

# Robotic Systems in Ophthalmologic Surgery



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## Abbreviations

FDA	Food and Drug Administration
ILM	Internal limiting membrane
IRISS	Intraocular robotic interventional surgical system
OCT	Optical coherence tomography
SHER	Steady-Hand Eye Robot
t-PA	Tissue plasminogen activators
US	United States

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J. P. Manzano, L. M. Ferreira (eds.), *Robotic Surgery Devices in Surgical  
Specialties*, [https://doi.org/10.1007/978-3-031-35102-0\\_12](https://doi.org/10.1007/978-3-031-35102-0_12)

## 1 Introduction

Robot-assisted surgery in a human patient was first reported by Kwoh in 1985 when the PUMA 560 robotic surgical arm was used for a neurosurgical needle biopsy while being guided by computed tomography [1]. Since then, robot-assisted surgery has found a growing niche in medicine, gradually becoming integral to improvements in surgical care, with potential applicability across numerous surgical specialties. Present and emerging robotic systems promise improvements in surgical scope, capability, efficacy, reproducibility, safety, and cost—over manually performed procedures. This is due in part to their increased precision, ability to reproducibly perform repetitive tasks, and the ability to overcome a number of human physiological limitations. Integrating robotics with other support capabilities such as imaging systems and sensors further extends the relevant competence of human-robot cooperation.

The expansion of robotic applications in the field of minimally invasive surgery has been marked by success, with systems such as the da Vinci (Intuitive Surgical Inc., Sunnyvale, CA, USA) being perhaps the most notable to date. Despite rapid implementation in surgery, the near-term intention is not for robots to replace surgeons, but that they function as assistants. Potential roles include but are not limited to working cooperatively directly with the surgeon or in the role of a specialized tool directed by the surgeon. Therefore, the concept of robot-assisted surgery is at present a most fitting framework by which to envision the role of robotics in microsurgery [2].

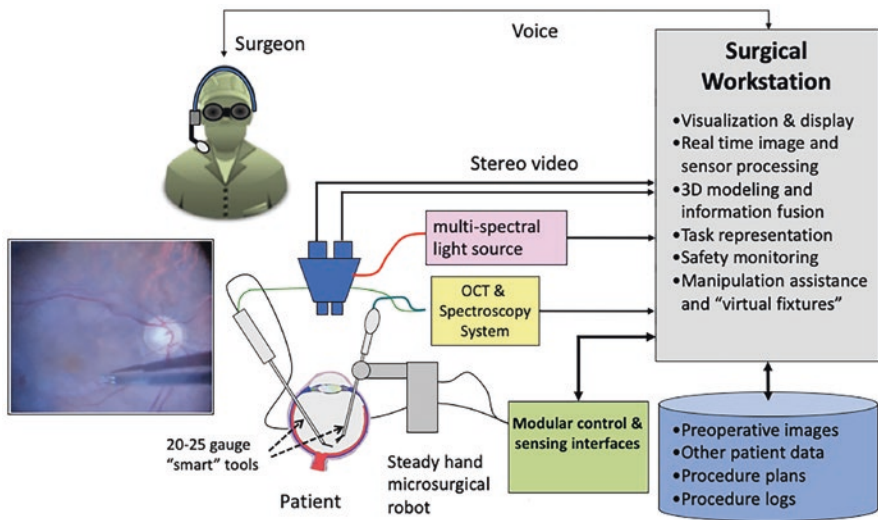
Ophthalmic microsurgery is a highly specialized microsurgical niche dealing with surgical procedures performed on the eye. Of the various ophthalmic microsurgical subspecialty areas, intraocular vitreoretinal microsurgery remains among the most technically challenging, despite recent advances in the field. The use of robotics offers numerous potential solutions to the challenges of retinal microsurgery, which include, but are not limited to, a confined space, a fragile and nonregenerative surgical target, micron-scale movement requirements, and visualization challenges [3].

Unassisted ophthalmic surgery requires a dexterous, stable, and precise surgical approach that lies at the limits of human motor function to perform [4]. Membrane peeling in vitreoretinal surgery, for instance, is known as one of the most delicate routinely performed surgical tasks, not only in ophthalmology but among all microsurgical disciplines. In this setting, microsurgical force measurement experiments show that typical intraoperative forces applied to retinal tissue by microsurgical instrument tips are routinely less than 7.5 mN. Forces on this order of magnitude are often below the threshold of the surgeon's tactile sensitivity [5–7]. Further complicating retinal membrane peeling is surgeon physiological hand tremor, which can prevent procedure completion and significantly increase the risk of iatrogenic retinal damage from unintentional tool-to-tissue contact [8]. Another challenge to be overcome encompasses the ergonomic aspects of ophthalmologic

surgical practice that may predispose ophthalmologists to a high rate of acquired musculoskeletal disorders at a relatively early career age.

With these and other factors in mind, robotic technology has continued to develop with current advancements nearing feasibility for routine clinical use. The barriers of dexterity, visualization, force perception, tremor, and ergonomics in ophthalmic surgery have all been significantly diminished by recent advancements in robotics for microsurgery [9–12]. Despite these and other improvements, vitreoretinal surgery still has many challenges to overcome. As a result, many studies developing robotic applications in ophthalmic surgery focus on vitreoretinal surgery. This chapter presents an overview of potential current vitreoretinal applications and the role of the prevalent robotic platforms developed to date (Fig. 1).

Robotic technology has only recently begun to be integrated into the ocular microsurgery field; therefore, its development, progress, and penetration are in their infancy relative to other surgical disciplines where the role is now better defined. This relative delay in robotic adoption is in part attributed to unique technological challenges present in ocular surgery. Barriers such as the need to operate on the order of millinewton (mN) forces and on single micron-scale surgical targets and others have delayed the full promise of a robotic system for vitreoretinal surgery [13]. Another potential explanation for delayed adoption of robotics into vitreoretinal surgery relates to application-specific challenges inherent in engineering machines that work safely and with micrometer precision, within a fragile and tightly confined anatomic work space. A high cost, intrinsic learning curves, longer surgical times, and patient acceptance present other current challenges to robotics in ophthalmology [14].



**Fig. 1** Flowchart showing possible interactions between the ophthalmic surgeon and the robotic assistant

## 2 Ophthalmic Diseases That May Benefit from Robot-Assisted Surgery

### 2.1 *Membrane Peeling*

In retinal microsurgery, precise manipulation of delicate and often transparent tissues is carried out by applying very small forces, the majority of which are below the surgeons' tactile sensory threshold [15]. Membrane peeling is a common task in vitreoretinal surgery, during which excessive peeling forces or inopportune maneuvers can lead to retinal trauma, hemorrhage, and tears. Iatrogenic operative trauma may be a cause of prolonged surgery times, failure to achieve surgical objectives, and suboptimal visual outcomes [16, 17]. Membrane peeling is among the essential tasks in vitreoretinal surgery and has generally been accepted as a fundamental step in prevalent procedures such as macular hole repair (internal limiting membrane (ILM) peeling) or in epiretinal membrane removal (epiretinal membrane peeling, which can also be associated, or not, with ILM peeling). The ILM is an approximately 2.5  $\mu\text{m}$  thick layer [18] formed by a basement membrane that constitutes the boundary between the retina and vitreous surface. It is adherent to the retinal surface and is transparent, requiring staining to visualize well. The goal of ILM peeling is to delaminate this micron-scale fibrous membrane from the inner retinal surface and relieve pathological tractional forces from the retinal surface.

With this background, Edwards et al. [19] reported the first-in-human study that used a teleoperated robotic device called Preceyes to perform membrane peeling surgery, in 2018. Twelve patients undergoing dissection of an epiretinal or internal limiting were randomly assigned to either robot-assisted or freehand surgery. Surgical outcomes were not significantly different in either group and the procedure took longer when performed with the robot. Despite no clear measurable early advantage for robotic assistance, high precision and minimal tremor maneuvers were clearly demonstrated in the human eye. As a result, this proof-of-concept series of robotic microsurgical procedures has opened the field of ophthalmic microsurgery to potential next-level improvements and applications in robotic microsurgery.

### 2.2 *Retinal Vein Cannulation*

Retinal vein occlusion is among the most prevalent retinal vascular disorders and a frequent cause of vision loss that is second only to diabetic retinopathy [20]. Current standard of care treatment options focus on mitigating downstream sequelae of the occluded vessel, such as macular edema, retinal neovascularization, vitreous hemorrhage, and traction retinal detachment, rather than directly addressing the retinal vascular occlusion. While each of the complications of retinal vein occlusion has management options that are variably effective (laser therapy, intraocular

injections of steroid or anti-VEGF drugs, and surgical approaches), none of these definitively addresses the underlying cause (vascular occlusion) and even when successful can leave the patient in chronic therapy and with some level of continued vision loss [20, 21].

Weiss et al. [22] demonstrated the relative safety of performing vitrectomy followed by freehand retinal vein cannulation for infusion of tissue plasminogen activators (t-PA) directly to the thrombus. The hypothesis was that this would improve vision. Twenty-eight patients with central retinal vein occlusion and vision loss were enrolled. However, 25% of this study population experienced procedure-related postoperative vitreous hemorrhages and one patient had a postoperative retinal detachment, demonstrating just some of the technical challenges inherent in this unassisted freehand approach.

Human retinal veins are at their largest most proximally just prior to entering the optic nerve. At this point they measure on the order of 125  $\mu\text{m}$ . By way of comparison the size of one of the smallest structures that vitreoretinal surgeons target for treatment, the ILM, is on the order of 2.5  $\mu\text{m}$  [18]. Human hand tremor is variable but it is not unusual for it to be on the order of 100  $\mu\text{m}$  when translated to the tip of a vitreoretinal instrument [23]. Therefore, for vitreoretinal microsurgery to be performed, human physiological tremor must be overcome. Robotic assistance using fully stabilized robotic tools is a logical potential approach. In the case of treating retinal vein occlusion, a further advantage of robotic assistance is not only the provision of efficient and safe cannulation, but also the intraluminal stabilization of the needle in the vein, allowing for the extended infusion period required for delivery of therapeutic agent to the thrombus [24].

Various robotic assistant modalities have been proposed over the past 20 years [25]. However in 2018 the world's first-in-human robot-assisted retinal vein cannulation study was performed [21]. Four patients diagnosed with retinal vein occlusion were treated using the KU Leuven robot, a co-manipulated robotic assistance device. This investigation demonstrated that it was technically feasible to safely inject an anticoagulant into a 100  $\mu\text{m}$  width retinal vein over a "prolonged period" of 10 min, using robotic assistance.

### **2.3 Subretinal Injections**

The field of gene therapy has made remarkable strides in recent years. The United States (US) Food and Drug Administration (FDA) approval of Luxturna in 2017 (the first US gene therapy for a genetic disease) marked a new cycle of innovation in ophthalmic therapy [26]. Luxturna is an intraocular suspension with a gene transfer vector that employs an adeno-associated viral vector capsid as a delivery vehicle for the human DNA necessary to replace the protein product of the RPE65 gene in the retinal pigment epithelium, via injection into the subretinal space. However, the emerging era of ocular gene therapy extends beyond Luxturna, bringing a broad array of new treatments for inherited retinal disease [27].

In this context, subretinal drug delivery has become increasingly useful and accepted in both scientific research and clinical application due to the more direct effects on the targeted cells in the subretinal space. This provides a new therapeutic method for vitreoretinal diseases, including but not limited to gene therapy [28]. Ideally, subretinal injection would result in the placement of the entire therapeutic solution in the subretinal space in immediate proximity to the targeted photoreceptors and RPE cells [29].

Unlike intravitreal drug delivery, which is relatively simple in practice, subretinal delivery is associated with a number of technical challenges. Moreover, its effectiveness relies on several factors, including the surgical delivery of drug to the subretinal space while minimizing eye trauma and any negative effects on the therapeutic agent. Similar to vein cannulation, subretinal injection not only involves accessing the correct anatomical space but also requires the ability to maintain the needle tip position stably in the correct position for the entire (sometimes prolonged) duration of drug injection. Among the challenges to performing minimally traumatic injections is the ability to form and maintain an injection bleb without drug refluxing throughout the duration of the injection phase. To achieve this, it is essential to minimize surgeon tremor to avoid enlargement of the needle entry point and injury to the associated tissues [30].

Faced with such novel surgical challenges, Ladha et al. [29] recently published a comparison between manual and robotic assistance in simulated subretinal injections in an artificial retina model using Preceyes Surgical System (Preceyes BV, Eindhoven, the Netherlands) as the robotic platform. They showed that the robotic device was associated with improved tremor, diminished retinal entry hole size, prolonged allowable injection times, and a higher rate of bleb formation with a reduction in drug reflux through the injection entry point. Edwards et al. [19] have used the Preceyes teleoperated robot to successfully inject recombinant t-PA beneath the retina to displace sight-threatening hemorrhage in three patients. This work reinforces the concept of robotic assistance for subretinal injections in the setting of retinal gene therapy.

### **3 Ophthalmic Robotic Devices**

The ophthalmic robots can be broadly categorized into three main groups: teleoperated systems, co-manipulated or cooperative platforms, and handheld robots.

#### ***3.1 Teleoperated Robots***

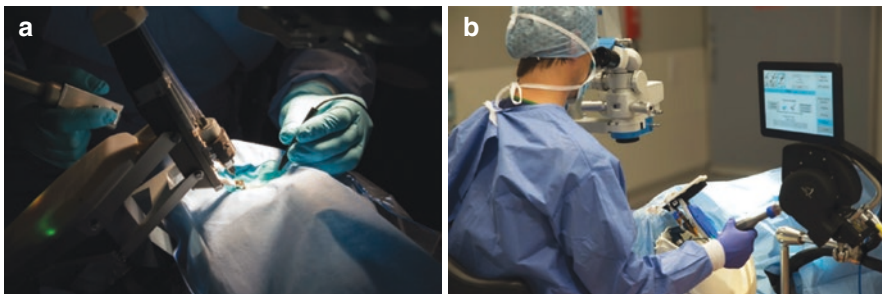
Telerobotic surgery represents a major area of interest and progress over the last decade due in part to the substantial number of potential high impact applications. Telepresence is the presentation of a remote environment in a natural way, thus

generating a sense of presence in remote locations. This concept describes the basis of both telemedicine and telerobotics [31]. The increasing acceptance of robot-assisted surgery commensurate with advances in telecommunications has led to progress in related technology and the further development and the use of telemedicine, extending from telepresence to telesurgery [32]. Teleoperated robotic surgical systems now allow a surgeon who is remotely located to provide various levels of training or patient care from a distance [16].

Teleoperated robotic platforms are divided into two main components: a master console, where the surgeon receives visual and tactile feedback, allowing him/her to control the active part of the robot, which is called the follower console and is located in a remote location [33]. The da Vinci Surgical System was the first telemanipulation robot to receive complete FDA approval [34] and has since been widely applied in various types of minimally invasive surgery. However, the microscopic scale of eye surgery and the rotational instability of the globe within the orbit place additional demands on the system that preclude the implementation of da Vinci-like systems in the ophthalmic surgical field [35].

To date, the Preceyes Surgical System is not only the first robotic device to be used in a safety and feasibility study for intraocular robotic surgery but also the first robotic surgery system dedicated to ophthalmology to become commercially available (Fig. 2) [19]. Originated in the Netherlands, the Preceyes robot positions the surgeon at the head of the operating table, where the robot is attached to a headrest. A motion controller positioned in the surgical field records the surgeon’s movements, which are filtered in real time and enhanced by a computer before being transmitted to the slave console. In addition, Preceyes utilizes a hybrid approach that allows intraoperative switching from freehand to robot-assisted surgical steps and to simultaneously operate the robot with one hand while manipulating a handheld instrument with the other.

The intraocular robotic interventional surgical system (IRISS) is another example of a teleoperated robot [36]. It was developed through a partnership between the Department of Mechanical and Aerospace Engineering of the University of California and the Jules Stein Eye Institute, motivated by the goal of performing



**Fig. 2** (a) The Preceyes Surgical System developed by the Preceyes BV, Eindhoven, the Netherlands. (b) Operating room setup. (Figure kindly provided by Dr. Gerrit Naus, CEO and Co-founder Preceyes BV, Eindhoven, the Netherlands)

complete, multistep, intraocular surgical procedures. The IRISS master console includes two joysticks and the robotic tissue manipulator (slave side) consists of two independently controllable arms, each capable of holding two automatically interchangeable surgical tools. These tools may consist of many types of commercially available microsurgical instruments that have been adapted to fit the surgical manipulator with a large range of motion. The robotic platform is positioned between the patient and surgeon in the surgical setup, in a way that the surgeon works from a surgical cockpit. The IRISS has been shown to be effective in completing many key steps in a variety of intraocular surgical procedures in postmortem porcine eyes, such as capsulorhexis, lens cortex removal, core vitrectomy, and retinal vein cannulation, and is now capable of performing an entire cataract extraction [37]. Therefore, this teleoperated system may eventually be suitable for performing both anterior and posterior segment ocular surgery.

### 3.2 *Co-manipulated/Cooperative Robots*

In a co-manipulated, also known as a cooperative robotic, system, the surgeon holds and maintains direct manual control over the motion of the surgical tool, which is simultaneously held by the robotic platform. The robot is then able to provide direct assistive compensation to the surgeon, e.g., physiologic human hand tremor or others, to meet the performance, accuracy, and safety requirements of microsurgery [13, 38–41]. Various surgical instruments, whether conventional or “smart,” can be attached to the robotic tool holder [38, 42, 43].

In this setting, the Steady-Hand Eye Robot (SHER) was developed by the Johns Hopkins University research team (Fig. 3) [44, 45]. This device is able to cooperatively guide instruments enabled to sense micro-forces exerted by the

**Fig. 3** The Steady-Hand Eye Robot developed by Johns Hopkins University





instrument to the eye, and to filter out any tremor via the robot's stiff mechanical structure, as it follows the user's motion [46–49]. In addition, the SHER is also capable of detecting tool tip micro-forces, in a way that provides effective assistance to perform surgical tasks safely and efficiently [44, 50–55]. Balicki et al. [56] went beyond the force sensing feature and integrated OCT-based distance sensors at the robot tool tip to enable vitreoretinal surgical interventions that utilized the maintenance of a constant distance from the retina, thereby avoiding inadvertent collision with tissue, as well as facilitating the targeting of anatomical structures inside of the eye.

Despite continuing improvements, the American SHER remains in preclinical development. The first, and for now the only one, co-manipulated robotic assistance device that has migrated to the living human eye environment as a clinically applicable robotic platform is a Belgian robot [57] that in 2018 successfully injected an anticoagulant into the retinal veins of four patients with retinal vein occlusion. The injections were carried out over 10 min in a phase 1 clinical trial [21]. This device consists of a parallel arm mechanism with a mechanical remote center of motion controlled through a spherical mechanism that provides motion scaling, tremor compensation, and scaled force feedback [13].

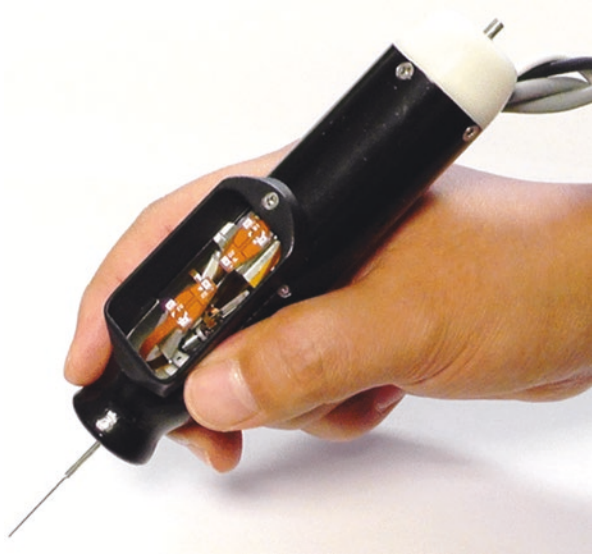
Although more complex than the handheld robots, the co-manipulated robots can still be built at a lower cost than teleoperated platforms due to the non-requirement for separate master and follower consoles [58]. A limitation of co-manipulated robots is their inability to provide variable motion scaling, semi-automation of surgical tasks, or improved ergonomic conditions for surgeons, as compared to teleoperated systems [35].

### **3.3 Handheld Robots**

The handheld robots are manually operated enhanced surgical instruments equipped with a limited distance sensing and servo action capability that allows autonomy. The tools provide the user with real-time information during each surgical maneuver, and a resulting automated response that, depending on the function, can compensate for the surgeon's physiological limits in the challenging surgical environment of the eye [59, 60]. While guided and manipulated by the surgeon's hand, the handheld robots can correct actions, attenuate interaction forces with the target tissue, and augment surgical capabilities to an optimized level during each step of the surgical procedure [61, 62].

An example of such a function is providing real-time force information during tissue manipulation at levels beneath human tactile abilities [63]. Tool action is programmed to respond to various force levels, potentially limiting excess force related to surgical complications. Visual, tactile, and auditory feedback are among the effective ways to communicate intraoperative forces to a surgeon [16, 64]. Similarly, obtaining live intraocular optical coherence tomography (OCT) scans during surgery can direct surgeon decision making based on intraoperative

**Fig. 4** The Micron handheld micromanipulator from Carnegie Mellon University



information [65]. An active handheld OCT imaging system developed by Yang et al. [66] is capable of canceling hand tremor, as is the Micron [67], which consists of an externally guided portable micromanipulator designed to remove tremor and increase positional accuracy (Fig. 4).

Handheld instruments are intrinsically intuitive for a surgeon to handle, mechanically simpler, and significantly less expensive to produce than large robotic platforms. Moreover, the motion control of the tool remains in the surgeon's hands, which may enhance safety, as the surgeon can manually finish a procedure in the case of robotic failure or unexpected patient movement. Alternatively handheld robots can simply be used to perform the portions of a procedure that are less effectively/efficiently executed freehand [68, 69]. An inherent limitation of handheld robots is the requirement to be continuously held and guided by the surgeon [58].

## 4 Conclusion

Ophthalmic surgery, and especially vitreoretinal surgery, represents a unique set of opportunities amenable to the potential advantages of robotic surgery. Increasingly widespread use of robotic platforms and a greater number of potential applications in the ophthalmologic surgical field are expected. Now however, the implementation of the full potential of surgical robotics in ophthalmology relies on the further development of technological platforms and integrated robotic systems that add significant value over current manual surgical techniques. Ultimately, the surgeon equipped with a robotic system will be able to perform procedures that are currently

impossible in a freehand environment. It is expected that further developments will improve the safety, efficiency, efficacy, and cost of these robot-assisted procedures.

**Acknowledgment** Dr. Roizenblatt reports receiving research funding from Lemann Foundation, Instituto da Visão, Latinofarma, and Coordination of Improvement of Higher Education Personnel. Dr. Gehlbach reports receiving research funding from Research to Prevent Blindness and gifts from the J. Willard and Alice S Marriott Foundation, the Gale Trust, Herb Ehlers, Bill Wilbur and Rajandre Shaw, Helen Nassif, Mary Ellen Keck, Don and Maggie Feiner, and Ronald Stiff. Dr. Maia and Dr. Belfort Jr. report receiving research funding from the National Council of Scientific and Technological Development. Dr. Iordachita reports receiving funding from US National Institutes of Health under grant numbers of 1R01EB023943-01 and 1R01EB025883-01. Ali Ebrahimi reports receiving funding from Link Foundation. The abovementioned institutions had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation; and review.

**Conflicts of Interest** No conflicting relationship exists for any author.

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