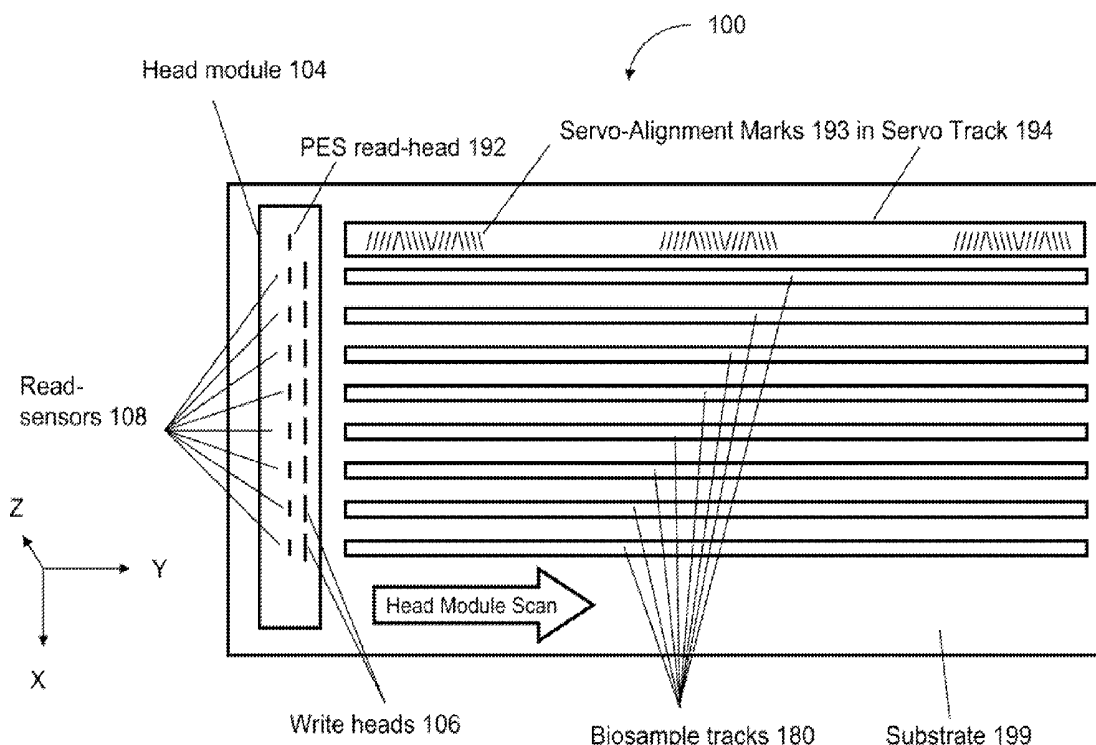




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**Boday et al.**(10) **Pub. No.: US 2011/0076670 A1**(43) **Pub. Date: Mar. 31, 2011**(54) **DETECTION OF ANALYTES VIA  
NANOPARTICLE-LABELED SUBSTANCES  
WITH ELECTROMAGNETIC READ-WRITE  
HEADS****Publication Classification**(51) **Int. Cl.**  
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28, 2009.(57) **ABSTRACT**

A first set of antibodies are bonded to a substrate, and are exposed to and bonded with target antigens. A second set of antibodies are bonded to nanoparticles, and the nanoparticle labeled antibodies are exposed to the targeted antigens. An electromagnetic write-head magnetizes the nanoparticles, and then a read-sensor detects the freshly magnetized nanoparticles. The substrate comprises a flexible film or a Peltier material to allow selective heating and cooling of the antigens and antibodies. Nanoparticles of different magnetic properties may be selectively paired with antibodies associated with different antigens to allow different antigens to be detected upon a single scan by the read-sensor.



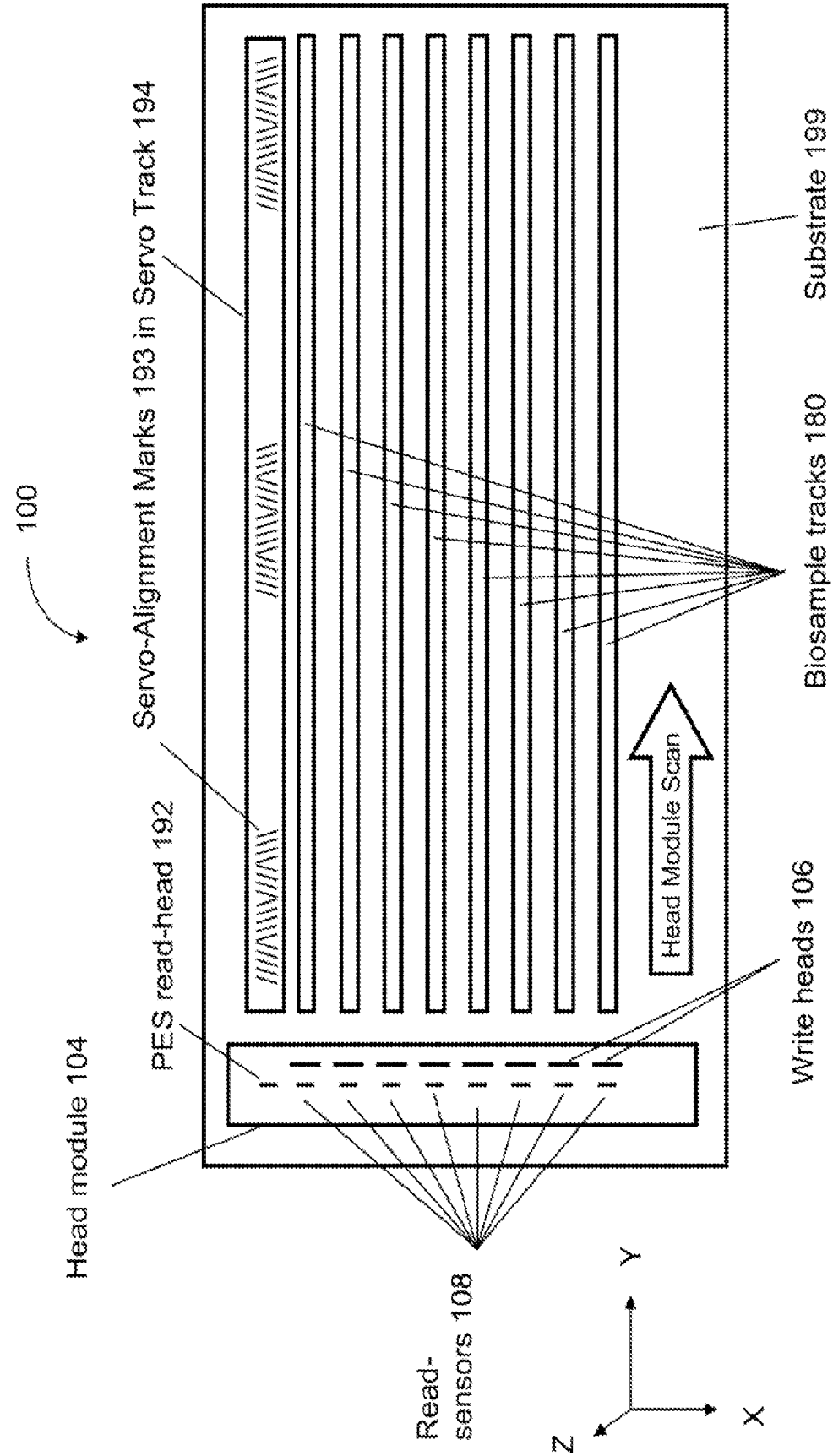


Figure 1

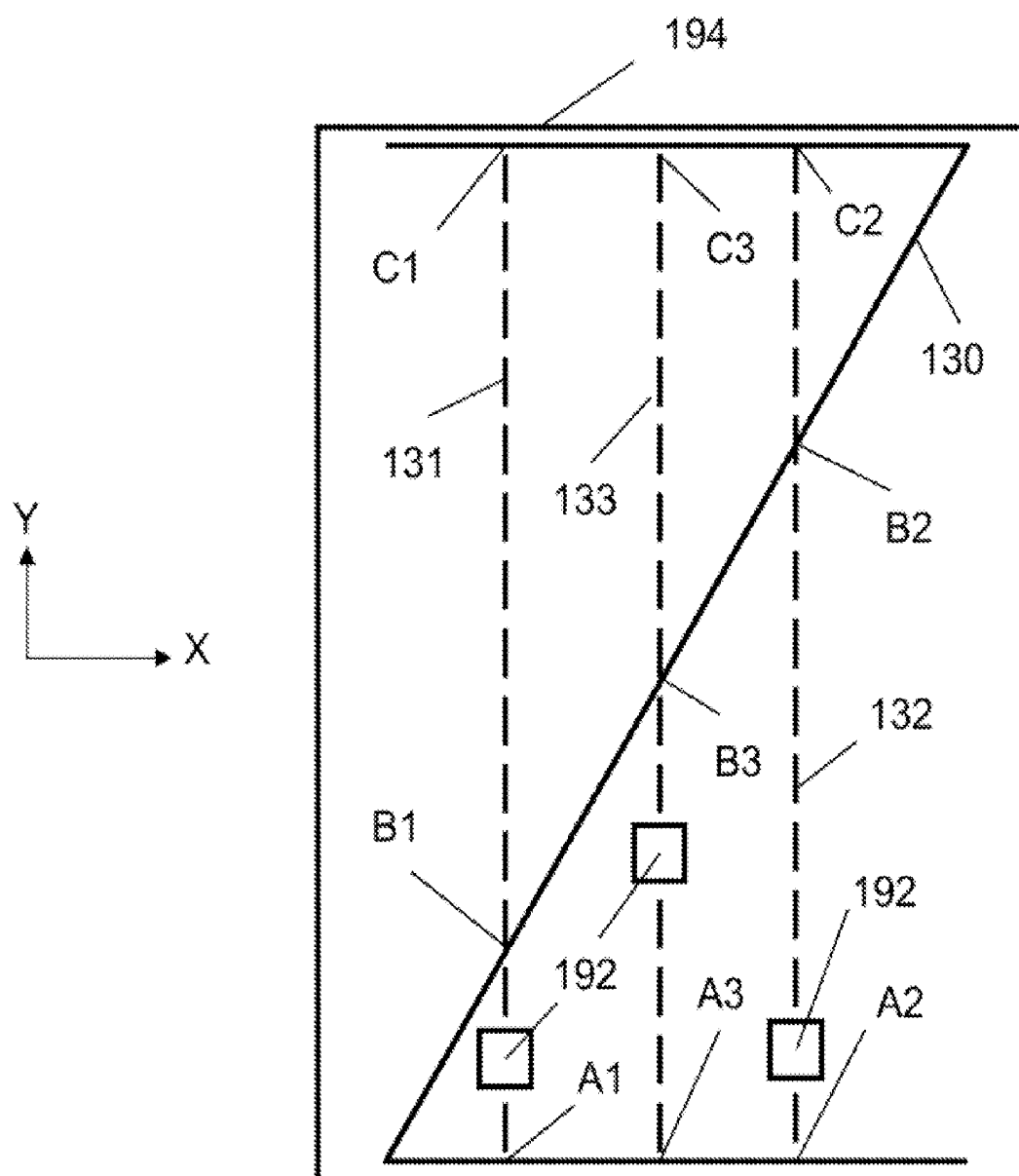


Figure 2

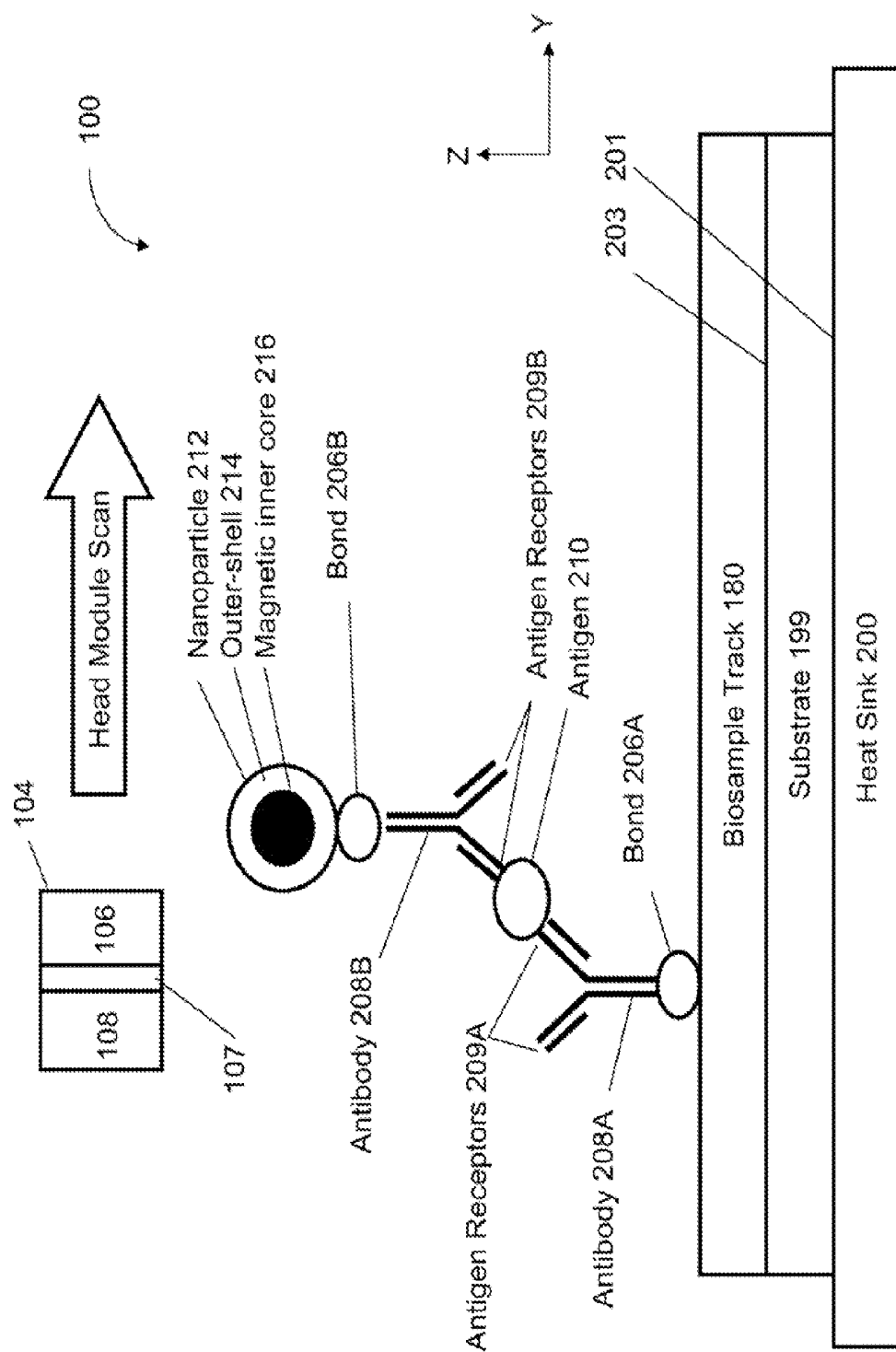


Figure 3

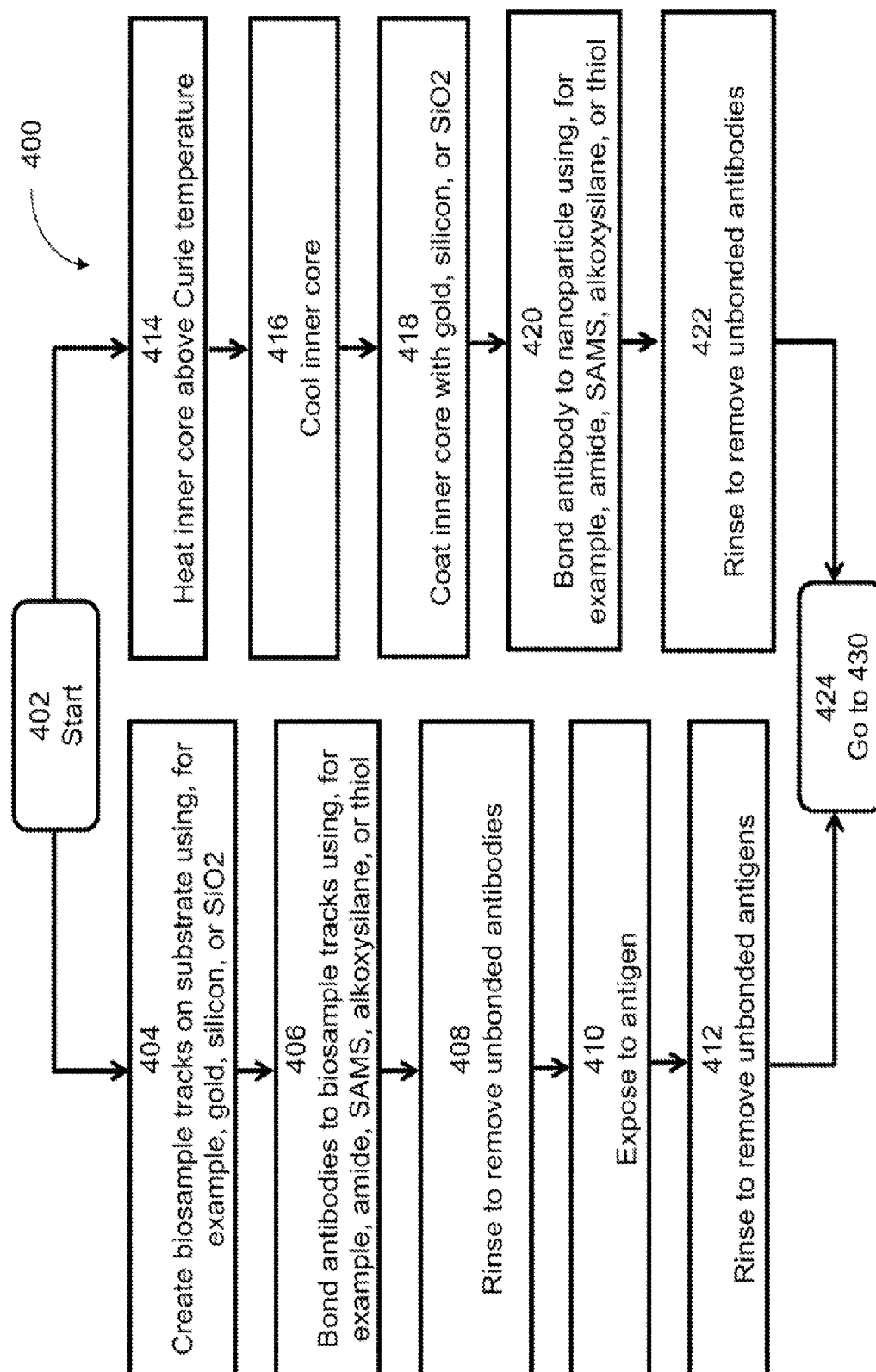


Figure 4A

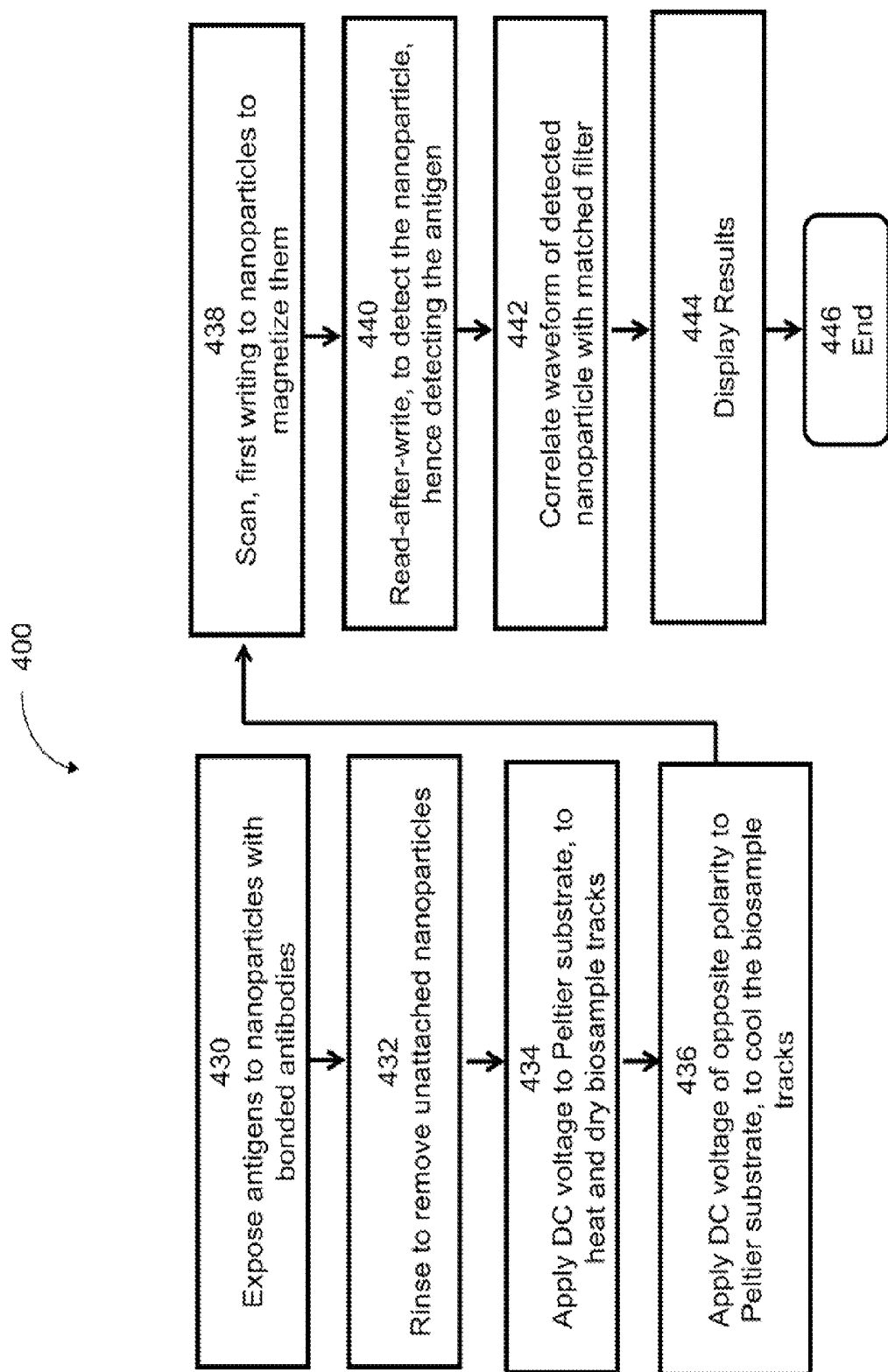


Figure 4B

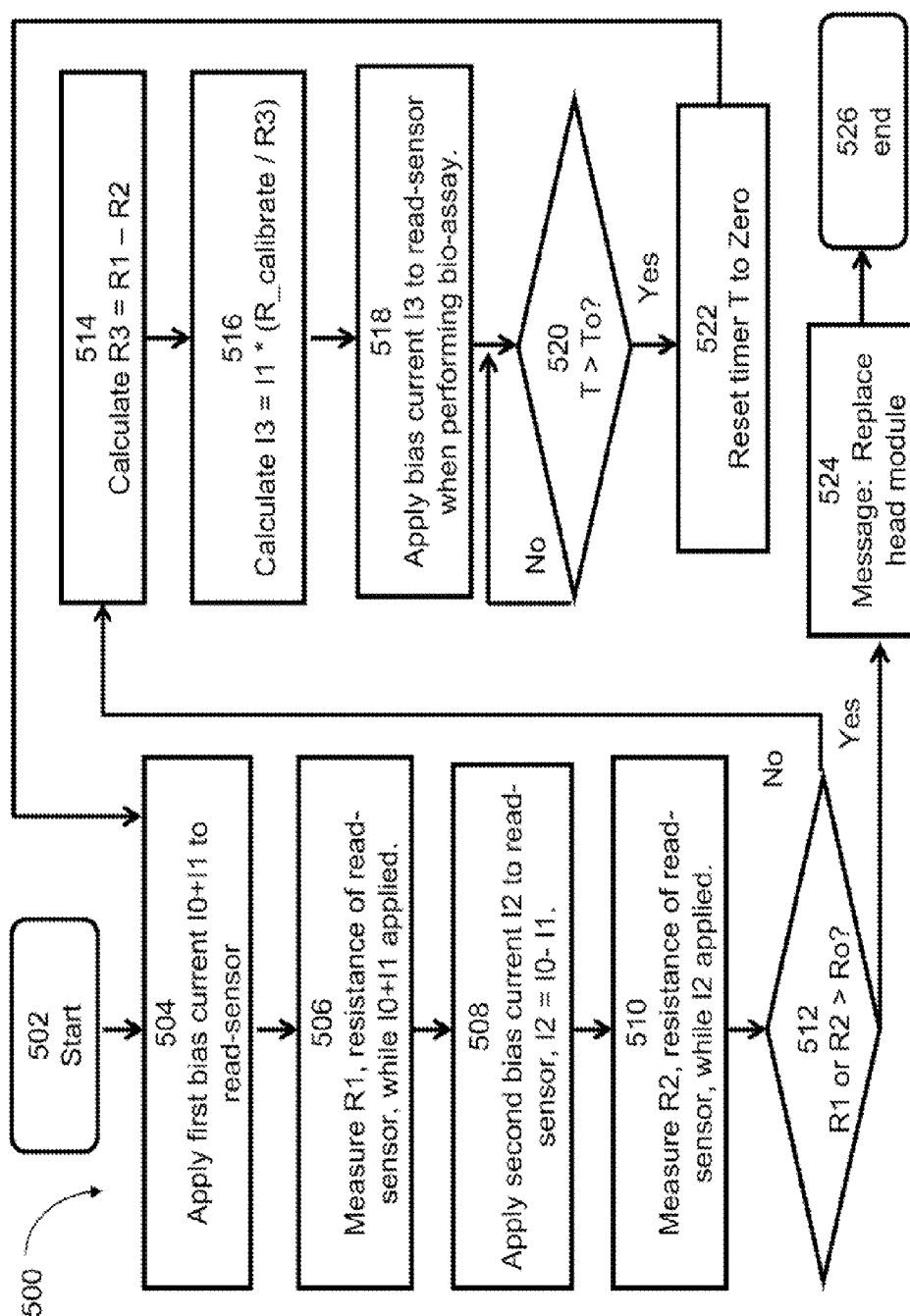


Figure 5

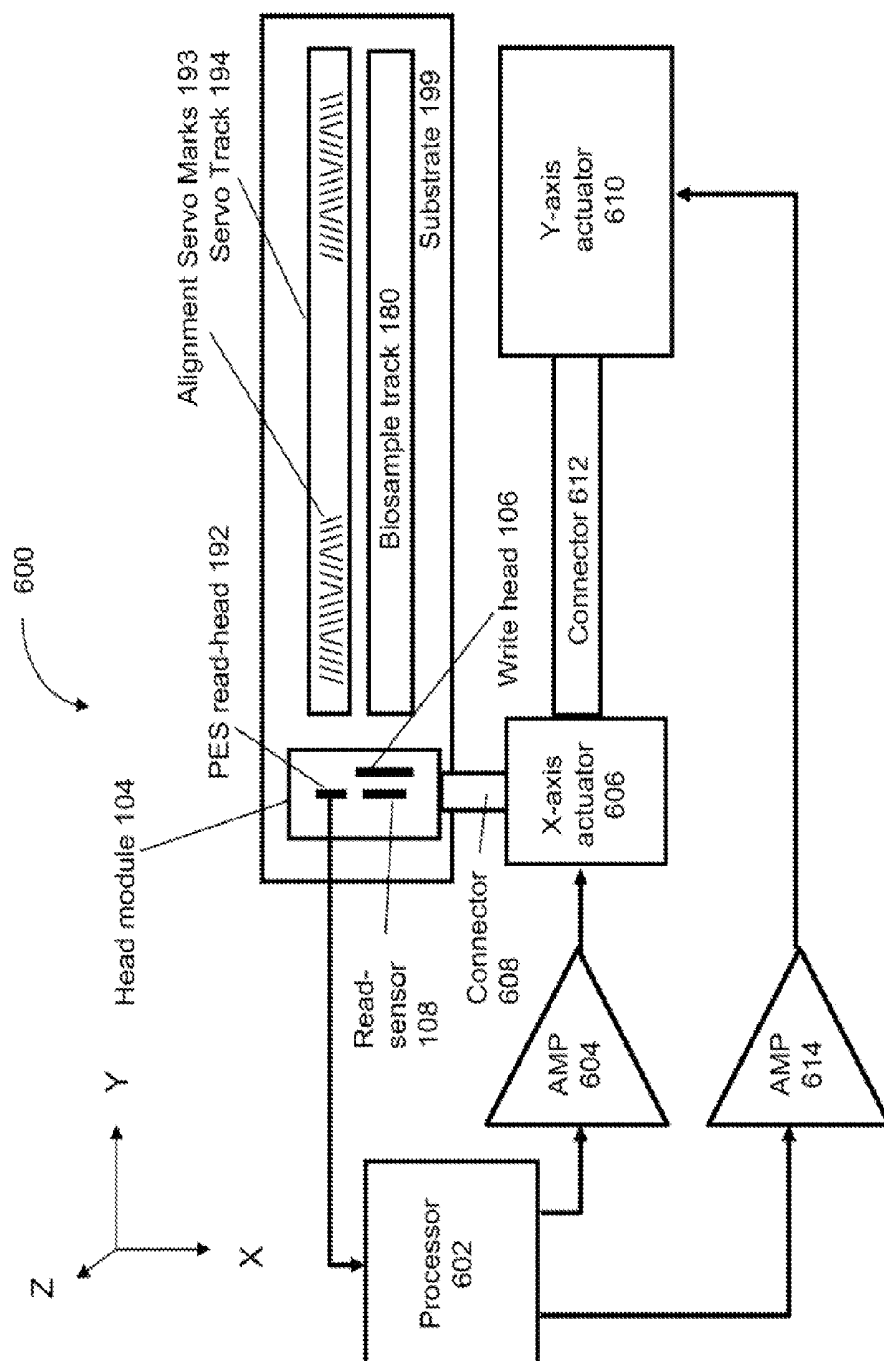


Figure 6



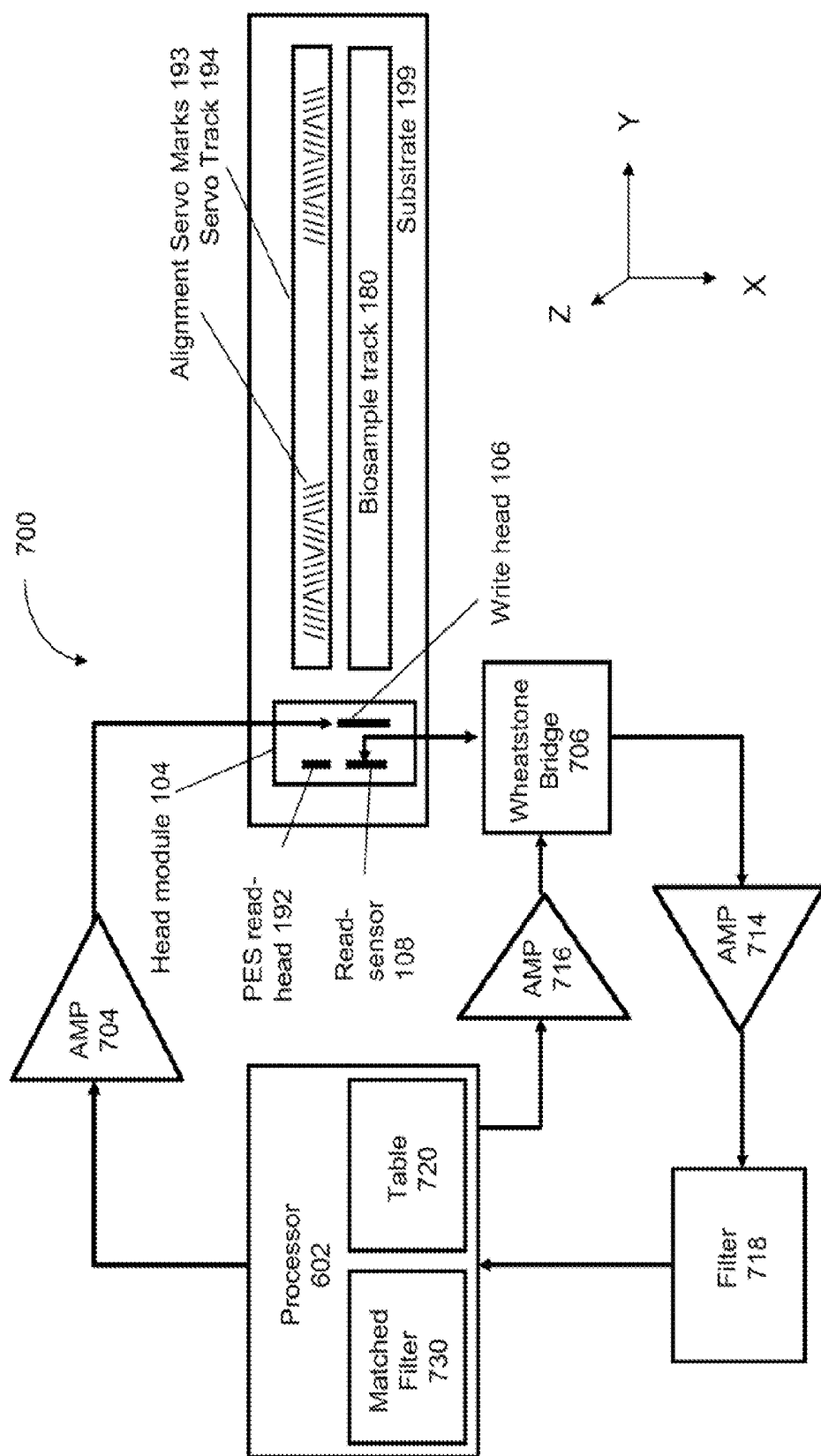


Figure 7

# DETECTION OF ANALYTES VIA NANOPARTICLE-LABELED SUBSTANCES WITH ELECTROMAGNETIC READ-WRITE HEADS

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application Ser. No. 61/246,329, entitled "READ-AFTER-WRITE DETECTION OF ANALYTES VIA NANOPARTICLE-LABELED SUBSTANCES" filed on Sep. 28, 2009, and is related to co-filed, co-pending and commonly assigned US patent application Ser. No. \_\_\_\_\_ entitled "READ-AFTER-WRITE DETECTION OF ANALYTES VIA NANOPARTICLE-LABELED SUBSTANCES", Ser. No. \_\_\_\_\_ entitled "A SERVO CONTROL CIRCUIT FOR DETECTING ANALYTES VIA NANOPARTICLE-LABELED SUBSTANCES WITH ELECTROMAGNETIC READ-WRITE HEADS", and Ser. No. \_\_\_\_\_ entitled "A CIRCUIT FOR DETECTING ANALYTES VIA NANOPARTICLE-LABELED SUBSTANCES WITH ELECTROMAGNETIC READ-WRITE HEADS," all of which are hereby incorporated by reference.

## BACKGROUND

[0002] The invention relates to analytical devices and processes, and more particularly, to devices and processes that incorporate electromagnetic write-heads and magneto-resistive read-sensors to detect analytes via nanoparticle-labeled substances.

[0003] It is known that antibodies bind with antigens as part of the human disease defense system. Presently, antigens are detected by such techniques as immunofluorescence, immunoperoxidase, or enzyme-linked immunosorbent assay (ELISA), each of which then employs a microscope for visual detection of the target antigen. It is desirable to exploit the use of magnetic signaling technology to automate the detection of analytes, such as antigens, and to further apply this technology to the detection of any biological matter.

## BRIEF SUMMARY

[0004] A first set of antibodies are bonded to a substrate, then this first set of antibodies are exposed to and bonded with target antigens. A second set of antibodies are bonded to demagnetized nanoparticles, and these nanoparticle labeled antibodies are exposed to the target antigens. The nanoparticles are then detected by the use of magneto-resistive read-sensors. Examples of read-sensors include anisotropic magneto-resistive (AMR), giant magneto-resistive (GMR), and tunnel magneto-resistive (TMR) read-sensors.

[0005] In an exemplary embodiment of the invention, an electromagnetic write-head first magnetizes the nanoparticles, and then a magneto-resistive read sensor, such as an AMR, GMR, or TMR read-sensor, detects the freshly magnetized nanoparticles.

[0006] In another exemplary embodiment, the first set of antibodies may be bonded to biosample tracks deposited on a substrate. The substrate may be a flexible film of polyethylene terephthalate (PET), such as used in conventional magnetic tape, or other polymeric film. Alternately, the substrate may be glass, or may be a Peltier material to allow selective heating and cooling of the substrate and the biological sample on the substrate.

[0007] Nanoparticles of differing magnetic properties are selectively paired with antibodies associated with different antigens, so that multiple types of antigens can be simultaneously detected upon a single scan of the read-sensor.

[0008] For a fuller understanding of the invention, reference is made to the following detailed description taken in conjunction with the accompanying drawings.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 is a block diagram of a top view of an analytic device according to an exemplary embodiment of the invention.

[0010] FIG. 2 is a block diagram of an exemplary Z-pattern servo-alignment mark according to an embodiment of the invention.

[0011] FIG. 3 is a block diagram of a side view of an exemplary analytic device according to an embodiment of the invention.

[0012] FIG. 4A is a flow chart illustrating an exemplary analytic process according to an embodiment of the invention.

[0013] FIG. 4B is a continuation of the flow chart in FIG. 4A, illustrating an exemplary analytic process according to an embodiment of the invention.

[0014] FIG. 5 is a flow chart illustrating an exemplary process for calibrating a read-sensor for use in detecting nanoparticle labeled antigens, according to an embodiment of the invention.

[0015] FIG. 6 is a block diagram of an exemplary circuit for controlling the X-axis and Y-axis motion of the head-module of an analytic device, according to an embodiment of the invention.

[0016] FIG. 7 is a block diagram of an exemplary write and read circuit for use with an analytic device, according to an embodiment of the invention.

## DETAILED DESCRIPTION

[0017] The invention is described in exemplary embodiments in the following description with reference to the Figures, in which like numbers represent the same or similar elements. While the invention is described in terms of the best mode for achieving the invention's objectives, it will be appreciated by those skilled in the art that variations may be accomplished in view of these teachings without deviating from the spirit or scope of the invention.

[0018] Referring to FIG. 1, there is illustrated a top view of an example substrate 199, which may comprise a Peltier hard-substrate, a glass substrate, a polyethylene terephthalate (PET, which is commonly known by the trade name of Mylar™) flexible-substrate, or other materials having similar properties. In an exemplary embodiment of the invention, head-module 104 scans across stationary substrate 199 from left-to-right, along the +Y-axis, individually sampling one or simultaneously sampling a plurality of biosample tracks 180. Alternately, substrate 199 may be swept across stationary head-module 104 from right-to-left, along the -Y-axis. If substrate 199 is of a flexible polyethylene terephthalate material, then in one embodiment, this right-to-left motion may be performed as data read-write operations in a magnetic tape drive. As an alternate embodiment of the invention, head-module 104 comprises a helical-scan rotary head-module, and the Y-axis of the biosample tracks 180 is at an angle to the substrate.

[0019] FIG. 1 shows electromagnetic write-heads **106** and magneto-resistive read-sensors **108** arranged in pairs in head-module **104**. The electromagnetic write-heads **106** first write to biosample tracks **180**, and then the adjacent magneto-resistive read-sensors **106** immediately read from biosample tracks **180**, which is referred to as a read-after-write operation. In an exemplary embodiment of the invention, substrate **199** comprises eight biosample tracks **180** corresponding to eight bits in a byte, and hence to eight electromagnetic write-head **106** and magneto-resistive read-sensor **108** pairs in a typical head-module **104** used in magnetic tape drive products. However, as alternatives, any number of biosample tracks **180** may be used. The number of electromagnetic write-head **106** and magneto-resistive read-sensor **108** pairs in head-module **104** may be any number ranging from a minimum of one to the number of electromagnetic write-head and magneto-resistive read-sensor pairs in the head-modules of the tape drives. For example, there are sixteen such electromagnetic write-head and magneto-resistive read-sensor pairs in a head module of an IBM 3480™ tape drive. Typically, the number of biosample tracks **180** is an integral multiple of the number of write-head **106** and read-sensor **108** pairs. In an alternate embodiment, a single device may perform the functions of both the write-head **106** and read-sensor **108**.

[0020] Write-heads **106** may comprise miniature electromagnets, with a coil sandwiched between to poles, such as taught without limitation by U.S. Pat. No. 5,452,164, entitled "Thin Film Magnetic Write-head," which is hereby incorporated by reference in its entirety. Write-heads **106** may comprise other structures with similar functionality.

[0021] Read-sensors **108** may be anisotropic magneto-resistive (AMR), giant magneto-resistive (GMR), or tunnel magneto-resistive (TMR) read-sensors, or other devices having similar functionality. AMR read-sensors are taught without limitation by U.S. Pat. No. 5,005,096, entitled "Magneto-resistive Read Transducer Having Hard Magnetic Shunt Bias," which is hereby incorporated by reference in its entirety. AMR read-sensors may comprise other structures having similar functionality. GMR read-sensors, which are also known as spin-valve read-sensors, are taught without limitation by U.S. Pat. No. 5,206,590, entitled "Magneto-resistive Sensor Based On The Spin Valve Effect," which is hereby incorporated by reference in its entirety. GMR read-sensors may comprise other structures having similar functionality. The GMR read-sensors typically have an internal antiparallel pinned layer for increased sensitivity, as taught without limitation by U.S. Pat. No. 5,465,185, entitled "Magneto-resistive Spin Valve Sensor With Improved Pinned Ferromagnetic Layer And Magnetic Recording System Using The Sensor," which is hereby incorporated by reference in its entirety. A recent form of read-sensor, TMR, uses a tunnel barrier layer to augment the GMR internal structure and to provide increased sensitivity, as taught without limitation by U.S. Pat. No. 5,764,567, entitled "Magnetic Tunnel Junction Device With Nonferromagnetic Interface Layer For Improved Magnetic Field Response," which is hereby incorporated by reference in its entirety. TMR read-sensors may comprise other structures having similar functionality.

[0022] In the exemplary embodiment illustrated in FIG. 1, write-head **106** is longer along the X-axis direction than read-sensor **108**. The active sensing portion of read-sensor **108** is smaller than write-head **106**, along the X-axis, as write-head **106** is used to magnetize nanoparticle **212** as described with

reference to FIGS. 3 and 4B, for detection of nanoparticles **212** by read-sensor **108**. If read-sensor **108** were too large in the X-axis direction, it could potentially encounter unmagnetized nanoparticles **212** and thus register an undesired false-negative detection of antigen **210**, as described with reference to FIG. 3.

[0023] Head-module **104** may be maintained in linear alignment with biosample tracks **180** along the X-axis by position-error-servo (PES) read-head **192**, which reads magnetically encoded servo-alignment marks **193** from servo track **194** on substrate **199**. PES read-head **192** may be, for example, an AMR, GMR, or TMR read-sensor. Magnetically encoded servo alignment marks **193** are encoded by the manufacturer of substrate **199** on either a piece of magnetic tape adhered to substrate **199** or encoded on a magnetic recording layer directly deposited on substrate **199**. In the example illustrated in FIG. 1, particular servo-alignment marks **193** shown in servo track **194** are Timing Based Servo (TBS) servo-alignment marks such as those used in IBM's Linear Tape Open (LTO) tape drive products, e.g., IBM tape drive models TS1120™ and TS1130™. TBS servo-alignment marks are taught without limitation by U.S. Pat. No. 6,320,719, entitled "Timing Based Servo System for Magnetic Tape Systems," which is hereby incorporated by reference in its entirety. Servo-alignment marks **193** may comprise other structures with similar functionality. The writing of TBS servo-alignment marks **193** in servo track **194**, as shown in FIG. 1, is taught without limitation by U.S. Pat. No. 6,282,051, entitled "Timing Based Servo System for Magnetic Tape Systems," which is hereby incorporated by reference in its entirety. TBS servo-alignment marks **193** may comprise other structures with similar functionality.

[0024] FIG. 2 illustrates another exemplary embodiment of servo-alignment marks **193** in the form of magnetically-encoded Z-pattern **130** that comprises servo-alignment marks in servo track **194**. Relative to the Y-axis, the distance between the top and bottom legs of Z-pattern **130** is constant and equal to the sum of line segments AB and BC, which is equal to the sum of line segments A1B1 and B1C1 in path **131**. This distance is also equal to the sum of line segments A2B2 and B2C2 in path **132**, and the sum of line segments A3B3 and B3C3 in path **133**. Thus, the velocity of head module **104** along the Y-axis relative to substrate **199** may be calculated by dividing the sum of line segments (AB+BC) by the time to transit Z-pattern **130** by head module **104**. This velocity calculation is not affected by the position of PES read-head **192** along the X-axis, because the top and bottom of Z-pattern **130** are both parallel to the X-axis.

[0025] The position-error-servo (PES) signal corresponding to the position of PES read-head **192**, and hence write-heads **106** and read-sensors **108**, along the X-axis may be determined by subtracting the distance AB from the distance BC each time a Z-pattern **130** is encountered by PES read-head **192**. As can be seen in FIG. 2, the PES signal from PES read-head **192** following path **132** is less than zero because the distance difference (B2C2-A2B2) is less than zero. Similarly, the PES signal from PES read-head **192** following path **131** is greater than zero because the difference (B1C1-A1B1) is greater than zero. Additionally, the value of (BC-AB) varies linearly as PES read-head **192** moves from left to right along the X-axis. Thus the PES signal, as calculated by the difference in distance (BC-AB), provides an X-axis PES signal for head-module **104** and its pairs of electromagnetic

write-heads **106** and magneto-resistive read-sensors **108**. This PES signal is incorporated into servo control circuit **600** shown in FIG. 6.

[0026] In an exemplary embodiment of the invention, the value of the line segment difference (BC-AB) is evaluated based on the time it takes for the PES read head **192** to cross segments AB and BC when the head-module **104** is moving at a constant velocity during its Y-axis seek operation. This is the case where the transit time for the PES read head **192** to cross each Z-pattern **130** is constant. In the exemplary embodiments of the invention shown in FIGS. 1 and 2, TBS servo-alignment marks **193** and Z-pattern **130** could be non-magnetic stripes, either lithographed, silk-screened, or ink-jet printed, and read with an optical laser. In FIG. 2, path **133** is the desired path for PES read-head **192** as electromagnetic write-heads **106** and magneto-resistive read-sensors **108** are aligned with biosample tracks **180**. With path **133**, the distance difference (B3C3-A3B3) is equal to zero, i.e., line segment B3C3 is equal to line segment A3B3. For path **131**, the distance difference (B1C1-A1B1) is greater than zero, which means that head-module **104** must be moved in the +X direction by X-axis actuator **606** so that electromagnetic write-heads **106** and magneto-resistive read-sensors **108** are aligned with biosample tracks **180**. The operation of the X-axis actuator **606** is described below with reference to FIG. 6. Similarly, for path **132**, the distance difference (B2C2-A2B2) is less than zero, which means that head-module **104** must be moved in the -X direction by X-axis actuator **606** so that electromagnetic write-heads **106** and magneto-resistive read-sensors **108** are aligned with biosample tracks **180**.

[0027] FIGS. 1 and 3 illustrate an exemplary analytic device **100**, and FIGS. 4A and 4B illustrate an exemplary analytic process **400**, respectively. In step **404**, biosample tracks **180** are deposited on substrate **199** with nonmagnetic materials such as gold, silicon, or SiO<sub>2</sub>, and other materials having similar magnetic properties. Deposition methods may include photolithography, silk-screening, and other similar processes. As shown in FIG. 1, biosample tracks **180** are deposited in stripes on substrate **199** with a track-to-track spacing along the X-axis, matching the read-sensor to read-sensor spacing on head-module **104**. Then, in step **406**, antibodies **208A** are bonded to biosample tracks **180**, for example, via amide, self-assembled-monolayers (SAMS), alkoxysilane, organic functional trialkoxysilane, or thiol bonds **206A**.

[0028] In one example of the bonding of the antibodies **208A** to the biosample tracks **180**, the bonding may comprise first coating substrate **199** with amide, self-assembled-monolayers (SAMS), alkoxysilane, or thiol and then placing a solution of antibodies **208A** on substrate **199** and gently rocking substrate **199** for a period of time, up to six hours. Amide refers to organic compounds that contain the functional group consisting of an acyl group, with the chemical notation C=O, linked to a nitrogen (N) atom. A SAM is an organized layer of amphiphilic molecules in which one end of the molecule, the "head group," shows a special affinity for a substrate, such as gold, silicon, or SiO<sub>2</sub> biosample tracks **180**. At the opposite end of the SAM from the "head group" is a functional group at the terminal end, and it is to this functional group that antibodies **208A** are attached in step **406**. Lastly, a thiol is a compound that contains the functional group composed of a sulfur atom and a hydrogen atom (-SH). Being the sulfur analog of an alcohol group (-OH), this functional group is referred to either as a thiol group or a mercaptan group.

[0029] There are generally five known isotopes (types) of antibodies **208A** and **208B** for mammals. In FIG. 3, the Y-shape of antibodies **208A** and **208B** are that of monomer antibodies. There are three isotopes of monomer antibodies: IgD, IgE, and IgG, where the prefix Ig is the symbol for Immunoglobulin. These monomer antibodies each have one unit of Ig. IgD antibodies function mainly as antigen receptors on B cells that have not been exposed to antigens. IgD antibodies have been shown to activate basophils and mast cells to produce antimicrobial factors. B cells are lymphocytes that play a large role in the humoral immune response, as opposed to the cell-mediated immune response, which is governed by T cells. The principal functions of B cells are to make antibodies against antigens, perform the role of Antigen Presenting Cells (APCs) and eventually develop into memory B cells after activation by antigen interaction. B cells are an essential component of the adaptive immune system. IgE antibodies binds to allergens and triggers histamine release from mast cells and basophils, and are involved in allergies. In its four forms, IgG antibodies provide the majority of antibody-based immunity against invading antigens, and thus IgG antibodies are the preferred antibodies **208A** and **208B**. IgG antibodies are the only antibody capable of crossing the placenta to give passive immunity to fetus.

[0030] In an exemplary embodiment of the invention, the base of the stem in a Y-shaped monomer antibody **208A** is bonded to biosample tracks **180** via amide, SAMS, alkoxysilane, organic functional trialkoxysilane, or thiol bonds. There is only one isotope of a dimer antibody, IgA, which has two Ig units. IgA antibodies can be found in mucous membrane areas, such as the gut, respiratory track, and urogenital track, as well as in saliva, tears, and maternal milk. Lastly, there is only one isotope of pentamer antibody, IgM, which has five Ig units. IgM antibodies are expressed on the surface of B cells. IgM antibodies eliminate antigens in the early stages of B cell humoral immunity before there are sufficient IgG antibodies in a person's body.

[0031] Other analytes may have different antibodies, such as the tetrameric antibody with four Ig units, an example of which is the IgM found in the teleost fish. Thus, analytic process **400** applies to biological analyses in medical and veterinary medicine, as well as to other biological applications. In the exemplary embodiments of the invention, nanoparticles **212** may be bonded to any biological matter and steps in analytic process **400** may be used to track and identify antigens present in a sample of the biological matter.

[0032] In the illustrated embodiment of analytic process **400**, step **408** comprises rinsing substrate **199** with water such as distilled water or other rinsing agent, which may have its surface tension reduced via a very mild surfactant such as a mild detergent solution. The rinsing removes any antibodies **208A** that are not specifically bonded to analytic tracks **180**. After rinse step **408**, antibodies **208A** are exposed to antigens **210** in step **410**. In one example, this may be accomplished by placing a blood sample or other biological sample on substrate **199** and then gently rocking substrate **199** for a period of time, up to six hours. Antigens **210** may comprise cancer cells, viruses such as Human Papilloma Virus (HPV), or bacteria. Human Papilloma Virus can lead to infections and cancers of the human reproductive organs. Antibodies **208A** are specifically chosen based on the targeted antigens **210**.

[0033] In step **410**, antigens **210** are bonded to monomer antibodies **208A** at antigen receptors **209A** which are diagrammatically shown to be at the v-shaped end of antibodies

**208A.** Each monomer antibody **208A** has two antigen receptors **209A**. Step **410** may include repetitive rocking of substrate **199** to facilitate the bonding of antigens **210** and antibodies **208A** at antigen receptors **209A**. Then, in step **412**, another rinse is performed on substrate **199** with water such as distilled water or other rinsing agent, which may have its surface tension reduced via a very mild surfactant such as a mild detergent solution. Step **412** is analogous to step **408**, but this time for removing antigens **210** not bonded to antibodies **208A**.

**[0034]** In parallel with steps **404**, **406**, **408**, **410**, **412** is the creation of nanoparticle-labeled antibodies in steps **414**, **416**, **418**, **420**, and **422** of the illustrated analytic process. In step **414**, magnetic inner cores, shown as inner core **216** in FIG. 2, may be heated above their Curie temperature to demagnetize the inner cores. The demagnetization keeps the nanoparticles that comprise the inner cores as individual particles by mitigating the forming of lumps which magnetized nanoparticles are prone to form. Magnetic inner cores **216** may comprise hard magnetic materials with high coercivity, such as  $\text{Fe}_2\text{O}_3$ ,  $\text{CrO}_2$ , and Barium Ferrite  $\text{BaFe}$ . As examples, magnetic inner cores **216** may comprise iron oxide based nanoparticle materials, including  $\text{MFe}_2\text{O}_4$  (where M may be Co, Ni, Cu, Zn, Cr, Ti, Ba, or Mg) nanomaterials, and iron oxide coated nanoparticle materials or other structures with similar functionality. The forming of such nanoparticles is taught without limitation by U.S. Pat. No. 6,962,685, entitled "Synthesis of Magnetite Nanoparticles and the Process of Forming," which is hereby incorporated by reference in its entirety. Then, in step **416**, the heated magnetic inner cores **216** are allowed to cool. Steps **414** and **416** are optional steps, as the manufacture of inner cores **216**, which may include high temperature sintering, may render inner cores **216** demagnetized during the manufacturing process.

**[0035]** Following step **416**, step **418** may comprise coating inner cores **216** with an outer-shell **214**, for example, of nonmagnetic gold, silicon, or  $\text{SiO}_2$ , to create nanoparticles **212**. The step of coating the inner cores **216** with outer-shells **214** is analogous to creating biosample tracks **180** in step **404**. Then, in step **420**, antibodies **208B** are bonded to nanoparticles **212** via amide, self-assembled-monolayers (SAMS), alkoxysilane, organic functional trialkoxysilane, or thiol bonds **206B**. This bonding is analogous to bonding antibodies **208A** to biosample tracks **180** in step **406**. The bonding of the antibodies **208B** may be accomplished by first coating nanoparticles **212** with amide, self-assembled-monolayers (SAMS), alkoxysilane, organic functional trialkoxysilane, or thiol and then placing nanoparticles **212** in a solution containing antibodies **208B** and gently rocking this solution for a period of time, up to six hours. Antibodies **208A** and **208B** are biologically identical, as both bond to the same antigen **210**. Following step **420**, step **422** comprises rinsing nanoparticles **212** with water, such as distilled water, or other rinsing agent, which may have its surface tension reduced via a very mild surfactant such as a mild detergent solution to remove unbonded antibodies. The rinsing step **422** is analogous to the rinsing step **408** above. At the conclusion of both steps **412** and **422**, process **400** converges at step **424** and continues with step **430** in FIG. 4B.

**[0036]** In step **430**, antigens **210** are exposed to nanoparticles **212** which have antibodies **208B** bonded to them. This may be done by placing a solution of nanoparticle-labeled antibodies **208B** on substrate **199** and then gently rocking substrate **199** for a period of time, up to six hours. Antigen

receptors **209B** of antibodies **208B** bond with antigen **210**. Step **432** comprises rinsing substrate **199** with water, such as distilled water, or other rinsing agent, which may have its surface tension reduced via a very mild surfactant such as a mild detergent solution. The rinsing in step **432** removes any nanoparticles **212** not bonded to an antigen **210** and is analogous to step **408**. If substrate **199** is a Peltier substrate, in optional step **434**, a DC voltage of a first polarity may be applied to the Peltier substrate, to heat surface **208** and hence dry both biosample tracks **180** and biological sample **206A-208A-210-208B-206B-212**. Then, in optional step **436**, a DC voltage of a second and opposite polarity, may be applied to the Peltier substrate, to cool surface **203** and hence cool both biosample tracks **180** and biological sample **206A-208A-210-208B-206B-212**. Heat sink **200** may be used to dissipate excess heat generated by the Peltier substrate along surface **201**.

**[0037]** In the exemplary embodiment of the analytical process of the invention shown in FIG. 4B, scan step **438** involves moving head-module **104** linearly in the +Y direction relative to substrate **199**, which could equally be done by moving substrate **199** linearly in the -Y direction relative to head-module **104**. In previous step **414**, inner cores **216** were demagnetized. Now, in step **438**, write-head **106** writes to nanoparticles **212** to magnetize inner cores **216**. Write-head **106** may write with a constant "DC" magnetic polarity for the duration of scan steps **438** and **440**, so that there are no unwritten regions of substrate **199**. Then in read-after-write step **440**, read-sensor **108** detects the freshly magnetized inner cores **216** of nanoparticles **212**, and hence detecting antigens **210** because nanoparticles **212** are bonded to antibodies **208B**, which in turn are bonded to antigens **210**. The adjacent logical-steps **438** and **440**, as well as the physical proximity of write-head **106** and read-sensor **108** in a typical electromagnetic head module, provide an advantage when using tape drive products to detect antigens. The inner cores **216** of nanoparticles **212** are magnetized by write-head **106** along the Y-axis, in what is called longitudinal-recording in the tape drive industry. This is the same direction that read-sensor **108** magnetically detects nanoparticles **212**. As a result, the nanoparticles **212** may be magnetized by write-head **106** and then magnetically detected by read-sensor **108** in the same scan of the biosample tracks **180**. Magnetic shield **107** separates write-head **106** and read-sensor **108** so that there is no meaningful cross-talk between write-head **106** and read-sensor **108** during steps **438** and **440**.

**[0038]** As an alternate embodiment of the invention, once steps **438** and **440** are completed by moving head-module **104** linearly in the +Y direction relative to substrate **199**, write-head **106** may be turned off as nanoparticles **212** are now magnetized. Step **440** may be repeated multiple times across biosample tracks **180** along both the +Y and -Y directions during which read-sensor **108** repeatedly checks for magnetized nanoparticles **212** and hence detecting antigens **210**. The multiple read operations insure that all antigens **210** on biosample tracks **180** are detected. As described above with reference to FIG. 1, the antigens **210** are attached to nanoparticles **212** through antibodies **208A** and **208B**.

**[0039]** In another exemplary embodiment of the invention where there are more biosample tracks **180** than write-head **106** and read-sensor **108** pairs in head-module **104**, head-module **104** may scan the biosample tracks **180** in a serpentine pattern. The head-module **104** performs a scan in the +Y direction, as head-module **104** only provides read-after-write capability in the +Y direction as illustrated in FIG. 1. Then a second head-module comprising a mirror image of head-module **104** may perform a read-after-write operation in the -Y direction.

[0040] The coercivity of a magnetic inner core 216 may be selectively chosen to have any of various values, depending upon the antigen 210 to be detected. The nanoparticles 212 with magnetic inner cores 216 of different coercivity values may be respectively bonded to different types of antibodies 208A and 208B to detect a various types of antigens 210 on the substrate 199 at the same time. A nanoparticle 212 thus may have different magnetic properties associated with each antigen-antibody combination. Read-sensor 108 detects the different magnetic properties of inner core 216 based on different materials used for that inner core, for example,  $\text{Fe}_2\text{O}_3$ ,  $\text{CrO}_2$ ,  $\text{BaFe}$ ,  $\text{M Fe}_2\text{O}_4$  (where M may be Co, Ni, Cu, Zn, Cr, Ti, Ba, or Mg), or other structures with similar functionality. Read-sensor 108 thus could detect different antigens 210 on the same scan of the biosample tracks 180, per steps 438 and 440 in FIG. 4B. To facilitate the detection of nanoparticles of different magnetic properties and hence the detection of different types of antigens, calibration of read-sensor 108 may be performed according to an exemplary calibration process 500 illustrated in FIG. 5.

#### Calibration of Read-Sensors

[0041] Referring to FIG. 5, in one exemplary embodiment of the calibration of read-sensor 108, calibration process 500 begins at step 502 and proceeds with step 504, where a first "DC" bias current ( $I_0+I_1$ ) is applied to read-sensor 108. This first bias current may consist of an offset DC current  $I_0$  plus a DC current  $I_1$ . In succeeding step 506, the process 500 measures resistance  $R_1$  of read-sensor 108 while DC current ( $I_0+I_1$ ) is applied. In step 508, second DC bias current  $I_2$  may be applied to read-sensor 108, where  $I_2=I_0-I_1$ . In steps 506 and 508, offset current  $I_0$  is typically zero milliamperes, but may have a positive or negative value. In succeeding step 510, the calibration process 500 measures resistance  $R_2$  of read-sensor 108 while DC current  $I_2$  is applied, where  $I_2=I_0-I_1$ . Then in step 512, a determination is made whether resistance  $R_1$  or  $R_2$  exceeds threshold resistance  $R_0$  and thus indicating a non-operational read-sensor 108. If resistance  $R_1$  or  $R_2$  exceeds the threshold, then process 500 branches to step 524 where a message is displayed to the user to replace head-module 104 as the read-sensor 108, which is an integral part of head-module 104, may be non-operational. If neither resistance  $R_1$  nor resistance  $R_2$  exceeds the threshold per the determination in step 512, then process 500 branches to step 514 and calculates resistance  $R_3$ , where  $R_3=R_1-R_2$ .

[0042] In step 516, calibration process 500 calculates a bias current  $I_3$ , where  $I_3=I_1*(R_{\text{calibrate}}/R_3)$  and  $R_{\text{calibrate}}$  is a preset value maintained by processor 602 shown in FIG. 7. In step 518, calibration process 500 applies bias current  $I_3$  to read-sensor 108 when performing step 440 as part of the bio-assay process 400. In step 520, a determination is made whether calibration time  $T$  exceeds a time threshold  $T_0$ , where  $T$  is the time elapsed during the calibration steps 504 to 518. If time  $T$  has not exceeded the threshold  $T_0$ , then calibration process 500 cycles back to step 520 and continues checking time  $T$  against the threshold  $T_0$ . Otherwise, process 500 resets time  $T$  to zero in step 522 before returning to step 504 to begin the calibration process again. Process 500 is executed by processor 602, as described below with reference to FIG. 7.

#### Mitigation of Corrosion in Head-Module

[0043] When read-sensor 108 is not in use for detecting magnetized nanoparticles 212, in one exemplary embodiment

of the invention, a current may be passed through read-sensor 108 in order to mitigate corrosive effects of ambient air. This current may be, for example, a direct current in the range of three to seven milliamperes. Alternately, the current may be a pulse-width-modulated (PWM) direct current or alternating current (AC) having an amplitude of, for example, three to seven milliamperes. This current causes read-sensor 108 to be sufficiently warm to minimize corrosive effects of water vapor, chlorine, and other gases present in ambient air in the vicinity of the biosample tracks 180. In one exemplary embodiment of the invention, this current may be applied based on signals sent by processor 602 to a power amplifier 716, as illustrated in FIG. 7. The power amplifier 716 supplies electric power to Wheatstone Bridge 706, where read-sensor 108 is a component of the Wheatstone Bridge 706.

[0044] Read-sensor 108 is essentially an impedance device, such as a resistor, which exhibits a change in resistance when exposed to a magnetic field. In the illustrated exemplary embodiment of the calibration, process 500 assumes that read-sensor 108 responds linearly when not saturated by the applied magnetic field, and to a first order approximation, read-sensor 108 does respond linearly. Correlation coefficients of up to 99.9% have been empirically measured, regarding the change in resistance in read-sensor 108 versus applied magnetic field, indicating a sufficiently high degree of linearity for application of calibration process 500.

[0045] Per Ohm's law,  $V=IR$ , voltage and current are directly proportional to each other in read-sensor 108. Thus, as an alternate embodiment of calibration process 500, first and second voltages  $V_1$ ,  $V_2$  could be used to obtain the first resistance  $R_1$  and second resistance  $R_2$ , respectively, without loss of generality.

#### A Servo Control Circuit

[0046] FIG. 6 shows an exemplary embodiment of a servo control system 600 for controlling the X-axis and Y-axis motion of head-module 104. As an example, FIG. 6 shows one biosample track 180, and one pair of write-head 106 and read-sensor 108. Processor 602 receives position-error-servo (PES) signals from PES read-head 192 when PES read-head 192 reads servo-alignment marks 193 in servo track 194. Based on this PES information, processor 602 sends a signal to power amplifier 604 to control X-axis actuator 606 which in turn controls the motion of head module 104 in the X-axis direction. With X-axis actuator 606 connected to head-module 104 via mechanical connector 608, head-module 104 may be positioned to center write-head 106 and read-sensor 108 on biosample track 180. Processor 602 may send signals to power amplifier 614 to control Y-axis actuator 610 for conducting a scan by head module 104 across substrate 199. With Y-axis actuator 610 connected to X-axis actuator via mechanical connector 612, head-module 104 can be moved along the Y-axis in a controllable manner.

[0047] As an example, when a predetermined number of servo-alignment marks 193 are read by PES read-head 192, processor 602 stops the Y-axis motion of head-module 104. A servo-system for control of X-axis actuator 606 and head-module 104 along the X-axis direction, particular to servo-alignment marks 193 shown in servo track 194 in FIG. 1, is taught without limitation by U.S. Pat. No. 5,689,384, entitled "Timing Based Servo System for Magnetic Tape System," which is hereby incorporated by reference in its entirety. The servo-system may comprise other structures with similar

functionality. As previously described regarding Z-pattern 130, the velocity of head module 104 relative to substrate 199 along the Y-axis can be calculated by dividing distance AB+BC by the time it takes for head module 104 to transit Z-pattern 130. This velocity measurement can be used by processor 602 to control Y-axis actuator 610 to keep head module 104 at a constant Y-axis velocity  $V_y$  relative to substrate 199. The position along the Y-axis of head module 104 relative to substrate 199 can be obtained by counting servo-alignment marks 193 or Z-pattern 130 by PES read-head 192 and processor 602.

#### A Write and Read Circuit

[0048] FIG. 7 shows an exemplary embodiment of a write and read circuitry 700 for writing to the biosample tracks 180 (i.e., for magnetizing nanoparticles 212) and reading from the biosample tracks 180 (i.e., for sensing and detecting the magnetized nanoparticles 212). Processor 602 may send signals to power amplifier 704 which provides power to write-head 106 for magnetizing nanoparticles 212. Processor 602 may further send signals to power amplifier 716 which powers Wheatstone bridge 706. Read-sensor 108 is one component in Wheatstone bridge 706 and thus receives DC current from Wheatstone bridge 706. Wheatstone bridge 706 serves the function of balancing out the zero-magnetism resistance of read-sensor 108 so that only the change in resistance of read-sensor 108 is passed onto amplifier 714. Such resistance change is due to the detection of a magnetized nanoparticle 212, which is sent to amplifier 714 and filter 718 before being received by processor 602.

[0049] Filter 718 filters out 60 Hz noise, which is pervasive noise in an office or laboratory with lighting where processes of the invention are typically performed. Processor 602 makes the determination of whether a nanoparticle 212 was detected, and hence an antigen 210 being detected. The change in resistance of read-sensor 108 is directly proportional to the magnetic field provided by nanoparticle 212, which may have different coercivities depending upon whether inner core 216 is  $\text{Fe}_2\text{O}_3$ ,  $\text{CrO}_2$ ,  $\text{BaFe}$ ,  $\text{M Fe}_2\text{O}_4$  ( $\text{M}=\text{Co}, \text{Ni}, \text{Cu}, \text{Zn}, \text{Cr}, \text{Ti}, \text{Ba}, \text{Mg}$ ), etc. In addition, particular antibodies 208A and 208B could be associated with inner cores 216 of nanoparticles 212 having a given coercivity. As a result, processor 602 could register the detection of different antigens 210 during steps 438 and 440 of process 400 depending on corresponding combinations of antibodies 208A and 208B and nanoparticles 212. The identification of the various antigens 210 simultaneously on the same biosample track 180 may be facilitated by a lookup table 720 in processor 602. In one exemplary embodiment of the invention, the lookup table 720 contains a list of (a) antigens 210, (b) the antibodies 208A and 208B used for bonding antigens and nanoparticles, and (c) the coercivity of the inner cores 216 of nanoparticles 212 bonded to the antibodies 208B.

#### Correlation of Detection Results

[0050] In another embodiment of the invention, a correlation calculation may be performed by the write and read circuit of FIG. 7 to improve the accuracy of the detection of magnetized nanoparticles 212. Referring to FIGS. 3, 4A, 4B, 6 and 7, processor 602 performs correlation calculation  $C(y)$  in equation [1] between a detection signal profile  $g(y)$  read by read-sensor 108 when a nanoparticle 212 is detected and a matched filter. The matched filter comprises an impulse

response  $h(y)$  of an ideal signal profile of a detected nanoparticle. Since  $h(y)$  is used repetitively, it may be calculated once and stored as matched filter 730 in processor 602. In equation [1],  $q$  is the integration variable along the Y-axis as read-sensor 108 scans along the Y-axis.

$$C(y)=\int g(\eta)h(\eta-y)d\eta$$

Equation [1]

[0051] The range of correlation  $C(y)$  is between  $-1$  and  $+1$ , where  $-1$  represents the ideal correlation of one hundred percent (100%). The electrical waveform  $g(y)$  of each potential detection of a nanoparticle 212 by read-sensor 108 has its correlation  $C(y)$  calculated in step 442 of FIG. 4A. Processor 602 then compares this correlation  $C(y)$  against a threshold correlation value  $C_0$  before accepting the signal  $g(y)$  as a valid detection of a nanoparticle 212. This correlation removes spurious electrical noise from actual detections of nanoparticles, and thus mitigates false-positive detections of antigens. In step 444 of FIG. 4B, the results of a scan may be displayed to a physician or clinician to inform the physician or clinician of the presence (or absence) of target antigens in the biological sample. The results may include items such as the antigen(s) tested for, the types of antibodies used, a simple positive-detection or negative-detection indication for each antigen, the number of nanoparticles counted for each antigen to give an indication of the prevalence of the targeted antigen, and the number of rejected detections based on the correlation calculation of step 442. In addition, the results may include patient name, date of test, time of test, and name of attending doctor or clinician. Process 400 ends at step 446 in FIG. 4B.

[0052] Those of skill in the art will understand that changes may be made with respect to the exemplary embodiments described above, including, but not limited to, changes to the ordering of the steps. Further, those of skill in the art will understand that differing specific component arrangements may be employed than those illustrated herein.

[0053] While the exemplary embodiments of the invention have been illustrated and described in detail, it should be apparent that modifications and adaptations to those embodiments may occur to one skilled in the art without departing from the scope of the invention.

What is claimed is:

1. A method for detecting target antigens in a biological sample, comprising:
  - bonding a first set of antibodies to a plurality of biosample tracks;
  - exposing the biological sample to the biosample tracks to allow the antigens to bind to the first set of antibodies;
  - bonding a second set of antibodies to magnetized nanoparticles wherein the first and second sets of antibodies are biologically identical;
  - exposing the nanoparticles to the antigens to allow the second set of antibodies to bind to the antigens; and
  - scanning the biosample tracks with a magneto-resistive read sensor to detect the antigens.
2. The method of claim 1, wherein the nanoparticles are initially demagnetized and the method further magnetizes the nanoparticles with an electromagnetic write head before scanning.
3. The method of claim 1, wherein the biosample tracks are of a nonmagnetic material.
4. The method of claim 3, wherein the nonmagnetic material is selected from the group consisting of gold, silicon, and  $\text{SiO}_2$ .

5. The method of claim 1, wherein the first set of antibodies are bonded to the biosample tracks with a bonding material selected from the group consisting of amide, self-assembled-monolayers (SAMS), alkoxysilane, organic functional tri-alkoxysilane, and thiol.

6. The method of claim 1, wherein the biosample tracks are deposited on a substrate.

7. The method of claim 6, wherein the biosample tracks are deposited using photolithography or silkscreening.

8. The method of claim 6, wherein the substrate is selected from the group consisting of a film, sheet, strip, flexible polymeric film, solid surface, glass, and peltier material.

9. The method of claim 6, wherein bonding the first set of antibodies comprises:

coating the biosample tracks with a bonding material;  
exposing a solution of the first set of antibodies to the biosample tracks; and  
gently rocking the substrate for a period of time to facilitate the bonding of the first set of antibodies to the biosample tracks.

10. The method of claim 9, further comprising rinsing the substrate with water or a rinsing agent to remove any antibodies not bonded to the biosample tracks.

11. The method of claim 1, wherein the first set of antibodies are Y-shape monomer antibodies each having a base and the monomer antibodies are bonded to the biosample tracks at the bases.

12. The method of claim 1, wherein the first and second sets of antibodies are Immunoglobulin (IgG) antibodies.

13. The method of claim 1, wherein the first and second sets of antibodies are selected from the group consisting of dimer antibodies IgA, pentamer antibodies IgM, and tetrameric antibodies.

14. The method of claim 1, wherein the first and second sets of antibodies are selected based on the target antigens.

15. The method of claim 1, wherein exposing the biological sample to the biosample tracks comprises placing the biological sample on the biosample tracks and rocking the biosample tracks for a period of time to facilitate the binding of the antigens to the first set of antibodies.

16. The method of claim 15, further comprising rinsing the biosample tracks with water or a rinsing agent to remove any antigens not bound to the first set of antibodies.

17. The method of claim 1, wherein the biological sample is selected from the group consisting of blood, blood products, bone marrow, bodily fluid, saliva, serum, plasma, urine, and milk.

18. The method of claim 1, wherein the target antigens are selected from the group consisting of cancer cells, viruses, and bacteria.

19. The method of claim 1, wherein bonding the second set of antibodies to the nanoparticles comprises coating a plurality of magnetic inner cores with a nonmagnetic material to create nanoparticles, and bonding the second set of antibodies to the nanoparticles with a bonding material.

20. The method of claim 19, wherein the inner cores comprise a hard magnetic material having a generally high coercivity.

21. The method of claim 20, wherein the hard magnetic material is selected from the group consisting of  $\text{Fe}_2\text{O}_3$ ,  $\text{CrO}_2$ ,  $\text{BaFe}$ , and  $\text{MFe}_2\text{O}_4$ , where M is selected from the group consisting of Co, Ni, Cu, Zn, Cr, Ti, Ba, and Mg.

22. The method of claim 19, wherein the inner cores of different magnetic properties are used to simultaneously detect different target antigens on the biosample tracks.

23. The method of claim 19, further comprising heating the inner cores above the Curie temperature of the inner cores to demagnetize the inner cores and then cooling the heated inner cores before bonding the second set of antibodies.

24. The method of claim 1, wherein exposing the second set of antibodies to the antigens comprises placing a solution of the second antibodies on the biosample tracks and gently rocking the biosample tracks for a period of time to facilitate the binding of the second antibodies to the antigens.

25. The method of claim 24, further comprising rinsing the biosample tracks with water or a rinsing agent to remove any antibodies not bound to the antigens.

26. The method of claim 25, wherein the biosample tracks are deposited on a substrate and the method further comprises:

applying a first DC voltage to the substrate to heat and dry the biosample tracks, antibodies, and antigens thereon; and

applying a second DC voltage to the substrate to cool the biosample tracks, antibodies, and antigens thereon, wherein the first and second DC voltages have opposite electrical polarities.

27. A method for detecting target antigens in a biological sample comprising:

bonding a first set of antibodies to a plurality of biosample tracks deposited on a magnetic tape media;

exposing the biological sample to the biosample tracks to allow the target antigens to bind to the first set of antibodies;

bonding a second set of antibodies to magnetized nanoparticles, wherein the first and second sets of antibodies are biologically identical;

exposing the nanoparticles to the antigens to allow the second set of antibodies to bind to the antigens; and  
reading the tape media with a magneto-resistive read sensor of a tape drive to detect the antigens through the magnetized nanoparticles.

28. The method of claim 27, wherein the nanoparticles are initially demagnetized and the method further magnetizes the nanoparticles with an electromagnetic write head of the tape drive before reading the tape media.

29. The method of claim 27, further comprising displaying an antigen detection to a user.

30. An apparatus for detecting target antigens, comprising:  
a biosample track having a first set of antibodies bonded thereon;

a biological sample exposed to the biosample track to allow antigens in the biological sample to bind to the first set of antibodies;

a plurality of magnetized nanoparticles bonded to a second set of antibodies, wherein the first and second sets of antibodies are biologically identical and the second set of antibodies bind to the antigens when the nanoparticles are exposed to the antigens; and

a magneto-resistive read sensor for detecting the target antigens through the magnetized nanoparticles when the read sensor scans the biosample track.

\* \* \* \* \*



专利名称(译)	通过带有电磁读写头的纳米颗粒标记物质检测分析物		
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#### 摘要(译)

第一组抗体与基质结合，并暴露于靶抗原并与靶抗原结合。第二组抗体与纳米颗粒结合，纳米颗粒标记的抗体暴露于靶抗原。电磁写头磁化纳米颗粒，然后读传感器检测新近磁化的纳米颗粒。基底包括柔性膜或Peltier材料，以允许选择性加热和冷却抗原和抗体。具有不同磁性的纳米颗粒可以选择性地与不同抗原相关的抗体配对，以允许在读取传感器的单次扫描中检测不同的抗原。

