(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 October 2012 (26.10.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/145159 A1

(51) International Patent Classification:
A61F 9/01 (2006.01) *A61F 9/008* (2006.01)

(21) International Application Number:
PCT/US2012/032024

(22) International Filing Date:
3 April 2012 (03.04.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/477,505	20 April 2011 (20.04.2011)	US
61/521,261	8 August 2011 (08.08.2011)	US
61/542,269	2 October 2011 (02.10.2011)	US
61/550,576	24 October 2011 (24.10.2011)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,

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(54) Title: CONTROLLED CROSS-LINKING INITIATION AND CORNEAL TOPOGRAPHY FEEDBACK SYSTEMS FOR DIRECTING CROSS-LINKING

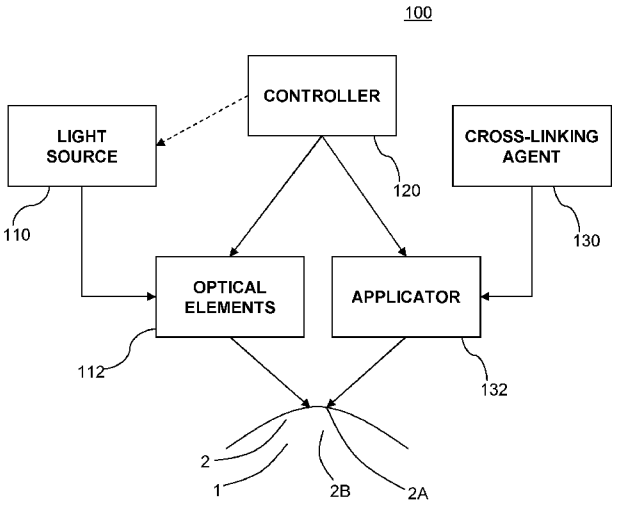

FIG. 1

(57) Abstract: Devices and approaches for activating cross-linking within corneal tissue to stabilize and strengthen the corneal tissue following an eye therapy treatment. A feedback system is provided to acquire measurements and pass feedback information to a controller. The feedback system may include an interferometer system, a corneal polarimetry system, or other configurations for monitoring cross-linking activity within the cornea. The controller is adapted to analyze the feedback information and adjust treatment to the eye based on the information. Aspects of the feedback system may also be used to monitor and diagnose features of the eye. Methods of activating cross-linking according to information provided by a feedback system in order to improve accuracy and safety of a cross-linking therapy are also provided.

WO 2012/145159 A1

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

CONTROLLED CROSS-LINKING INITIATION AND CORNEAL TOPOGRAPHY FEEDBACK SYSTEMS FOR DIRECTING CROSS-LINKING

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention pertains to systems and methods for stabilizing corneal tissue, and more particularly, systems and methods for applying and activating a cross-linking agent in corneal tissue and monitoring the activation of the cross-linking agent.

Description of Related Art

[0002] A variety of eye disorders, such as myopia, keratoconus, and hyperopia, involve abnormal shaping of the cornea. Laser-assisted in-situ keratomileusis (LASIK) is one of a number of corrective procedures that reshape the cornea so that light traveling through the cornea is properly focused onto the retina located in the back of the eye. During LASIK eye surgery, an instrument called a microkeratome is used to cut a thin flap in the cornea. The cornea is then peeled back and the underlying cornea tissue ablated to the desired shape with an excimer laser. After the desired reshaping of the cornea is achieved, the cornea flap is put back in place and the surgery is complete.

[0003] In another corrective procedure that reshapes the cornea, thermokeratoplasty provides a noninvasive procedure that applies electrical energy in the microwave or radio frequency (RF) band to the cornea. In particular, the electrical energy raises the corneal temperature until the collagen fibers in the cornea shrink at about 60°C. The onset of shrinkage is rapid, and stresses resulting from this shrinkage reshape the corneal surface. Thus, application of energy according to particular patterns, including, but not limited to, circular or annular patterns, may cause aspects of the cornea to flatten and improve vision in the eye.

[0004] The success of procedures, such as LASIK or thermokeratoplasty, in addressing eye disorders, such as myopia, keratoconus, and hyperopia, depends on the stability of the changes in the corneal structure after the procedures have been applied.

BRIEF SUMMARY

[0005] Aspects of the present disclosure further provide a system for applying a controlled amount of cross-linking in corneal tissue of an eye. The system includes an

applicator adapted to apply a cross-linking agent to the eye. The system also includes a light source adapted to emit a photoactivating light. The system also includes a targeting system adapted to create targeting feedback information indicative of a position of a cornea of the eye. The system also includes a mirror array having a plurality of mirrors arranged in rows and columns. The plurality of mirrors are adapted to selectively direct the photoactivating light toward the eye according to a pixelated intensity pattern having pixels corresponding to the plurality of mirrors in the mirror array. The system also includes an interferometer adapted to monitor an amount of cross-linking in the corneal tissue. The interferometer monitors the amount of cross-linking in the corneal tissue by interfering a beam of light reflected from a surface of the eye with a reference beam of light reflected from a reference surface. The interferometer monitors the amount of cross-linking in the corneal tissue by also capturing, via an associated camera, a series of images of interference patterns due to optical interference between the beam of light and the reference beam of light. The series of images are indicative of a plurality of profiles of the surface of the eye. The system also includes a head restraint device for restraining a position of a head associated with the eye. The head restraint device thereby aligns the eye with respect to the interferometer. The system also includes a controller. The controller is adapted to receive the targeting feedback information and receive the generated series of intensity patterns. The controller is also adapted to analyze the generated series of intensity patterns to determine the plurality of profiles of the surface of the eye associated therewith. The controller is also adapted to determine an amount of cross-linking of the corneal tissue based on a dynamic deformation of the surface of the eye. The dynamic deformation of the eye is indicated by the plurality of profiles of the surface of the eye. The controller is also adapted to adjust the pixelated intensity pattern according to data. The data includes at least one of: the targeting feedback information and the determined amount of cross-linking.

[0006] These and other aspects of the present disclosure will become more apparent from the following detailed description of embodiments of the present disclosure when viewed in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1 provides a block diagram of an example delivery system for delivering a cross-linking agent and an activator to a cornea of an eye in order to initiate molecular cross-linking of corneal collagen within the cornea.

[0008] FIG. 2A provides a flowchart showing an example embodiment according to aspects of the present disclosure for activating cross-linking within cornea tissue using a cross-linking agent and an initiating element.

[0009] FIG. 2B provides a flowchart similar to FIG. 2A where Riboflavin may be applied topically as the cross-linking agent and UV light may be applied as the initiating element.

[0010] FIG. 2C provides a flowchart similar to FIG. 2A, but with an additional step for placing a mask on the eye described in FIGS. 10A and 10B.

[0011] FIG. 3 provides an example delivery system for delivering light to the cornea 2 employing laser scanning technology.

[0012] FIG. 4 illustrates a delivery system incorporating a feedback system.

[0013] FIG. 5A illustrates a delivery system for activating cross-linking in the cornea with the laser scanning device and having a video camera feedback system.

[0014] FIG. 5B illustrates an exemplary operation of the delivery system shown in FIG. 5A.

[0015] FIG. 6 illustrates an example delivery system for applying light to an eye from a laser light source.

[0016] FIG. 7A illustrates an optical power contour map of an eye prior to initiation of cross-linking therapy.

[0017] FIG. 7B illustrates an optical power contour map of the eye shown in FIG. 7A following treatment by cross-linking therapy according to an aspect of the present disclosure.

[0018] FIG. 7C illustrates a contour map of the difference between the contour map in FIG. 7B and the contour map shown in FIG. 7A.

DETAILED DESCRIPTION

[0019] FIG. 1 provides a block diagram of an example delivery system 100 for delivering a cross-linking agent 130 and an activator to a cornea 2 of an eye 1 in order to initiate molecular cross-linking of corneal collagen within the cornea 2. Cross-linking can stabilize corneal tissue and improve its biomechanical strength. The delivery system 100 includes an applicator 132 for applying the cross-linking agent 130 to the cornea 2. The delivery system 100 includes a light source 110 and optical elements 112 for directing light to the cornea 2. The delivery system 100 also includes a controller 120 that is coupled to the applicator 132 and the optical elements 112. The applicator 132 may be an apparatus adapted to apply the cross-linking agent 130 according to particular patterns on the cornea 2 advantageous for causing cross-linking to take place within the corneal tissues. The applicator 132 may apply

the cross-linking agent 130 to a corneal surface 2A (*e.g.*, an epithelium), or to other locations on the eye 1. Particularly, the applicator 132 may apply the cross-linking agent 130 to an abrasion or cut of the corneal surface 2A to facilitate the transport or penetration of the cross-linking agent through the cornea 2 to a mid-depth region 2B.

[0020] As described below in connection with FIGS. 2A-2B, which describe an exemplary operation of the delivery system 100, the cross-linking agent 130 is applied to the cornea 2 using the applicator 132. Once the cross-linking agent 130 has been applied to the cornea 2, the cross-linking agent 130 is initiated by the light source 110 (*i.e.* the initiating element) to cause cross-linking agent 130 to absorb enough energy to release free oxygen radicals within the cornea 2. Once released, the free oxygen radicals (*i.e.* singlet oxygen) form covalent bonds between corneal collagen fibrils and thereby cause the corneal collagen fibrils to cross-link and change the structure of the cornea 2. For example, activation of the cross-linking agent 130 with the light source 110 delivered to the cornea 2 through the optical elements 112 may result in cross-linking in the mid-depth region 2B of the cornea 2 and thereby strengthen and stiffen the structure of the cornea 2.

[0021] Although eye therapy treatments may initially achieve desired reshaping of the cornea 2, the desired effects of reshaping the cornea 2 may be mitigated or reversed at least partially if the collagen fibrils within the cornea 2 continue to change after the desired reshaping has been achieved. Indeed, complications may result from further changes to the cornea 2 after treatment. For example, a complication known as post-LASIK ectasia may occur due to the permanent thinning and weakening of the cornea 2 caused by LASIK surgery. In post-LASIK ectasia, the cornea 2 experiences progressive steepening (bulging).

[0022] Aspects of the present disclosure provide approaches for initiating molecular cross-linking of corneal collagen to stabilize corneal tissue and improve its biomechanical strength. For example, embodiments may provide devices and approaches for preserving the desired corneal structure and shape that result from an eye therapy treatment, such as LASIK surgery or thermokeratoplasty. In addition, aspects of the present disclosure may provide devices and approaches for monitoring the shape, molecular cross-linking, and biomechanical strength of the corneal tissue and providing feedback to a system for providing iterative initiations of cross-linking of the corneal collagen. As described herein, the devices and approaches disclosed herein may be used to preserve desired shape or structural changes following an eye therapy treatment by stabilizing the corneal tissue of the cornea 2. The devices and approaches disclosed herein may also be used to enhance the strength or biomechanical structural integrity of the corneal tissue apart from any eye therapy treatment.

[0023] Therefore, aspects of the present disclosure provide devices and approaches for preserving the desired corneal structure and shape that result from an eye treatment, such as LASIK surgery or thermokeratoplasty. In particular, embodiments may provide approaches for initiating molecular cross-linking of the corneal collagen to stabilize the corneal tissue and improve its biomechanical strength and stiffness after the desired shape change has been achieved. In addition, embodiments may provide devices and approaches for monitoring cross-linking in the corneal collagen and the resulting changes in biomechanical strength to provide a feedback to a system for inducing cross-linking in corneal tissue.

[0024] Some approaches initiate molecular cross-linking in a treatment zone of the cornea 2 where structural changes have been induced by, for example, LASIK surgery or thermokeratoplasty. However, it has been discovered that initiating cross-linking directly in this treatment zone may result in undesired haze formation. Accordingly, aspects of the present disclosure also provide alternative techniques for initiating cross-linking to minimize haze formation. In particular, the structural changes in the cornea 2 are stabilized by initiating cross-linking in selected areas of corneal collagen outside of the treatment zone. This cross-linking strengthens corneal tissue neighboring the treatment zone to support and stabilize the actual structural changes within the treatment zone.

[0025] With reference to FIG. 1, the optical elements 112 may include one or more mirrors or lenses for directing and focusing the light emitted by the light source 110 to a particular pattern on the cornea 2 suitable for activating the cross-linking agent 130. The light source 110 may be an ultraviolet light source, and the light directed to the cornea 2 through the optical elements 112 may be an activator of the cross-linking agent 130. The light source 110 may also alternatively or additionally emit photons with greater or lesser energy levels than ultraviolet light photons. The delivery system 100 also includes a controller 120 for controlling the operation of the optical elements 112 or the applicator 132, or both. By controlling aspects of the operation of the optical elements 112 and the applicator 132, the controller 120 can control the regions of the cornea 2 that receive the cross-linking agent 130 and that are exposed to the light source 110. By controlling the regions of the cornea 2 that receive the cross-linking agent 130 and the light source 110, the controller 120 can control the particular regions of the cornea 2 that are strengthened and stabilized through cross-linking of the corneal collagen fibrils. In an implementation, the cross-linking agent 130 can be applied generally to the eye 1, without regard to a particular region of the cornea 2 requiring strengthening, but the light source 110 can be directed to a particular region of the cornea 2 requiring strengthening, and thereby control the region of the

cornea 2 wherein cross-linking is initiated by controlling the regions of the cornea 2 that are exposed to the light source 110.

[0026] The optical elements 112 can be used to focus the light emitted by the light source 110 to a particular focal plane within the cornea 2, such as a focal plane that includes the mid-depth region 2B. In addition, according to particular embodiments, the optical elements 112 may include one or more beam splitters for dividing a beam of light emitted by the light source 110, and may include one or more heat sinks for absorbing light emitted by the light source 110. The optical elements 112 may further include filters for partially blocking wavelengths of light emitted by the light source 110 and for advantageously selecting particular wavelengths of light to be directed to the cornea 2 for activating the cross-linking agent 130. The controller 120 can also be adapted to control the light source 110 by, for example, toggling a power switch of the light source 110.

[0027] In an implementation, the controller 120 may include hardware and/or software elements, and may be a computer. The controller 120 may include a processor, a memory storage, a microcontroller, digital logic elements, software running on a computer processor, or any combination thereof. In an alternative implementation of the delivery system 100 shown in FIG. 1, the controller 120 may be replaced by two or more separate controllers or processors. For example, one controller may be used to control the operation of the applicator 132, and thereby control the precise rate and location of the application of the cross-linking agent 130 to the cornea 2. Another controller may be used to control the operation of the optical elements 112, and thereby control with precision the delivery of the light source 110 (*i.e.* the initiating element) to the cornea 2 by controlling any combination of: wavelength, bandwidth, intensity, power, location, depth of penetration, and duration of treatment. In addition, the function of the controller 120 can be partially or wholly replaced by a manual operation. For example, the applicator 132 can be manually operated to deliver the cross-linking agent 130 to the cornea 2 without the assistance of the controller 120. In addition, the controller 120 can operate the applicator 132 and the optical elements 112 according to inputs dynamically supplied by an operator of the delivery system 100 in real time, or can operate according to a pre-programmed sequence or routine.

[0028] Referring to FIG. 2A, an example embodiment 200A according to aspects of the present disclosure is illustrated. Specifically, in step 210, the corneal tissue is treated with the cross-linking agent 130. Step 210 may occur, for example, after a treatment is applied to generate structural changes in the cornea and produce a desired shape change. Alternatively, step 210 may occur, for example, after it has been determined that the corneal tissue requires

stabilization or strengthening. The cross-linking agent 130 is then activated in step 220 with an initiating element 222. In an example configuration, the initiating element 222 may be the light source 110 shown in FIG. 1. Activation of the cross-linking agent 130, for example, may be triggered thermally by the application of microwaves or light.

[0029] As the example embodiment 200B of FIG. 2B shows further, Riboflavin may be applied topically as a cross-linking agent 214 to the corneal tissue in step 210. As also shown in FIG 2B, ultraviolet (UV) light may be applied as an initiating element 224 in step 220 to initiate cross-linking in the corneal areas treated with Riboflavin. Specifically, the UV light initiates cross-linking activity by causing the applied Riboflavin to release reactive oxygen radicals in the corneal tissue. In particular, the Riboflavin acts as a sensitizer to convert O_2 into singlet oxygen which causes cross-linking within the corneal tissue.

[0030] According to one approach, the Riboflavin may be applied topically to the corneal surface, and transepithelial delivery allows the Riboflavin to be applied to the corneal stroma. In general, the application of the cross-linking agent sufficiently introduces Riboflavin to mid-depth regions of the corneal tissue where stronger and more stable structure is desired.

[0031] Where the initiating element is UV light, the UV light may be generally applied to the corneal surface 2A (*e.g.* the epithelium) of the cornea 2 to activate cross-linking. However, regions of the cornea 2 requiring stabilization may extend from the corneal surface 2A to a mid-depth region 2B in the corneal stroma 2C. Generally applying UV light to the corneal surface 2A may not allow sufficient penetration of the UV light to activate necessary cross-linking at a mid-depth region of the cornea. Accordingly, embodiments according to aspects of the present disclosure provide a delivery system that accurately and precisely delivers UV light to the mid-depth region 2B where stronger and more stable corneal structure is required. In particular, treatment may generate desired changes in corneal structure at the mid-depth region 2B.

[0032] FIG. 3 provides an example delivery system adapted as a laser scanning device 300 for delivering light to the cornea 2 employing laser scanning technology. The laser scanning device 300 has the light source 110 for delivering a laser beam through an objective lens 346 into a small focal volume within the cornea 2. The laser scanning device 300 also includes the controller 120 for controlling the intensity profile of the light delivered to the cornea 2 using a mirror array 344 and for controlling the focal plane of the objective lens 346. The light source 110 can be an ultraviolet (UV) light source that emits a UV laser. A beam of light 341 is emitted from the light source 110 (*e.g.*, UV laser) and passes to the mirror array 344. Within the mirror array 344, the beam of light 341 from the light source 110 is scanned

over multiple mirrors adapted in an array. The beam of light 341 can be scanned over the mirrors in the mirror array 344 using, for example, one or more adjustable mirrors to direct the beam of light 341 to point at each mirror in turn. The beam of light 341 can be scanned over each mirror one at a time. Alternately, the beam of light 341 can be split into one or more additional beams of light using, for example, a beam splitter, and the resultant multiple beams of light can then be simultaneously scanned over multiple mirrors in the mirror array 344.

[0033] By rapidly scanning the beam of light 341 over the mirrors in the mirror array 344, the mirror array 344 outputs a light pattern 345, which has a two dimensional intensity pattern. The two dimensional intensity pattern of the light pattern 345 is generated by the mirror array 344 according to, for example, the length of time that the beam of light 341 is scanned over each mirror in the mirror array 344. In particular, the light pattern 345 can be considered a pixilated intensity pattern with each pixel represented by a mirror in the mirror array 344 and the intensity of the light in each pixel of the light pattern 345 proportionate to the length of time the beam of light 341 scans over the mirror in the mirror array 344 corresponding to each pixel. In an implementation where the beam of light 341 scans over each mirror in the mirror array 344 in turn to create the light pattern 345, the light pattern 345 is properly considered a time-averaged light pattern, as the output of the light pattern 345 at any one particular instant in time may constitute light from as few as a single pixel in the pixelated light pattern 345. In an implementation, the laser scanning technology of the delivery system 300 may be similar to the technology utilized by Digital Light Processing™ (DLP®) display technologies.

[0034] The mirror array 344 can include an array of small oscillating mirrors, controlled by mirror position motors 347. The mirror position motors 347 can be servo motors for causing the mirrors in the mirror array 344 to rotate so as to alternately reflect the beam of light 341 from the light source 340 toward the cornea 2. The controller 120 can control the light pattern 345 generated in the mirror array 344 using the mirror position motors 347. In addition, the controller 120 can control the depth within the cornea 2 that the light pattern 345 is focused to by controlling the location of the focal depth of the objective lens 346 relative to the corneal surface 2A. The controller can utilize an objective lens position motor 348 to raise and/or lower the objective lens 346 in order to adjust the focal plane 6 of the light pattern 345 emitted from the mirror array 344. By adjusting the focal plane 6 of the light pattern 345 using the objective lens motor 348, and controlling the two-dimensional intensity profile of the light pattern 345 using the mirror position motors 347, the controller 120 is

adapted to control the delivery of the light source 110 to the cornea 2 in three dimensions. The three-dimensional pattern is generated by delivering the UV light to selected regions 5 on successive planes (parallel to the focal plane 6), which extend from the corneal surface 2A to the mid-depth region 2B within the corneal stroma. The cross-linking agent 130 introduced into the selected regions 5 is then activated as described above.

[0035] By scanning over selected regions 5 of a plane 6 at a particular depth within the cornea 2, the controller 120 can control the activation of the cross-linking agent 130 within the cornea 2 according to a three dimensional profile. In particular, the controller 120 can utilize the laser scanning technology of the laser scanning device 300 to strengthen and stiffen the corneal tissues by activating cross-linking in a three-dimensional pattern within the cornea 2. In an implementation, the objective lens 346 can be replaced by an optical train consisting of mirrors and/or lenses to properly focus the light pattern 345 emitted from the mirror array 344. Additionally, the objective lens motor 348 can be replaced by a motorized device for adjusting the position of the eye 1 relative to the objective lens 346, which can be fixed in space. For example, a chair or lift that makes fine motor step adjustments and adapted to hold a patient during eye treatment can be utilized to adjust the position of the eye 1 relative to the objective lens 346.

[0036] Advantageously, the use of laser scanning technologies allows cross-linking to be activated beyond the corneal surface 2A of the cornea 2, at depths where stronger and more stable corneal structure is desired, for example, where structural changes have been generated by an eye therapy treatment. In other words, the application of the initiating element (*i.e.*, the light source 110) is applied precisely according to a selected three-dimensional pattern and is not limited to a two-dimensional area at the corneal surface 2A of the cornea 2.

[0037] Although the embodiments described herein may initiate cross-linking in the cornea according to an annular pattern defined, for example, by a thermokeratoplasty applicator, the initiation pattern in other embodiments is not limited to a particular shape. Indeed, energy may be applied to the cornea in non-annular patterns, so cross-linking may be initiated in areas of the cornea that correspond to the resulting non-annular changes in corneal structure. Examples of the non-annular shapes by which energy may be applied to the cornea are described in U.S. Patent Serial No. 12/113,672, filed on May 1, 2008, the contents of which are entirely incorporated herein by reference.

[0038] Some embodiments may employ Digital Micromirror Device (DMD) technology to modulate the application of initiating light, *e.g.*, UV light, spatially as well as a temporally. Using DMD technology, a controlled light source projects the initiating light in a precise

spatial pattern that is created by microscopically small mirrors laid out in a matrix on a semiconductor chip, known as a (DMD). Each mirror represents one or more pixels in the pattern of projected light. The power and duration at which the light is projected is determined as described elsewhere.

[0039] Embodiments may also employ aspects of multiphoton excitation microscopy. In particular, rather than delivering a single photon of a particular wavelength to the cornea 2, the delivery system (*e.g.*, 100 in FIG. 1) delivers multiple photons of longer wavelengths, *i.e.*, lower energy, that combine to initiate the cross-linking. Advantageously, longer wavelengths are scattered within the cornea 2 to a lesser degree than shorter wavelengths, which allows longer wavelengths of light to penetrate the cornea 2 more efficiently than shorter wavelength light. For example, in some embodiments, two photons may be employed, where each photon carries approximately half the energy necessary to excite the molecules in the cross-linking agent 130 that release oxygen radicals. When a cross-linking agent molecule simultaneously absorbs both photons, it absorbs enough energy to release reactive oxygen radicals in the corneal tissue. Embodiments may also utilize lower energy photons such that a cross-linking agent molecule must simultaneously absorb, for example, three, four, or five, photons to release a reactive oxygen radical. The probability of the near-simultaneous absorption of multiple photons is low, so a high flux of excitation photons may be required, and the high flux may be delivered through a femtosecond laser. Because multiple photons are absorbed for activation of the cross-linking agent molecule, the probability for activation increases with intensity. Therefore, more activation occurs where the delivery of light from the light source 110 is tightly focused compared to where it is more diffuse. The light source 110 may deliver a laser beam to the cornea 2. Effectively, activation of the cross-linking agent 330 is restricted to the smaller focal volume where the light source 310 is delivered to the cornea 2 with a high flux. This localization advantageously allows for more precise control over where cross-linking is activated within the cornea 2.

[0040] Referring again to FIG. 1, embodiments employing multiphoton excitation microscopy can also optionally employ multiple beams of light simultaneously applied to the cornea 2 by the light source 110. For example, a first and a second beam of light can each be directed from the optical elements 112 to an overlapping region of the cornea 2. The region of intersection of the two beams of light can be a volume in the cornea 2 where cross-linking is desired to occur. Multiple beams of light can be delivered to the cornea 2 using aspects of the optical elements 112 to split a beam of light emitted from the light source 310 and direct the resulting multiple beams of light to an overlapping region of the cornea 2. In addition,

embodiments employing multiphoton excitation microscopy can employ multiple light sources, each emitting a beam of light that is directed to the cornea 2, such that the multiple resulting beams of light overlap or intersect in a volume of the cornea 2 where cross-linking is desired to occur. The region of intersection may be, for example, in the mid-depth region 2B of the cornea 2, and may be below the corneal surface 2A. Aspects of the present disclosure employing overlapping beams of light to achieve multi-photon microscopy may provide an additional approach to controlling the activation of the cross-linking agent 130 according to a three-dimensional profile within the cornea 2.

[0041] Aspects of the present disclosure, *e.g.*, adjusting the parameters for delivery and activation of the cross-linking agent, can be employed to reduce the amount of time required to achieve the desired cross-linking. In an example implementation, the time can be reduced from minutes to seconds. While some configurations may apply the initiating element (i.e., the light source 110) at a flux dose of 5 J/cm^2, aspects of the present disclosure allow larger doses of the initiating element, *e.g.*, multiples of 5 J/cm^2, to be applied to reduce the time required to achieve the desired cross-linking. Highly accelerated cross-linking is particularly possible when using laser scanning technologies (such as in the delivery system 300 provided in FIG. 3) in combination with a feedback system 400 as shown in FIG. 4, such as a rapid video eye-tracking system, described below.

[0042] To decrease the treatment time, and advantageously generate stronger cross-linking within the cornea 2, the initiating element (*e.g.*, the light source 110 shown in FIG. 1) may be applied with a power between 30 mW and 1 W. The total dose of energy absorbed in the cornea 2 can be described as an effective dose, which is an amount of energy absorbed through a region of the corneal surface 2A. For example the effective dose for a region of the cornea 2 can be, for example, 5 J/cm^2, or as high as 20 J/cm^2 or 30 J/cm^2. The effective dose delivering the energy flux just described can be delivered from a single application of energy, or from repeated applications of energy. In an example implementation where repeated applications of energy are employed to deliver an effective dose to a region of the cornea 2, each subsequent application of energy can be identical, or can be different according to information provided by the feedback system 400.

[0043] Treatment of the cornea 2 by activating cross-linking produces structural changes to the corneal stroma. In general, the optomechanical properties of the cornea changes under stress. Such changes include: straightening out the waviness of the collagen fibrils; slippage and rotation of individual lamellae; and breakdown of aggregated molecular superstructures into smaller units. In such cases, the application of the cross-linking agent 130 introduces

sufficient amounts of cross-linking agent to mid-depth regions 2B of the corneal tissue where stronger and more stable structure is desired. The cross-linking agent 130 may be applied directly to corneal tissue that have received an eye therapy treatment and/or in areas around the treated tissue.

[0044] To enhance safety and efficacy of the application and the activation of the cross-linking agent, aspects of the present disclosure provide techniques for real time monitoring of the changes to the collagen fibrils with a feedback system 400 shown in FIG. 4. These techniques may be employed to confirm whether appropriate doses of the cross-linking agent 130 have been applied during treatment and/or to determine whether the cross-linking agent 130 has been sufficiently activated by the initiating element (*e.g.*, the light source 110). General studies relating to dosage may also apply these monitoring techniques.

[0045] Moreover, real time monitoring with the feedback system 400 may be employed to identify when further application of the initiating element (*e.g.*, the light source 110) yields no additional cross-linking. Where the initiating element is UV light, determining an end point for the application of the initiating element protects the corneal tissue from unnecessary exposure to UV light. Accordingly, the safety of the cross-linking treatment is enhanced. The controller 120 for the cross-linking delivery system can automatically cease further application of UV light when the real time monitoring from the feedback system 400 determines that no additional cross-linking is occurring.

[0046] FIG. 4 illustrates a delivery system incorporating the feedback system 400. The feedback system 400 is adapted to gather measurements 402 from the eye 1, and pass feedback information 404 to the controller 120. The measurements 402 can be indicative of the progress of strengthening and stabilizing the corneal tissue. The measurements 402 can also provide position information regarding the location of the eye and can detect movement of the cornea 2, and particularly the regions of the corneal tissue requiring stabilization. The feedback information 404 is based on the measurements 402 and provides input to the controller 120. The controller 120 then analyzes the feedback information 404 to determine how to adjust the application of the initiating element, *e.g.*, the light source 110, and sends command signals 406 to the light source 110 accordingly. Furthermore, the delivery system 100 shown in FIG. 1 can be adapted to incorporate the feedback system 100 and can adjust any combination of the optical elements 112, the applicator 132, or the light source 110 in order to control the activation of the cross-linking agent 130 within the cornea 2 based on the feedback information 404 received from the feedback system 400.

[0047] The feedback system 400 can be a video eye-tracking system as shown in FIG. 5A, which illustrates a delivery system 500 for activating cross-linking in the cornea 2 with the laser scanning device 300. The delivery system 500 of FIG. 5A includes a video camera 510 for capturing digital video image data 504 of the eye 1. The video camera 510 generates the video image data 504 of the eye 1 in real time and tracks any movement of the eye 1. The video image data 504 generated by the video camera 510 is indicative of photons 502 reflected from the eye 1. The photons 502 can be reflected from the eye 1 from an ambient light source, or can be reflected from the eye 1 by a light source that is incorporated into the delivery system 500 adapted to direct light to the eye 1 for reflecting back to the video camera 510. Delivery systems including the light source can optionally be adapted with the light source controlled by the controller 120. The delivery system 500 may minimize movement of the eye 1 by minimizing movement of the head, such as, for example, by use of a bite plate described below. However, the eye 1 can still move in the socket, relative to the head.

[0048] The real time video image data 504 (*e.g.*, the series of images captured by the video camera 510) are sent to the controller 120, which may include processing hardware, such as a conventional personal computer or the like. The controller 120 analyzes the data from the video camera 10, for example, according to programmed instructions on computer-readable storage media, *e.g.*, data storage hardware. In particular, the controller 120 identifies the image of the cornea 2 in the video image data 504 and determines the position of the cornea 2 relative to the delivery system 500, and particularly relative to the laser scanning device 300. The controller 120 sends instructions 506 to the laser scanning device 300 to direct a pattern of UV light 508 to the position of the cornea 2. For example, the instructions 506 can adjust optical aspects of the laser scanning device 300 to center the pattern of UV light 508 output from the laser scanning device 300 on the cornea 2. The pattern of UV light 508 activates the cross-linking agent 130 in desired areas and depths of corneal tissue according to aspects of the present disclosure described herein.

[0049] In addition, the video image data 504 can optionally include distance information and the controller 130 can be adapted to further analyze the video image data 504 to determine the distance to the cornea 2 from the laser scanning device 508 and can adjust the focal plane of the pattern of UV light 508 directed to the cornea 2. For example, the distance to the cornea 2 may be detected according to an auto-focus scheme that automatically determines the focal plane of the cornea 2, or may be determined according to an active ranging scheme, such as a laser ranging or radar scheme. In an implementation, the video

image data 504 can be a series of images, and the controller 120 can be adapted to analyze the images in the series of images individually or in combination to detect, for example, trends in the movement of the cornea 2 in order to predict the location of the cornea 2 at a future time.

[0050] FIG. 5B illustrates an exemplary operation of the delivery system 500 shown in FIG. 5A. In step 512, the video camera 510 captures the video image data 504 of the eye 1 based on the photons 502 reflected from the eye 1. In step 514, the video image data 504 is sent to the controller 120. In step 516, the controller 120 sends the instructions 506 to the laser scanning device 300 according to the detected position of the cornea 2. In step 518, the initiating element (*e.g.*, UV light) is applied to the cornea 2 according to the detected position of the cornea 2. Following step 518, a decision is made whether to continue to gather feedback data using the video monitoring system. If feedback data continues to be desired, the exemplary operation returns to step 512 and repeats until it is determined that feedback information is no longer required, at which point the exemplary operation ceases. In an implementation, the delivery system 500 can be adapted to operate according to the steps illustrated in FIG. 5B in real time, and can provide position data about the location of the cornea 2 continuously, or in response to queries from, for example, the controller 120.

[0051] In general, the system 500 shown in FIG. 5A can correlate pixels of the video camera 510 with the pixels of the laser scanning device 300, so the real time video image date 504 from the video camera 120 can be employed to direct the pattern of UV light 508 from the laser scanning device 300 accurately to the desired corneal tissue even if there is some movement by the eye 1. The system 500 can be employed to map, associate, and/or correlate pixels in the video camera 510 with pixels in the laser scanning device 300. Advantageously, the system 500 does not require mechanical tracking of the eye 1 and mechanical adjustment (of the laser scanning device 300) to apply the pattern of UV light 508 accurately to the cornea 2.

[0052] In sum, implementations of aspects of the present disclosure stabilize a three-dimensional structure of corneal tissue through controlled application and activation of cross-linking in the corneal tissue. For example, the cross-linking agent 130 and/or the initiating element (*e.g.*, the pattern of UV light 508) are applied in a series of timed and controlled steps to activate cross-linking incrementally. Moreover, the delivery and activation of the cross-linking agent 130 at depths in the cornea 2 depend on the concentration(s) and diffusion times of the cross-linking agent 130 as well as the power(s) and bandwidths of the initiating element. Furthermore, systems may employ laser scanning technologies in combination with

a video eye-tracking system to achieve accurate application of the initiating element 222 to the cornea 2.

[0053] Another technique for real time monitoring of the cornea 2 during cross-linking treatment employs interferometry with a specialized phasecam interferometer (*e.g.,* manufactured by 4dTechnology, Tucson, AZ). The interferometer takes up to 25 frames per second with a very short exposure so as to substantially minimize motion during an exposure duration. In an example, the exposure time can be less than one millisecond. As the heart beats, the intraocular pressure (IOP) in the eye 1 increases and causes the corneal surface to extend outwardly by a slight amount. The deflection of the cornea 2 is determined by developing a difference map between the peaks and valleys of the cardiac pulsate flow cycles. The deflection of the cornea provides an indicator for the strength of the corneal tissue. The deflection of the cornea 2 may be used to measure changes in the biomechanical strength, rigidity, and/or stiffness during cross-linking treatment. Additionally, comparisons of an amount of deflection observed before and after cross-linking treatment is applied to a cornea 2 may be used to determine a change in biomechanical strength, rigidity, and/or stiffness of the corneal tissue. In general, however, interferometry may be employed to measure corneal strength before and after an eye surgery, before and after any eye treatment, or to monitor disease states. Thus, aspects of the present disclosure employ interferometry as a non-contact technique to determine the surface shape of the cornea 2 and develop a difference map to measure the deflection from IOP. The deflection of the cornea can then be used to determine changes in corneal strength during cross-linking treatment.

[0054] To provide control over cross-linking activity, aspects of the present disclosure provide techniques for real time monitoring of the changes in the strength of the corneal tissue. These techniques may be employed to confirm whether appropriate doses of the cross-linking agent have been applied during treatment. Moreover, real time monitoring may be employed to identify when further application of the initiating element yields no additional cross-linking. Where the initiating element is UV light, determining an end point for the application of the initiating element protects the corneal tissue from unnecessary exposure to UV light. Accordingly, the safety of the cross-linking treatment is enhanced. The controller 120 for the cross-linking delivery system (*e.g.*, the delivery system 100 in FIG. 1) can automatically cease further application of UV light when the real time monitoring determines that no additional cross-linking is occurring.

[0055] In addition the video systems and interferometry systems discussed above, still further examples of systems suitable to be included in the feedback system 400 of FIG. 4

include the OCT systems and supersonic shear imaging systems discussed below, which can be operated to provide real-time feedback on the biomechanical properties of the corneal tissue. The information can then be used to develop a treatment plan or dynamically adjust a treatment plan that is suited to the monitored characteristics of the corneal tissue. The treatment plan can be characterized by applications of cross-linking agent, energy doses of initiating element, and selective patterns and/or distributions therefore in order to controllably activate cross-linking in the corneal tissue.

[0056] FIG. 6 illustrates an example delivery system 1400 for applying light to an eye 1 incorporating a laser light source 1410 and a beam conditioning system 1420. The laser light source 1400 can emit, for example, ultraviolet or green light suitable for activating a cross-linking agent that is applied to the eye 1. The output of the laser light source 1410 is transferred to the beam conditioning system 1420 via an optical path 1415. The optical path 1415 can include, for example, an optical fiber adapted for delivering the laser light from the laser light source 1410 to the beam conditioning system 1420. The beam conditioning system 1420 receives the output of the laser light source 1410 and emits output light 1422 that is collimated or nearly collimated. In an example implementation of the system 1400, the output light 1422 is reflected by the mirror 1402 and directed to the eye 1. According to an aspect of the system 1400, the intensity of the output light 1422 does not decrease according to the inverse of the square of the distance from the laser light source 1422. By incorporating the laser light source 1422, the system 1400 provides a desired intensity of light to the eye 1 with relatively little sensitivity to the optical distance between the eye 1 and the system 1400. In other words, systems incorporating light sources having intensities that decrease according to an inverse distance squared may require careful alignment of the eye 1 at a particular optical plane to ensure a desired intensity of illumination of the eye 1 is achieved; however, the output light 1422 of the system 1400 provides an intensity that is substantially stable over a range of distances between the eye 1 and the system 1400.

[0057] The beam conditioning system 1420 can generally include lenses, mirrors, apertures, and/or other optical elements to condition the beam of light such that the resulting output light 1422 has a non-uniform time-averaged intensity profile. The output light 1422 can activate cross-linking in the eye 1 according to a non-uniform pattern that is related to the non-uniform time-averaged intensity profile. For example, regions of the eye 1 illuminated by portions of the output light 1422 having a relatively greater energy flux can experience more cross linking than regions of the eye 1 illuminated by portions of the output light 1422 having a relatively lesser energy flux.

[0058] Aspects of the beam conditioning system 1420 can be similar to the system 300 such that the non-uniform time-averaged intensity profile of the output light 1422 can be generated at least in part by scanning the laser light over an array of selectively alignable mirrors to create a pixelated intensity profile. Additionally or alternatively, the laser light can be diverged or converged and directed to a digital micro mirror device having an array of selectively alignable mirrors to generate a pixelated intensity profile with the digital micro mirror device being imaged to the eye 1.

[0059] The laser light may also be passed through one or more fixed or moving apertures to selectively block portions of the beam of light thereby generating the non-uniform time-averaged intensity profile of the output light 1422 imaged on the eye 1. Dynamic adjustments to the non-uniform time-averaged intensity profile can be provided in part by translating and/or rotating apertures adapted to be programmatically positioned to generate the non-uniform time averaged intensity profile. In an implementation, the positions, translations, and/or rotations of the apertures may be carried according to instructions from a controller. Generally, the apertures can be manipulated such that greater amounts of light are blocked, on a time-averaged basis, from regions of the beam corresponding to low-intensity areas of the desired intensity profile, and vice versa. For example, light-blocking portions of the apertures can move relatively more rapidly through regions of the beam corresponding to high-intensity areas of the desired intensity profile and relatively more slowly through regions of the beam corresponding to low-intensity areas of the desired intensity profile. The apertures can include rotating screens having cut-out portions shaped as wedges, shapes similar to a nautilus shell pattern, and/or other shapes. The screens can be rotated in an optical path of the beam of light from the laser 1410. As the cut-out portion of the screen sweeps through regions of the beam of light corresponding to relatively high intensity regions of the non-uniform intensity profile, the angular rotation of the screen can be slowed to a low rate, and while the cut-out portion sweeps through regions of the beam of light corresponding to relatively low intensity regions of the non-uniform time-averaged intensity profile, the angular rotation of the screen can be slowed to a high rate. The same principal can be applied to translating apertures with high rates of motion of a cut-out portion corresponding to low intensity regions of a resulting intensity profile and vice versa.

[0060] The beam conditioning system may also have a set of beam steering optics that can scan a converging or diverging beam of light with a specific spot size imaged on the eye 1. The spot intensity distribution, size and shape being modified by the methods described herein.

[0061] In implementations, the beam conditioning system 1420 can be programmatically adjusted and controlled by a controller (such as the controller 120 described herein). Generally, similar to aspects described herein in reference to iterative approaches for activating cross-linking, the output light 1422 can be delivered to the eye 1 in one or more doses characterized by a power, bandwidth, duration, and/or intensity profile. Furthermore, aspects of the beam conditioning system 1420 can be automatically adjusted to modify, for example, the overall intensity or power, the non-uniform intensity pattern, the duration, and/or the bandwidth of the output light 1422 for each dose of the output light 1422 delivered to the eye 1. In implementations, the automatic adjustment of each dose of the output light 1422 can be carried out according to feedback information, such as the feedback information provided by the interferometry systems, polarimetry systems, and multi-slit lamp configurations described herein for providing feedback.

[0062] Furthermore, ocular coherence tomography (OCT) systems can be employed to provide feedback to the controller (e.g., 120). An OCT system generally utilizes low coherence interferometry of white optical light or near-infrared light interfered with light from a reference surface to characterize regions of interest within a narrow coherence length. OCT systems can employ time domain or frequency domain scanning to generate a high resolution (micrometer scale), three-dimensional (to millimeter depths) profile of the corneal tissue. Examples of OCT systems providing feedback for an eye therapy system are disclosed, for example, in U.S. Provisional Patent Application No. 61/542,269, filed October 2, 2011; and U.S. Provisional Patent Application No. 61/550,576, filed October 24, 2011, each of which is hereby incorporated herein by reference in its entirety.

[0063] Aspects of the present disclosure also provide systems and methods for treating myopia (i.e., near-sightedness) and/or astigmatism of a patient by activating cross-linking in the patient's corneal tissue. Clinical observations have revealed that myopia can be treated by applying a cross-linking agent (e.g., Riboflavin) to an eye with an applicator, and then activating cross-linking in the corneal tissue of the eye by applying an initiating element, such as UV light. The resulting cross-lining activity in the corneal tissue of the eye has been observed to flatten the shape of the eye, thereby advantageously reducing the corneal power of the cornea so as to correct for myopia. Furthermore, asymmetric flattening of an eye has been observed in patients suffering from astigmatism. In an example clinical treatment, which is discussed next in connection with FIGS. 7A-7C, a patient's astigmatism was observed to be corrected by 0.8 diopters after cross-linking therapy was applied.

[0064] FIG. 7A illustrates an optical power contour map of an eye prior to initiation of cross-linking therapy. The contour map in FIG. 7A illustrates the optical power of the eye measured in diopters with contour lines illustrating regions having uniform optical power. The contour map in FIG. 7A (and FIG. 7B) was produced by an Oculus Pentacam system utilizing rotating Scheimplug cameras to measure corneal thickness and topography (i.e., elevation of the posterior and anterior corneal surface along an axis oriented normal through the center of the eye). Such Pentacam systems are available, for example, from Oculus USA (Lynnwood, WA). The measurements of the elevations of the cornea are converted to axial (Sagittal) radius values within the Pentacam system and the power of the corneal lens is computed based on the axial radius values and based on ray tracing calculations.

[0065] As shown in FIG. 7A, the contour map of the eye is characterized by an astigmatism. In particular, a meridian oriented at 159.6 degrees with respect to the horizontal axis is referred to as the flattest meridian (e.g., K1) and has a characteristic optical power of 42.5 diopters. The meridian perpendicular to the flattest meridian (e.g., K2) has a characteristic optical power of 46.1 diopters. Thus, the optical power of the eye is non-uniform about the central optical axis of the eye, and is characterized by a difference of 3.6 diopters between the flattest meridian (K1) and the perpendicular meridian (K2). Thus, the lack of axial uniformity in corneal power about the central point of the corneal contour map shown in FIG. 7A illustrates that the patient suffered from astigmatism.

[0066] FIG. 7B illustrates an optical power contour map of the eye shown in FIG. 15A following treatment by cross-linking therapy according to an aspect of the present disclosure. In particular, a cross-linking agent including Riboflavin and benzalkonium chloride (BAC) was applied to the eye. The cross-linking agent was then activated ("initiated") by applying UV light to the cornea in a 3 mm diameter treatment zone approximately centered on the cornea. The UV light was applied in the treatment zone in a dose of 10.8 J/cm^2 at a rate of 30 mW/cm^2. In particular, according to an aspect of the present disclosure, the dose of the applied UV light exceeded 5 J/cm^2. As shown by the contour map in FIG. 7B, the corneal power of the eye was reduced by the cross-linking therapy, thus addressing the patient's myopia observed pre-therapy (FIG. 7A). Furthermore, the astigmatism observed pre-therapy (FIG. 7A) was partially corrected by the cross-linking therapy as well. In particular, in the post-therapy contour map shown in FIG. 7B a meridian oriented at 158.3 degrees with respect to the horizontal axis is referred to as the flattest meridian (e.g., K1) and has a characteristic optical power of 39.8 diopters. The meridian perpendicular to the flattest meridian (e.g., K2) has a characteristic optical power of 42.6 diopters. While the optical power of the eye is non-

uniform about the central optical axis of the eye, it is characterized by a difference of only 2.8 diopters between the flattest meridian (K1) and the perpendicular meridian (K2) post-therapy. Thus, the cross-linking therapy improved the patient's pre-therapy astigmatism by 0.8 diopters.

[0067] FIG. 7C illustrates a contour map of the difference between the contour map in FIG. 7B and the contour map shown in FIG. 7A. As shown in FIG. 7C, the amount of corneal power adjusted by the cross-linking therapy decreased the corneal power in the treatment zone by approximately 3.4 diopters.

[0068] The present disclosure provides techniques for addressing astigmatism that contrast with LASIK techniques for correcting astigmatism. LASIK techniques treat astigmatism by removing corneal tissue from bulging regions of the cornea (i.e., from regions having high corneal power) in order to flatten those regions of the cornea. The removal of corneal tissue from the bulging regions further weakens those regions and undesirably thins those regions of the cornea, making them potentially more susceptible to bulging in the future. In contrast, the cross-linking therapy described herein corrects astigmatism by flattening (and strengthening) bulging regions of the cornea by activating cross-linking therapy in those regions. According to aspects of the present disclosure, corneal thickness and corneal strength is not sacrificed in order to provide optical corrections to the cornea. Aspects of the present disclosure provide for strengthening weakened regions of the cornea (e.g., regions of the cornea that are bulging so as to cause non-uniformities in corneal power) through cross-linking. Furthermore, it has been observed that cross-linking therapy applied to an eye in a uniform treatment zone results in preferential flattening of regions of the treatment zone having relatively greater corneal power (e.g., regions of the cornea with greater axial curvature). This effect of preferential cross-linking activity in higher curvature regions of the corneal tissue results in a partial correction of corneal astigmatism even when cross-linking therapy is initiated according to a uniformly applied pattern within the treatment zone.

[0069] While particular clinical results are described in connection with FIGS. 7A through 7C, generally the treatment of the corneal tissue by cross-linking therapy is not limited to flattening corneal tissue to treat myopia and/or astigmatism. Cross-linking therapy can be applied to adjust the optical power of the cornea by selectively flattening and/or strengthening regions of the cornea. It is particularly noted that hyperopia (i.e., "far-sightedness") can be corrected, for example, by activating cross-linking in a ring-shaped region surrounding a central portion of the cornea so as to pinch the cornea and cause the

central portion to have an increased optical power, thereby addressing the hyperopia. Furthermore, cross-linking therapy can be applied to an eye principally for the purpose of strengthening the cornea to address corneal thin-ness, weakness, or to reinforce structural changes to the eye applied previously, such as by Photo-Refractive Keratectomy (PRK), LASEK, LASIK, thermokeratoplasty, cataract, scar removal by PRK or Photo-Therapeutic Keratectomy (PTK) or some other form of refractive or ocular surgery. In some examples, cross-linking is activated according to a pattern that corresponds to a region of measured corneal thinness or weakness or according to a pattern that corresponds to a region of expected corneal thinness or weakness based on a previous treatment (e.g., LASIK) to selectively strengthen regions of the corneal tissue known or expected to be relatively weaker than other regions.

[0070] According to aspects of the present disclosure, cross-linking therapy treatments applied to an eye can be tuned according to one or more biomechanical properties of the eye, such as the corneal topography (i.e., shape), corneal strength (i.e., stiffness), and/or corneal thickness. Based on the received one or more biomechanical properties, (e.g., corneal thickness), the cross-linking treatment is accordingly adjusted to provide treatment based on the received biomechanical properties. For example, the amount of cross-linking agent and/or dosage of cross-linking activation can be increased for patients having larger corneal thickness. Generally optical correction and/or strengthening of the cornea is applied similar to the descriptions of iterative cross-linking therapy treatments discussed above where the cross-linking agent and/or cross-linking initiating element are each applied in one or more iterations with adjustable characteristics for each iteration. Furthermore, the treatment can be adapted based on feedback information of the biomechanical properties of the cornea that is gathered in real-time during treatment or during breaks in treatment. Generally the developed treatment plan can include a number of applications of the cross-linking agent (e.g., the cross-linking agent 130 shown in FIGS. 1 and 2A), the amount and concentration of the cross-linking agent for each application, the number of treatments of the initiating element (e.g., the initiating element 222 of FIG. 2A), and the timing, duration, power, energy dosage, and pattern of the initiating element for each treatment with the initiating element. As discussed herein, the initiating element can be patterned to apply the initiating element non-uniformly according to a mirror array of digitally controlled micro-mirrors (e.g., FIG. 3 and accompanying description), according to multi-photon excitation microscopy and/or according to the use of masks to selectively block the initiating element.

[0071] Additionally and/or alternatively, the non-uniform pattern of the initiating element can also be realized by applying the initiating element to the eye in separate treatment zones with different doses sequentially or continuously applied. For example, one treatment zone can turn off (i.e., ceases to receive the initiating element) while another stays on (i.e., continues to receive the initiating element). The zones can be, for example, annularly shaped about a center point of the eye. There can also be discontinuous zones where no initiating element is applied (e.g., a central zone surrounded by an annulus of no light surrounded by an annulus of light, etc.). The widths of the annular zones ("rings") can be of different dimensions, such as where one annular zone has a width of 1 mm and another has a width of 2 mm. Applying the initiating element in rings on the periphery of the eye without a central spot can result in a hyperopic correction by causing the central region of the eye to have an increased curvature while the periphery is strengthened. Furthermore, the central and surrounding annular treatment zones can be elliptical in shape to correct for astigmatism by preferentially initiating cross-linking in regions of the cornea to correct the astigmatism. Such elliptically shaped annular treatment zones are preferentially oriented with the axis of the annular treatment zones aligned according to the orientation of the astigmatism. The elliptically shaped treatment zones can also be irregularly asymmetric (i.e., having major and minor axis that are not perpendicular and can be situated with distinct center points (centers of mass)). The elliptically shaped treatment zones can also be dictated by the biomechanical properties of the cornea, for example, the corneal topography, the corneal thickness, and/or the corneal strength. These zones may also be defined by the irregular and translating shaped apertures as described herein.

[0072] Furthermore, the distribution of the cross-linking agent can be adjusted prior to or during initiation of the cross-linking agent according to the techniques and systems described in commonly assigned U.S. Patent Application No. 13/086,019, filed April 13, 2011, the contents of which is incorporated entirely herein by reference.

[0073] The one or more biomechanical properties of the eye can be observed pre-treatment or can be actively observed during treatment by a feedback system, such as the interferometric feedback system, Oculus Pentacam, 4 slit lamp apparatus, OCT system, and other feedback systems described herein. Additionally and/or alternatively, biomechanical properties of the cornea may be provided according to information from a Supersonic Shear Imaging ("SSI") corneal elasticity measurement system, such as described in, for example, M. Tanter et al., High-Resolution Quantitative Imaging of Cornea Elasticity Using Supersonic Shear Imaging, *IEEE Transactions on Medical Imaging*, vol. 28, no. 12, Dec.

2009, pp. 1881-1893, the contents of which is hereby incorporated entirely herein by reference. Additionally or alternatively, biomechanical properties of the cornea may be provided according to information from an Ocular Response Analyzer for measuring corneal hysteresis in response to a changing optical pressure, available from Reichert, Inc., and as described in Michael Sullivan-Mee, The Role of Ocular Biomechanics In Glaucoma Management, *Review of Optometry*, Oct. 15, 2008, pp. 49-54, the contents of which is hereby incorporated entirely herein by reference.

[0074] The cross-linking agent 122 may be applied to the corneal tissue in an ophthalmic solution, *e.g.*, in the form of eye drops. In some cases, the cross-linking agent 122 is effectively applied to the corneal tissue by removing the overlying epithelium before application. However, in other cases, the cross-linking agent 122 is effectively applied in a solution that transitions across the epithelium into the underlying corneal tissue, *i.e.*, without removal of the epithelium. For example, a transepithelial solution may combine Riboflavin with approximately 0.1% benzalkonium chloride (BAC) in distilled water. Alternatively, the transepithelial solution may include other salt mixtures, such as a solution containing approximately 0.4% sodium chloride (NaCl) and approximately 0.02% BAC. Additionally, the transepithelial solution may contain methyl cellulose, dextran, or the like to provide a desired viscosity that allows the solution to remain on the eye for a determined soak time.

[0075] Although embodiments of the present disclosure may describe stabilizing corneal structure after treatments, such as LASIK surgery and thermokeratoplasty, it is understood that aspects of the present disclosure are applicable in any context where it is advantageous to form a stable three-dimensional structure of corneal tissue through cross-linking. Furthermore, while aspects of the present disclosure are described in connection with the re-shaping and/or strengthening of corneal tissue via cross-linking the corneal collagen fibrils, it is specifically noted that the present disclosure is not limited to cross-linking corneal tissue, or even cross-linking of tissue. Aspects of the present disclosure apply generally to the controlled cross-linking of fibrous matter and optionally according to feedback information. The fibrous matter can be collagen fibrils such as found in tissue or can be another organic or inorganic material that is arranged, microscopically, as a plurality of fibrils with the ability to be reshaped by generating cross-links between the fibrils. Similarly, the present disclosure is not limited to a particular type of cross-linking agent or initiating element, and it is understood that suitable cross-linking agents and initiating elements can be selected according to the particular fibrous material being reshaped and/or strengthened by cross-linking.

[0076] The present disclosure includes systems having controllers for providing various functionality to process information and determine results based on inputs. Generally, the controllers (such as the controller 120 described throughout the present disclosure) may be implemented as a combination of hardware and software elements. The hardware aspects may include combinations of operatively coupled hardware components including microprocessors, logical circuitry, communication/networking ports, digital filters, memory, or logical circuitry. The controller may be adapted to perform operations specified by a computer-executable code, which may be stored on a computer readable medium.

[0077] As described above, the controller 120 may be a programmable processing device, such as an external conventional computer or an on-board field programmable gate array (FPGA) or digital signal processor (DSP), that executes software, or stored instructions. In general, physical processors and/or machines employed by embodiments of the present disclosure for any processing or evaluation may include one or more networked or non-networked general purpose computer systems, microprocessors, field programmable gate arrays (FPGA's), digital signal processors (DSP's), micro-controllers, and the like, programmed according to the teachings of the exemplary embodiments of the present disclosure, as is appreciated by those skilled in the computer and software arts. The physical processors and/or machines may be externally networked with the image capture device(s), or may be integrated to reside within the image capture device. Appropriate software can be readily prepared by programmers of ordinary skill based on the teachings of the exemplary embodiments, as is appreciated by those skilled in the software art. In addition, the devices and subsystems of the exemplary embodiments can be implemented by the preparation of application-specific integrated circuits or by interconnecting an appropriate network of conventional component circuits, as is appreciated by those skilled in the electrical art(s). Thus, the exemplary embodiments are not limited to any specific combination of hardware circuitry and/or software.

[0078] Stored on any one or on a combination of computer readable media, the exemplary embodiments of the present disclosure may include software for controlling the devices and subsystems of the exemplary embodiments, for driving the devices and subsystems of the exemplary embodiments, for enabling the devices and subsystems of the exemplary embodiments to interact with a human user, and the like. Such software can include, but is not limited to, device drivers, firmware, operating systems, development tools, applications software, and the like. Such computer readable media further can include the computer program product of an embodiment of the present disclosure for performing all or a

portion (if processing is distributed) of the processing performed in implementations. Computer code devices of the exemplary embodiments of the present disclosure can include any suitable interpretable or executable code mechanism, including but not limited to scripts, interpretable programs, dynamic link libraries (DLLs), Java classes and applets, complete executable programs, and the like. Moreover, parts of the processing of the exemplary embodiments of the present disclosure can be distributed for better performance, reliability, cost, and the like.

[0079] Common forms of computer-readable media may include, for example, a floppy disk, a flexible disk, hard disk, magnetic tape, any other suitable magnetic medium, a CD-ROM, CDRW, DVD, any other suitable optical medium, punch cards, paper tape, optical mark sheets, any other suitable physical medium with patterns of holes or other optically recognizable indicia, a RAM, a PROM, an EPROM, a FLASH-EPROM, any other suitable memory chip or cartridge, a carrier wave or any other suitable medium from which a computer can read.

[0080] While the present disclosure has been described in connection with a number of exemplary embodiments, and implementations, the present disclosure is not so limited, but rather covers various modifications, and equivalent arrangements. In addition, although aspects of the present invention may be described in separate embodiments, it is contemplated that the features from more than one embodiment described herein may be combined into a single embodiment.

WHAT IS CLAIMED IS:

1. A system for activating cross-linking in an eye, the system comprising:
a feedback system configured to monitor a biomechanical property of the eye and generate signals indicative of the monitored biomechanical property;
an applicator for applying cross-linking agent to the eye;
a light source for directing light to the eye to activate the cross-linking agent according to the monitored biomechanical property.

2. A system for activating cross-linking according to claim 1, further comprising a controller configured to:
analyze the indication of the monitored biomechanical property,
determine, based on the monitored biomechanical property, a pattern of cross-linking activation in the eye, and
direct the light to the eye, via the light source, according to the determined pattern of cross-linking activation.

3. A system for activating cross-linking according to claim 1, wherein the system is configured to correct an astigmatic condition of the eye by preferentially activating cross-linking in regions of a cornea of the eye that are relatively thin, compared to other regions.

4. A system for activating cross-linking according to claim 1, wherein the system is configured to correct a myopic condition of the eye by strengthening a cornea of the eye so as to generally flatten the topography of the cornea.

5. The system for activating cross-linking according to claim 1, wherein the feedback system includes a rotating scheimpflug system and the biomechanical properties include corneal thickness and topography.

6. The system for activating cross-linking according to claim 1, wherein the monitored biomechanical property is indicative of an orientation of astigmatism of the eye, and wherein the system is configured to apply the light source in a non-uniform pattern with an orientation defined by the orientation of the astigmatism.

7. The system for activating cross-linking according to claim 1, wherein the biomechanical properties include an indication of an astigmatism of the eye.

8. The system for activating cross-linking according to claim 7, wherein the light source is configured to apply the light in a treatment zone that is elliptical and oriented according to the indication of astigmatism.

9. The system for activating cross-linking according to claim 1, wherein the light source includes a laser generating the light applied to the eye such that the intensity of the light delivered to the eye from the light source is substantially insensitive to an optical distance between the light source and the eye.

10. The system for activating cross-linking according to claim 9, further comprising a beam conditioning system for receiving light from the light source and outputting a beam of light to the eye, the beam of light output to the eye having a non-uniform time-averaged intensity profile such that cross-linking is activated in the eye according to the non-uniform time-averaged intensity profile.

11. A method of controllably activating a cross-linking agent applied to an eye, comprising:

receiving feedback information comprising electronic signals output from a feedback system adapted to monitor the eye, the feedback information indicative of a biomechanical strength of corneal tissue of the eye;

automatically analyzing the feedback information to determine a dosage of light to be applied to the eye; and

activating the cross-linking agent by conveying light to the eye according to the determined dosage.

12. The method of claim 1, further comprising:

receiving targeting information indicative of an alignment of the eye with respect to the conveyed light; and

automatically adjusting the alignment of the eye with respect to the conveyed light according to the received targeting information.

13. The method of claim 1, wherein the feedback system comprises an interferometer adapted to interfere a beam of light reflected from a surface of the eye with a reference beam of light reflected from a reference surface, the interfered with beams of light passing through a polarizing filter and creating an intensity pattern detected by a camera associated with the feedback system, the feedback system adapted to allow the associated camera to detect a plurality of intensity patterns, and wherein the feedback information comprises the plurality of detected intensity patterns, and wherein the automatically analyzing the feedback information is carried out by:

receiving the plurality of detected intensity patterns,

determining a plurality of surface profiles of the surface of the eye associated with the plurality of detected intensity patterns based on the plurality of detected intensity patterns and based on a distance between the surface of the eye and the interferometer, and

determining an amount of dynamic deformation of the surface of the eye based on the determined plurality of surface profiles, the amount of dynamic deformation related to the dosage of light to be applied to the eye.

14. The method of claim 13, wherein the polarizing filter includes a pixelated polarizing filter for capturing intensity patterns associated with four polarization states, and wherein intensity patterns associated with four different polarizations states are simultaneously detected by the associated camera.

15. The method of claim 13, further comprising:

capturing, via a photosensitive detector, a specular reflection related to the plurality of intensity patterns detected by the associated camera;

analyzing the specular reflection to determine targeting information associated with the alignment of the eye with respect to the conveyed light;

adjusting the alignment of the eye with respect to the conveyed light according to the determined targeting information.

16. The method of claim 14, wherein targeting information is determined by solving for a centroid position of the captured specular reflection.

17. The method of claim 14, wherein the targeting information is determined by solving for an energy distribution of the captured specular reflection.

18. The method of claim 14, wherein the adjusting the alignment and the receiving the targeting information are carried out in real time to stabilize an initial fringe pattern captured by the associated camera.

19. The method of claim 1, wherein the feedback system is adapted to direct light emitted by a light source to complete a double-pass of the corneal optics, direct emerging light that emerges from the eye through a polarizing filter, and capture an intensity pattern indicative of a degree of polarization of the emerging light, and wherein the feedback information comprises the degree of polarization.

20. The method of claim 1, wherein the receiving feedback information, the automatically analyzing the feedback information, and the activating the cross-linking agent are carried out repeatedly.

21. The method of claim 20, wherein the repeated carrying out of the activating the cross-linking agent is ceased responsive to the biomechanical strength of the cornea indicated by the feedback information attaining a desired value.

22. The method of claim 1, wherein the light is conveyed to the eye via a laser scanning device.

23. The method of claim 1, wherein the light is conveyed to the eye according to a multi-photon technology.

24. The method of claim 1, wherein the cross-linking agent is Riboflavin or Rose Bengal and the light conveyed to the eye is ultraviolet light.

25. A method for activating cross-linking in corneal tissue of an eye, comprising:

applying a cross-linking agent having a first concentration to the eye;

allowing, during a first diffusion time, the cross-linking agent having the first concentration to diffuse within the eye;

activating the cross-linking agent with a photoactivating light applied according to a first dose, the first dose specified by a first power and a first bandwidth;

activating the cross-linking agent with the photoactivating light applied according to a second dose, the second dose specified by a second power and a second bandwidth.

26. The method of claim 25, wherein the second dose is applied responsive to monitoring the corneal tissue with a feedback system to determine an amount of cross-linking of the corneal tissue.

27. The method of claim 25, further comprising:

applying a cross-linking agent having a second concentration to the eye; and

allowing, during a second diffusion time, the cross-linking agent having the second concentration to diffuse within the eye.

28. The method of claim 25, wherein the applying, the allowing, and one or more of the activating the cross-linking agent are carried out repeatedly.

29. The method of claim 25, wherein the first dose or the second dose is applied such that an amount of energy of the photoactivating light is applied to a surface of the eye exceeding 5 J/cm^2.

30. A method of activating a cross-linking agent applied to an eye, comprising:

emitting photoactivating light;

directing the photoactivating light to be scanned across a mirror array having a plurality of mirrors arranged in rows and columns, the plurality of mirrors adapted to selectively direct the photoactivating light toward the eye according to a pixelated intensity pattern having pixels corresponding to the plurality of mirrors in the mirror array, the plurality of mirrors alignable according to one or more control signals; and

generating the one or more control signals for programmatically aligning the plurality of mirrors in the mirror array according to the pixelated intensity pattern.

31. The method of claim 30, further comprising:

receiving, from a feedback system, feedback information indicative of an amount of cross-linking in the corneal tissue; and

adjusting the one or more control signals based on the feedback information to thereby modify the pixelated intensity pattern applied to the eye via the mirror array.

32. The method of claim 30, further comprising:

receiving video images of the eye from a video camera, the video images having pixels mapped to the pixels corresponding to the plurality of mirrors.

33. The method of claim 30, further comprising:

conveying the pixelated intensity pattern to the surface of the eye via one or more optical elements;

receiving an image of the eye from a camera;

analyzing the received video images to determine targeting information; and

adjusting an alignment of the eye to the one or more optical elements according to the determined targeting information.

34. The method of claim 30, wherein the photoactivating light activates cross-linking in the corneal tissue by exciting the cross-linking agent to produce a reactive singlet oxygen from oxygen content in corneal tissue of the eye.

35. A method of activating a cross-linking agent applied to an eye, comprising:

emitting photoactivating light; and

directing the photoactivating light to pass through a mask adapted to selectively allow the photoactivating light to be transmitted therethrough, the regions of the mask allowing the photoactivating light to be transmitted defining a pattern of activation of the cross-linking agent.

36. The method of claim 35, wherein the mask comprises a circular lens adapted to be placed on a surface of the eye, the circular lens having a coating applied to at least a portion of the circular lens, the coating substantially blocking the photoactivating light from being transmitted through the circular lens to the eye.

37. The method of claim 36, wherein the coating is applied according to a predetermined or prescribed pattern.

38. The method of claim 35, wherein the photoactivating light activates cross-linking in the corneal tissue by exciting the cross-linking agent to produce a reactive singlet oxygen from oxygen content in corneal tissue of the eye.

39. A method of monitoring an eye, comprising:

emitting a beam of light from a light source having a known polarization;

splitting the beam and directing a first portion to be reflected from a surface of the eye, and directing a second portion to be reflected from a reference surface;

interfering the first portion of the beam and second portion of the beam to create a superimposed beam;

directing the superimposed beam through a polarizing filter;

capturing an intensity pattern of the superimposed beam emerging from the polarizing filter;

analyzing the captured intensity pattern to determine a surface profile of the surface of the eye.

40. The method of claim 39, wherein the polarizing filter includes a pixelated polarizing filter for simultaneously capturing, via an associated camera, intensity patterns associated with four polarization states.

41. The method of claim 39, wherein the analyzing the captured intensity pattern includes:

determining a phase offset, for a plurality of points in the captured intensity pattern, between the reflected first portion and the reflected second portion based on the captured intensity pattern;

determining an optical path length difference between the reflected first portion and the reflected second portion for the plurality of points from the phase offsets determined for the plurality of points; and

determining a surface profile of the eye by comparing a profile of the reference surface to the optical path length differences determined for the plurality of points.

42. The method of claim 39, further comprising:

capturing a plurality of sequential intensity patterns;

determining a plurality of surface profiles of the surface of the eye associated with the plurality of detected intensity patterns; and

determining an amount of dynamic deformation of the surface of the eye based on the determined plurality of surface profiles.

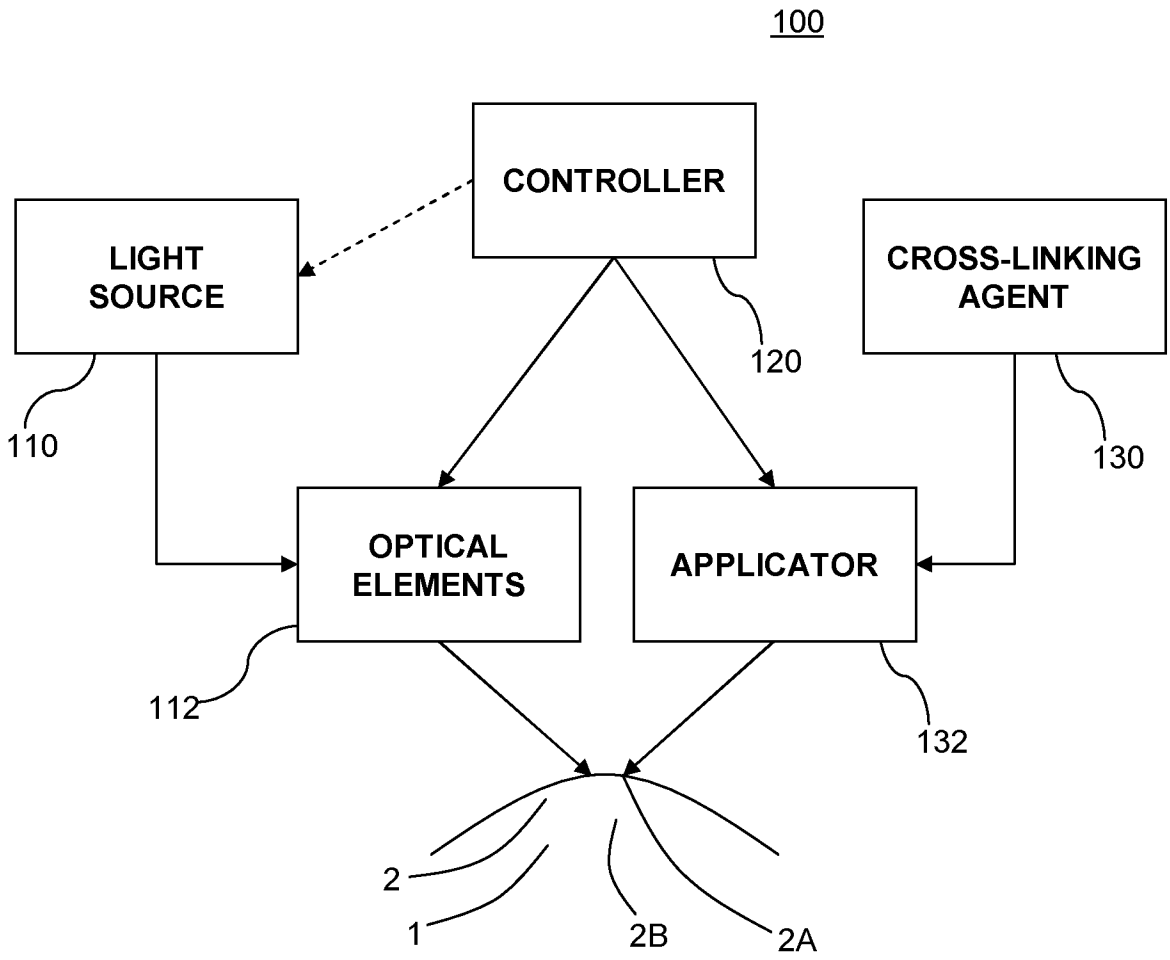
100
CONTROLLER
LIGHT SOURCE
CROSS-LINKING AGENT
120
110
130
OPTICAL ELEMENTS
APPLICATOR
112
132
2
1
2B
2A

FIG. 1

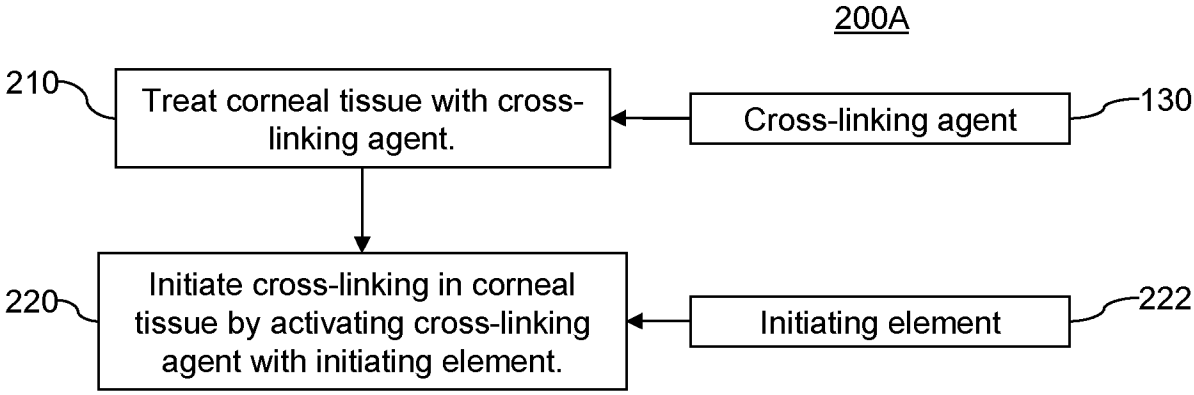
200A
210
Treat corneal tissue with cross-linking agent.
Cross-linking agent
130
220
Initiate cross-linking in corneal tissue by activating cross-linking agent with initiating element.
Initiating element
222

FIG. 2A

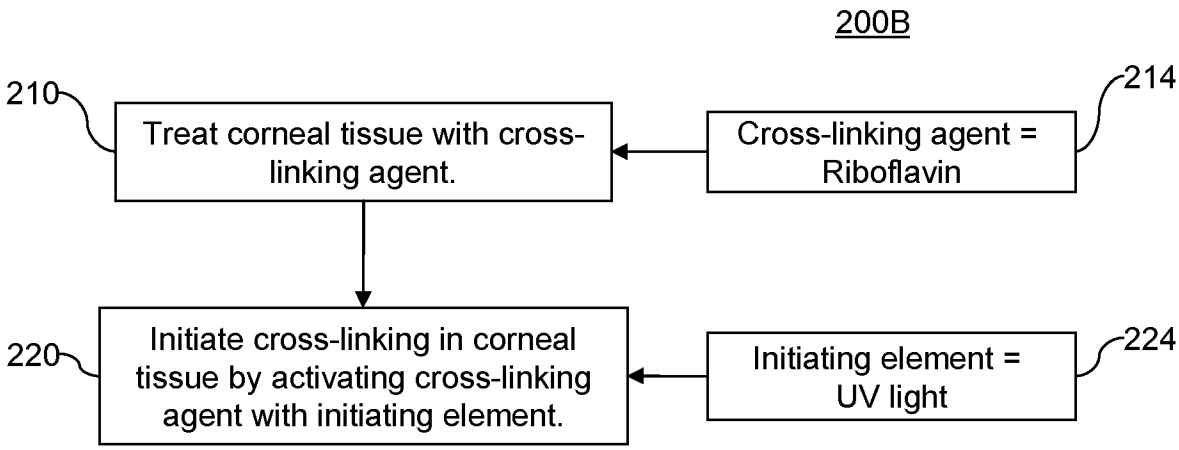
200B
210
Treat corneal tissue with cross-linking agent.
Cross-linking agent = Riboflavin
214
220
Initiate cross-linking in corneal tissue by activating cross-linking agent with initiating element.
Initiating element = UV light
224

FIG. 2B

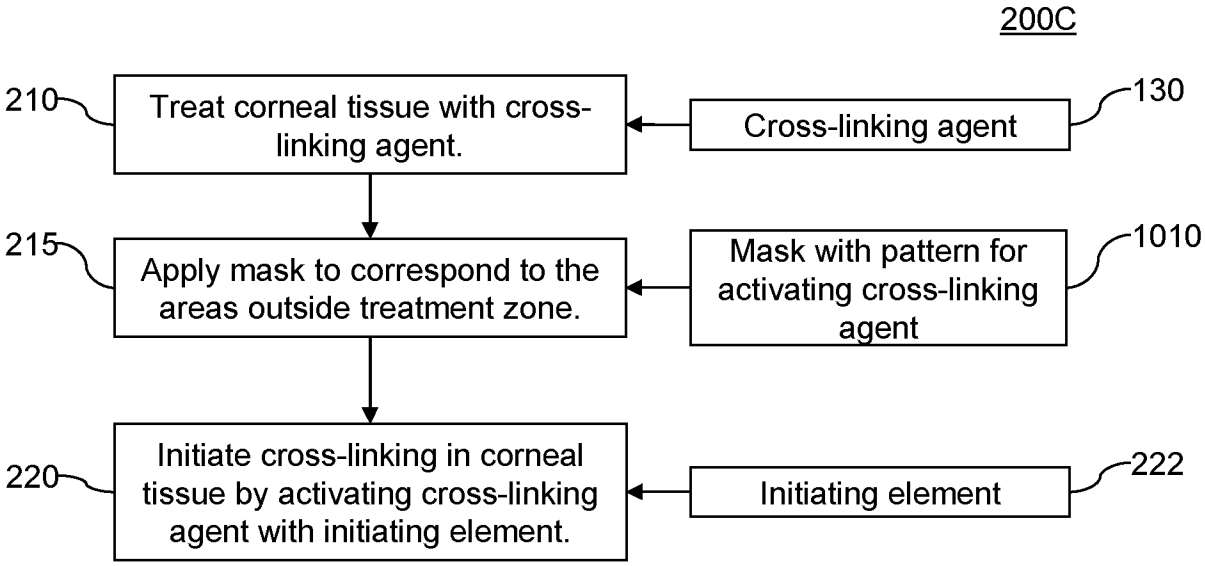
200C
210
Treat corneal tissue with cross-linking agent.
Cross-linking agent
130
215
Apply mask to correspond to the areas outside treatment zone.
Mask with pattern for activating cross-linking agent
1010
220
Initiate cross-linking in corneal tissue by activating cross-linking agent with initiating element.
Initiating element
222

FIG. 2C

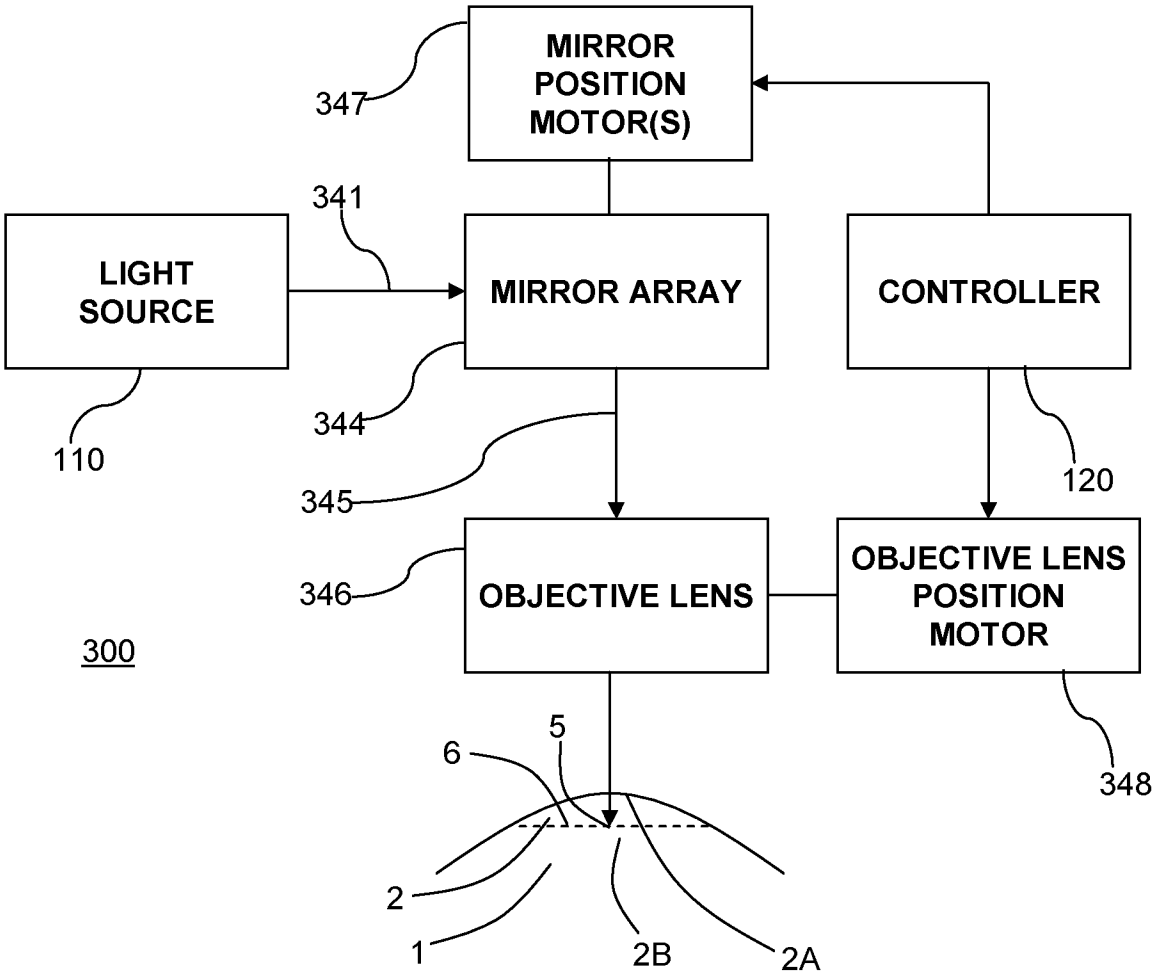
MIRROR POSITION MOTOR(S)
347
341
LIGHT SOURCE
MIRROR ARRAY
CONTROLLER
110
344
120
345
346
OBJECTIVE LENS
OBJECTIVE LENS POSITION MOTOR
300
348
5
6
2
1
2B
2A

FIG. 3

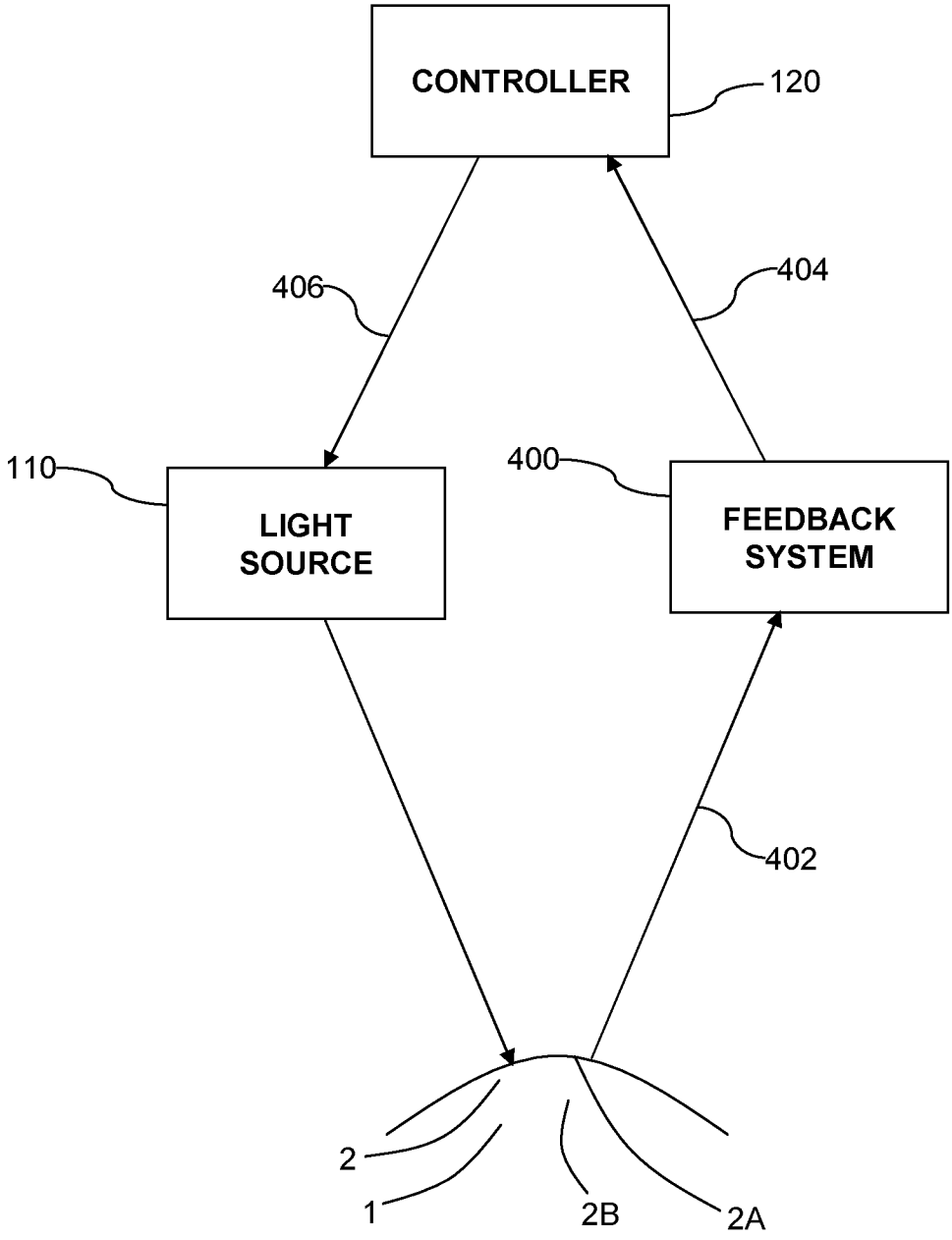
CONTROLLER
120
406
404
110
LIGHT SOURCE
400
FEEDBACK SYSTEM
402
2
1
2B
2A

FIG. 4

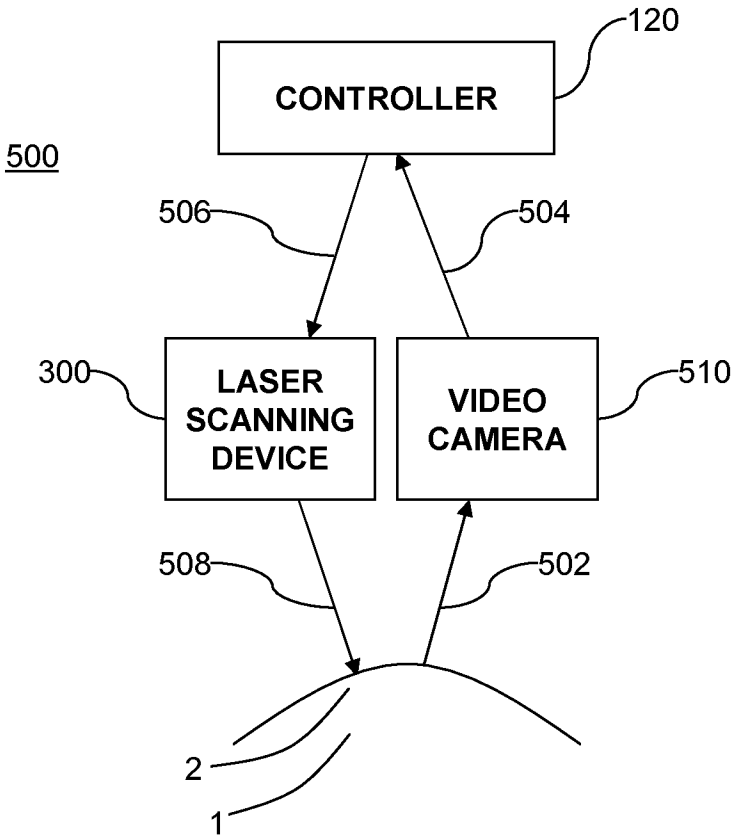
120
CONTROLLER
500
506
504
300
LASER SCANNING DEVICE
VIDEO CAMERA
510
508
502
2
1

FIG. 5A

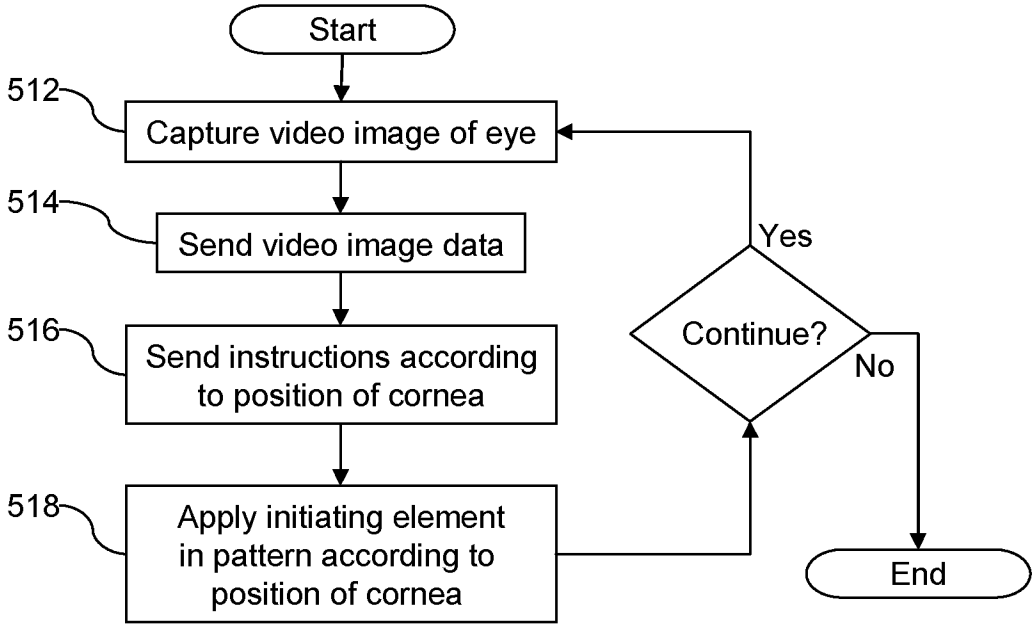
Start
512
Capture video image of eye
514
Send video image data
516
Send instructions according to position of cornea
518
Apply initiating element in pattern according to position of cornea
Continue?
Yes
No
End

FIG. 5B

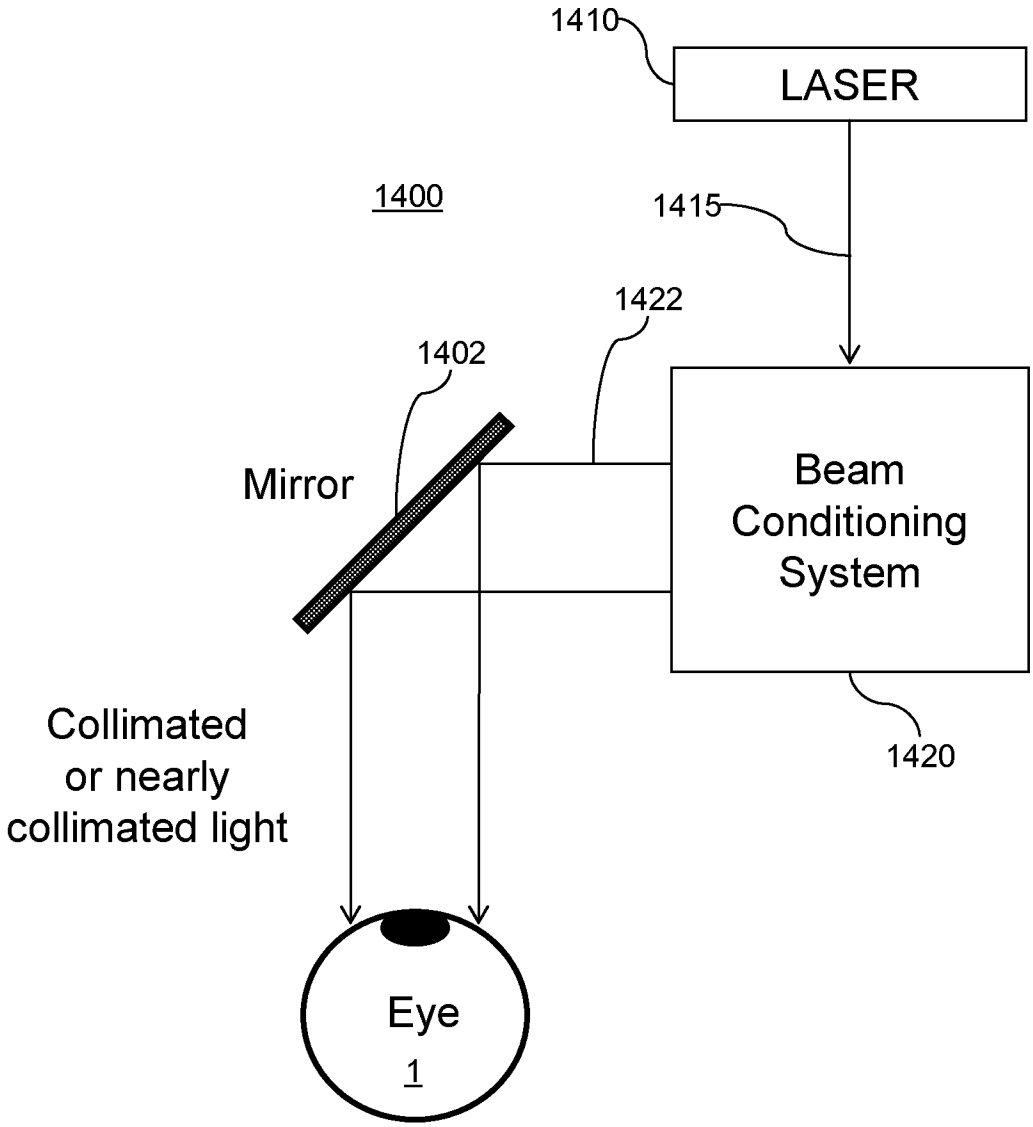
1410
LASER
1400
1415
1422
1402
Mirror
Beam
Conditioning
System
1420
Collimated
or nearly
collimated light
Eye
1

FIG. 6

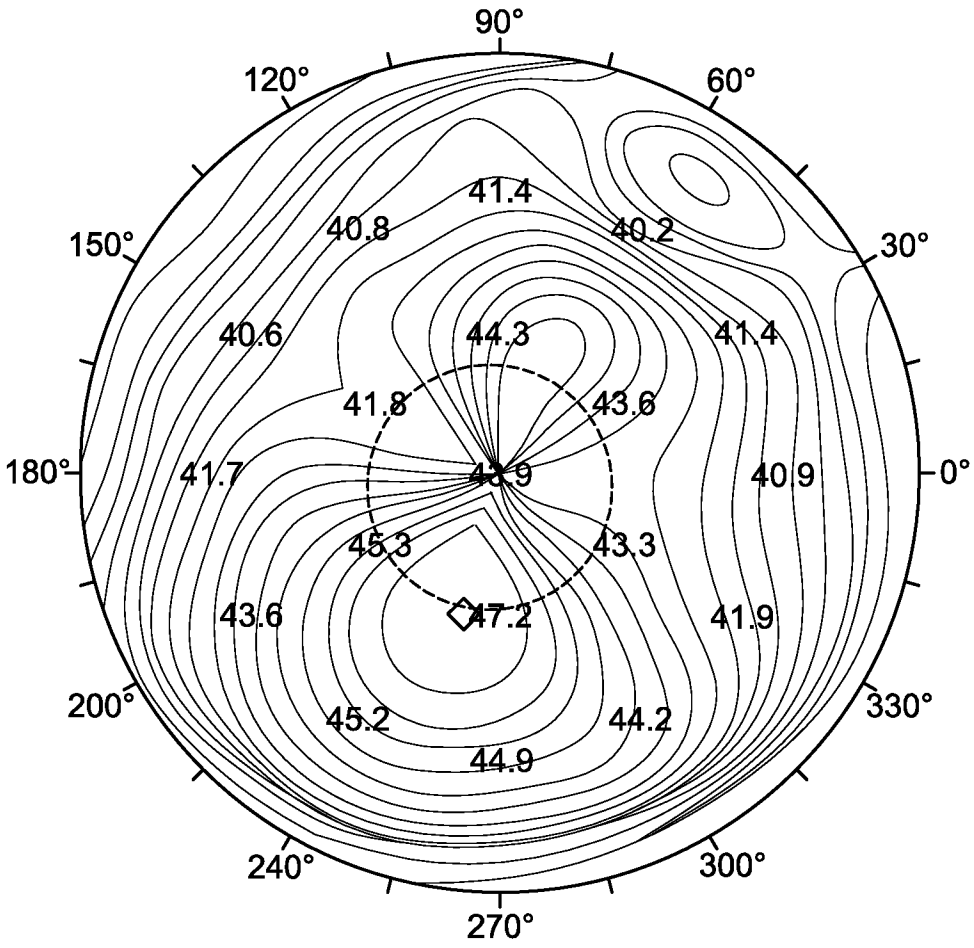
90°
120°
60°
150°
30°
180°
0°
200°
330°
240°
300°
270°
41.4
40.8
40.2
40.6
44.3
41.4
41.8
43.6
41.7
40.9
45.3
43.3
43.6
47.2
41.9
45.2
44.2
44.9

FIG. 7A

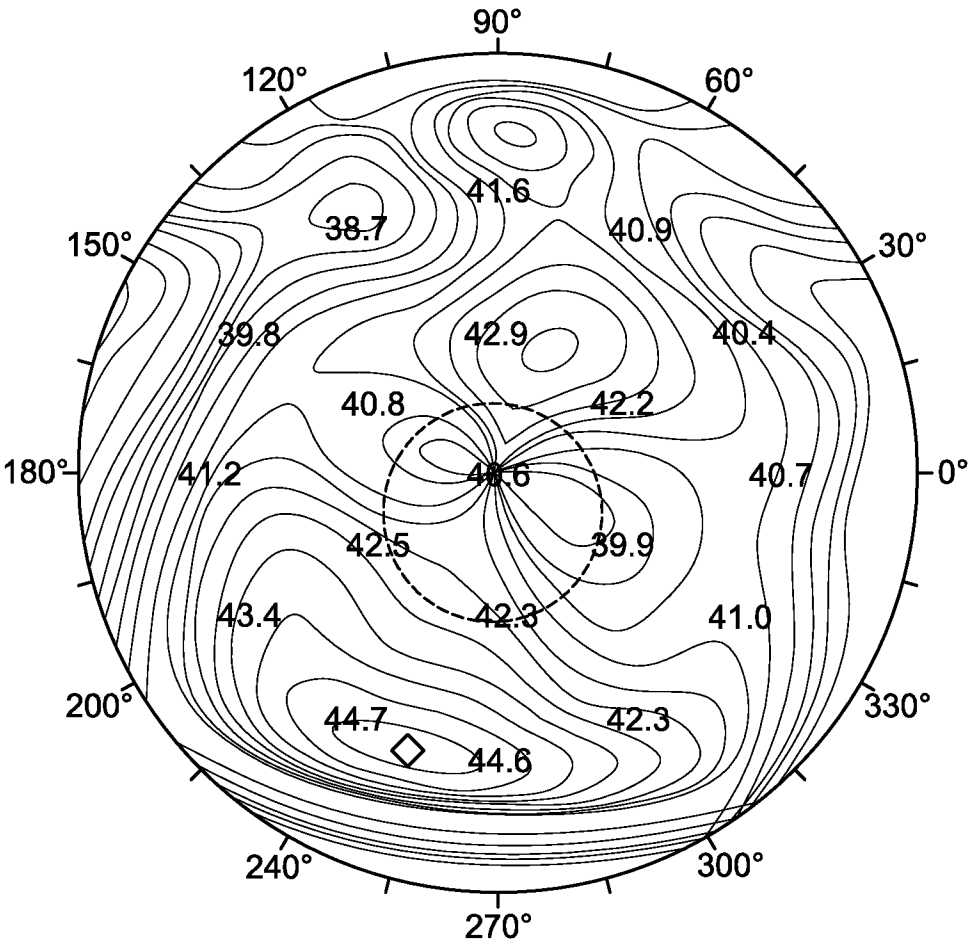
90°
120°
60°
150°
30°
180°
0°
200°
330°
240°
300°
270°
41.6
38.7
40.9
39.8
42.9
40.4
40.8
42.2
41.2
40.7
42.5
39.9
43.4
42.3
41.0
44.7
42.3
44.6

FIG. 7B

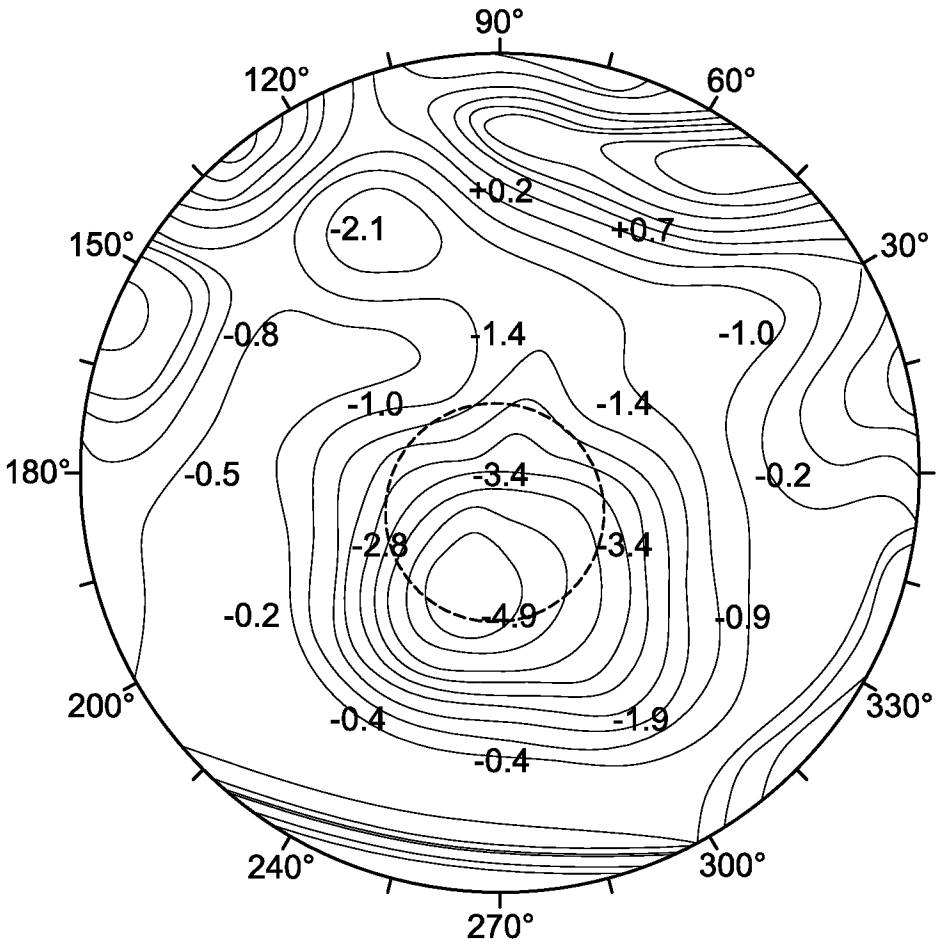
90°
120°
60°
150°
30°
180°
200°
330°
240°
300°
270°
+0.2
+0.7
-2.1
-0.8
-1.4
-1.0
-1.0
-1.4
-0.5
-3.4
-0.2
-2.8
-3.4
-0.2
-4.9
-0.9
-0.4
-1.9
-0.4

FIG. 7C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/032024

A. CLASSIFICATION OF SUBJECT MATTER

A61F 9/01(2006.01)i, A61F 9/008(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F 9/01; A61B 3/113; A61B 3/107; A61F 9/00; A61N 5/06; A61F 9/008; A61F 9/013; A61B 18/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: eye therapy, cross-linking, light.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2009-0171305 A1 (SAMI G. EL HAGE) 02 July 2009 See abstract; paragraphs 7, 8, 12, 13, 49, 53, 54, 63-70, 87, 94, 97, 98, 112, 115 and 116; and claims 1-3, 15-19.	1,3-10 2
Y A	US 2009-0149842 A1 (DAVID MULLER et al.) 11 June 2009 See abstract; paragraphs 8, 10, 32-46; claims 1-7, 14-19; and figures 1, 3A-6.	2 1,3-10
A	US 2009-0149923 A1 (SATISH V. HEREKAR) 11 June 2009 See abstract; paragraphs 10, 11, 21, 22; claim 12; and figure 1.	1-10
A	US 2009-0275929 A1 (LEANDER ZICKLER) 05 November 2009 See abstract, paragraphs 15, 16, 34, 40, 43, 50, 52, 54, 64, 68, 102, 105, 112; claims 1, 3, 6-7, 9-12, 14-17; and figures 1-11.	1-10
A	US 2010-0318017 A1 (SCOTT E. LEWIS et al.) 16 December 2010 See the whole document.	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 SEPTEMBER 2012 (21.09.2012)	**24 SEPTEMBER 2012 (24.09.2012)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer YOO Min Jeong Telephone No. 82-42-481-3463

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/032024

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-42
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 11-42 pertain to methods for treatment of the human body by surgery or therapy (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/032024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009-0171305 A1	02.07.2009	WO 2007-082127 A2	19.07.2007
		WO 2007-082127 A8	12.06.2008
US 2009-0149842 A1	11.06.2009	EP 2227197 A1	15.09.2010
		EP 2227197 A4	22.06.2011
		EP 2346457 A1	27.07.2011
		JP 2012-502668 A	02.02.2012
		JP 2012-502763 A	02.02.2012
		US 2010-0076423 A1	25.03.2010
		WO 2009-073213 A1	11.06.2009
		WO 2010-033804 A1	25.03.2010
US 2009-0149923 A1	11.06.2009	GB 2465666 A	02.06.2010
		JP 03-158398 U	10.03.2010
		KR 20-2010-0005924 U	10.06.2010
		US 2010-0057060 A1	04.03.2010
		WO 2009-073600 A1	11.06.2009
US 2009-0275929 A1	05.11.2009	WO 2009-135084 A1	05.11.2009
US 2010-0318017 A1	16.12.2010	None	