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Robotic Assistance for Intraocular Microsurgery: Challenges and Perspectives

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Abstract

Intraocular surgery, one of the most challenging discipline of microsurgery, requires sensory and motor skills at the limits of human physiological capabilities combined with tremendously difficult requirements for accuracy and steadiness. Nowadays, robotics combined with advanced imaging has opened conspicuous and significant directions in advancing the field of intraocular microsurgery. Having patient treatment with greater safety and efficiency as the final goal, similar to other medical applications, robotics has a real potential to fundamentally change microsurgery by combining human strengths with computer and sensor-based technology in an information-driven environment. Still in its early stages, robotic assistance for intraocular microsurgery has been accepted with precaution in the operating room and successfully tested in a limited number of clinical trials. However, owing to its demonstrated capabilities including hand tremor reduction, haptic feedback, steadiness, enhanced dexterity, micrometer-scale accuracy, and others, microsurgery robotics has evolved as a very promising trend in advancing retinal surgery. This paper will analyze the advances in retinal robotic microsurgery, its current drawbacks and limitations, as well as the possible new directions to expand retinal microsurgery to techniques currently beyond human boundaries or infeasible without robotics.

Index Terms

Medical robotics; robotic surgery; vitreoretinal surgery; sensing; control

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I. Introduction

Microsurgery, a type of surgery performed using miniaturized instruments and a microscope (or other type of magnification) for intricate and highly precise surgical tasks, requires specialised skills and capabilities only acquired through extensive training [1]. The miniaturization of sensors and actuators, combined with real-time computer processing, optics, and robotics has the potential to transform the way modern microsurgical interventions are performed. In micro-surgery, robotic assistance can provide significantly increased dexterity, controllability and precision, allowing surgeons to execute more precise and safer operations, or even pioneering previously impossible procedures. Applications of precision medicine based on robotic microsurgery already include a large range of surgical specialties like plastic and reconstructive operations, paediatric and fetal surgery, ophthalmology, otolaryngology, and urology. In vitreoretinal surgery, arguably the most demanding type of ophthalmic surgery, robotic assistance has reached a turning point, with clinically proven systems but with less visible market successes [2]–[4].

Therefore, this article intends to review typical and recent advances in robot-assisted retinal microsurgery, including an analysis of the challenges in modern retinal surgical practice and a rigorous evaluation of the current robotic systems used worldwide in research and, more important, in clinical applications. Equally important, the article emphasises the need of various instruments with embedded measurement functionality to complement vision toward a more profound real-time understanding of the tool-tissue interaction that in combination with different control strategies, could enable safe tissue manipulation under human control and, potentially, autonomous control. Furthermore, current barriers in clinical translation are identified along with real opportunities to address them such that, in addition to fine robotics, it could be possible to open the operating room door for robot-assisted retinal microsurgery.

This article is organized as follows. Section II reviews relevant intraocular surgical procedures, challenges associated with human factors, and the motivation for robotic assistance in retinal microsurgery. Section III discusses the current approaches in robotic systems for retinal surgery, state of the art, and clinical use cases. Section IV presents sensorized instruments for contact and proximity sensing, force sensing and puncture detection. Section V reviews robot guidance and control strategy while Section VI deals with clinical translation aspects. Finally, Section VII includes discussion on future directions and concluding remarks are presented in Section VIII.

II. Need of Robotic Assistance for Intraocular Microsurgery

Ophthalmic surgery, also known as eye surgery, is a type of microsurgery performed on the eye by an ophthalmic surgeon. Among the subspecialties of eye surgery, vitreoretinal surgery deals with surgical treatment of retinal and posterior segment diseases. It is recognized that vitreoretinal surgery is one of the most technically difficult types of microsurgery [5]. As one of the very fragile organs of the body, the eye requires extreme care before, during, and after a surgical procedure. Intraocular microsurgery requires surgeons to operate minimally invasive, manipulating slender instruments through small incisions in the sclera (sclerotomy), Fig.1. Inside the eye visualization happens through an operative stereo-microscope under difficult hand-eye coordination. Fine and very precise motion is essential to safely manipulate delicate tissue within the constrained space of the eye. The surgical forces are often below human tactile perception [6]. The main technical limitations include: inadequate spatial resolution and depth perception of targeted microstructures; imprecise movements during micromanipulation of tissue, often on the order of tens of microns, due to physiological hand tremor; and lack of force sensing since the movements required for dissection are below the surgeon's sensory threshold [5]. The challenges of retinal microsurgery are further exacerbated by the possibility of patient movement during surgery, leading to a higher risk of complications [4]. Last but not least, operating through a surgical microscope is associated with poor ergonomics that could lead to an elevated risk for back and neck injuries among ophthalmologists [7], and that further increase the difficulty of hand-eye coordination.

Some of the most relevant retinal procedures that may benefit from the use of robotic assistance are epiretinal membrane peeling, retinal vein cannulation, and subretinal injections [4]. Membrane peeling is an essential and challenging component of the surgical treatment of advanced diabetic retinopathy [9], macular pucker [10], and macular holes [11]. Epiretinal membrane surgery is the most common vitreoretinal surgery performed [12]. The procedure involves pars-plana vitrectomy, followed by lifting and peeling of the epiretinal membrane (on average $61 \pm 28\ \mu m$ [13] without harming the underlying retina [14]. The incidence of intra and postoperative complications ranges from 2% to 30%. The main complication here is that the surgeon easily can place the tool too deep, which traumatizes the retina and can result in hemorrhages or even in retinal injury.

Retinal vein occlusion (RVO) is one of the most common retinovascular diseases worldwide [15] and typically occurs when there is thickening of the crossing artery, low flow, hyper-coagulability, or thrombosis in the central retinal vein or its branches. The available treatments for RVO – including photocoagulation, hemodilution, radial optic neurotomy, vitrectomy and intra-vitreal injections – currently are focused on limiting the damage induced by the occlusion, rather than directly resolving the occlusion [16]. Retinal vein cannulation (RVC) is an experimental surgical procedure proposed to treat RVO by direct delivery of therapeutic agent to the site of occlusion. The procedure steps are: (1) accurately bringing a sharp-tipped cannula onto the occluded retinal vein, (2) puncturing through the vein wall and precisely halting the cannula tip at the right depth, and (3) maintaining the cannula inside the vein for several minutes, during which time the therapeutic agent – presently tissue plasminogen activator (t-PA) [17] or ocriplasmin [18] – is delivered to dissolve the obstructing thrombus. This is a very demanding and risky procedure because of the small size and fragility of retinal veins – especially if the occlusion is at a branch retinal vein (typically diameters $< 200 \mu m$) rather than the central vein. This is the key reason that this procedure is not employed in everyday surgical practice, as it is too challenging to perform manually.

Subretinal injection is a proposed method of accessing the subretinal space and providing treatment approaches to prevalent blinding diseases including but not limited to age-related macular degeneration (AMD), which is the leading cause of blindness in developed countries [19]. A number of stem cell-based therapies and gene therapies for the treatment of AMD have progressed to human clinical trials [20], [21]. Currently, the major technical challenge in these types of therapy is safe delivery of effective doses of substances to the target area. Following conventional pars plana vitrectomy, the surgeon penetrates the retina with a micro-cannula and injects controlled and precisely localized volumes into the subretinal space, whose thickness is under 250 μm [22]. Subretinal surgery raises significant safety issues, as the microstructural anatomy of the retina in AMD patients is fragile and the surgery can induce mechanical damage, reactive gliosis, and loss of function. Today's approach to ensure safety and performance of the first commercially available surgical protocols is to select and train dedicated surgeons per state or country. This approach is intrinsically limited to smaller indications that cannot be translated to broader applications such as AMD.

Similar to other types of surgery, robotic platforms offer potential advantages in the field of retinal microsurgery. They are able to filter physiological tremor and allow for motion scaling, thereby enhancing surgical precision. Furthermore, robotic platforms have the ability to keep instruments steady and, if necessary and safe, immobilized for prolonged periods, and offer better manipulation of instruments in smaller and confined spaces that are difficult to visualize due to challenging anatomy. Robotic platforms could be integrated with "smart instruments" and could provide real-time feedback on tool-to-anatomy interaction (force, position) enhancing safe surgical procedures. Owing to its precision, robotic assistance could enable surgical tasks currently beyond human capabilities, like microcannulation and subretinal injection. Similarly, robotic assistance could facilitate safe manipulation of more than two instruments, providing clear advantages in complicated cases (e.g., delaminations). Combined with narrower and/or flexible instruments, robotic platforms could assist the surgeon in performing advanced microsurgical procedures and have potential to decrease complication rates. Moreover, robotic assistance can improve the work and productivity of retinal surgeons: (1) by reducing the drawbacks related to human fatigue, offering enhanced dexterity for surgeons and allowing them to perform more operations per day at the same level of performance; and (2) by extending surgeons' professional careers with high levels of precision and dexterity, and allowing them to reach expert levels of performance earlier in their careers.

III. State-of-the-Art Robotic Systems for Intraocular Microsurgery

Numerous robotic systems have been conceived in the past decades by researchers across the globe. This section offers an encompassing overview of all governing platforms and discusses recent experiences in clinical experiments. Some basic requirements for a retinal microsurgery robotic assistant are that it should [2]: (1) be lightweight and compliant, allowing intimate and safe interaction between patient, clinician, and robot; (2) be easy to attach to the surgical table or fit into the hand and to be operated by clinical personnel; (3) incorporate or be interfaced with a visualization system providing the necessary resolution for microsurgical tasks; (4) provide hardware and software constraints to guarantee safe instrument manipulation outside and inside the eye; and (5) be safe and able to react appropriately to involuntary patient movements.

A. Different approaches

Three fundamentally different approaches can be distinguished: (1) telemanipulation, which provides tremor filtering and motion scaling; (2) comanipulation control, which focuses on tremor filtering, but lacks motion scaling; and (3) handheld, smart surgical tools, which focus on minimal impact on the workflow. In addition, a fourth concept of magnetically controlled microrobots, targeting minimally invasive approaches, should be mentioned [23], [24]. Remote magnetic navigation to control microsurgical instrumentation poses a different actuation paradigm to existing robotic approaches. It could allow for high dexterity and a (semi-) automated approach, while maintaining the benefits of micrometer precision, hand tremor removal, and telemanipulation. Research into specific tasks yields some promising results [25]. Nevertheless, the layout of a magnetic navigation system would intrinsically limit integration in the standard surgical workflow and the interaction forces would limit application to specific tasks. For retina surgery, this approach has not yet been considered other than in bench tests. Current commercial initiatives are focused on the before-mentioned assistive robotic approaches. Some advantages and disadvantages of these approaches are summarized in Table I.

1) Telemanipulation systems: In the telemanipulation approach or so-called leader-follower design, instruments can be attached to a separate robotic manipulator, whilst a motion controller is operated by the surgeon. The motion controller can be positioned either adjacent to the surgical site or at a separate console, and a computer translates the commands from the motion controller to the manipulator [26]–[30]. Telemanipulation robots provide tremor filtering and the ability to position an instrument at a predefined position for prolonged time. The main advantages of a telemanipulation robot include variable motion scaling and the possibility to provide (semi) automation of tasks. These advantages make the design particularly suited for a wide range of both static and dynamic tasks. The PRECEYES Surgical System [29] (Fig. 2) and the Intraocular Robotic Interventional Surgical System (IRISS) [30] (Fig. 3) are two relevant examples of telemanipulation systems, among many others.

2) Hand-over-hand or comanipulation systems: In the comanipulation or so-called hand-over-hand approach, a robotic manipulator is fitted with an instrument that is simultaneously held by the surgeon. During a surgical maneuver, the manipulator dampens movements, thereby limiting tremor. It can also maintain a stable position independent of the surgeon’s grip, further extending the physiologic reach of a surgeon. Notable examples of comanipulation robotic systems are the Johns Hopkins Steady-Hand Eye Robot [31] (Fig. 4) and the robot developed by KU Leuven [32] (Fig. 5). The comanipulation approach is applied in particular to the cannulation of retinal veins. The stability and possibility to maintain a static position is particularly needed during injection of drugs, e.g., during retinal vein cannulation [18], [33], [34].

3) Handheld, smart surgical tools: A final approach is to create smart surgical tools that are still manually operated by the surgeon but augment his/her surgical capabilities [35]–[37]. The tools typically support limiting hand tremor, providing micrometer precision and accuracy, as well as scaling of motion and forces. The most relevant example in this category is Micron [38] (Fig. 6), a handheld micromanipulator developed by the Robotics Institute, Carnegie Mellon University. The approach is intrinsically intuitive for a surgeon; however, the tools are often an engineering challenge, especially in terms of the ability to deliver a wide range of instruments. More complex, intelligent instruments can extend their applicability. Examples include optical tracking systems and ‘snake-like’ systems, providing additional degrees of freedom [39], [40]. One inherent limitation to this approach is the requirement that the devices need to be continuously held by the surgeon. On the other hand, the approach also has the inherent benefit that it does not require immobilization of the head.

B. State of the art

The field of robotic eye surgery has been active since the mid-1950’s. Table II gives an overview of relevant initiatives in the field, including research as well as commercial initiatives. Today, over 60 initiatives are and/or have been active in the field. The large majority involves research initiatives. Initial commercial initiatives include Acusurgical (FR), ForSight (IL), LIV Medtech (US), Ophthorobotics (a spin-off of ETH Zurich, CH) and Preceyes (NL). Notable research groups include the Johns Hopkins University (JHU) LCSR lab (US), the Jules Stein Eye Institute in collaboration with UCLA’s CASIT lab (US), the Surgical Mechatronics Laboratory at Carnegie Mellon University (US), the department of Robotics and Embedded Systems of University of Technology Munich (DE), the Robot-Assisted Surgery group of KU Leuven (BE), the ARMA lab of Vanderbilt University (US), the Telerobotics Laboratory at the University of Utah (US), and the Chinese research groups of Harbin Institute of Technology (CN) and Wenzhou University (CN).

C. Clinical use cases

To date, only the PRECEYES Surgical System (see Fig. 2) of Preceyes BV (NL) has a CE mark for everyday use in ocular surgery, with retina surgery as its intended use [41]. The system was used in the successful first human intraocular robotic surgery (for further references see Preceyes BV or go to https://www.preceyes.nl/) [42] and has been used in multiple clinical studies since. Fig. 7 shows a typical setup with the PRECEYES Surgical System in the operating room. Next after Preceyes, KU Leuven (BE) executed a preliminary clinical feasibility study (see MYNUTIA) [34]. Their developments are also focusing on retina surgery.

Robotic assistance promises multiple benefits for retina surgery. On one hand, stability and (semi)automation allows optimizing and standardizing of existing surgical procedures. This is much like medical robotics in other fields of application that are generally focused on optimizing existing procedures. Optimization and standardization of surgical procedures and tasks provides several benefits; real-time as well as data-based assessment of procedures and their validity, elimination of complications and, potentially most importantly, a limited learning curve for surgeons at all levels of experience. Simulators have shown, both in ophthalmology and beyond, that robotics levels the playing field between experienced and novice surgeons [43], [44].

On the other hand, the precision and accuracy that robotics provide, which can be 10 to 20 times better than manually operated instrumentation, could actually enable developing and executing novel high-precision procedures that cannot be performed manually. This is a key differentiator with respect to medical robotics in other fields of application and it is anticipated to be an important driver of robotics in retina surgery; surgeons are working at the limit of what is manually possible and numerous novel treatments and therapies that are under development require an even better level of precision.

Treatment of retinal vein occlusions by cannulation of the vein is a typical example of a treatment that would be enabled by robotic precision and stability. Today’s approaches involve repetitive treatment of symptoms secondary to the occlusions as opposed to the envisioned one-time treatment of the actual occlusion itself [18], [34]. Another example is gene therapy, a highly priced treatment, which requires delivery to the subretinal space without reflux, using a slow infusion over several minutes. This can be done safely and reproducibly using robotics [42], [45]. The first therapies are marketed today. It is anticipated that gene (and cell) therapies will be able in the near future to address several major indications that are currently without adequate treatment, including age-related macular degeneration, the number one cause of blindness and vision loss in industrialized countries.

The potential benefits of robotic assistance are not limited to retina surgery and can be expanded to other fields of ocular surgery with procedures that have a high level of reproducibility. High reproducibility generally results in intrinsically high efficiency and safety. Examples include glaucoma stent insertion, refractive and cataract surgery. These fields typically have relatively large numbers and cost efficiency is an even more important factor than for other applications. Robotics are historically used in highly reproducible settings and full automation will enable cost efficiency [30]. Data-based approaches and advanced AI algorithms will allow benchmarking and optimization of surgical procedures based on real-time recordings, supporting automation and promising to provide surgeons with standardization and best practice options as they perform surgery.

IV. Sensorized Instruments for Robotic Intraocular Microsurgery

Generally, surgical procedures require some physical interaction with patient anatomy through a surgical instrument [46]. Today, retinal surgeons have access to a wide variety of instrumentation and commonly used diameters are around 0.65 mm (23-gauge), 0.5 mm (25-gauge), and even 0.4 mm (27-gauge) [47]. Small diameter (0.5 mm or smaller) instruments have the advantage of self-sealing incisions but are more compliant and bend in contact with the tissue. Larger diameter (0.65 mm or bigger) instruments are stiffer, provide more room for integrating force and other sensors to capture tool-tissue interactions, and may be used to develop sensorized instruments. Similar to other types of surgery, in retinal surgery excessive tool-tissue interaction forces could result in tissue damage, while insufficient forces could prevent task completion [48]. Force measurement can provide a quantitative metric of surgical skills and characterize the safe range of forces for specific maneuvers and tasks. Furthermore, these data can be used to control robotic platforms or provide real-time feedback to human operators.

A. Instrument tip interaction forces

Retinal surgery instruments could come in contact with tissue inside the eye (e.g., tool-tip to retina interaction) or outside the eye, at the sclerotomy (tool-shaft to sclera interaction). The interaction forces at the retina are difficult to estimate at the instrument handle: as shown in [6], around 75% of the measured forces in retinal surgery are less than 7.5 mN, well below the human sensory thresholds. Furthermore, sclera forces are typically an order of magnitude larger [49] and obscure the retinal forces. Consequently, to correctly measure the forces at the instrument tip, the sensors must be embedded into the intraocular segment of the shaft. Various studies have been carried out to develop intraocular force-sensing capabilities into surgical instruments based on fiber optic sensors (FOS) [4], [50]. Beside advantages such as high resolution, biocompatibility, sterilizability, electrical immunity, etc., FOS could come in very small size (diameter 60–250μm) [51], providing feasible solutions for sub-millimeter sensorized instruments. Whereas the majority of FOS-based sensorized instruments involve FBG (Fiber Bragg Grating) sensors [52], some employ the Fabry-Perot Interferometry (FPI) measurement principle instead [53].

Employing FBGs, some works focused on development and evaluation of 2-degree-of-freedom (DOF) [54]–[57] and 3-DOF force sensing pick tools. He *et al.* [58] proposed a 3-DOF force sensing pick tool, using a superelastic Nitinol flexure to provide axial force-sensitivity with 1 mN resolution in a 0.9 mm (20 gauge) shaft diameter. In a second design iteration (see Fig. 8(b)) [59] they proposed a new type of flexure to achieve high axial force sensing sensitivity and low crosstalk.

Other works introduced FBG-based force sensing micro-needles that could be used for vein cannulation or subretinal injection procedures: 2-DOF micro-needles are presented in [60]–[65] while [50] proposed a 3-DOF sensorized instrument. Furthermore, by analyzing the vessel puncture force transient, Gijbels *et al.* [61] and Gonenc *et al.* [62], [63] implemented algorithms to detect puncture in real-time with almost 100% success.

Using FBG technology, some works developed force sensing capabilities in micro-forceps that could be used for membrane peeling force detection [64], [66], [67]. He *et al.* [66] proposed a 2-DOF, 20 gauge sensorized forceps, with 0.25 mN resolution, and evaluated it during membrane peeling experiments with chicken embryos and rabbit eyes *in vivo*. With similar micro-forceps, by applying micro-vibrations, Gonenc *et al.* [67] proved that it is possible to reduce the peeling force while increasing the delamination speed of raw chicken egg membranes. Furthermore, Gonenc *et al.* [64], developed a 20 gauge motorized micro-forceps (see Fig. 8(c)) with 3-DOF force sensing capabilities and demonstrated force measurement RMS error under 0.15 mN in the transverse plane and with 2-mN accuracy in the axial direction.

B. Scleral interaction forces

The use of a robot to manipulate surgical tools inserted into the eye, greatly interferes with the surgeon’s ability to feel the forces at the sclerotomy, increasing the potential for eye injury. Consequently, some research works [68] investigated integration of FBG force sensors at the tool-tip and also into the tool shaft, outside the eye, to simultaneously measure forces at the retina, the sclera contact location (tool-tip insertion depth), and the corresponding contact force (scleral force), Fig. 8(a). The information from such multi-function force sensing tools could be used to augment cooperatively controlled robot behavior with variable admittance control and create an adaptive remote center-of-motion (RCM) constraint to minimize the eye motion and the potential damage on the eye-wall at the sclerotomy [69]. A similar control-framework and force-sensing light pipe [70] were used to provide automatic illumination of the target area in bimanual robot-assisted retinal surgery [71].

C. Instruments with OCT for depth perception

Owing to its resolution, Optical Coherence Tomography (OCT) has become a popular intraoperative imaging modality for retinal surgery [4]. OCT-based sensorized retinal picks have been developed to visualize retina layers [73], [74] and assess the tool-tip distance to anatomy in real time [56]. Employing the same concept, [75] developed a motorized microforceps and [76] proposed a microinjector able to conduct subretinal injections at specific depths. Recently, a cannulation needle with FBG-based force sensing combined with OCT-based distance-sensing was developed [77] and tested in pig eyes *in vivo* [78] (see Fig. 9). Furthermore, Preceyes BV developed an OCT-based distance sensor (see Fig. 10) that was clinically validated at the Eye Hospital Rotterdam [44].

D. Dexterous vitreoretinal instruments

Beside the straight surgical instruments, several works focused on tools with distal dexterity [79]–[84]. Due to their flexible distal end, these instruments have large manipulating workspace, could reach targets from different angles and hence reduce the force at sclerotomy. Recently, [85] combined both distal dexterity and force sensing within a miniature continuum manipulator with two rotational DOFs and 3-DOF intraocular force sensing capabilities.

Incorporating different types of sensors, “smart instruments” can extend robots’ functionality, increase safety, and improve surgical performance. In particular, force and distance sensing could enhance safety from inadvertent eye movement and enable better control of instrument motion in depth. More information about the use of sensorized instruments for safe manipulation in robotic intraocular microsurgery could be found herein, sections V-E and VII, and in [4].

V. Guidance and Control Strategies

Image-guided robotics has the potential to significantly reduce the surgeon’s burden by guiding the surgeon past obstacles and difficulties, potentially automating parts of the intervention. This section introduces the contributions that have been made in visual servoing and active constraints. Furthermore, by introducing smart instruments in robotic intraocular microsurgery, it becomes possible to establish high-bandwidth real-time feedback schemes that adjust to the changing anatomy. This section also describes different feedback and guidance schemes including haptic feedback and other force-servoing schemes. Through sensor fusion it becomes possible to setup multi-rate estimation schemes that mix global models derived from preoperative or intraoperative imaging with local sensor measurements.

A. Visual servoing

The transparent nature of the interior of the eye creates opportunities for visual servoing using video cameras installed in the microscope. This is facilitated by the fact that many modern operating microscopes are already equipped with cameras, independent of whether robotic assistance is used. Visual servoing to targets such as the optic disc for drug delivery has been demonstrated using untethered microrobots actuated by remote magnets [86]. Visual servoing can also be used in combination with other approaches; an example is “semi-automated” patterned laser photocoagulation using Micron, performed by manual scanning of the instrument over the retina combined with visual servoing for coagulation of individual targets as they come within range of the manipulator [40], [87]. Visual servoing can also be performed using OCT images; for example, Del Giudice *et al.* [88] have used it to demonstrate retinal vessel cannulation in an artificial phantom using a continuum robot. Additional examples of control strategies using OCT are presented in the next section.

B. Virtual boundaries

Virtual boundaries can be utilized inside the eye for safety purposes, such as to prevent unwanted penetration below the retina. OCT is the sensing modality used most often for this purpose. Enforcement of a constant distance offset from the retina was demonstrated using the Johns Hopkins Steady Hand system using a 1-D OCT sensor in 2009 [56]. More recently, the PRECEYES Surgical System has also incorporated a similar sensor [44]. Such sensing has also been incorporated within a vein cannulation needle and has been used in the KU Leuven eye surgery robot to demonstrate cannulation in an animal model *in vivo* [78]. Kang *et al.* [76] have also demonstrated subretinal injections at controlled depth using a single-degree-of-freedom OCT-equipped handheld instrument. This approach was also used to control distance to the retina during membrane peeling [75]. An alternative approach using less expensive hardware has been demonstrated in the Micron system. This approach involves the use of a laser aiming beam of the sort that is typically incorporated within therapeutic laser systems; the reflection of the aiming beam from the retinal surface is detected by a camera within the surgical microscope. When combined with tracking of the instrument tip, this technique enables estimation of the distance from tip to retina. The technique has been used in Micron to maintain constant standoff distance during patterned laser photocoagulation in porcine eyes *ex vivo* [89] and to prevent penetration of the retina during membrane peeling in an eye phantom [90]. A similar technique has also been used in a vessel tracing task in an eye phantom using the JHU Steady Hand robot [91].

C. Tremor cancellation

The idea of tremor canceling or filtering for accuracy enhancement in microsurgery is over 30 years old [92]. The earliest robotic systems designed for tremor cancellation were telerobotic [93], [94], since the principle of teleoperation allows any desired filter to be interposed between the master interface and the teleoperated manipulator, and telerobotics continues to be the approach taken by the majority of such systems. In the cooperatively controlled systems at Johns Hopkins [31] and KU Leuven [34], virtual damping serves to attenuate hand tremor. The handheld nature of the Micron system recasts tremor cancellation as an active noise control problem. Because the instrument is handheld, transmission of hand motion to the tip is immediate. Active compensation of tremor is the only possibility, therefore low latency is essential. Tremor filtering in Micron is performed by a low-pass shelving filter [35]. This filter fully suppresses frequencies above 3 Hz, while in the band of approximately 0.2–2.0 Hz, where there is considerable overlap between intended motion and tremor, it has a flat “shelf” with −10 dB gain, which provides a relative form of motion scaling. To maximize canceling performance, a feedforward control element is included, using Kalman-filter-based tremor estimation [95], as shown in Fig. 11, and care is taken during the design of the internal model controller used in Micron in order to minimize delay in the system [35]. Tremor canceling in a single-degree-of-freedom axially actuated instrument has also been demonstrated using OCT-based sensing of the distance between instrument tip and retina as input [96].

D. Haptic guidance

In teleoperative and cooperatively controlled robotic systems, which support force feedback to the user, haptic virtual fixtures can be used for guidance. In an early example, Dewan *et al*. [97] used stereo vision-based reconstruction with the JHU Steady-Hand robot to implement virtual fixtures for surface following, alignment, targeting (motion constrained toward a target point), and insertion/extraction (constrained translation along the tool axis) in an “open-sky” eye phantom. Similar haptic guidance in a cooperatively controlled robotic system during patterned laser photocoagulation has also been demonstrated in an open-sky experiment [98]. Haptic guidance with an off-the-shelf Phantom Premium master interface has also been used in teleoperation of a hybrid parallel-serial manipulator, with separate control modes for translation and rotation [99]. More recently, distance measurement based on intraoperative OCT has been used in order to provide haptic guidance for prevention of retinal penetration during membrane peeling. This technique demonstrated a significant reduction in retinal penetration in operations in a virtual environment using a master interface inspired by the PRECEYES Surgical System [100]. Haptic feedback is generally viewed as having considerable potential to improve performance of ophthalmologic surgical robotics, but in most regards conclusive proof of such benefits remains to be demonstrated [101].

E. Automatic execution

Autonomous operation in robotic retinal surgery is still in its infancy, and examples to date involve subtasks or portions of surgical procedures rather than entire procedures. Where clinically feasible, its positioning accuracy often outperforms other approaches to robot-assisted surgery via teleoperation, cooperative control, or actively compensated handheld instruments. One of the earliest efforts involved automated generation of OCT scans and automated positioning above a prespecified OCT-registered target, performed with the JHU Steady Hand system in artificial phantoms [56]. Similar automated OCT scans were later repeated using the Micron system [74]. Autonomous retinal vein cannulation using the Intraocular Robotic Interventional Surgical System (IRISS) under guidance from an OCT probe and microscope video has been demonstrated in silicone phantoms [102]. A laser aiming-beam or “spotlight” technique based on a fiberoptic light pipe that allows distance to the retina to be determined from spot size and location tangential to the retina to be determined from spot location on the surface has been used for guidance of Micron in autonomous patterned laser photocoagulation in porcine eyes *ex vivo* [89]. The automated technique yielded faster and more accurate results than manual scanning of Micron with visual servoing to individual laser targets whenever they came within range [40]. The "spotlight"-based guidance has also been used for vessel tracking (as an intermediate step toward cannulation) with the Steady Hand system. This technique outperformed manual execution and cooperative control of the Steady Hand in a head-to-head comparison [91]. The Steady Hand system has also been used in a demonstration of autonomous mimicking of expert-generated trajectories toward selected targets on the retina, utilizing a learning-from-demonstration approach based on deep learning [103], [104] (see Fig. 12 for the overall scheme of the proposed framework). Microrobots have performed autonomous positioning and drug delivery in animal models in vivo using remote magnetic actuation with microscope video guidance [24], [105]. The small payload of such devices is a challenge, however.

In addition to automatic execution of clinical tasks, retinal surgery robots can also autonomously perform assistive functions that are not in themselves surgical tasks but that promote safety or improve accuracy. One example would be the tremor canceling techniques described earlier. Another such example is adaptive control of the Steady Hand to minimize scleral contact force whilst actively monitoring the insertion depth [69]–[72]. The control strategy used in these studies is summarized in Fig. 13 [72]. In a preliminary study on eye phantoms for robot-assisted bilateral vein cannulation [72], He *et al.* showed that the proposed controller was able to command the robotic manipulators to maintain the tool-tip and sclera forces for both forceps and cannula within predefined ranges, even when the eyeball was subjected to rotational disturbances.

VI. Clinical Translation Aspects

Owing to its relevant capabilities, including tremor cancellation, enhanced dexterity, micron-scale sensing and accuracy, robotics has become one of the most promising trends in advancing retinal surgery [3], [5]. Despite the technological feats, there is a broad lack of trust and clinical experience among surgeons, and robotic assistance is associated with clinical implementation challenges, including robotic surgical training and learning curves, cost, risk, complications, and difficulties regarding regulatory compliance [106].

Related to the learning curve, recent works [43], [44] proved that robotic assistance could reduce the training time for surgeons at all levels of experience. In a study on simulated subretinal injections using an artificial retina model, Ladha *et al.* [45] showed that robotic assistance is effective in helping surgeons to succeed in surgical tasks. Moreover, in the first-in-human study of the safety and viability of robotic-assisted retinal surgery, Edwards *et al.* [42] proved that surgical outcomes were equally successful in robotic surgery and manual surgery. Furthermore, He *et al.* [107] proposed a curriculum and credentialing process for robotic surgical training in ophthalmology.

Similar to other surgical applications, where the use of robotic assistance has increased the surgical time, clinical acceptance of robotics in retinal surgery depends on the balance between benefits and cost [2]. Some ways for reducing the cost and preserving the benefits are: reduce the set-up time, use robotic assistance only for specific high-precision tasks, reduce surgical time by increasing the speed and safety when moving the instruments toward an intraocular target, etc. For the current procedures that are intrinsically efficient and safe, full automation is technologically achievable and it may be considered to justify the necessary investments. Such devices will also require a different regulatory path: it is very likely that fully automated systems will be considered Class III devices by US FDA. Therefore, these devices will require a premarket approval (PMA) (https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma) under section 515 of the FD&C Act in order to obtain marketing approval, with considerable cost increase [108].

VII. Future Directions

Nowadays, robotic assistance is rapidly extending and evolving, especially in microsurgery, where robotic technology has begun to significantly impact many surgical specialities. Among these, the highly technical field of robotic retinal surgery has witnessed increasing growth in technological developments and capabilities [3]. In light of the most recent evidence it is becoming prominent that robotics may increase surgical capabilities beyond current freehand practice. To realize the potential of robotic assistance in retinal surgery it is important that research should continue to address known limitations, discover others still unknown, and expand the benefits of previous achievements. Besides addressing the clinical translation aspects presented above, future developments may be focused on, but not limited to: multi-arm robotic assistance, robots with extended surgical capabilities, robot autonomy, safety enhancement, and use of machine learning.

Currently, most studies focus on assisting the manipulation of dominant instruments. On the other hand, the bilateral approach has the potential to lead to new surgical support methods, such as increasing surgical efficiency and facilitating complex tasks. Wei *et al.* proposed a method to control the posture of the eye using the coordinated manipulation of two surgical tools [84]. He *et al.* developed a research platform for the bilateral approach (Fig. 14) [70], [72] and an automated method for lightguide-side operation [71]. It is expected that the future will see increasing attention on the bilateral approach and even on multi-arm robotic assistance.

A possible way to reduce the cost and facilitate the adoption of robotic retinal surgery in current practice is the development of robotic systems with extended surgical capabilities. A good example in this direction is the IRISS, a robot designed for various tasks in ophthalmic surgery [30], [109], [110]. Another desired feature for extended surgical capabilities is the possibility to quickly exchange tools such as developed by Nambi et al. in [111]. As shown above, many research efforts have been focused on supporting only specific tasks, such as peeling and cannulation tasks. It is expected that this trend will continue in the future; however, robotic systems able to assist with multiple types of procedures will very likely become the norm.

As in other surgical specialties, more automated and even autonomous surgery is likely to be implemented [2]. One possible scenario is to enable surgeons to supervise multiple robots that perform routine procedures autonomously, on one or multiple patients, and only call on clinician expertise and guidance during complex tasks. However, as shown in [112], there are significant challenges involved in autonomy in medical robotics and consequently, existing surgical robots have lower degrees of autonomy. In vitreoretinal surgery, there is no example of achieving automation of all surgical steps; the relevant research is focused on automation or semi-automation of specific tasks [113], [114]. In addition, at present, accurate automatic positioning of surgical instruments is difficult, and is a subject of active research. Taking advantage of its high resolution, OCT has been widely used [115]–[117] to guide instruments. For the same purpose, other researchers have employed stereo cameras [118] or reflections of a spotlight [40], [87], [89], [119]. Whereas numerous studies have demonstrated the ability to estimate the distance to the eyeground; few studies [40], [89], [103], [120] have actually achieved automated positioning. It is very likely that in the future more surgical tasks will be automated, but this will require robust methods to estimate the exact position of the surgical tool inside the eye.

In much robotic surgery, the surgeons do not directly hold the surgical tool, and therefore they cannot receive force feedback from the tissue, which is a major safety issue. As mentioned in section IV, sensorized instruments have been developed that can measure the force applied to the sclera at the insertion point and the contact force with the eyeground tissue. Ebrahimi *et al*. proposed a system to feedback excessive force loads to the surgeon based on the force information from such surgical tools [69], [121], [122]. Currently, there are research efforts focusing on the addition of sensors to surgical instruments to enhance safety. It is expected that this trend will continue with the final goal being to develop “smart instruments” able to provide real-time feedback to the surgeons on dangerous tasks or even to anticipate and inform the human operator about possible safety failures that may happen in the future, in order to make the necessary corrections.

Future ophthalmic surgery will very likely make use of automated robotic systems, potentially governed by artificial intelligence (AI) [124]. The challenge is the need of the system to detect, anticipate, and take actions to eliminate the possible failure modes [112], and deep learning will likely be useful to this end [2], [125]. Following this direction, recent studies [103], [123], [126] incorporate machine learning in robot control. For example He *et al*. [123] used a recurrent neural network (RNN)-based active interventional control framework to increase operation safety by monitoring scleral force, predicting the surgeon’s manipulation, and intervening in the operation to avoid exertion of excessive forces (see Fig. 15). Other works [127]–[130] apply machine learning or simultaneous localization and mapping techniques to microscopic and OCT images to extract information in order to guide the surgical instruments. Beyond these first steps, the use of AI in robot-assisted retinal surgery will likely require collection and analysis of data from a broad number of surgical procedures in order to develop the algorithms necessary to correctly, robustly, and reproducibly address the complex decisions required in surgery.

VIII. Conclusion

After more than three decades of assiduous and sustained research work with various, exciting, and consistent results, robotics has become one of the most promising trends in advancing the field of intraocular microsurgery. No doubt, the achievements of robot-assisted retinal surgery are tremendous and relevant capabilities include, but are not limited to, tremor canceling, enhanced dexterity, micron-scale distance sensing and positioning precision, haptic feedback, sub-millinewton force sensing, sensor servoing-based functions, and other. With the development of novel surgical interventions such as subretinal injections in gene therapy, the technical requirements of intraocular robotic surgery are becoming greater and more varied. Pioneering robotic eye surgery interventions have been successfully performed in a limited number of clinical trials, opening the possibility of robotic technology translation into clinical practice. However, medical robotics is still associated with implementation challenges related to learning curves, cost, risks, and complications, and there is a broad lack of clinical experience among potential users. Consequently, future developments will likely focus on improving clinical outcomes, reducing cost and operating time, and employing larger scale clinical trials. In the end, robotic intraocular microsurgery, potentially augmented with artificial intelligence, could enhance and expand the surgeon’s physical capabilities at superhuman levels and provide advanced and safe surgical care for patients.

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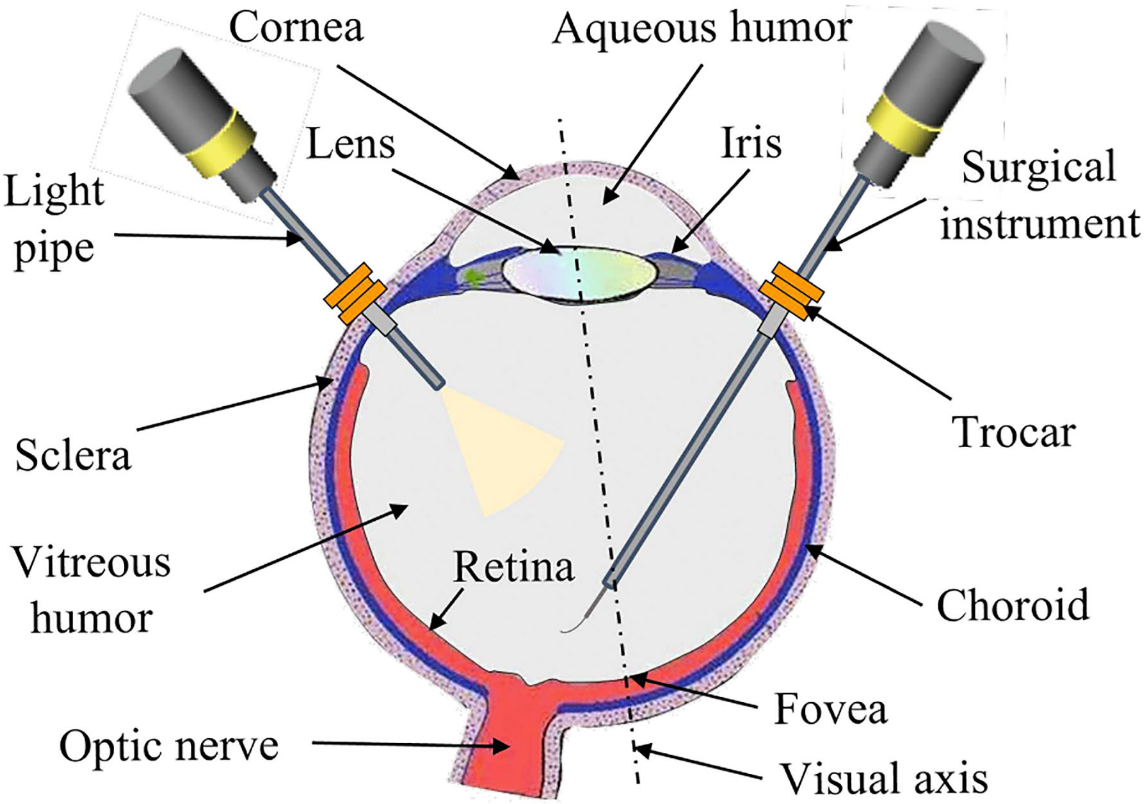

Fig. 1.

Simplified illustration of human eye cross-section and surgical instruments setup for retinal surgery. The size of the human adult eye is approximately 24.2 mm (transverse) × 23.7 mm (sagittal) × 22.0–24.8 mm (axial) [8].

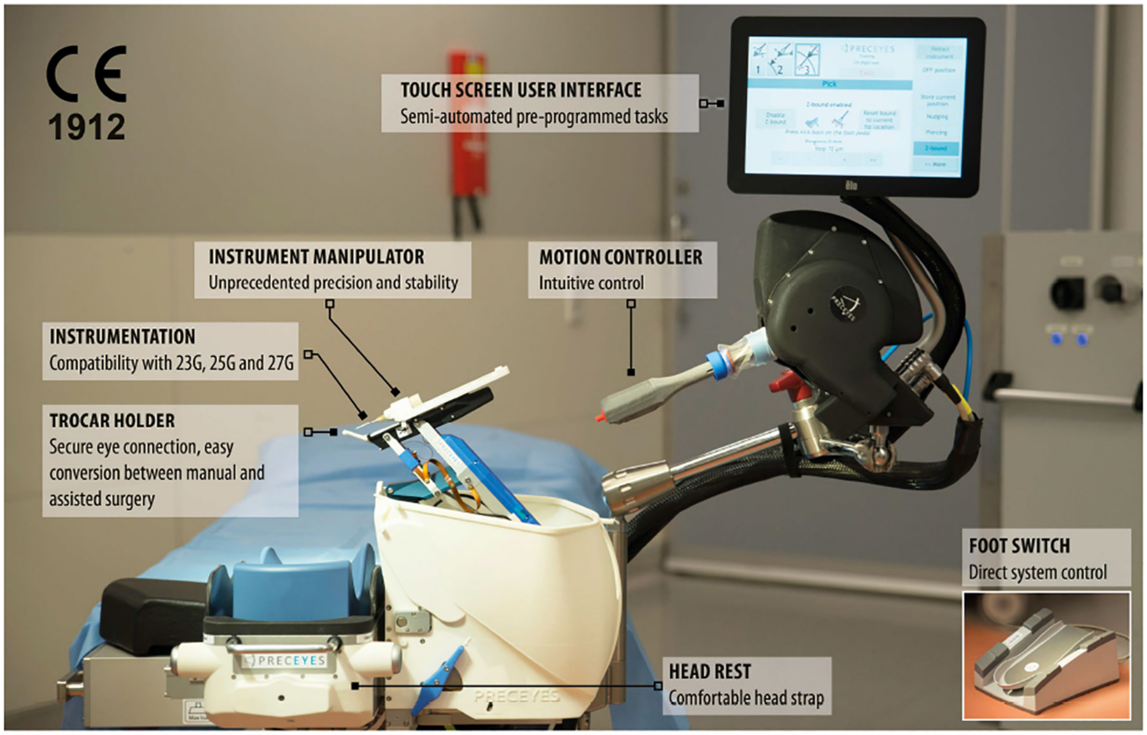

Fig. 2.

PRECEYES Surgical System: a telerobotic surgical system developed by PRECEYES BV in the Netherlands. This is the only commercially available robotic surgical system developed for intraocular surgery. Photo © PRECEYES BV.

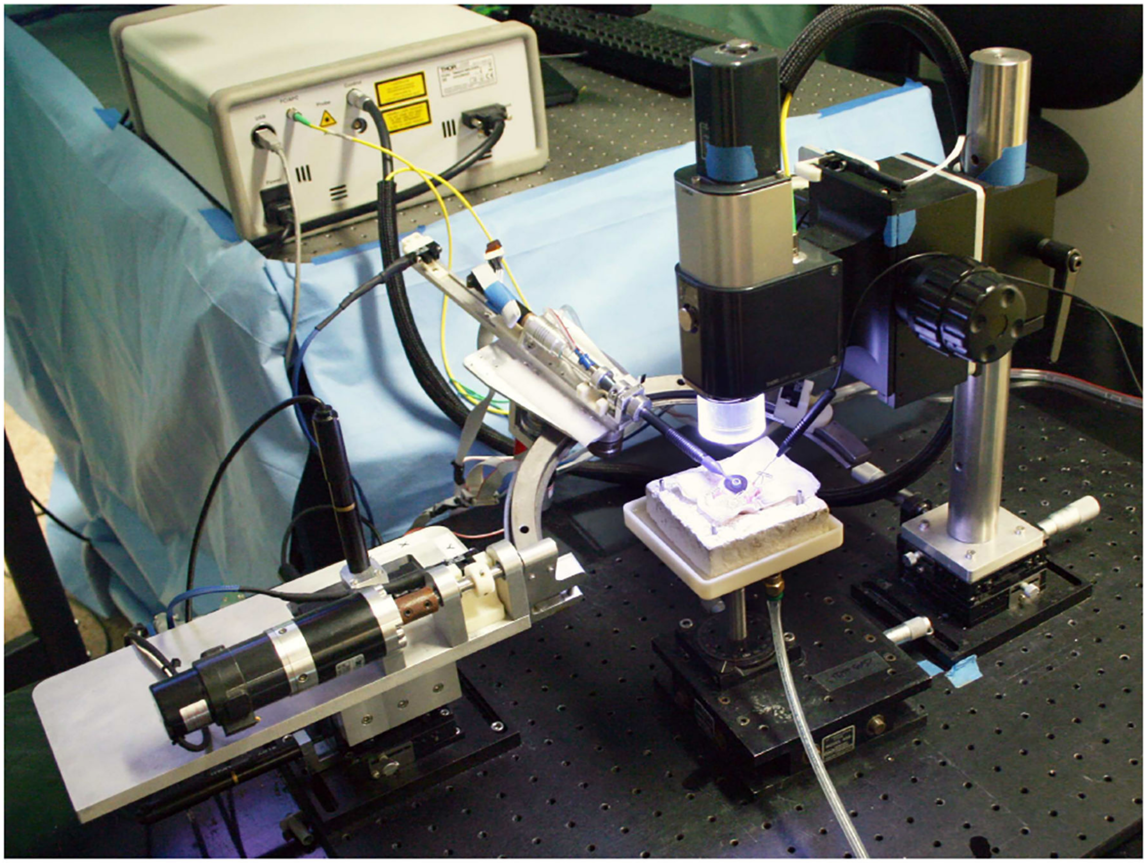

Fig. 3.

The Intraocular Robotic Interventional Surgical System (IRISS) is a robotic system developed by the Jules Stein Eye Institute and the University of California, Los Angeles, for ophthalmic surgery. Image by courtesy of Matthew J. Gerber and Tsu-Chin Tsao.

Fig. 4.

The Steady-Hand Eye Robot (SHER): a cooperative robotic system developed by the Laboratory for Computational Sensing and Robotics at Johns Hopkins University, for retinal surgery. Image © Iulian Iordachita.

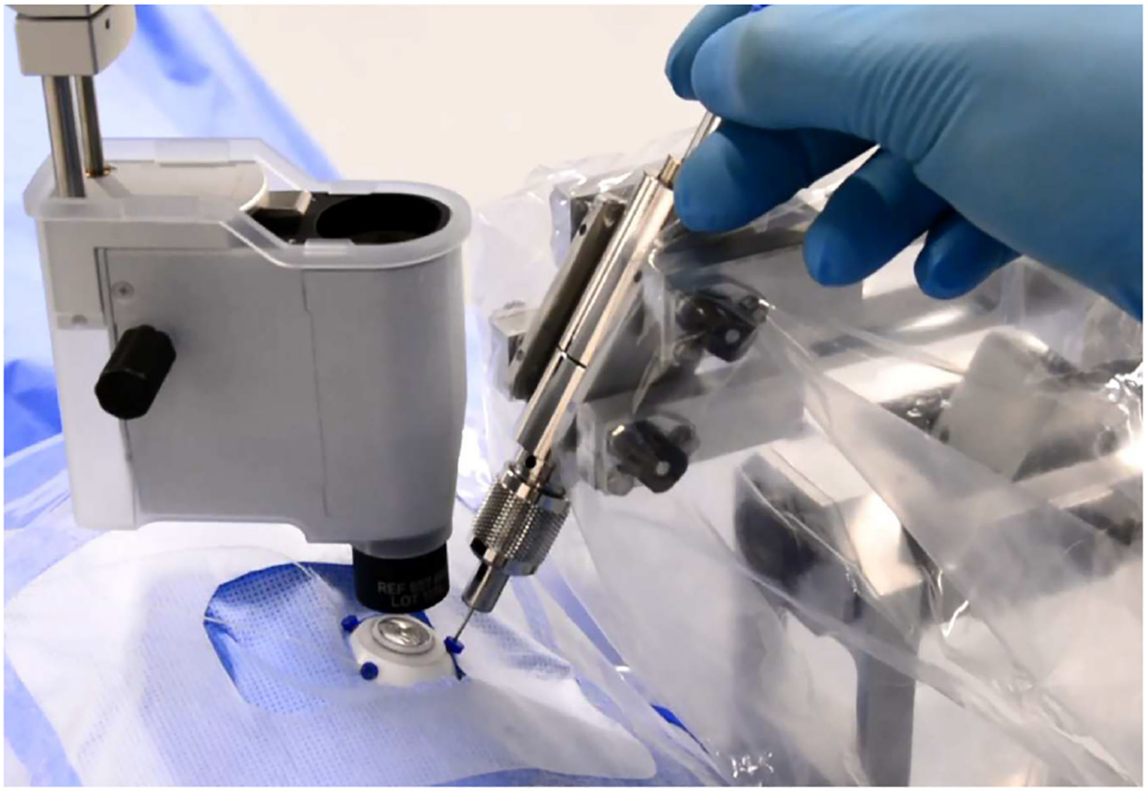

Fig. 5.

The comanipulation robot developed by KU Leuven for retinal surgery. Image by courtesy of Emmanuel Vander Poorten.

Fig. 6.

The Micron: a handheld micromanipulator developed by Carnegie Mellon University. Image © Cameron Riviere.

Fig. 7.

PRECEYES Surgical System in operating room setting. Image © 2019 Preceyes BV.

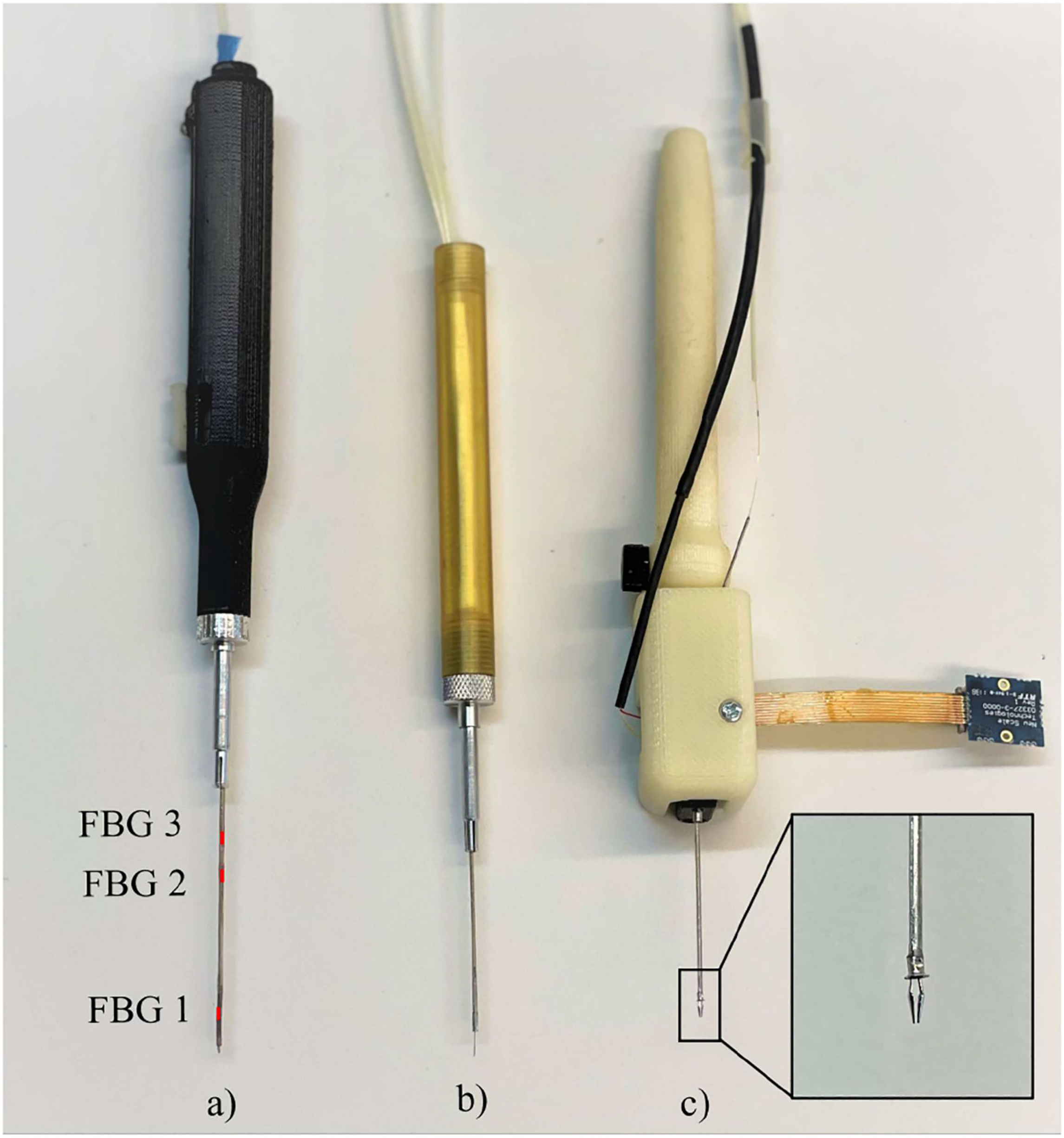

Fig. 8.

JHU FBG-based sensorized microsurgical instruments: (a) Multi-function force-sensing microneedle for vein cannulation [72] capable to simultaneously measure forces at retina (FBG 1, location of the active area is marked with a red line), sclera contact location (tool-tip insertion depth), and the corresponding contact force (scleral force, FBG 2 and FBG 3, red lines) [68]; (b) 3-DOF force-sensing pick tool with high axial force-sensing sensitivity and low crosstalk noise [59]; (c) 3-DOF force sensing motorized micro-forceps [64]. Image © Iulian Iordachita.

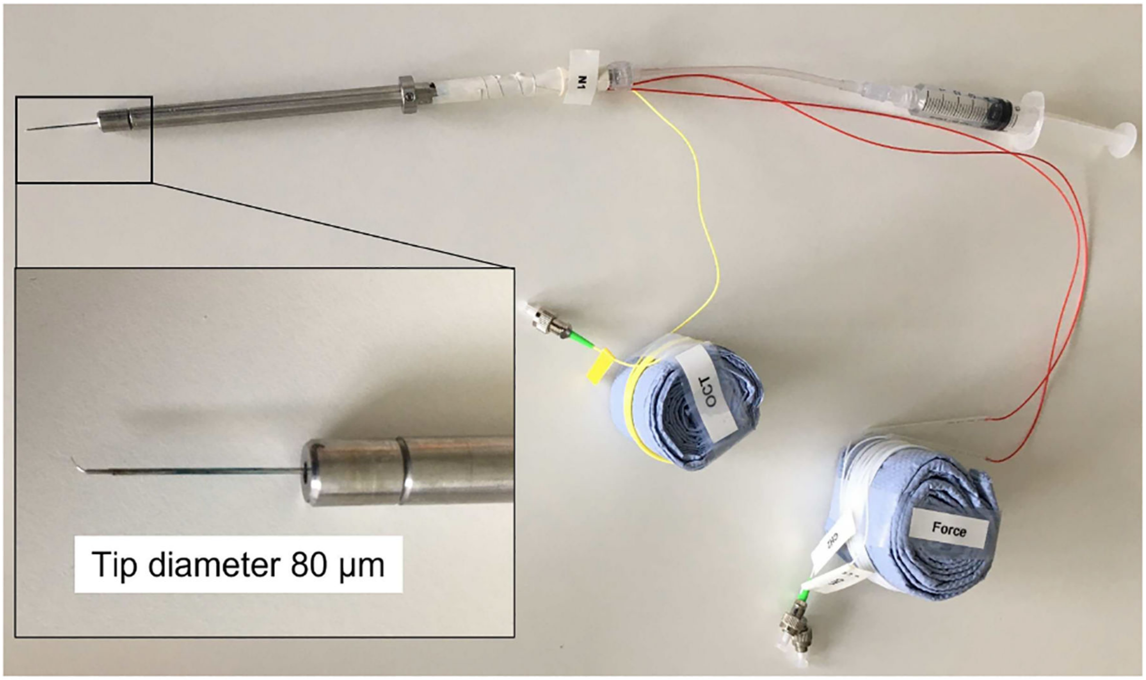

Fig. 9.

KU Leuven combined force and distance sensing cannulation microneedle: needle-tip contact forces are measure with two FBG sensors and an OCT A-scan fibre provides the distance sensing [78]. Images by courtesy of Emmanuel Vander Poorten.

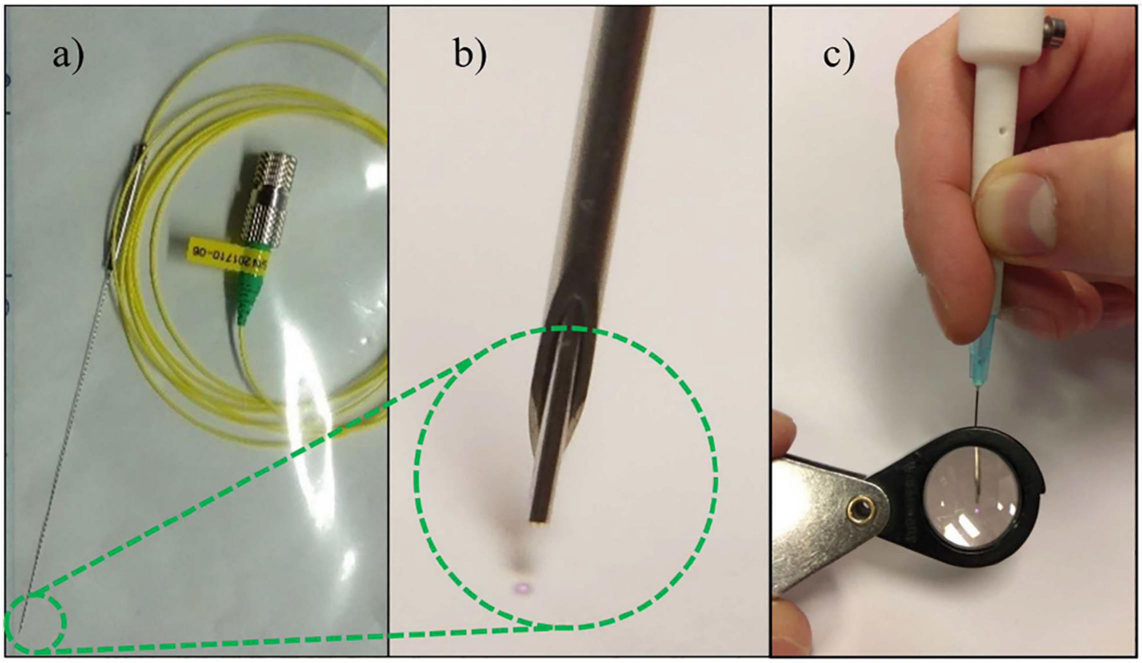

Fig. 10.

PRECEYES BV iiOCT probe for distance sensing: (a) The iiOCT fiber in its packaging; (b) The iiOCT fiber inserted into a 23 gauge needle; (c) Needle mounted to an instrument body for connection to the robot. Images by courtesy of Gerrit Naus.

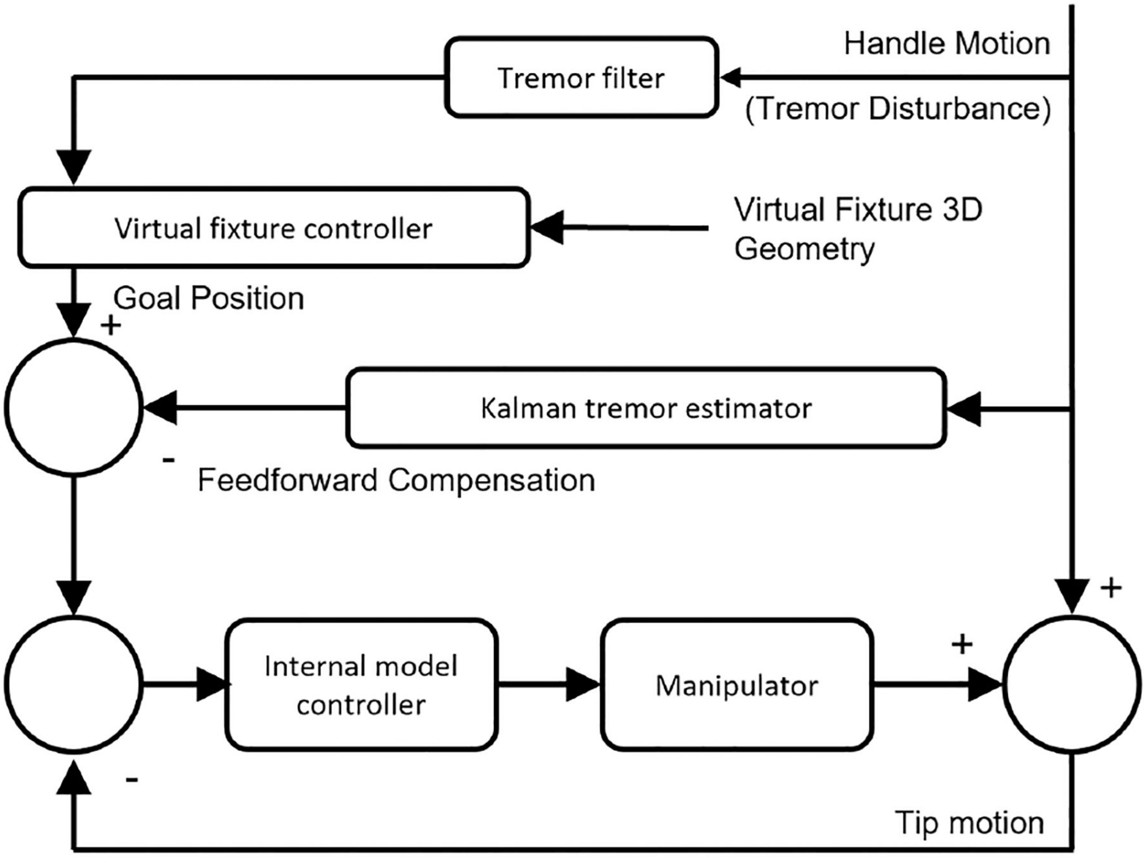

Fig. 11.

Micron block diagram: with handle motion, including tremor, as input, the goal position is set by the tremor filter (and, if present, the virtual fixture). Kalman filter-based tremor prediction is incorporated as a feedforward element to adjust the goal position to overcome manipulator latency. The latency-compensated goal position is used as the set point for the internal model controller of the manipulator. Image © Cameron Riviere.

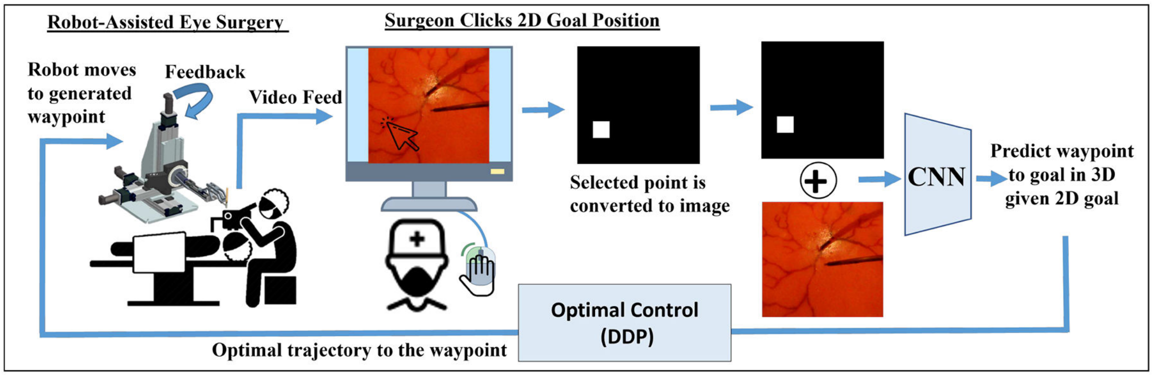

Fig. 12.

Control loop for autonomous surgical tool navigation using a convolutional neural network (CNN) and optimal control. The network is trained to navigate the surgical tool to the desired position on the retina using only monocular images and top-down 2D goals specified by the surgeon. The surgeon does not specify the depth position of the target position, which is one of the advantages of this approach. The challenging task of depth estimation is solved by the network based on its training experience, enabling the surgeon to focus on other important aspects of the surgery [104]. Image © Ji Woong Kim.

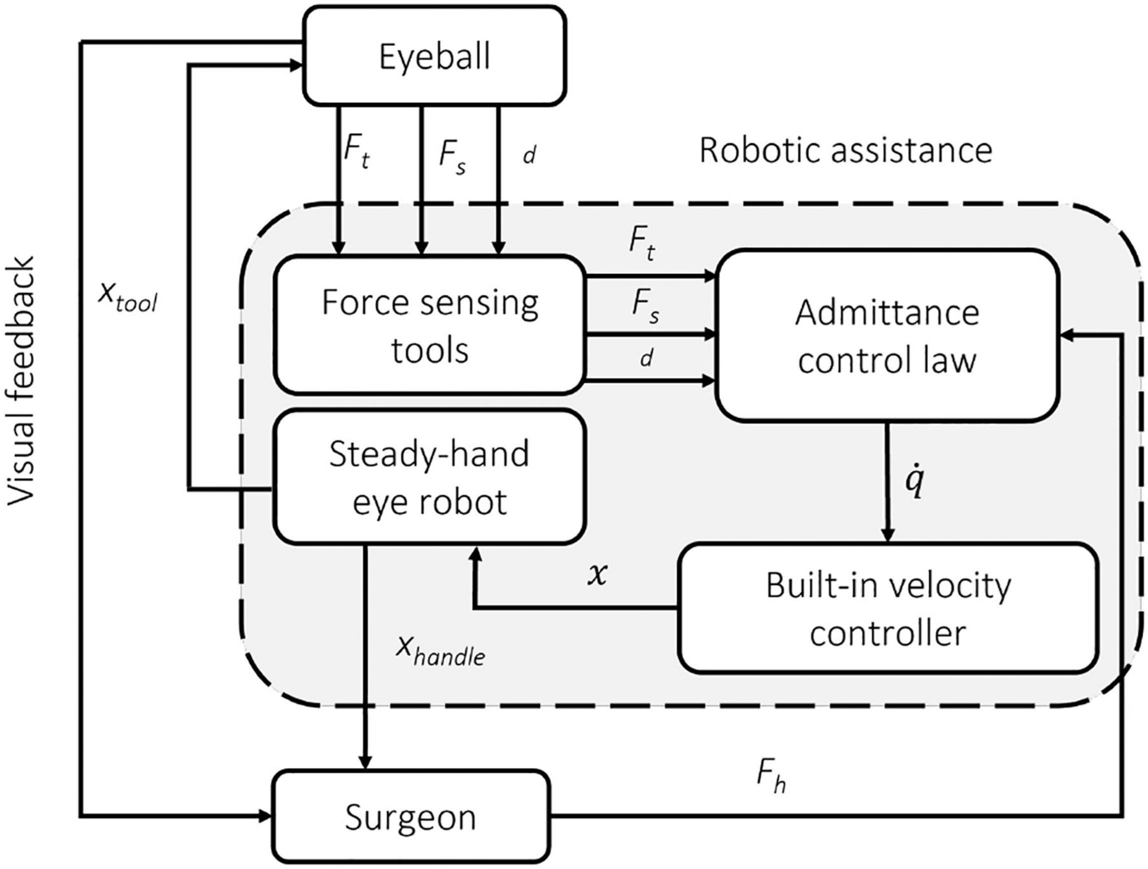

Fig. 13.

JHU SHER control block diagram: the admittance controller takes the tip force F_t, scleral force F_s, insertion depth d, and the surgeon's maneuvering forces F_h as inputs and outputs desired velocities to command the robot and maintain the dual force constraints [72]. Image © Iulian Iordachita.

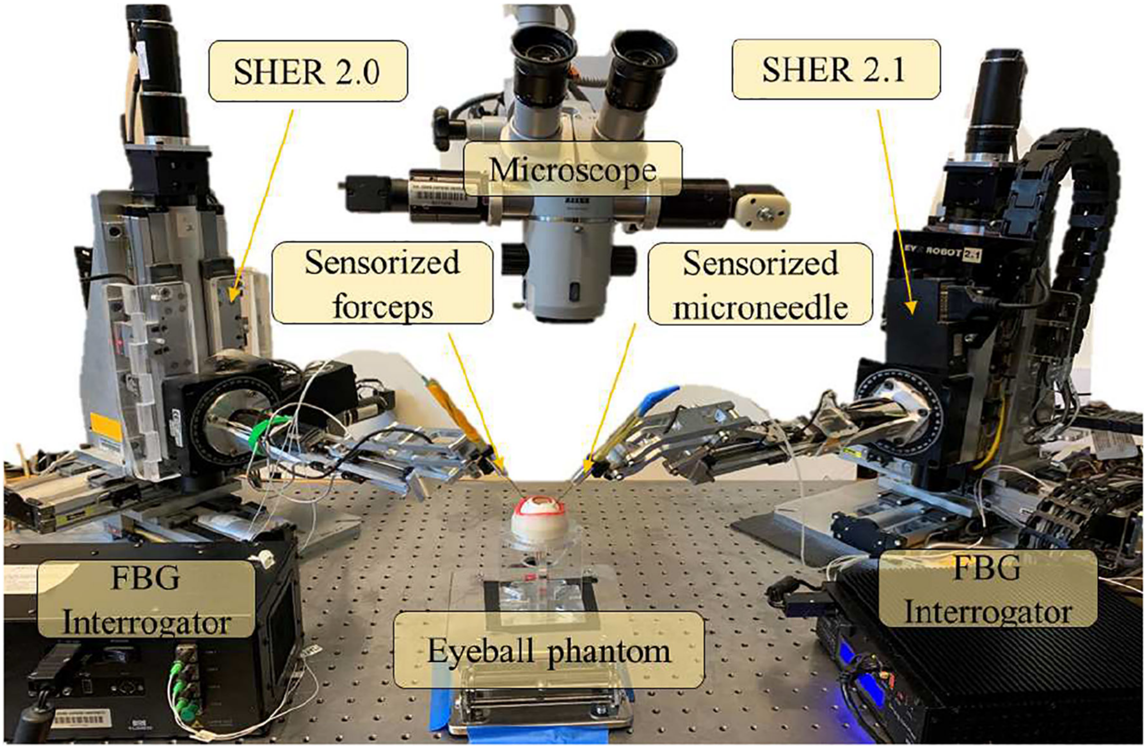

Fig. 14.

Experimental setup for robot-assisted bilateral vein cannulation with two JHU SHER robots and two multi-function forces-sensing instruments [72]. A third robotic arm could be used to automatically move a sensorized light pipe and illuminate the target area following the tool-tip motion [71]. Image © Iulian Iordachita.

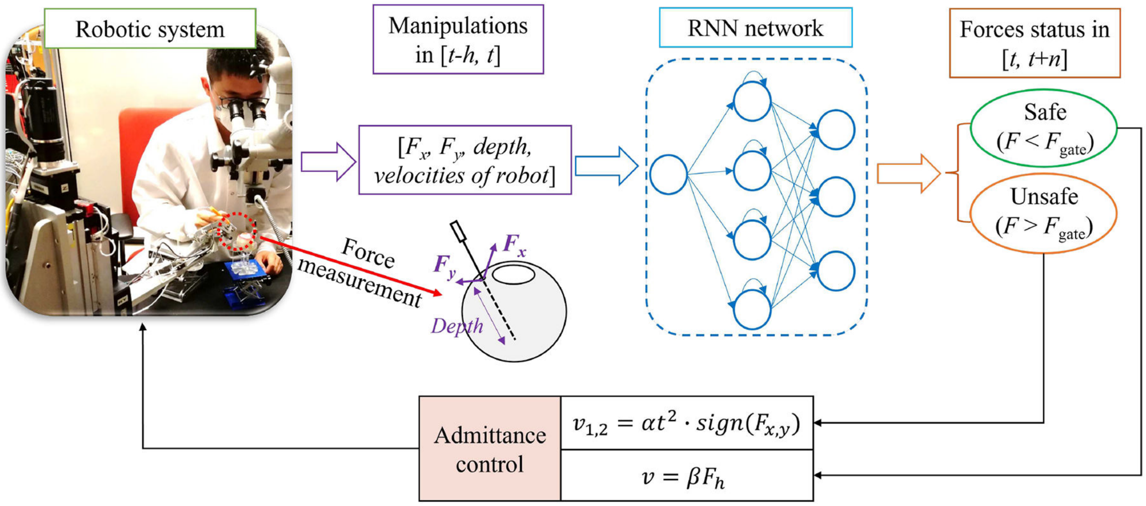

Fig. 15.

Overview of the control framework consisting of a multi-function force-sensing tool, an RNN predictor, an admittance control system, and the SHER research platform.The robotic manipulator is activated to move at a varying speed in order to decrease the resulting scleral forces. The results in multi-user experiment suggest that active interventional control framework can effectively predict excessive-force instances and augment performance of the user to avoid undesired events during robot-assisted microsurgical tasks [123]. Image © Iulian Iordachita.

TABLE I

Robotic design approaches in eye surgery and their level of achievement for relevant desired functionality [2]

Feature	**Telemanipulation**	**Comanipulation**	**Hand held**	**Microrobots**
Tremor filtering	+	+	+	+/−
Motion scaling	+	−	+/−	+
Motion mirroring	+	+	−	+
Eye stabilization	+	+	−	−
Motion profiles and task automation	+	−	+/−	+
Dynamic/static tasks	+/+	−/+	+/−	−/+
Remote control option	+	−	−	−
Rapid exit	+	−	+	−

TABLE II

Overview of relevant robotic systems developed for retinal surgery

Key players	Tech	Testing	Motion scaling	Tremor filtering	RCM	Table/patient mounted	Robot-trocar connection	Precision	(Semi-) automatic motion profiles
Acusurgical (FR)	TM	A	yes	o	yes	no	o	o	o
Carnegie Mellon (US)	HH	A	yes	yes	yes	no	no	$13\mu m$ RMSE	yes
JHU LCSR lab (US)	CM	A	no	yes	yes	no	no	$5\mu m$	no
ForSight (IL)	AM	o	o	o	o	o	o	o	yes
Harbin Inst Tech (CN)	o	o	o	o	yes	yes	o	o	o
King’s College (UK)	TM	B	yes	no	yes	yes	no	o	o
KU Leuven (BE)	CM	C	no	yes	yes	yes	yes	$<= 1\mu m$ (res)	no
LIV Medtech (US)	HH	B	no	yes	no	no	no	$< 5\mu m$ RMSE	yes
Ophthorobotics (CH)	AM	B	no	no	no	no	yes	o	yes
Preceyes (NL)	TM	C	yes	yes	yes	yes	yes	$1 - 2\mu m$	yes
TU Munich (DE)	TM	B	no	no	yes	yes	no	$10\mu m$	o
UCLA (US)	TM	A	yes	yes	yes	o	no	$5\mu m$	yes
Univ. of Utah (US)	TM	B	yes	yes	yes	yes	no	$< 1\mu m$	yes
Vanderbilt (US)	TM	B	yes	yes	yes	no	no	$< 5\mu m$	o
Wenzhou Univ. (CN)	TM	A	yes	yes	yes	no	no	$13\mu m$ (res)	o

List of abbreviations: TM = telemanipulation, CM = comanipulation, HH = handheld, AM = automated, o = unknown, C = clinical, A = animal, B = bench tests.