



(51) International Patent Classification:

G01L 1/24 (2006.01) G01N 21/64 (2006.01)

G01B 11/16 (2006.01) G01L 5/18 (2006.01)

(21) International Application Number:

PCT/US2024/061325

(22) International Filing Date:

20 December 2024 (20.12.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/613,919 22 December 2023 (22.12.2023) US

(71) Applicants: CZ BIOHUB SF, LLC [US/US]; 499 Illinois Street, San Francisco, California 94158 (US). THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY [US/US]; Office of the General Counsel, Bldg. 170, Third Floor, Main Quad, P. O. Box 20386, Stanford, California 94305-2038 (US).

(72) Inventors: CASAR, Jason; c/o The Board of Trustees of the Leland Stanford Junior University, Office of the Gener-

al Counsel, Bldg. 170, Third Floor, Main Quad, P.O. Box 20386, Stanford, California 94305 (US). DIONNE, Jennifer A.; c/o The Board of Trustees of the Leland Stanford Junior University, Office of the General Counsel, Bldg. 170, Third Floor, Main Quad, P.O. Box 20386, Stanford, California 94305 (US). GOODMAN, Miriam B.; c/o The Board of Trustees of the Leland Stanford Junior University, Office of the General Counsel, Bldg. 170, Third Floor, Main Quad, P.O. Box 20386, Stanford, California 94305 (US).

(74) Agent: ZIGMANT, John M. et al.; Kilpatrick Townsend & Stockton LLP, Mailstop: IP Docketing - 22, 1100 Peachtree Street, Suite 2800, Atlanta, Georgia 30309 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,

(54) Title: METHOD AND SYSTEM FOR FORCE SENSORS INCLUDING UPCONVERTING NANOPARTICLES IN A POLYMERIC HOST

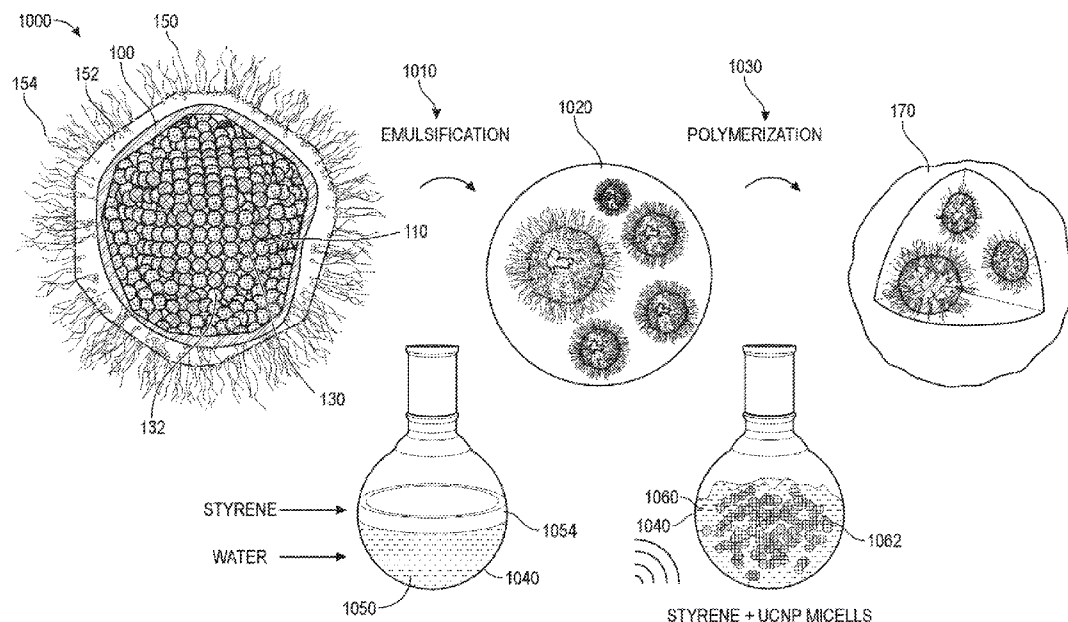


FIG. 10

(57) Abstract: A force sensor includes one or more upconverting nanoparticles. Each of the one or more upconverting nanoparticles include an emitter. The force sensor also includes a polymeric host at least partially around the one or more upconverting nanoparticles. The polymeric host exhibits electronic-vibrational coupling with the emitter in a stress dependent manner.

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

**METHOD AND SYSTEM FOR FORCE SENSORS INCLUDING
UPCONVERTING NANOPARTICLES IN A POLYMERIC HOST**

**STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY
SPONSORED RESEARCH AND DEVELOPMENT**

[0001] This invention was made with Government support under contract GM129879 awarded
by the National Institutes of Health and contract DGE-1656518 awarded by The National
Science Foundation. The Government has certain rights in the invention.

CROSS-REFERENCES TO RELATED APPLICATIONS

[0002] This application claims priority to United States provisional application number
63/613,919, filed December 22, 2023, which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0003] It is often desirable to measure and track forces and pressures in an in-vivo or in-vitro
environment. For example, being able to measure and track forces in a heart can help to identify
a cause of high blood pressure or other health anomaly. It can also be desirable to measure a
force between an immune cell and an antigen presenting cell. These measurements can be used
for diagnostics, for determining treatment efficacy, and other purposes.

[0004] Taking such measurements can be an invasive process, including the use of force or
pressure measurement devices having connections that can include wires or other conduits. For
example, physical connections can be needed to direct a measurement device to a specific region.
Electrical connections can be needed to provide power and receive data from the measurement
devices. These connections can be made from outside the organism to inside the organism,
thereby passing through a surface of the organism. This can create regions on the organism that
are likely to become infected and can necessitate the removal of the measurement device once
measurements are completed.

[0005] Instead of providing power through a connection, a measurement device can include a battery. However, such a battery can limit the lifetime of the measurement device to that of the battery. Alternatively, a battery can be wirelessly charged, but that can greatly increase the costs and complexity of the measurement device.

5 [0006] Thus, there is a need in the art for improved force and/or pressure measurement sensors, including sensors that can operate without the need for an external connection or power supply.

SUMMARY OF THE INVENTION

10 [0007] Embodiments of the present invention relate generally to force measurement devices, such as force sensors. More specifically, embodiments disclosed herein include force sensors that can operate without the need for an external connection or power supply. Merely by way of example, some embodiments provide a force sensor including one or more upconverting nanoparticles in a host structure. One or more force sensors can be positioned in an organism at
15 locations at which the organism can apply a force or pressure. The force sensors can provide an output that can be used to measure and track force applied by the organism.

[0008] Mechanical forces regulate many important biological processes from stem cell differentiation to digestion. The ability to measure forces on very small physical scales could help uncover novel biomarkers of disease that go undetected with traditional chemical, optical
20 and electrical sensing modalities. However, existing mechanosensing tools, such as atomic force microscopy or traction force microscopy, are either too large and invasive to operate in vivo, while others, such as FRET tethers, which operate below 100 pN, are limited in their dynamic range and propensity to rapidly photobleach.

[0009] Accordingly, embodiments of the present invention can provide force sensors that
25 include mechanosensitive upconverting nanoparticles (UCNP). These force sensors can be used study micronewton scale biological forces because they are small, for example less than 20 nm, relatively non-toxic, photostable and exhibit a strong anti-Stokes shift that allow them to be excited in the near-IR biological window (980 nm). Embodiments of the present invention can provide force sensors that include UCNPs that are embedded in polystyrene microbeads. These
30 force sensors, which can also be referred to as microgauges, exhibit a micronewton colorimetric

sensitivity to applied compressive force that is linear and robust across multiple compression-relaxation cycles. These force sensors can be fabricated via an emulsion polymerization and sized to mimic the natural bacterial food source of the *C. elegans* worm; thus, they accumulate readily in the pharyngeal and intestinal lumen when made accessible to a freely feeding worm, without adversely affecting worm fecundity or pharyngeal pumping rate. This allows for rapid imaging at greater than 40 Hz of pharyngeal muscle contraction induced force dynamics in gently immobilized, actively pumping worms. The resulting ratiometric changes induced during the contraction-relaxation cycle are further correlated with the muscle membrane depolarizations that induce them via a simultaneous electropharyngeogram.

[0010] In a particular embodiment of the present invention, a force sensor includes one or more upconverting nanoparticles, wherein each of the one or more upconverting nanoparticles include an emitter, and a host at least partially around the one or more upconverting nanoparticles, wherein the host is chosen such that its vibrational modes couple with the electronic modes of the emitter. In another embodiment, a device for use in measuring force or pressure is provided. The device includes a sensitizer configured to receive energy from first photons in a first wavelength range, an emitter configured to receive energy from the sensitizer and to emit second photons in a second wavelength range and third photons in a third wavelength range, and a host including the sensitizer and the emitter, wherein the vibrational transitions of the host are capable of coupling to the electronic states of the emitter.

[0011] Numerous benefits are achieved by way of the present disclosure over conventional techniques. For example, embodiments of the present invention can provide force sensors that can be used to detect forces and/or pressures over short measurement times in in-vivo or intracellular applications. The impact of photobleaching is decreased for embodiments of the present invention compared to other optical measurement techniques. Embodiments of the present invention combine the optical stability, color-based mechanosensitivity and potential nanometer scale footprint of upconverting nanoparticles within a range of optically transparent, biocompatible, non-toxic, and readily scalable polymer constructs to enable local, nonperturbative mechanosensing with light. Thus, embodiments of the present invention provide force sensors that are novel optical mechanosensors with a demonstrated sensitivity to compressive forces in the super-nanoNewton range. The multiphoton process utilized herein

affords the platform long-term photostability, distinct anti-Stokes shifts, and negligible autofluorescence background even through millimeters of tissue. These and other embodiments, along with many of its advantages and features, are described in more detail in conjunction with the text below and attached figures.

- 5 **[0012]** Various embodiments of the present invention can incorporate one or more of these and the other features described herein. A better understanding of the nature and advantages of the present invention can be gained by reference to the following detailed description and the accompanying drawings.

10 **BRIEF DESCRIPTION OF THE DRAWINGS**

[0013] FIG. 1A illustrates an upconverting nanoparticle according to an embodiment of the present invention.

[0014] FIG. 1B illustrates a force sensor including a plurality of upconverting nanoparticles according to an embodiment of the present invention.

- 15 **[0015]** FIG. 2A illustrates a core of an upconverting nanoparticle according to an embodiment of the present invention.

[0016] FIG. 2B illustrates a crystal lattice that can be used in the core illustrated in FIG. 2A.

[0017] FIG. 3 illustrates the operation of a force sensor according to an embodiment of the present invention.

- 20 **[0018]** FIG. 4 illustrates an electron energy level diagram for an upconverting nanoparticle and a corresponding emission profile according to an embodiment of the present invention.

[0019] FIG. 5A is a plot 500 of light emission intensity (in arbitrary units) as a function of energy for a polymeric host according to an embodiment of the present invention.

- 25 **[0020]** FIG. 5B is a plot of the peak center of the light emission intensity curve as a function of pressure for a polymeric host according to an embodiment of the present invention.

[0021] FIG. 5C is a plot of one of the Raman peaks, corresponding to the aromatic C-H stretch for the polystyrene at three pressures, fit to a Gaussian function according to an embodiment of the present invention.

[0022] FIG. 6 illustrates an electronic energy level diagram for a force sensor according to an embodiment of the present invention.

[0023] FIG. 7 illustrates another electronic energy level diagram for a force sensor and a corresponding emission profile according to an embodiment of the present invention.

[0024] FIG. 8 is a plot of light intensity as a function of wavelength for a force sensor according to an embodiment of the present invention.

[0025] FIG. 9 is a plot of the output response of a force sensor according as a function of force according to an embodiment of the present invention.

[0026] FIG. 10 graphically illustrates a method of manufacturing a force sensor according to an embodiment of the present invention.

[0027] FIG. 11 is a flowchart illustrating a method of manufacturing force sensors according to an embodiment of the present invention.

[0028] FIG. 12A is a simplified schematic diagram illustrating a test system and operation of a force sensor according to an embodiment of the present invention.

[0029] FIG. 12B is a plot of voltage and the percentage change in intensity ratio as a function of time for a force sensor according to an embodiment of the present invention.

[0030] FIG. 13 is a flowchart illustrating a method of using a force sensor according to an embodiment of the present invention.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

[0031] Embodiments of the present invention relate generally to force measurement devices, such as force sensors. More specifically, embodiments disclosed herein include force sensors that can operate without the need for an external connection or power supply. Merely by way of example, some embodiments provide a force sensor including one or more upconverting

nanoparticles in a host structure. One or more force sensors can be positioned in an organism at locations at which the organism can apply a force or pressure. The force sensors can provide an output that can be used to measure and track force applied by the organism.

[0032] FIG. 1A illustrates an upconverting nanoparticle according to an embodiment of the present invention. Upconverting nanoparticle 100 can include core 110, core shell 140, and ligands 150. Core 110 can be formed of a crystal lattice host 120, doped with sensitizers 130 and emitters 132. The crystal lattice can be formed of sodium yttrium fluoride (NaYF_4), which is shown further in FIG. 2B. Material for the crystal lattice host 120, including the sensitizers 130 and emitters 132, is available from American Elements of Los Angeles, California. In addition to NaYF_4 , other materials can be used to form crystal lattice host 120, including SrLiF_4 , BaF_3Li , NaGdF_4 , CaLuF_4 , CaYF_4 , SrLuF_4 , SrYF_4 , BaLuF_4 , BaYF_4 , materials including Group 2 elements such as Sr, Ba, and Ca and a range of lanthanides such as Lu, Yb, Y, etc. Sensitizers 130 and emitters 132 can be dopants in crystal lattice host 120. For example, sensitizers 130 and emitters 132 can be dopants that can replace sodium or yttrium atoms in crystal lattice host 120 of core 110. For example, sensitizers 130 can be ytterbium ions (Yb^{3+}) while emitters 132 can be erbium ions (Er^{3+}). Sensitizers 130 and emitters 132 can be other types of dopants, for example they can be other types of lanthanide dopants. The operation of sensitizers 130 and emitters 132 is discussed more fully in relation to FIGS. 3 - 9 below.

[0033] Although ytterbium and erbium as discussed herein as examples of lanthanides, other lanthanides including thulium, holmium, and the like can be utilized as sensitizers 130 and emitters 132 and embodiments of the present invention are not limited to the use of ytterbium and erbium as dopants. Furthermore, in addition or in place of lanthanides, some embodiments can utilize D-metal dopants, i.e., transition metal dopants such as cobalt or manganese, to impact the energy transfer between the upconverting nanoparticle and the host described more fully below. The dopants can be added to either upconverting nanoparticle 100 or a host, such as polymer host 170 (shown in FIG. 1B.) One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

[0034] Upconverting nanoparticle 100 can further include core shell 140. Core shell 140 can be formed of an undoped material, including the same ceramic or material as found in core 110. For example, core shell 140 can be formed of a sodium yttrium fluoride crystal lattice. Core

shell 140 can completely or partially surround core 110. In some embodiments, core shell 140 can improve the brightness of light produced by upconverting nanoparticle 100. That is, core shell 140 can act to increase the number of photons produced by the core 110 in response to upconversion excitation.

5 **[0035]** Upconverting nanoparticle 100 can further include ligands 150, for example, oleic acid ligands that are attached to core shell 140. Each ligand 150 can have a carboxylic acid terminus 152 attached to core shell 140 and a hydrophobic alkyl chain 154 extending away from core shell 140. Ligands 150 can cause upconverting nanoparticle 100 to be hydrophobic such that they can remain suspended in a liquid during formation of the polymer host as shown in FIGS. 10 and 11.

10 **[0036]** As described more fully below in relation to FIG. 3, upconverting nanoparticle 100 can absorb light in a first wavelength range (e.g., 980 nm) and emit light at shorter wavelengths. The emitted light, particularly, the ratio of light in a second wavelength range to light in a third wavelength range can be a function of the force applied to a host containing the upconverting nanoparticle, for instance, a polymeric host including one or more upconverting nanoparticles.

15 Accordingly, by measuring the characteristics of the light emitted by the upconverting nanoparticle, force measurements can be made using embodiments of the present invention.

[0037] FIG. 1B illustrates a force sensor including a plurality of upconverting nanoparticles according to an embodiment of the present invention. As illustrated in FIG. 1B, one or more upconverting nanoparticles 100 can be supported by polymer host 170 to form force sensor 160.

20 Polymer host 170 can have a size on the order of microns. (Note that the nanoparticles in FIG. 1B are not to scale but are enlarge for visibility.) The one or more upconverting nanoparticles 100 are illustrated in FIG. 1B as a plurality of, i.e., three, upconverting nanoparticles 100. However, in some embodiments, a single upconverting nanoparticles 100 is supported by polymer host 170.

25 **[0038]** Polymer host 170 can be a biocompatible material. For example, polymer host 170 can be formed of a polymer or polymeric material such as polystyrene. Additionally, polymer host 170 can be formed of other materials, for example, polymer host 170 can be a thin poly (maleic anhydride-alt-1-octadecene) (PMAO) shell, polydimethylsiloxane (PDMS) pellets, polyethylene glycol (PEG), or other material. In some embodiments, polymer host 170 can be formed of

30 polyvinyl alcohol hydrogel for lower kilopascal pressure applications, or epoxy resin for higher

gigapascal pressure applications. Polymer host 170 can be formed completely or partially around one or more upconverting nanoparticles 100. Polymer host 170 can also include polylactic acid (PLA), polymethyl methacrylate (PMMA), acrylonitrile butadiene styrene (ABS), softer polymers with different geometries, for example, a thin film of a soft gel (e.g. alginate, PAA, or the like), etc.

[0039] Polymer host 170 can interact with emitters 132 in core 110 illustrated in FIG. 1A in order to increase a sensitivity of upconverting nanoparticles 100. For example, vibrational modes of polymer host 170 can be coupled to electronic transitions in emitter 132 in upconverting nanoparticles 100 and can interact with emitters 132 in upconverting nanoparticles 100 to increase a change in an amount of photons released by emitters 132 in core 110 when a force or pressure is applied to force sensor 160. Thus, polymer host 170 can interact with emitters 132 in upconverting nanoparticles 100 to cause a change in a ratio of photons at two different ranges of wavelengths released by emitters 132 in core 110 when a force or pressure is applied to force sensor 160. An example of the operation of force sensor 160 is discussed more fully in relation to FIGS. 3 - 9 below.

[0040] In these and other embodiments of the present invention, core 110 illustrated in FIG. 1A can be formed of various materials having various structures. An example is shown in the following figures.

[0041] FIG. 2A illustrates a core of an upconverting nanoparticle according to an embodiment of the present invention. As illustrated in FIG. 2A, sensitizers 130 and emitters 132 are present in core 110. In this example, the upconverting nanoparticle is $\text{NaY}_{0.8}\text{Yb}_{0.18}\text{Er}_{0.02}\text{F}_4$ surrounded by a NaYF_4 shell, though other concentrations can be used in these and other embodiments of the present invention. The higher concentration of emitters 132 improves the transfer of energy from sensitizers 130 to emitters 132, as discussed more fully in relation to FIG. 3. In the example core 110 shown in FIG. 2A, sensitizers 130 and emitters 132 are lanthanide atoms. Thus, sensitizers 130 can be formed of a first lanthanide dopant such as ytterbium ions while emitters 132 can be formed of a second lanthanide dopant such as erbium ions. In addition to Yb^{3+} and Er^{3+} , other dopants can be utilized including d-metal dopants including Mn, Cr, or Fe.

[0042] FIG. 2B illustrates a crystal structure of the core illustrated in FIG. 2A. The crystal lattice host 120 shown in FIG. 2B can also be referred to as a lattice structure or a crystal structure.

[0043] Referring to FIG. 2B, a dopant 230 has taken the place of a sodium/yttrium atom 210 in crystal lattice host 120. Fluoride atoms 220 are also included in crystal lattice host 120, which can be a cubic crystal lattice. Dopant 230 can be one of a number of different dopants. For example, crystal lattice host 120 can include sensitizers 130 and emitters 132 (as shown in FIG. 1A), represented here as dopant 230. Sensitizers 130 and emitters 132 can be lanthanide dopants as discussed above. Sensitizers 130 can have a higher concentration than emitters 132. In other embodiments, emitters 132 can have a higher concentration than sensitizers 130. In yet other embodiments, sensitizers 130 and emitters 132 can have equal or substantially equal concentrations. Merely by way of example, sensitizers 130 can have an 18% concentration while emitters 132 can have a 2% concentration. Sensitizers 130 can be ytterbium ions while emitters 132 can be erbium ions.

[0044] Although a cubic crystal lattice made of columns of nonahedrons is illustrated in FIG. 2B, this is not required by embodiments of the present invention. Other types of materials having various structures can be employed by these and other embodiments of the present invention. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

[0045] As described more fully herein, embodiments of the present invention can implement a force sensor 160 based on a multi-photon upconversion and emission process. For instance, sensitizers 130 can receive energy, for example from a long wavelength light source producing infrared light. Sensitizers 130 can absorb this energy and then pass this absorbed energy to emitters 132. Emitters 132 can then emit photons in two or more ranges of wavelengths. As discussed in relation to FIG. 1, elements of core 110, including emitters 132, can be chosen to electronically couple to vibrational modes of polymer host 170. This coupling can enhance or increase the number of photons emitted from core 110 when a force or pressure is applied to force sensor 160 illustrated in FIG. 1B. This coupling can change a ratio of photons emitted by core 110 at two different wavelength ranges in response to a force or pressure being

applied to force sensor 160. An example of these absorption, energy transfer, and optical emission processes is shown in the following figure.

[0046] FIG. 3 illustrates the operation of a force sensor according to an embodiment of the present invention. In FIG. 3, diagram 300 illustrates the operation of a force sensor, such as force sensor 160 in FIG. 1B. Photons 310 in a first wavelength range (e.g., infrared photons at 980 nm) can be provided to and received by sensitizers 130. Sensitizers 130 are shown here as ytterbium ions. Sensitizers 130 can absorb the infrared photons and pass the absorbed energy to emitters 132 via energy transfer process 330. Emitters 132 are shown here as being erbium ions. The emitters 132 can emit photons 370 and photons 372 in the green wavelength range and photons 374 in the red wavelength range.

[0047] Electronic transitions of emitters 132 can be coupled to vibrational transitions of polymer host 170 via energy transfer processes 350. This interaction or coupling between emitters 132 and polymer host 170 can increase or decrease a number of photons 370, photons 372, and photons 374 that are emitted by emitters 132. In particular, this coupling can increase or decrease the number of photons 370, photons 372, and photons 374 released by emitters 132 when a force or pressure is applied to a force sensor including sensitizer 130, emitters 132, and polymer host 170. This coupling can modify (e.g., increase) the ratio of photons 374 to photons 370 and photons 372 emitted by emitters 132 when a force or pressure is applied to the force sensor. Moreover, this coupling can also modify (e.g., decrease) the ratio of photons 374 to photons 370 and photons 372 emitted by emitters 132 when a force or pressure is removed from the force sensor. Polymer host 170 can be implemented using polystyrene as shown in FIG. 3.

[0048] Referring to FIG. 3, sensitizer 130 can absorb energy from lower energy (e.g., infrared) photons having a wavelength of ~980 nm, while emitters 132 can emit visible (e.g., red) photons having a wavelength of ~660 nm and additional visible (e.g., green) photons having a wavelength of ~520 nm and ~540 nm. Thus, embodiments of the present invention provide the advantage of using stimulus light that is not visible, thereby allowing the photons emitted by emitters 132, i.e., the visible light corresponding to the output response of the force sensor, to be observed more clearly. In other embodiments of the present invention, detectors other than visible light detectors can be used to receive light emitted by emitters 132, for example light that

is not in the visible spectrum. This can allow the use of photons in the visible spectrum to be used as the stimulus photons that are provided to the sensitizer 130.

[0049] As shown in FIG. 3, energy from long wavelength photons can be absorbed by sensitizer 130 (e.g., a first lanthanide such as sensitizers 130 shown in FIG. 1A), the absorbed energy can be transferred to emitters 132 (e.g., a second lanthanide such as emitters 132), and then, after interaction with polymer host 170, for example, a polystyrene host, visible light at higher energies can be emitted as an output of the force sensor. This process is shown further in the following figure.

[0050] FIG. 4 illustrates an electronic energy level diagram for an upconverting nanoparticle and a corresponding emission profile according to an embodiment of the present invention. The electronic energy level diagram shown in FIG. 4 corresponds to an upconverting nanoparticle alone, i.e., that is not yet embedded in a polymer host, such as polymer host 170 shown in FIG. 1B. Referring to FIG. 4, sensitizers 130 absorb infrared photons 410 via an energy transition 412 corresponding to an electron moving from the $^2F_{7/2}$ state to the $^2F_{5/2}$ state. Two such energy transitions are shown as energy transition 414 and energy transition 416. An energy transition can then occur between sensitizers 130 and emitters 132 to transition an electron in the emitter from the $^4I_{15/2}$ state to the $^4S_{3/2}$ state or higher. The energized electron can relax into one of the $^2H_{11/2}$, $^4S_{3/2}$, or $^4F_{9/2}$ state. Emission processes will occur in conjunction with the electrons returning to the $^4I_{15/2}$ state, including the emission of a green photon at 520 nm (energy transition 420 and emitted photon 430), the emission of a green photon at 540 nm (energy transition 422 and emitted photon 432), or the emission of a red photon at 660 nm (energy transition 424 and emitted photon 434), respectively.

[0051] The corresponding emission profile for emitted photons represented by emitted photon 430, emitted photons represented by emitted photon 432, and emitted photons represented by emitted photon 434 is shown on the right side of FIG. 4. Specifically, the amplitude of the intensity of the emitted light (in arbitrary units) emitted by the erbium ions includes peak 440 in the green wavelength (i.e., 520 nm) range, peak 442 in the green wavelength (i.e., 540 nm) range, and peak 444 in the red wavelength (i.e., 660 nm) range is plotted as a function of wavelength in nanometers.

[0052] As discussed in relation to FIG. 3, force sensor 160 shown in FIG. 1B includes both upconverting nanoparticle 100 (including sensitizer 130 and emitters 132) and polymer host 170. Thus, in addition to coupling between sensitizers and emitters as shown in FIG. 3, emitters 132 are also coupled to polymer host 170. This coupling enables the host to couple energy to the emitter when force sensor 160 is exposed to force or pressure. This additional energy can increase an intensity ratio of photons at different wavelength ranges emitted by emitters 132 when force or pressure is applied to force sensor 160. An example of a behavior of polymer host 170 when a force or pressure is applied to force sensor 160 is shown in the following figure.

[0053] FIG. 5A is a plot 500 of light emission intensity (in arbitrary units) as a function of energy for a polymeric host according to an embodiment of the present invention. In this example, the polymeric host is polystyrene and the light emission corresponds to vibrational modes of the polymeric host. As shown in FIG. 5A, curve 510 is a Raman spectrum that represents the light emission intensity from the polystyrene for an applied pressure (i.e., the pressure applied to the polymeric host) of 0.0001 GPa. Curve 520 is a Raman spectrum that represents the light emission intensity from the polystyrene for an applied pressure (i.e., the pressure applied to the polymeric host) of 3.1 GPa. As the applied pressure is increased, the center energy of the light intensity peak of the light emission intensity curve for these vibrational modes shifts to higher energies.

[0054] FIG. 5B is a plot of the peak center of the light emission intensity curve as a function of pressure for a polymeric host according to an embodiment of the present invention. As shown in FIG. 5B, the peak center (i.e., the center energy of the light intensity peak of the light emission intensity curve) increases in a substantially linear manner as the applied pressure is increased. At atmospheric pressure, the peak center is $\sim 3058 \text{ cm}^{-1}$ and at a pressure of $\sim 3 \text{ GPa}$, the peak center is $\sim 3085 \text{ cm}^{-1}$.

[0055] Fig. 5c is a plot of one of the Raman peaks, corresponding to the aromatic C-H stretch for the polystyrene at three pressures, fit to a Gaussian function. In this figure, the light emission intensity peak corresponding to the aromatic C-H stretch for the polystyrene at a given pressure is represented by an idealized curve. In a manner consistent with the shift of the light intensity peak of the light emission intensity curve to higher energies at higher applied pressures shown in FIGS. 5A and 5B, FIG. 5C illustrates peak 570 corresponding to an applied pressure of 0.0001

GPa shifting to become peak 572 corresponding to an applied pressure of 1.3 GPa. Peak 572 then shifts as the pressure is increased further to become peak 574 corresponding to an applied pressure of 3.1 GPa. Thus, as the applied pressure is increased, the center energy of the relative peak energy of the vibrational mode for a polymeric host shifts to higher energies.

5 [0056] FIG. 6 illustrates an electronic energy level diagram for a force sensor according to an embodiment of the present invention. As discussed above, emitters 132 (e.g. erbium ions) receive energy non-radiatively from excited sensitizers 130 (e.g. ytterbium ions excited to $2F_{5/2}$), multiple times, resulting in energy transition 610 and subsequently energy transition 612 moving, for Er^{3+} , an electron from the $4I_{15/2}$ state to the $4I_{11/2}$ state, and then from there to the 10 $4F_{7/2}$ state. The energized electron can relax into one of the $^2H_{11/2}$, $^4S_{3/2}$, or $^4I_{9/2}$ state. The presence of electronic-vibrational coupling between polymer host 170 and emitters 132 in upconverting nanoparticle 100 can impact the relaxation processes into the $^2H_{11/2}$, $^4S_{3/2}$, or $^4I_{9/2}$ states. In particular, as the applied pressure increases, the increased vibrational coupling between polymer host 170 and the emitter can increase the population at the $^4I_{9/2}$ level compared 15 to the populations at the $^2H_{11/2}$ level and the $^4S_{3/2}$ level. This change in populations decreases the probability of a green emission at either the 520 nm wavelength represented by energy transition 620 or the 540 nm wavelength represented by energy transition 622, while increasing the probability of a red emission at the 660 nm wavelength represented by energy transition 624. Thus, under pressure, the ratio of the percentage of red emissions with respect to the green 20 emissions (i.e., $\%I_{\text{Red}}/I_{\text{Green}}$) increases. As the pressure is decreased, the opposite population change occurs, with the population at the $^4I_{9/2}$ level decreasing compared to the populations at the $^2H_{11/2}$ level and the $^4S_{3/2}$ level. As a result, as the pressure is decreased, the ratio of the red emissions with respect to the green emissions (i.e., $I_{\text{Red}}/I_{\text{Green}}$) decreases.

[0057] FIG. 7 illustrates another electronic energy level diagram for a force sensor and a 25 corresponding emission profile according to an embodiment of the present invention. In the more detailed electron energy level diagram shown in FIG. 7, one or more upconverting nanoparticles are supported by a host, such as polymer host 170 to form force sensor 160 as shown in FIG. 1B.

[0058] Referring to FIG. 7, sensitizers 130 (e.g., ytterbium ions) absorbs infrared photons 410 30 resulting in energy transition 412 corresponding, for Yb^{3+} , to an electron moving from the $^2F_{7/2}$

state to the $^2F_{5/2}$ state. An energy transition can then occur between sensitizers 130 and emitters 132 (e.g., erbium ions) to transition an electron in emitter 132, for Er^{3+} , from the $^4I_{15/2}$ state to the $^4S_{3/2}$ state or higher. Two such energy transitions are shown as energy transition 414 and energy transition 416. The energized electron can relax into one of the $^2H_{11/2}$, $^4S_{3/2}$, or $^4F_{9/2}$ state.

5 [0059] The electronic-vibrational coupling between the emitter and polymer host 170 (e.g., between the upconverting nanoparticle and the polymeric host in which the upconverting nanoparticle is embedded) can change the electron populations at the relevant energy levels: $^2H_{11/2}$, $^4S_{3/2}$, and $^4F_{9/2}$. As discussed above, the likelihood of electrons making energy transition 770 to state $^4F_{9/2}$ can be increased by the application of pressure via the electrical and vibrational
10 coupling between the emitter and the host. Emission processes will occur in conjunction with the electrons returning to the $^4I_{15/2}$ state, including the emission of a green photon at 520 nm (energy transition 720 and emitted photon 730), the emission of a green photon at 540 nm (energy transition 722 and emitted photon 732), or the emission of a red photon at 660 nm (energy transition 724 and emitted photon 734), respectively.

15 [0060] Thus, as pressure or force is applied to force sensor 160, the populations at the $^4F_{9/2}$ state increase, resulting in additional emission at red wavelengths and the populations at the $^2H_{11/2}$ and $^4S_{3/2}$ states decrease, resulting in reduced emission at green wavelengths. The net-effect of this variation in population as a function of pressure is that the ratio of the number of photons emitted at red wavelengths to the number of photons emitted at green wavelengths
20 increases.

[0061] The change in this ratio (i.e., $\Delta\%I_{Red}/I_{Green}$) can be measured as an output response from force sensor 160. This output response as a function of applied force can then be used to calibrate the force sensor 160. That is, known forces can be applied to force sensor 160 and the output measured to determine an output response as a function of force. When force sensor 160
25 is used in an organism, the output response can be observed and used to determine the force or pressure applied by the organism to the force sensor 160. Further details regarding the output response of force sensor 160 is shown in the following figure.

[0062] FIG. 8 is a plot of light intensity as a function of wavelength for a force sensor according to an embodiment of the present invention. The data shown in plot 800 can be used to
30 characterize the output response of force sensor 160 described herein. In plot 800, the light

intensity in arbitrary units is plotted as a function of wavelength in nanometers. The measurements made in FIG. 8 correspond to a force sensor 160 implemented using $\text{Yb}^{3+}/\text{Er}^{3+}$ in a cubic NaYF_4 crystal lattice as the core 110 in a polymeric host.

[0063] As shown in FIG. 8, the upconverting nanoparticles, in response to excitation using near infrared light, emit light in two wavelength bands: green photon emission in the wavelengths ranges of 520 nm and 540 nm and red photon emission in the wavelength range around 660 nm and peaks 814 at green wavelengths around 520 nm and 540 nm. These photon emissions are shown with force sensor 160 (shown in FIG. 1B) operating under two different pressures, specifically 0.4 GPa and 2.1 GPa. Curve 820 corresponds to the lower pressure and includes peaks 822 at green wavelengths around 540 nm and peaks 824 at red wavelengths around 660 nm. When pressure is increased, not only are additional photons emitted, but the ratio of the intensity of red emission to green emission increases. At higher pressure, the emission intensity corresponds to curve 810, which includes peaks 812 at red wavelengths around 660 nm and peaks 814 at green wavelengths around 520 nm and 540 nm. In this example, the increase from 0.4 GPa to 2.1 GPa causes a 0.8% reduction in the lattice constant of the upconverting nanoparticles 100 (shown in FIG. 1A) in force sensors 160.

[0064] As shown in FIG. 8, the number of red photons emitted by force sensor 160 increases with increasing pressure. That is, the area under curve 810 is larger than the area under curve 820. Accordingly, the intensity of red light produced by force sensor 160 can be used as an output response from force sensor 160. Also, the total number of green and red photons emitted by force sensor 160 increases with increasing pressure. That is, the sum of the area under curve 810 (i.e., peak 812 and peak 814) is larger than the sum of the area under curve 820 (i.e., peak 822 and peak 824). Accordingly, the intensity of the combined light emitted by force sensor 160 can be used as an output response from force sensor 160. Moreover, while the number of red photons and the number of green photons both increase with increasing pressure, the number of red photons increases at a faster rate. As a result, the ratio of the intensity of red photons to the intensity of green photons increases with increasing pressure. Accordingly, this ratio can be used as an output response from force sensor 160. That is, embodiments of the present invention can provide methods and systems to measure $I_{\text{Red}}/I_{\text{Green}}$ and compute the corresponding force as the intensity ratio varies linearly with applied force.

[0065] Using the ratio of the intensity of red photons at 660 nm to the intensity of green photons at 540 nm and 520 nm as an output response has an advantage in that this output response can be linear. This output response as a function of pressure, or force per unit area, can also be linear. This output response as a function of force can also be linear. An example is shown in the following figure.

[0066] FIG. 9 is a plot of the output response of a force sensor according as a function of force according to an embodiment of the present invention. The plot 900 shown in FIG. 9, the force illustrated on the abscissa applied to a force sensor is cycled from 0.4 μN to 15.2 μN at 3.4 μN intervals, and then back to 0.4 μN . Three cycles, Cycle 1, Cycle 2, and Cycle 3 are illustrated in FIG. 9. The change in percentage of the ratio of the intensity of photon emission at red wavelengths to the intensity of photon emission at green wavelengths is plotted as a function of force over three cycles, i.e., cycle 1 960, cycle 2, 962, and cycle 3 964. Data points 930 are collected during the three cycles. In this example, upconversion luminescence for 12 samples ($N=12$) with three replicates at each force point ($N=3$) was collected at eight different force conditions over three cycles and averaged to generate the linear output response shown in the figure.

[0067] The change in the ratio of the intensity of photon emission at red wavelengths to the intensity of photon emission at green wavelengths ($\Delta\%I_{\text{Red}}/I_{\text{Green}}$) increases linearly along line 910 for a first portion of cycle 1 960, cycle 2 962, and cycle 3 964 as the force is increased from 0.4 μN to 15.2 μN . Then, as the force decreases from 15.2 μN to 0.4 μN , the percentage change in the ratio $I_{\text{Red}}/I_{\text{Green}}$ decreases linearly along line 920, having identical slope magnitude as line 910, for a second portion of cycles cycle 1 960, cycle 2 962, and cycle 3 964. In some implementations, force sensors 160 exhibited a response of 0.52% $I_{\text{Red}}/I_{\text{Green}}$ per μN , i.e., 5.6% per GPa. The force measurements (i.e., 0.52% per μN) were obtained using a confocal-AFM procedure described herein. The pressure measurements (i.e., 5.6% per GPa) were obtained using a diamond anvil cell (DAC) procedure. It can also be seen that little or no permanent offset occurs in the output response after several cycles. That is, force sensor 160 can exhibit a micronewton colorimetric sensitivity to applied compressive force that is linear and robust across multiple compression-relaxation cycles.

[0068] FIG. 10 graphically illustrates a method of manufacturing a force sensor according to an embodiment of the present invention. In the process 1000 illustrated in FIG. 10, one or more upconverting nanoparticles including sensitizers 130 and emitters 132 are supported in core 110, illustrated by upconverting nanoparticle 100, described more fully in relation to FIG. 1A, can be provided. As discussed in relation to FIG. 1A, upconverting nanoparticle 100 can include ligands 150. Since ligands 150 can be hydrophobic, the ligands can be suspended in styrene 1054 or other hydrophobic material. Styrene 1054 can be contained in container 1040 with water 1050. An emulsification process 1010 can be used to suspend or emulsify upconverting nanoparticle 100 in a hydrophobic medium to generate emulsion 1020. Ultrasonic energy can be applied to the styrene 1054 and water 1050 during a polymerization process 1030 to form micelles 1062. A thermal initiator 1060 can then be added to container 1040. The thermal initiator 1060 can be potassium persulfate. The heat provided can convert the micelles into polystyrene beads forming hosts 170 around one or more upconverting nanoparticles to form force sensor 160. That is, the heat provided by thermal initiator 1060 can cause polymerization of the micelles to form polystyrene hosts around one or more upconverting nanoparticles to form force sensor 160. As will be evident to one of skill in the art, more than one upconverting nanoparticle can be included in each force sensor and multiple force sensors can be fabricated. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

[0069] FIG. 11 is a flowchart illustrating a method of manufacturing force sensors according to an embodiment of the present invention. The method 1100 includes providing cores 110, each having sensitizers 130 and emitters 132 (1110). In an embodiment of the present invention, a thermal decomposition is used to grow an optically active $\text{NaY}_{0.8}\text{Yb}_{0.18}\text{Er}_{0.02}\text{F}_4$ core 110. A core shell 140 is formed at least partially surrounding each of the cores 110 (1120), for example, using a hot injection method to grow an inert, epitaxial layer of NaYF_4 surrounding core 110. The inert ~ 3 nm NaYF_4 shell can serve to physically separate the sensitizers 130 and emitters 132 from surface states and vibrational modes of the solvent that would otherwise decrease upconversion quantum yield (UCQY) by siphoning luminescence via nonradiative energy transfer. In some implementations, the mean core diameter is 10.9 ± 0.9 nm and the mean core shell diameter is 17.5 ± 1.3 nm. The method 1100 also includes attaching a plurality of oleic acid ligands 150 to each core shell (1130). This can complete the method of manufacturing upconverting nanoparticles 100 for force sensors 160.

[0070] As previously discussed in relation to FIG. 10, an emulsion polymerization method can be used to package the upconverting nanoparticles in polystyrene microspheres. Hydrophobic OA-capped upconverting nanoparticles can be transferred into a styrene micelle in an aqueous continuous phase. Polystyrene is particularly attractive as polymer host 170, also referred to as a host matrix, because its hydrophobicity minimizes aqueous infiltration, protecting upconverting nanoparticles 100 from both water and dissolved electrolytes. By packaging upconverting nanoparticles 100 at high density in an environment that limits the rate of competing energy transfer events from upconverting nanoparticles 100 to the aqueous media in the *C. elegans* pharyngeal lumen, embodiments of the present invention can achieve a brightness that is compatible with high frame rates (50 Hz) and rapid imaging appropriate to the rapid pharyngeal pumping dynamics (up to 5 Hz).

[0071] Referring once again to FIG. 11, the method further includes suspending upconverting nanoparticles 100 in a hydrophobic medium (1140). The hydrophobic medium can be styrene 1054 or other material. The hydrophobic medium can be contained using a container 1040 and water 1050. The method also includes applying ultrasonic energy to the hydrophobic medium (e.g., styrene 1054 contained by water 1050) to form micelles 1062 (1150). A thermal initiator (not shown) can then be used (e.g., added to the micelles) to convert the micelles 1062 into force sensors 160 (1160). The thermal initiator can be potassium persulfate. The heat provided to the thermal initiator can convert the hydrophobic medium (e.g., styrene) into polystyrene beads forming hosts 170 around one or more upconverting nanoparticles 100 to form force sensor 160.

[0072] It should be appreciated that the specific steps illustrated in FIG. 11 provide a particular method of manufacturing force sensors according to an embodiment of the present invention. Other sequences of steps may also be performed according to alternative embodiments. For example, alternative embodiments of the present invention may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in FIG. 11 may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step. Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

[0073] FIG. 12A is a simplified schematic diagram illustrating a test system and operation of a force sensor according to an embodiment of the present invention. In FIG. 12A, light source

1210 can emit light 1212 toward support 1214. Organism 1216 can be placed on support 1214. As an example, organism 1216 can be an optically transparent *C. elegans* worm immobilized in an electropharyngeogram (EPG) chip (not shown).

[0074] Force sensor 160 can be placed such that organism 1216 can apply a force or pressure on the force sensor 160. For example, the force sensor 160, which can be one of a plurality of force sensors 160, can be fed to organism 1216, which can be a *C. elegans* worm or other organism. In some embodiments, to encourage feeding on the force sensors, the host (e.g., polystyrene bead) can have a texture and size that mimics bacteria that a *C. elegans* worm often consumes. As discussed in relation to FIGS. 7 and 9, light 1240, which can include both red and green wavelengths, can be generated by upconversion and emission in the force sensor 160. Light 1240 can then be separated into different wavelength ranges by dichroic filter 1220, resulting in the emission of green photons 1250 at 520 nm, green photons 1252 at 540 nm, and red photons 1254 at 660 nm.

[0075] The light intensity at red wavelengths can be measured using camera 1232, which can be referred to as the red channel. The light intensity at green wavelengths can be measured using camera 1234, which can be referred to as the green channel. Thus, the ratio of the intensity of red emission to the intensity of green emission can be tracked and used to determine a pressure applied to the force sensor 160 by organism 1216. An amplifier 1230 can be connected to electrodes in the vicinity of organism 1216 to track the electrical signals generated by organism 1216 to produce the force that is measured using force sensors 160.

[0076] FIG. 12B is a plot of voltage and the percentage change in intensity ratio as a function of time for a force sensor according to an embodiment of the present invention. FIG. 12B illustrates measurements that can be taken using the test system illustrated in FIG. 12A.

[0077] Referring to FIG. 12B, the right ordinate represents the voltage measured at amplifier 1230 as a function of time. The left ordinate represents the percentage change in the ratio of the intensity of red light to the intensity of green light emitted by force sensor 160 as a function of time. As described more fully below, an analysis of the amplifier voltage and the change in the intensity ratio enables a correlated electrical-mechanical imaging of feeding forces in live worms.

[0078] Referring to the right ordinate, the voltage 1270 received from electrodes electrically coupled to organism 1216 (i.e., an electropharyngeogram) provide information about muscle activity in organism 1216. The voltage 1270 can increase to a value of $\sim 200 \mu\text{V}$ at the start of a bite at time 1272 (E) to a trough of $\sim -600 \mu\text{V}$ at the end of the bite when the muscles relax (R) at time 1274. Thus, in this example, the release of the bite at time 1274 as the muscles relax (R) is defined as time $t=0$ and the start of the bite occurs at $\sim 80 \text{ ms}$ at time 1272 (E). Of course, other baseline times can be utilized as appropriate to the particular application. Thus, the timing of the bite can be determined by monitoring voltage 1270 as a function of time, i.e., the time between E and R.

[0079] Referring to the left ordinate, the intensity ratio 1260 of emission from the region in which the mouth of the organism is located increases as force is applied by organism 1216 to force sensor 160, for example during chewing. That is, the intensity ratio increases from a baseline value of zero to a peak value 1262 of $\sim 10\%$ during the bite and then decreases after the end of the bite at time 1274. Thus, by considering both the voltage 1270 and the intensity ratio 1260 as shown in FIG. 12B, it is evident that the peak voltage from a bite at time 1274 corresponds to the peak in the intensity ratio 1260, i.e., the percentage change in the ratio of the intensity of red light to the intensity of green light emitted by force sensor 160. Moreover, the correlation between the electrical measurements and the optical measurements enables not only the timing of the bite, but measurements of the force applied by the organism at different times during the bite.

[0080] FIG. 13 is a flowchart illustrating a method of using a force sensor according to an embodiment of the present invention. The method 1300 includes providing an organism 1216 (1310) and providing force sensors 160 (1320). The organism 1216 can be a *C. elegans* worm or other organism or to a biological or engineered 3D tissue. Force sensors 160 can each include a polymer host 170 including one or more upconverting nanoparticles 100. The method also includes positioning force sensors 160 in a location where organism 1216 can provide a force to force sensors 160 (1330).

[0081] The method further includes providing light in a first wavelength range to force sensors 160 (1340), receiving light in a second wavelength range from force sensors 160 (1350), and receiving light in a third wavelength range from force sensors 160 (1360). Because the light in

the first wavelength range can be infrared light (e.g., at 980 nm), some embodiments can be utilized in applications where deep penetration into tissue is utilized in order for the light in the first wavelength range to reach force sensors 160. Thus, operating in a water transparency window, embodiments of the present invention provide benefits not available using systems that
5 utilize visible light or other wavelengths absorbed by water for sample illumination. The method also includes determining an intensity ratio for the intensity of light in the second wavelength range to the intensity of light in the third wavelength range (1370). The intensity ratio can be measured and tracked over time.

[0082] It should be appreciated that the specific steps illustrated in FIG. 13 provide a particular
10 method of using a force sensor according to an embodiment of the present invention. Other sequences of steps may also be performed according to alternative embodiments. For example, alternative embodiments of the present invention may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in FIG. 13 may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step.

15 Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

[0083] Accordingly, embodiments of the present invention can provide force sensors that can operate without the need for an external connection or power supply. An illustrative
embodiment of the present invention can provide a force sensor including one or more
20 upconverting nanoparticles in a host structure. One or more force sensors can be positioned in an organism where the organism can apply a force or pressure. The force sensors can provide an output that can be used to measure and track force applied by the organism.

[0084] These and other embodiments of the present invention can provide force sensors that do not require a power source. Instead, each force sensor can include one or more unconvert
25 nanoparticles. Photons in a first range of wavelengths can be provided to the upconverting nanoparticles. The photons in the first range of wavelengths can move electrons in the unconvert
nanoparticles to a more energetic state. This energy can be released as photons
having higher energy and shorter wavelengths. For example, the unconvert
nanoparticles in a host can release photons in a second range of wavelengths, the second range of wavelengths
30 shorter than the first range of wavelengths. The unconvert
nanoparticles can release photons

in a second range of wavelengths and a third range of wavelengths, the second range of wavelengths and the third range of wavelengths shorter than the first range of wavelengths. The unconvertng nanoparticles can release photons in a second range of wavelengths, a third range of wavelengths, and a fourth range of wavelengths, the second range of wavelengths, the third
5 range of wavelengths, and the fourth range of wavelengths shorter than the first range of wavelengths. In this way, force sensors can receive photons in the first range of wavelengths and then upconvert the received photons to provide photons at one or more energetic wavelengths without the need of a power supply connection, internal battery, or other power source.

[0085] In these and other embodiments of the present invention, the force sensors can be
10 pressure sensitive. That is, the upconverted photons provided by the upconverting nanoparticles in a force sensor can vary as a function of force or pressure applied to the upconverting nanoparticles.

[0086] In these and other embodiments of the present invention, the upconverted photons provided by upconverting nanoparticles in a force sensor can vary in different ways in response
15 to a force or pressure. For example, when a force or pressure is applied to a force sensor, a number of photons provided by the upconverting nanoparticles at a second range of wavelengths can increase. When a force or pressure is applied to a force sensor, a number of photons provided by the upconverting nanoparticles at a second range of wavelengths can decrease. When a force or pressure is applied to a force sensor, a number of photons provided by the
20 upconverting nanoparticles at a second range of wavelengths and at a third range of wavelengths can increase. When a force or pressure is applied to a force sensor, a number of photons provided by the upconverting nanoparticles at a second range of wavelengths and at a third range of wavelengths can decrease. When a force or pressure is applied to a force sensor, a ratio of a number of photons provided by the upconverting nanoparticles at a second range of wavelengths
25 to a number of photons at a third range of wavelengths can increase. When a force or pressure is applied to a force sensor, a ratio of a number of photons provided by the upconverting nanoparticles at a second range of wavelengths to a number of photons at a third range of wavelengths can decrease. These changes in either the number of photons, ratios of photons, or other relationships among number of photons can vary. These changes, or relationships among
30 these changes, can be used as an output response for the force sensors.

[0087] In these and other embodiments of the present invention, this variability can be used to determine a force on a force sensor. For example, forces can be applied to upconverting nanoparticles, the force can be measured, and the resulting response can be measured. The output response as a function of applied force can be used to calibrate the force sensors. When
5 the force sensors are used in an organism, the output response can be observed and used to determine the force or pressure applied to by the organism to the force sensors.

[0088] The relationship between the output response and the force or pressure applied to a force sensor can vary in different embodiments of the present invention. For example, the relationship between the output response and the force or pressure applied to a force sensor can
10 be linear, that is, a change in output response can be proportional to a change in force or pressure at the force sensor. The relationship between the output response and the force or pressure applied to a force sensor can be reciprocal, that is, the output response can follow the reciprocal of the applied force or pressure. This relationship can be geometrical, exponential, the inverse of these functions, or other functions or their inverse.

[0089] Various types of nanoparticles and hosts can be employed in these and other
15 embodiments of the present invention. The upconverting nanoparticles can have a core. The core can be ceramic or other material. The core can be a sodium yttrium fluoride lattice. The core can be doped. For example, the core can be doped with lanthanide, though other materials can be used to dope the core. The core can include a first lanthanide dopant and a second
20 lanthanide dopant. The first lanthanide dopant can be ytterbium or other material. The second lanthanide dopant can be erbium or other material. The core can be at least partially surrounded by a shell. The shell can be formed of an undoped version of the material used for the core. Oleic acid ligands can be attached to each core shell. Each ligand can have a carboxylic acid terminus attached to the core shell and a hydrophobic alkyl chain extending away from the core
25 shell. One or more of these upconverting nanoparticles can be supported in a host. The host can be formed of a polymer. That is, a polymeric host can be formed around one or more upconverting nanoparticles. For example, the host can be formed of polystyrene or other polymer.

[0090] Force sensors provided by these and other embodiments of the present invention can
30 operate in various ways. For example, a force sensor can include a sensitizer, an emitter, and a

polymer host. Energy can be absorbed by the sensitizer. For example, energy from photons in a first range of wavelengths can be absorbed by the sensitizer. The sensitizer can provide this energy to the emitter, which can provide photons in a second range of wavelengths and in a third range of wavelengths. The emitter and polymer host can be electronically-vibrationally coupled to the polymer host. The polymer host can increase a sensitivity of the emitter to force or pressure.

[0091] In these and other embodiments of the present invention, the ytterbium dopants in the core can serve as a sensitizer. The ytterbium dopants can receive energy from infra-red photons at or around the 980 nm wavelengths. The ytterbium dopants can provide this energy to the emitter, which can be formed of erbium dopants in the core. The erbium dopants and the host, which can be implemented as a polymeric host, can be electronically-vibrationally coupled to the sensor, which can be implemented as a polymeric host. The polymeric host can be formed of polystyrene or other polymer. The erbium dopants can provide red photons at or around the 660 nm wavelengths and green photons at or around the 540 nm wavelengths. When the force sensors experience a force or pressure, the emitters can emit an increased number of green photons and red photons. The increase in these photons can be used to indicate an amount of force or pressure on the force sensor. When the force sensors experience a force or pressure, the ratio of the number of red photons at or around the 660 nm wavelengths to the number of green photons at or around the 540 nm wavelengths emitted by the emitter can increase. The increase in this ratio can be used to indicate an amount of force or pressure on the force sensor.

[0092] In these and other embodiments of the present invention, sensitizers can receive energy from infra-red photons at or around the 980 nm wavelengths, while the emitters can provide red photons at or around the 660 nm wavelengths and green photons at or around the 540 nm wavelengths. This has the advantage of using stimulus light that is not visible, allowing the visible light of the output response to be observed more clearly. In these and other embodiments of the present invention other detectors can be used to receive light from the emitters, for example light that is not in the visible spectrum. This can allow the stimulus photons provided to the sensitizers to be in the visible spectrum.

[0093] Embodiments of the present invention can provide various methods of manufacturing force sensors. For example, material for ceramic cores can be provided. These cores can be

ceramic or other material and can have a first lanthanide dopant and a second lanthanide dopant. The ceramic core can be sodium yttrium fluoride or other material. The first lanthanide dopant can be ytterbium or other material. The second lanthanide dopant can be erbium or other material. The core and dopants can be commercially available.

5 [0094] The core can be at least partially encased in a shell. The shell can be formed of an undoped version of the material used for the core. The presence of the shell can increase brightness, that is, it can increase the number of photons emitted by the erbium. Oleic acid ligands can be attached to each core shell. Each ligand can have a carboxylic acid terminus attached to the core shell and a hydrophobic alkyl chain extending away from the core shell to
10 complete the formation of the upconverting nanoparticles. These ligands can cause the upconverting nanoparticles to be hydrophobic such that they can remain suspended in a liquid during formation of the polymer hosts.

[0095] The upconverting nanoparticles can be place in styrene, which can be suspended in water. Ultrasonic energy can be applied to the suspended styrene and the upconverting
15 nanoparticles to generate micelles. A thermal initiator can be used to convert the styrene micelles to polystyrene beads. The individual beads can then be used as force sensors.

[0096] These and other embodiments of the present invention can be used in various types of measurements. For example, an organism can be provided. Force sensors can be provided. These force sensors can each include one or more upconverting nanoparticles in a polymeric
20 host. The force sensor can be positioned where the organism can provide a force or pressure to the force sensors. Photons in a first range of wavelengths can be provided to the force sensors. Photons in a second range of wavelengths can be received, as can photons in a third range of wavelengths. A ratio of an intensity of light in the second range of wavelengths to an intensity of light in the third range of wavelengths can be found. This ratio can be used to estimate a force
25 or pressure on the force sensors applied by the organism. A voltage at the organism can be measured as well, if applicable.

[0097] Various embodiments of the present invention can incorporate one or more of these and the other features described herein. A better understanding of the nature and advantages of the present invention can be gained by reference to the above detailed description and the
30 accompanying drawings.

[0098] The above description of embodiments of the invention has been presented for the purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form described, and many modifications and variations are possible in light of the teaching above. The embodiments were chosen and described in order to best
5 explain the principles of the invention and its practical applications to thereby enable others skilled in the art to best utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Thus, it will be appreciated that the invention is intended to cover all modifications and equivalents within the scope of the following claims.

WHAT IS CLAIMED IS:

- 1 1. A force sensor comprising:
2 one or more upconverting nanoparticles, wherein each of the one or more
3 upconverting nanoparticles include an emitter; and
4 a polymeric host at least partially around the one or more upconverting
5 nanoparticles, wherein the polymeric host exhibits electronic-vibrational coupling with the
6 emitter in a stress dependent manner.
- 1 2. The force sensor of claim 1 wherein the one or more upconverting
2 nanoparticles comprises one upconverting nanoparticle.
- 1 3. The force sensor of claim 1 wherein the one or more upconverting
2 nanoparticles comprises at least one thousand upconverting nanoparticles.
- 1 4. The force sensor of claim 1 wherein at least one of the one or more
2 upconverting nanoparticles has a diameter between 1 and 100 nanometers.
- 1 5. The force sensor of claim 1 wherein each of the one or more upconverting
2 nanoparticles comprise a ceramic core including:
3 a crystal lattice;
4 a first dopant in the crystal lattice, wherein the first dopant is operable to receive
5 energy from photons in a first wavelength range; and
6 a second dopant in the crystal lattice, wherein the second dopant is operable to:
7 receive energy from the first dopant;
8 emit a first number of photons in a second wavelength range; and
9 emit a second number of photons in a third wavelength range different
10 from the second wavelength range.
- 1 6. The force sensor of claim 5 wherein the crystal lattice comprises a
2 ceramic.
- 1 7. The force sensor of claim 6 wherein the ceramic comprises sodium
2 yttrium fluoride.

1 8. The force sensor of claim 5 wherein the first dopant and the second dopant
2 are lanthanides.

1 9. The force sensor of claim 5 wherein the first dopant is ytterbium and the
2 second dopant is erbium.

1 10. The force sensor of claim 5 further comprising a ceramic shell
2 surrounding the crystal lattice.

1 11. The force sensor of claim 10 wherein the ceramic shell is undoped.

1 12. The force sensor of claim 1 wherein the polymer comprises polystyrene.

1 13. A device for use in measuring force or pressure, the device comprising:
2 a sensitizer configured to receive energy from first photons in a first wavelength
3 range;

4 an emitter configured to receive energy from the sensitizer and to emit second
5 photons in a second wavelength range and third photons in a third wavelength range; and

6 a host including the sensitizer and the emitter, wherein the host is chosen such
7 that its vibrational modes couple with the electronic modes of the emitter.

1 14. The device of claim 13 wherein the host is polystyrene.

1 15. The device of claim 13 wherein the host interacts with the emitter such
2 that the emitter emits an increased amount of third photons in the third wavelength range as
3 compared to an amount of third photons in the third wavelength range that the emitter emits in
4 the absence of the host.

1 16. The device of claim 15 wherein the emitter emits an increased amount of
2 third photons in the third wavelength range as compared to an amount of second photons in the
3 second wavelength range in response to force applied to the device.

1 17. The device of claim 15 wherein the emitter emits an increased amount of
2 third photons in the third wavelength range relative to second photons in the second wavelength
3 range in response to force or pressure applied to the device.

1 18. The device of claim 13 wherein the device is located in a cardiovascular
2 pressure measuring system.

1 19. The device of claim 13 wherein the device is located in an apparatus
2 configured to measure a force between an immune cell and an antigen presenting cell.

1 20. A method of measuring an in-vivo force, the method comprising:
2 providing an organism;
3 providing one or more force sensors, where each force sensor comprises one or
4 more upconverting nanoparticles positioned in a polymeric host,
5 positioning the one or more force sensors such that the organism exerts a force on
6 the one or more force sensors;
7 illuminating the one or more force sensors with first photons in a first wavelength
8 range;
9 receiving second photons emitted by the one or more force sensors in a second
10 wavelength range;
11 receiving third photons emitted by the one or more force sensors in a third
12 wavelength range;
13 separating the second photons in the second wavelength range from the third
14 photons in the third wavelength range; and
15 determining a ratio of an intensity of light in the second wavelength range to the
16 intensity of light in the third wavelength range.

1 21. The method of claim 20 further comprising tracking the determined ratio
2 for a first duration.

1 22. The method of claim 20 further comprising measuring a voltage associated
2 with the force exerted by the organism.

1 23. The method of claim 20 wherein each of the one or more upconverting
2 nanoparticles comprise a ceramic core including:
3 a crystal lattice;
4 a first dopant in the crystal lattice, wherein the first dopant is operable to receive
5 energy from the first photons in the first wavelength range; and
6 a second dopant in the crystal lattice, wherein the second dopant is operable to:
7 receive energy from the first dopant;
8 emit second photons in the second wavelength range; and
9 emit third photons in the third wavelength range different from the second
10 wavelength range.

1 24. The method of claim 20 wherein at least one of the one or more
2 upconverting nanoparticles has a diameter between 1 and 100 nanometers.

1 25. The method of claim 20 wherein the first wavelength range comprises
2 infrared wavelengths and the second wavelength range and the third wavelength range comprise
3 visible or near-infrared wavelengths.

1 26. A method of manufacturing a force sensor, the method comprising:
2 providing one or more ceramic cores, the ceramic cores each having a first
3 lanthanide dopant and a second lanthanide dopant;
4 suspending the one or more ceramic cores in a hydrophobic medium;
5 suspending the one or more ceramic cores and the hydrophobic medium in water;
6 applying ultrasonic energy to the suspended hydrophobic medium to generate
7 micelles; and
8 using a thermal initiator to convert the micelles into force sensing devices.

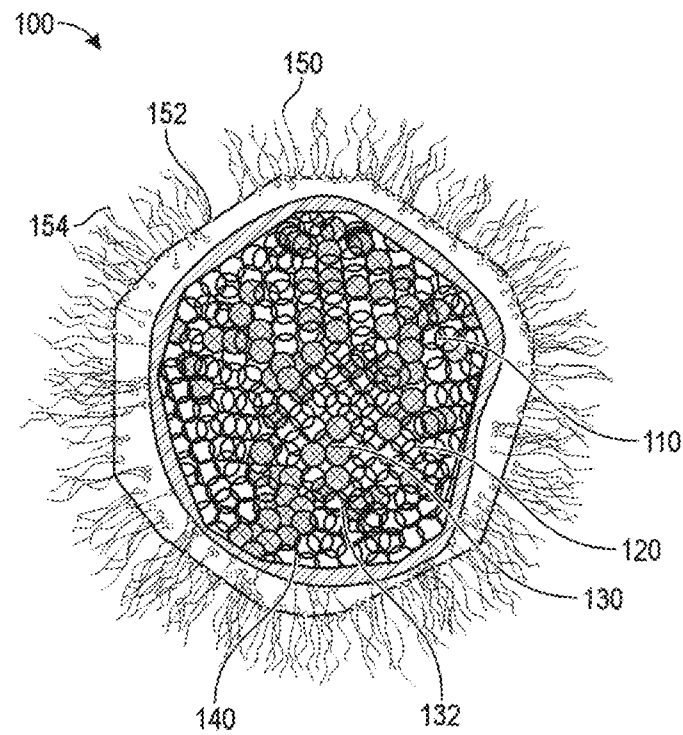
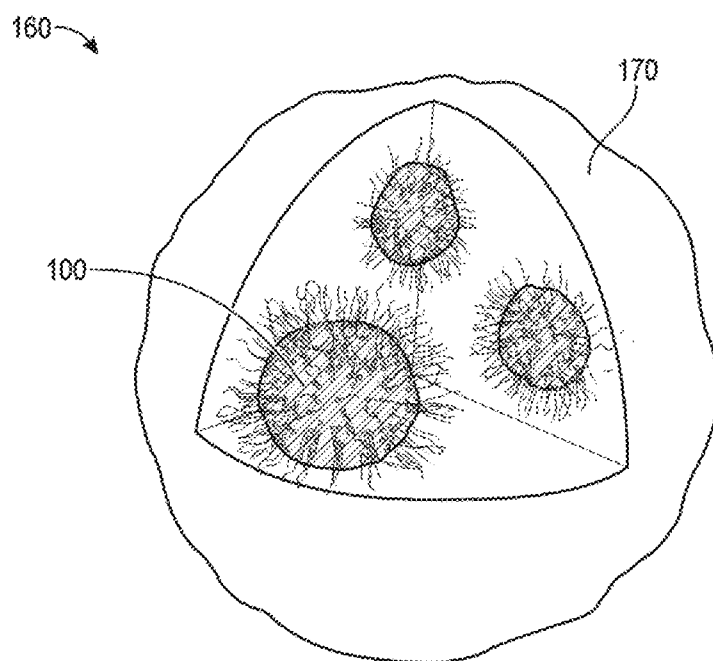
1 27. The method of claim 26 wherein providing one or more ceramic cores, the
2 ceramic cores each having a first lanthanide dopant and a second lanthanide dopant comprises:
3 for at least one of the one or more ceramic cores, providing a sodium yttrium
4 fluoride lattice, wherein the first lanthanide dopant is ytterbium at an 18 percent concentration
5 and the second lanthanide dopant is erbium at a 2 percent concentration.

1 28. The method of claim 26 wherein the hydrophobic medium comprises
2 styrene.

1 29. The method of claim 26 wherein the thermal initiator comprises potassium
2 persulfate.

1 30. The method of claim 29 wherein the hydrophobic medium is styrene, the
2 micelles are styrene micelles, and the styrene micelles are converted into polystyrene beads using
3 the potassium persulfate.

1 31. The method of claim 26 further comprising:
2 before suspending the one or more ceramic cores in the hydrophobic medium,
3 forming a core shell around each of a corresponding one of the one or more ceramic cores; and
4 attaching a plurality of oleic acid ligands to each core shell, each ligand having a
5 carboxylic acid terminus attached to the core shell and a hydrophobic alkyl chain extending away
6 from the core shell.

**FIG. 1A****FIG. 1B**

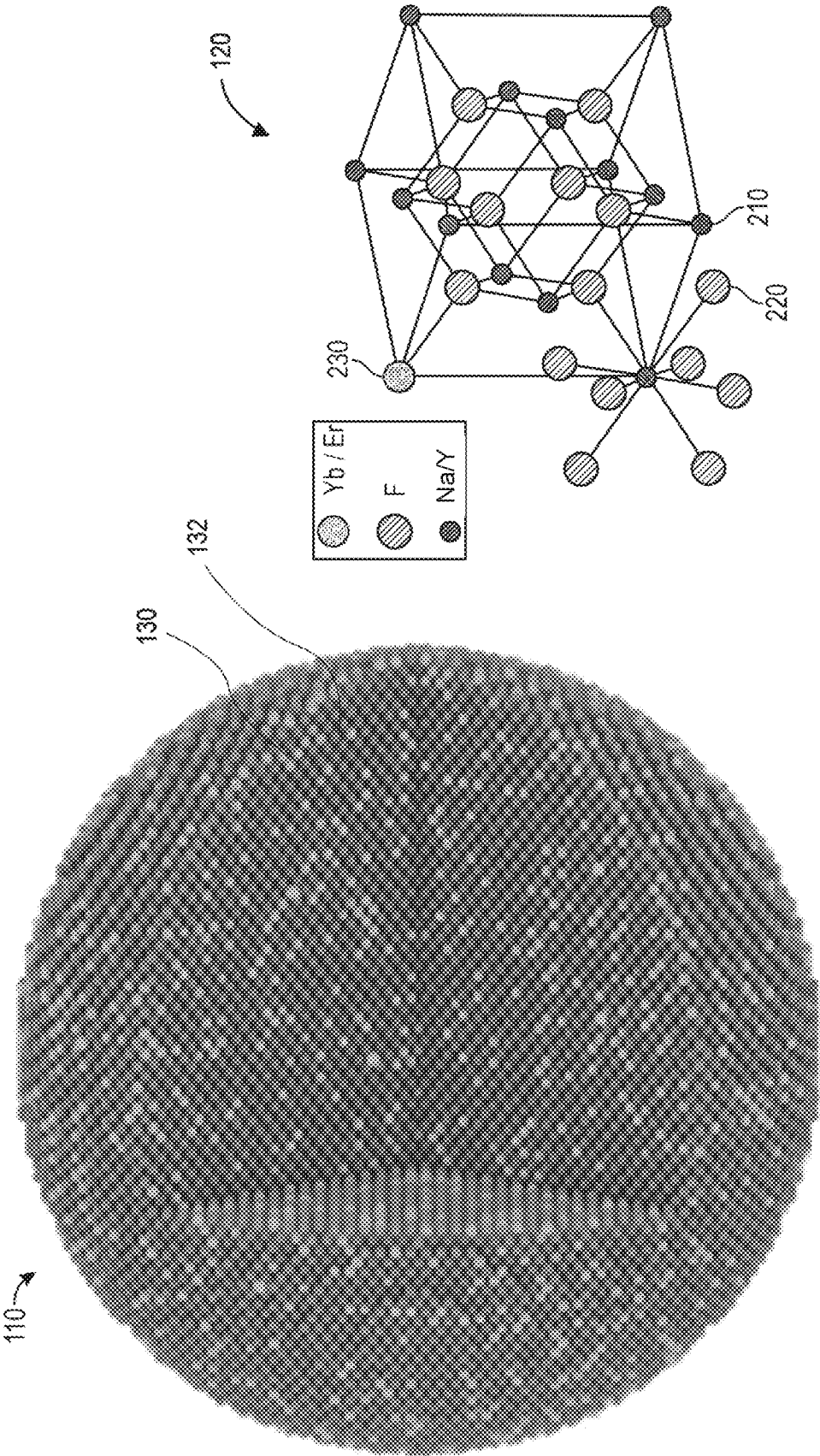


FIG. 2B

FIG. 2A

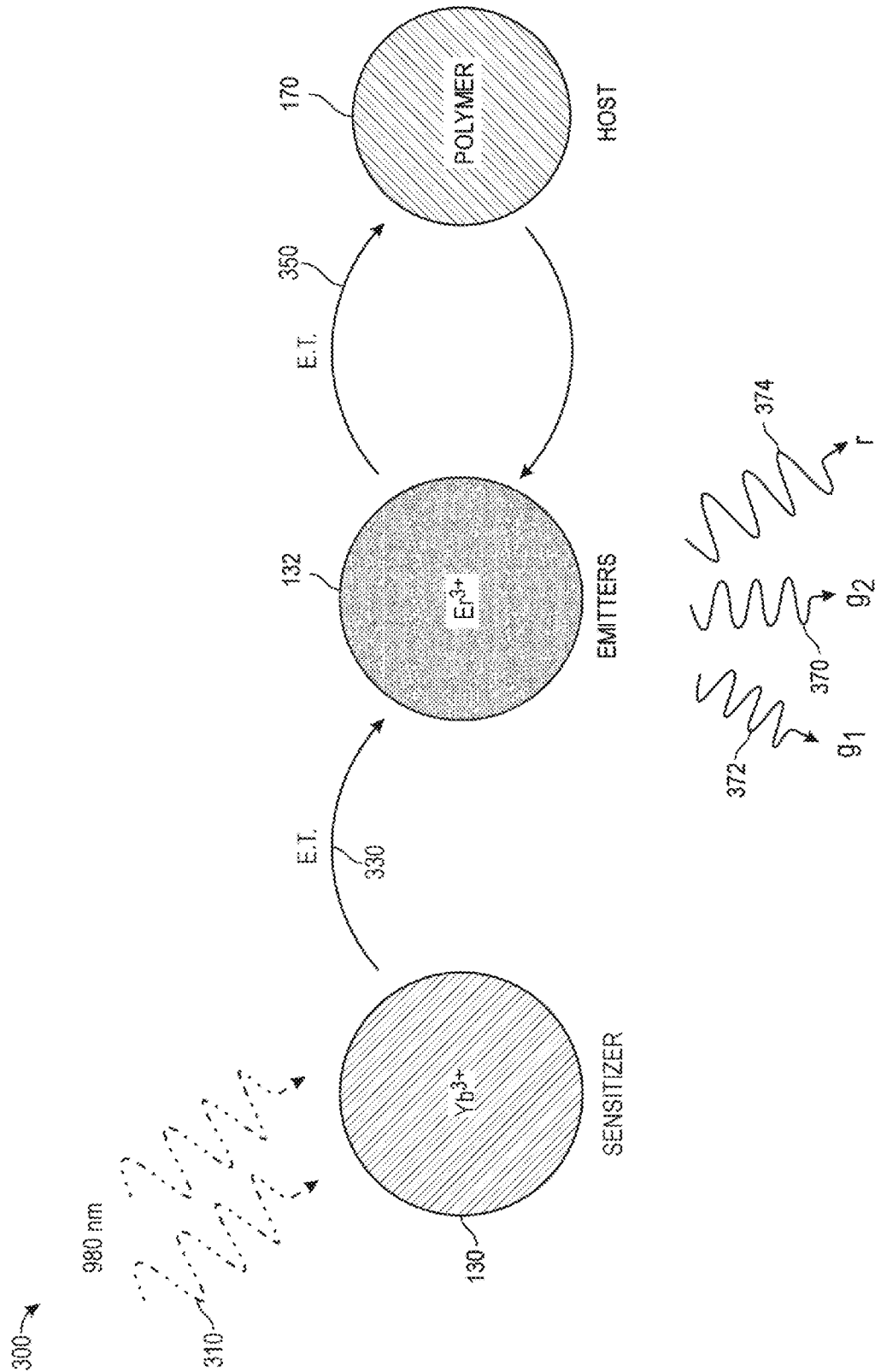


FIG. 3

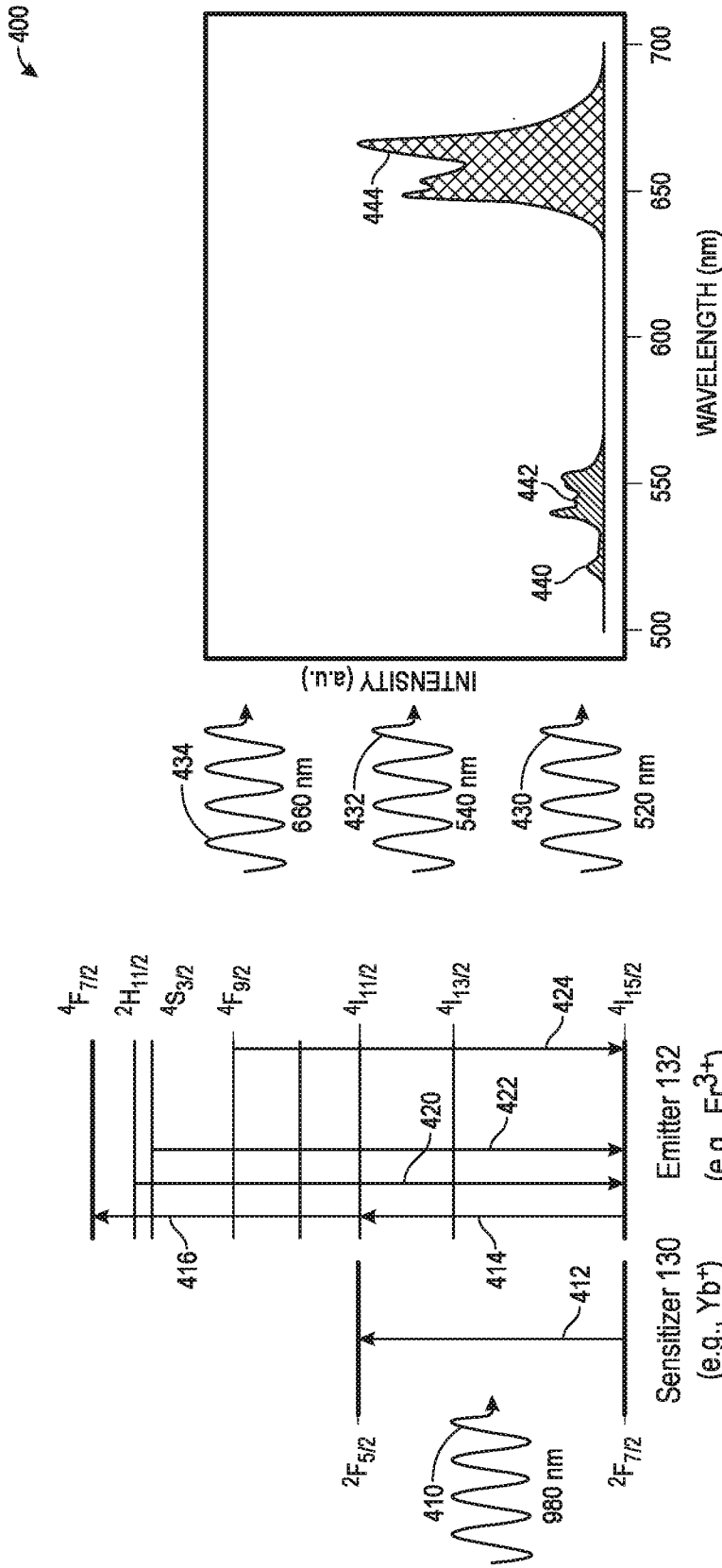


FIG. 4

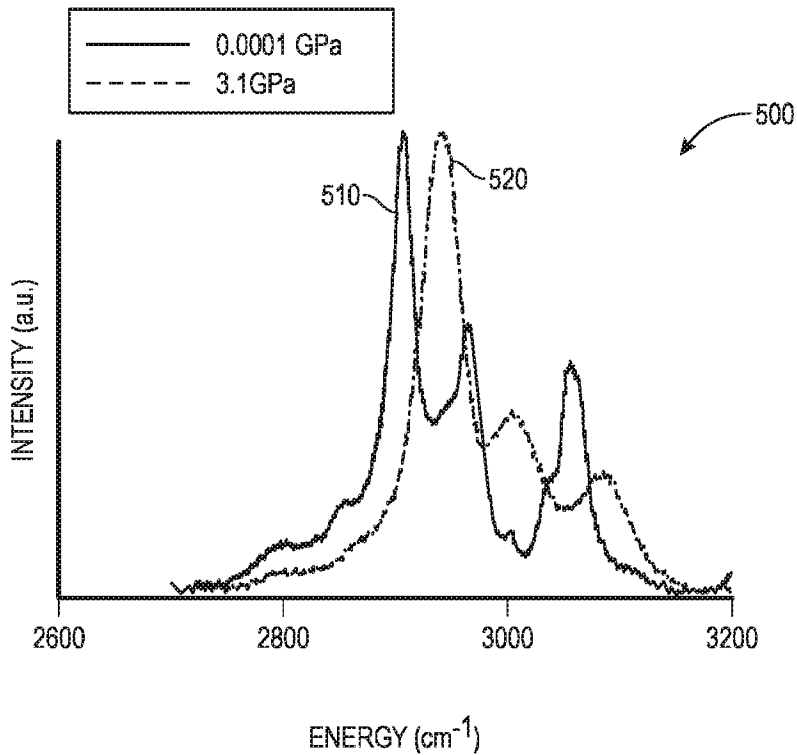


FIG. 5A

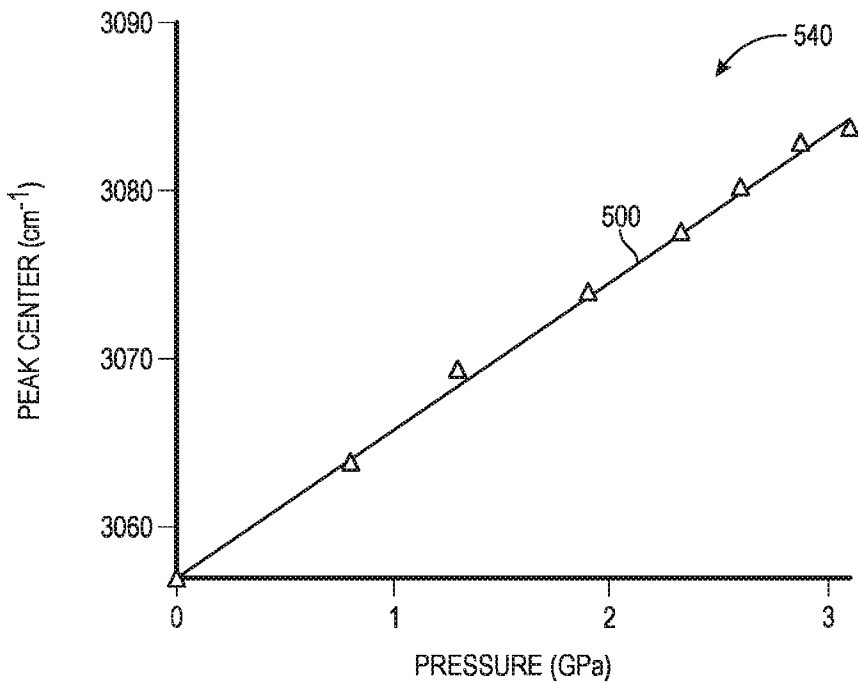
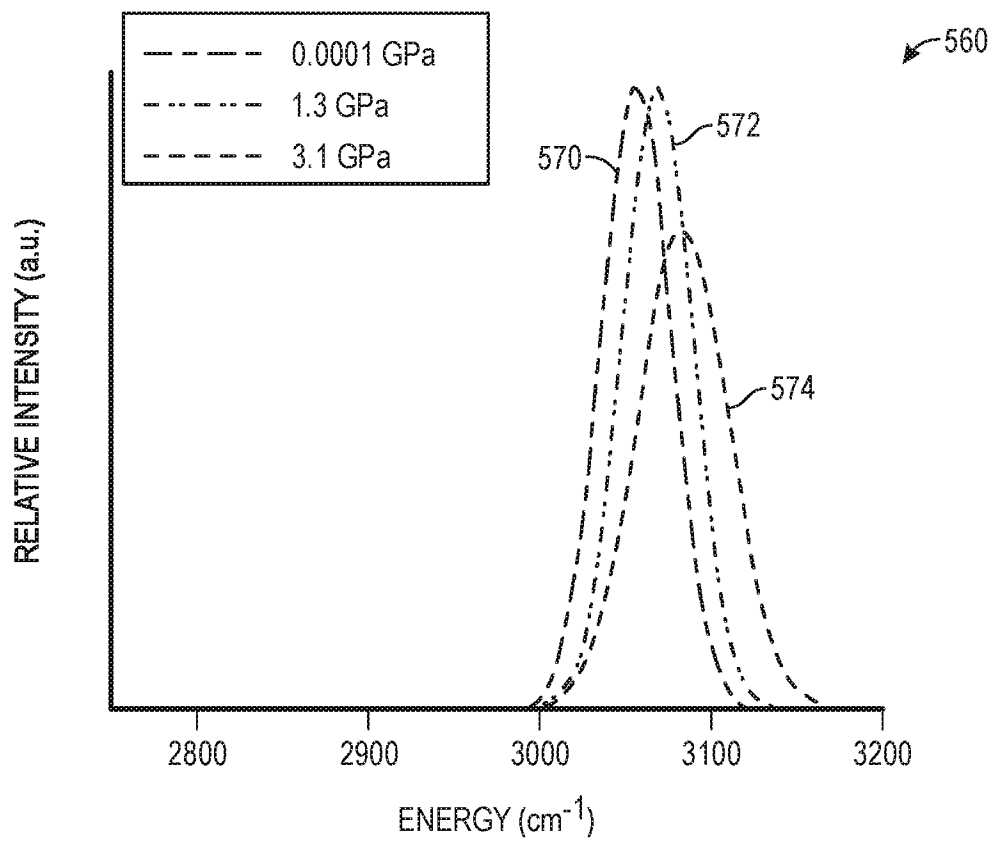
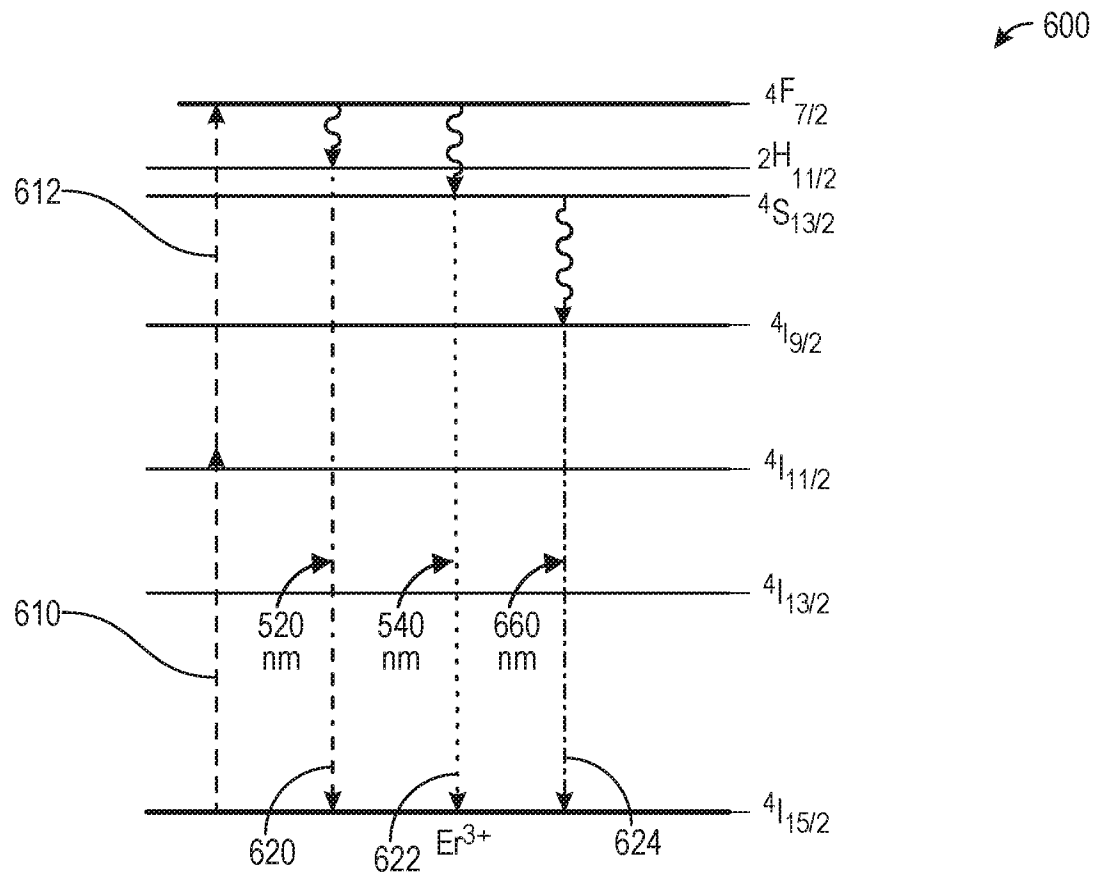


FIG. 5B

**FIG. 5C**

**FIG. 6**

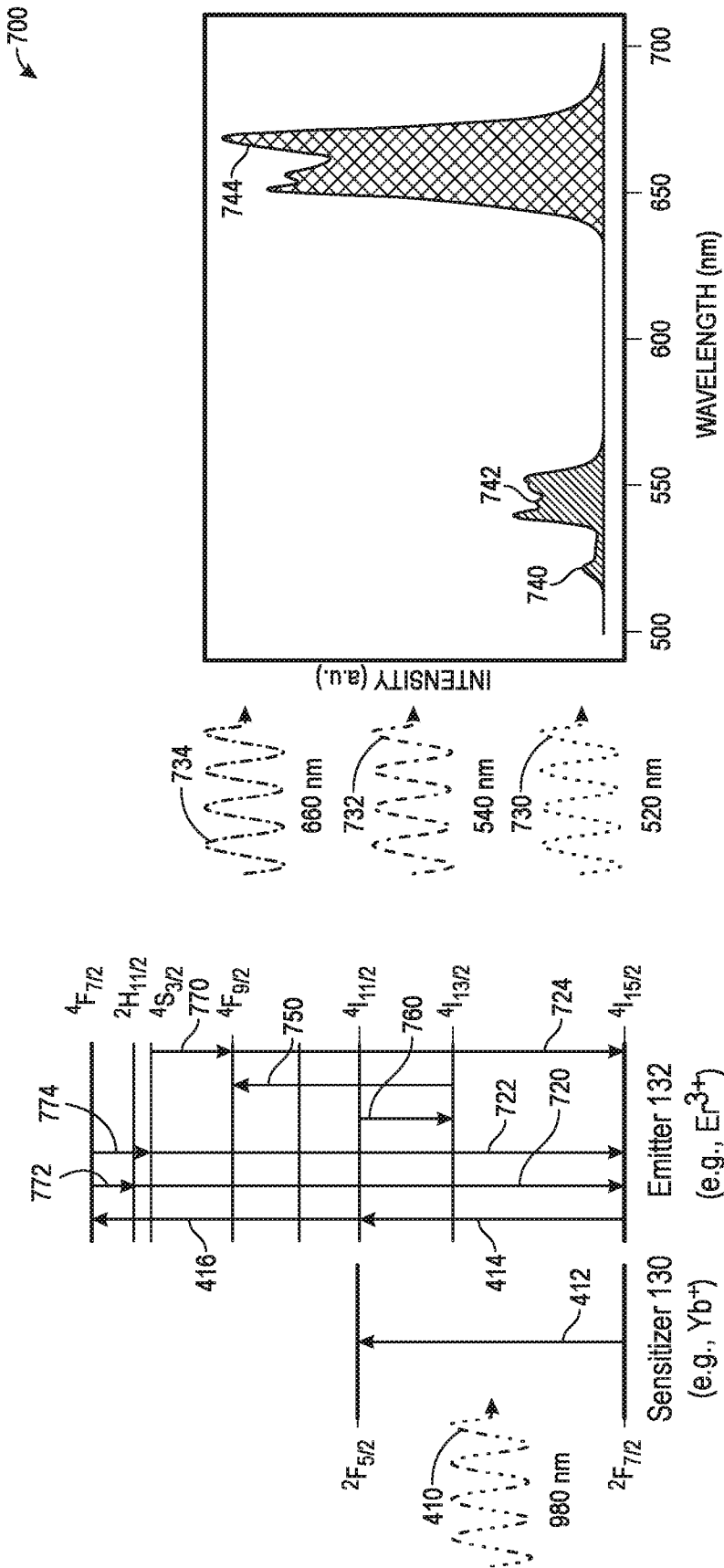
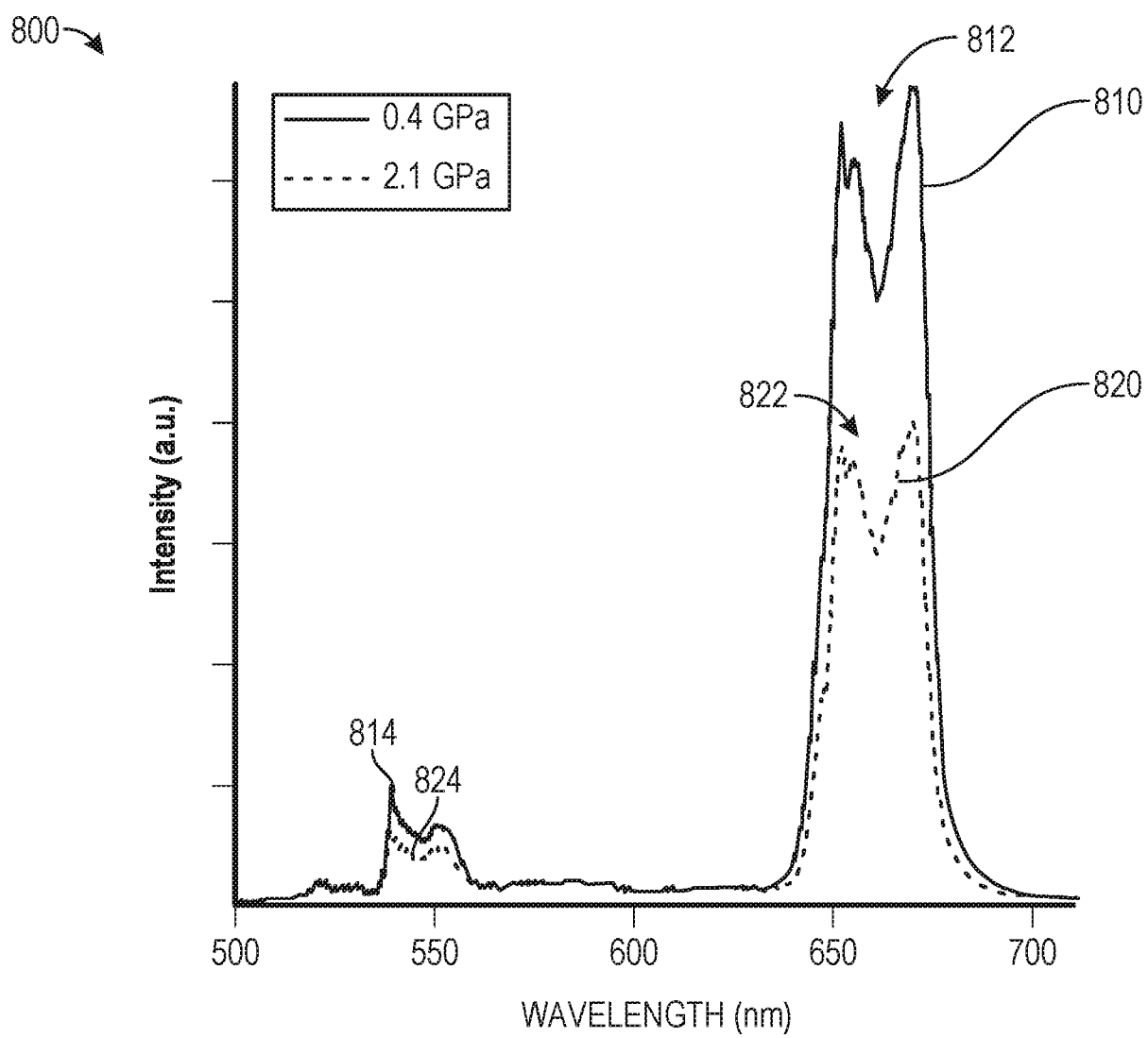
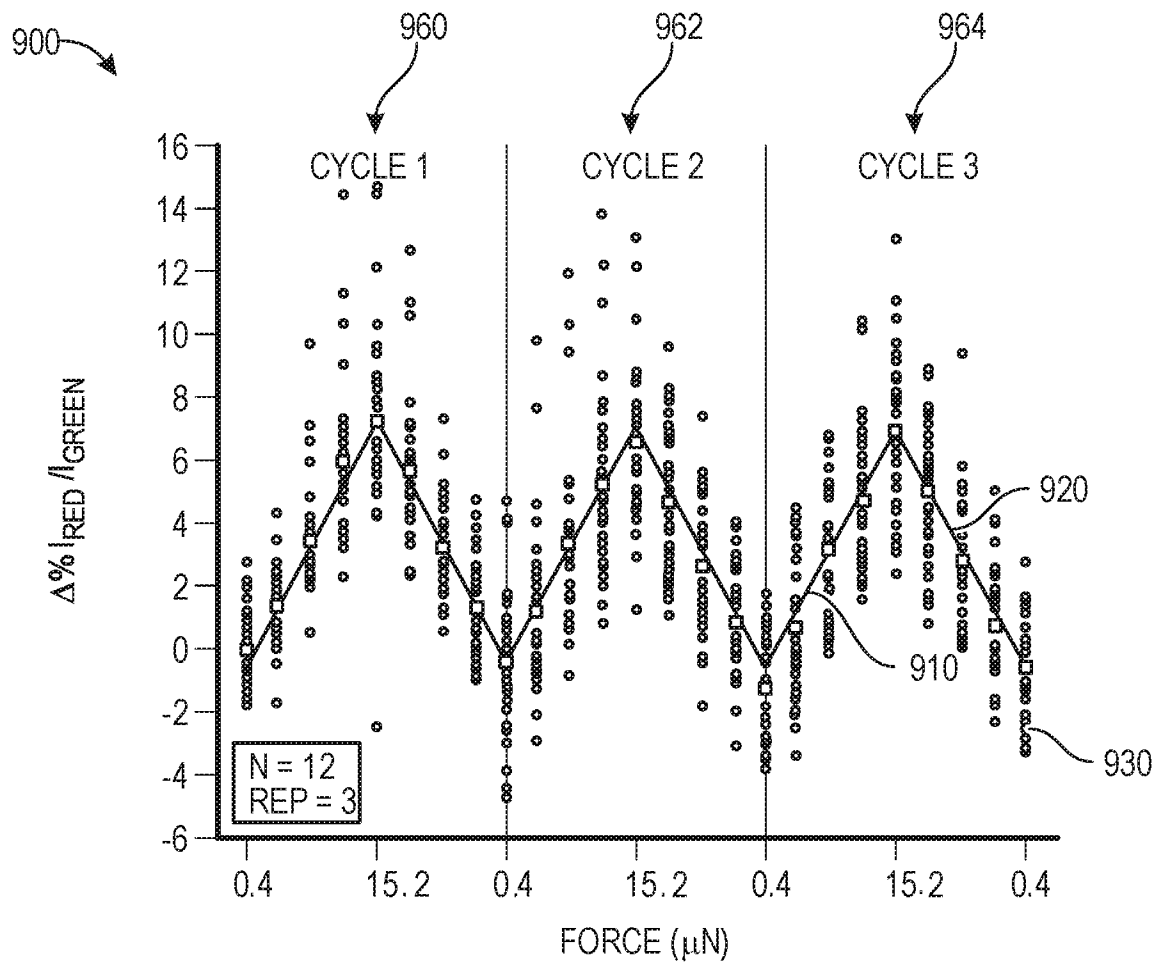


FIG. 7

**FIG. 8**

**FIG. 9**

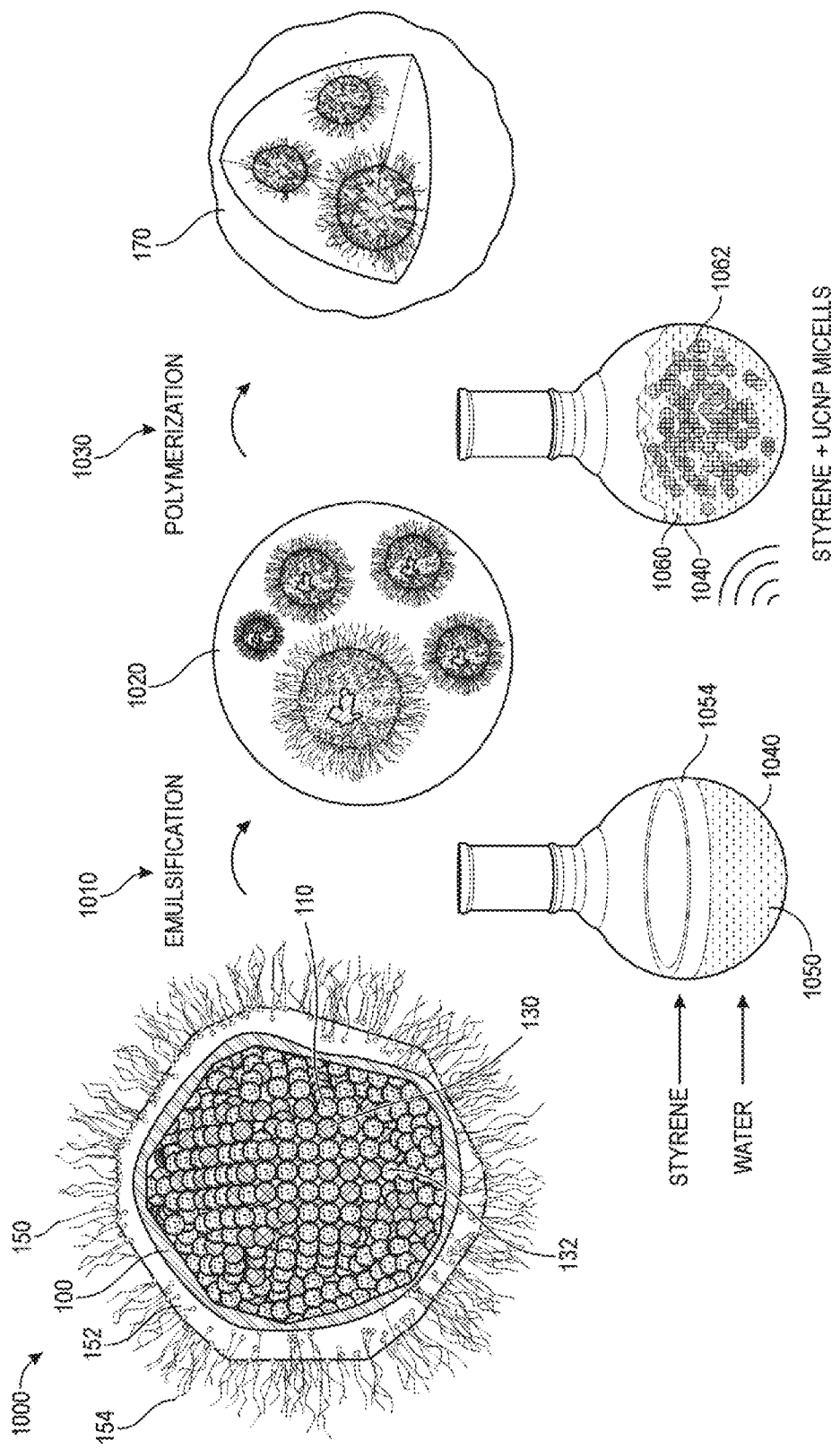
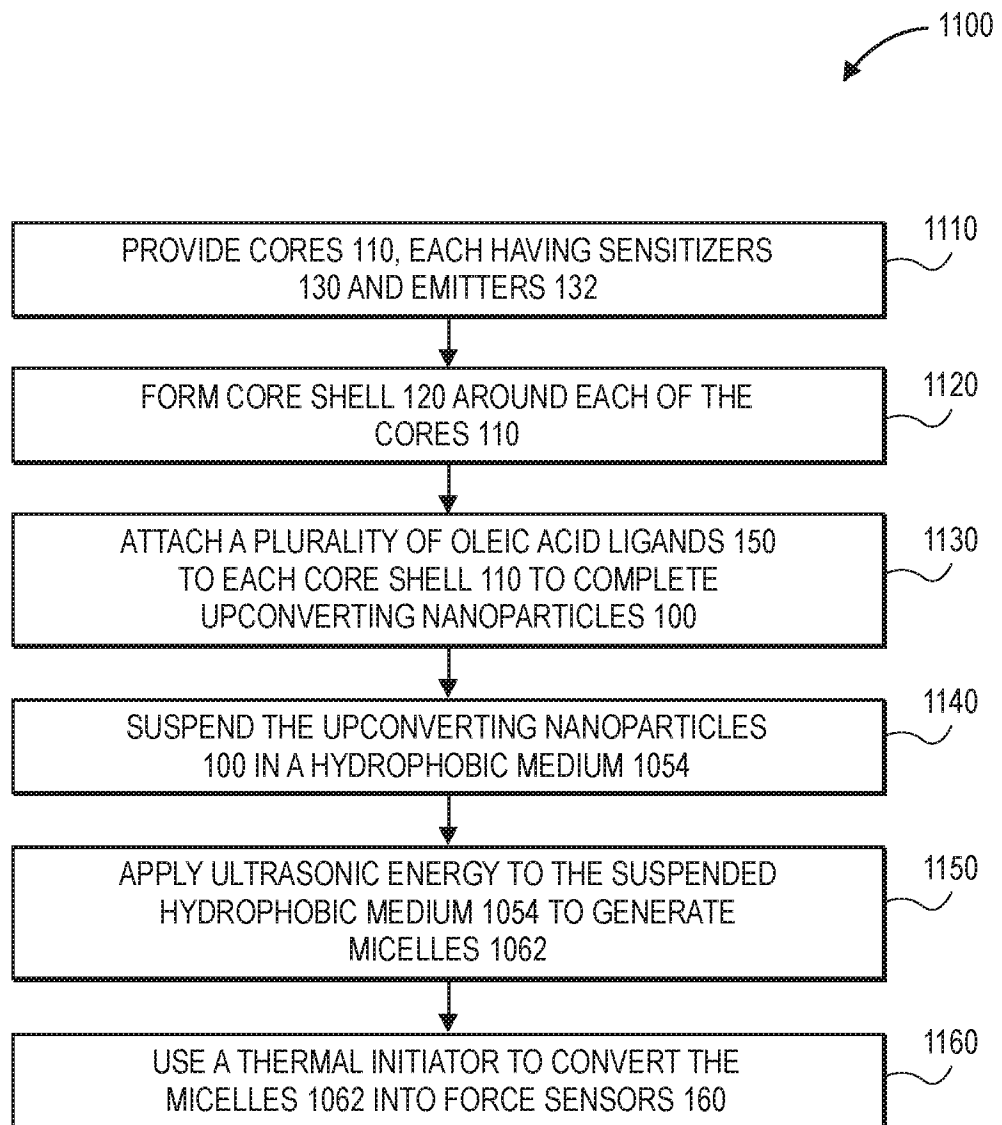


FIG. 10

**FIG. 11**

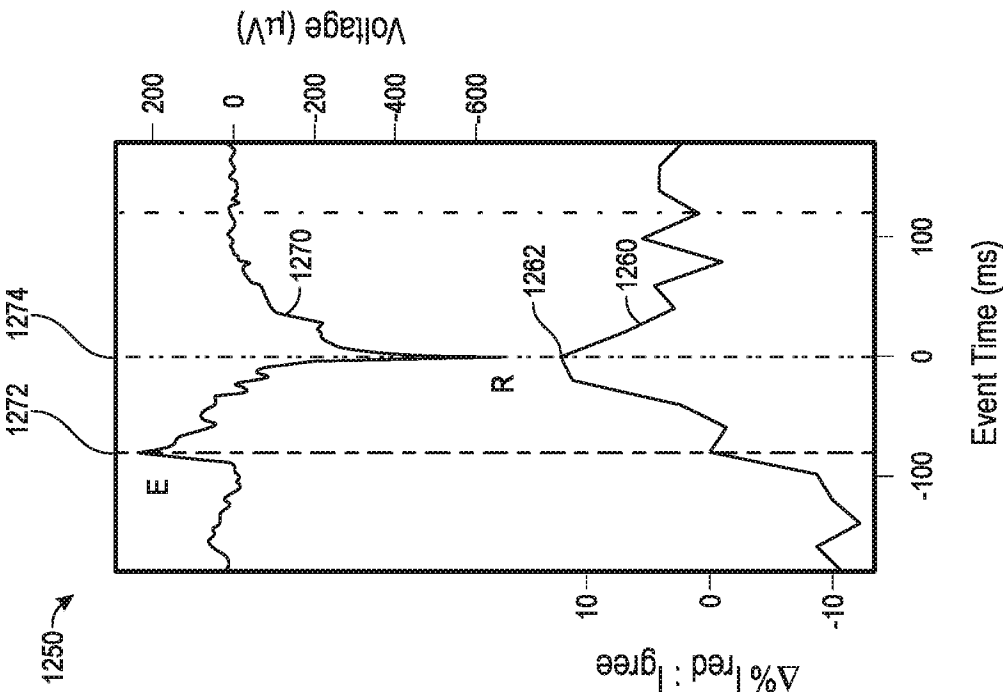


FIG. 12B

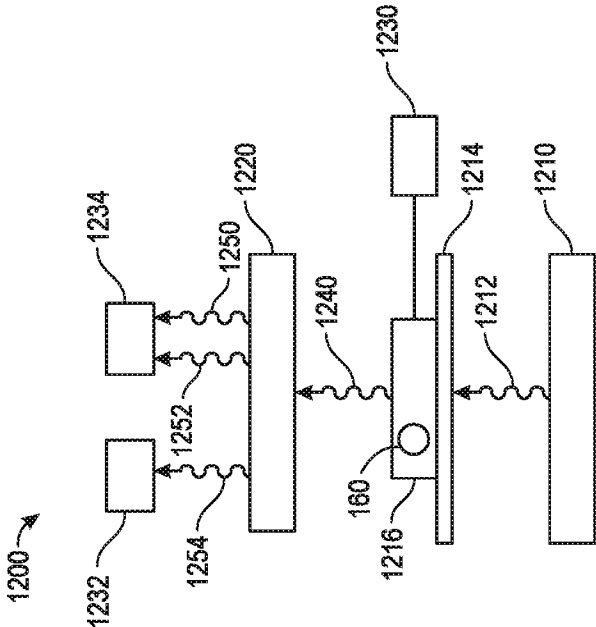
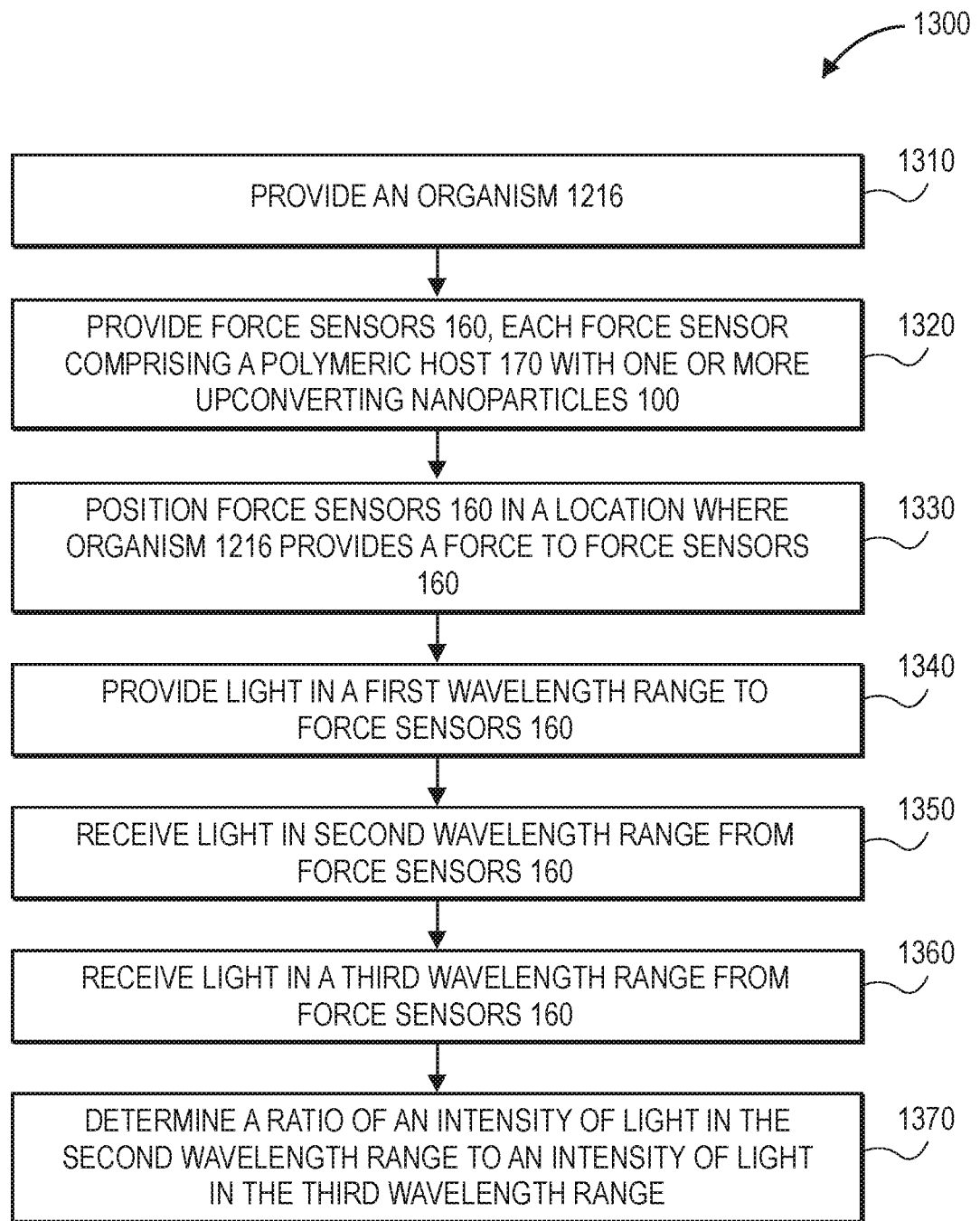


FIG. 12A

**FIG. 13**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/061325

A. CLASSIFICATION OF SUBJECT MATTER IPC: G01L 1/24 (2025.01); G01B 11/16 (2025.01); G01N 21/64 (2025.01); G01L 5/18 (2025.01) CPC: G01L 1/24 ; G01N 21/64 ; G01B 11/16 ; G01L 5/18 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	WO 2022/236104 A1 (THE REGENTS OF THE UNIVERSITY OF COLORADO A BODY CORPORATE) 10 November 2022 (10.11.2022) entire document	1-12
Y	US 2016/0263393 A1 (IMMUNOLIGHT LLC et al.) 15 September 2016 (15.09.2016) entire document	1-12
Y	US 2013/0236555 A1 (SONY CORPORATION) 12 September 2013 (12.09.2013) entire document	12
A	US 2022/0306888 A1 (LIQUID X PRINTED METALS INC.) 29 September 2022 (29.09.2022) entire document	1-12
A	US 2020/0072787 A1 (LG CHEM LTD. et al.) 05 March 2020 (05.03.2020) entire document	1-12
A	US 2022/0003676 A1 (MAZED) 06 January 2022 (06.01.2022) entire document	1-12
☒ 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 21 February 2025 (21.02.2025)		Date of mailing of the international search report 08 April 2025 (08.04.2025)
Name and mailing address of the ISA/US COMMISSIONER FOR PATENTS MAIL STOP PCT, ATTN: ISA/US P.O. Box 1450 Alexandria, VA 22313-1450 UNITED STATES OF AMERICA Facsimile No. 571-273-8300		Authorized officer TAINA MATOS Telephone No. 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/061325

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0268943 A1 (UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE ARMY) 21 September 2017 (21.09.2017) entire document	1-12

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

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-12, is drawn to a force sensor comprising: the polymeric host exhibits electronic-vibrational coupling with the emitter in a stress dependent manner.

Group II, claims 13-19, is drawn to a device for use in measuring force or pressure, the device comprising: a sensitizer configured to receive energy from first photons in a first wavelength range.

Group III, claims 20-25, is drawn to a method of measuring an in-vivo force- the method comprising: providing an organism.

Group IV, claims 26-31, is drawn to a method of manufacturing a force sensor, the method comprising: providing one or more ceramic cores.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention: the polymeric host exhibits electronic-vibrational coupling with the emitter in a stress dependent manner as claimed therein is not present in the invention of Groups II, III or IV. The special technical feature of the Group II invention: a sensitizer configured to receive energy from first photons in a first wavelength range; an emitter configured to receive energy from the sensitizer and to emit second photons in a second wavelength range and third photons in a third wavelength range; and a host including the sensitizer and the emitter, wherein the host is chosen such that its vibrational modes couple with the electronic modes of the emitter as claimed therein is not present in the invention of Groups I, III or IV. The special technical feature of the Group III invention: positioning the one or more force sensors such that the organism exerts a force on the one or more force sensors; illuminating tie one or more force sensors with first photons in a first wavelength range; receiving second photons emitted by the one or more force sensors in a second wavelength range; receiving third photons emitted by the one or more force sensors in a third wavelength range; separating the second photons in the second wavelength range from the third photons in the third wavelength range; and determining a ratio of an intensity of light in the second wavelength range to the intensity of light in the third wavelength range as claimed therein is not present in the invention of Groups I, II or IV. The special technical feature of the Group IV invention: providing one or more ceramic cores, the ceramic cores each having a first lanthanide dopant and a second lanthanide dopant, suspending the one or more ceramic cores in a hydrophobic medium; suspending the one or more ceramic cores and the hydrophobic medium in water; applying ultrasonic energy to the suspended hydrophobic medium to generate micelles; and using a thermal initiator to convert the micelles into force sensing devices as claimed therein is not present in the invention of Groups I- III.

Groups I-IV lack unity of invention because even though the inventions of these groups require the technical feature of a force sensor comprising: one or more upconverting nanoparticles positioned in a polymeric host, this technical feature is not a special technical feature as it does not make a contribution over the prior art.

Specifically, US 2022/0306888 to Liquid X Printed Metals, Inc. teaches a force sensor comprising: one or more upconverting nanoparticles positioned in a polymeric host (flexible force sensitive resistors, or force sensors, that may be directly printed on a flexible substrate, para. 0026. Certain conducting organic polymers are known to be excellent hosts for metal nanoparticles where cured nanoparticles may be embedded in the polymer matrix, para. 0113).

Since none of the special technical features of the Group I-IV inventions are found in more than one of the inventions, unity of invention is lacking.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/061325

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-12**

Remark on Protest

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