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Initial *in vivo* results of a hybrid retinal photocoagulation system

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Abstract. We describe initial *in vivo* experimental results of a new hybrid digital and analog design for retinal tracking and laser beam control. An overview of the design is given. The results show *in vivo* tracking rates which exceed the equivalent of 38°/s in the eye. A robotically assisted lesion pattern is created for laser surgery to treat conditions such as diabetic retinopathy and retinal breaks. © *2000 Society of Photo-Optical Instrumentation Engineers.* [S1083-3668(00)00501-3]

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1 Introduction

A computer-assisted system known as CALOSOS (computer aided laser optical system for ophthalmic surgery) is being developed that will rapidly and safely place multiple therapeutic lesions of consistent size at desired locations on the retina in a matter of seconds with little or no human intervention. Previous work related to the development of CALOSOS has been published;[1–3] this paper discusses initial *in vivo* results using the system.

The two main improvements CALOSOS can provide are:

- the ability to track the retina and thereby compensate for any eye movement with sufficient speed during photocoagulation such that the laser always remains on the desired location on the retina, and
- the ability to detect and compensate for variations in the retinal absorption of laser energy across the retina such that irradiation time may be adjusted as needed in real time to produce consistent lesions.

A side benefit of CALOSOS is an improvement in the user interface which the clinician uses to perform the photocoagulation procedures.

With regard to tracking the retina, two different design approaches have been developed and tested *in vivo*: a digital imaging system and an analog optical system, each with its own advantages and disadvantages. When both tracking techniques are combined into an integrated hybrid system, they complement each other quite effectively. Details of each of these tracking methods, and eye phantom tests using the combined hybrid approach, have been described.[2]

The results of using this hybrid design to place *in vivo* lesions in the rabbit retina are described in this paper. The system can also acquire a real-time, motion-stabilized dynamic reflectance signal from the therapeutic lesion as it forms. This signal may be used to control lesion growth (and thus mitigate undesirable variability) during photocoagulation. While the acquisition of the lesion reflectance signal is described briefly in this paper, the required signal processing and the derivation of a reliable lesion control algorithm to produce consistently sized lesions will be described in a subsequent article.

The CALOSOS system requirements and our design approach to meet them have been discussed.[2,3] They are: retinal tracking rate of 10°/s[†] or faster, 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 should register a loss-of-lock condition, immediately close the laser shutter, and attempt to reestablish system lock.

2 System Description

2.1 Lesion Pattern Generation

One of the advantages of CALOSOS from the clinician's point of view (aside from increased patient safety) is the improvement in the user interface. For example, it is quite tedious to manually identify the often thousands of lesion locations required for treatment of diabetic retinopathy. Each location must be chosen not only for its therapeutic value, but also to avoid critical areas such as the macula and major retinal blood vessels. CALOSOS incorporates a single-monitor,

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[†]Since the average human adult eye measures 291.5 μm/deg at the posterior pole, this equates to a tracking velocity of 2.915 mm/s on the retinal surface.

[‡]Note that typical therapeutic lesions used to treat diabetic retinopathy and retinal tears are approximately 200 μm diameter.[4]

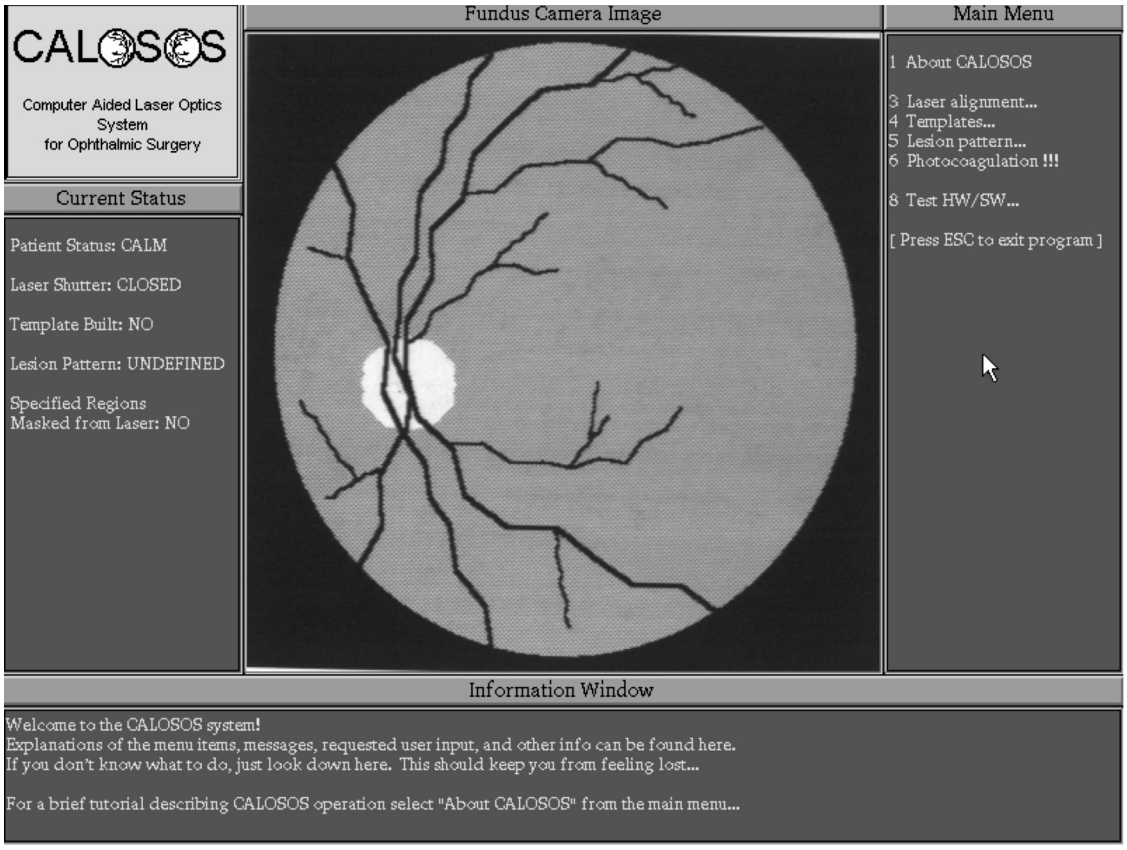

Fig. 1 An example of the user interface for CALOSOS. The fundus camera signal shown is a simulated retinal image.

mouse-driven human-computer interface which aides the clinician in designating the desired lesion locations and in performing the surgical procedure. A snapshot of this user interface is shown in Figure 1.

Note that Figure 1 is *not* the familiar MICROSOFT WINDOWS 9X or NT interface; in order to meet the real-time interrupt-driven processing requirements of CALOSOS, a low-level 32-bit (protected mode) extended DOS library of windowing, mouse, and other hardware/software interface routines has been developed by the authors.

When an ophthalmologist uses CALOSOS, the retinal image is shown in a large window of the computer monitor as seen in the center of Figure 1. The clinician uses the mouse to designate the area in which the lesion pattern should be formed, specifies the pattern shape and number of lesions, and the computer does the rest. In less than 1 s, the prospective lesion pattern is displayed superimposed on the retinal image for the ophthalmologist's approval; the proposed order of irradiation is also optimized to minimize steering mirror movements. Individual lesion sites can be added or deleted using the mouse, and the clinician can have the computer automatically detect major blood vessels and deconflict any of the potential lesion sites. The final result is usually a somewhat randomized lesion pattern, for which the optimal order of irradiation is not easily determined (as a special case of the classic traveling salesman problem). CALOSOS overcomes this by implementing a simulated annealing algorithm[5] which finds the global optimized path through all the desired lesion sites, a path that results in the smallest average mirror movement between lesion sites. This statistically based optimization technique reduces the need to insert pauses in steering mirror movements that would normally be needed allow the mirrors to ''settle'' into the proper position, thus reducing the time a patient must concentrate on fixation. While CALOSOS is a hybrid analog/digital design, the user interface and lesion pattern generation (with the associated steering mirror pointing) described above relies solely upon the digital part of the system. This is one factor that led to the hybrid approach; tracking speed is the other main factor.

2.2 Retinal Tracking

Several methods have been devised for eye tracking, but most are designed to track the anterior eye and cornea. The eye is not a rigid object, so relative motion can occur between the anterior and posterior regions during eye movements. In order to place lesions with acceptable accuracy on the retina, a system must directly track the retina.[6] A few methods have been devised in recent years for tracking the retina directly.[6–9] For CALOSOS, however, the choice of tracking methods is quite limited. In order to combine (at the lowest reasonable cost) a laser control and pointing subsystem, an automatic lesion pattern generation subsystem, a lesion growth monitoring and control subsystem, *and* the retinal tracking subsystem of choice, with response times of 5 ms or less—and have them all work together seamlessly—the authors found that most of the known tracking techniques must be discarded. While we are pursuing, as a parallel effort, the development of an all-

digital version of CALOSOS due to its potential simplicity,[10] as of this writing a more complex digital/analog hybrid system is the only way to meet the requirements of CALOSOS for an acceptable system cost.

2.2.1 *Digital tracking*

The digital portion of the hybrid system relies upon efficient image registration techniques. The retinal image is acquired from a fundus camera video port→charge coupled device (CCD) camera→frame grabber setup. A detailed description of this digital tracking technique, which uses blood vessel templates, has been discussed.[1,10] For the purpose of this discussion, we need only summarize the advantages and disadvantages of this form of retinal tracking.

Disadvantage. Relying upon an industry-standard RS-170 CCD camera which operates at 30 frames/s (fps), the tracking updates cannot occur in less than 33 ms, which does not meet the 5 ms response time needed. Cameras with a >200 fps capability as would be needed to satisfy the specified requirements of CALOSOS are much too expensive for our targeted system cost.

Advantage. While too slow by itself, this method of digital tracking has two critical advantages: it is a ''global'' tracker which can relock itself automatically, and it provides the necessary information to the lesion pattern generation subsystem and the graphical user interface. However, digital tracking by itself does not meet the tracking requirements of CALOSOS.

2.2.2 *Analog tracking*

As mentioned above, the primary limitation of the digital tracking method is the unavoidable dependence upon the frame rate of the CCD camera. To overcome this, we developed an analog tracking technique that lends itself well to the needs of CALOSOS. This analog optical technique, relying upon a confocal reflectometer signal, has been described in detail.[2] For the purpose of this discussion, we need only summarize the advantages and disadvantages of this form of retinal tracking.

Advantage. Because the analog tracking technique does not rely upon a camera frame rate, it allows the system to track retinal movements at very high speeds. It was shown[2] that the equivalent of over 68°/s at the retinal plane can be achieved with *in vitro* tests using eye phantoms. The response time of the analog tracker is 5 ms and it can resolve tracking displacements on the eye phantom of better than a 100 μm error radius at this maximum velocity. However, *in vivo* tracking performance will be somewhat lower, as described in Sec. 4.

Disadvantage. At very high retinal velocities, the tracking beam may ''lose'' the reference lesion, a condition which must be detected. If the tracking beam has ''fallen off'' the reference point on the retina a loss of lock condition can be easily detected. Unfortunately, the analog tracker can only *detect* loss of lock—it cannot relock itself as it is a ''local'' tracking method. The analog tracker also provides none of the information needed by the lesion pattern generation subsystem and the graphical user interface. The analog tracker also cannot detect rotation, but this is not a problem. The patient remains stationary in a standard chin cup and forehead bar, with the conguate eye fixated on a light emitting diode target. In this situation, human eye rotation has been shown to be negligible.

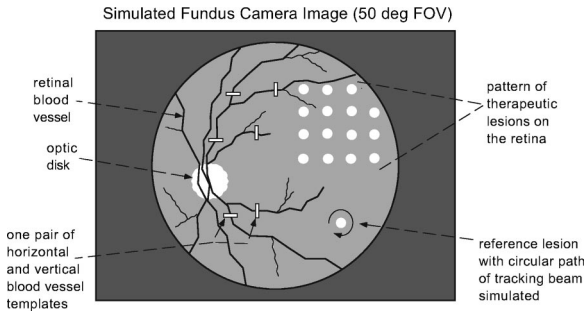

Fig. 2 Pictorial representation of the digital and analog tracking methods working together as in the hybrid implementation of CALOSOS.

2.2.3 *Hybrid tracking*

While extremely fast compared to the digital tracking method, the analog optical tracker lacks a global coordinate system necessary for seamless integration of retinal tracking, lesion pattern creation, laser pointing, and graphical user interface subsystems. Even more importantly, the analog tracker, as noted above, has no way to relock the tracking beam if needed. Because of this we combined the digital and analog designs into a single hybrid tracking system. The combination of the digital and analog designs compensates for the limitations and capitalizes on the strengths of each individual tracking approach. A pictorial representation on a simulated retina of the combined digital and analog tracking modalities is shown in Figure 2.

The six subtemplates on the retinal blood vessels are used by the digital tracker, and the arrow indicates the circular path around the reference lesion of the low-power tracking beam which is used by the analog tracker.

The functionality of the digital tracking subsystem is contained within a desktop Pentium computer,[1] and the signal processing and control part of the analog tracking subsystem is implemented with inexpensive, off-the-shelf analog electronics.[2] The hybrid tracking system processes images and reflectance signals from the retina and produces the control signals to the shutters, the dither mirrors, and the main steering mirrors to maintain the coagulating beam on the prescribed therapeutic lesion site on the retinal surface. Since the integration and handshaking in the latest hybrid design goes well beyond the previous implementation described,[2] the process is described below. Note that two laser beams are used: a low power tracking beam and a higher power coagulating beam, pointing at any given time to two different locations on the retina.

• The digital tracking subsystem obtains a digital map of the retina from a CCD camera attached to the fundus camera and a frame grabber inside the system computer. A ''fingerprint'' of six retinal blood vessel templates is locked into a fixed orientation to one another and is used to establish a global coordinate system and track retinal movement. The desired therapeutic lesion sites are selected in reference to this coordinate system using the graphical user interface and mouse. Critical vision anatomy (fovea, optic disk, and major

retinal vessels) and the vessel template locations are then designated as laser ''stay out'' regions. At this point, the analog tracking subsystem is not engaged.

• Initial tracking lock is then accomplished by the digital tracking subsystem by correlating the retinal fingerprint with live video from the fundus camera. Correction signals are sent to the main steering mirrors to point the coagulating laser beam at the desired location of the *reference lesion*.[2] The reference lesion has no therapeutic value. In fact, it is intentionally separated from the therapeutic lesion locations. The laser shutter is then opened for a fixed irradiation time to form the reference lesion. Note that this step is optional; a suitable lesion or other object with high contrast may already exist on the retinal surface. The electronics can detect a light object on darker background (as in the case of a reference lesion) or a dark object on a lighter background (such as an intersection point of blood vessels).

• Correction signals are then sent by the digital tracking subsystem to the dither mirrors to place the analog subsystem's tracking beam on the reference object. Correction signals are also sent to the main steering mirrors to place the main coagulating beam on the first desired therapeutic lesion site.

• If the analog system achieves tracking lock, tracking control is transferred from the digital tracking subsystem to the faster analog tracking subsystem. The shutter is then opened to irradiate the first therapeutic lesion site. In the final system, the coagulating beam's confocal reflectometer signal (different from the tracking signal) indicates when the lesion has reached desired therapeutic parameters on the retina (discussed below). When the lesion is complete, the laser shutter is closed and the digital tracking subsystem regains tracking control. Correction signals are then issued to the main mirrors to place the coagulating beam on the next therapeutic lesion site. This step repeats until all desired therapeutic lesion sites are irradiated.

• Should the analog tracking subsystem lose lock while it has tracking control, the laser shutter is closed within 5 ms and control is transferred back to the digital tracking subsystem. The digital system, using its global coordinate system and knowledge of the location of the reference object, attempts to re-establish analog tracking lock. If successful, the procedure continues; if not, the procedure is aborted and the clinician is notified of the error condition. Should the digital tracking subsystem lose lock while it has control, it attempts to reestablish lock of the blood vessel templates. As with the analog tracking, if relock is successful, the procedure continues; if not, the procedure is aborted and the clinician is notified of the error condition.

This is an abbreviated discussion of hybrid tracking system operation but it provides enough detail to illustrate the handshaking that takes place between the digital tracking subsystem and the analog tracking subsystem in the hybrid design. Other key areas are laser pointing and lesion control, but those have already been discussed in detail.[1,2]

3 Experimental Design

Tests reported previously[11] of the analog subsystem on moving albumen eye phantoms demonstrated a maximum tracking velocity of 68.6°/s with a maximum error radius of less than 166 μm. To test the hybrid system under more stringent *in vivo* conditions, we used two Dutch Belted rabbits that were only lightly sedated to allow reflexive eye movements which would stress the tracking system. Both animals survived without harm. Each rabbit was secured on a specialized animal platform in front of the fundus camera with their eye aligned similarly to that of a typical human patient. The rabbit's nose rested in a padded annular holder which elevated the animal's chin and positioned the eye at the optimum location for the test. A digital template was established by CALOSOS using the retinal blood vessels of the rabbit; this template was then used by the computer to establish the retinal coordinate system reference. Lesion patterns were then defined as needed according to this coordinate system.

A single photocoagulation was performed to create the reference lesion, and the tracking beam was then manually directed to the reference lesion where it established lock (at the time of this test, the digital tracking subsystem was not yet able to direct the analog tracking subsystem tracking beam automatically). Various lesions (individual and patterns) were created in the rabbit fundus. The loss of lock signal for the analog tracking subsystem was temporarily disconnected to allow an intentional loss of lock condition during some tests for comparison with results when locked. The laser parameters were: argon laser ($\lambda = 488$ nm, 514 nm), 175 mW at the cornea, and an approximately 275 μm diam spot on the retina. All irradiations were 100 ms in duration. The tracking beam confocal reflectometer signal was sampled at 1 kHz and stored. No attempt was made to control the lesion depth with this signal, since the control algorithm is still under development. However, such a motion-stabilized *in vivo* lesion reflectance signal had never before been obtained.

4 Results

An unretouched scan from a fundus photograph of one of the rabbits is shown in Figure 3. In Figure 3 the tracking lesion used is the lesion closest to the center of the frame. Two 3 $\times$4 patterns of laser-induced lesions were specified via the graphical user interface and created during eye motion of up to 32°/s. Each lesion is approximately 250–300 μm in diameter. The pattern on the left was created after intentionally forcing the analog tracker to lose lock but with the loss of lock signal disconnected; this pattern illustrates the relative movement of the fundus during irradiation and the need for high speed tracking. The irregular lesion placement is due only to eye movement of the rabbit during the irradiation of the pattern. The lesion pattern on the right was created when the tracking system was locked. This pattern shows the benefit of high speed motion compensation provided by the analog tracking updates during irradiation, as well as the accuracy of the lesion pattern which can be created using the digital tracking method's coordinate system. This lesion pattern on the right, when compared to the computer coordinates specified on the graphical user interface for the desired pattern location and adjusted for image registration between frames, was no more than ± 2 pixels ($\pm 64\,\mu$m on the retina) from the intended location. In a frame-by-frame analysis of the fundus camera video tape of the entire experiment, the various velocities of the rabbit's reflexive eye movements were determined. The maximum velocity the system could track without

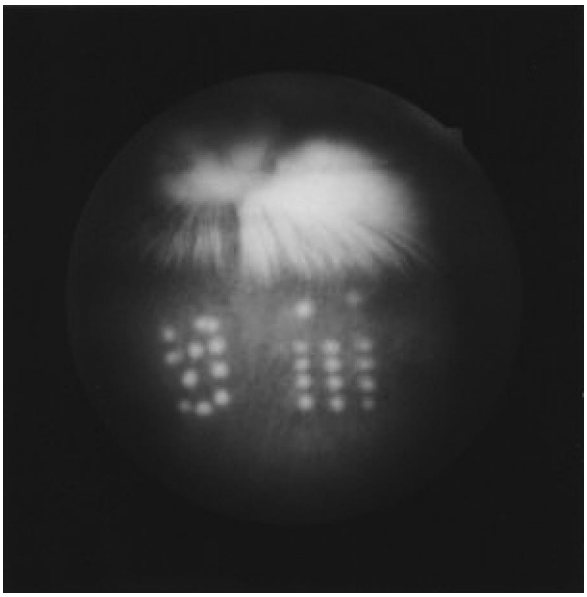

Fig. 3 Photocoagulation on a rabbit fundus, unlocked and locked tracking, eye motion of up to 32°/s. Argon laser (λ = 488 nm, 514 nm), 175 mW at the cornea, approximately 275 μm diam spot on the retina.

losing lock varied according to the optical condition of the cornea, and the location of the reference lesion in the fundus field of view (FOV). A clearer cornea permitted faster velocities, as did a reference lesion near the center of the FOV. The lowest velocity at which tracking lock was broken was 30°/s, during a short, highly impulsive movement. The highest velocity at which tracking lock was maintained was 38°/s, during a relatively smooth movement. A motion-stabilized confocal reflectometer signal obtained of a lesion forming in 100 ms is shown in Figure 4. During the irradiation of Figure 4, the rabbit's eye exhibited motion at up to 14°/s.

5 Discussion

The maximum tracking velocity demonstrated *in vivo* was lower than that found *in vitro* using eye phantoms,[2] but still faster than the minimum system requirements for CALOSOS.

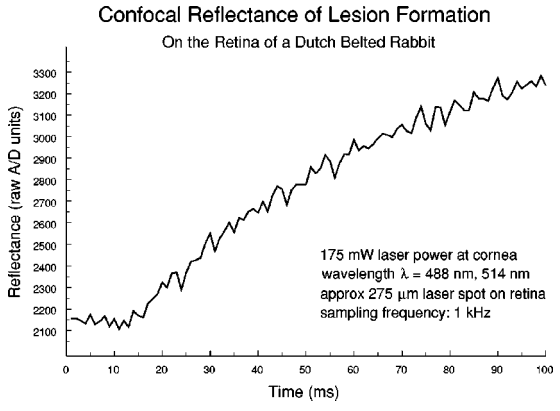

Fig. 4 Measured *in vivo* reflectance signal for a 100 ms irradiation on a rabbit fundus during tracked motion of up to 14°/s.

Even more important than tracking velocity, the hybrid system response time was 5 ms, which is currently beyond the ability of an affordable all-digital implementation. The reduced tracking performance *in vivo* is attributed to the poorer characteristics of the total optical path. While the earlier *in vitro* results seemed to depend only upon retinal velocity, loss of lock *in vivo* was observed for impulsive movements that otherwise were within the normal tracking velocity limits. We hypothesize this acceleration sensitivity is due to some residual imbalances between the tracking and steering control in the analog subsystem which are only manifested in the poorer optical conditions found *in vivo*. This effect requires further investigation.

The confocal reflectometer signal shown in Figure 4 is relatively free from motion artifact. The random noise seen in the plot is not motion induced (confirmed by motionless tests which also had this level of noise). Figure 4 represents the first time a true motion-stabilized reflectance signal has been obtained *in vivo* for a clinically significant irradiation time. This now removes the primary obstacle to using this reflectance signal for real-time lesion control; this next step of perfecting the control algorithm is currently under investigation.

Other applications of the hybrid tracking approach described in this paper are also possible. CALOSOS has already been used to control an ultrashort pulsed laser (femtosecond pulses) for eye damage threshold studies, and may also be useful for photodynamic therapy treatments of macular degeneration. It has also been suggested that the technology could be adapted to certain dermatology treatments, where precise motion-stabilized placement of laser energy is required such as port-wine stain treatment and tatoo removal.

While CALOSOS has been in development for some time, this hybrid technique for retinal tracking (when combined with other subsystems of CALOSOS) may soon make possible robotically assisted laser surgery to treat ophthalmic conditions such as diabetic retinopathy and retinal breaks under clinical conditions with the requisite safety margin and at a reasonable system cost.

Acknowledgments

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References

1. S. F. Barrett, C. H. G. Wright, M. R. Jerath, R. S. Lewis II, B. C. Dillard, H. G. Rylander III, and A. J. Welch, ''Computer-aided retinal photocoagulation system,'' *J. Biomed. Opt.* **1**, 83–91 (1996).
2. C. H. G. Wright, R. D. Ferguson, H. G. Rylander III, A. J. Welch, and S. F. Barrett, ''Hybrid approach to retinal tracking and laser aiming for photocoagulation,'' *J. Biomed. Opt.* **2**, 195–203 (1997).
3. C. Wright, E. Oberg, and S. Barrett, ''Hybrid retinal tracking and coagulation system,'' *Proc. SPIE* **3246**, 185–191 (Jan. 1998).
4. T. A. Deutsch and D. B. Feller, *Patton and Goldberg's Management of Ocular Injury*, pp. 205–207, Sanders, Philadelphia, PA, 1985.

5. S. Kirkpatrick, C. D. Gelatt, and M. P. Vecchi, ''Optimization by simulated annealing,'' *Science* **220**, 671–680 (1983).
6. D. P. Wornson, G. W. Hughes, and R. H. Webb, ''Fundus tracking with the scanning laser ophthalmoscope,'' *Appl. Opt.* **26**, 1500–1504 (1987).
7. S. F. Barrett, M. R. Jerath, H. G. Rylander III, and A. J. Welch, ''Digital tracking and control of retinal images,'' *Opt. Eng.* **33**, 150–159 (1994).
8. T. Bantel, D. Ott, and M. Rueff, ''Global tracking of the ocular fundus pattern imaged by scanning laser ophthalmoscopy,'' *Int. J. Biomed. Comput.* **27**, 59–69 (1990).
9. M. S. Markow, H. G. Rylander III, and A. J. Welch, ''Real-time algorithm for retinal tracking,'' *IEEE Trans. Biomed. Eng.* **40**, 1269–1281 (1993).
10. S. F. Barrett, C. H. G. Wright, E. D. Oberg, B. A. Rockwell, C. P. Cain, H. G. Rylander III, and A. J. Welch, ''Digital imaging-based retinal photocoagulation system,'' *Proc. SPIE* **2971**, 118–128 (Feb. 1997).
11. R. D. Ferguson, C. H. G. Wright, S. F. Barrett, H. G. Rylander III, and A. J. Welch, ''Hybrid tracking and control system for computer-aided retinal surgery,'' *Proc. SPIE* **2673**, 32–41 (Feb. 1996).