Computer-assisted laser photocoagulation of the retina—a hybrid tracking approach

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1 Introduction
1.1 Background

Laser photocoagulation has been used to treat retinal disorders such as diabetic retinopathy, macular degeneration, and retinal tears for several decades.1 Typical treatment protocols require placement of multiple (often several thousand) therapeutic lesions on the retina in an outpatient environment. Lesion placement is determined by the ophthalmologist, and the patient is fully awake during the procedure. Although the patient’s head is supported in a chin cup and the conjugate eye is stabilized with a fixation target, considerable retinal movement may occur. The procedure is currently performed manually and suffers from several drawbacks including:2 it often requires many clinical visits, it is very tedious for both patient and ophthalmologist, and the laser pointing accuracy and safety margin are limited by a combination of the ophthalmologist’s manual dexterity and the patient’s ability to hold their eye still. Furthermore, there is a large variability in lesion size even with identical irradiation parameters due to the nonhomogeneous retinal tissue properties. The goal of this research is to develop a computer-assisted laser delivery system to aid the ophthalmologist in therapeutic lesion placement and parameter control. This paper concentrates on the development of a second hybrid system prototype to accomplish the project goal. The paper begins with a brief review of laser photocoagulation treatment for retinal disorders followed by a description of the hybrid system. The remainder of the paper then describes each subsystem in detail and outlines the progress toward a clinically significant prototype.

1.2 Photocoagulation for Retinal Disorders

Laser photocoagulation is used to treat various retinal disorders. In laser photocoagulation, the absorption of laser light by tissue generates heat which causes molecular denaturation and necrosis in the absorbing and surrounding tissue. Typically an argon laser (λ = 488,514 nm) is used. The argon wavelength has been found to provide the most desirable penetration depth through the neural retina and high absorption in the retinal pigment epithelium (RPE).3,4 The generated heat transfers to the neighboring tissue and a therapeutic lesion is thus formed. The lesion developed appears highly reflective compared to the surrounding tissue when viewed via a fundus camera. The lesion will reflect light more effectively than the undamaged parts of the retina due to an increase in the scattering coefficient of the tissue optical properties. Light reflected from the lesion is used to track retinal movement and is also used to control the depth of the lesion. Lesion formation is not uniform across the retinal surface due to varying absorption characteristics. It has been shown that absorption of laser energy in the RPE typically varies up to 200% across the retinal surface.5 It is imperative that the lesion depth does not approach close to the inner surface of the retina which can damage the nerve fiber layer and may lead to arcuate scotoma.6 Furthermore, deep lesion growth may result in hemorrhage into the vitreous chamber while a shallow lesion...
provides limited therapeutic effect. There are several disorders currently treated with laser photocoagulation. These disorders include diabetic retinopathy, macular degeneration, and retinal tears.

Diabetic retinopathy is the most common of all retinal diseases. It is one of the leading causes of blindness in the Western hemisphere. It is a direct result of diabetes mellitus. Retinopathy is an alteration of blood vessels that provide nourishment to the retina. These blood vessels may leak, develop irregular branches, or become enlarged causing poor vision. To treat this disease, an ophthalmologist directs the laser through the pupil onto the retina at different locations. Each laser "shot" to the retina creates a tiny burn or lesion (approximately 200 μm in diameter) that, if successful, can stop abnormal leakage or bleeding and generally mitigate the retinopathy. This procedure may require up to 3000 lesions per eye, involving repeated clinical visits, and can be very tedious to both patient and ophthalmologist.

Macular degeneration often associated with aging, it is a common retinal disease, and the most common cause of legal blindness in the United States for people over 60 years old. With this problem, the central area of the retina deteriorates causing poor central vision and requires prompt evaluation. As with diabetic retinopathy, a laser is directed on the retina at different locations to stop abnormal leakage or bleeding and generally improve the condition. One problem with this disease is that the diseased area is sometimes very close to the fovea (the area where our most acute vision takes place), and damage to the fovea can cause permanent blindness. Therefore, placing lesions in this area requires extreme caution.

Retinal detachments can be caused by disease or injury and involve a segment of the retina actually being separated or peeled away from the back wall of the eye. This usually results in the immediate loss (partial or complete) of vision. Retinal detachment is the stage that normally occurs after retinal tears. It first starts with a tear in the retina, which eventually leads to a detachment. The procedure for laser treatment of retinal detachment/tears is to direct the laser to locations surrounding the damaged area in order to stop the tears from progressing to a wider area of the eye.

1.3 The Computer Aided Laser Optical System for Ophthalmic Surgery

In the late 1980’s, Markow et al. at the University of Texas (UT) proposed an automated system to treat retinal disorders with the following goals.

1. Development of a clinically significant photocoagulation system to provide a user-friendly interface for the ophthalmologist, to quickly and safely place therapeutic laser-induced lesions of desired parameters at desired retinal coordinates (while compensating for patient retinal movement), and
2. permit consistent retinal lesion formation (compensating for variations in the retinal absorption coefficient).

Considerable research has been accomplished at the UT, University of Wyoming, and the University of Wyoming to develop a clinically significant system capable of treating retinal disorders. This research effort is known as CALOSOS for computer aided laser optical system for ophthalmic surgery. The requirements for this system have evolved to: retinal tracking rates equal to or better than 10^-6 s, laser pointing accuracy better than 100 μm at the retinal surface, uniform lesion formation within 5% of apparent size and depth, and system reaction time of no more than 5 ms. Should retinal movement exceed the ability of the system (or other anomalous condition occurs such as patient blinking), the tracking system must register a loss-of-lock condition, immediately close the laser shutter, and attempt to re-establish system lock.

The CALOSOS system has been subdivided by function into three main subsystems.

1. The digital tracking system—provides a global retinal tracking capability.
2. The analog tracking system—provides a fast, local tracking capability.
3. The lesion control system—controls laser dosimetry in real time to produce consistent therapeutic lesions across the retina.

When integrated together, these three subsystems provide a hybrid system capable of mapping desired lesion placement sites, tracking and compensating for retinal movement, and controlling laser irradiation time to provide for consistent therapeutic lesions. In this paper we will present the progress made in each of the subsystems toward realization of a clinically significant system.

2 Digital Tracking Subsystem

2.1 Overview

The digital tracking subsystem uses a standard 640×480 pixel resolution, 30 frames per second (fps), and a monochrome charge coupled device (CCD) video camera attached to a mydriatic fundus camera to obtain an image of the retina. The CCD camera is connected to a frame grabber hosted by a standard desktop PC. The frame grabber converts the CCD camera signal into a series of images compatible with a personal computer. The digital tracking system provides a global retinal tracking capability using a blood vessel template matching scheme to update the position of the irradiating laser on the retinal surface.

2.2 The Optical Configuration

The digital tracking subsystem and the analog tracking subsystem share an optical configuration illustrated in Figure 1. The details of this optical configuration have been described elsewhere. A diagram and a brief description of the optical configuration is provided here for completeness. An all lines argon laser is introduced to the system via a laser delivery fiber. The irradiating beam is routed to the retinal surface via mirrors M1 and M2, passing without deviation through a dither mirror (a beamsplitter), and the main steering mirrors. The dither mirror and the main steering mirrors are under galvanometer control. From the main steering mirrors the beam is directed to the beam splitter (BS4) at the fundus camera through the patient’s dilated pupil and to the retina. On this path, the beam passes through other optical com-
ments, which are used to condition and control the beam and to split off a portion of the main beam for use as the tracking beam, including several shutters and a beam splitter. A portion of the main beam is also reflected off of beam splitter BS1 to the laser power reflectometer which measures instantaneous laser power.

As the therapeutic lesion begins to form on the retinal surface, the retinal tissue coagulates, the scattering coefficient increases, and the lesion reflects an increasing portion of the irradiating beam back along the same optical path. The signal is reflected off of BS1 to the coagulating beam reflectometer and is used to derive an indication of lesion depth.

A low-power tracking beam is obtained by tapping off a portion of the main coagulating beam in the forward direction of the light path at beam splitter BS1. The dither beam is significantly attenuated by beamsplitters BS1 and BS2 (both 80/20) and the neutral density filter. The tracking beam reflects off beam splitter BS2 to the dither mirrors. The dither mirrors are driven by quadrature related sinusoid signals such that the tracking beam is driven in a circular dither pattern. The tracking beam then passes through the main mirrors and on to the retina. The low power dithering tracking signal reflects off of a reference lesion. The reference lesion is used for analog tracking purposes. It may be a lesion of therapeutic value or a low level marker lesion placed at the beginning of the surgical procedure under the control of the digital tracking system. The reflectance from the dithering signal follows the reverse path back to the tracking beam reflectometer.

The prototype optical configuration has been significantly reduced in footprint to approximately 30 cm by 30 cm, a reduction in area of almost 16:1. This makes the system more clinically practical and easily adaptable to an existing ophthalmic fundus camera. The set-up, shown in Figure 2, was constructed with LINOS Photonics Microbench optical components. Various components were used to focus (L1–L6, LS) and direct the beam (M1, M2, main mirrors, and BS4). Lenses L1, L3, L5, and L6 are planoconvex with \( f = 25 \text{ mm} \); whereas, L2 and L4 are planoconvex lenses with \( f = 250 \text{ mm} \). Lens LS is an aspheric lens with \( f = 53 \text{ mm} \). All lenses were AR coated.

2.3 Digital System Software

The software is the fundamental part of the CALOSOS system. It controls the building of the tracking template, the laying out of the lesion sites, and controlling the retinal surgery. The tracking template consists of three sets of horizontal and vertical blood vessel templates locked into known orientation to one another to form a unique, two-dimensional template of the retina’s vessel pattern. An individual blood vessel tem-

![Optical configuration for the digital tracking subsystem and the analog tracking subsystem.](https://www.spiedigitallibrary.org/journals/Journal-of-Biomedical-Optics)
plate consists of the leading and trailing edge of a blood vessel at a known distance from one another. In addition, the software also drives the graphical user interface for the operator. Figure 3 shows the software language chosen for this project was Microsoft Visual C++ 6.0 with the Windows NT 4.0 operating system. The software interacts with three hardware PCI boards: a frame grabber board from MuTech MV-1000 and two data acquisition cards from National Instruments PCI-6025E, which control the operation of the shutters and galvanometers. A standard, monochrome, RS-170 640 × 480, 30 fps camera (Sony XC-75) is used to capture the images of the retina.

The software controls the retinal surgical procedure and provides the operator an easy to use interface. The operator will choose where the tracking templates should be created and then choose to accept the tracking templates or to discard them. The same is the case for lesion placement. The software will automatically layout the lesion sites after the operator designates the area, in addition to masking the optic disk, fovea, blood vessels, and tracking templates from laser irradiation. The optic disk location is automatically detected using Hough Transform techniques. This masking is done to prevent putting lesion sites on critical locations which may damage the eye. However, the operator has the option to delete and/or to add new lesion sites before accepting the lesion placement.

Upon starting the surgical procedure, the software will control the movement of the laser from one lesion site to another. It will also make necessary adjustments to the laser position at a rate of 30 times per second (determined by the camera frame rate), based on template registration within each video frame. If retinal movement is detected, the software will move the mirrors in the appropriate direction to ensure the laser stays at the designated lesion location. If the software cannot establish digital lock, it will shut off the main coagulating beam until it has re-established lock or else halt the surgical procedure. The update every 33.3 ms is not fast enough for the required system response of 5 ms. This is where the analog tracking subsystem is used to achieve faster position updates and response time. The tracking and control functions are implemented with three PCI boards. Two boards are identical data acquisition (DAQ) boards from National Instruments PCI-6025E. Each PCI-6025E has two analog output channels (−10 to +10 V) and one eight-bit digital I/O channel (0 to +5 V). Since the software is controlling four galvanometers, two DAQ boards are required.

2.4 Digital Tracking Subsystem Testing
In order to characterize the tracking parameters of the digital tracking subsystem, several tests were performed using a retinal phantom. The retinal phantom consisted of an X–Y plotter with a retinal image affixed to the plotting pen carriage. Using this configuration, known scaled retinal movements could be produced in the retinal phantom. The results of a representative test (where the retinal speed was increased until the digital tracking subsystem lost lock and then attempted to regain lock) are shown in Figure 4. The tracking system was
able to keep up with equivalent retinal velocities up to 23.83 °/s. The system then successfully re-established system lock when the phantom velocity was decreased.

As previously mentioned, the digital tracking subsystem provides a global view of the retina and also a retinal tracking capability beyond the desired 10 °/s requirement. However, the response time of the system is limited by the camera frame rate at 33 ms and, hence, does not meet the overall system requirement of a 5 ms response time. Although faster camera frame rates are available, retinal image quality would suffer due to reduced pixel integration time and digital retinal tracking would no longer be possible. To achieve the required system response time, a fast analog tracking system is required.

3 Analog Tracking Subsystem
3.1 The Analog Tracking Subsystem Overview
The analog tracking subsystem of CALOSOS includes three features: fast retinal tracking, lesion parameter control, and generation of the system loss of lock signal. Recall from our earlier discussion that the digital tracker is able to produce a 33 ms response time when a standard 30 fps camera is employed. To compensate for the frame rate limitation and provide a 5 ms response time, analog tracking was added to CALOSOS. The technique was developed as a stand-alone method to eliminate retinal motion induced artifacts from confocal reflectometer signals obtained during laser photocoagulation. The heart of the design is a closed loop control system.

The analog tracking subsystem employs a small, laser-induced retinal lesion with a reflectance significantly different than the surrounding tissue. This feature can be used for tracking, by “dithering” a low-power secondary laser beam in a small circle around the inside edge of the reference lesion and detecting the returning light with a confocal reflectometer (see Figure 5). When this dithered beam is pointed on the reference lesion, the reflectometer signal is high. When the beam is pointed off the lesion, the reflectometer signal is low. Thus, the reflectometer output signal varies synchronously with the periodic dither signal which drives the dithering mirrors. This

![Fig. 3 GUI layout after tracking algorithm and lesion placement algorithm have been performed.](https://www.spiedigitallibrary.org/journals/Journal-of-Biomedical-Optics)

![Fig. 4 Tracking loss at retinal movements >23.83 °/s. The tracking speed is slowly increased until a loss of lock occurs. The system then attempts to re-establish lock. In the above chart relock did not occur until the speed was brought down again to under 23 °/s.](https://www.spiedigitallibrary.org/journals/Journal-of-Biomedical-Optics)
output is processed to yield $X$ and $Y$ error correction signals from the confocal reflectometer. In this synchronous detection technique, the error signals contain all the information needed to redirect the tracking beam back to the center of the reference lesion, thereby minimizing the error signal. These error signals are integrated over time and used as correction signals to drive the main steering mirrors in the tracking beam path. Therefore, the motion of the reference lesion due to retinal movement can be detected and tracked.

When this closed loop control system has lost lock with the eye due to an abrupt retinal movement, it will provide the hybrid system with a “lost lock signal.” The normal “lock signal” is high as long as the dither beam is tracking the reference lesion, and goes low if the dither is off the reference lesion. When the analog system loses lock, the loss of lock condition immediately causes the main shutter to close so that no harm is done to the patient.

### 3.2 Analog Tracking Subsystem Description

Figure 6 provides a block diagram of the analog tracking subsystem. The subsystem is divided into five sections. The input section amplifies and filters the reflectance signals from the coagulation beam reflectometer, the laser power reflectometer, and the tracking beam reflectometer. In the normalization section, the laser power reflectometer signal is used to normalize the other two reflectance signals to compensate for laser source variation. The quadrature generator is the third section and provides reference signals for synchronous detection and the drive signals for the dithering galvanometers. The $X$ and $Y$ channel sections provide drive signals to regulate two pairs of galvanometer-controlled mirrors so that the laser dithering beam always illuminates a reference lesion keeping the therapeutic laser at the correct location on the retinal surface. These signals have been designated $X$-galvo-out and $Y$-galvo-out for the therapeutic laser beam control and $X$-dither galvo-out and $Y$-dither galvo-out for the dithering beam control.

### 3.3 Input and Signal Normalization Blocks

The input block consists of three reflectometers followed by a filter and an amplification stage. Each reflectometer is a Burr Brown photodetector consisting of a high performance silicon photodiode and precision, field-effect transistor-input transim
pedance amplifier integrated on a single monolithic chip. The output of the photodetector is a voltage proportional to the intensity of the light illuminating it. All three input channels are equipped with a third order low pass filter to prevent aliasing when the signal is sampled by the lesion control subsystem. The last part of the input block is the amplification stage. It is necessary to employ low noise amplifiers in this stage since the photodiodes within the reflectometers produce low-level signals. The laser power input also has a direct current (dc) blocking circuit. The purpose is to normalize the two other reflectance signals by the laser power source. Due to the requirements of the specific analog divider used in the normalization process, it was necessary to retain the alternating current portion of the signal, and remove the dc bias signal. A dc 10 V level was then added to meet the input requirements of the analog divider.

3.4 The Quadrature Generator

The quadrature generator provides two outputs: a sine wave for driving the X channel, and a cosine wave for the Y channel. When driving the dither mirrors with these two signals, a circular beam motion results. This is referred to as the dithering beam. These signals are also used for synchronous detection.

The quadrature related signals are generated using two EPROMs erasable programable read only memories (EPROMs). One EPROM has a digital representation of a sine signal stored within it while the other has the cosine signal. Analog sine and cosine signals were reconstructed from the digital representations stored in the EPROMs by sequentially scanning through the EPROMs memory locations. Each digitized sample of the wave form is fed into an analog-to-digital
converter followed by a low pass smoothing filter. The overall results are sine and cosine signals precisely locked into a quadrature relationship with one another. This is called direct digital synthesis.

3.5 X and Y Channel Detection and Error Generation
The X and Y error signals are generated in this stage via synchronous detection. The sine and cosine reference signals from the quadrature generator are separately multiplied with the signal from tracking beam reflectometer. The result is an X-error and Y-error signal that when filtered may be used as a compensation signal to maintain the coagulating beam and the dithering beam on the desired location on the retina.

3.6 Analog Tracking Subsystem Simulation and Testing
During development, the analog tracking subsystem circuit was first simulated under a variety of test conditions using Electronics Workbench. The results of a representative test are illustrated in Figure 7. The simulation illustrated depicts a scenario where the eye has moved to the left. The chopped sine wave is caused by a portion of the dither beam reflection signal falling off the reference lesion. Note that the error is integrated over time and increases accordingly until the movement effects have been eliminated and the dither signal is back on the reference lesion. As expected, when a portion of the dither signal falls off the reference lesion, a corresponding error signal is generated. The response time of this system is well within the 5 ms system requirement. A 1 kHz dither signal was used. The system response time is limited primarily by the mechanical movement of the galvanometers.

Once a prototype was completed, the analog tracking subsystem was also put through a battery of tests. The results of a step response test is shown in Figure 8. An analog switch was used to engage a dc voltage step that would simply be added to the dither drive signal. The input step, the reflectometer output, the error generated on channel x, and the error generated on channel y were then captured with an oscilloscope.

The tracking beam reflectometer output in response to the step deflection input is the top trace. The corresponding Y channel and X channel error correction signals generated by the analog tracking subsystem are also shown along with the step response signal. A step input in the negative x direction was used to test the circuit. In reality this would be the same as if the eye moved to the right. The first signal to respond to the step function is at the bottom of the display (delta-x). The reflectometer detected the movement by providing a signal that indicated the dither beam was about to fall off the reference lesion. The error generated at the X channel is increasing, which means the dc signal added to the X channel dither was increasing. This means the dither is returning to the reference lesion. The error signal generated stabilizes after a short time, which means the system had compensated for the step input. Also note that the Y channel generated an error signal. This was due to the dither signal not being perfectly placed in the middle of the reference lesion when the step was input.

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Fig. 7 Sample of dither with displacement, eye moved to the left.

Fig. 8 Step response test.
executed. The dither was forced slightly to the left. This deflection triggered a low level of compensation in the $Y$ channel, forcing a small positive error signal. This process stabilized the dither signal back on the reference lesion and resulted in no error.

4 Lesion Control Subsystem

The final CALOSOS subsystem to be discussed is the lesion control subsystem. The purpose of this subsystem is to dynamically control irradiation dosimetry to provide consistent lesions across the surface of the retina. Our goal is to use measurable lesion reflectance parameters to determine non-measurable lesion depth. Efforts to measure lesion parameters and correlate them with depth are reported elsewhere.\textsuperscript{26–28} The following section presents the current work in this area. For completeness we have provided a typical lesion reflectance curve in Figure 9.

Previous work determined the correlation of the latency period to lesion depth and the slope of the reflectance curve to lesion depth in a retinal phantom. These investigations yielded a good (0.66–0.99) correlation coefficient between these lesion reflectance parameters and lesion depth. However, this correlation was not enough to be reliably used to consistently control lesion depth parameters. At the suggestion of Dr. Jay Miller (Brooks AFB, TX), the correlation between the integrated lesion reflectance (simply put, the area under the lesion reflectance curve) and lesion depth was investigated. We formed a number of lesions using the same experimental apparatus from previous studies\textsuperscript{26,29} under many different experimental conditions. We purposely tried to inject a significant amount of electronic noise onto the reflectance signal to test the robustness of this technique. The results were excellent. Over the course of these experiments the correlation coefficient between central lesion reflectance and lesion depth
varied between 0.9 and 0.99. A representative result is provided in Figure 10.

We are very encouraged by these preliminary results in an egg white retinal phantom. We are currently repeating these experiments in vitro on porcine retina using clinically significant laser parameters. Preliminary results indicate the lesion reflectance curves have a virtually identical profile to those of the egg white phantom.

5 Discussion and Conclusions

In this paper we have reported on the considerable progress made on a clinically significant prototype system to safely place therapeutic lesions on the retina for the treatment of retinal disorders. To fully implement a clinical prototype, the following tasks must be accomplished:

- Fully integrate the digital and analog tracking subsystems,
- Fully characterize the lesion control subsystem and integrate it with the two tracking subsystems, and
- Test the hybrid prototype system in vitro on porcine retinas and in vivo on pigmented rabbits.

Efforts to integrate the lesion control subsystem are underway. Ludwig designed and implemented a stand-alone controller which collects confocal reflectance data from a forming reference lesion in real time. When the ophthalmologist verifies the reference lesion is acceptable, the collected reference parameters from the reference lesion are then used as a benchmark to form remaining therapeutic lesions. That is, when the reflectance area of a forming lesion matches the reflectance area of the reference lesion, the laser shutter is closed. The overall result will be consistent lesions across the retinal surface, even under retinal tissue absorbance variation. Ludwig has extensively tested the prototype controller under laboratory conditions. Testing on retinal tissue is yet to be accomplished.28,29 We hope to have a fully functional prototype system capable of rapidly and safely placing therapeutic laser lesions for the treatment of retinal disorders in the near future.

The tracking algorithms and concepts developed for this project have tremendous potential for application in many other areas of biomedical engineering. We have already adapted the basic tracking system for recording eye movements directly from the retina for Department of Defense studies.31,32 tracking rats in a water maze for psychophysical studies,33–34 and stabilizing a laser for computer-assisted tattoo removal.

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References


