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(54) **IMAGE-GUIDED DELIVERY OF OPHTHALMIC THERAPEUTICS**

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A61F 9/00	(2006.01)
A61B 3/10	(2006.01)
G16H 10/60	(2018.01)

(52) **U.S. Cl.**

CPC ***A61F 9/0017*** (2013.01); ***A61B 3/102*** (2013.01); ***A61F 9/0026*** (2013.01); ***G16H 10/60*** (2018.01)

(58) **Field of Classification Search**

CPC A61F 9/0008–9/0026; A61F 9/00736–9/00763; A61F 9/0017; A61M 5/142–5/155; A61M 2205/33–2205/3396;

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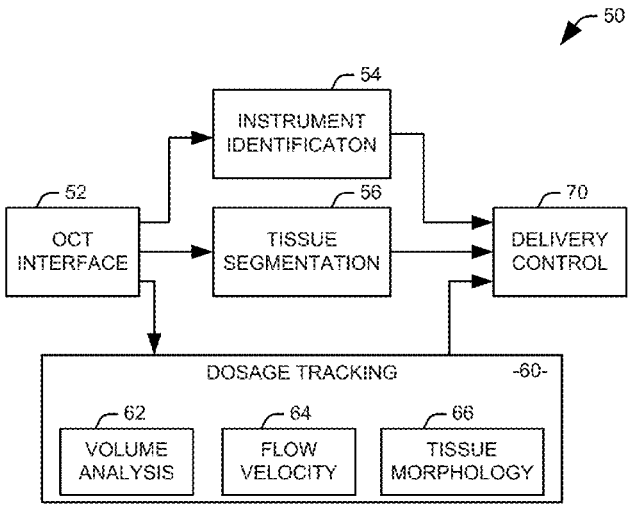
(57) **ABSTRACT**

Systems and methods are provided for image-guided delivery of therapeutics to an eye. An optical coherence tomography (OCT) imager is configured to produce at least one OCT image of the eye. A therapeutic delivery system is configured to deliver a therapeutic to the eye through a distal end of a delivery mechanism. A system control is configured to determine a position of the distal end of the delivery mechanism and control the therapeutic delivery system according to at least the determined position.

12 Claims, 3 Drawing Sheets



(58) **Field of Classification Search**
CPC A61M 5/172–2005/1726; A61B 3/102; G06F 19/322; G16H 10/60
USPC 604/521
See application file for complete search history.

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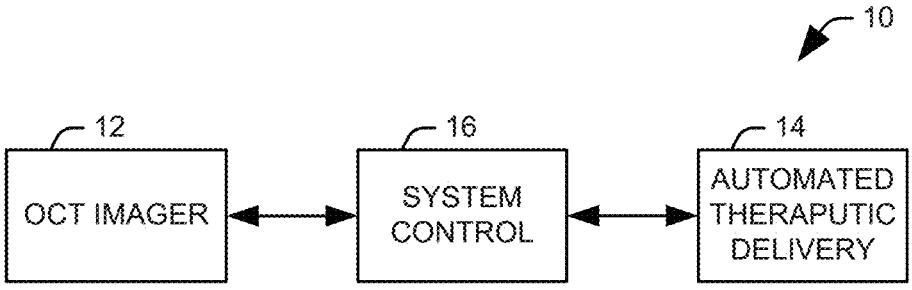

10
12
OCT IMAGER
16
SYSTEM CONTROL
14
AUTOMATED THERAPUTIC DELIVERY

FIG. 1

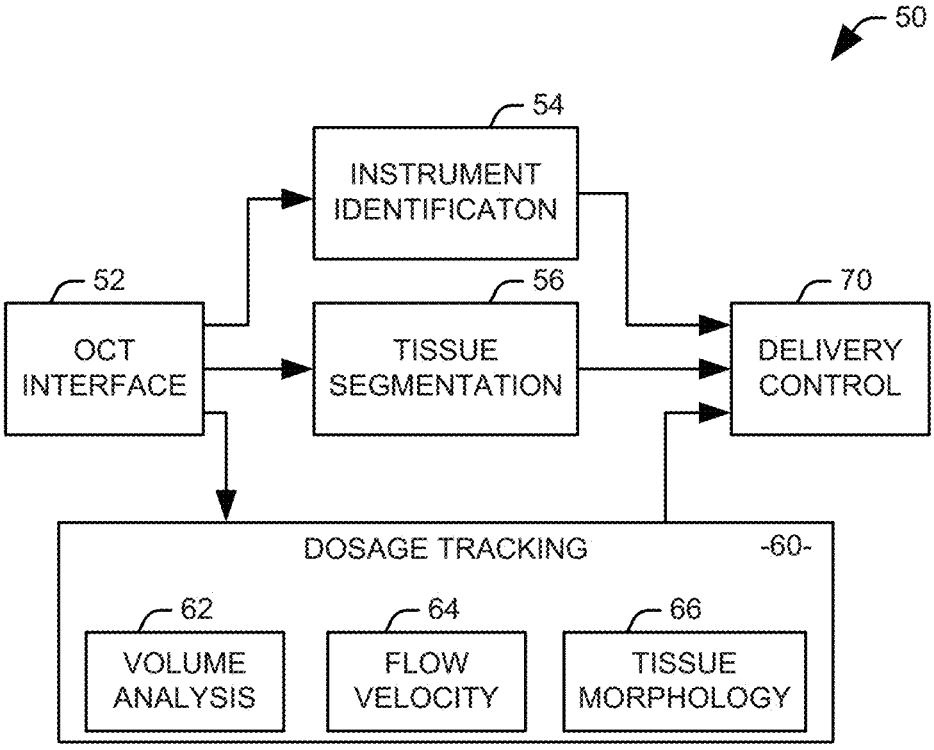

50
54
INSTRUMENT IDENTIFICATON
52
OCT INTERFACE
56
TISSUE SEGMENTATION
70
DELIVERY CONTROL
DOSAGE TRACKING
-60-
62
VOLUME ANALYSIS
64
FLOW VELOCITY
66
TISSUE MORPHOLOGY

FIG. 2

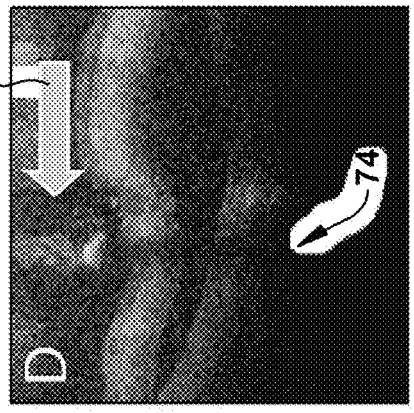
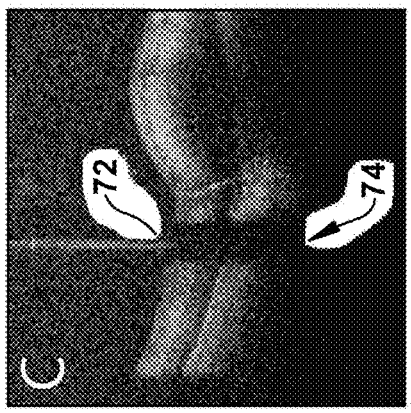


FIG. 3D



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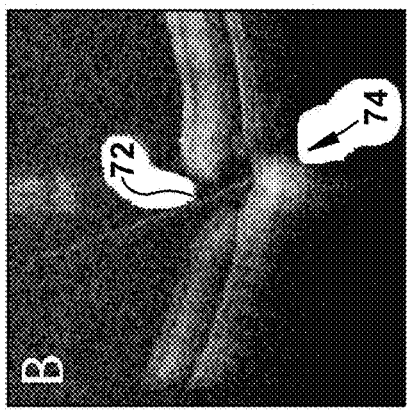

FIG. 3B

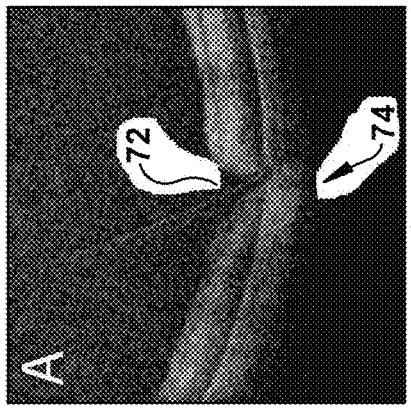

FIG. 3A

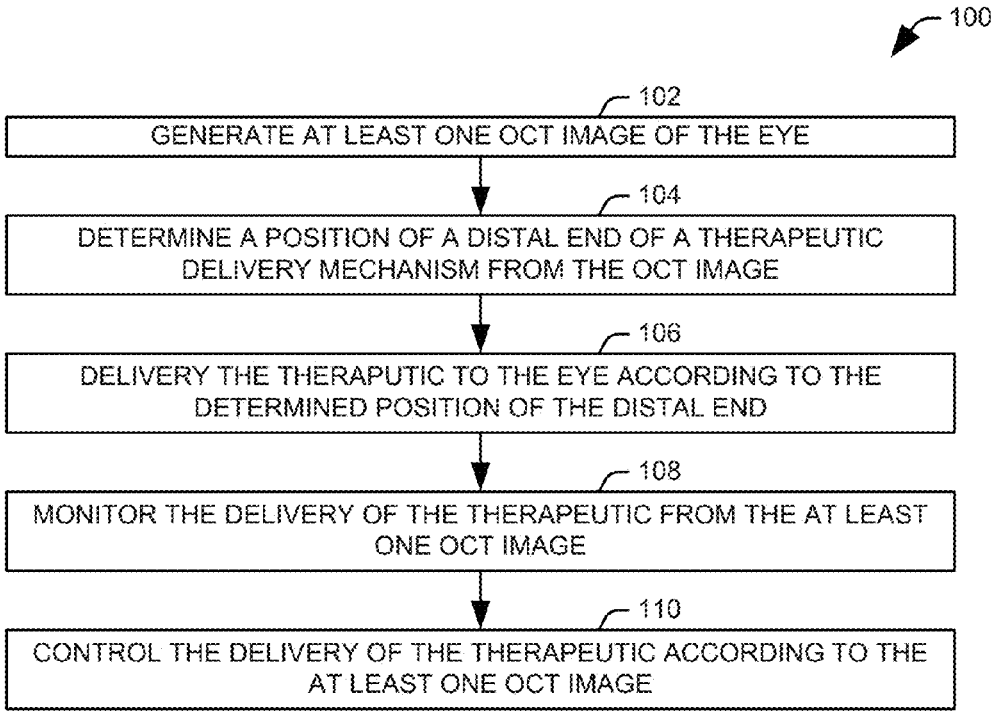
100
102
GENERATE AT LEAST ONE OCT IMAGE OF THE EYE
104
DETERMINE A POSITION OF A DISTAL END OF A THERAPEUTIC DELIVERY MECHANISM FROM THE OCT IMAGE
106
DELIVERY THE THERAPUTIC TO THE EYE ACCORDING TO THE DETERMINED POSITION OF THE DISTAL END
108
MONITOR THE DELIVERY OF THE THERAPEUTIC FROM THE AT LEAST ONE OCT IMAGE
110
CONTROL THE DELIVERY OF THE THERAPEUTIC ACCORDING TO THE AT LEAST ONE OCT IMAGE

FIG. 4

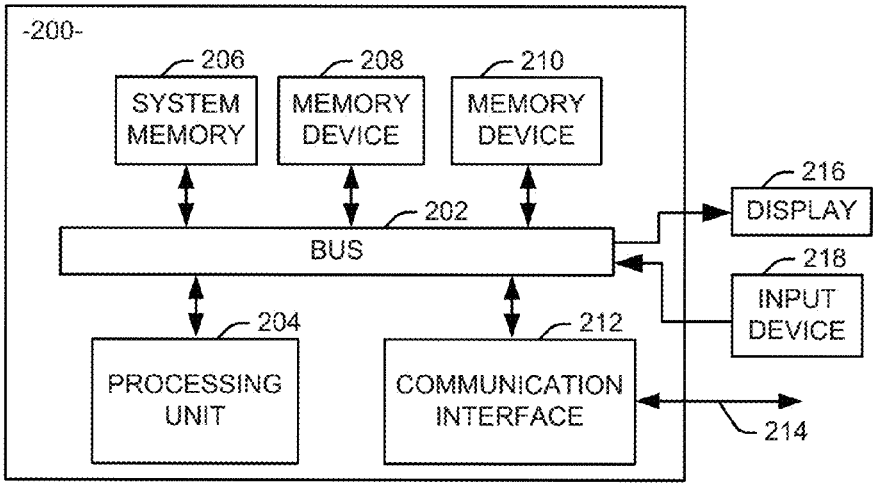
-200-
206
SYSTEM MEMORY
208
MEMORY DEVICE
210
MEMORY DEVICE
202
BUS
216
DISPLAY
218
INPUT DEVICE
204
PROCESSING UNIT
212
COMMUNICATION INTERFACE
214

FIG. 5

IMAGE-GUIDED DELIVERY OF OPHTHALMIC THERAPEUTICS

RELATED APPLICATIONS

This application claims priority from U.S. Patent Application Ser. No. 62/065,444, filed 17 Oct. 2014, which is incorporated herein in its entirety.

GOVERNMENT INTEREST

This invention was made with government support under EY022947 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

This invention relates to medical systems, and more particularly, to image-guided delivery of ophthalmic therapeutics.

BACKGROUND

Novel therapeutics in ophthalmology are currently going through a massive expansion in disease applications and mechanisms. Numerous diseases ranging from inherited retinal degenerations to acquired diseases, such as macular degeneration, are potentially amenable to many of these therapeutics, including stem cell delivery, gene therapy, small molecule pharmacotherapy, and other biologics. Many of these therapies are highly dependent on precision delivery to the area of interest.

SUMMARY OF THE INVENTION

In accordance with an aspect of the present invention, a system is provided for image-guided delivery of therapeutics to an eye. An optical coherence tomography (OCT) imager is configured to produce at least one OCT image of the eye. A therapeutic delivery system is configured to deliver a therapeutic to the eye through a distal end of a delivery mechanism. A system control is configured to determine a position of the distal end of the delivery mechanism and control the therapeutic delivery system according to at least the determined position.

In accordance with another aspect of the present invention, a method is provided for image-guided delivery of a therapeutic to an eye. At least one optical coherence tomography (OCT) image of the eye is generated. A position of a distal end of a therapeutic delivery mechanism is determined from the at least one OCT image of the eye. The therapeutic is delivered to the eye through the therapeutic delivery mechanism according to the determined position of the distal end of the therapeutic delivery mechanism. The delivery of the therapeutic is monitored from the at least one OCT image. The therapeutic delivery system is controlled according to the monitored delivery of the therapeutic.

In accordance with yet another aspect of the present invention, a system is provided for automated delivery of therapeutics to an eye. An optical coherence tomography (OCT) imager is configured to produce at least one OCT image of the eye. A therapeutic delivery system is configured to deliver a therapeutic to the eye through a distal end of a delivery mechanism. A system control is configured to monitor the delivery of the therapeutic from the at least one OCT image and control the therapeutic delivery system according to at least one of a determined flow velocity of the therapeutic, a determined delivered volume of the therapeutic, a determined leakage of the therapeutic from the delivery site, and a determined stress on tissue at the delivery site, and a determined strain on tissue at the delivery site.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** illustrates one example of system for image-guided delivery of therapeutics to an eye;

FIG. **2** illustrates one example of a system control in accordance with an aspect of the present invention;

FIGS. **3**A-**3**D illustrate an example a subretinal cannulation and injection in a porcine eye;

FIG. **4** illustrates a method for image-guided delivery of a therapeutic to an eye; and

FIG. **5** is a schematic block diagram illustrating an exemplary system of hardware components capable of implementing examples of the systems and methods

DETAILED DESCRIPTION

In accordance with an aspect of the present invention, methods and systems are provided for image-guided and targeted delivery of ophthalmic therapeutics utilizing a microscope integrated OCT system, a surgeon or clinician can target these therapeutics to the area of interest. The resolution of the OCT allows for visualization both the target area as well as the instrument delivery system. The integrated OCT system provides immediate feedback of the cross-sectional location of the delivery system. Additionally, the volumetric nature of the integrated platform system allows for accurate measurement of the volume of the delivered therapeutic agent. Using a comprehensive image-guided OCT surgeon feedback system, expansion of the surgical manipulation is possible, including vibration dampened instruments, robotic assistance or guidance based on the image-guided feedback system.

FIG. **1** illustrates one example of system **10** for image-guided delivery of therapeutics to an eye. It will be appreciated that the system **10** can be configured to assist a user in manually performing a delivery of therapeutics to the eye or to partially or completely automate the delivery of therapeutics. It will be appreciated that the delivered therapeutic can include stem cells, nucleic acid polymers, pharmaceuticals, and other biologics.

The system **10** includes an optical coherence tomography (OCT) imager **12** configured to produce at least one OCT image of the eye. The OCT scanner **12** can be include any appropriate arrangement for providing OCT images, such as time domain OCT, swept source OCT, spatially encoded frequency OCT, and Doppler OCT. The system **10** further includes a therapeutic delivery system **14** configured to deliver the therapeutic to the eye through a distal end of a delivery mechanism. In one implementation, the therapeutic delivery system **14** includes a syringe with an injection tip that can be inserted into the eye and a pump to deliver the therapeutic at the injection site. As discussed previously, the therapeutic delivery system **14**, in some implementations, will further include actuators for automatically inserting and withdrawing the injection tip into the eye.

A system control **16** is configured to determine a position of the distal end of the delivery mechanism and control the therapeutic delivery system **14** according to at least the determined position. It will be appreciated that the system control **16** can be implemented as a stand-alone unit operatively connected to each of the OCT scanner **12** and the therapeutic delivery system **14**, or as part of either of the

OCT scanner or the therapeutic delivery system **14**. The system control **14** can be implemented as dedicated hardware, software instructions executed by an associated processor, or a combination of software and dedicated hardware. In one implementation, the position of the instrument tip can be tracked, with the system control **14** instructing haptic, audible, or visual feedback provided to the user when a desired location, such as a retinal layer of interest, is reached. Feedback can also be provided to stop the therapeutic delivery when a desired volume has been delivered.

In another implementation, real-time automated tissue segmentation algorithms can be applied to intraoperative OCT cross-sectional B-scan or volumetric datasets to guide automated drug delivery. It will be appreciated that this implementation, although referred to herein as "fully automated," does not preclude supervision and correction of the delivery process by a human operator. To this end, the position of instrument tips may be identified using en face OCT shadowing, cross-sectional contrast, or instrument-tracked imaging methods to locate specific treatment positions, and specific tissue layers targeted for therapeutic delivery may be identified before or during surgery and used as real-time triggers to control the therapeutic delivery system. To this end, a subretinal tissue layer of interest is targeted and injection automatically begins as the tip of the needle arrives at the layer-of-interest on OCT B-scans. If the instrument tip moves out of the subretinal space as a result of global motion or tremor, injection automatically stops. Finally, real-time volumetric segmentation can be used to precisely quantify the injected volume and stop or withdraw therapeutics as required.

FIG. **2** illustrates one example of a system control **50** in accordance with an aspect of the present invention. In the illustrated implementation, the system control **50** is implemented as software instructions executed by an associated processor in a stand-alone general purpose computer, although it will be appreciated that other configurations are possible. It will further be appreciated that the illustrated system control **50** is intended for a fully automated implementation, although the functional modules can operate similarly for a less-automated system.

The system control **50** includes an optical coherence tomography (OCT) interface **52** configured to receive at least one OCT image of the eye from an OCT system (not shown) and format the at least one OCT image for analysis by the system control **50**. It will be appreciated that the OCT images can be provided in any form suitable for analysis, with examples including volumetric images and B-scans. Further, the OCT interface **52** can include digital filters and other components for conditioning the images for analysis as well as instructions for returning instructions to the OCT system. In one implementation, the OCT interface **52** can instruct the scanner to use specific scanning protocols to sparsely image the injection site for rapid measurements of injection volume in real-time, including variation of radial scans.

The received images are provided to each of an instrument identification component **54**, a tissue segmentation component **56**, and a dosage tracking component **60**. The instrument identification component **54** is configured to determine a position of the distal end of the delivery mechanism within the at least one OCT image. For example, the instrument identification component **54** can utilized en face iOCT shadowing, cross-sectional contrast, or any other appropriate instrument tracking method. The tissue segmentation component **56** can be configured to determine a set of boundaries for tissue layers within the eye. In one implementation, the tissue layers are sub-surface retinal sublayers. It will be appreciated that these boundaries can be used to determine an appropriate delivery depth for the therapeutic. For example, the system control **50** can to instruct the therapeutic delivery system to deliver the therapeutic when it is determined that the tracked distal end is within a desired tissue layer.

The dosage tracking component **60** is configured to monitor the delivery of the therapeutic from the at least one OCT image. The dosage tracking component **60** includes a volume analysis component **62** configured to identify the delivered therapeutic within the at least one OCT image and determine a delivered volume from the identified therapeutic. For example, the volume analysis component **62** can include an edge recognition algorithm that determines a spatial extent of the delivered therapeutic within the image and calculates a volume from the spatial extent of the therapeutic. The volume analysis component **62** can further be configured to measure leakage of the delivered therapeutic from a site of delivery, allowing for a net delivery of the therapeutic to the delivery site to be calculated.

A flow velocity component **64** is configured to determine a flow velocity of the therapeutic from the at least one OCT image and determine an injection speed for the therapeutic. For example, the flow velocity component **64** can utilize any of Doppler OCT speckle variance, phase variance, or appropriate blood flow imaging techniques to acquire flow velocity measurements in real-time on cross-sectional B-scans at the injection site to calculate a therapeutic injection speed. A tissue morphology component **66** configured to measure one of stress and strain on tissue layers of interest. Specifically, changes in the tissue morphology can be monitored intraoperatively via real-time measurements of stress-strain on tissue layers-of-interest and used as real-time biomechanical feedback on acceptable rates of drug delivery.

The outputs of the instrument identification component **54**, the tissue segmentation component **56**, and the dosage tracking component **60** can be provided to a delivery control component **70** configured to provide an interface with the therapeutic delivery system allowing for control of the delivery system according to these outputs. For example, the delivery control component **70** can be configured to stop delivery of the therapeutic when the dosage tracking component **60** indicates that a desired dosage is achieved or if a measured stress or strain exceeds a predetermined threshold value. Alternatively, the delivery control **70** can select a delivery speed of the therapeutic according to the measured one of stress and strain.

The systems of FIGS. **1** and **2** significantly advance the field of targeted delivery of gene therapy, stem cells and regenerative medicine, and other biologics in the field of ophthalmology, particularly in the treatment of retinal diseases and degenerations. No current technologies exist for quantitating and confirming delivery of these therapeutics while confirming optimal location. Using live imaging of instrument/tissue interactions during surgical maneuvers in the eye. The high lateral and axial resolution of intraoperative OCT, down to several microns, allows for precision delivery of therapeutics to specific layers of interest intraoperatively. Effectively, automated therapeutic delivery can be performed by using OCT-guided feedback, including a position or depth of injection site and a volume of therapeutic delivered, to control a programmable syringe pump or similar device.

FIGS. **3**A-**3**D illustrate an example **70** a subretinal cannulation and injection in a porcine eye. Each of FIGS. **3**A-**3**D is a cross-sectional image of a subretinal region of

the eye. FIG. **3**A shows a needle tip **72** entering the subretinal space **74**. FIG. **3**B shows an initial injection volume displacing tissue surrounding the injection site. FIG. **3**C illustrates the injection of the therapeutic into the subretinal space, with an accompanying elevation of the retina. In FIG. **3**D, excess fluid and triamcinolone **76** is observed leaking from the injection site.

In view of the foregoing structural and functional features described above in FIGS. **1-3**, an example method will be better appreciated with reference to FIG. **4**. While, for purposes of simplicity of explanation, the method of FIG. **4** is shown and described as executing serially, it is to be understood and appreciated that the present invention is not limited by the illustrated order, as some actions could in other examples occur in different orders and/or concurrently from that shown and described herein.

FIG. **4** illustrates a method **100** for image-guided delivery of a therapeutic to an eye. At **102**, at least one optical coherence tomography (OCT) image of the eye is generated. A position of a distal end of a therapeutic delivery mechanism is determined from the at least one OCT image of the eye at **104**. In one example, this is done via en face OCT shadowing, although it will be appreciated that other methods for locating the distal end can be utilized. In one implementation, a set of boundaries are determined for tissue layers within the eye, with the position of the distal end determined relative to the tissue layer boundaries.

The therapeutic is delivered to the eye through the therapeutic delivery mechanism according to the determined position of the distal end of the therapeutic delivery mechanism at **106**. For example, a syringe pump associated with the delivery mechanism can be activated when a desired delivery location is reached. For example, the therapeutic delivery system can be instructed to deliver the therapeutic when the distal end is within a desired tissue layer. Alternatively, the therapeutic delivery system can be instructed to provide one of haptic, audible, or visible feedback to the user to instruct the user to begin delivering the therapeutic.

At **108**, delivery of the therapeutic is monitored from the at least one OCT image. It will be appreciated that at least one OCT image can include a time series of images, such that the delivery can be monitored over a period of time. In one implementation, an amount of therapeutic delivered to the eye can be tracked to determine a total dosage. This tracked volume can be refined by measuring leakage of the delivered therapeutic from the delivery site, such that a net delivered dosage can be calculated. Alternatively or additionally, a flow velocity of the delivered therapeutic can be measured. This can be used to compute or confirm a volume of delivered material or simply monitored to ensure that the flow velocity does not become sufficient to damage the tissue at the delivery site. A stress or strain on the tissue at the delivery site can also be monitored to determine an appropriate delivery velocity and to ensure that the tissue is not damaged during delivery of the therapeutic.

At **110**, the therapeutic delivery system is controlled according to the at least one OCT image. Specifically, the observations from the monitoring at **108** can be applied to alter the manner in which the therapeutic is delivered to the patient. In one implementation, this can include stopping delivery of the therapeutic when a desired dosage is achieved. In another implementation, this can include adjusting a delivery speed, such as a flow velocity, according to a detected stress or strain on the tissue.

FIG. **5** is a schematic block diagram illustrating an exemplary system **200** of hardware components capable of implementing examples of the systems and methods disclosed in FIGS. **1-4**, such as the system control **16** illustrated in FIG. **1**. The system **200** can include various systems and subsystems. The system **200** can be a personal computer, a laptop computer, a workstation, a computer system, an appliance, an application-specific integrated circuit (ASIC), a server, a server blade center, a server farm, etc.

The system **200** can includes a system bus **202**, a processing unit **204**, a system memory **206**, memory devices **208** and **210**, a communication interface **212** (e.g., a network interface), a communication link **214**, a display **216** (e.g., a video screen), and an input device **218** (e.g., a keyboard and/or a mouse). The system bus **202** can be in communication with the processing unit **204** and the system memory **206**. The additional memory devices **208** and **210**, such as a hard disk drive, server, stand alone database, or other non-volatile memory, can also be in communication with the system bus **202**. The system bus **202** interconnects the processing unit **204**, the memory devices **206-210**, the communication interface **212**, the display **216**, and the input device **218**. In some examples, the system bus **202** also interconnects an additional port (not shown), such as a universal serial bus (USB) port.

The processing unit **204** can be a computing device and can include an application-specific integrated circuit (ASIC). The processing unit **204** executes a set of instructions to implement the operations of examples disclosed herein. The processing unit can include a processing core.

The additional memory devices **206**, **208** and **210** can store data, programs, instructions, database queries in text or compiled form, and any other information that can be needed to operate a computer. The memories **206**, **208** and **210** can be implemented as computer-readable media (integrated or removable) such as a memory card, disk drive, compact disk (CD), or server accessible over a network. In certain examples, the memories **206**, **208** and **210** can comprise text, images, video, and/or audio, portions of which can be available in formats comprehensible to human beings.

Additionally or alternatively, the system **200** can access an external data source or query source through the communication interface **212**, which can communicate with the system bus **202** and the communication link **214**.

In operation, the system **200** can be used to implement one or more parts of a therapeutic delivery system in accordance with the present invention. Computer executable logic for implementing the diagnostic system resides on one or more of the system memory **206**, and the memory devices **208**, **210** in accordance with certain examples. The processing unit **204** executes one or more computer executable instructions originating from the system memory **206** and the memory devices **208** and **210**. The term "computer readable medium" as used herein refers to a medium that participates in providing instructions to the processing unit **204** for execution, and can, in practice, refer to multiple, operatively connected apparatuses for storing machine executable instructions.

What have been described above are examples of the present invention. It is, of course, not possible to describe every conceivable combination of components or methodologies for purposes of describing the present invention, but one of ordinary skill in the art will recognize that many further combinations and permutations of the present invention are possible. Accordingly, the present invention is intended to embrace all such alterations, modifications, and variations that fall within the scope of the appended claims.

What is claimed is:

1. A system for image-guided delivery of therapeutics to an eye comprising:

an optical coherence tomography (OCT) imager configured to produce at least one OCT image of the eye;

a therapeutic delivery system configured to deliver a therapeutic to the eye through a distal end of a delivery mechanism; and

a system control having a processor configured to determine a position of the distal end of the delivery mechanism and control the therapeutic delivery system according to at least the determined position;

wherein the system control comprises a dosage tracking component configured to monitor the delivery of the therapeutic to a target area representing a biological area of interest from the at least one OCT image, the system control being configured to control the therapeutic delivery system according to the monitored delivery of the therapeutic.

2. The system of claim 1, the system control comprising a tissue segmentation component configured to determine a set of boundaries for tissue layers within the eye, the system control being configured to instruct the therapeutic delivery system to deliver the therapeutic when the system control determines that the distal end is within a desired tissue layer.

3. The system of claim 2, wherein the tissue segmentation component is configured to determine the set of boundaries for sub-surface retinal sublayers.

4. The system of claim 1, the dosage tracking component being configured to determine an amount of the therapeutic delivered to the eye, the system control being configured to stop delivery of the therapeutic when a desired dosage is achieved.

5. The system of claim 1, the dosage tracking component comprising a volume analysis component configured to identify the delivered therapeutic within the at least one OCT image and determine a delivered volume from the identified therapeutic.

6. The system of claim 5, the volume analysis component being further configured to measure leakage of the delivered therapeutic from a site of delivery, wherein the leakage is the amount of the delivered therapeutic that has not been injected to the target area.

7. The system of claim 1, the dosage tracking component comprising a flow velocity component configured to determine a flow velocity of the therapeutic from the at least one OCT image and determine an injection speed for the therapeutic.

8. The system of claim 1, the dosage tracking component comprising a tissue morphology component configured to measure one of stress and strain on tissue layers of interest, the system control being configured to slow delivery of the therapeutic if the measured one of stress and strain exceeds a predetermined threshold value.

9. The system of claim 1, the dosage tracking component comprising a tissue morphology component configured to measure one of stress and strain on tissue layers of interest, the system control selecting a delivery speed of the therapeutic according to the measured one of stress and strain.

10. A system for automated delivery of therapeutics to an eye comprising:

an optical coherence tomography (OCT) imager configured to produce at least one OCT image of the eye;

a therapeutic delivery system configured to deliver a therapeutic to the eye through a distal end of a delivery mechanism; and

a system control having a processor configured to monitor the delivery of the therapeutic to a target area representing a biological area of interest from the at least one OCT image and control the therapeutic delivery system according to at least one of a determined flow velocity, a determined delivered volume of the therapeutic, a determined leakage of the therapeutic from the delivery site, and a determined stress on tissue at the delivery site, and a determined strain on tissue at the delivery site.

11. The system of claim 10, the system control comprising an instrument identification component configured to determine a position of the distal end of the delivery mechanism, the system control being further configured to control the therapeutic delivery system according to at least the determined position of the distal end of the delivery mechanism.

12. The system of claim 11, the system control comprising a tissue segmentation component configured to determine a set of boundaries for tissue layers within the eye, the system control being configured to instruct the therapeutic delivery system to deliver the therapeutic when the system control determines that the distal end is within a desired tissue layer.

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