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(54) **Title:** IMAGING SYSTEM AND METHODS OF HIGH RESOLUTION CHERENKOV DOSE IMAGES

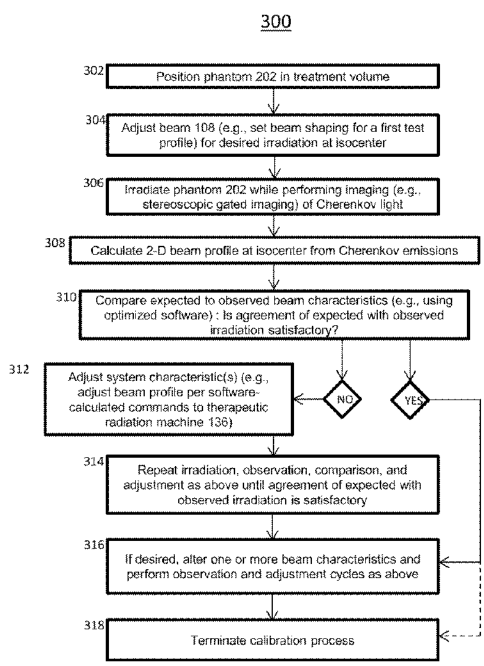


Fig. 3

(57) **Abstract:** A Cherenkov imaging system includes a high-speed radiation detector configured to provide a first timing signal synchronized with pulses of radiation to control operation of at least one pulse-gated, multiple-pulse-integrating, (PG-MPI) CMOS camera synchronized through the digital time signal to pulses of the radiation beam source, to image Cherenkov radiation; and a digital image-processing system. The high-speed radiation detector is either a solid-state radiation detector or a scintillator with a photodetector. The system images Cherenkov light emitted by tissue by using a timing signal synchronized to pulses of a pulsed radiation beam to control the PG-MPI camera by integrating light received by the PG-MPI camera during multiple pulses of the radiation beam while excluding light received by the camera between pulses of the radiation beam.

IMAGING SYSTEM AND METHODS OF HIGH RESOLUTION CHERENKOV DOSE IMAGES

PRIORITY CLAIM

[001] The present application claims priority to United States Provisional Patent Application No. 62/967,302 filed 29 January 2020. The entire contents of the aforementioned provisional application are hereby incorporated herein by reference.

GOVERNMENT SUPPORT

[002] This invention was made with government support under grant numbers R01 EB023909 and grant subcontract (Doseoptics LLC) R44 CA232879 awarded by National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[003] High-energy particle or photon beams are used in treatment of many cancers. Such beams are typically provided by a linear accelerator (LINAC), or related apparatus. When treating cancers with radiation it is desirable to target the beam in time and space such that there is a high net ratio of energy deposited in the tumor relative to energy deposited in normal tissues outside the tumor, resulting in a high therapeutic ratio of tumor to normal tissue dose.

[004] When treating patients with a high-energy radiation beam it is desirable to verify that the beam shape is as planned. Additionally, when beams enter tissue it is important to accurately predict how radiation beam shape varies with depth in tissue, to ensure adequate dosage to tumor tissue while minimizing dosage to surrounding normal tissues. If beam shape and orientation are adjusted, such as by positioning deflection magnets or shielding devices, it is important to confirm the resulting beam shape and dosage profile are as desired. Radiation treatment centers may therefore desire to confirm beam shape and dose profile for each patient or as part of routine calibration and maintenance. Moreover, aiming, shaping, timing, and other characteristics of therapeutic radiation beams should be verified during routine quality assurance or quality audit and recalibration prior to the administration of treatment to patients, where inadvertent exposure of non-tumor tissue to radiation must be minimized.

[005] In fact, manufacturers of radiation treatment devices routinely document beam shapes and dosage profiles produced by common configurations of their devices for training and guiding operators in using their machines. Further, they must seek regulatory approvals of their machines, and, as part of the regulatory approvals process, must provide documentation of beam shapes and dosage profiles achievable by their machines. Manufacturers therefore also need to accurately verify and document beam profiles for this regulatory approval process.

[006] Cherenkov light emitted by tissue, or by media with radiological properties similar to those of tissue (such as water), can be used as a proxy for radiation delivered to tissue and to other media. Cherenkov light has been used for qualitative applications, in systems that detect Cherenkov radiation emitted by tissue and other media in real-world clinical settings, however, these systems required direct interfacing to the LINAC.

[007] Current Cherenkov imaging camera systems require interfacing with LINAC timing signals to support Cherenkov imaging synchronized to during beam pulses and background imaging with beam off. Such synchronized operation with the LINAC allows imaging optically weak Cherenkov light emissions in well-lit rooms. Although these synchronization signals are accessible through standard LINAC service panels, electrical interfaces must be carefully designed to make sure there is no interference with normal LINAC operations. Access to these signals requires rigorous verification and validation requirements on interfacing electronics, as well as approvals from LINAC vendors and regulatory authorities.

[008] As mentioned above, Cherenkov light emissions from a medical LINAC's beam in water or tissue are weak and appear in brief pulses. These pulses are short enough, and the Cherenkov emissions weak enough, that typical CMOS image sensors fail to provide adequate images. An imaging technology that has successfully imaged Cherenkov light is an image-intensified, gated, electronic camera with a gated image intensifier tube positioned to intensify light received from the tissue, and an electronic camera positioned to record images from the image intensifier tube.

SUMMARY

[009] The present system is a Cherenkov-based imaging system that may use a remote, beam sensing, radio-optical triggering unit (RTU) which does not require an electrical interface to a LINAC. The RTU provides trigger signals for Cherenkov and background imaging. The radio-optical triggering unit, as well as related systems and methods, leverages scattered radiation present in the room during radiation treatment with high-speed, highly sensitive radio-optical sensing to generate a digital timing signal synchronous with the treatment beam for use in triggering Cherenkov radiation cameras.

[0010] The system and method provides for rapid and economic characterization of complex radiation treatment plans prior to patient exposure, utilizing a radio-optical triggering unit (RTU). Further, the system and method provide for economically imaging Cherenkov radiation emitted by tissue and other media in real-world clinical settings, such as settings illuminated by visible light, utilizing the RTU.

[0011] The present system is also directed to Cherenkov-based imaging systems that use a pulse-gated, multiple-pulse-integrating, (PG-MPI) CMOS image sensor array synchronized to radiation pulses provided by the LINAC using either the remote, beam-sensing, (RTU) triggering solution for timing or a direct electrical interface to the LINAC for timing.

[0012] In an embodiment, a Cherenkov imaging system includes a high-speed radiation detector configured to provide a first timing signal synchronized with pulses of radiation provided by a pulsed radiation beam source; the timing signal coupled to control operation of at least one camera capable of imaging Cherenkov radiation; and a digital image-processing system; where the high-speed radiation detector is selected from the group consisting of solid-state radiation detectors and radiation detectors of the type comprising a scintillator and a photodetector; and where the at least one camera capable of imaging Cherenkov radiation is a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera synchronized through the digital time signal to pulses of the radiation beam source.

[0013] An imaging unit has a trigger input adapted for connection to a beam-on output signal provided by a pulsed radiation beam source, the trigger input receiving a digital timing signal; apparatus configured to communicate the digital timing signal to trigger operation of at least one camera capable of imaging Cherenkov radiation; where the camera

capable of imaging Cherenkov radiation is a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera synchronized through the digital time signal to pulses of the radiation beam source.

[0014] In another embodiment, a method of imaging Cherenkov light emitted by a phantom or tissue includes providing a timing signal synchronized to pulses of a pulsed radiation beam; applying the pulsed radiation beam to the phantom or tissue, the pulsed radiation beam causing the phantom or tissue to emit the Cherenkov light; imaging the Cherenkov light with a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera; imaging the Cherenkov light being performed by integrating light received by the PG-MPI camera during multiple pulses of the radiation beam and not integrating light received by the PG-MPI camera between pulses of the radiation beam.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] In the drawings, like reference characters generally refer to the same parts throughout the different views. The drawings are not to scale, emphasis instead being placed upon illustrating principles of the system and method.

[0016] FIG. 1A schematically depicts an illustrative system for performing monitored radiotherapy with time-controlled room lighting and camera sensing of light emissions from a subject.

[0017] FIG. 1B is a diagram showing the approximate relationships of room lighting, beam pulses, light emissions, and camera shutter windows in the system of FIG. 1A.

[0018] FIG. 2 is a schematic block diagram of an apparatus for coordinated direct feedback observation and adjustment/control of high-energy beam profiles in a therapeutic radiation system while imaging the beam depositing dose in a phantom.

[0019] FIG. 3 is a flow chart of an illustrative method of operation of the system of FIG. 2.

[0020] FIG. 4A is a schematic block diagram of an apparatus for the calibration of Cherenkov observations to in situ, high-accuracy radiation measurements in a therapeutic radiation system and phantom.

[0021] FIG. 4B is a more detailed view of portions of the system of FIG. 4A.

[0022] FIG. 5 is a schematic block diagram of an apparatus for coordinated Cherenkov and non-Cherenkov observation of high-energy beam profiles in a therapeutic radiation system.

[0023] Figure 6A shows a schematic of one embodiment of a radio-optical triggering unit, which comprises a high speed, highly sensitive radio-optical sensing system to generate a digital timing signal which is synchronous with the treatment beam.

[0024] FIG. 6B is a schematic of two radio-optical triggering units with outputs AND-ed to suppress spurious triggers.

[0025] FIG. 7A is a schematic depicting one embodiment where the RTU placed within a central interface box, which distributes the synchronization signal to multiple connected cameras along with power.

[0026] FIG. 7B is a schematic depicting one embodiment where the RTU is housed within a camera enclosure.

[0027] FIG. 8 is a representation of the case and components certain embodiments of the RTU.

[0028] FIG. 9 is a graph that depicts an optical trigger signal matching both TARG-I and KLY-V signals.

[0029] FIG.10A provides multiple Cherenkov images indicating optical triggering matching TARG-I triggering.

[0030] FIG. 10B provides multiple Cherenkov images and data indicating optical triggering matches the TARG-I triggering in location and intensity.

[0031] FIG. 11 is a block diagram of a versatile RTU providing raw pulses indicative of detected radiation pulses, synthesized pulses synchronized to detected radiation pulses, synthesized pulses immediately following detected radiation when fluorescent emissions are expected, and synthesized pulses leading expected radiation pulses for background image capture.

[0032] FIG. 12 is a timing diagram of the versatile RTU of FIG. 11.

[0033] FIG. 13 is a flowchart of operation of the versatile RTU of FIG. 11.

[0034] FIG. 14 is a timing diagram of an enhanced RTU.

[0035] FIG. 15 is an exemplary schematic diagram of a photosensor cell of a pulse-gated, multiple-pulse-integrating, photodiode detector.

[0036] FIG. 16 is an exemplary timing diagram of operating a pulse-gated photodiode detector to integrate received Cherenkov light generated over multiple pulses of a particle-accelerator beam.

[0037] Fig. 17 is an exemplary composite photograph of Cherenkov radiation and background image captured sequentially with a gated, multiple-pulse-integrating, CMOS image sensor.

[0038] Fig. 18A is an exemplary single-frame photograph of Cherenkov radiation corrected by subtracting an integrated background.

[0039] Fig. 18B is an exemplary photograph of Cherenkov radiation captured with a gated, multiple-pulse-integrating, CMOS image sensor over 200 frames corrected by subtracting background, showing significant improvement in image quality over the single-frame photograph of Fig. 18A.

[0040] Fig. 19 is an exemplary integrated background image captured over 200 beam pulses.

[0041] Fig. 20 is an exemplary flowchart of a method of using a pulse-gated, multiple-pulse-integrating, camera with background subtraction to image Cherenkov radiation.

DETAILED DESCRIPTION

[0042] Embodiments of the present system are directed to Cherenkov-based imaging systems for high resolution radiation dose images using a remote, beam sensing triggering solution which does not require an electrical interface to a pulsed radiation beam source for timing. In embodiments, the pulsed radiation beam source may be a linear accelerator (LINAC), cyclotron, synchrotron, or similar device.

[0043] Embodiments of the present system are directed to Cherenkov-based imaging systems that use a gated, multiple-pulse-integrating, CMOS image sensor array with either the remote, beam-sensing, triggering solution or a direct electrical interface to a LINAC for timing.

[0044] Charged particles (*e.g.*, electrons, positrons, protons, alpha particles) moving faster than the speed of light in a dielectric medium decelerate while emitting photons. These photons are termed Cherenkov (a.k.a. “Cerenkov” and similar spellings) radiation. In particular, charged particles moving with sufficient speed cause Cherenkov radiation emission in human tissue or water. Cherenkov radiation can also result from irradiation by high-energy photons used in cancer therapy (*e.g.*, 6–18 MV), because Compton scatter of these photons produce secondary electron emission having sufficient kinetic energy to produce Cherenkov radiation in the medium. Cherenkov emission in human tissue has been detected with incident radiation in the range of 6 to 24 MeV energies for electrons and x-ray photons. Although no particle of nonzero mass can move at or above the speed of light in vacuum (velocity c), it is common that particle velocities can exceed the speed of light v in a material media, v being less than c, when excited to kinetic energies greater than a few hundred kiloelectron volts (keV). Since Cherenkov emission depends on particle velocity, more-massive particles (*e.g.*, protons, alpha particles) need correspondingly higher energies to produce Cherenkov radiation in a given medium, and so Cherenkov is only emitted from larger-mass charged particles such as protons at considerably higher kinetic energy than required for electrons.

[0045] Cherenkov radiation (or "Cherenkov light") is emitted at an acute angle θ to the path of a particle moving at velocity v_p, where $\cos\theta = c/(nv_p)$ and n is the refractive index of the medium; when numerous charged particles move at suitable velocity in a collimated beam, a Cherenkov glow is emitted in a conic pattern at angle θ to the beam, which is approximately 41 degrees from the direction of travel. Cherenkov emission has a continuous spectrum across the entire ultraviolet, visible, and near-infrared spectrum with intensity varying as the inverse square of the wavelength (up to a cutoff frequency). Thus, Cherenkov emission at higher frequencies (shorter wavelengths) is more intense, giving rise to Cherenkov light's characteristic blue color when viewed by eye or camera.

[0046] When Cherenkov light is induced locally inside water or tissue, it is predominantly blue in color, but with a broad spectrum which tapers off into the green, red, and near-infrared (NIR) with an inverse square wavelength dependence given by the Frank-Tamm formula. This light when emitted within tissue is attenuated by absorbers significantly reducing the blue green wavelengths and largely just leaving the red and NIR wavelengths for transmission over a few millimeters. This light in the tissue can also excite other molecular species within the tissue to induce photo-luminescence (*i.e.*, fluorescence or phosphorescence).

[0047] Cherenkov light is of significance for medical radiation systems because its intensity at any given point in a volume of tissue, as captured by imaging equipment, correlates with the intensity at that point of radiation that meets the criteria for inducing Cherenkov light. Cherenkov light emission is thus a proxy for high-energy radiation intensity. Therefore, Cherenkov light enables quantitative and relative observation of a high-energy radiation beam by an imaging device (*e.g.*, camera) not aligned directly with the beam and thus not subject to damage by it.

[0048] Accordingly, we describe systems, tools, and methods for using Cherenkov light emission from an intersection of a pulsed radiation beam from a standard linear accelerator, or other pulsed accelerator, with a subject or phantom, including emission of fluorescent light from fluorophores stimulated by Cherenkov light, to localize and quantify the radiation beam. In certain embodiments, operative feedback including Cherenkov imaging, *e.g.*, of a phantom (nonliving test object), is employed to enable a human operator or computational system to adjust a therapeutic radiation machine or plan of treatment for purposes of design, commissioning, quality auditing, adjustment, treatment plan verification, or the like in real-time.

[0049] In certain other embodiments, localized high-accuracy measurements of therapeutic radiation flux by an additionally available measurement device such as an external portal imaging device, ionization chamber, or diode, are integrated with Cherenkov imaging to produce Cherenkov visualizations of dose delivery calibrated to accurate dose units. In some embodiments, high resolution dose images are provided in tomographic or otherwise enhanced characterizations of therapeutic radiation beam profiles.

[0050] The Cherenkov-based imaging systems, tools, and related methods are described with reference to the following definitions that, for convenience, are set forth below:

I. Definitions

[0051] As used herein, the term "a," "an," "the" and similar terms used herein are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[0052] The term "camera" herein describes an electronic camera capable of imaging Cherenkov radiation and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation.

[0053] The term pulse-gated, multiple-pulse-integrating, (PG-MPI) camera herein describes a camera as described above with the ability to image light received during a pulse of a timing signal, while ignoring light received at times other than during pulses of the timing signal. Further, the PG-MPI camera can integrate light detected during multiple pulses of the repetitive timing signal to provide a stronger image than can be achieved by imaging light only during a single pulse of the timing signal. We have discovered that a commercial-grade time-domain Time-of-Flight (ToF) CMOS image sensor, the Teledyne e2v BORA® 1.3-megapixel image sensor, can be configured as a PG-MPI image sensor in a way that is capable of detecting Cherenkov light from tissue. It is expected that similar image sensors may become available with greater numbers of pixels, and other technologies may be able to produce future PG-MPI image sensors. A PG-MPI image sensor may be synchronized to pulses of the radiation beam source to selectively capture images of light either during pulses of the radiation beam while ignoring light received between pulses of the radiation beam for Cherenkov images, or alternatively synchronized to capture images of light received between, but not during, pulses of the radiation beam source for background images.

[0054] The term "interface" is used herein to describe a shared boundary across which two separate components of a system exchange information, which can be between software, computer hardware, peripheral devices, humans and combinations of these. Moreover, the operation of two separate components across the boundary, as in the interaction of the camera interface which is designed to interface with the camera, is referred to herein as "interfacing." In certain embodiments, the interfacing may be bi-directional. In other embodiments, the interfacing may be unidirectional. In specific embodiments, the term "interface" may reference a user interface such as a graphic user display and keyboard.

[0055] The term "high-energy radiation" is used herein to describe radiation that, considering the mass of particles involved, contains enough energy to generate Cherenkov radiation upon entry into a given medium with a given refractive index. As such, the use of the language "high-energy radiation" herein considers both the delivered particle and the medium irradiated.

[0056] The term “isocenter” herein references a point in space relative to the treatment machine which indicates the center of the treatment volume, *e.g.*, in a system where various components system rotate, the isocenter is the point about which the components rotate. Location of the isocenter plays an important role in treatment planning, since ideally the isocenter should be centered in the target volume such as centered in a tumor; thus, patient positioning with respect to the isocenter is a significant factor for successful irradiation of cancerous tissue and consequently for treatment outcome.

[0057] The language “machine-readable medium” describes a medium capable of storing data in a format readable by a machine. Examples of machine-readable media include magnetic media such as magnetic disks, cards, tapes, and drums, punched cards and paper tapes, optical disks, barcodes, magnetic ink characters, and solid-state devices such as flash-based thumbdrives, solid-state disks, etc. In a particular embodiment, the machine-readable medium is a network server disk or disk array. In specific embodiments, the machine-readable medium occupies more than one network server disks.

[0058] The term “subject” as used herein is to describe the object being irradiated with radiation, such as a phantom or human tissue.

[0059] The term “user” or “operator” are used interchangeably to describe any person that operates the systems of the present system by interfacing with a user interface.

II. Advancements in Cherenkov-Based Imaging Systems

[0060] Cherenkov-based imaging systems offer instantaneous radiation surface imaging of a subject exposed with high-energy radiation, to qualitatively record and verify accuracy of treatment at the time of exposure. Such systems generally include at least one camera capable of imaging Cherenkov light, an image processor, and a machine-readable medium designed to record and store the information; capture of the Cherenkov light from the subject is typically triggered by a signal tapped directly from a pulsed radiation beam source such as a LINAC that provides pulsed radiation to the subject.

[0061] In contrast, the advanced Cherenkov-based imaging systems herein described use a radio-optical triggering unit (RTU) instead of a signal tapped directly from a LINC and provide enhanced system features that afford the systems to more actively use this information through (1) feedback presentation of this information to control the radiation beam source; (2) quantification of dose based on Cherenkov imaging, providing high resolution images; and (3) improved dynamic range image capture through use of the beam sensing triggering solution described herein.

[0062] As such, one embodiment provides an advanced Cherenkov-based imaging system including:

a radiation beam source (*e.g.*, a particle accelerator or other device for providing high-energy radiation, which, for example, may be cross-sectionally shaped by a beam-shaping apparatus, *e.g.*, a multi-leaf collimator);

at least one camera capable of imaging Cherenkov radiation (and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation); and

one or more processing units that enables the control of the radiation beam source,

wherein the Cherenkov radiation is detected by the camera after exposure of a subject to high-energy radiation from the radiation beam source. In certain embodiments, systems have desirable properties such as rapidity, three- and four-dimensionality, and water equivalence.

[0063] In certain embodiments, the systems include an illumination system adapted to substantially reduce interference with wavelengths of interest by using an LED illumination system.

[0064] FIG. 1A, FIG. 1B, and FIG. 2, described further herein below, depict certain aspects of systems that are relevant to various embodiments.

[0065] FIG. 1A schematically depicts portions of an illustrative external-beam radiation therapy system 100 like a system described in US Provisional Patent Application No 62/153,417. System 100 provides context relevant to various embodiments described herein. System 100 depicts high-sensitivity electronic cameras or groups of cameras 102, 104 used to image Cherenkov light and/or light emitted by fluorescent substances (fluorophores) excited by Cherenkov light and to localize locations on or in a human subject 106 from where this light is emitted. In certain embodiments, the subject 106 is preferably located within an environment from which light from uncontrolled sources, such as the sun and incandescent lamps, is excluded or minimized. In certain embodiments of the system

100 depicted in FIG. 1A, the subject 106 is placed in the path of a radiation beam 108 so that the beam 108 irradiates tissue 110 of the subject in need of radiation treatment, such as a tumor. Beam 108 is provided by a radiation beam source 112, *e.g.*, a particle accelerator or other device for providing high-energy radiation, and typically is cross-sectionally shaped by a beam-shaping apparatus 114, *e.g.*, a multi-leaf collimator.

[0066] In the illustrative system 100 of FIG. 1A, the source 112 is an accelerator that provides a beam 108 of electrons having energy of between 6 million electron volts (6 MeV) and 24 MeV, such as is used to deliver treatment energy to deep tumors as opposed to treatment of surface skin. Various other therapeutic systems could produce, for example, a photon beam of 6 MeV or higher or a high-energy proton beam. In general, various embodiments are combined with therapeutic radiation systems that produce beams capable of inducing Cherenkov radiation emission in human tissue, including but not limited to systems described explicitly herein.

[0067] In certain embodiments like system 100, cameras 102, 104 image the subject 106 from fewer or more points of view than are depicted in FIG. 1A, or non-stereoscopic cameras are used, or a single camera is arranged to move to more than one position with respect to the subject, or the subject 106 is supported in a manner that permits their rotation with respect to one or more cameras, or some combination of one or more of these or other imaging arrangements is employed. Cherenkov and/or fluorescent radiation emission occurs where the tissues (or tissue equivalent) of the subject 106 are irradiated by the beam 108, a volume herein termed the emission volume 116. Fluorescent light emissions can be induced by Cherenkov-light excitation of fluorophores in tissue, where such fluorophores are present, and are radiated isotropically rather than directionally as is the case with Cherenkov radiation.

[0068] In certain embodiments, the cameras 102, 104 are aimed to image at least part of the emission volume 116 and are coupled to a camera interface 118 of an image-processing system 120. Camera connections to the camera interface 118 may be wired or wireless and are not depicted in FIG. 1A for clarity. Herein, in certain embodiments, camera connections may serve both to transfer image data from a camera to the camera interface 118 and to convey commands (*e.g.*, for setting shutter timing, exposure) from the camera interface 118 to the camera. In certain embodiments like system 100, light-modifying components such as filters and light intensifiers are aligned with cameras, or included in cameras, to intensify and/or selectively admit Cherenkov and/or fluorescence light; however, such light-modifying devices are omitted from FIG. 1A for simplicity. The camera interface 118 captures and stores digital images from the cameras 102, 104 in memory 122 for later retrieval and processing by at least one processor 124 of the image processing system 120. The processor 124 can exchange information not only with the camera interface 118 and memory 122 but with a timing interface 126, a display subsystem 128, and potentially other devices as well. The display subsystem 128 communicates with a user interface 130 through which a user 132 can interact with the imaging-processing system 120. In certain embodiments, timing interface 126 is adapted to communicate with a system interface 134 of the radiation therapy device 136 to determine timing of pulses of radiation from the beam source 112 and to control pulsed room lighting 138 to mitigate interference from room lighting during imaging of Cherenkov emissions and/or fluorescence by synchronizing lighting with image capture by cameras 102, 104, as discussed below with reference to FIG. 1B.

[0069] In certain embodiments of the system 100 of FIG. 1A, the imaging system cameras 102, 104 are spectrally-sensitive cameras capable of providing spectral data permitting distinction between Cherenkov and fluorescent light. Emitted Cherenkov and fluorescent light is subject to attenuation by absorbance as it propagates through and emitted by tissue, and in some embodiments spectrally-sensitive cameras permit distinction between light absorbed by oxyhemoglobin and by deoxyhemoglobin.

[0070] In certain embodiments of the systems, for example in the system 100 of FIG. 1A, raw or de-noised images from the imaging system are recorded in one or more suitable digital memory systems (*e.g.*, memory 122) as documentation of the radiation treatment.

[0071] In certain embodiments, prior to each session for which monitoring of radiation delivery is desired, an enhancing and indicating agent is administered to the patient. In a particular example, the enhancing and indicating agent is a dose in the range of 20 milligrams per kilogram body weight of 5-delta-aminoievulinic acid (5-ALA), administered for an incubation time of approximately four hours before each divided radiotherapy session begins. In specific embodiments with a metabolically active tumor in tissue 110 of the subject, some of the 5-ALA is metabolized to protoporphyrin IX (PpIX), which fluoresces when illuminated by Cherenkov light. PpIX production in normal tissue and metabolically active tissues 110 is generally understood to be proportional to metabolic processes in those tissues; thus, a metabolically active tumor will tend to contain more PpIX and fluoresce more brightly. Other enhancing agents may be developed or utilized with the system described herein.

[0072] The system and method provide simple, accurate, quick, robust, real-time, water-equivalent characterization of beams from LINACs and other systems producing external-therapy radiation utilizing a radio-optical triggering unit (RTU) for purposes including optimization, commissioning, routine quality auditing, R&D, and manufacture.

[0073] The radio-optical triggering unit, as well as related systems and methods, leverages the scattered radiation present in the room during the treatment and employs high-speed, highly sensitive radio-optical sensing to generate a digital timing signal which is synchronous with the treatment beam for use in triggering Cherenkov radiation detection and does not rely on any electrical signal from the LINAC itself.

A. Radio-Optical Triggering Unit (RTU)

[0074] As such, one embodiment provides a radio-optical triggering unit (RTU) that performs a method including steps of:

detection of scattered radiation by a fast response time scintillator (SCI) coupled with a high speed, single-photon sensitive silicon photomultiplier module (SiPM) to detect exposure of a subject to high-energy radiation from a radiation beam source;

the SCI performs conversion and amplification of the scattered radiation into optical photons, while the SiPM generates an analog electrical signal;

processing the analog signal to a digital timing signal, *e.g.*, a transistor-transistor logic signal, wherein the digital timing signal is synchronized with the radiation beam source; and

communication of the digital timing signal to trigger the operation of at least one camera capable of imaging one or more signals, *e.g.*, Cherenkov radiation or scintillation signals (*e.g.*, from scintillation patches placed on the patient’s body).

[0075] In an alternative embodiment, the RTU times pulses of the high-energy radiation to provide a timing signal of improved accuracy, to provide interpolated signals early in each interval between beam pulses when fluorescent emission is present, and to provide interpolated signals late in each interval between beam pulses when only background illumination is present.

[0076] In one embodiment, the timing signal generated by the RTU may be used to perform synchronous imaging of Cherenkov radiation produced by the treatment beams in tissue or other synthetic materials, as detailed herein. In an alternative embodiment, the timing signal generated by the RTU is used to perform synchronous imaging of scintillation signals produced by the treatment beams in tissue or other synthetic materials in the same manner as imaging the Cherenkov signals.

[0077] Figure 6A shows a schematic of one embodiment of a radio-optical triggering unit, including a high speed, highly sensitive radio-optical sensing system to generate a digital timing signal synchronous with the treatment beam. For example, the RTU converts and amplifies scattered ionizing radiation into optical photons, which is detected by a fast response time scintillator coupled with a high speed, single photon sensitive silicon photomultiplier module (SiPM), and the analog electrical signal generated by the SiPM is conditioned and converted to a digital (transistor-transistor logic) TTL signal by the signal processing unit (SPU).

[0078] In certain embodiments of the radio-optical triggering unit (RTU), the time signal is synchronized with the radiation beam source to trigger the operation of at least one camera capable of imaging Cherenkov radiation to detect Cherenkov radiation during beam pulses and imaging background images at times when beam pulses are not present. In particular embodiments, such synchronized operation with the LINAC allows imaging optically weak Cherenkov light emissions in well-lit rooms.

[0079] In certain embodiments of the radio-optical triggering unit (RTU), the step of communication is capable of instructing modification of additional downstream electronics and imaging system functions.

[0080] In certain embodiments of the radio-optical triggering unit (RTU), the rising edge of the timing signal is synchronous with the radiation beam source and is used to trigger the operation of at least one camera capable of imaging Cherenkov radiation. In certain embodiments, the rising edge of the timing signal is used for gating additional downstream electronics and imaging systems, *e.g.*, such as the camera, *e.g.*, C-Dose™ camera.

[0081] In certain embodiments of the radio-optical triggering unit (RTU), the fast response scintillator SCI is encapsulated in a light tight enclosure.

[0082] In certain embodiments, the signal from RTU fully substitutes for the LINAC supplied sync signals, such as TARG-I (typically used for imaging photon beams) or KLY-V (typically used for imaging electrons), which are typically used to synchronize the operation of prior cameras for imaging Cherenkov radiation with LINAC operation. In this respect, Figure 9 depicts the optical trigger signals matching both TARG-I and KLY-V signals. Furthermore, Figures 10A shows optical triggering matching the TARG-I triggering visually and 10B shows the optical triggering matches the TARG-I triggering in location and intensity.

[0083] In certain embodiments with the RTU, the system further comprises a communication tool with one or more processing units that enables the control of a radiation beam source.

[0084] In certain embodiments of the system, the system includes a radiation beam source. In certain embodiments, the radiation beam source is a particle accelerator, LINAC, or other device for providing high-energy radiation. In particular embodiments, the radiation beam source may be cross-sectionally shaped by a beam-shaping apparatus. In specific embodiments, the beam-shaping apparatus is a multi-leaf collimator.

[0085] In certain embodiments of the advanced triggering systems, the system further comprises one or more additional radio-optical triggering units, multiple RTU modules being used to implement a co-incidence triggering mechanism. This design allows rejection of possible spurious triggering of the SCI, and coupled SiPM due to spontaneous emissions from the scintillator crystal or cosmic ray interactions. Figure 6B below shows a schematic of this implementation employing two RTUs, where each of these modules are shown to be sensing a spurious trigger during the normal operational mode. In particular embodiments the outputs from two RTU modules are combined using a logical AND gate. Since spurious triggers occur randomly in time the AND gate effectively suppresses them at the output; but the radiation beam is sensed by both the RTUs and valid triggers synchronous with each other are passed to the cameras. In certain additional embodiments, the two RTUs are spatially separated, to reduce potential for spurious triggers.

[0086] The RTUs may be compact and independent sensing modules, and as such, they may be configured in many ways to improve redundancy, and support self-contained operation of Cherenkov imaging camera systems. Accordingly, and without intending to limit the system architecture including an RTU a system may include multiple RTUs, each RTU may be encompassed within camera units or may be separate from the camera. Figure 7A shows one configuration where the RTU module is placed within a central interface box, which distributes the synchronization signal to multiple connected cameras along with the power. The RTU module in this depiction may be a basic unit or a coincidence triggering variant, which offers additional redundancy in the case of one of the RTU units failing. In an alternative embodiment, as shown in Figure 7B, an RTU is housed within each camera enclosure. This configuration offers camera level redundancy and enables simple single camera designs with built-in triggering capabilities.

[0087] In certain embodiments of the advanced triggering systems, the system further comprises an integrated power supply unit (PSU), *e.g.*, that provides power to the radio-optical triggering unit, *e.g.*, SCI and, *e.g.*, coupled SiPM.

B. Direct Feedback Interface Control Units and Systems

[0088] In certain advanced Cherenkov-based imaging systems utilizing a radio-optical triggering unit (RTU), the system further provides direct feedback of the image information derived from capturing real-time Cherenkov radiation administration to instruct on the control of the beam source and/or beam shape. In certain embodiments, this is accomplished by means of incorporation of a direct feedback interface (DFI) control unit, wherein the DFI control unit is designed to provide direct/real-time communication between the camera and the radiation beam source unit and/or beam shaping unit (*e.g.*, collimator), *e.g.*, via a user display. Moreover, the Cherenkov-based feedback to the radiation beam source and/or beam shaping unit, may be used by developers or service people to optimize the radiation beam source and/or beam shaping unit.

[0089] As such, another embodiment provides a direct feedback interface (DFI) control unit including a processor configured by firmware to perform a method comprising:

detection of Cherenkov radiation (and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation) after exposure of a subject to high-energy radiation from a radiation beam source;

creation of an image (*e.g.*, image information);

comparative analysis of the image to a reference image; and

communication of the results of the comparative analysis to the radiation beam source unit, wherein such communication is capable of instructing modification of the beam profile. In this way, the detected Cherenkov radiation may be used to directly control the linear accelerator, and the beam output. Another embodiment uses a radio-optical triggering unit (RTU) as herein described, further provides an advanced Cherenkov-based imaging system comprising a direct feedback interface (DFI) control unit. In certain embodiments, a direct feedback interface (DFI) control unit is incorporated into any system described herein. In certain embodiments, the system includes a Cherenkov-based imaging system including:

a radiation beam source which, for example, may produce a beam cross-sectionally shaped by a beam-shaping apparatus such as a multi-leaf collimator;

at least one camera capable of imaging Cherenkov radiation (and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation);

one or more processing units that enable the control of the radiation beam source; and

a direct feedback interface (DFI) control unit,

wherein the Cherenkov radiation is detected by the camera after exposure of a subject to high-energy radiation from the radiation beam source.

[0090] In certain embodiments, a beam profile based on detected Cherenkov light or Cherenkov-stimulated fluorescence is directly fed to the radiation beam source unit or a designer, operator, or maintainer who is testing therapeutic radiation machine design, commissioning a newly installed therapeutic radiation machine, or performing periodic quality auditing and/or adjustment of a therapeutic radiation machine, or who wishes for any other purpose (*e.g.*, treatment-plan verification) to characterize the spatial and temporal delivery of radiation by a therapeutic radiation machine to a treatment volume. In certain embodiments, a LINAC machine delivering radiation in the form high-energy electrons is described as an illustrative therapeutic radiation system, but no restriction is intended by this usage; all other radiation systems capable of inducing Cherenkov radiation in tissue are contemplated and within the scope of the invention.

[0091] FIG. 2 is a schematic depiction of portions of an illustrative system 200 for the coordinated observation and adjustment of a device providing radiotherapy based on direct feedback control. In certain embodiments, system 200 is equipped with a subsystem interface for determining beam profiles and dynamics by observation and analysis of Cherenkov radiation. For example, in certain embodiments, a beam-calibration phantom 202 is placed in a zone where it is desired to measure a profile of a radiation beam 108 provided by a radiation therapy device 136. In particular embodiments, the zone may be a volume above or beside a treatment table (not depicted). In certain embodiments, the phantom 202 is a fluid-filled tank, the fluid in the tank being a translucent or transparent fluid having an index of refraction greater than that of air; in a particular embodiment, the fluid is water. In certain embodiments portions of the walls of the phantom 202 are transparent to Cherenkov light, *e.g.*, the top and sides of phantom 202 consist largely of glass or transparent plastic. In a particular embodiment, the phantom 202 has sides constructed of acrylic sheets; another particular embodiment has sides constructed of polycarbonate panels. In a specific embodiment, a small amount of scattering agent and/or fluorophore is added to the liquid in the phantom 202 to enhance scatter of Cherenkov light without significantly affecting propagation of the radiation beam 108, overcoming the inherent directionality of Cherenkov light from a collimated radiation beam and allowing more light to be detected laterally around the phantom 202. The system 200 may also include an apparatus for preventing interference by room lighting or may be blacked out to prevent interference of ambient light with measurements of the Cherenkov radiation. However, room blackout for relatively long periods (*e.g.*, a multi-image acquisition interval) is in general more feasible with a phantom 202 rather than a patient because live subjects may find blackout disturbing (*e.g.*, claustrophobic) and workers cannot observe a patient’s condition during blackout, which raises safety concerns.

[0092] In an alternative embodiment, the tank is filled with a transparent fluid such as silicone oil. In yet another embodiment, the phantom is formed from a high-index, transparent, material, such as a cast high-index plastic, *e.g.*, plastic water or solid water (*e.g.*, anthropomorphic), and may have both fluorophores and light-scattering additives embedded within it.

[0093] In certain embodiments, the system 200 also includes one camera or a multiplicity of cameras; the illustrative embodiment of FIG. 2 includes two cameras 208, 210. For graphic simplicity the two cameras 208, 210 are depicted as being coplanar, but in certain embodiments, the cameras have lines of sight (*e.g.*, line of sight 212 of camera 208) that are orthogonal to each other, *e.g.*, in a plane that is orthogonal to the treatment beam 108. In certain embodiments, two orthogonal views suffice for the tomographic reconstruction of the three-dimensional light field intensity in the emission region 214 (cross-hatched region) from each simultaneously acquired pair of images from the cameras 208, 210. In particular embodiments, where only Cherenkov light is emitted from the emission region 214, the cameras 208, 210 may lie in a plane that is at angle θ with respect to the beam 108, where $\cos\theta = c/(nv_p)$, c being the velocity of light in a vacuum, n the index of refraction of the material filling the phantom 202 (assumed herein for illustrative purposes to be homogeneous, but not necessarily so), and v_p being the velocity of particles in the beam 108. In various other embodiments, a single camera is arranged to move to more than one position with respect to the phantom 202, or the phantom 202 is supported in a manner that permits its rotation with respect to one or more cameras, or some combination of one or more of these or other imaging arrangements is employed to obtain sufficient information for beam profile characterization (*e.g.*, tomography). In certain embodiments where the beam 108 is known to have a radially symmetric spatial profile), a single camera may be used to fully characterize the spatial profile of the beam 108. Also in other embodiments, the particle beam source 112 and beam shaping subsystem 114 are attached to a gantry that enables them to move about a phantom 202 or a patient in the irradiation zone, delivering radiation to and from a range of angles.

[0094] The cameras 208, 210 are aimed to image at least part of the emission volume 214 and are coupled to a camera interface 118 of an image-processing system 120. (Camera connections to the camera interface 118 may be wired or wireless and are not depicted in FIG. 2 for clarity.) In certain embodiments, the camera interface 118 captures and stores digital images from the cameras 102, 104 in memory 122 for processing by at least one processor 124 of an image processing system 120. The processor 124 is capable of exchanging information not only with the camera interface 118 and memory 122 but with a timing interface 126, a display subsystem 128, and potentially other devices. The display subsystem 128 communicates with a user interface 130 through which a user 132 can interact with the image-processing system 120. Timing interface 126 is adapted to communicate with a system interface 134 of the radiation therapy device 136 to determine timing of pulses of radiation from the beam source 112 and potentially to control pulsed room lighting 138 to avoid interference from room lighting during imaging of Cherenkov emissions and/or fluorescence by synchronizing lighting.

[0095] In certain embodiments, the phantom 202 is located within an environment that excludes significant amounts of daylight and light from other bright source such as room illuminators. In particular embodiments, the walls of the phantom 202 are coated on their interior surface with a light-absorbing coating except for camera viewing windows positioned in front of each camera, the coating being provided to absorb both stray light originating from outside the phantom 202 and to prevent emissions light from being reflected from the interior walls of the phantom 202 into a camera 208, 210.

[0096] In certain embodiments, a beam source 112 (*e.g.*, particle accelerator or other device for providing high-energy radiation) is aimed to provide a beam 108 of radiation through beam-shaping apparatus 114 to phantom 202. In a particular embodiment, the beam source 112 provides a beam of electrons having energy of 6 million electron volts (6 MeV) or greater; in a particular embodiment, the beam energy lies between 6 and 24 MeV. In an alternative embodiment, the source 112 produces a photon beam of 6 MeV or greater. In another alternative embodiment, the source 112 provides a proton or heavy charged particle beam. In yet another alternative embodiment, the source 112 produces a beam of electrons or photons having a substantial percentage of electrons or photons having energy of 1 MeV or greater. In the illustrative embodiment of FIG. 2, the radiation therapy device 136 is a LINAC providing a beam of 6 MEV electrons.

[0097] Reference is now made to FIG. 1B, which schematically depicts the timing relationships of certain embodiments of the system 100 of FIG. 1 according to some methods of operation. In signal diagrams given in FIG. 1B and elsewhere herein, timing relationships are not necessarily drawn to scale: *e.g.*, the width of a pulse may be exaggerated relative to the delay between pulses, or the duration (width) of a pulse depicted for one signal may not be proportional to that depicted for another signal. With emphasis on the sequence of events, *i.e.*, which signals are On and which are Off at any given moment, Cherenkov radiation is emitted during high-energy radiation beam pulses 140; timing and intensity of Cherenkov emission closely correlates to timing and intensity of radiation pulses 140. Cherenkov-stimulated secondary fluorescent light 142 emitted from naturally occurring, artificially administered, or drug-metabolite fluorescent materials can lag the radiation beam 140 and can decay exponentially 141 after each pulse of the beam turns off, as illustrated. The time of this decay depends upon the emission lifetime of the biochemical species that was excited.

[0098] In one illustrative mode of operation, an effective Cherenkov shutter interval 144 that includes beam pulse 140 is used to image light primarily emitted by Cherenkov mechanisms, and an effective fluorescent shutter interval 146 is used to capture light emitted from the human subject or phantom by fluorescent and/or phosphorescent mechanisms. In this exemplary arrangement and mode of operation, room lighting 148 is pulsed Off for the duration of Cherenkov light emission (*i.e.*, for duration of radiation pulse 140) and fluorescent emission 142 so that the relatively weak optical signals of interest may not be swamped by ambient light: in effect, the optical signal to noise ratio is improved by turning room lighting 148 off during emissions imaging. If the period of such pulses is significantly shorter than the flicker perception threshold of human vision, some dimming of room lighting relative to an unpulsed mode of operation may be visible, but no irritating flicker would be observed. In another exemplary mode of operation, room light is not pulsed, but an intensification step of image acquisition (not depicted) is gated On only during Cherenkov light emission, thus effectively rejecting most of the ambient light. In an example, during Cherenkov and/or fluorescent light acquisition, light imaged by cameras 102, 104 in FIG. 1A is recorded as pairs of consecutive images, with a first image of each pair recording of Cherenkov light emitted during beam pulse 140 and a second image of each pair recording light emitted during the fluorescent shutter interval 146. In certain embodiments, processor 124 of FIG. 1A executes machine-readable instructions in associated memory, such as memory 122, to reconstruct first (Cherenkov) tomographic image sets of the subject from the first images of all image pairs captured, to reconstruct second (fluorescence) tomographic image sets of the subject from the second images of all image pairs captured, and to produce an image set of fluorophore distribution in the subject based upon some mathematical relationships (*e.g.*, ratio) between the first and second tomographic image sets. In various other, similar systems and/or modes of operation, non-tomographic imaging is performed, optionally enhanced by signal-processing steps such as background subtraction and median filtering to remove saturated pixels.

[0099] In modes of operation such as those where 5-ALA is administered, the fluorophore distribution is related to metabolic activity in the subject, and the tomographic image set of fluorophore distribution in the subject is indicative of metabolic activity throughout the imaged volume of the subject. The processor 124, or a processor of another computer device (not depicted), can further execute machine-readable instructions in memory 122 to compare the tomographic image set of fluorophore distribution in the subject against a tomographic image set of fluorophore distribution in the subject obtained during a prior radiation treatment session to produce a tomographic image set indicative of treatment effectiveness, *i.e.*, changes (if any) in tumor metabolic activity.

[00100] In certain embodiments of system 100 an enclosure (not depicted herein) surrounds the subject and excludes ambient light from the subject, supporting the imaging of faint Cherenkov and fluorescence emissions. Additionally, or alternatively, the coordinated functioning of timing interfaces 126 of system 100 (FIG. 1A) and pulsed room lighting 148 (FIG. 1B) serve to mitigate or prevent interference of ambient lighting with measurement of Cherenkov light and fluorescent light from an emission volume in the subject. The term “apparatus for preventing interference by room lighting” as used herein shall mean either or both of an enclosure surrounding and excluding ambient light from the subject, and the combination of timing interfaces 126 and pulsed room lighting 148.

[00101] In certain embodiments, Cherenkov radiation and/or associated fluorescent emissions, which are proxies for radiation deposition by high-energy photons and charged particles, may be employed in spatial (*i.e.*, one-dimensional, two-dimensional, or three-dimensional) and temporal beam characterization or profiling. Herein, “temporal beam profiling” refers to the characterization of variations in beam intensity over time, whether during single pulses or averaged over portions of pulses or whole pulses, and "spatial beam profiling" refers to characterization of the distribution of beam intensity across the two-dimensional beam cross-section, or as a function of depth in a phantom or living subject, or both. The fullest possible profile of a beam pulse, which is acquired in various embodiments, consists of a three-dimensional spatial profile re-acquired at time intervals sufficiently frequent to capture all temporal beam behavior of interest for a given purpose: in effect, such data constitute a three-dimensional movie of pulse intensity, herein termed a four-dimensional beam profile. Herein, unmodified reference to a "beam profile" may denote a one-, two-, three-, or four-dimensional beam profiles.

[00102] The illustrative embodiment of FIG. 2 includes a LINAC user interface 214 that is capable of exchange information with a user 132. In certain embodiments, the information thus exchanged may include settings of control parameters for beam shaping system 114, particle beam source 112, movements of a gantry (not depicted) for directing the beam 108, and other measurable and/or controllable aspects of the radiation therapy device 136, whose readings or behaviors may in general be made known to the user 132 and modified by the user 132. In certain embodiments, the user 132 may, in several examples, be a designer monitoring the performance of a LINAC machine under development, a technician performing commissioning of a newly installed LINAC system, a technician performing periodic or scheduled quality auditing and/or adjustment of the LINAC system, a technician validating the delivery of a patient treatment plan using a phantom 202 prior to administration of the plan to a living subject, or a person who wishes for any other purpose to study and possibly adjust the temporal, spatial, and other characteristics of a beam 108 produced by therapeutic radiation therapy device 136 in various modes of operation, and the interactions of such a beam with a phantom 202 and possibly with additional phantoms, living subjects (*e.g.*, animal or human), or other targets.

[00103] In certain embodiments, Cherenkov-based imaging enabled by the image processing subsystem 120 supports visual, qualitative, and relative quantification characterization of profiles (one, two, three, or four-dimensional) of the beam 108, including such aspects as translations and rotations of the beam 108, shaping of the beam 108 by various settings of the beam-shaping subsystem 114, changes in particle energy (Cherenkov spectra and emission angles are both functions of particle energy, making such properties detectable in principle by the imaging subsystem), alterations in beam intensity (detectable because for a given particle energy, beam intensity and Cherenkov light brightness are proportional), and other aspects. Unlike methods used in the prior art for the characterization of beam profiles, the Cherenkov-based system 200 of FIG. 2 and other embodiments can acquire two- or three-dimensional beam profiles at rates limited only by the optical and other technical characteristics of the cameras (*e.g.*, cameras 208, 210) and associated equipment (shutters, intensifiers, etc.): Cherenkov light (and/or fluorescent emissions stimulated by Cherenkov light) is intrinsically a continuous, high-resolution, four-dimensional source of information about radiation flux in the irradiated volume 214. Four-dimensional characterization of individual beam pulses is possible in various embodiments. Such data can be processed by the processor 124—*e.g.*, in a tomographic manner, or using various model-based and other imaging approaches that will be familiar to persons versed in the art of medical image processing—to reveal features of interest in one, two, three, and four dimensions (*e.g.*, derivative images and comparative images, delivered-dose maps) that are not available from existing technologies. In further examples, temporal performance of the radiation therapy device 136 can be assessed within a single pulse, or between pulses, or during the warm-up phase of operation of the LINAC. This information can be used by the user 132 to adjust the performance of system 134. For example, the user 132 can issue commands to alter beam shaping by the beam-shaping subsystem 114. In another example, the user 132 or another person may make mechanical or electrical adjustments to the beam-generating mechanism of the beam source 112. In certain embodiments, all adjustable aspects of the operation of radiation therapy device 136 can be adjusted in a manner informed by the Cherenkov-derived information collected and processed by the image-display subsystem 128. In certain embodiments, such information may be transmitted to other computing and memory devices (not depicted) for post-processing, long-term storage, studies comparing different therapeutic machines or configurations, simulation, and other purposes. Advantageously, certain embodiments enable the rapid, high-resolution, four-dimensional characterization of radiation delivery to the phantom 202, without need to reposition the cameras 208 210 or the phantom 202, as well as adjustments of radiation therapy device 136 in a manner informed by such detailed and timely characterization.

[00104] Moreover, certain embodiments enable efficient positioning of a phantom 202, or of other targets, with respect to the isocenter of the LINAC 136 (or other pulsed therapeutic therapy device), in order that beam characterization or other tasks may be performed. In certain embodiments, the therapeutic radiation system indicates its isocenter location using intersecting visible lasers. In various embodiments, these lasers can be imaged by the same cameras (*e.g.*, cameras 208 and 210) that are used to image Cherenkov and/or fluorescent light. Software control and feedback as described herein (*e.g.*, through the system interface 134 and image processing subsystem 120) provide isocenter alignment information to the user 132. In a particular example, isocenter alignment laser images may be compared to physical or virtual registration marks on the phantom 202 as imaged to the user 132, and the phantom's position is adjusted accordingly: for example, control of platform positioning of the radiation therapy device 136 is conducted through the system interface 134, either manually by the user 132 or as determined by software computed by the image processing subsystem 120 or another computing device, to produce satisfactory alignment of isocenter of the phantom 202 or a region or target therein. Such embodiments minimize the time required for phantom setup and offer, for example, advantageous time savings for quality audit processes compared to lower-resolution electronic beam-locating systems. Because the camera or cameras of various embodiments have relatively very high spatial resolution and can be dual-used for both laser observation and Cherenkov observation, embodiments have a flexibility of set-up which exceeds that of known electronic diode or ionization chamber ionization processes.

[00105] In certain embodiments, the user interfaces 130 and 214 are supplemented or replaced by direct informatic communications interfaces and the human user 132 is supplemented or replaced by a computational system, such as a software program or artificial intelligence, that is configured to exchange information with image-processing subsystem 120, with the system interface of the radiation treatment device 136, and potentially with other measuring devices, mechanical systems, computing devices, and other devices or systems. In such embodiments, the software program or artificial intelligence performs some or all the functions of evaluation, comparison, and adjustment that in the embodiment of FIG. 2 are performed by the human user 132.

[00106] In certain embodiments the operation of system is as illustrated by the flowchart of method 300 of FIG. 3, adjustment of the radiation therapy device 136 is performed to produce a beam of desired characteristics within a specified accuracy range. In a preliminary positioning step 302 that may entail imaging of the system isocenter, the phantom 202 may be positioned within the treatment space of the radiation therapy device 136 so that the center of the phantom 202, or some other point within the phantom 202, is located at the system isocenter. In a beam-programming or adjustment step 304, the radiation therapy device 136 may be set to produce a beam 108 of a given character for irradiation of the phantom 202: such characteristics as intensity, pulse duration, pulse frequency, number of pulses, and two-dimensional beam profile as determined by the beam-shaping subsystem 114, among other characteristics, may be set to predetermined values. The predetermined values may be specified to serve a manufacturer's test plan, or as part of a patient treatment plan, or according to other criteria. In an irradiation step 306, one or more pulses of radiation are supplied by the radiation therapy device 136, while imaging (*e.g.*, stereoscopic gated imaging) of the Cherenkov light and/or secondary fluorescent light induced in the phantom by the radiation is performed. In an image-processing or beam-profile calculation step 308, data from the cameras 208, 210 is processed by the image processing subsystem 120 to produce, in this illustrative method, a two-dimensional irradiation pattern or beam profile at the system isocenter. In a display and comparison step 310, an expected profile and the observed profile are compared. Such comparison may be visual and ad hoc, or quantitative, or may combine several modes of comparison: in any case, such comparison produces a judgement, whether ad hoc or numerical, as to whether the expected irradiation pattern is sufficiently like the observed radiation pattern or not. If it is sufficiently similar, then the method may proceed to the testing 316 of another configuration of the radiation therapy device 136 or may terminate. If agreement between expected and observed radiation is unsatisfactory, then an adjustment step 312 is performed, in which one or more adjustable aspects of the mechanism and/or operation of the radiation therapy device 136 is performed by one or more of the user 132, software, or an additional person. In a looping or convergence phase 314, irradiation and observation 306, beam profile calculation 308, comparison 310, and possibly adjustment 312, as described above, are repeated until satisfactory agreement between expected and observed radiation delivery is observed, a different system configuration is set up for testing 316, or the operator elects to end the procedure 318.

[00107] The calibration method 300 is illustrative of a broad class of procedures and methods by which the system 200 or various other embodiments may be operated. The systems and methods of most embodiments entail rapid and information-rich feedback to characteristics of the radiation therapy device 136 based on observed and processed Cherenkov light or secondary fluorescence induced in the phantom 202 by the radiation beam 108.

C. Enhanced Beam Characterization: Integration of Cherenkov and Non-Cherenkov Sensing

[00108] Another embodiment provides high resolution dose quantified Cherenkov-based images, through enhanced beam characterization. Certain embodiments use a radio-optical triggering unit (RTU), further address the challenges of fast 3D dosimetry utilizing a technique that allows for real-time dose imaging, *e.g.*, in water phantoms. While known non-Cherenkov radiation measurement devices, such as external portal imaging devices (EPID), can provide a 2D transverse distribution of a transmitted beam, and the Cherenkov imaging provides an accurate lateral view of the dose; the tools and methods described herein provide the integration of these measures by providing for the simultaneous acquisition of EPID images and lateral Cherenkov images. In certain embodiments, the integration of these measures produces a consistent 3D distribution of the deposited dose. In particular embodiments the non-Cherenkov radiation measurement device, *e.g.*, EPID, and the Cherenkov techniques provide images with high frame rates (~10 fps) which permits real-time 3D beam reconstruction. As such, and in particular embodiments, this affords the ability to perform pre-treatment plan verification and quality assurance due to the high spatial and temporal resolution of the measured 3D dose distributions produced.

[00109] Traditionally, measurement methods for therapeutic radiation beams have depended on radiographic or Gafchromic film dosimetry for obtaining planar two-dimensional (2D) dose distributions inside a dosimetry phantom placed inside the treatment zone. Although film dosimetry is high-resolution, the process is cumbersome, not real-time, and may exhibit processing-dependent variability. Other known techniques include electronic portal imaging devices (EPIDs), ionization chamber arrays, and semiconductor arrays. For example, Theraview Technology's EPID images over a 40×40 cm square planar array with 1024×1024 pixels and 12-bit acquisition. A digital analogue to film dosimetry, EPID imaging is easy to use—EPIDs can be integrated with therapeutic systems and software-controlled—but the true experimental measurement may only be made at a single planar slice: thus, for EPIDs and other planar-type dosimetry methods, fully three-dimensional beam characterization is difficult and time-consuming to perform or may be impossible, while beam characterization in 3D over time (herein referred to as "four-dimensional" characterization) is extremely difficult and rarely, if ever, performed. Also, planar array-based systems have inherently limited resolution due to the finite spacing of the detectors.

[00110] Additional dosimetry methods currently under development include gel and plastic or liquid scintillation dosimetry. Despite several advantages, gel dosimetry is time consuming and requires post-processing and a readout mechanism such as optical computed tomography or magnetic resonance imaging, while scintillation methods require careful calibration and suppression of the stem effect. Finally, none of the currently known techniques are truly water equivalent, as the active medium is not water itself, which is of importance, as water is the gold-standard dosimetry medium due to its radiological close equivalence to tissue, cheap abundance, high purity, and ease of interinstitutional standardization.

[00111] As such, another embodiment uses a radio-optical triggering unit (RTU), to provide a quantifier integration (QI) unit to perform a method comprising:

detection of Cherenkov radiation (and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation) after exposure of a subject to high-energy radiation from a radiation beam source, and establishment of a Cherenkov radiation image;

detection of non-Cherenkov radiation after exposure of a subject to high-energy radiation from a radiation beam source, and establishment of a non-Cherenkov radiation measurement; and

integration of the non-Cherenkov (*i.e.*, quantitative) radiation measurements (*e.g.*, from an ionization chamber or an EPID) with the Cherenkov radiation image (*e.g.*, tomography), to produce a quantitatively calibrated high-resolution Cherenkov image. The language "high resolution" as used herein describes high spatial and temporal resolution of the measured dose distribution, *e.g.*, three-dimensional dose distribution. The quantitatively calibrated Cherenkov images represent beam geometry and intensity that are labeled with absolute dose units. These images may be used to establish a calibration where a given intensity of Cherenkov light at a given point of the phantom is experimentally associated with a particular intensity of ionization radiation in absolute dose units as measured by, for example, an EPID or ionization chamber. Further, in particular embodiments, non-Cherenkov radiation measurements (such as ionization chamber measurements) at sampling of discrete locations within the phantom or treatment volume (*e.g.*, along the beam axis) can be used to produce a table or map (one-, two-, or three-dimensional) of local conversion factors that link units of observed Cherenkov brightness to absolute dose units in different portions of a beam.

[00112] In certain embodiments of the quantifier integration (QI) unit, the non-Cherenkov radiation measurement device is selected from the group consisting of an ionization chamber, EPID, diodes, and any combination thereof. In certain embodiments, the method may further comprise the step of communication of the quantitatively calibrated high-resolution Cherenkov image to the radiation beam source unit. In this way, in certain embodiments, the detected Cherenkov radiation may be used to directly control the linear accelerator, and the beam output. In certain embodiments, the quantitatively calibrated high-resolution Cherenkov image may be stored on a second a machine-readable medium (*e.g.*, wherein the second machine-readable medium is the machine-readable medium of a DFI control unit). In certain embodiments, the non-Cherenkov radiation measurements allow quantitative estimation of the depth-vs.-dose curve from the Cherenkov radiation image.

[00113] Another embodiment provides an advanced Cherenkov-based imaging system utilizing a radio-optical triggering unit (RTU), including a quantifier integration unit. In certain embodiments, a quantifier integration (QI) unit may be incorporated into any system described herein. In certain embodiments, an advanced Cherenkov-based imaging system includes:

a radiation beam source (*e.g.*, a particle accelerator or other device for providing high-energy radiation, which, for example, may be cross-sectionally shaped by a beam-shaping apparatus, *e.g.*, a multi-leaf collimator);

at least one camera capable of imaging Cherenkov radiation (and/or radiation emitted by fluorescent substances (fluorophores) excited by Cherenkov radiation);

one or more processing units that enables the control of the radiation beam source;

a non-Cherenkov radiation measurement device; and

a quantifier integration unit,

wherein the Cherenkov radiation is detected by the camera and non-Cherenkov radiation is detected by the non-Cherenkov radiation measurement device after exposure of a subject to high-energy radiation from the radiation beam source.

[00114] Alternatively, in certain embodiments, the quantifier integration unit is implemented and integrated into an existing system via a supplemental kit, including for example, the quantifier integration unit and any component of the system described herein not present in the existing system to which the kit will be added.

[00115] Reference is now made to FIG. 4A, which schematically depicts portions of an illustrative system 400 according to certain embodiments. System 400 resembles system 200 of FIG. 4A but with the addition of a non-Cherenkov radiation measurement device 502. In certain embodiments, the non-Cherenkov radiation measurement device is an ionization chamber. For example, a typical ionization chamber is a gas-filled chamber in which high-energy (ionizing) radiation creates free charges that can be detected and whose rate of appearance corresponds to the intensity of high-energy radiation within the ionization chamber. The term “ionization chamber” is often applied to denote entire radiation-probe systems that include an ionization chamber, not only to the chamber per se. Ionization chamber probes are generally considered the gold standard for calibration of therapeutic radiation systems because they give a precise and highly localized measure of the ionizing radiation delivered by a therapeutic system at a given point, *e.g.*, a point within a water-filled phantom. In particular embodiments, the ionization chamber is the cylindrical, waterproof Farmer-type ion ionization chamber, which is recommended by various dosimetry protocols for dose measurement of radiotherapy beams. The chambers of such probes typically have volumes of 0.6–0.65 cm^3 and can report measured calibrated exposure accurate to National Institute of Standards & Technology (NIST) certified standards, which can be directly mapped to dose delivery at that point. The value of having one or more measures of exposure or dose allows calibration of the Cherenkov intensity into similar intensity units.

[00116] In certain embodiments, measurements from ionization chamber are combined/integrated with Cherenkov imaging (*e.g.*, tomography) to produce accurately calibrated Cherenkov images or non-image measurements. In certain embodiments, a localized, highly precise measurement of radiation intensity is obtained by an ionization chamber at a given point (*e.g.*, a point inside a water-filled phantom), the ionization chamber is removed, and the intensity of Cherenkov light emitted under identical radiation conditions by the sub-volume of the phantom corresponding to that previously occupied by the ionization chamber is observed. (This order of events may be varied; *e.g.*, Cherenkov imaging may precede ionization chamber measurement.) A calibration is thus enabled by which a given intensity of Cherenkov light at a given point of the phantom is experimentally associated with a particular intensity of ionization radiation as measured by ionization chamber in absolute dose units. Ionization chamber measurements at sampling of discrete locations within the phantom or treatment volume (*e.g.*, along the beam axis) can be used to produce a table or map (one-, two-, or three-dimensional) of local conversion factors that link units of observed Cherenkov brightness to absolute dose units in different portions of a beam. In an example, the resulting mapping of units is depth-dependent; in another example, the mapping is dependent on depth and on radial distance from beam center; in another example, the mapping is dependent on depth, radial distance from beam center, and distance from beam center. Thus, in certain embodiments, the tools and methods herein described enable the production of Cherenkov images of beam geometry and intensity that are labeled with absolute dose units, not merely with units of optical brightness.

[00117] In certain embodiments, for example in the illustrative system 400 of FIG. 4A, the non-Cherenkov radiation detection device 402 is a Farmer-type ionization probe inserted into the liquid-filled phantom 202. The actual gas chamber 404 of the probe 402 is at one tip of the probe 402. In particular embodiments, the volume of the chamber 404 is presumed to be sufficiently small relative to the irradiated volume 214 to permit meaningfully localized characterization of beam 108 intensity.

[00118] FIG. 4B depicts a closer view of one embodiment of the phantom 202 and probe 402, omitting cameras and other apparatus for clarity. In one illustrative method of operation of the system 400, the probe 402 may be moved so that the ion chamber 404 occupies a series of positions along the axis of the beam 108. In FIG. 4B, these points (*e.g.*, position 406) are depicted as evenly spaced along a line and seven in number, but in general need not be evenly spaced and may be of any number or spatial arrangement. In certain methods of operation, either the entire phantom 202 may be moved along the axis of the beam 108 or the location of the chamber 404 may be moved. For clarity, only positions of the chamber 404, not the whole probe 402, are depicted in FIG. 4B.

[00119] In certain embodiments, and in the illustrative method partly illustrated in FIG. 4B, ionization chamber measurements of radiation intensity are made centrally along the axis of beam 108. In certain embodiments, after all measurements, the probe 402 is removed from the phantom 202 and one or more Cherenkov images (*i.e.*, images of Cherenkov light or secondarily emitted fluorescent light) of the irradiation volume 214 are acquired. The average intensity of the observed light from within each of the seven measurement volumes is then directly correlated with radiation intensity as measured by ionization chamber. In one example, a continuous one-dimensional calibrative function can be calculated (*e.g.*, by interpolation) from the discretely measured correspondences of radiation intensity to light intensity and applied to subsequent Cherenkov images of the phantom to accurately associate radiation intensity units with light-intensity units. In certain other methods of operation, radiation intensity measurements may be made within the irradiation volume 214 according to various geometric schemes other than or addition to that depicted in FIG. 4B (*e.g.*, measurements may be located to sample a planar cross-section, or more than one planar cross-section, or a given sub-volume of the irradiation volume 214, or multiple one-dimensional transects like that depicted in FIG. 4B).

[00120] Certain embodiments advantageously combine the features of ionization chambers or other high-precision radiation tools with those of Cherenkov imaging. Ionization chamber dose measurements are highly accurate but slow and typically not acquired in more than one dimension (*e.g.*, along beam axis for depth versus dose curves, or orthogonally to beam axis for beam profile measurements) at a time. In comparison, Cherenkov imaging has the inherent strengths of rapidity and provision of two-, three-, and four-dimensional data very quickly. Cherenkov imaging does, however, require calibration for quantitative accuracy of dose estimation. Using the tools and methods described herein, combining the two types of measurements—*i.e.*, high-accuracy point or small-volume dose measurements and Cherenkov imaging—allows exploiting the strengths of both modalities while mitigating their weaknesses.

[00121] Reference is now made to FIG. 5, which schematically depicts portions of an illustrative system 500 according to certain embodiments. System 500 resembles system 200 of FIG. 2 but with the addition of a non-Cherenkov radiation measurement device 502. In one example, the imaging device 502 is an external portal imaging device (EPID). One type of EPID consists essentially of a converter layer that converts incident radiation into light and a two-dimensional array of electronic sensors capable of sensing the light thus produced. In certain embodiments, the converter layer may consist essentially of some form of metal plate in contact with either an ionization medium or a phosphor screen. Further, in certain embodiments, the detection array may be in a camera trained upon the converter, or in extended solid-state array (active matrix flat panel) parallel and close to the converter. In some EPID technologies, conversion is omitted in favor of direct detection by active matrix flat-panel devices. In essence, an EPID serves as a piece of electronic film whose image may be retrieved, in the form of digital data, at relatively high speed and without the need for development.

[00122] Regardless of technological basis, a typical EPID is capable of imaging a rectangular two-dimensional cross-section of the beam 108 (typically orthogonal to the beam 108) at a given distance from the beam source 112. In one illustrative system 500, data from the EPID may be routed to the memory 122 and processor 124 of the Cherenkov image processing subsystem 120, *e.g.*, via a quantifier integration unit described herein; in certain alternative embodiments, EPID data may be separately processed through a different interface, memory, and processing system (not depicted), such as is already provided in an integral manner with some LINAC or other therapeutic-radiation systems, before being routed to or integrated with the Cherenkov image processing subsystem 120. Provisions for mounting, moving, and communicating with the EPID are for simplicity omitted from FIG. 5, but the nature of such provisions will be familiar to persons versed in the construction of such devices, considering the disclosure herein.

[00123] Certain embodiments employ one or more non-Cherenkov measurement devices, which may employ one or more sensing modalities (*e.g.*, ionization, direct-detection flat panel), to acquire beam information. In one example, the EPID of FIG. 5 acquires lateral beam information, *i.e.*, one- or two-dimensional radiation intensity information in the plane of the non-Cherenkov device, which is orthogonal to the beam 108. In addition to non-Cherenkov dose information, Cherenkov emission information is acquired from one or more viewpoints, *e.g.*, by a moving camera, or a camera fixed relative to a moving irradiation target, or by a multiplicity of cameras. Thus, in certain embodiments, information on delivered dose is obtained from a plurality of viewpoints using at least two distinct sensing modalities, one of which is Cherenkov imaging. In one example, the lateral profile or extent of the beam at the back of the treatment area (*i.e.*, in the position of the EPID 502 depicted in FIG. 5) can be measured and, with assumptions based on lateral beam divergence and penumbra, estimates of the three-dimensional image of beam 108 can be made. This information, combined with axial decay of the signal from lateral Cherenkov imaging, can be used to estimate full four-dimensional dosimetry in a water tank or other phantom.

[00124] Advantageously, the system enables measurements to be made in real time, allowing characterization of phantom-delivered complex treatment plans at all points in the treatment. This can be a valuable tool for routine patient plan verification prior to delivery in the patient; verification could be performed on each plan prior to delivery. This is especially important for complex treatment plans, where verification is not only necessary but is reimbursed by some systems of health-care funding (*e.g.*, by Medicare in the US, as “pretreatment simulation”).

[00125] In addition, in certain embodiments of the system, the EPID or other non-Cherenkov imaging information is combined with Cherenkov imaging acquired during actual patient irradiation. Although Cherenkov light cannot typically be detected from deep within human tissue, surficial Cherenkov light may be imaged as a proxy for skin dose. In effect, Cherenkov light emitted at or just below the skin surface upon beam entry serves as a cross-sectional (through the generally non-planar skin surface) image of the incident beam, conveying information both on intensity profile and overall geometry: this information can be combined with beam profile data transmitted through the medium and detected by EPID or other non-Cherenkov information using a variety of mathematical modeling procedures to produce estimates of internal patient dose geometry, and in certain embodiments, with high temporal resolution, that are more accurate than those achievable from either Cherenkov or non-Cherenkov sensing alone. It is advantageous for patient safety and treatment efficacy to have improved knowledge of internal dosage geometry.

III. Methods of Cherenkov-Based Imaging

[00126] We provide methods using a radio-optical triggering unit (RTU). Such methods include, methods of radio-optical triggering comprising:

detection of scattered radiation by a fast response time scintillator (SCI) coupled with a high speed, single photon sensitive, silicon photomultiplier module (SiPM)) upon exposure of a subject to high-energy radiation from a radiation beam source;

conversion and amplification of the scattered radiation into optical photons, generating an analog electrical signal;

processing the analog signal to a digital timing signal, wherein the digital timing signal is synchronized with the radiation beam source; and

communication of the digital timing signal to trigger the operation of at least one camera capable of imaging Cherenkov radiation,

such that the operation of said camera is triggered to detect Cherenkov radiation for Cherenkov imaging purposes.

Versatile RTU

[00127] With reference to FIGs. 11, 12, and 13, a versatile RTU 1000 includes a fast-response radiation detector 1002. In an embodiment, the fast-response radiation detector 1002 uses a fast-response scintillator coupled to a fast-response photodetector, in an alternative embodiment the fast-response radiation detector 1002 is a semiconductor radiation detector. The fast-response radiation detector 1002 provides a raw output 1016 synchronized to pulses of the radiation and which may be used as above described to trigger cameras to detect Cherenkov radiation.

[00128] Signals from the fast response radiation detector 1002 are not well timed for detecting background images or fluorescent images, in addition there may be shutter delays and risetime delays. In an embodiment, signals from the fast response radiation detector 1002 are detected 1050 and measured 1052 as to time 1030 of occurrence, and width 1032 by pulse timing and measurement circuits 1004, providing this information to processor 1008. Processor 1008, operating under control of machine readable instructions of firmware in memory 1010, determines a pulse rate and pulse width from the time of occurrence of multiple radiation pulses, and predicts 1054 a time 1024 of occurrence for each next radiation pulse, instructing pulse generator circuits 1006 to generate 1056 a synchronized pulse 1028 output 1018 during each next radiation pulse. Processor 1008 also instructs pulse generator circuits 1006 to provide a signal 1022, bearing a pulse 1023 just after an end of the radiation pulse to be used for imaging fluorescent emissions before they decay, and an output 1020 bearing a pulse 1021 late in each pulse-to-pulse interval to trigger capture of background images for background subtraction.

[00129] To prevent interference by room lighting, when the fast response radiation detector 1002 incorporates a scintillator and photodetector, those components are encapsulated in a light shield 1014 configured to exclude light from other sources. Further, to prevent stray or scattered high energy radiation or x-rays from erasing data in electrically-programmable or reprogrammable memory devices, or corrupting data in dynamic RAM memory devices, of memory 1010, memory 1010 is enclosed in radiation shield 1012.

Unintensified, Multi-pulse-integrating Camera

[00130] Due to the weak efficiency of Cherenkov light generation, the surface fluence ranges from 1-100 nW/cm2, and therefore is not easily observed under the standard treatment conditions. However, the pulsed nature of the beam can be leveraged to suppress the background and improve signal-to-noise ratio using synchronized gated imaging. In most therapeutic LINAC systems, the radiation dose is delivered to the patient in a form of a sequence of x-ray or electron pulse bursts with microsecond pulse duration and with millisecond repetition rate. In past systems, a gated image intensifier coupled with CCD or CMOS imaging sensors was the sole technology capable of suppressing the background-only light while amplifying the weak Cherenkov light during the microsecond gating periods. The amplified image from the gated image intensifier was imaged by a CCD or CMOS photodiode-array imaging sensor. In addition to requiring high voltages and vacuum for operation, the image intensifier portions of these cameras were found to exhibit long-term non-linearity and high sensitivity to stray x-ray noise, which is abundant in the treatment room and caused unwanted image artifacts.

[00131] We discovered that a commercial-grade time-domain Time-of-Flight (ToF) CMOS image sensor, the Teledyne e2v BORA® (trademark of Teledyne Technologies, Thousand Oaks, California) 1.3-megapixel image sensor, can be configured as a pulse-gated, multi-pulse integrating, image sensor in a way to be capable of detecting Cherenkov light from tissue. It is expected that similar image sensors may become available with greater numbers of pixels. The BORA ToF image sensor is operated in a gated multi-integration mode, where the photo-sensitive component (photodiode 1502) (FIG. 15) of the pixels is repeatedly connected (gated) by a transfer gate 1506 to a storage node (capacitor 1504) within each pixel during each beam pulse, and both isolated from the storage node and precharged by a precharge gate 1508 between beam pulses to prevent transferring charges accumulated on the photodiode from background illumination between beam pulses from reaching the storage node. The electronic signal from a multitude of light pulses is stored on the storage node 1504 in the pixels prior frame readout. Accumulation of the signal in pixels prior readout helps overcome the readout noise when reading a Cherenkov or scintillation image acquired during beam pulses by integrating the dim Cherenkov or scintillation light over multiple beam pulses while excluding that portion of background light that is received between beam pulses.

[00132] Additionally, the gated operation also allows to be used to record background light received between beam pulses only. This is achieved by introducing a phase shift or delay between the X-ray or electron pulses, and the gate signal to acquire light from the treatment zone and patient under background illumination with the beam off. Background-only acquisition of a background correction image frame allows subtraction, as controlled by firmware in the DSP, of the background light from the Cherenkov or scintillation image in the DSP. This allows quantitative imaging and remote dose measurement even in the presence of arbitrary background light from room lighting; imaging with room lights on is desired by many patients because they can become claustrophobic when left in a strange room in the dark.

[00133] The general imaging setup is depicted if FIG. 1A. Subject 106 is irradiated by a beam of X-rays or electrons 108, generated in a pulsed linear accelerator (LINAC serving as beam source 112. Cherenkov emissions are emitted from tissue, and scintillation light is emitted from scintillator, if present. One or more cameras 102, 104, which uses the gated BORA CMOS ToF image sensor array and a lens system, observes the beam interaction area of the patient. The gating signal is driven either by directly interfacing the LINAC, or by using a remote trigger detector RTU as described above, for a trigger signal to which the gate signal is synchronized. Gated images are processed in the camera and image processing subsystem 120, which also displays the background-subtracted Cherenkov or scintillation image and related metrics.

[00134] In one embodiment, the architecture of single pixel in a gated CMOS light sensor array is depicted in FIG. 15, and operates according to the corresponding timing diagram is outlined in FIG. 16. Image frame acquisition begins with resetting the charge of storage capacitor 1504 C by applying a “reset” pulse to a reset device 1510, typically charging the capacitor to a reference voltage Vr. During the gated exposure of the Cherenkov or scintillation frame, the gate pulse *gate 1604* is repetitively applied to the sensor during beam pulses 1602 to allow photocurrent flow from photodiode PD and transfer gate 1506 to collect as charge on capacitor 1504. To erase stray charges accumulated between beam pulses on photodiode PD 1502, the *buffer* signal 1608 may be used to turn on a precharge gate transistor 1508 to precharge the photodiode PD 1502. Once charge from a suitable number of radiation pulses have accumulated on the storage capacitor 1504, charge on the storage capacitor 1504 is read through source follower 1512 and selection 1514 transistors by a select line 1610 to a data readout line.

[00135] This action substitutes for the combination of image intensifier gating and a single exposure in conventional Cherenkov cameras. Once light is acquired for a necessary number of pulses is acquired, the gate line is set inactive, and the 2D charge matrix is read out as described through the source follower 1512 and selection transistors 1514. In embodiments, light is acquired during at least ten to twenty pulses but in some embodiments light may be acquired and integrated during as many as 200 or more beam pulses for each image.

[00136] The concept of intensifier-less Cherenkov imaging was demonstrated using a 1.3-megapixel Teledyne BORA ToF sensor and an optical lens in a camera imaging a square 6MV X-ray beam intersecting a white ABS plate and captured at a rate of 20 frames per second. A representative single frame of an image stream capturing Cherenkov radiation is shown in FIG. 17. A static background frame was captured prior to capturing the Cherenkov frame, subtracted from the Cherenkov frame, and the resulting Cherenkov-only image is displayed in FIG. 17 in light color 1700, while the background image is displayed in grayscale.

[00137] FIG. 19 is an exemplary integrated background image of a target 1900 captured over 200 beam pulses. FIG. 18A is an exemplary single-frame image of Cherenkov radiation corrected by subtracting the integrated background image of FIG. 19; FIG. 18B is an exemplary image of Cherenkov radiation captured with a gated, multiple-pulse-integrating, CMOS image sensor over 200 beam pulses corrected by subtracting an integrated background image of FIG. 19, showing the significant improvement in image quality over the single-frame photograph of FIG. 18A attainable with the BORA ToF image sensor array operated in the pulse-gated, multiple-pulse integrating (PG-MPI), mode herein described and showing a region 1800 of a target emitting Cherenkov radiation where a pulsed radiation beam intersects the target.

[00138] Advantages of the system and method herein include that the multi-integration mode of a gated time-of-flight imaging sensor, herein known as a pulse-gated, multiple-pulse-integrating, CMOS image sensor or camera can image the weak Cherenkov and/or scintillation light with a performance and image quality sufficient for commercial application. Our system eliminated image artifacts and signal nonlinearity caused by image intensifiers. Further, the complexity of the Cherenkov camera is decreased over prior systems, as there is no need of a fragile, complex, and expensive image intensifier. The commercially-available image-sensor chip that we used in this demonstration allowed nearly 100-fold price reduction of the imaging system, and holds significant potential for commercialization of Cherenkov cameras for safety applications in radiotherapy.

[00139] We anticipate better images may be obtained by cooling the image sensor.

[00140] In summary, the system is operated according to a radiation exposure determination method 2000 (FIG. 20) where the pulsed radiation beam source 112 (FIG. 1A) provides 2002 a regularly-spaced sequence of pulses of a radiation beam 108 to tissue 110 of the subject 106. In embodiments using the radio-optical triggering units (RTUs) illustrated with reference to FIGS. 6A or 6B, scattered radiation from pulses of the radiation beam 108 is detected 2004 in a high-speed radiation detector of the RTU to provide a signal “A”. In some embodiments using dual RTUs as illustrated with reference to FIG. 6B, scattered radiation from pulses of the radiation beam is detected in a second high-speed radiation detector to provide 2006 a second signal “B”, signals “A” and “B” are then logically “AND”-ed to generate a composite radiation detection signal “C. As illustrated with reference to FIG. 13, the composite signal “C” in dual RTU systems, the signal “A” in single RTU systems, or a pulse output of the pulsed radiation beam source in systems without an RTU is processed to measure time and duration of pulses and to generate 2008 a “beam-ON” pulse signal.

[00141] The PG-MPI camera is then reset 2012 and the “beam-ON” signal used to trigger the PG-MPI camera to integrate 2014 received Cherenkov light received from tissue 110, the Cherenkov light emitted during pulses of the pulsed radiation beam, the Cherenkov light being integrated in the PG-MPI camera over a sequence of multiple pulses of the pulsed radiation beam, while ignoring light received between pulses of the pulsed radiation beam, to generate a Cherenkov light image. In some embodiments, the Cherenkov light is integrated over at least 10 and in some embodiments at least 200 pulses of the pulsed radiation beam while forming the Cherenkov light image.

[00142] As discussed with reference to FIG. 13, a “Beam OFF” signal is also generated 2010, the “Beam OFF” signal being timed to be between, and not overlapping, pulses of the radiation beam, this signal may be derived from RTU output signals A or C, from the “beam ON” signal, or directly from a signal provided by the pulsed radiation beam source 112 as appropriate for the system. The PG-MPI camera is then reset 2016 and the PG-MPI camera is used to generate 2018 a background image of light received from tissue of the subject when pulses of the radiation beam are not present and thus no Cherenkov light is being emitted from tissue of the subject.

[00143] The background image is scaled if necessary and subtracted 2020 from the Cherenkov light image to generate 2024 a corrected Cherenkov light image.

[00144] Separately, a set of calibration tables has been generated 2022, in embodiments these calibration tables are generated using a non-Cherenkov-based dose-quantifier device or system; these tables need only be generated once and can be reused for converting many corrected Cherenkov light images to dose maps.

[00145] The calibration tables are then used with overall beam pulse counts to convert 2024 the corrected Cherenkov light image into a calibrated current dose map and a calibrated cumulative dose map. Generation of these dose maps may be repeated many times during a radiation treatment session. Once generated, the calibrated current and calibrated cumulative dose maps may be displayed 2026 to a user or operator to verify correct treatment is being applied to the subject, or automatically compared against thresholds and alarms generated whenever a dose map shows areas of excessive dose.

COMBINATIONS

[00146] The features herein described can be combined in a multitude of different ways while forming various embodiments of the system. Among combinations anticipated by the inventors are:

[00147] A Cherenkov imaging system designated A including a high-speed radiation detector configured to provide a first timing signal synchronized with pulses of radiation provided by a pulsed radiation beam source; the timing signal being coupled to control operation of at least one camera capable of imaging Cherenkov radiation; and a digital image-processing system; where the high-speed radiation detector is selected from the group consisting of solid-state radiation detectors and radiation detectors of the type comprising a scintillator and a photodetector; and where the at least one camera capable of imaging Cherenkov radiation is a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera synchronized through the digital time signal to pulses of the radiation beam.

[00148] A Cherenkov imaging system designated AA including the Cherenkov imaging system designated A wherein a plurality of pixels of the PG-MPI camera comprises a photodiode coupled through a precharge gate to a precharge level signal, the photodiode also coupled through a transfer gate to a capacitor associated with the storage node, the storage node also coupled through a reset transistor to a reset voltage signal, the storage node also coupled to a gate of a source follower, the source of the source follower being coupled through a select transistor to a data readout line.

[00149] A Cherenkov imaging system designated AB including the Cherenkov imaging system designated A or AA further comprising a second high-speed radiation detector configured to provide a second timing signal, and the camera capable of imaging

Cherenkov radiation is controlled to image Cherenkov radiation when both the first and second high-speed radiation detectors detect radiation.

[00150] A Cherenkov imaging system designated AC including the Cherenkov imaging system designated AB, AA, or A wherein the digital image-processing system is configured to use the PG-MPI camera to capture an image of Cherenkov emissions and a background image, and to subtract the background image from the image of Cherenkov emissions to generate a corrected Cherenkov image.

[00151] A Cherenkov imaging system designated AD including the Cherenkov imaging system designated AC wherein the digital image-processing system is further configured to apply calibration tables to the corrected Cherenkov image to generate a dose map.

[00152] An imaging unit designated B and including a trigger input adapted for connection to a beam-on output signal provided by a pulsed radiation beam source, the trigger input receiving a digital timing signal; apparatus configured to communicate the digital timing signal to trigger operation of at least one camera capable of imaging Cherenkov radiation; where the camera capable of imaging Cherenkov radiation is a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera synchronized through the digital time signal to pulses of the radiation beam source.

[00153] A Cherenkov imaging system designated BA including the system designated B wherein each pixel of a plurality of pixels of the PG-MPI camera comprises a photodiode coupled through a precharge gate to a precharge level signal, the photodiode also coupled through a transfer gate to a capacitor associated with the storage node, the storage node also coupled through a reset transistor to a reset voltage signal, the storage node also coupled to a gate of a source follower, the source of the source follower being coupled through a select transistor to a data readout line.

[00154] A Cherenkov imaging system designated BB including the system designated B or BA wherein the digital image-processing system is configured to use the PG-MPI camera to capture an image of Cherenkov emissions and a background image, and to subtract the background image from the image of Cherenkov emissions to generate a corrected Cherenkov image.

[00155] A Cherenkov imaging system designated BC including the system designated BB wherein the digital image-processing system is further configured to apply calibration tables to the corrected Cherenkov image to generate a dose map.

[00156] A method of imaging Cherenkov light emitted by a phantom or tissue designated C includes providing a timing signal synchronized to pulses of a pulsed radiation beam; applying the pulsed radiation beam to the phantom or tissue, the pulsed radiation beam causing the phantom or tissue to emit the Cherenkov light; imaging the Cherenkov light with a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera; imaging the Cherenkov light being performed by integrating light received by the PG-MPI camera during multiple pulses of the radiation beam and not integrating light received by the PG-MPI camera between pulses of the radiation beam.

[00157] A method of imaging Cherenkov light designated CA including the method designated C where the timing signal synchronized to pulses of the pulsed radiation beam is provided by a radio-optical triggering unit (RTU) configured to detect scattered radiation from pulses of the radiation beam.

[00158] A method of imaging Cherenkov light designated CB including the method designated C where the timing signal synchronized to pulses of the pulsed radiation beam is provided by a source of the pulsed radiation beam.

[00159] A method of imaging Cherenkov light designated CC including the method designated C where the timing signal synchronized to pulses of the pulsed radiation beam is provided by logically "AND"-ing signals from two radio-optical triggering units configured to detect scattered radiation from pulses of the radiation beam.

[00160] A method of imaging Cherenkov light designated CD including the method designated CC, CB, or CA wherein the PG-MPI camera is configured to integrate the Cherenkov light over at least 10 pulses of the pulsed radiation beam while forming the Cherenkov light image.

[00161] A method of imaging Cherenkov light designated CE including the method designated C, CA, CB, CC, or CD wherein the PG-MPI camera is used to generate a background image of light received from tissue of the subject when pulses of the radiation beam are not present; and further comprising subtracting the background image from the Cherenkov light image to form a corrected Cherenkov image.

[00162] A method of imaging Cherenkov light designated CF including the method designated CE further comprising using calibration tables to convert corrected Cherenkov light images to dose maps.

[00163] A method of imaging Cherenkov light designated CG including the method designated CF further comprising using the dose maps to verify correct treatment is being applied to a subject.

[00164] Changes may be made in the above methods and systems without departing from the scope hereof. It should thus be noted that the matter contained in the above description or shown in the accompanying drawings should be interpreted as illustrative and not in a limiting sense. The following claims are intended to cover all generic and specific features described herein, as well as all statements of the scope of the present method and system, which, as a matter of language, might be said to fall therebetween.

CLAIMS

What is claimed is:

1. A Cherenkov imaging system comprising:

a high-speed radiation detector configured to provide a first timing signal synchronized with pulses of radiation provided by a pulsed radiation beam source;

the first timing signal is coupled to control operation of at least one camera capable of imaging Cherenkov radiation; and

a digital image-processing system;

where the high-speed radiation detector is selected from the group consisting of solid-state radiation detectors and radiation detectors of the type comprising a scintillator and a photodetector;

where the at least one camera capable of imaging Cherenkov radiation comprises a pulse-gated, multiple-pulse-integrating, (PG-MPI) CMOS image sensor synchronized through the first time signal to pulses of the radiation beam source.

2. A Cherenkov imaging system of claim 1 wherein a plurality of pixels of the PG-MPI CMOS image sensor each comprise a photodiode coupled through a precharge gate to a precharge level signal, the photodiode also coupled through a transfer gate to a capacitor associated with a storage node, the storage node also coupled through a reset transistor to a reset voltage signal, the storage node also coupled to a gate of a source follower, the source of the source follower being coupled through a select transistor to a data readout line.

3. The Cherenkov imaging system of claim 1 further comprising a second high-speed radiation detector configured to provide a second timing signal, and the camera capable of imaging Cherenkov radiation is controlled to image Cherenkov radiation when both the first and second high-speed radiation detectors simultaneously detect radiation.

4. The Cherenkov imaging system of claim 1, 2, or 3 wherein the digital image-processing system is configured to use the camera capable of imaging Cherenkov radiation to capture an image of Cherenkov emissions and a background image, and to subtract the background image from the image of Cherenkov emissions to generate a corrected Cherenkov image.

5. The Cherenkov imaging system of claim 4 wherein the digital image-processing system is further configured to apply calibration tables to the corrected Cherenkov image to generate a dose map.

6. An imaging unit comprising:

a trigger input adapted for connection to a beam-on output signal provided by a pulsed radiation beam source, the trigger input receiving a digital timing signal;

apparatus configured to communicate the digital timing signal to trigger operation of at least one camera capable of imaging Cherenkov radiation;

where the camera capable of imaging Cherenkov radiation is a pulse-gated, multiple-pulse-integrating, (PG-MPI) CMOS camera synchronized through the digital time signal to pulses of the radiation beam source.

7. A Cherenkov imaging system of claim 6 wherein each pixel of a plurality of pixels of the PG-MPI CMOS camera comprises a photodiode coupled through a precharge gate to a precharge level signal, the photodiode also coupled through a transfer gate to a capacitor associated with the storage node, the storage node also coupled through a reset transistor to a reset voltage signal, the storage node also coupled to a gate of a source follower, the source of the source follower being coupled through a select transistor to a data readout line.

8. The Cherenkov imaging system of claim 6 or 7 wherein the digital image-processing system is configured to use the PG-MPI CMOS camera to capture an image of Cherenkov emissions and a background image, and to subtract the background image from the image of Cherenkov emissions to generate a corrected Cherenkov image.

9. The Cherenkov imaging system of claim 8 wherein the digital image-processing system is further configured to apply calibration tables to the corrected Cherenkov image to generate a dose map.

10. A method of imaging Cherenkov light emitted by a phantom or tissue comprising:

providing a timing signal synchronized to pulses of a pulsed radiation beam;

applying the pulsed radiation beam to the phantom or tissue, the pulsed radiation beam causing the phantom or tissue to emit the Cherenkov light;

imaging the Cherenkov light with a pulse-gated, multiple-pulse-integrating, (PG-MPI) camera; imaging the Cherenkov light being performed by integrating light received by the

PG-MPI camera during multiple pulses of the radiation beam and not integrating light received by the PG-MPI camera between pulses of the radiation beam.

11.The method of claim 10 where the timing signal synchronized to pulses of the pulsed radiation beam is provided by a radio-optical triggering unit (RTU) configured to detect scattered radiation from pulses of the radiation beam.

12. The method of claim 10 where the timing signal synchronized to pulses of the pulsed radiation beam is provided by a source of the pulsed radiation beam.

13.The method of claim 10 where the timing signal synchronized to pulses of the pulsed radiation beam is provided by logically "AND"-ing signals from two radio-optical triggering units configured to detect scattered radiation from pulses of the radiation beam.

14. The method of claim 10, 11, 12 or 13 wherein the PG-MPI camera is configured to integrate the Cherenkov light over at least 10 pulses of the pulsed radiation beam while forming the Cherenkov light image.

15. The method of claim 14 wherein the PG-MPI camera is used to generate a background image of light received from tissue of the subject when pulses of the radiation beam are not present; and further comprising subtracting the background image from the Cherenkov light image to form a corrected Cherenkov image.

16. The method of claim 15 further comprising using calibration tables to convert corrected Cherenkov light images to dose maps.

17. The method of claim 16 further comprising using the dose maps to verify correct treatment is being applied to a subject.

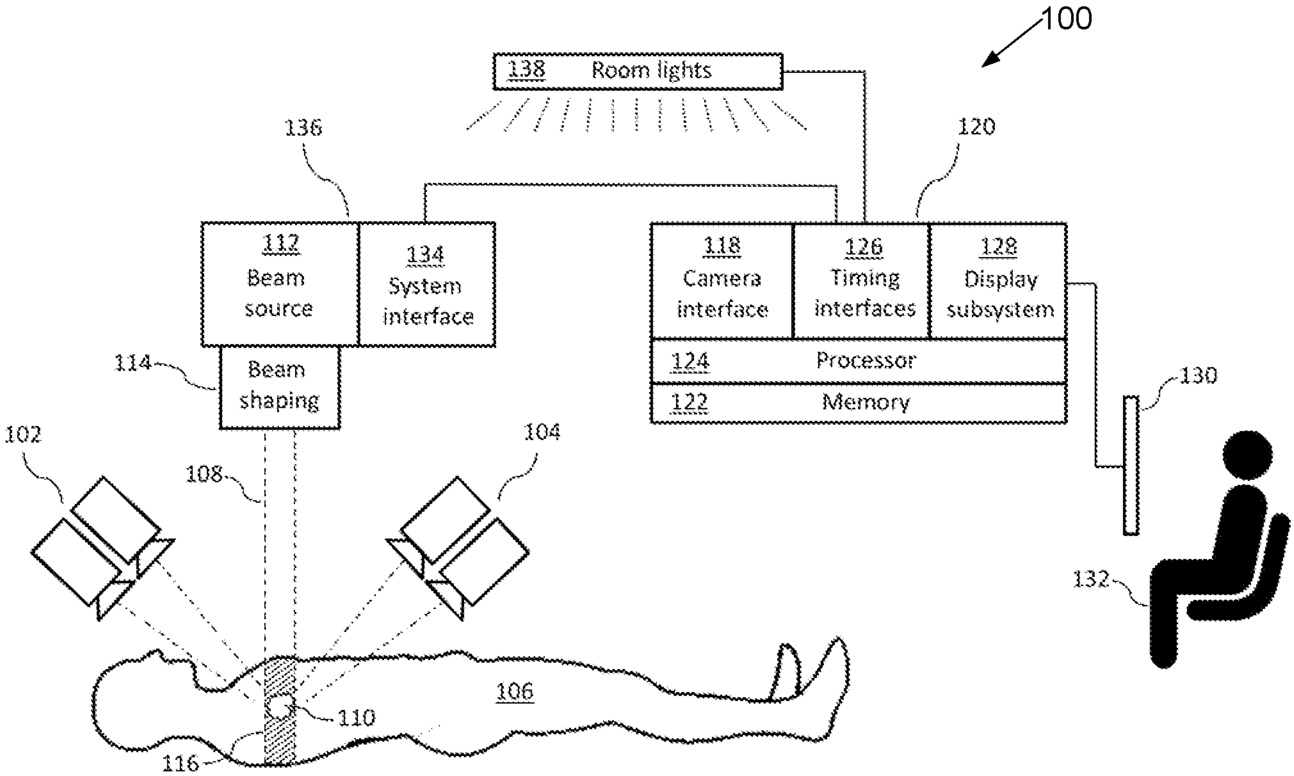

100
138 Room lights
136
120
112 Beam source
134 System interface
118 Camera interface
126 Timing interfaces
128 Display subsystem
114
Beam shaping
124 Processor
122 Memory
130
102
108
104
132
106
110
116

Fig. 1A

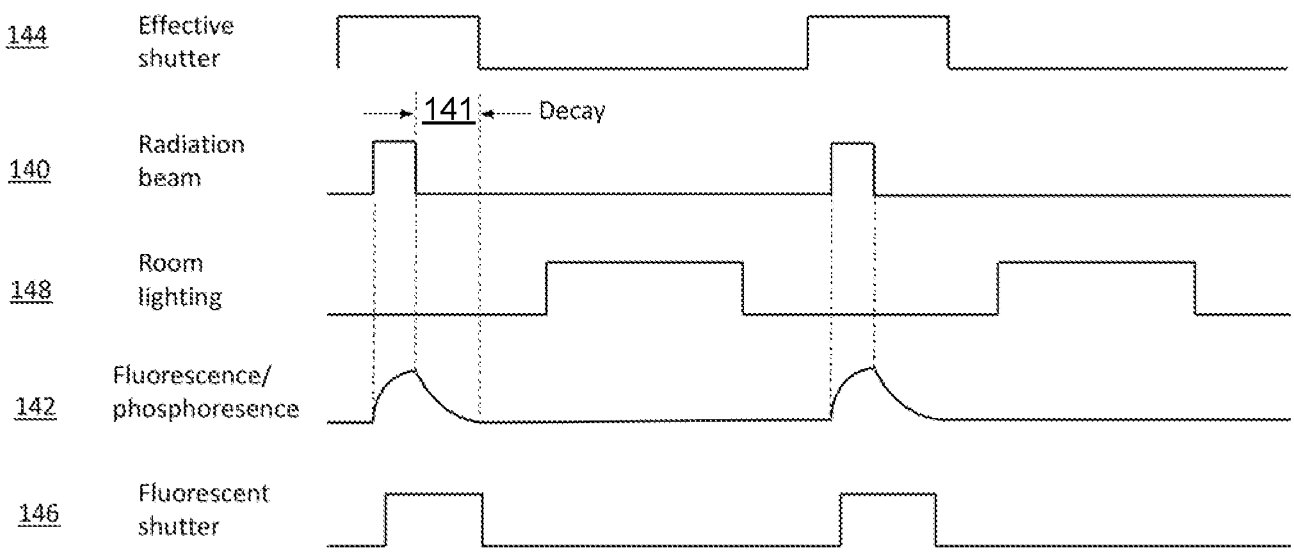

144 Effective shutter
141
Decay
140 Radiation beam
148 Room lighting
142 Fluorescence/ phosphoresence
146 Fluorescent shutter

Fig. 1B

200

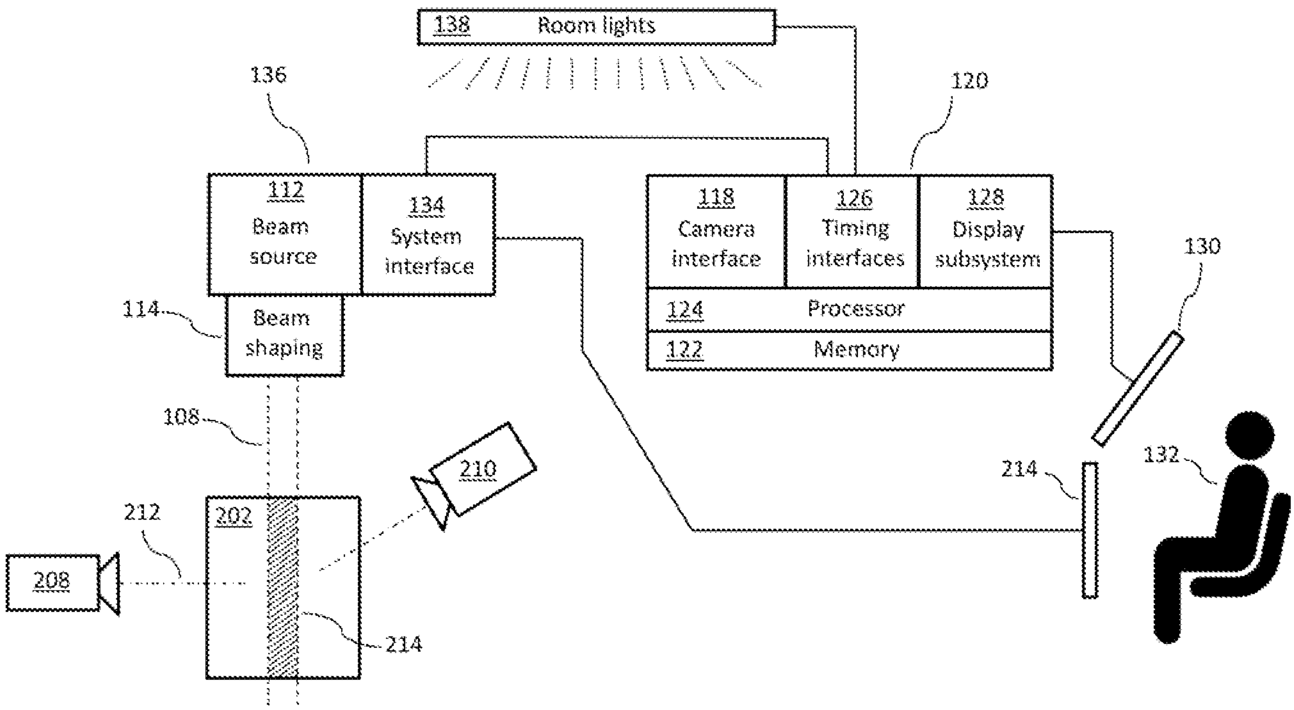


Fig. 2

400

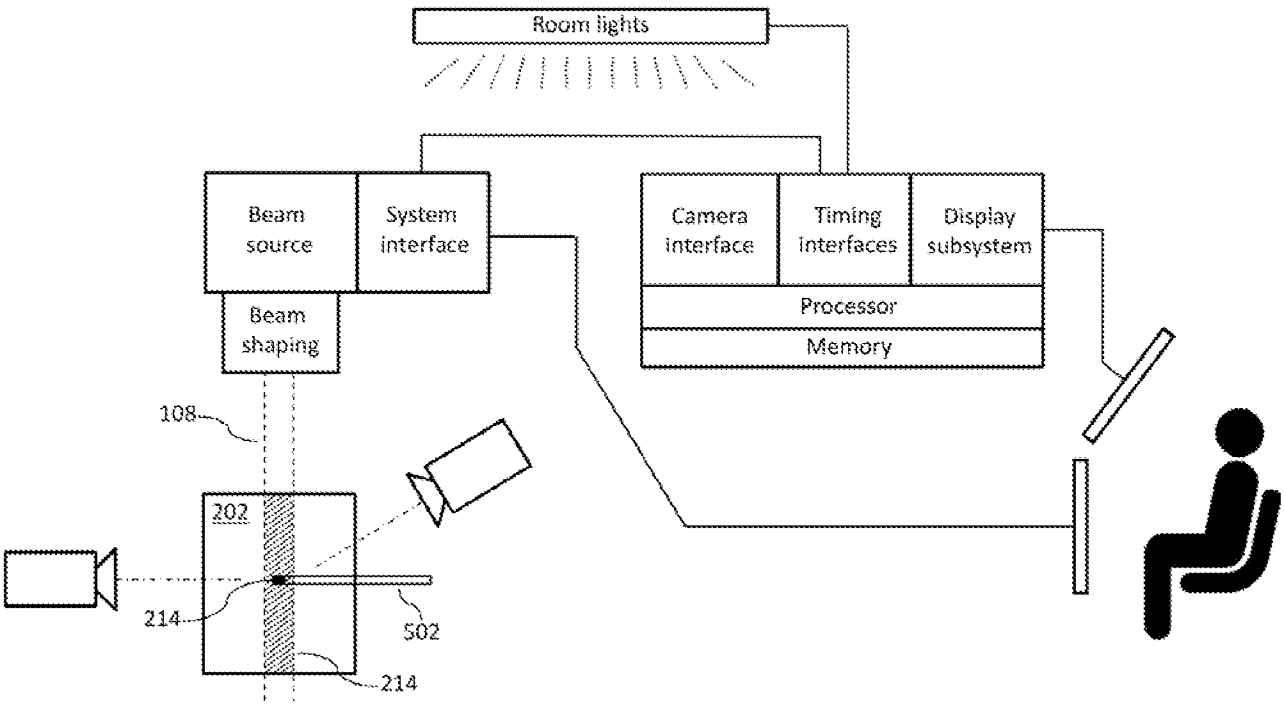


Fig. 4A

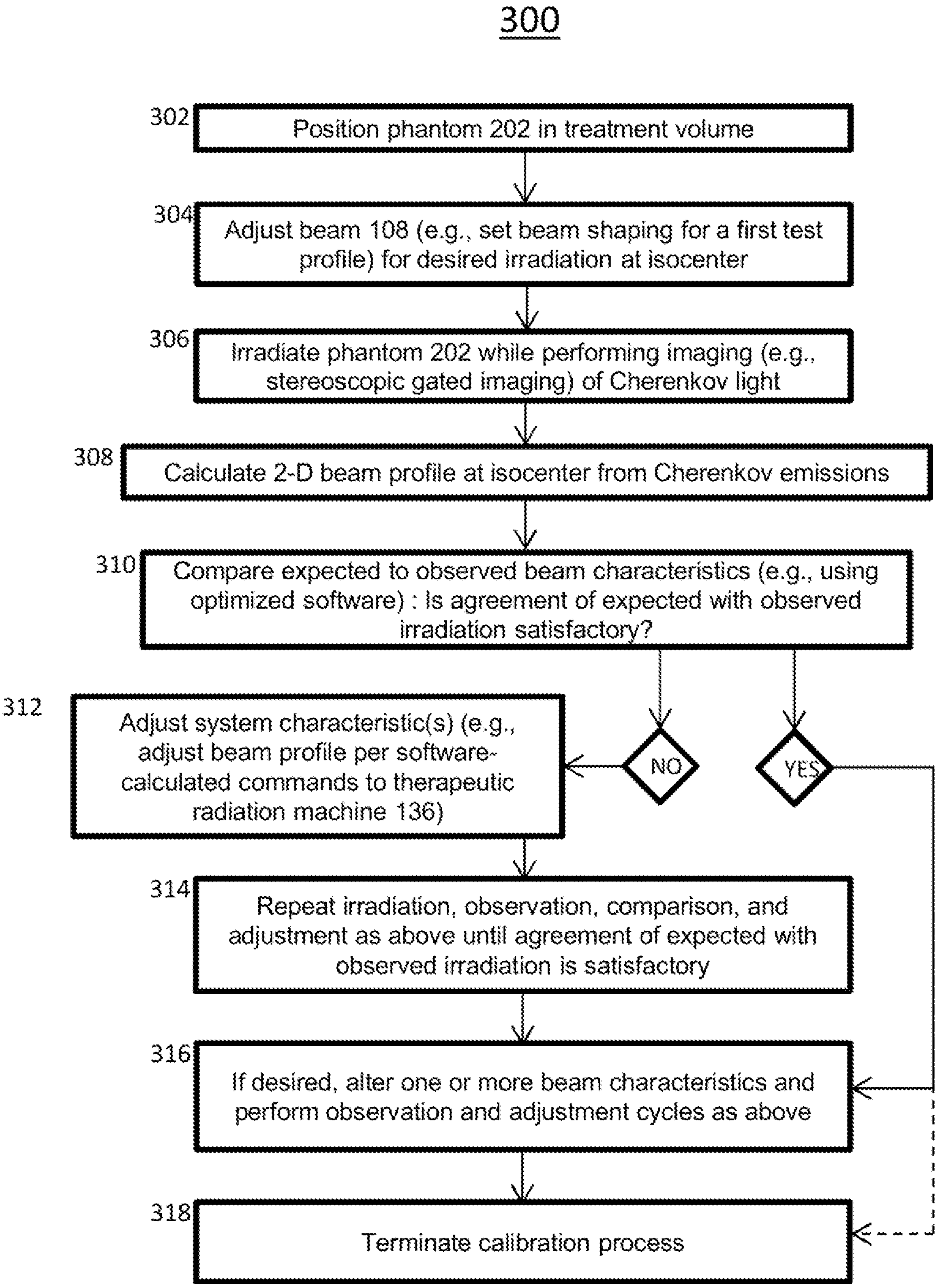

300
302
Position phantom 202 in treatment volume
304
Adjust beam 108 (e.g., set beam shaping for a first test profile) for desired irradiation at isocenter
306
Irradiate phantom 202 while performing imaging (e.g., stereoscopic gated imaging) of Cherenkov light
308
Calculate 2-D beam profile at isocenter from Cherenkov emissions
310
Compare expected to observed beam characteristics (e.g., using optimized software) : Is agreement of expected with observed irradiation satisfactory?
312
Adjust system characteristic(s) (e.g., adjust beam profile per software-calculated commands to therapeutic radiation machine 136)
NO
YES
314
Repeat irradiation, observation, comparison, and adjustment as above until agreement of expected with observed irradiation is satisfactory
316
If desired, alter one or more beam characteristics and perform observation and adjustment cycles as above
318
Terminate calibration process

Fig. 3

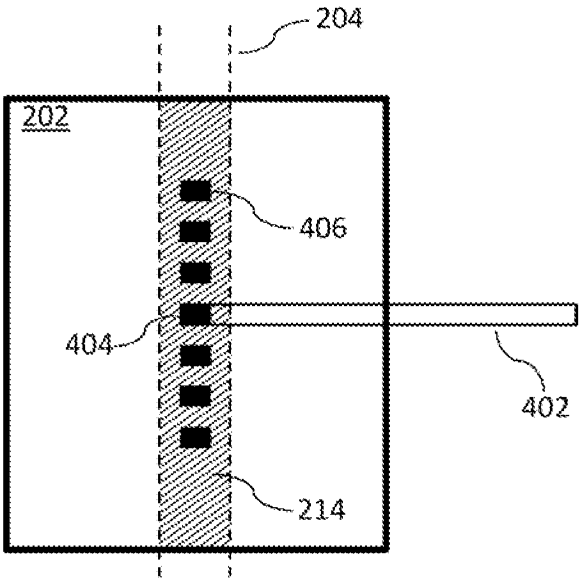

204
202
406
404
402
214

Fig. 4B

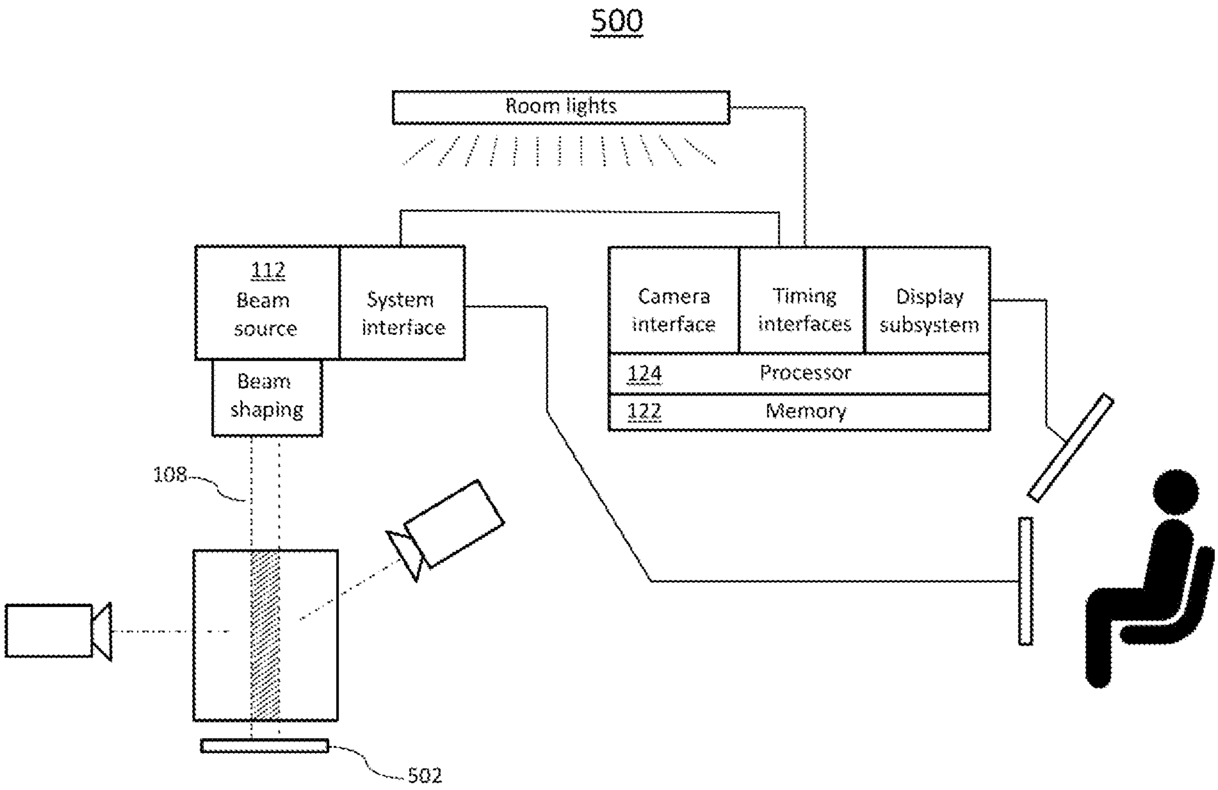

500
Room lights
112
Beam
source
System
interface
Camera
interface
Timing
interfaces
Display
subsystem
124 Processor
122 Memory
Beam
shaping
108
502

Fig. 5

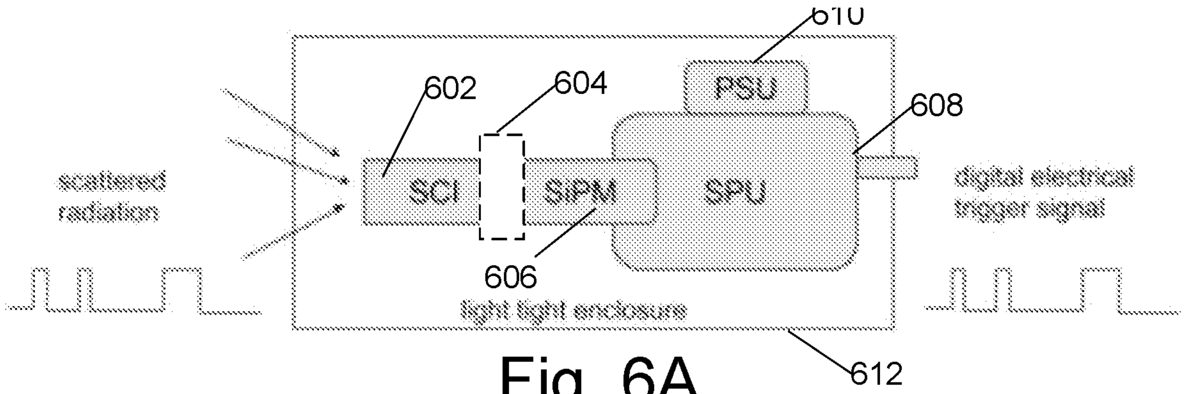

610
602
604
608
PSU
scattered radiation
SCI
SiPM
SPU
digital electrical trigger signal
606
light tight enclosure
612

Fig. 6A

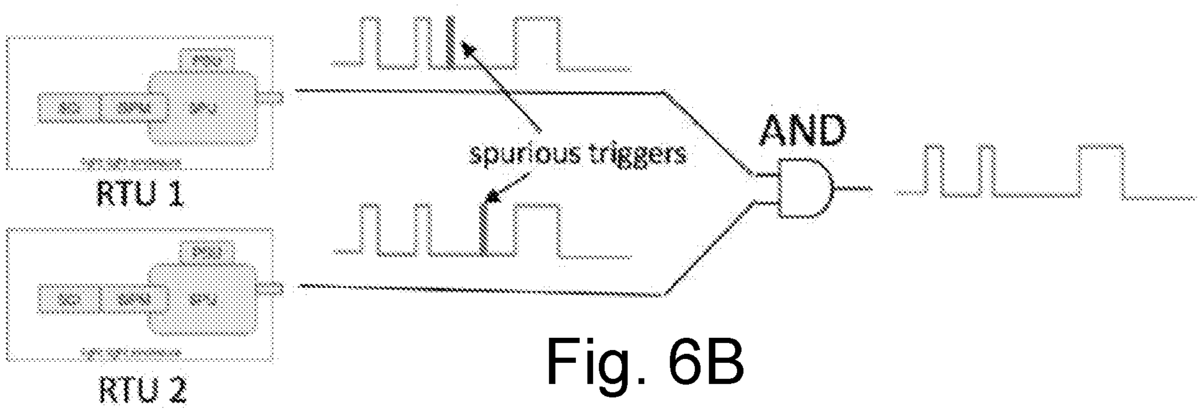

AND
spurious triggers
RTU 1
RTU 2

Fig. 6B

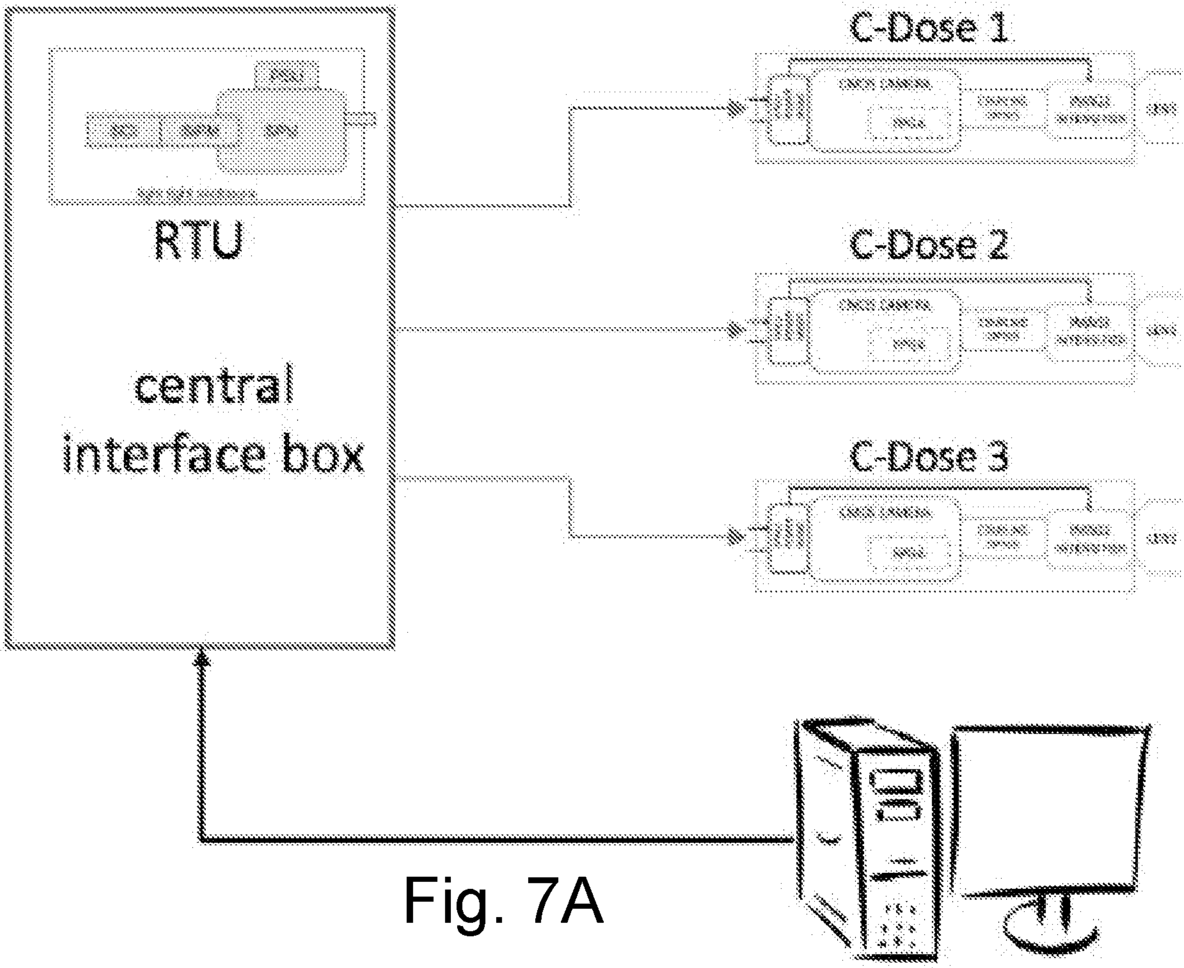


Fig. 7A

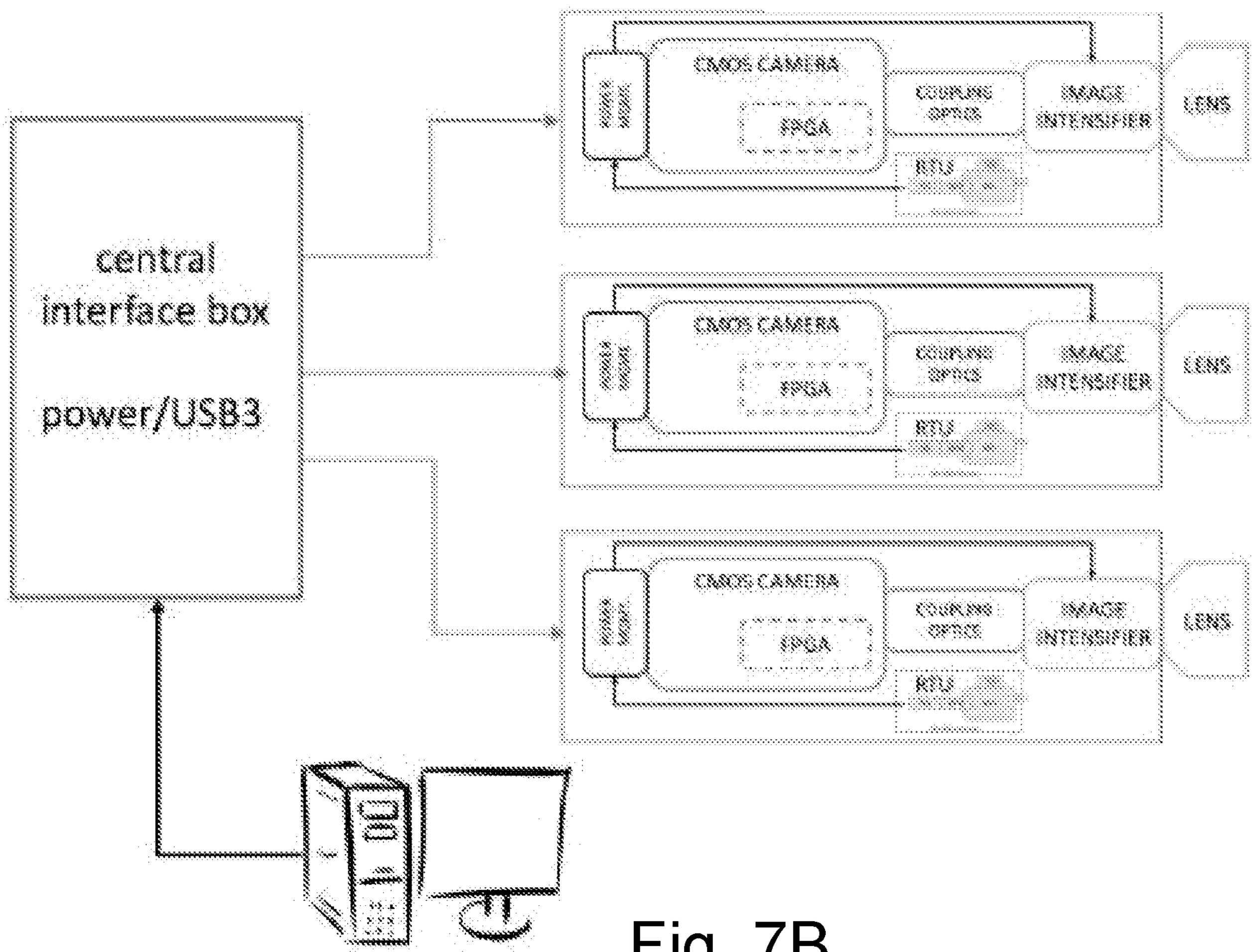

central
interface box
power/USB3
CMOS CAMERA
FPGA
COUPLING
OPTICS
IMAGE
INTENSIFIER
LENS
RTU

Fig. 7B

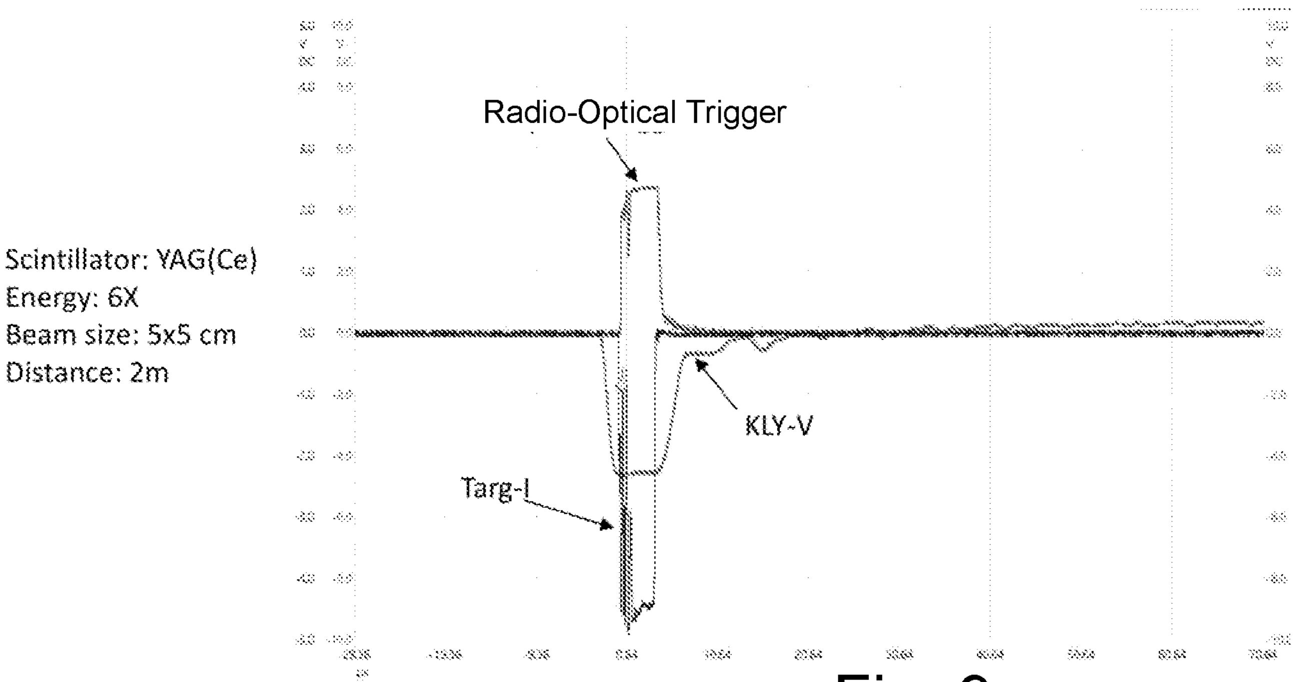
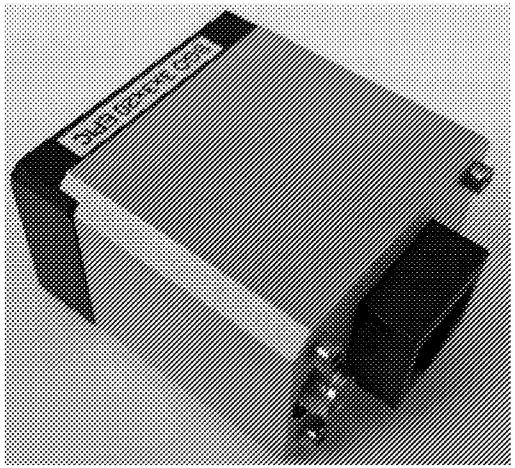

Radio-Optical Trigger
Scintillator: YAG(Ce)
Energy: 6X
Beam size: 5x5 cm
Distance: 2m
KLY-V
Targ-I

Fig. 9

Casing



Scintillator housing

Electronics

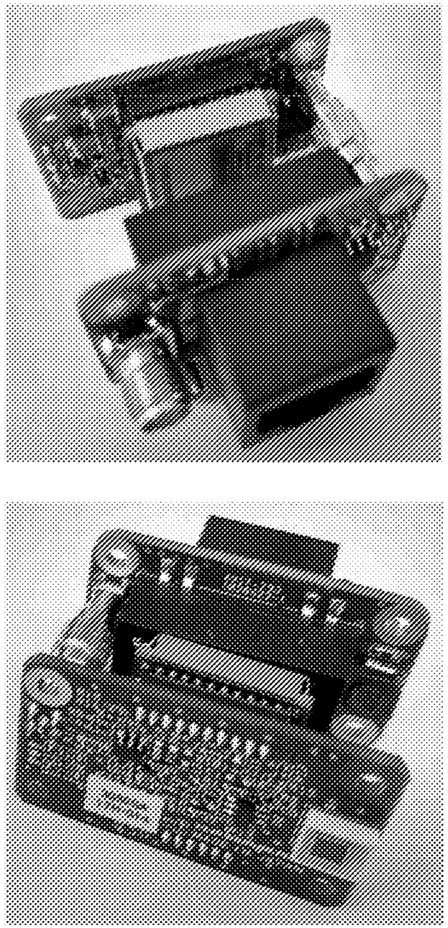


Fig. 8

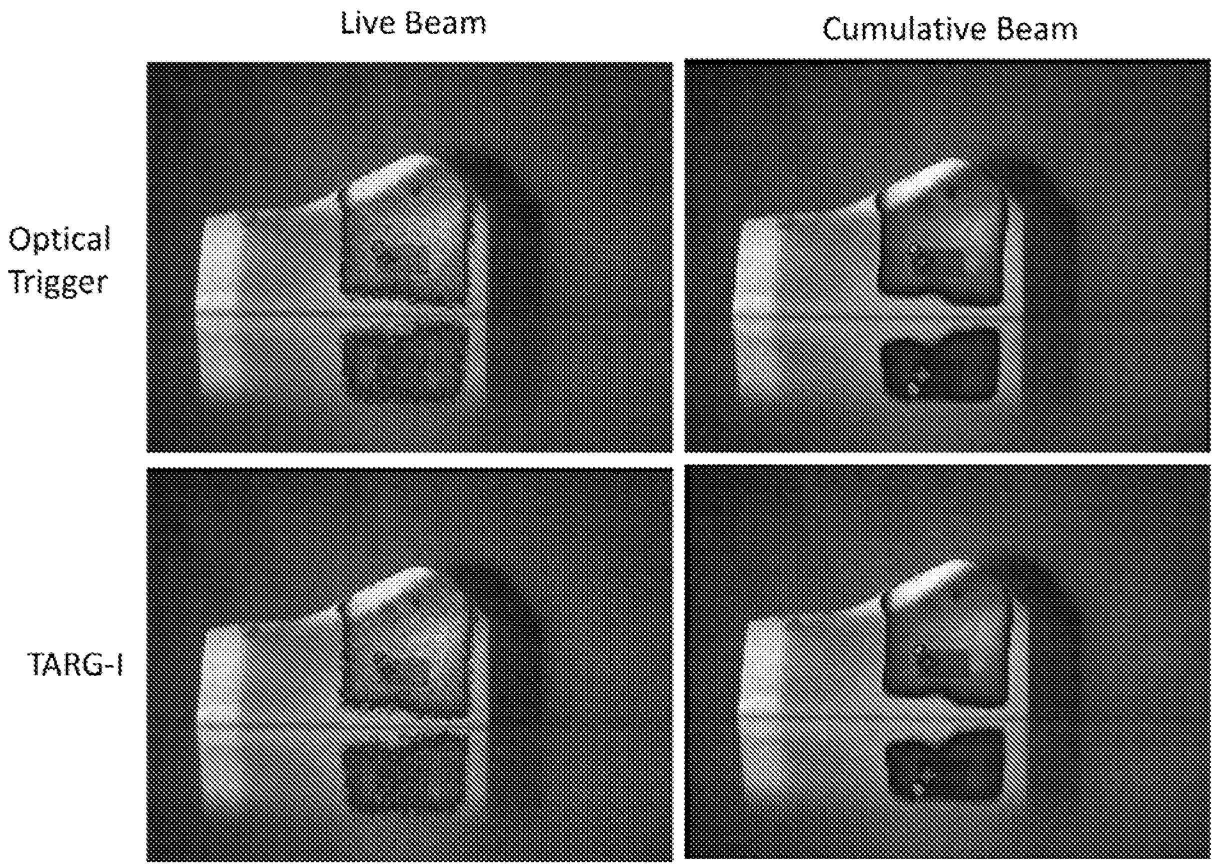


Fig. 10A

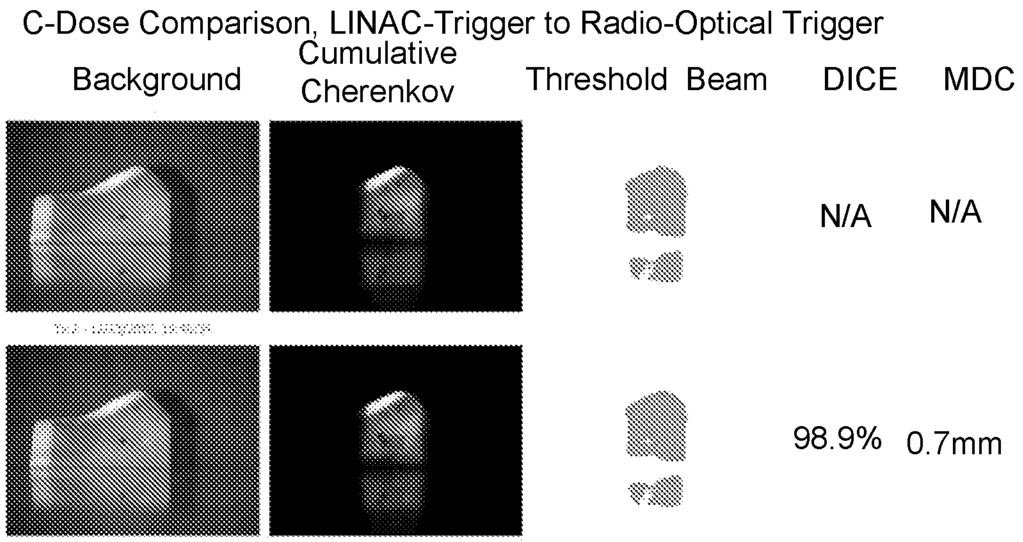


Fig. 10B

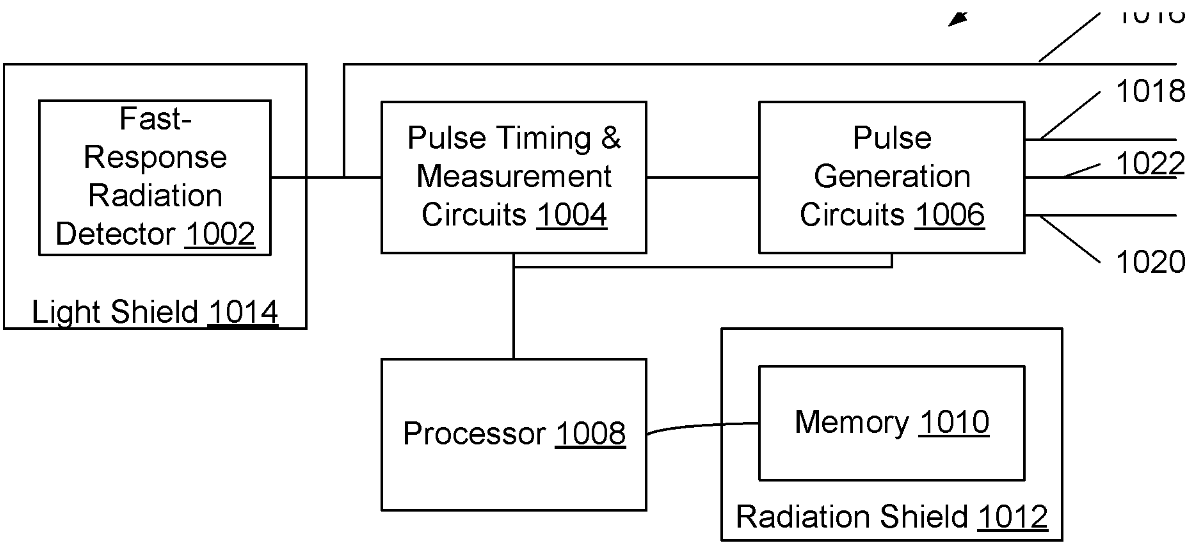


Fig. 11

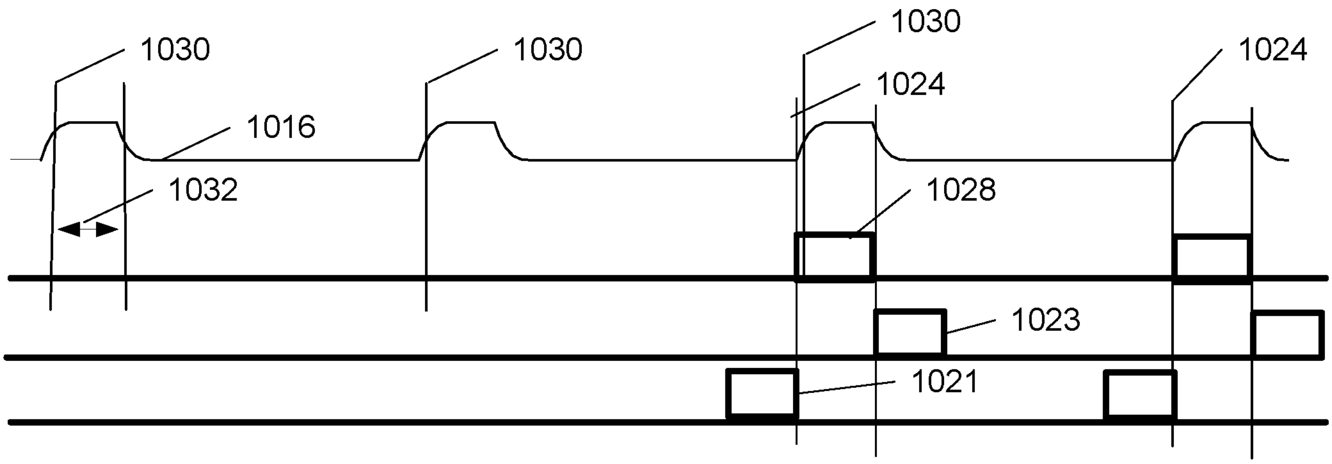


Fig. 12

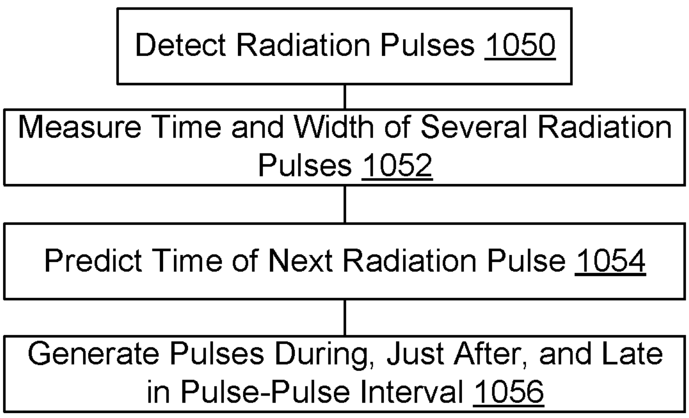


Fig. 13

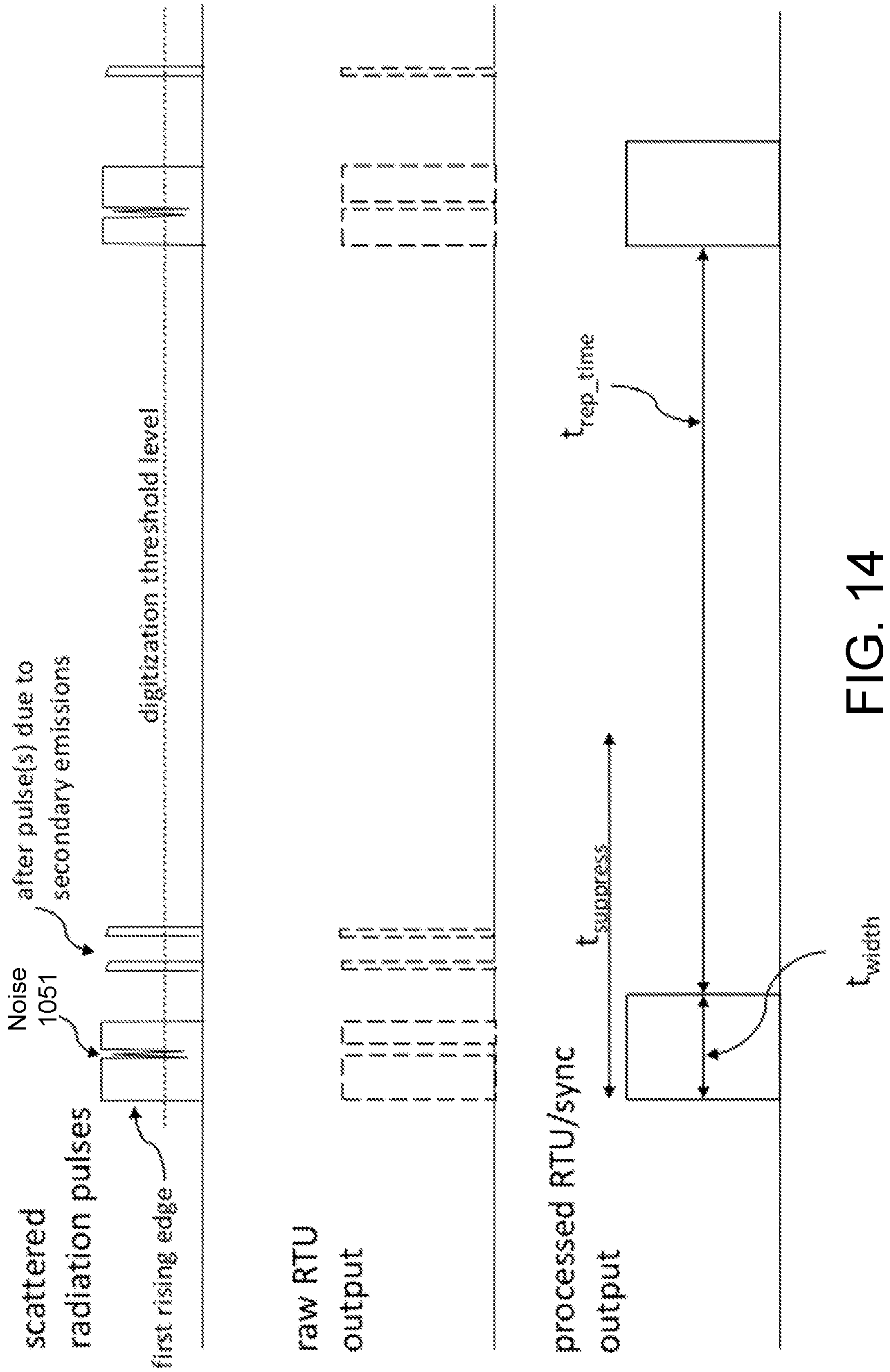
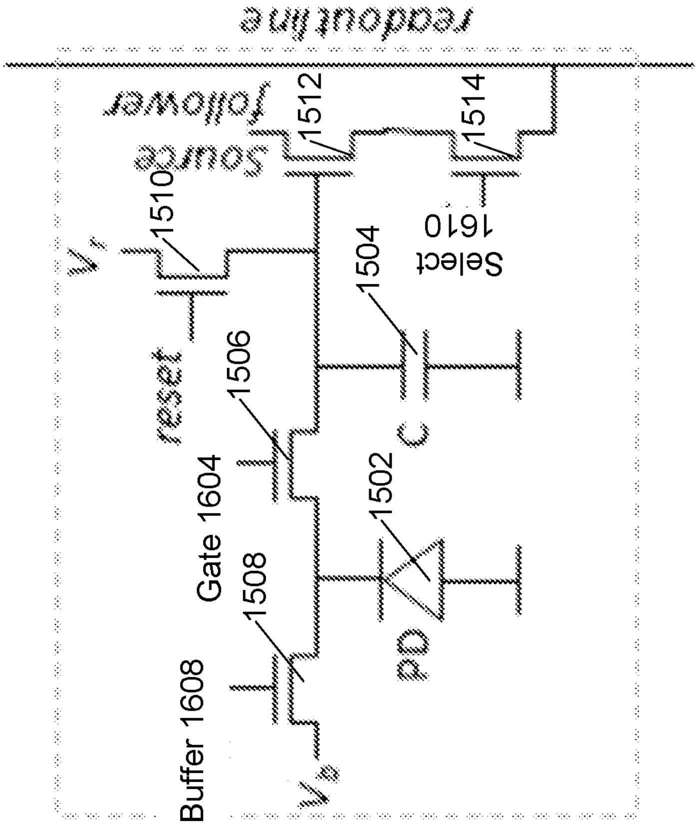

scattered radiation pulses
first rising edge
Noise 1051
after pulse(s) due to secondary emissions
digitization threshold level
raw RTU output
processed RTU/sync output
$t_{suppress}$
t_{rep_time}
t_{width}

FIG. 14



1512

FIG. 15

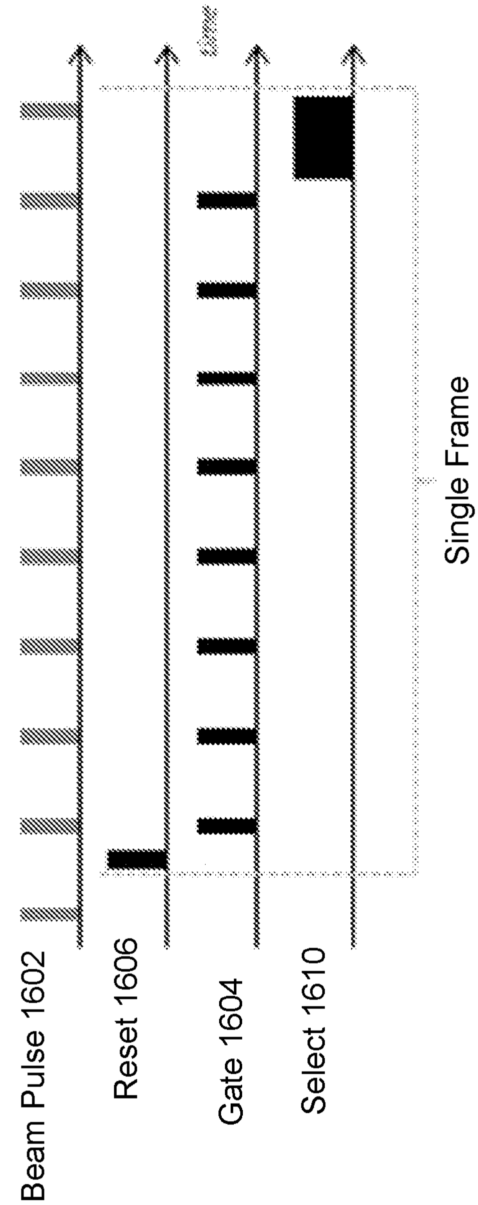


FIG. 16

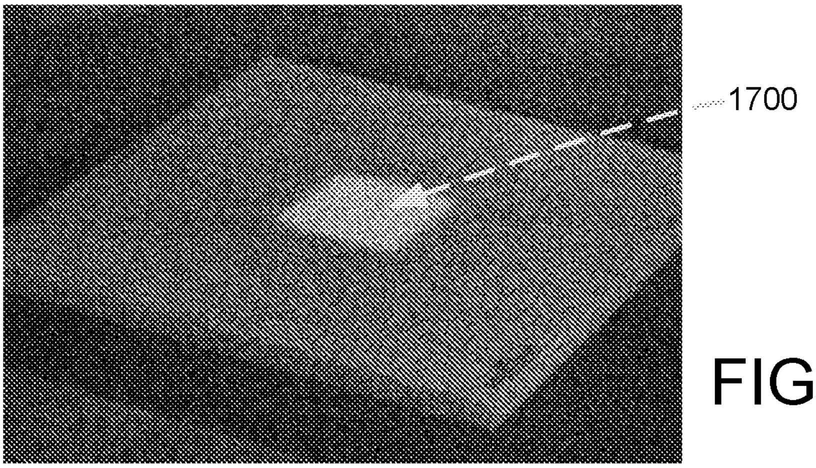


FIG. 17

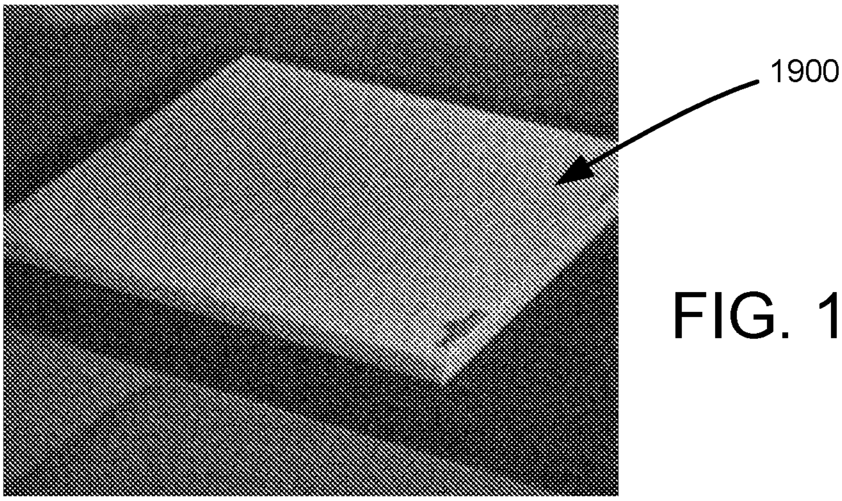


FIG. 19

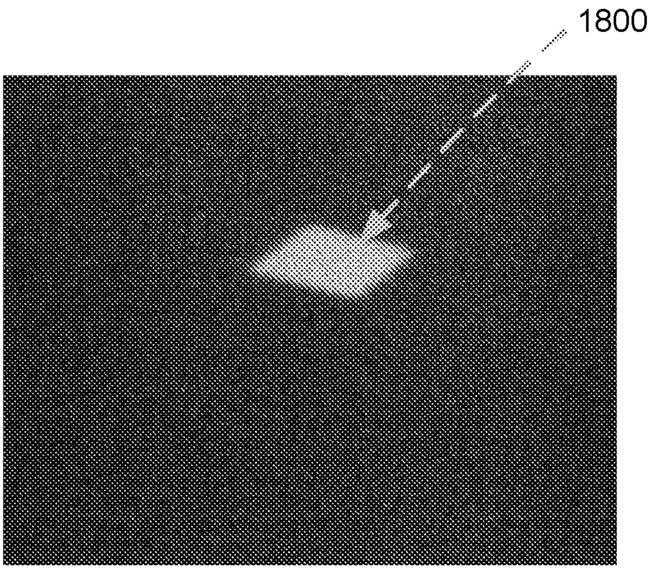


FIG. 18B

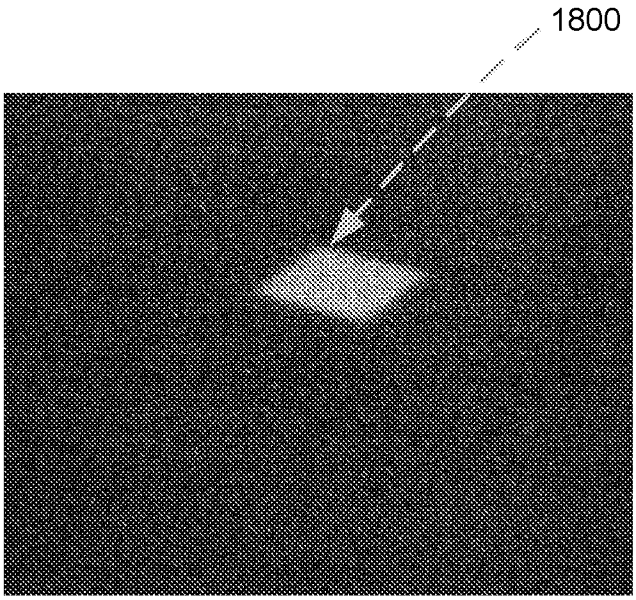


FIG. 18A

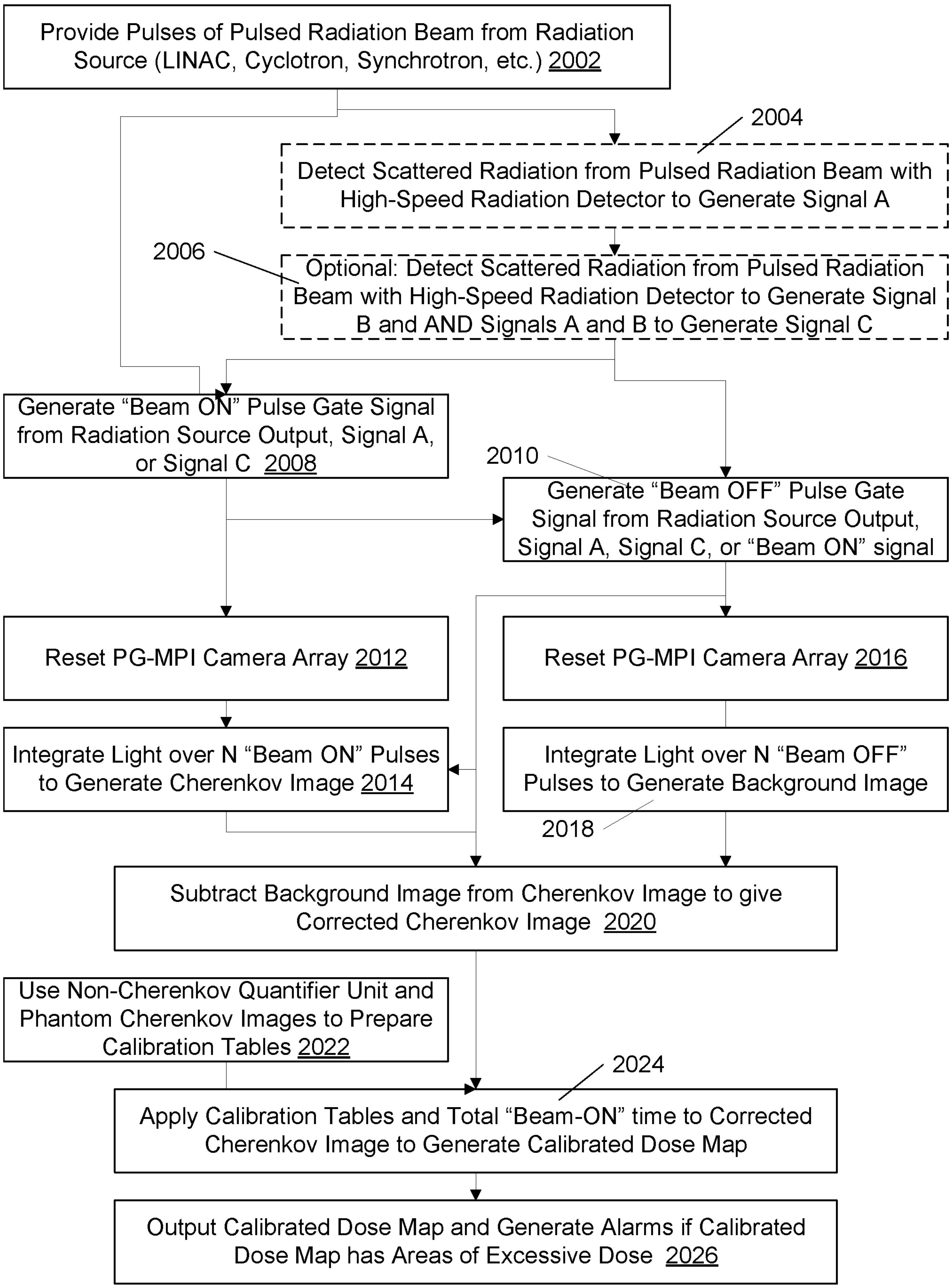

Provide Pulses of Pulsed Radiation Beam from Radiation Source (LINAC, Cyclotron, Synchrotron, etc.) 2002
2004
Detect Scattered Radiation from Pulsed Radiation Beam with High-Speed Radiation Detector to Generate Signal A
2006
Optional: Detect Scattered Radiation from Pulsed Radiation Beam with High-Speed Radiation Detector to Generate Signal B and AND Signals A and B to Generate Signal C
Generate "Beam ON" Pulse Gate Signal from Radiation Source Output, Signal A, or Signal C 2008
2010
Generate "Beam OFF" Pulse Gate Signal from Radiation Source Output, Signal A, Signal C, or "Beam ON" signal
Reset PG-MPI Camera Array 2012
Reset PG-MPI Camera Array 2016
Integrate Light over N "Beam ON" Pulses to Generate Cherenkov Image 2014
Integrate Light over N "Beam OFF" Pulses to Generate Background Image
2018
Subtract Background Image from Cherenkov Image to give Corrected Cherenkov Image 2020
Use Non-Cherenkov Quantifier Unit and Phantom Cherenkov Images to Prepare Calibration Tables 2022
2024
Apply Calibration Tables and Total "Beam-ON" time to Corrected Cherenkov Image to Generate Calibrated Dose Map
Output Calibrated Dose Map and Generate Alarms if Calibrated Dose Map has Areas of Excessive Dose 2026

FIG. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/15655

A. CLASSIFICATION OF SUBJECT MATTER
IPC - G01T 1/22 (2021.01)

CPC - G01T 1/22; A61N 5/1071; A61N 5/1075; A61N 2005/1076

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0263402 A1 (THE TRUSTEES OF DARTMOUTH COLLEGE) 15 September 2016 (15.09.2016) Fig 1, 3, 5, abstract, para [0049], [0082], [0088], [0089], [0121], [0131], [0132], [0201]	1-17
Y	US 2016/0084703 A1 (PHILIPS GMBH, et al.) 24 March 2016 (24.03.2016) abstract, para [0001], [0009], [0065]	1-17
Y	US 2019/0355782 A1 (BAE SYSTEMS IMAGING SOLUTIONS INC.) 21 November 2019 (21.11.2019) Fig 2, abstract, para [0017], [0020], [0027]	2, (4-5)/(2), 7, (8-9)/(7)
Y	US 2008/0094626 A1 (BECKER-ROSS et al.) 24 April 2008 (24.04.2008) Fig 1, abstract, para [0036], [0037]	3, (4-5)/(3)
Y	WO 2019/143972 A2 (THE TRUSTEES OF DARTMOUTH COLLEGE) 25 July 2019 (25.07.2019) Fig 6A, 6B, abstract, para [0063], [0071]	11, 13, (14-17)/(11,13)

☐ 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
"D" document cited by the applicant in the international application
"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 another 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
26 March 2021	APR 14 2021

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee Young Telephone No. PCT Helpdesk: 571-272-4300