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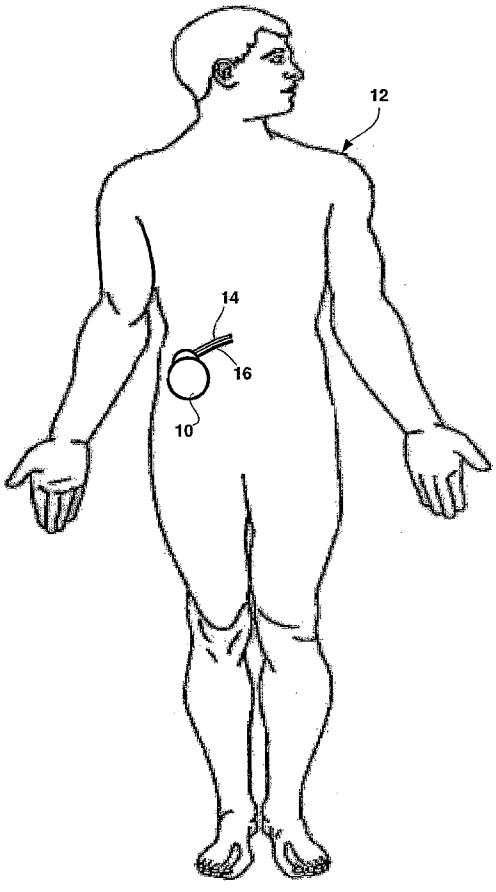

(57) Abstract: Activation of an enzyme in a bodily fluid is detected based on the amount of cleavage of a substrate for the enzyme. The substrate is tagged with two fluorescent dyes - a donor and an acceptor. The tagged substrate is presented to the bodily fluid. A device emits energy at a first wavelength into the bodily fluid, and detects energy at second and third wavelengths emitted by the dyes in response to the energy at the first wavelength. Prior to enzymatic cleavage of the substrate, the acceptor emits energy at the third wavelength in response to energy at the second wavelength received through fluorescent resonant energy transfer (FRET) from the donor. After enzymatic cleavage of the substrate, the donor emits energy at the second wavelength. The device can determine the concentration of activated enzyme within the bodily fluid based on the relative intensities of energy at the second and third wavelengths.

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OPTICAL DETECTOR FOR ENZYME ACTIVATION

The invention relates to medical devices, and more particularly, to medical devices that detect enzymes within bodily fluid.

In general, the activities of various enzymes within bodily fluids, such as the blood or lymph, are of clinical interest. Some enzymes exist in bodily fluids as an inactive precursor until an event or condition triggers their activation. For example, the enzymes kallikrein and thrombin are present in blood as their respective inactive precursors, prekallikrein and prothrombin, until activated. The activation of enzymes, such as kallikrein and thrombin, can indicate clinically significant underlying events or conditions.

Kallikrein is involved in the processes of signaling painful events or stimuli to the nervous system via the extrinsic pain pathway. When an agent, such as heat, force, or radiation, causes a cell to rupture, that cell releases its internal components into the surrounding environment. Among these cell components are proteins that activate kallikrein, i.e., convert inactive prekallikrein to kallikrein. Kallikrein in turn activates a protein called bradykinin, which acts on free nerve endings to signal pain in the area. Bradykinin can also induce pain by causing tissue to swell, e.g. by causing edema.

Thrombin is involved in the process of blood coagulation. Specifically, thrombin converts fibrinogen into fibrin, which in turn forms thrombi. Prothrombin is converted to thrombin as part of an intricate cascade of enzymatic activities. Generally speaking, patients with conditions that lead to pooling of the blood within vessels, such as atrial fibrillation, or patients with implanted foreign matter exposed to blood flow, such as artificial heart valves, are at increased risk of developing potentially life-threatening thrombi. Such patients often receive anticoagulants to reduce the likelihood of thrombus formation.

In general, the invention is directed to techniques for optically detecting activation of an enzyme within a bodily fluid. The bodily fluid can be blood, and the detected enzyme can be, for example, kallikrein or thrombin. Activation of the enzyme can indicate a medically significant event or condition. In some embodiments, detecting

activation of the enzyme within the bodily fluid according to the invention enables clinical diagnosis, chronic monitoring, and/or closed-loop therapy delivery.

Activation of the enzyme in a bodily fluid is detected based on the amount of cleavage of a substrate for the enzyme. The substrate is tagged with two fluorescent dyes, such that each of two products that will result from cleavage of the substrate by the enzyme is tagged with one of the dyes. The absorption spectrum of one of the dyes, the acceptor, overlaps the emission spectrum of the other dye, the donor.

The tagged substrate is presented to the bodily fluid. A device emits energy at a first wavelength into the bodily fluid, and detects energy, emitted by the dyes in response to the energy emitted by the device at the first wavelength, at a second and a third wavelength. The donor absorbs energy emitted by the device at the first wavelength. Prior to enzymatic cleavage of the substrate, the acceptor receives energy at the second wavelength from the donor through fluorescent resonant energy transfer (FRET), and emits energy at the third wavelength. After enzymatic cleavage, FRET does not occur and the donor emits energy at the second wavelength in response to absorbing energy at the first wavelength.

The same device that emits energy at a first wavelength can also present the tagged substrate to the bodily fluid from a reservoir using a pump and a catheter. The device can emit and detect energy via an optical fiber with a distal end located in the bodily fluid. In some embodiments, the substrate is presented to the bodily fluid on a substrate tape, or is linked to the optical fiber.

The rate of cleavage of the substrate is determined based on the relative intensities of energy at the second and third wavelengths over time. In some embodiments, the device determines a ratio between the intensities of energy at the second and third wavelengths, and determines the amount of activated enzyme within the bodily fluid based on the value of the determined ratio over time. Information describing relationships between amount of activated enzyme and ratios can be stored within a memory as one or more look-up tables, equations, curves, or the like. The amount of activated enzyme can, for example, be expressed as a concentration of activated enzyme, e.g., units per milliliter of bodily fluid. Information describing relationships between concentration of activated enzyme and ratios over time can be determined experimentally.

In some embodiments, the device stores determined amounts of activated enzyme in the memory for later retrieval by a clinician. In some embodiments, the device stores one or more thresholds in the memory and activates an alarm if the amount of activated enzyme or a rate of change of the amount of activated enzyme exceeds or falls below the threshold. Therapy, such as anticoagulant or pain relieving drug therapy, or neurostimulation, may be delivered based on determined amounts of activated enzyme.

In one embodiment, the invention is directed to a method in which energy is emitted at a first wavelength into a bodily fluid. A tagged substrate within the bodily fluid emits energy at a second wavelength and a third wavelength in response to the energy at the first wavelength, and the energy emitted by the tagged substrate is detected. Activation of an enzyme that cleaves the substrate within the bodily fluid is detected based on the detected energy. A ratio between a first detected intensity of energy at the second wavelength and a second detected intensity of energy at the third wavelength may be determined, and the concentration of activated enzyme within the bodily fluid may be determined based on the ratio.

In another embodiment, the invention is directed to a device that includes an emitting element to emit energy at a first wavelength into a bodily fluid, and a detector to detect energy emitted at a second wavelength and a third wavelength by products of a tagged substrate in the bodily fluid in response to the energy at the first wavelength. The device further includes a processor to control the emitting element to emit energy at the first wavelength, receive indications of intensities of energy detected by the detector, and detect activation of an enzyme that cleaves the substrate within the bodily fluid based on the indicated energy intensities. The device may also include an optical fiber optically coupled to the emitting element and the detector. A distal end of the optical fiber may be located in the bodily fluid. The emitting element may emit energy into the bodily fluid via the optical fiber, and the detector may detect energy emitted by products of the tagged substrate in the fluid via the optical fiber.

In another embodiment, the invention is directed to a system that includes a first medical device to optically detect activation level of an enzyme within a bodily fluid of a patient, and a second medical device to deliver a therapy to the patient based on the detection of enzyme activation. The second medical device may be, for example, a drug pump that delivers drugs to the patient based on the concentration of activated enzyme

within the bodily fluid, or a neurostimulation device that delivers neurostimulation therapy to the patient based on the concentration of activated enzyme within the bodily fluid.

In another embodiment, the invention is directed to an optical fiber that includes a core and a cladding. The cladding is partially removed from a section of the fiber to expose a section of the core, and a substrate for an enzyme within a bodily fluid is linked to the exposed section of the core.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic diagram illustrating an example implantable medical device for optically detecting enzyme activation.

FIG. 2 is a conceptual diagram illustrating use of fluorescent resonant energy transfer to detect enzyme activation according to the invention.

FIG. 3 is a schematic diagram illustrating an example operation of the implantable medical device of FIG. 1 to detect enzyme activation.

FIG. 4 is a block diagram illustrating an example configuration of an implantable medical device for optically detecting enzyme activation.

FIG. 5 is a timing diagram illustrating example ratio curves used to determine an amount of activated enzyme.

FIG. 6 is a flowchart illustrating an example method for detecting enzyme activation.

FIG. 7 is a perspective diagram illustrating an example optical fiber that includes a substrate for use in optically detecting enzyme activation.

FIG. 8 is a perspective diagram illustrating an example optical fiber and a substrate tape for use in optically detecting enzyme activation.

FIG. 9 is a block diagram illustrating an example system for optically determining an amount of activated enzyme and delivering therapy to a patient based on the determined amount of activated enzyme.

FIG. 1 is a perspective diagram illustrating an example implantable medical device (IMD) 10 implanted within a patient 12. IMD 10 optically detects enzyme activation within a bodily fluid of patient 12. The bodily fluid can be blood within a blood vessel (not shown) of patient 12. Further, IMD 10 can, in some embodiments, detect activation of protease enzymes, such as kallikrein or thrombin, within blood.

IMD 10 is coupled to a catheter 14 and an optical fiber 16. The distal ends of catheter 16 and optical fiber 18 extend into the bodily fluid to enable IMD 12 to detect activation of the enzyme within the bodily fluid. For example, the distal ends of catheter 14 and optical fiber 16 can extend into a blood vessel so that IMD 10 can detect activation of kallikrein or thrombin within the blood of patient 12.

In general, when the target enzyme is activated within the bodily fluid, it acts to cleave a specific protein within the bodily fluid. For example, kallikrein cleaves kininogen to release bradykinin, and thrombin cleaves fibrinogen to release fibrin. According to the Michaelis-Menten model, the amount of cleaved protein depends on the concentration of activated enzyme, the turnover rate of the enzyme, and the amount of accessible protein.

IMD 10 uses a substrate to detect activation of the target enzyme. In addition to cleaving the protein, the target enzyme cleaves the substrate. IMD 10 determines the level of enzyme activation based on the extent of substrate cleavage. The substrate is presented to the bodily fluid via catheter 14.

The enzyme cleaves the protein and the substrate by breaking selected bonds within the molecular structures of the protein and the substrate. Specifically, both kallikrein and thrombin are serine-proteases and selectively target the peptide bonds between arginine and lysine or arginine and glysine. Thus, a suitable substrate for kallikrein or thrombin includes a peptide bond that can be broken by the target enzyme to cleave the substrate.

Examples of suitable substrates for kallikrein and thrombin are listed in Tables 1 and 2, respectively. However, the invention is not limited to detection of enzyme activation using these exemplary substrates. Nor is the invention limited to detection of the activation of kallikrein or thrombin. Suitable substrates for detection of the activation of any particular enzyme can be identified based on the bond selectivity of that particular enzyme.

H—D Pro—HHT—Arg—pNA
H—D—Pro—Phe—Arg—pNA
H—D—But—CHA—Arg—pNA.2AcOH
Pro—Phe—Arg—MCA
H—D—Val—Leu—Arg—AFC, 2HCL

Table 1: Kallikrein Substrates

Protein C
Secretin
Lysozyme
Growth Hormone
Actin
d—FPRX (where x=paranitroanilide)
d—FPKX (where x=paranitroanilide)
d—FGRX (where x=paranitroanilide)
d—VGKX (where x=paranitroanilide)

Table 2: Thrombin Substrates

IMD 10 detects the amount of substrate cleavage, and thus enzyme activation, optically. IMD 10 emits energy into the bodily fluid via optical fiber 16 when the substrate is presented to the bodily fluid. The substrate is tagged with fluorescent dyes. IMD 10 detects energy that is emitted by the fluorescent dyes in response to absorbing the energy emitted by IMD 10 via optical fiber 16. As will be described in greater detail below, IMD 10 detects the amount of substrate cleavage based on the level of fluorescent resonant energy transfer (FRET) between the dyes. The energy emitted and detected by IMD 10 may be visible light.

The distal ends of catheter 14 and optical fiber 16 can, as shown in FIG. 1, be located substantially proximate to each other within the bodily fluid. In some embodiments, catheter 14 and optical fiber 16 are contained within a common sheath (not shown) that facilitates and maintains their placement proximate to each other. However, catheter 14 and optical fiber 16 need not be collocated. For example, IMD 10 can present the tagged substrate to a blood flow via catheter 14 at a point that is "upstream" from the location of optical fiber 16. Moreover, in some embodiments IMD 10 is not coupled to a catheter 14. In such embodiments, the tagged substrate can be presented to the bodily

fluid via manual injection using a hypodermic syringe and needle, via an external drug pump delivering an intravenous bolus, via a substrate tape, or linked to optical fiber 16.

FIG. 2 is a conceptual diagram illustrating use of FRET to detect enzyme activation according to the invention. An exemplary substrate molecule 20 includes a first product 22 and a second product 24. The first product 22 of substrate molecule 20 is tagged with a first fluorescent dye, which is a donor dye 26. The second product 24 of substrate molecule 20 is tagged with a second fluorescent dye, which is an acceptor dye 28.

An absorption spectrum 30 and emission spectrum 32 for donor dye 26 are illustrated in FIG. 2. An absorption spectrum 34 and emission spectrum 36 for acceptor dye 28 are also illustrated. As illustrated, donor dye 26 emits energy at a wavelength λ_1 in response to the absorption of energy at a wavelength λ_0. Acceptor dye 28 emits energy at a wavelength λ_2 in response to the absorption of energy at a wavelength λ_1. Thus, the absorption spectrum of acceptor dye 28 overlaps the emission spectrum of donor dye 26.

When donor dye 26 and acceptor dye 28 are sufficiently proximate, e.g., between approximately 10 and 100 Angstroms, and their dipole orientations are approximately parallel, acceptor 28 will resonantly receive energy at wavelength λ_1 from donor 26 via FRET. Acceptor 28 will emit energy at wavelength λ_2 in response to absorbing the energy at wavelength λ_1. As illustrated in FIG. 2, donor 26 and acceptor 28 are sufficiently proximate and properly oriented prior to enzymatic cleavage of substrate molecule 20, and acceptor 28 emits energy at wavelength λ_2 in response to donor absorbing energy at wavelength λ_0. When substrate molecule 20 is enzymatically cleaved, donor 26 and acceptor 28 are no longer sufficiently proximate or properly oriented, and donor 26 emits energy at wavelength λ_1 in response to absorbing energy at wavelength λ_0.

FIG. 3 is a perspective diagram illustrating an example operation of IMD 10 to detect enzyme activation. The distal ends of catheter 14 and optical fiber 16 are deployed within a blood vessel 40. The blood within blood vessel 40 includes enzyme 42. Enzyme 42 includes activated enzyme molecules and inactive precursor molecules for the enzyme. For example, enzyme 42 can include prekallikrein and kallikrein molecules, or prothrombin and thrombin molecules. For ease of illustration, only a single enzyme molecule 42 is labeled.

IMD 10 presents substrate 20, which includes a product tagged with donor dye 26 and a product tagged with acceptor dye 28, to the blood flow within vessel 40 via catheter

14. As shown in FIG. 3, activated enzyme molecules 42 cleave substrate 20 such that the products tagged with dyes 26 and 28 are separated. For ease of illustration, only a single substrate molecule 20 and a single instance of products tagged with donor and acceptor dye 26 and 28 are labeled.

IMD 10 emits energy at wavelength λ_0 into the blood stream of vessel 40 via optical fiber 16. Donor dye 26 absorbs energy at wavelength λ_0. When substrate molecules 20 are intact in the blood stream, acceptor dye 28 will, through FRET, emit energy at wavelength λ_2 in response to the donor 26 absorbing energy at wavelength λ_0, as described above. When activated enzyme molecules 42 cleave substrate molecules 20, dyes 26 and 28 are physically separated preventing FRET from occurring. When substrate molecules 20 are cleaved, donor 26 emits energy at wavelength λ_1 in response to absorbing the energy emitted by IMD 10 at wavelength λ_0.

IMD 10 detects energy emitted by donor 26 at wavelength λ_1 and energy emitted by acceptor 28 at wavelength λ_2 via optical fiber 16. The intensities of energy detected at wavelengths λ_1 and λ_2 are related to the amount of cleaved and uncleaved substrate 20 within vessel 40. The amount of cleaved and uncleaved substrate 20 within vessel 40 depends on the amount of activated enzyme 42 within the blood.

IMD 10 detects activation of enzyme 42 based on the ratio between the intensities of energy detected at wavelengths λ_1 and λ_2. By detecting activation of enzyme 42 based on a ratio, IMD 10 is less susceptible to errors caused by signal degradation, e.g., fibrous tissue growth on optical fiber 16. In some embodiments, IMD 10 can monitor the overall intensity of the detected energy and compensate for reduced signal intensity by increasing the intensity of the emitted energy.

Suitable donor 26/acceptor 28 pairs for use with the exemplary substrates listed in Tables 1 and 2 include AMCA/FITC and FITC/TRITC. The invention is not, however, limited to these dye pairs. Suitable dye pairs include any dye pair that has an acceptor whose absorption spectrum overlaps the emission spectrum of the donor. Suitability of a dye pair may also depend on its ability to bond to the products of a selected substrate.

FIG. 4 is a block diagram illustrating an example configuration of IMD 10. In the example configuration of IMD 10 illustrated in FIG. 4, IMD 10 includes a reservoir 50 and a pump 52 in fluid communication with reservoir 50 and catheter 14. Reservoir 50 contains tagged substrate 20. A processor 54 controls pump 52 to present substrate 20 to

bodily fluid via catheter 14. With respect to the presentation substrate 20, IMD 10 can correspond substantially to an implantable drug pump, such as Synchromed™ drug pumps sold by Medtronic Corporation. Reservoir 50 can be refillable, e.g., via a syringe, to enable chronic implantation and enzyme activation detection.

IMD 10 also includes an emitter 56 and detectors 58 and 60 that are optically coupled to optical fiber 16. Processor 54 controls emitter 56 to emit energy at wavelength λ_0 in conjunction with the presentation of substrate 20 by pump 52. Detector 58 detects energy emitted by substrate 20 in the bodily fluid at wavelength λ_1, and detector 60 detects energy emitted by substrate 20 in the bodily fluid at wavelength λ_2. Processor 54 receives an indication of the intensities of the energy at wavelengths λ_1 and λ_2 from detectors 58 and 60.

Detectors 58 and 60 can take the form of electro-optical transducers. In some embodiments, a single detector detects energy at wavelengths λ_1 and λ_2. In such embodiments, the detector can include analog or digital signal processing components in addition to an electro-optical transducer to determine the intensities at wavelengths λ_1 and λ_2 and indicate the intensities to processor 54.

An optical coupler 62 couples emitter 56 and detectors 58 and 60 the fiber 16. A filter 64 filters energy emitted by emitter 56 to assure that energy at wavelength λ_0 is delivered to the bodily fluid. Filters 66 and 68 filter energy received from substrate 20 in the bodily fluid to assure that detectors 58 and 60 receive energy at wavelengths λ_1 and λ_2, respectively. In some embodiments, filters 64-68 take the form of dichroic band-pass filters.

Energy delivered to detectors 58 and 60 can be amplified. One or more amplifiers (not shown), such chopper stabilized amplifiers, can be used to amplify the energy to improve the signal to noise ratio for the energy delivered to detectors 58 and 60.

Processor 54 detects activation of an enzyme, and can, in some embodiments, determines the amount of activated enzyme within a bodily fluid based on the indicated intensities at wavelengths λ_1 and λ_2. Specifically, processor 54 can calculate a ratio between the intensities at wavelengths λ_1 and λ_2, and determine the amount of activated enzyme based on the ratio. The amount of activated enzyme can be expressed as a concentration of the activated form of the enzyme within the bodily fluid, e.g., units per milliliter of bodily fluid.

Processor 54 can store the determined ratio in a memory 70. Memory 70 also stores information used by processor 54 to determine an amount of activated enzyme based on the ratio. For example, in some embodiments, memory 70 includes a look-up table or equation that describes a relationship between the ratio and enzyme concentration.

The determined amount of activated enzyme, e.g., concentration of activated enzyme, can be stored in memory 70 for later retrieval by a clinician. In exemplary embodiments, the clinician retrieves one or more concentrations from memory 70 using a programmer via a telemetry circuit 72, as is known in the art. Where the target enzyme is kallikrein, the clinician can use the concentrations to more accurately identify the intensity and frequency of pain, for example, and, depending on the position of optical fiber 16, the location of pain. This information may allow the clinician to more accurately diagnose the underlying cause of the pain, and prescribe more effective pain therapies for patient 12. Where the target enzyme is thrombin, the clinician can use the enzyme concentrations collected over time to, for example, better determine a dosage for anticoagulant therapy for patient 12. Telemetry can also be used to communicate information relating to the status or performance of IMD 10, such as battery and reservoir status, to clinician.

Memory 70 can store threshold values, and processor 54 can activate an alarm 74 when the ratio, concentration, rate of change of the ratio over time, or rate of change of concentration over time, exceeds or falls below a threshold value. Alarm 74 is detectable by patient 12, e.g., audibly or through vibration. Alarm 74 can be used to cause patient 12 to seek immediate medical attention when enzyme activation concentration of activated enzyme indicates an emergency medical condition, such as a thrombin concentration that indicates a dangerously high probability of thrombi formation. Increased thrombin activation can in some cases indicate a coagulation cascade preceding a heart attack.

Memory 70 can also store program instructions that control processor 54 to perform the functions ascribed to it herein. Memory 70 may include a variety of magnetic, optical, or electronic media, such as random access memory (RAM), read-only memory (ROM), electronic erasable programmable read-only memory (EEPROM), flash memory, or the like. Processor 54 may include one or more microprocessors, digital signal processors (DSPs), application specific integrated circuits (ASICs), field-programmable gate arrays (FPGAs), or the like.

In some embodiments, processor 54 controls delivery of therapy to patient 12 based on determined amounts of activated enzyme. In some embodiments, IMD 10 includes an additional reservoir, pump and catheter for the delivery of one or more drugs to patient 12. Processor 54 can control the additional pump to initiate delivery of a drug or change the dosage for a drug based on the determined amount of activated enzyme. For example, delivery of a pain relieving drug may be initiated upon determination of increased kallikrein activation, or the dosage of an anticoagulant, such as heparin, may be altered based on a determination of increased thrombin activation. In other embodiments, IMD 10 is part of system that includes a therapy delivery device that is either controlled by processor 54 or acts in response to activated enzyme amounts received from processor 54, as will be described in greater detail below. In this manner, IMD 10 can enable closed-loop delivery of therapy to patient 12.

FIG. 5 is a timing diagram illustrating example ratio curves 80-86 used to determine activated enzyme amount. Each of ratio curves 80-86 is associated with an amount of activated enzyme, e.g., a concentration of activated enzyme. Ratio curves 80-86 are generated by measuring λ_1/λ_2 ratios over a period of time, e.g., one to ten minutes, after introduction of a known concentration of activated enzyme with a tagged substrate. In some embodiments, memory 70 stores information representing curves 80-86, and processor 54 uses the information to determine the current activation level based on one or more λ_1/λ_2 ratios calculated at known times subsequent to presentation of substrate 20 to the bodily fluid. The information describing curves 80-86 may be stored as one or more look-up tables or equations.

FIG. 6 is a flowchart illustrating an example method that may be employed by IMD 10 to detect enzyme activation. Tagged substrate 20 is presented to the bodily fluid (90). In some embodiments, processor 54 controls pump 52 to present substrate 20 via catheter 14, as described above. IMD 10 then emits energy at wavelength λ_0 by, for example, processor 54 controlling emitter 56 to emit energy at wavelength λ_0 (92).

IMD 10 detects energy at wavelengths λ_1 and λ_2, which is emitted by donor and acceptor dyes 26 and 28 tagged to substrate 20 in response to absorption of the energy emitted by IMD 10 at wavelength λ_0 (94). For example, in some embodiments, processor 54 receives indications of the intensities of energy at wavelengths λ_1 and λ_2 from detectors 58 and 60, as described above. Processor 54 compares the intensities of energy at

wavelengths λ_1 and λ_2 (96), e.g., by calculating a λ_1/λ_2 ratio, and determines an amount of activated enzyme, e.g. concentration of activated enzyme, as a function of the comparison (98).

The frequency with which the method is performed can depend on the application. For example, the method can be performed one or more times during a clinic visit as a diagnostic test under the control of a clinician using a programmer. In some embodiments, the method may be performed periodically as indicated by the condition or enzyme being monitored. For example, the method may be performed one or more times per day or week, or may be performed hourly. The invention is not limited to any particular frequency of enzyme activation detection.

FIG. 7 is a perspective diagram illustrating an example optical fiber 100 that can be coupled to IMD 10 according to some embodiments of the invention. As shown in FIG. 7, optical fiber 100 includes substrate 20 linked thereto. Optical fiber 100 is used to present substrate 20 to a bodily fluid. Optical fiber 100 can, for example, be used with embodiments of IMD 10 that do not include a pump 52 and reservoir 50 for presenting substrate 20 to the bodily fluid.

Substrate 20 is linked to a region 102 of optical fiber 100 where a cladding 104 of fiber 100 is partially removed to expose a core 105 of optical fiber 100. In general, cladding 104 reflects and refracts energy to direct the energy to travel within core 105 to the distal end of fiber 100. At region 102 where cladding 104 is partially removed, energy may exit and enter core 105 of fiber 100. In other words, IMD 10 may emit energy at wavelength λ_0 into a bodily fluid via region 102 such that the donor 26 presented to the bodily fluid may absorb the energy. When substrate 20 is uncleaved, as illustrated in FIG. 7, the acceptor 28 emits energy at wavelength λ_2 through FRET, as described above. The energy at wavelength λ_2 emitted by the acceptor 28 enters fiber 100 via region 102 for detection by IMD 10.

Donor tagged product 22 and acceptor tagged product 24 of substrate 20 are linked to core 105 at region 102 by cross-linkers 106A and 106B, respectively (collectively "cross-linkers 106"). Cross-linkers 106 can take the form of heterobifunctional cross-linkers, such as SPDP (N-Succinimidyl-3-(2-pyridyldithio)propionate). Region 102 of fiber 100 is treated with aminosilanes, such as 3-aminopropyltriethoxysilane, or proteins

with modified amine groups that yield sulfhydryl-reactive intermediates to promote binding of cross-linkers 106 to region 102.

Substrate 20 is exposed to the bodily fluid, which contains an enzyme. When the enzyme cleaves substrate 20, donor tagged product 22 and acceptor tagged product 24 are separated such that FRET no longer occurs between dyes 26 and 28. The separation between donor tagged product 22 and acceptor tagged product 24 can be due in part to a springing action of cross-linkers 106. When substrate 20 is cleaved, the donor 26 will emit energy at wavelength λ_1 in response to energy emitted by IMD 10 at wavelength λ_0 via region 102, as described above.

In some embodiments, fiber 100 can be used a single time and thereafter discarded. Thus fiber 100 is particularly suitable for use with external devices capable of practicing the invention as described herein. Fiber 100 may be used percutaneously or in an in vitro sample of bodily fluid. Although it is understood that multiple substrate molecules 20 are linked to the exposed region 102, a single substrate molecule 20 is shown for ease of illustration. Further, region 102 need not be located at the distal end of fiber 100 as illustrated in FIG. 7.

FIG. 8 is a perspective diagram illustrating an example optical fiber 110 and a substrate tape 112 for use in optically detecting enzyme activation according to some embodiments of the invention. As shown in FIG. 8, fiber 110 may include a region 114 of optical fiber 110 where a cladding 116 of fiber 100 is partially removed to expose a core 117 of fiber 110. As described above with reference to FIG. 7, an implantable medical device 118 may emit energy and detect energy emitted by dyes 26 and 28 via region 114.

Substrate 20 is linked to tape 112 via cross-linkers 106. Tape 112 travels between reels 120A and 120B. Tape 112 can travel on a path that is substantially parallel and proximate to optical fiber 110, such the substrate 20 and dyes 26 and 28 are proximate to region 114. Reel 120B can be attached to fiber 110 by a support member 122 that allow reel 120B rotational freedom in a single direction. Reel 120A is coupled to a reel rotation mechanism 124 that rotates reel 120 to move tape 112 along the indicated path between reels 120A and 120B.

A processor (not shown) of IMD 118 can control reel rotation mechanism 124 to move tape 112 in order to present new substrate 20 for each new determination of enzyme activation. Tape 112 is spooled on reel 120B, and substrate molecules 20 are insulated

from the bodily fluid while spooled on reel 120B. Substrate molecules 20 become exposed to the bodily fluid as the tape is drawn from reel 120B by the action of reel rotation mechanism 124.

IMD 118 can include components, such as a processor, emitter and detectors similar to IMD 10, as described above with reference to FIG. 4. However, for ease of illustration, only reel rotation mechanism 124 and reel 120A are shown in FIG. 8. Although it is understood that multiple substrate molecules 20 are linked to tape, a single substrate molecule 20 is shown for ease of illustration. Further, region 114 and reel 120B need not be located at the distal end of fiber 110 as illustrated in FIG. 8.

FIG. 9 is a block diagram illustrating an example system 130 for optically detecting enzyme activation and delivering therapy to patient 12 based on the determined level of enzyme activation. System 130 includes IMD 10 coupled to catheter 14 and optical fiber 16. IMD 10 optically determines an amount of activated enzyme as described above.

System 130 also includes a therapy delivery device 132 for delivering therapy to patient 12 based on amounts of activated enzyme as determined by IMD 10. Therapy delivery device 132 can be an implantable or external device. Therapy delivery device 132 can be, for example, an implantable drug pump that delivers a drug as a function of determined enzyme activation levels, such as a Synchromed™ drug pump. In other embodiments, therapy delivery device 132 takes the form of an implantable neurostimulation device, such as an implanted pulse generator. In such embodiments, therapy delivery device 132 delivers neurostimulation to patient 12 via one or more electrodes 136 included on a lead 134.

Drug or neurostimulation therapy can be provided to treat pain. When operated in concert with IMD 10, therapy delivery device 132 can treat pain in a closed-loop fashion, with adjustments to pain therapy based on an objective assessment of pain. In other embodiments, anticoagulation therapy is provided via a drug pump embodiment of therapy delivery device 132. In general, anticoagulant dosage is adjusted only after the coagulation status of the patient is measured, which occurs during infrequent clinic visits. Infrequently made measurements may miss changes to the condition of the patient that would require a change in the anticoagulant dosage. Too much anticoagulant can cause problematic bleeding, while too little can leave patient subject to formation of thrombi.

System 130 may enable a more accurate, closed-loop determination of proper coagulation dose.

Processor 54 of IMD 10 can control therapy delivery device 132 to deliver therapy based on determined enzyme activation levels, or in other embodiments can simply communicate determined activated enzyme amounts to therapy delivery device 132 which in turn adjusts the therapy based on the communicated amounts. Processor 54 can control or communicate with device 132 via wired or RF telemetry communications. In some embodiments, IMD 10 and device 132 are a single device sharing one or more processors, or a single device with processors dedicated to either the enzyme activation detection functions or therapy delivery functions described herein.

Various embodiments of the invention have been described. For example, implantable medical devices for optically detecting enzyme activation have been described. However, one skilled in the art will recognize that the invention is not limited to the described embodiments, and that various modifications can be made to the described embodiments without departing from the scope of the invention. For example, although the invention has been primarily described herein as detecting the activation of the enzymes kallikrein and thrombin, the invention may be used to detect the activation of any enzyme within bodily fluid.

Further, although the invention has been described with reference to an implantable medical device, non-implanted embodiments are within the scope of the invention. For example, devices according to the invention can optically detect enzyme activation via percutaneous leads, or within bodily fluid samples in vitro. Some external device embodiments within the scope of the invention can utilize an optical fiber 100 linked to substrate 20 as described with reference to FIG. 7. Such embodiments may take the form of diagnostic devices within clinics for use with multiple patients or fluid samples. A new optical fiber 100 can be used for each patient or fluid sample. These and other embodiments are within the scope of the following claims.

CLAIMS

1. A method of detecting enzyme activation in an implantable medical device, comprising:

emitting energy at a first wavelength into a bodily fluid that contains an enzyme and a substrate tagged with at least two fluorescent dyes;

detecting energy emitted by a first one of the dyes at a second wavelength based on fluorescent resonant energy transfer from a second one of the dyes in response to the emitted energy at the first wavelength; and

detecting activation of the enzyme based on the detected energy.

2. The method of claim 1, wherein the bodily fluid is blood, and emitting and detecting energy comprises emitting and detecting energy via an optical fiber that includes a distal end located in a blood vessel of a patient.

3. The method of claim 1, further comprising detecting energy emitted by the second one of the dyes at a third wavelength in response to the emitted energy at the first wavelength, wherein detecting activation of the enzyme comprises:

determining a ratio between a first detected intensity of energy at the second wavelength and a second detected intensity of energy at the third wavelength; and

detecting a concentration of activated enzyme within the bodily fluid based on the ratio.

4. The method of claim 3, wherein the substrate includes a first product and a second product, the first product tagged with the first one of the dyes, and the second product tagged with the second one of the dyes, and

wherein the enzyme cleaves the substrate, and the first one of the dyes absorbs energy received from the second one of the dyes at the third wavelength via fluorescent resonant energy transfer and emits energy at the second wavelength in response to receiving the energy at the third wavelength prior to cleavage of the substrate by the enzyme.

5. The method of claim 1, further comprising presenting the substrate to the bodily fluid.

6. The method of claim 5, wherein the bodily fluid is blood, and presenting the substrate to the bodily fluid comprises controlling a pump to present the substrate to the blood via a catheter with a distal end located in a blood vessel of a patient.

7. The method of claim 1, wherein the energy is visible light.

8. The method of claim 1, wherein the enzyme is a protease enzyme.

9. The method of claim 8, wherein the enzyme is one of thrombin and kallikrein.

10. The method of claim 1, further comprising:

storing information relating to the detection of enzyme activation; and

delivering the information to a user.

11. The method of claim 1, further comprising activating an alarm in response to the detection of enzyme activation.

12. The method of claim 1, further comprising delivering therapy to the patient based on the detection of enzyme activation.

13. The method of claim 12, wherein delivering therapy comprises delivering at least one of an anticoagulant, a pain relieving drug, and neurostimulation therapy.

14. An implantable medical device comprising:

an emitting element to emit energy at a first wavelength into a bodily fluid that contains an enzyme and a substrate tagged with at least two fluorescent dyes;

a detector to detect energy emitted by a first one of the dyes at a second wavelength based on fluorescent resonant energy transfer from a second one of the dyes in response to the emitted energy at the first wavelength; and

a processor to control the emitting element to emit energy at the first wavelength, receive an indication of an intensity of energy detected by the detector, and detect enzyme activation based on the indicated energy intensity.

15. The device of claim 14, wherein the detector detects energy emitted by the second one of the dyes at a third wavelength in response to the emitted energy at the first wavelength, and

wherein the processor receives an indication of an intensity of energy detected by the detector at the second and third wavelengths, determines a ratio between a first detected intensity at the second wavelength and a second detected intensity at the third wavelength, and determines a concentration of activated enzyme within the bodily fluid based on the ratio.

16. The device of claim 15, wherein the substrate includes a first product and a second product, the first product tagged with the first one of the dyes, and the second product tagged with the second one of the dyes, and

wherein the enzyme cleaves the substrate, and the first one of the dyes absorbs energy received from the second one of the dyes at the third wavelength via fluorescent resonant

energy transfer and emits energy at the second wavelength in response to receiving the energy at the third wavelength prior to cleavage of the substrate by the enzyme.

17. The device of claim 15, wherein the detector comprises a first detector to detect energy emitted at the second wavelength and a second detector to detect energy at the third wavelength, the device further comprising:

a first filter to pass energy at the second wavelength to the first detector; and

a second filter to pass energy at the third wavelength to the second detector.

18. The device of claim 14, further comprising an optical fiber optically coupled to the emitting element and the detector, wherein a distal end of the optical fiber is located in the bodily fluid, the emitting element emits energy into the bodily fluid via the optical fiber, and the detector detects energy emitted by the first one of the dyes via the optical fiber.

19. The device of claim 18, wherein the fluid is blood and the distal end of the optical fiber is located within a blood vessel of a patient.

20. The device of claim 18, wherein the optical fiber includes a cladding, and wherein the optical fiber includes a region at which the cladding is removed from the optical fiber, and wherein the substrate is linked to the region of the optical fiber where the cladding is removed.

21. The device of claim 20, wherein the region is a distal region of the fiber.

22. The device of claim 18, further comprising:

a first reel;

a second reel; and

a reel rotation mechanism to move a tape between the first reel and the second reel along a path that is substantially parallel and proximate to the optical fiber,

wherein the substrate is linked to the tape, the optical fiber includes a cladding, the cladding is removed from a portion of the optical fiber, and the processor controls the reel rotation mechanism to move the tape such that uncleaved substrate is proximate to the unclad portion of the optical fiber.

23. The device of claim 22, wherein at least one of the first and second reels is coupled to the optical fiber.

24. The device of claim 14, further comprising:

a reservoir that contains the substrate;

a pump in fluid communication with the reservoir; and

a catheter that includes a proximal end in fluid communication with the pump and a distal end located in the bodily fluid,

wherein the processor controls the pump to present the substrate to the bodily fluid via the catheter.

25. The device of claim 24, wherein the bodily fluid is blood and the distal end of the catheter is located in a blood vessel of a patient.

26. The device of claim 14, wherein the energy is visible light.

27. The device of claim 14, wherein the enzyme is a protease enzyme.

28. The device of claim 27, wherein the enzyme is one of thrombin and kallikrein.

29. The device of claim 14, further comprising:

a memory to store information relating to the detection of enzyme activation; and

a telemetry circuit,

wherein the processor delivers the information to a user via the telemetry circuit.

30. The device of claim 14, further comprising an alarm, wherein the processor activates the alarm based on the detection of enzyme activation.

31. The device of claim 14, further comprising:

a reservoir containing a drug;

a pump in fluid communication with the reservoir; and

a catheter with a proximal end in fluid communication with the pump and a distal end located within a patient,

wherein the processor controls the pump to deliver the drug to the patient via the catheter based on the detection of enzyme activation.

32. The device of claim 31, wherein the drug comprises one of an anticoagulant and a pain relieving drug.

33. The device of claim 14, wherein the device is implanted in a patient.

34. An implantable medical device system comprising:

a first medical device to optically detect activation of an enzyme within a bodily fluid of a patient; and

a second medical device to deliver a therapy to the patient based on the detection of enzyme activation.

35. The system of claim 34, wherein the first medical device comprises:

an emitting element to emit energy at a first wavelength into a bodily fluid;

a detector to detect energy emitted at a second wavelength and a third wavelength by products of a tagged substrate in the bodily fluid in response to the energy at the first wavelength; and

a processor to control the emitting element to emit energy at the first wavelength, receive indications of intensities of energy detected by the detector, and determine a concentration of activated enzyme that cleaves the substrate within the bodily fluid based on the indicated energy intensities, wherein the second medical device delivers the therapy to the patient based on the determined concentration.

36. The system of claim 34, wherein the second medical device comprises a drug pump to deliver a drug based on the detection of enzyme activation.

37. The system of claim 34, wherein the second medical device comprises a neurostimulation device to deliver neurostimulation therapy based on the detection of enzyme activation.

38. The system of claim 34, wherein the first and second medical devices are integrated within a single housing.

39. The system of claim 34, wherein at least one of the first and second medical devices are implanted in a patient.

40. An optical fiber comprising:

a core; and

a cladding surrounding the core,

wherein the cladding is partially removed from a section of the fiber to expose a section of the core, and a substrate for an enzyme within a bodily fluid is linked to the section of the core.

41. The optical fiber of claim 40, wherein the section of the fiber is proximate to a distal end of the fiber.

42. The optical fiber of claim 40, wherein the enzyme is one of kallikrein and thrombin.

43. The optical fiber of claim 40, wherein the substrate is linked to the core by cross-linkers.

44. The optical fiber of claim 43, wherein the substrate is tagged with at least two fluorescent dyes.

45. The optical fiber of claim 44, wherein the absorption spectrum of a first one of the dyes overlaps an emission spectrum of a second one of the dyes.

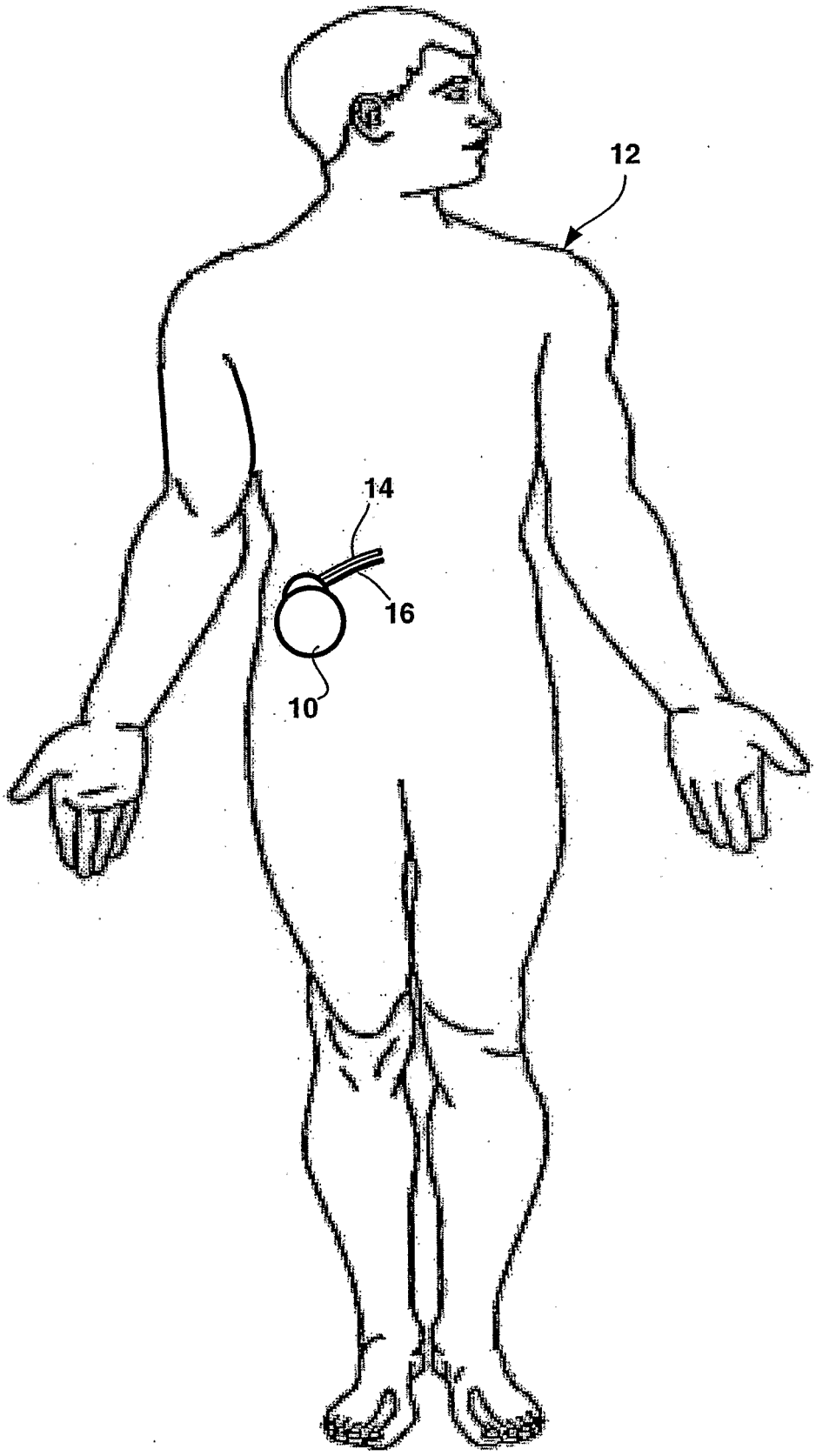


FIG. 1

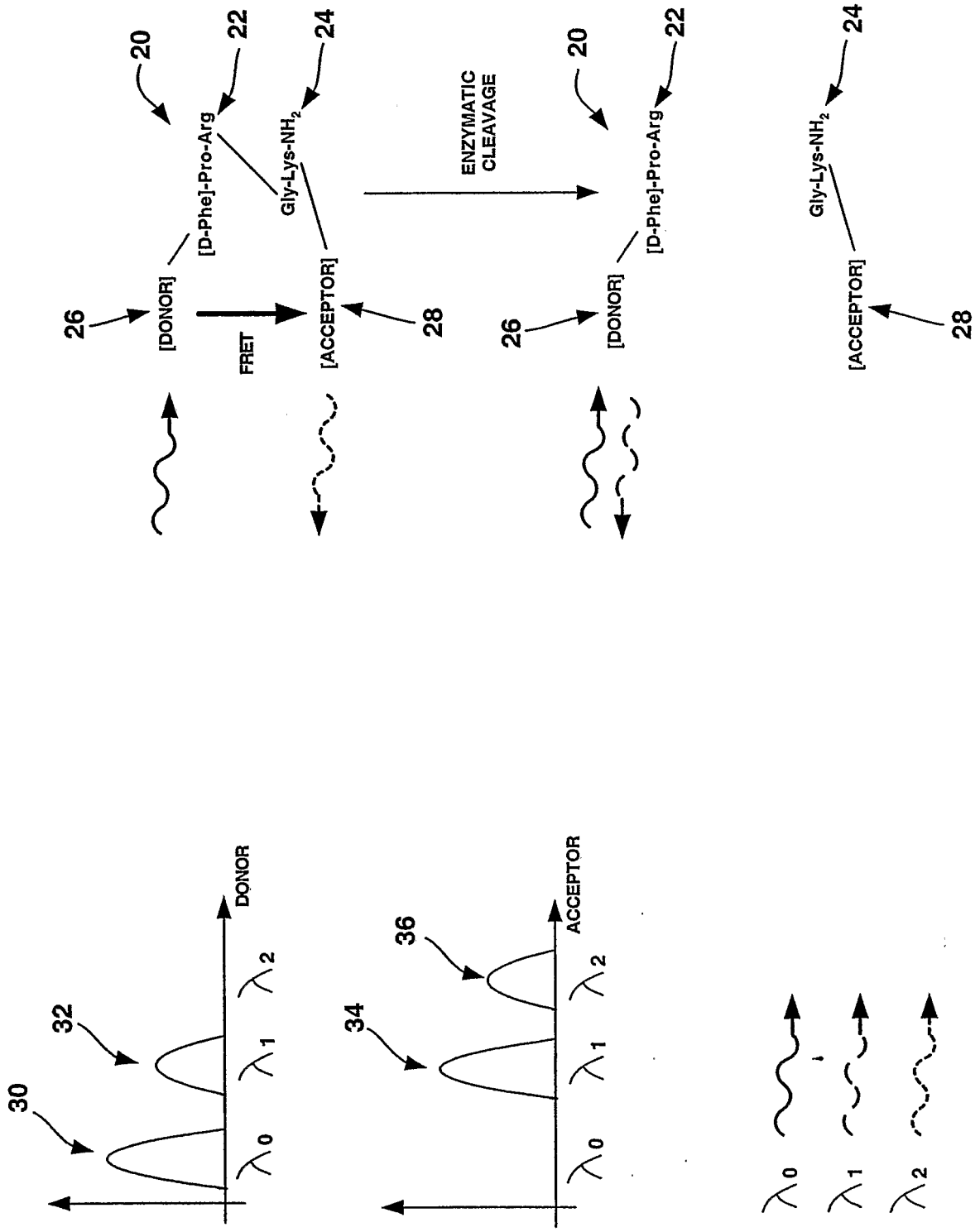

20
22
24
[D-Phe]-Pro-Arg
Gly-Lys-NH2
ENZYMATIC CLEAVAGE
26
[DONOR]
FRET
[ACCEPTOR]
28
30
32
DONOR
λ0
λ1
λ2
34
36
ACCEPTOR

FIG. 2

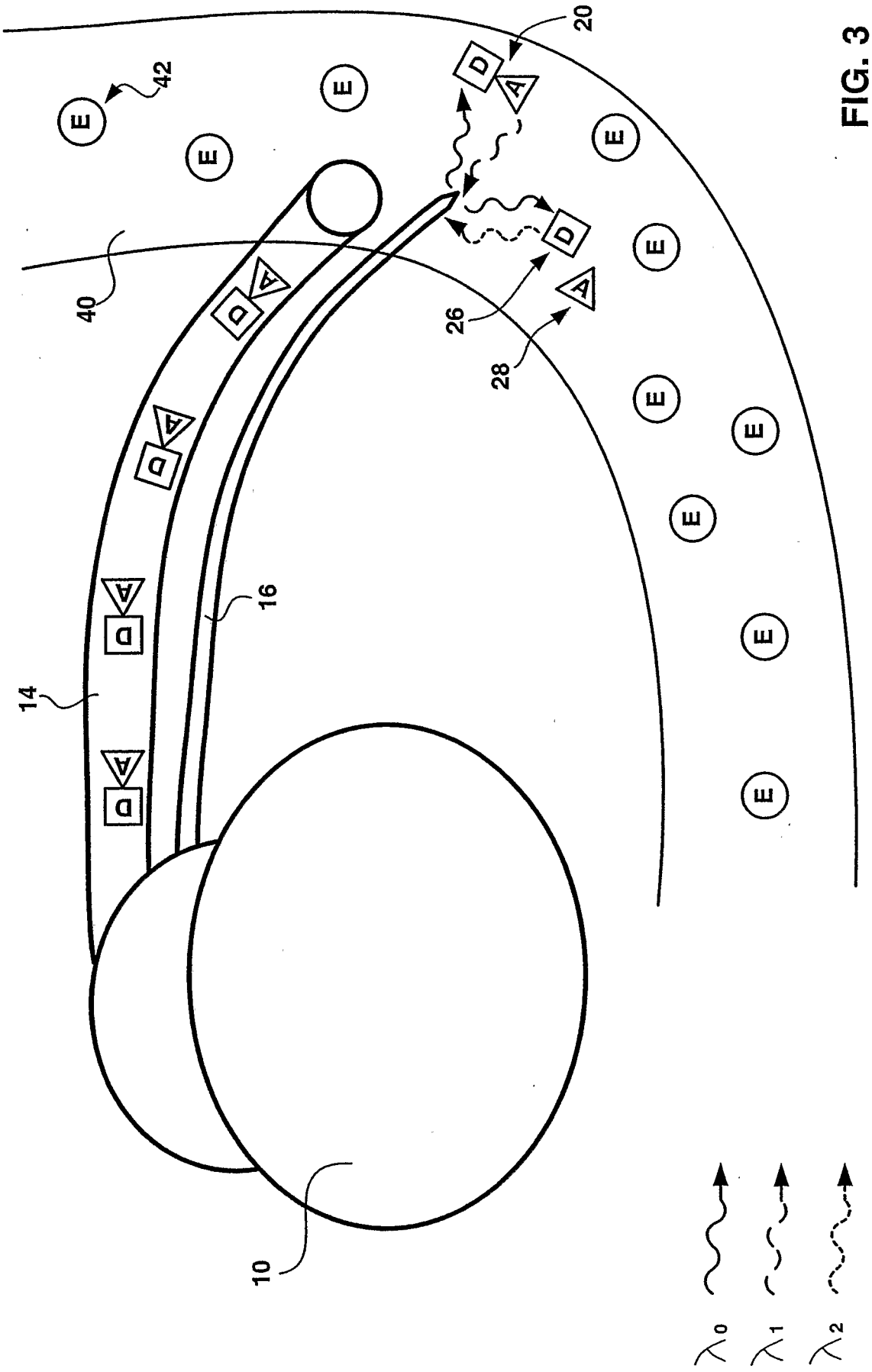
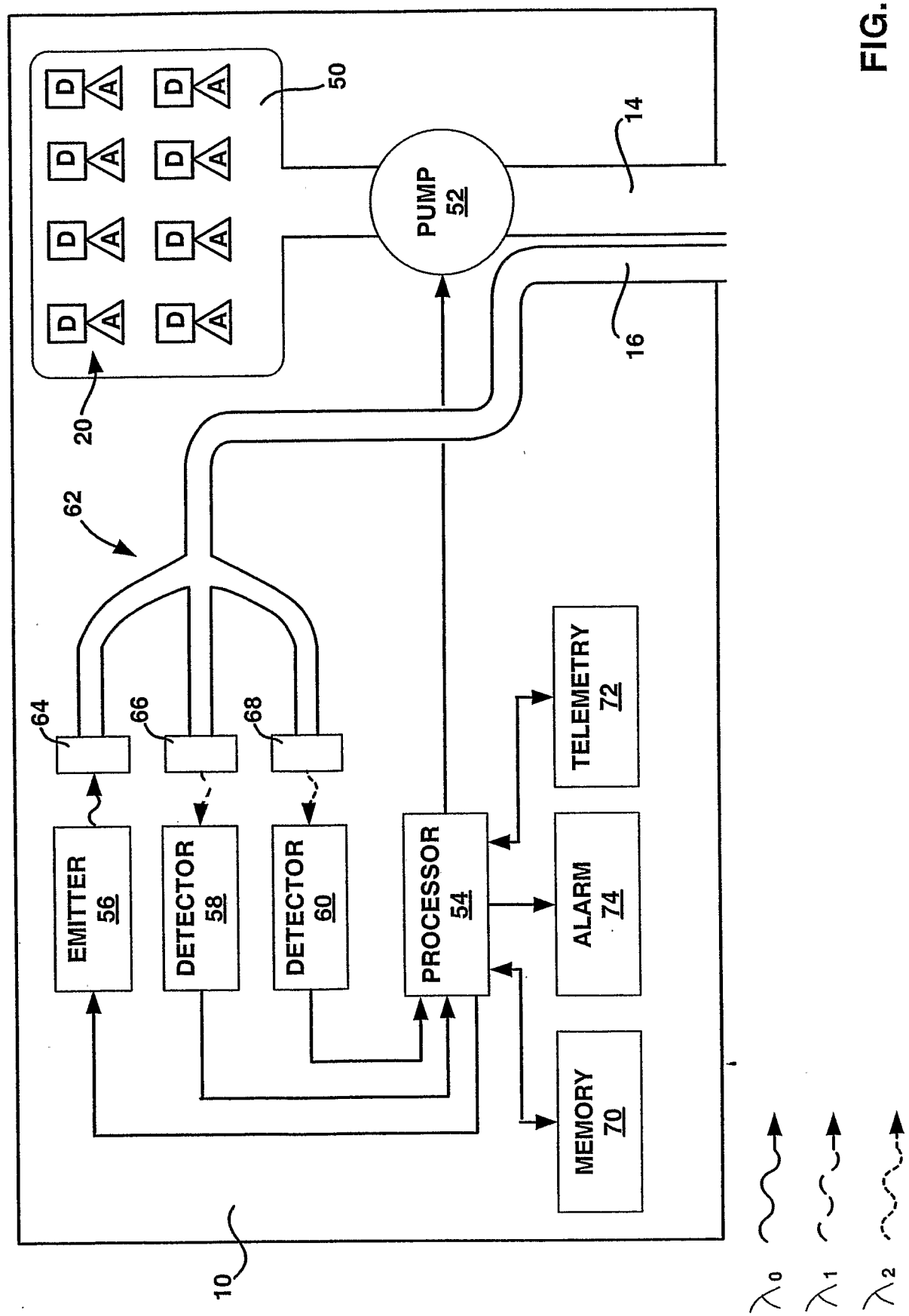


FIG. 3


D
A
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PUMP
52
14
16
20
62
64
66
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EMITTER
56
DETECTOR
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DETECTOR
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TELEMETRY
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ALARM
74
MEMORY
70
10
λ0
λ1
λ2

FIG. 4

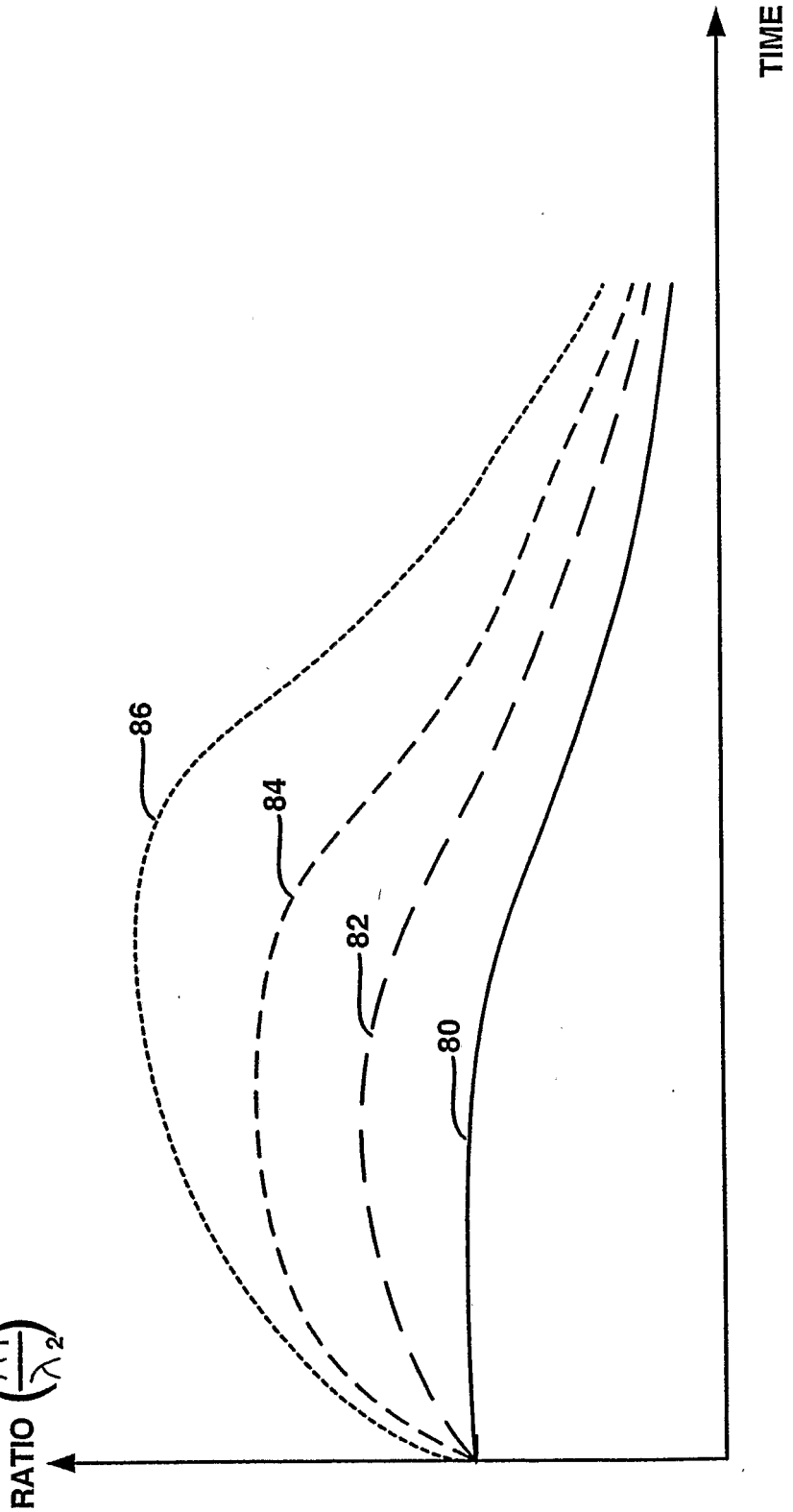

FIG. 5

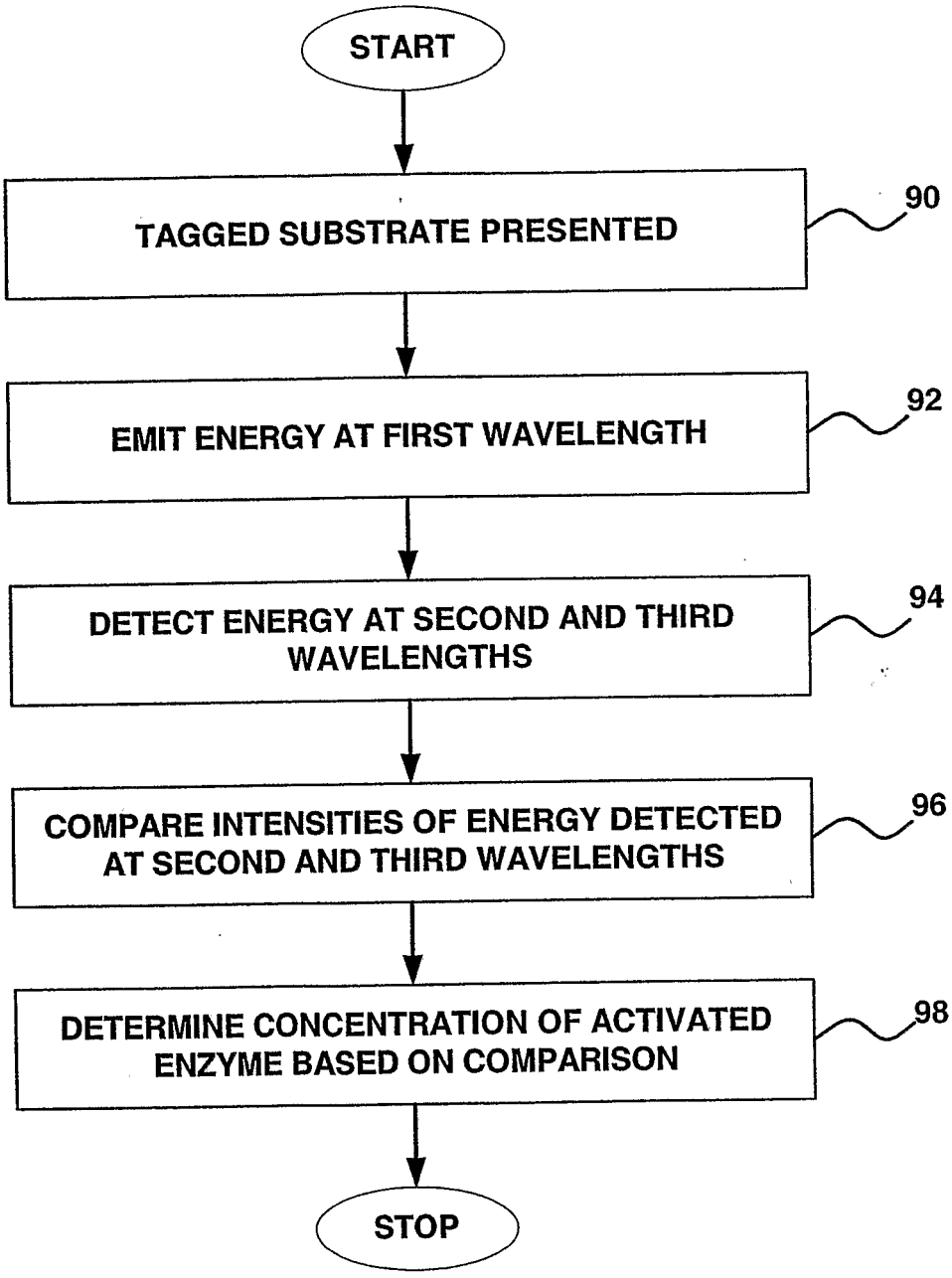
START
TAGGED SUBSTRATE PRESENTED
90
EMIT ENERGY AT FIRST WAVELENGTH
92
DETECT ENERGY AT SECOND AND THIRD WAVELENGTHS
94
COMPARE INTENSITIES OF ENERGY DETECTED AT SECOND AND THIRD WAVELENGTHS
96
DETERMINE CONCENTRATION OF ACTIVATED ENZYME BASED ON COMPARISON
98
STOP

FIG. 6

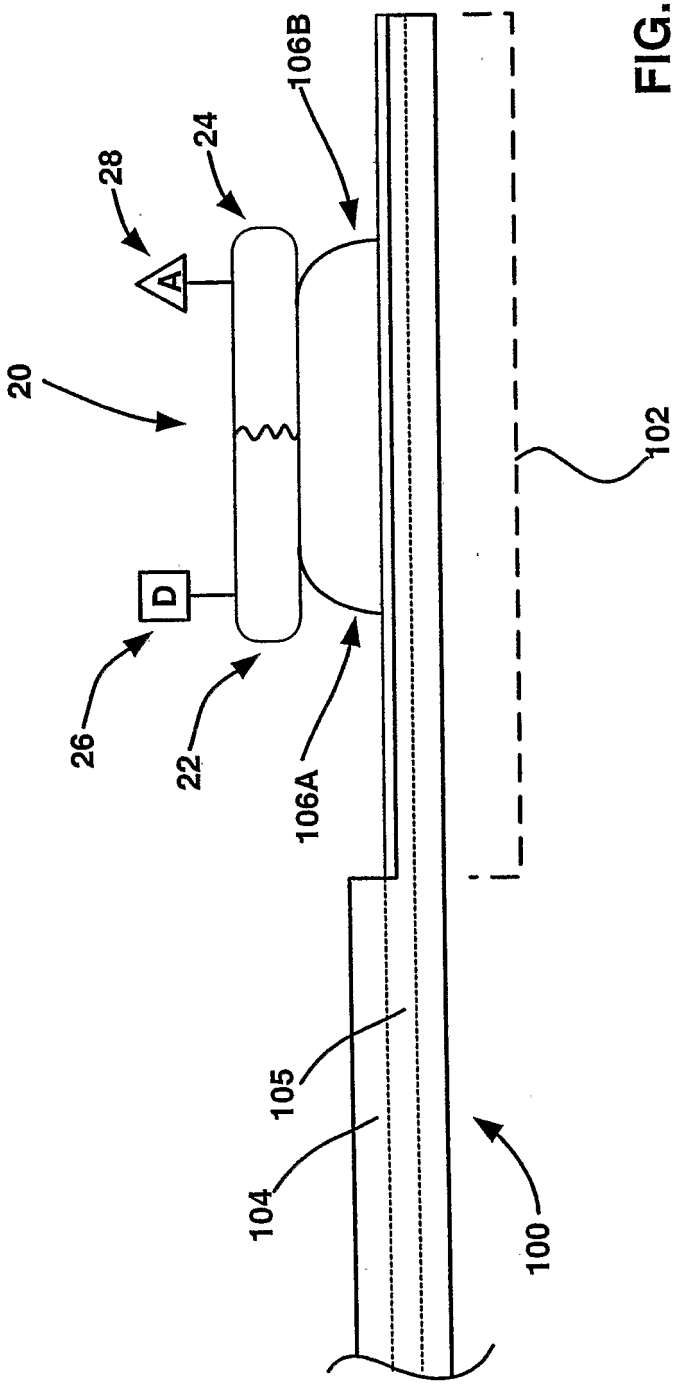

FIG. 7

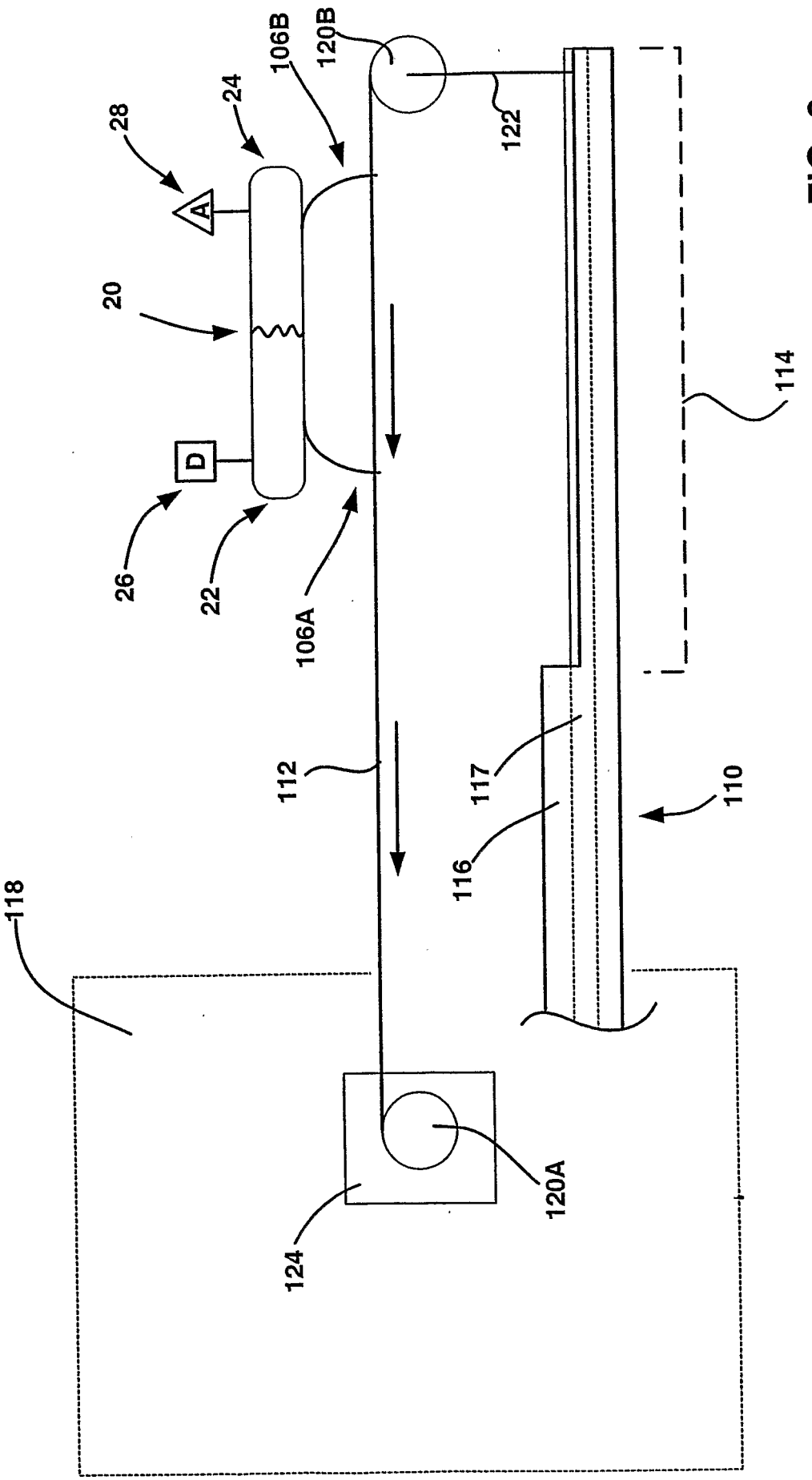
106B
120B
24
28
122
A
20
114
D
26
22
106A
112
117
110
116
118
120A
124

FIG. 8

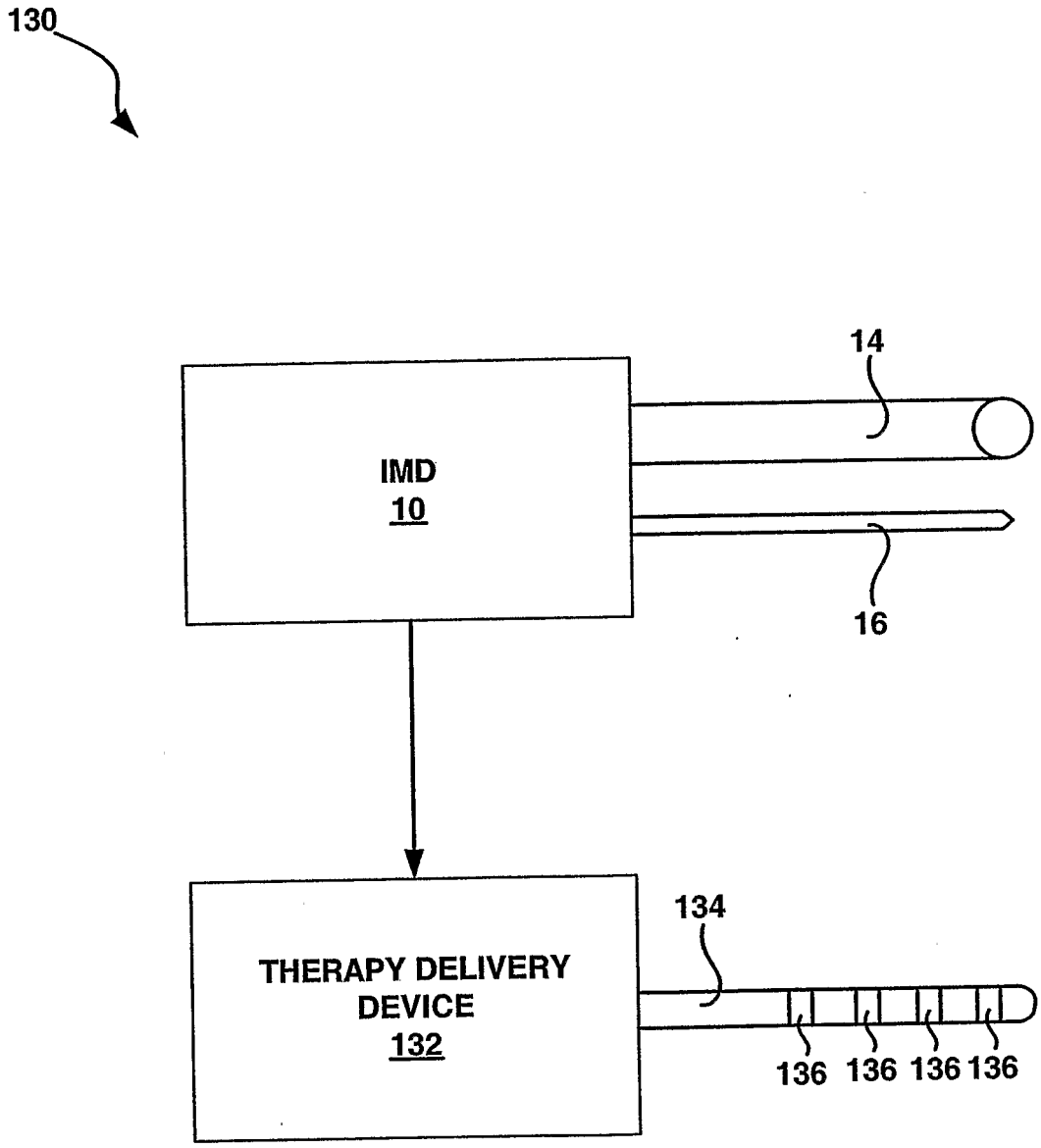
130
14
IMD
10
16
THERAPY DELIVERY
DEVICE
132
134
136
136
136
136

FIG. 9

专利名称(译)	用于酶活化的光学检测器		
公开(公告)号	EP1618367A2	公开(公告)日	2006-01-25
申请号	EP2004760246	申请日	2004-04-09
[标]申请(专利权)人(译)	美敦力公司		
申请(专利权)人(译)	美敦力公司，INC.		
当前申请(专利权)人(译)	美敦力公司，INC.		
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发明人	SOYKAN, ORHAN DONOVAN, MAURA, G. THOMPSON, AMY, ELIZEBETH		
IPC分类号	G01N21/64 C12Q1/37 A61B5/00 G02B6/02 C12Q1/56 G01N21/85 G01N33/86		
CPC分类号	A61B5/14546 A61B5/0071 A61B5/0075 A61B5/0084 A61B5/4839 A61B5/7203 C12Q1/37 C12Q1/56 G01N21/6428 G01N21/8507 G01N33/86 G01N2021/6415 G01N2021/6441 G01N2021/6484 G01N2021/8528		
优先权	10/423112 2003-04-25 US		
其他公开文献	EP1618367B1		
外部链接	Espacenet		

摘要(译)

基于酶的底物的切割量来检测体液中酶的活化。基质用两种荧光染料标记 - 供体和受体。标记的基质呈现给体液。装置以第一波长将能量发射到体液中，并且响应于第一波长的能量检测由染料发射的第二和第三波长的能量。在酶促切割底物之前，受体通过来自供体的荧光共振能量转移（FRET）接收的第二波长的能量发射第三波长的能量。在酶促切割底物后，供体以第二波长发射能量。该装置可以基于第二和第三波长处的能量的相对强度来确定体液内活化酶的浓度。