor filter results in a binary iris code\[^{25}\] that can be compared to the saved image codes in the database. In a next step, the degree of similarity of two codes is determined by deriving the Hamming distance as a ratio between disagreeing bits to the total number of bits in the binary codes.

**Pupil Tracking**

A tracking algorithm has been implemented to track the position of the pupil of the eye. During the injection process, several cameras continuously take images of the targeted eye. An algorithm analyzes the images and outputs the relative position and orientation of the eye. Pupil tracking, as illustrated in Figure 3, has been implemented to supply visual feedback to the motor controllers. The pupil and its center are tracked from different angles, such that the eye’s orientation can be determined in 3-D. Additionally, pupil tracking offers increased safety to the patient. As soon as the eye moves more than the allowed distance or if the eye moves fast, the system...

![Figure 5. Four examples of successful iris segmentation under demanding conditions, such as eyelash and eyelid occlusions and changing light conditions.](image-url)
detects the eye motion and automatically stops the injection procedure.

**Eye and Head Fixation**

The standard of care to fixate the patient’s direction of gaze is to ask to look at a specific point in the room during manual injection. To fixate the eye during an automated injection process, a screen is integrated into the system. The patient can choose to view a personal image. Alternatively, the patient is given a task, such as counting the red stars on the screen. This small activity helps to focus the patient’s attention to the screen rather than to the injection needle and fixates the eye in a predetermined orientation.

As illustrated in Figure 2, the patient lays on his or her back during the procedure. The patient’s head is placed on a surgical pillow with an indentation for the head to prevent backward or sideward head movement. Additionally, by tracking the pupil, the automated system has knowledge of the relative position of the patient’s eye, despite any small head or body motion, and can adjust. In the case that the patient’s head or eye movement exceeds a velocity or position threshold, the system terminates the procedure and retreats to its initial position.

**Intravitreal Injection**

The assistive device automatically suggests a point for safe injection on the pars plana that lies within a range of 3.5 mm to 4 mm from the limbus and within an angle of ± 80° on the temporal side of the eye, as illustrated in Figure 4. This region is chosen to avoid injecting into the crystalline lens of the eye on the one side and the retina on the other (Figure 4A) and allows for an additional safety margin. The preselected injection position can be altered manually by the treating physician on a user interface (UI). When all changes and data are submitted, the ophthalmologist initiates the injection procedure on the UI. To account for patient comfort, the system allows for direct visual and auditive interaction between physician and patient through the use of a screen, microphone, speaker, and two cameras.

After initialization of the injection process, the system first centers itself over the treated eye. Then, the injection needle is aligned with the intended injection point on the sclera with a predetermined orientation. Finally, the needle is moved linearly into the eye and medication is delivered intravitreally. The positioning accuracy during fine adjustment of the system is 0.05 µm with a bidirectional repeatability of 1.6 µm. The theoretical positioning resolution of orienting the syringe over the injection point is $6.8 \times 10^{-5}$ degrees. Presumably, the precision is lowered during actuation due to backlash in the mechanical system or uncertainties during visual tracking.

**Patient Data Documentation**

A Swiss survey shows that the average time a physician spends on documentation and administrative tasks increased from 15.8% in 2011 to 17.1% in 2013, leaving less time for patient interaction. In
practice, the average time for one intravitreal injection process, including preparation and documentation time, is approximately 10 minutes, of which the actual injection procedure only takes 1 minute to 2 minutes. To decrease the time needed for documentation, a system is implemented that allows to directly save a patient’s personal and medical data into a database. These data may include the patient’s name, date of birth, and patient number, as well as his/her medical condition, suggested treatment, and type and amount of the injected drug. After each intravitreal injection process, the physician can submit all changes made to the patient database, where information is saved as binary code to account for storage space. Storing patient data in a database has the advantage that information is made available and searchable throughout the injection process efficiently.

EXPERIMENTAL VALIDATION

To evaluate the injection system, the iris recognition algorithm and the injection process are demonstrated through experiments.

Iris Recognition

The iris recognition was tested by evaluating the segmentation and recognition performance. Segmentation performance is evaluated by applying the algorithm to 2,739 images from an eye database, which offers demanding conditions as images feature eyelash and eyelid occlusions combined with changing illumination conditions. The algorithm achieved a 93.39% correct segmentation rate. However, in practice, the iris recognition algorithm will be used on images of patients’ eyes held open by a speculum, reducing occlusions and increasing the success rate. Examples of iris segmentation featuring eyelash and eyelid occlusions under changing light conditions are shown in Figure 5. To analyze the recognition performance, 100 images of 20 different eyes (ie, five images per eye) were taken and the Hamming distance was derived for all possible intraclass (same eyes) and interclass (different eyes) combinations. The resultant distributions are normalized and shown in Figure 6. The two distributions are completely separated, such that a Hamming distance threshold of 0.4 would result in 100% correct recognition rate.

Injection Procedure

To demonstrate the functions of the proposed assistive device for intravitreal injections, porcine eyes are injected during ex vivo experiments. The experimental setup is illustrated in Figure 7. Cadaver eyes were obtained from the local abattoir and experiments took place less than 10 hours postmortem. A porcine eye was fixed in a rubber holder and placed within the reach of the passive arm. First, a human opera-
The robotic system moved the passive arm coarsely over the pig eye and fixed it in position. Then the positioning module centered the injection module over the eye. Prior to injection, a region for safe injection was defined on the eye. Then the injection process was started, ignoring eye recognition.

Figure 8 depicts the steps of the injection procedure. Figure 8A shows the end-effector with the attached injection needle in its initial position. In a next step, the injection needle is aligned with the targeted point of injection on the pars plana by controlling the injection module (Figure 8B). By actuating the linear actuator in the end-effector, the injection is accomplished. Finally, the needle is retracted linearly and the assistive device moves back to its initial position. The experimental process was repeated 10 times and the true injection point was compared to the targeted point for safe injection during post-processing. It was found that all 10 injections were within the safe region for injection on the cadaver eye.

**DISCUSSION**

Since initial developments in the mid-1980s, the use of robotic technology in surgery has increased dramatically. Specialty areas that adopted robotics for assistance were first explored in neurology, urology, and gynecology, and more recently, in ophthalmology. A historical review of these developments can be found in Ballantyne et al. and Lanfranco et al., and a more present overview is given in Bergeles et al. Advantages that robotic technologies have over traditional, human-operated procedures include an improved access to the surgical site, a higher technical precision of instrumentation positioning, and the possibility of tactile and visual feedback beyond human capabilities. Moreover, robotic devices enable teleoperation whereby the surgeon does not need to be present at the patient site, eliminating physiological tremor and fatigue while improving dexterity of the surgery. Furthermore, a surgical robot may be sterilized whereas a human surgeon provides limited sterility.

Despite these clear advantages for patient and surgeon, few automated medical assistive devices have made it past clinical trials and are routinely being used in hospitals. The disadvantages of robot-assisted surgery include limited adaptability of a system to a situation; thus, only simple surgical tasks are currently possible utilizing robots. Additionally, acquisition...
cost of a robot-assisted system for surgery is relatively high, adding cost to procedures with low throughput. However, surgical procedures with a high patient throughput, such as intravitreal injections, may become more efficient in terms of time and cost.

As demonstrated in an experimental setting, intravitreal injections can be performed by automated, remotely controlled systems in a most safe and precise manner. The requirements as listed in the Table can be technically fulfilled. Compared to today’s practice, the proposed system has multiple advantages. First, the precision of the intravitreal injection can be increased with regard to location, depth, and volume of the injection. Second, safety with regard to human errors, specifically in highly repetitive tasks, can be increased. The system recognizes the correct patient and eye using an iris scan. In clinics, treating large numbers of patients per day produces, despite all safety measures, imminent risk for human error such as selecting the wrong drug, treating the wrong patient (eg, poor hearing of elderly patients presuming their name to be called), or confusing left and right eye. An automated system with iris recognition avoids these risks. By having a closed drug-delivery system, mistakes in handling the drug (volume, air-bubbles, wrong drug) and bacterial contamination can be avoided. The most serious complication of an IVT is a bacterial infection in the eye, which can lead to rapid loss of not only vision but also of the whole eye. Off-label drugs used for intravitreal injections (eg, bevacizumab and ziv-aflibercept) are frequently compounded by external pharmacies. In the past, multiple series of severe infections in the eye occurred due to misconduct in compounding.22

In addition to the features mentioned above, further development of the assistive system includes a closed laminar airflow system. Laminar airflow is capable of reducing air contamination twentyfold compared to conventional operation room ventilation and removes 99.9% of particles larger than 3 µm.23 Moreover, since disinfection is needed only at the point of injection a disinfecting patch, through which the injection is given, is currently being developed in addition to a specific needle that is only exposed once it enters the eye. These features should minimize the risk of contamination and endophthalmitis.

The key aspect that makes an automated system attractive to clinics and physicians is the dramatic reduction in the physician’s time performing and documenting IVTs, and thus, a reduction in cost. In the setting of a large clinic in Zurich, Switzerland, (Department of Ophthalmology, City Hospital Triemli), performing more than 7,000 IVTs per year, the doctor’s time associated with the injection can be reduced from 10 minutes to a maximum of 1 minute. This frees up physicians’ time, allowing them to replace a tiring and very repetitive task by more valuable and demanding tasks, as well as leaving them more time for essential patient care. The cost of an automated device for intravitreal injections is similar to other technological systems used for ophthalmic surgery. Considering the saved physician time, the system amortizes within a time period of 2 years, without taking into account other high-value procedures, which may be conducted in the freed time. Moreover, by creating a local sterile environment (ie, closed laminar airflow) around the patient’s head, an expensive operating room becomes obsolete. Furthermore, the system allows the ophthalmologist to control and supervise the IVT from outside the injection/operating room. It is therefore possible to integrate performing IVTs in a regular outpatients clinic or even to perform them from remote locations. In addition, a very precise documentation of the procedure is amendable to electronic records, as well as automated billing. Both aspects can be easily integrated in the controlled conduction and surveillance of the procedure by the physician. In future, fingerprint recognition of the doctor performing the injections may help avoid situations where an untrained personnel member conducts an IVT with the system.

One of the key challenges will remain the acceptance of automated systems in medicine. The centerpiece of the patient-doctor relationship is the trust in the expertise and skills of the treating physician. With an automated system, the misperception of an anonymous robot taking over the medical care of a doctor could arise. It is therefore important that communication with the patient is part of the proposed system, allowing the patient to see his or her treating physician in a high-resolution screen and hear his or her voice. This will help to strengthen the fact that the doctor is treating an individual patient. Today, most patients understand that automated systems can be much more precise than a physician’s hand. Some automated systems, such as the da Vinci system for prostate surgery, have become the standard of care and the doctor’s use of an automated system is a sign for excellence and state of the art care.24 In ophthalmology, automated laser systems were first introduced many years ago. The first automated corneal laser surgeries were reported in the 1980s and have continuously been refined.25 No ophthalmologist would consider today removing corneal tissue manually for achieving ideal optical properties in refractive surgery. Relevant steps in cataract surgery are also now conducted by automated laser systems (ie, femto-phaco surgery).26 The trend for automated sys-
tems that allow better precision and safety is evident throughout medicine, but especially in the field of ophthalmology. An automated intravitreal injection system is, in our eyes, the next logical step.

CONCLUSION

This work outlines the potential of an automated assistive system for intravitreal therapy for the treatment of AMD and other chronic ocular diseases. The development of an injection system is demonstrated that consists of a positioning and injection module. Experiments with ex vivo porcine eyes show that the system allows for precise injection into the previously defined safe region for injection, such that neither the crystalline lens nor the retina is damaged. In conclusion, technical feasibility of an automated system for IVT is shown that offers a wide range of advantages in today’s care of the growing number of patients with medically treatable ocular diseases.

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