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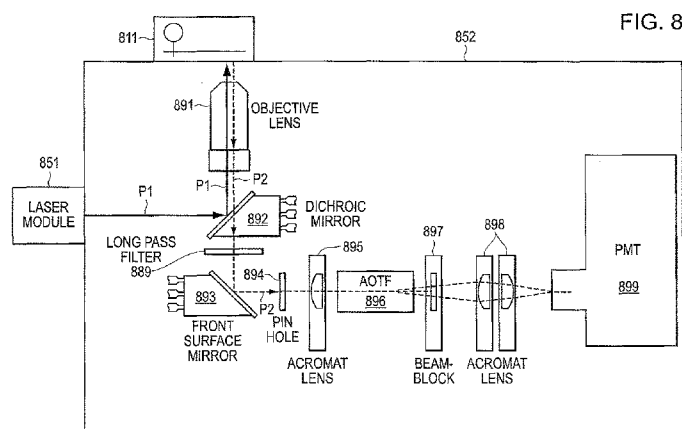
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(54) Title: OPTICAL APPROACH FOR MICROFLUIDIC DNA ELECTROPHORESIS DETECTION



(57) Abstract: Aspects of the disclosure provides a DNA analyzer to facilitate an integrated single-chip DNA analysis. The DNA analyzer includes an interface for coupling a microfluidic chip to the DNA analyzer. The microfluidic chip includes a first domain configured for polymerase chain reaction (PCR) amplification of DNA fragments, and a second domain fluidically coupled to the first domain to receive the DNA fragments and perform electrophoretic separation of the DNA fragments. The DNA fragments are tagged with fluorescent labels. The DNA analyzer includes a detection module to excite the fluorescent labels to emit fluorescence and detect the emitted fluorescence. The detection module includes a laser source, a set of optical elements, a filter module and a photo-detector.

OPTICAL APPROACH FOR MICROFLUIDIC DNA ELECTROPHORESIS DETECTION

INCORPORATION BY REFERENCE

[0001] This application claims the benefit of U.S. Provisional Applications No. 61/213,405, "Fast Sample to Answer DNA Analyzer (Analytical Microdevice)" filed on June 4, 2009, No. 61/213,406, "Optical Approach for Microfluidic DNA Electrophoresis Detection" filed on June 4, 2009, and No. 61/213,404, "Multiple Sample, Integrated Microfluidic Chip for DNA Analysis" filed on June 4, 2009, which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] DNA is recognized as the "ultimate biometric" for human identification. DNA analysis can provide evidence for solving forensic and medical cases, such as in areas of criminal justice, identifications of human remains, paternity testing, pathogen detection, disease detection, and the like.

SUMMARY

[0003] Aspects of the disclosure can provide a DNA analyzer to facilitate DNA analysis. The DNA analyzer includes an interface for coupling a microfluidic chip to the DNA analyzer. The microfluidic chip includes a first domain configured for polymerase chain reaction (PCR) amplification of DNA fragments, and a second domain fluidically coupled to the first domain to receive the DNA fragments. The second domain includes a separation channel for electrophoretic separation of the DNA fragments. The microfluidic chip may include other domains, such as purification domain, post-PCR domain, and the like.

[0004] The DNA fragments are tagged with fluorescent labels during the PCR amplification. The DNA analyzer includes a detection module optically coupled with the microfluidic chip to excite the fluorescent labels to emit fluorescence and to detect the emitted fluorescence. The detection module can include a laser source, a set of optical elements, a filter module and a photo-detector.

[0005] The laser source generates a laser beam. The set of optical elements direct the laser beam to the separation channel to excite the fluorescent labels to emit fluorescence while the DNA fragments migrate in the separation channel. In addition, the set of optical elements collect the emitted fluorescence into an optical signal. The filter module filters the optical signal to allow a first portion of the optical signal having a first wavelength to pass,

and the photo-detector generates an electrical detection signal in response to the filtered optical signal.

[0006] In an embodiment, the photo-detector includes a photo-multiplier tube configured to generate the electrical detection signal in response to the filtered optical signal. The set of optical elements include an objective lens aligned with the separation channel to direct the laser beam to the separation channel and to collect the emitted fluorescence from the separation channel. The objective lens can be aligned with the separation channel by a motor.

[0007] The filter module can include an acousto-optic tunable filter (AOTF). The AOTF can filter the optical signal to allow the first portion of the optical signal having the first wavelength to pass based on an electrical tuning signal having a first tuning frequency. The first wavelength satisfies a matching condition of the AOTF with the first tuning frequency.

[0008] In an embodiment, the DNA analyzer includes a controller configured to generate a control signal indicative of the first tuning frequency, and a synthesizer configured to generate the electrical tuning signal having the first tuning frequency based on the control signal.

[0009] The controller can adjust the control signal to be indicative of a second tuning frequency. Then, the electrical tuning signal generated by the synthesizer has the second tuning frequency. Based on the electrical tuning signal, the AOTF filters the optical signal to allow a second portion of the optical signal having a second wavelength to pass. The second wavelength satisfies the matching condition of the AOTF with the second tuning frequency.

[0010] In an embodiment, the DNA analyzer includes a modulation signal generator configured to generate a modulation signal having a modulation frequency, and a reference signal having the modulation frequency. The modulation signal being used by the AOTF to modulate the filtered optical signal. Further, the DNA analyzer includes a phase-sensitive detector configured to receive the reference signal and the electrical detection signal corresponding to the modulated filtered optical signal and to demodulate the electrical detection signal based on the reference signal.

[0011] It is noted that the DNA analyzer can include other modules to act on the microfluidic chip to perform integrated single-chip DNA analysis. For example, the DNA analyzer can include a pressure module configured to flow liquid in the microfluidic chip, a

thermal module configured to induce thermal cycling at the first domain of the microfluidic chip for the PCR amplification, a power module configured to generate voltages to be applied to the second domain of the microfluidic chip for the electrophoretic separation, and a controller module. The controller module is configured to control the pressure module, the thermal module, the power module, and the detection module according to a control procedure to act on the microfluidic chip for a single-chip DNA analysis.

[0012] Aspects of the disclosure can provide a method of DNA analysis. The method includes selecting a first wavelength corresponding to a first fluorescent label used to label DNA fragments during polymerase chain reaction (PCR) amplification in a first domain of a microfluidic chip. The DNA fragments have been fluidically directed from the first domain to a second domain of the microfluidic chip having a separation channel for electrophoretic separation. The method further includes exciting at least the first fluorescent label to emit fluorescence in the second domain, and tuning a detection module to detect the emitted fluorescence having the first wavelength.

[0013] To excite the first fluorescent label to emit the fluorescence, the method includes generating a laser beam, and directing the laser beam to the separation channel to excite the first fluorescent label to emit the fluorescence while the DNA fragments migrate in the separation channel. The emitted fluorescence can be collected into an optical signal.

[0014] Further, to tune the detection module to detect the emitted fluorescence having the first wavelength, the method includes generating an electrical tuning signal having a first tuning frequency, providing the electrical tuning signal to an acousto-optic tunable filter (AOTF) in the detection module to filter the optical signal and pass a first portion of the optical signal having the first wavelength, and detecting the filtered optical signal. The first wavelength satisfies a matching condition of the AOTF with the first tuning frequency.

[0015] In addition, the method includes selecting a second wavelength corresponding to a second fluorescent label used to label the DNA fragments during the (PCR) amplification in the first domain, and adjusting the electrical tuning signal to have a second tuning frequency. The adjustment causes the AOTF to filter the optical signal and pass a second portion of the optical signal having the second wavelength. The second wavelength satisfies the matching condition of the AOTF with the second tuning frequency.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Various exemplary embodiments of this disclosure will be described in detail with reference to the following figures, wherein like numerals reference like elements, and wherein:

[0017] Fig 1 shows a block diagram of an exemplary DNA analyzer according to an embodiment of the disclosure;

[0018] Fig. 2A and 2B show a swab example and a sample cartridge example according to an embodiment of the disclosure;

[0019] Fig. 3 shows a schematic diagram of a microfluidic chip example according to an embodiment of the disclosure;

[0020] Fig. 4 shows a prototype implementation of a DNA analyzer according to an embodiment of the disclosure;

[0021] Fig. 5 shows a flow chart outlining a process example for using a DNA analyzer to perform DNA analysis according to an embodiment of the disclosure;

[0022] Fig. 6 shows a flow chart outlining a process example for a DNA analyzer to perform DNA analysis according to an embodiment of the disclosure;

[0023] Fig. 7 shows a block diagram of a detection module according to an embodiment of the disclosure;

[0024] Fig. 8 shows a block diagram of an optical design according to an embodiment of the disclosure;

[0025] Fig. 9 shows a block diagram for signal processing according to an embodiment of the disclosure; and

[0026] Fig. 10 shows a flow chart outlining a process example for a controller to control a multi-color fluorescence detection according to an embodiment of the disclosure.

DETAILED DESCRIPTION OF EMBODIMENTS

[0027] Fig. 1 shows a block diagram of an exemplary DNA analyzer 100 according to an embodiment of the disclosure. The DNA analyzer 100 includes a microfluidic chip module 110, a thermal module 120, a pressure module 130, a high voltage module 140, a detection module 150, a power module 160, a computing module 170, and a controller module 180. Additionally, the DNA analyzer 100 can include a magnetic module 190. These elements can be coupled together as shown in Fig. 1.

[0028] The DNA analyzer 100 is capable of processing sample-to-answer DNA analysis on an integrated single-chip. Thus, using the DNA analyzer 100 to perform DNA analysis does not need substantial experience and knowledge of DNA processes. In an example, the appropriate procedures to use the DNA analyzer 100 to perform DNA analysis can be learned in an hour. Additionally, the integrated single-chip DNA analysis requires a reduced volume of reagents, for example, in the order of a micro-liter. Further, the reduced volume of reagents can reduce thermal inputs for inducing thermal cycles in the DNA analysis, and thus reduce the time for DNA analysis.

[0029] The microfluidic chip module 110 includes a microfluidic chip 111. The microfluidic chip 111 can be suitably coupled with other elements of the DNA analyzer 100 to perform integrated single-chip DNA analysis. In an example, the microfluidic chip module 110 is implemented as a disposable cartridge, and a cartridge interface that can couple the disposable cartridge with other components of the DNA analyzer 100 that are not included as part of the disposable cartridge. The disposable cartridge includes the microfluidic chip 111 and a micro-to-macro interface. The micro-to-macro interface couples the microfluidic chip 111 to macro structures on the disposable cartridge. The disposable cartridge can be separately stored, and can be installed in the DNA analyzer 100 at a time of DNA analysis. After the DNA analysis, the disposable cartridge can be suitably thrown away.

[0030] The microfluidic chip 111 includes various domains that can be suitably configured to enable the integrated single-chip DNA analysis. In an embodiment, DNA analysis generally includes a step of PCR amplification, and a step of electrophoretic separation. The microfluidic chip 111 can include a first domain 111a for the PCR amplification and a second domain 111b for the electrophoretic separation. In addition, the microfluidic chip 111 can include other domains that are suitably integrated with the first domain 111a and the second domain 111b. In an example, the microfluidic chip 111 includes a purification domain fluidically coupled with the first domain 111a. The purification domain can be used to extract and purify a template DNA. It is noted that any suitable techniques, such as solid-phase extraction, liquid-phase extraction, and the like, can be used to purify the template DNA in the purification domain.

[0031] In another example, the microfluidic chip 111 includes a post-PCR clean-up/dilution domain that is fluidically coupled with the first domain 111a and the second

domain 111b. The post-PCR clean-up/dilution domain can be used for any suitable process after the PCR amplification and before the electrophoretic separation.

[0032] The first domain 111a includes a reservoir configured for PCR amplification. In an embodiment, the first domain 111a includes multiple separated reservoirs to enable simultaneous PCR amplification for multiple DNA samples. The temperature at the first domain 111a can be controlled by the thermal module 120 to enable the PCR amplification. According to an embodiment of the disclosure, the PCR amplification on the microfluidic chip 111 requires only a small volume of reagents, and the PCR amplification can achieve rapid thermal cycling. In an example, the volume of reagents used for the PCR amplification can be in the order of sub-micro-liter, and the time required for the PCR amplification can be under 20 minutes.

[0033] The second domain 111b can include a plurality of micro channels. The plurality of micro channels can be configured for electrophoretic separation. More specifically, each micro channel can be filled with, for example, polymer sieving matrix. Further, an electric field can be induced in the micro channel. Thus, when DNA fragments are injected in the micro channel, the DNA fragments can migrate by force of the electric field at different speeds based on the sizes of the DNA fragments.

[0034] Additionally, the second domain 111b can be configured to facilitate DNA fragments detection in the DNA analysis. In an example, DNA fragments are tagged with fluorescent labels during PCR, before being injected in the micro channels. The fluorescent labels can emit fluorescence of pre-known wavelength when excited by a laser beam. The second domain 111b includes a detection window configured for detection. The laser beam can be directed to pass through the detection window to excite the fluorescent labels in the micro channels. The emitted fluorescence can pass through the detection window to be collected and detected.

[0035] The microfluidic chip 111 can include additional structures to facilitate the integrated single-chip DNA analysis. For example, the microfluidic chip 111 can include microfluidic channels that can direct DNA fragments from the first domain 111a to the second domain 111b. Through the microfluidic channels, the DNA fragments flow in a solution from the first domain 111a to the second domain 111b. In addition, the microfluidic chip 111 can include inlets for receiving reagents and the template DNA. The microfluidic chip 111 can also include additional reservoirs for additional processing steps, such as dilution, cleanup, and the like.

[0036] The microfluidic chip 111 can be constructed from any suitable material. In an example, the microfluidic chip 111 is constructed from glass. In another example, the microfluidic chip 111 is constructed from plastic or polymeric material.

[0037] In addition to the microfluidic chip 111, the disposable cartridge can include a sample acceptor and a reagent carrier. In an example, the sample acceptor accepts a swab used for taking DNA sample, such as from saliva, bloodstains, cigarettes, and the like. Further, the sample acceptor extracts a template DNA from the swab. The sample acceptor can use any suitable mechanism, such as solid-phase extraction, liquid-phase extraction, and the like to obtain and/or purify the template DNA from the swab. In an embodiment, the sample acceptor uses a solid-phase DNA extraction method, such as silica beads based DNA extraction.

[0038] In another embodiment, the sample acceptor uses a liquid-phase DNA extraction method. The liquid-phase DNA extraction method can simplify the purification and extraction process, and reduce a total cost of the DNA analyzer 100. In an example, the sample acceptor uses an enzymatic DNA-isolation method to extract and purify the template DNA. The enzymatic DNA-isolation method can achieve liquid phase purification without a need of centrifugation. In addition, the sample acceptor can be suitably designed to maintain sample integrity.

[0039] More specifically, the sample acceptor can include a plurality of separated wells for taking swabs, for example. Thus, the DNA analysis can simultaneously process multiple DNA samples. Each well includes a liquid phase mixture that is sealed by a membrane at a bottom portion of the well. The liquid phase mixture can conduct enzymatic digestion of all proteins and other cellular interferences, with the exception of DNA. For example, the liquid phase mixture can include thermostable proteinases from thermophilic *Bacillus* species, such as disclosed in U.S. Patent Application Publication No. 2004/0197788, which is incorporated herein by reference in its entirety. Thus, the liquid phase mixture can perform DNA extraction and purification when a swab is immersed in the liquid phase mixture. The liquid phase method can achieve comparable DNA quality to other methodologies in both DNA concentration and purity. In an example, a final DNA concentration by the liquid phase method is in a range of 0.5-2 ng/ μ L.

[0040] Further, using the liquid phase extraction method instead of the silica solid phase method can reduce the overall hydraulic pressure requirement to induce solution flow through the microfluidic chip 111. In an embodiment, the liquid phase extraction can enable

a valveless design for the microfluidic chip 111. Thus, the liquid phase extraction can simplify the DNA analyzer 100 and simplify the manufacturing and testing steps in association with the solid-phase extraction.

[0041] Before taking DNA sample, a swab can be sealed in a hard case to avoid contamination. The swab can be attached to a seal cap that can seal the hard case. The swab can be identified by various mechanisms. In an example, a barcode label is attached to the hard case to identify the swab. In another example, the seal cap has a radio frequency identification (RFID) tag implanted. The RFID tag can identify the swab attached to the seal cap throughout the process. After the swab is used to take DNA sample, the swab can be placed in one of the plurality of separated wells, and can be sealed in the well, for example, by the seal cap attached to the sampled swab. In an embodiment, the seal cap is a stepped seal cap that can seal the well in a first step, and a second step. When the seal cap seals the well in the first step, the swab does not puncture the membrane. When the seal cap seals the well in the second step, the swab punctures the membrane and is immersed in the liquid phase mixture. The liquid phase mixture can then extract template DNA from the swab.

[0042] The reagent carrier can house a plurality of reagents for DNA analysis, such as reagents for polymerase chain reaction (PCR) amplification, solutions for electrophoretic separation, and the like. In an STR typing example, the reagent carrier houses reagents for multiplexed STR amplification. The reagents can perform multiplexed STR amplification and can use multiple fluorescent dyes to label STR alleles. The reagents can be commercially available reagent kits or can be tailored to the micro-scale chip environment to further facilitate the integrated single-chip DNA analysis.

[0043] In addition, the reagent carrier houses solutions that are suitable for electrophoretic separation in the micro-scale chip environment. For example, the reagent carrier houses a coating solution, such as poly-N-hydroxyethylacrylamide, and the like. The coating solution can be used to coat micro channel walls prior to the separation to reduce electro osmotic flow and enable single base pair resolution of amplified DNA fragments. In another example, the reagent carrier houses a dilution solution, such as water and/or Formamide, and the like. The dilution solution can be used to reduce the ionic strength of the sample in order to promote better electro-kinetic injection. In another example, the reagent carrier houses an internal lane standard (ILS). The ILS can be used for accurate size measurements. The reagent carrier also houses a polymer solution for electrophoretic separation in the micro-scale chip environment. The polymer solution is used as gels to

provide a physical separation of DNA fragments according to chain length. For example, the polymer solution can include a sieving or non-sieving matrix, such as that disclosed in U.S. Patents No. 7,531,073, No. 7,399,396, No. 7,371,533, No. 7,026,414, No. 6,811,977 and No. 6,455,682, which are incorporated herein by reference in their entirety. In an example, a polymer sieving matrix can be used to yield a single-base resolution in a total separation length of 8 cm and in less than 400 seconds.

[0044] The thermal module 120 receives control signals from the controller module 180, and induces suitable temperatures for DNA analysis, such as a temperature for DNA extraction, thermal cycles for the PCR amplification, a temperature for electrophoretic separation, and the like. In an example, the thermal module 120 includes a resistance heater to control a temperature in the wells of the sample acceptor for the DNA extraction and purification. In another example, the thermal module 120 includes another resistance heater to control a temperature at the second domain 111b.

[0045] In another example, the thermal module 120 includes a heating unit, a cooling unit and a sensing unit to induce the thermal cycles for the PCR amplification at the first domain 111a. The heating unit can direct heat to the first domain 111a, the cooling unit can disperse heat from the first domain 111a, and the sensing unit can measure a temperature at the first domain 111a. The controller module 180 can control the heating unit and the cooling unit based on the temperature measured by the sensing unit.

[0046] In an embodiment, the thermal module 120 performs non-contact thermal controls. For example, the thermal module 120 includes an infrared light source as the heating unit, a cooling fan as the cooling unit, and an infrared pyrometer as the temperature sensing unit. The infrared light source, such as a halogen light bulb, can excite, for example, the 1.3 μm vibrational band of liquid. Thus, the infrared light source can heat a small volume of solution within a reservoir in the first domain 111a independent of the reservoir to achieve rapid heating and cooling. The infrared pyrometer measures blackbody radiation from an outside of the reservoir. In an example, the reservoir is designed to have a thinner side for the infrared pyrometer measurements. The infrared pyrometer measurements at the thinner side can more accurately reflect the temperature of solution within the reservoir. Thus, the DNA analyzer 100 can achieve a precise temperature control along with rapid thermal cycles. In an example, the DNA analyzer 100 can achieve a temperature fluctuation of less than $\pm 0.1^\circ\text{C}$, and a time of the thermal cycles for the PCR amplification can be less than 20 minutes.

[0047] The pressure module 130 receives control signals from the controller module 180, and applies suitable pressures to the microfluidic chip module 110 to enable fluid movement. In an embodiment, the pressure module 130 receives a sensing signal that is indicative of a pressure applied to the microfluidic chip module 110, and suitably adjusts its operation to maintain the suitable pressure to the microfluidic chip module 110.

[0048] The pressure module 130 can include a plurality of pumps. The plurality of pumps control the injection of the various reagents and the template DNA solutions into the microfluidic chip 111. According to an embodiment of the disclosure, the plurality of pumps can be individually controlled to achieve any possible timing sequence.

[0049] The pressure module 130 may include other pressure components to suit the integrated single-chip integrated DNA analysis. In an embodiment, the microfluidic chip 111 has membrane valves. The pressure module 130 can include a hydrodynamic pressure/vacuum system to suitably control the closing and opening of the membrane valves to enable fluid movement through the microfluidic chip 111.

[0050] In another embodiment, the microfluidic chip 111 is valveless. For example, the DNA analyzer 100 uses a liquid phase DNA extraction instead of a silica solid phase DNA extraction. The liquid phase DNA extraction can be integrated with following DNA processes on a valveless microfluidic chip. Thus, the hydrodynamic pressure/vacuum system is not needed. The pressure module 130 can be simplified to reduce the footprint, the weight, the cost, and the complexity of the DNA analyzer 100.

[0051] The power module 160 receives a main power, and generates various operation powers for various components of the DNA analyzer 100. In an example, the DNA analyzer 100 is implemented using a modular design. Each module of the DNA analyzer 100 needs an operation power supply, which can be different from other modules. The power module 160 receives an AC power input, such as 100-240 V, 50-60 Hz, single phase AC power from a power outlet. Then, the power module 160 generates 5 V, 12 V, 24 V, and the like, to provide operation powers for the various components of the DNA analyzer 100.

[0052] In addition, the power module 160 generates high voltages, such as 1000 V, 2000 V, and the like, for suitable DNA processes on the microfluidic chip 111, such as electro-kinetic injection, electrophoretic separation, and the like.

[0053] Further, the power module 160 can implement various protection techniques, such as power outage protection, graceful shut-down, and the like, to protect the

various components and data against power failure. It is noted that the power module 160 may include a back-up power, such as a battery module, to support, for example, graceful shut-down.

[0054] The high voltage module 140 can receive the high voltages from the power module 160 and suitably apply the high voltages on the microfluidic chip 111. For example, the high voltage module 140 includes interfaces that apply the high voltages to suitable electrodes on the microfluidic chip 111 to induce electro-kinetic injection and/or electrophoretic separation.

[0055] The detection module 150 includes components configured to suit the integrated single-chip DNA analysis. In an embodiment, the detection module 150 is configured for multicolor fluorescence detection. The detection module 150 includes a laser source unit, a set of optics and a detector unit.

[0056] The laser source unit emits a laser beam. In an example, the laser source unit includes an argon-ion laser unit. In another example, the laser source unit includes a solid state laser, such as a coherent sapphire optically pumped semiconductor laser unit. The solid state laser has the advantages of reduced size, weight and power consumption.

[0057] The set of optics can direct the laser beam to pass through the detection window at the second domain 111b of the microfluidic chip 111. The laser beam can excite fluorescent labels attached to DNA fragments to emit fluorescence. Further, the set of optics can collect and direct the emitted fluorescence to the detector unit for detection. In an STR typing example, STR alleles are separated in the second domain 111b according to sizes. STR alleles of different sizes pass the detection window at different times. In addition, STR alleles of overlapping sizes can be tagged with fluorescent labels of different colors. The detector unit can be configured to detect an STR allele having a fluorescent label based on a time of fluorescence emitted by the fluorescent label and a color of the emitted fluorescence.

[0058] In another example, internal lane standard (ILS) is added to migrate in the micro channel with the STR alleles. The ILS includes DNA fragments of known sizes, and can be tagged with a pre-determined fluorescent dye. The detector unit detects fluorescence emitted from the ILS to set up a size scale. In addition, the detector unit detects fluorescence emitted from the STR alleles. The detector unit can suitably convert the detected fluorescence into electrical signals. The electrical signals can be suitably stored and/or analyzed. In an example, a processor executes DNA analysis software instructions to identify the STR alleles by their sizes and emitted fluorescence colors (wavelengths).

[0059] The computing module 170 includes computing and communication units. In an example, the computing module 170 includes a personal computer. The personal computer can be coupled with the controller module 180 to provide a user interface. The user interface can inform the status of the DNA analyzer 100, and can receive user instructions for controlling the operation of the DNA analyzer 100. The personal computer includes various storage media to store software instruction and data. The personal computer can include DNA analysis software that can perform data processing based on raw data obtained from the detection module 150. In addition, the personal computer can be coupled to external processing units, such as a database, a server, and the like to further process the data obtained from the DNA analyzer 100.

[0060] The magnetic module 190 can enable a magnetic solid phase for the integrated single chip DNA analysis. In an embodiment, the magnetic solid phase can be suitably incorporated in the integrated single chip DNA analysis to facilitate a volume reduction to suit for low copy numbers of template DNAs. In another embodiment, the magnetic solid phase can be suitably incorporated into an integrated single chip sequencing DNA analysis.

[0061] The controller module 180 can receive status signals and feedback signals from the various components, and provide control signals to the various components according to a control procedure. In addition, the controller module 180 can provide the status signals to, for example, the personal computer, to inform the user. Further, the controller module 180 can receive user instructions from the personal computer, and may provide the control signals to the various components based on the user instructions.

[0062] During operation, the controller module 180 receives user instructions from the personal computer to perform a STR typing analysis, for example. The controller module 180 then monitors the microfluidic chip module 110 to check whether a suitable disposable cartridge has been installed, and whether swabs have been identified and suitably immersed in the liquid phase mixture to extract template DNA. When the controller module 180 confirms the proper status at the microfluidic chip module 110, the controller module 180 starts a control procedure corresponding to the STR typing analysis. In an example, the controller module 180 can control the thermal module 120 to maintain an appropriate temperature at the wells of the sample acceptor for a predetermined time. The liquid phase mixture in the wells can extract template DNAs from the swabs. Then, the controller module 180 can control the pressure module 130 to pump the extracted template DNAs into the first

domain 111a of the microfluidic chip 111. In addition, the controller module 180 can control the pressure module 130 to pump reagents for multiplexed STR amplification into the first domain 111a.

[0063] Further, the controller module 180 can control the thermal module 120 to induce thermal cycling for the multiplexed STR amplification at the first domain 111a. The reagents and the thermal cycling can cause DNA amplification. In addition, the DNA amplicons can be suitably tagged with fluorescent labels.

[0064] Subsequently, the controller module 180 can control the pressure module 130 to flow the DNA amplicons to the second domain 111b. The controller module 180 may control the pressure module 130 to pump a dilution solution into the microfluidic chip 111 to mix with the DNA amplicons. In addition, the controller module 180 may control the pressure module 130 to pump an ILS into the microfluidic chip 111 to mix with the DNA amplicons.

[0065] Further, the controller module 180 controls the high voltage module 140 to induce electro-kinetic injection to inject DNA fragments into the micro channels. The DNA fragments include the amplified targets, and the ILS. Then, the controller module 180 controls the high voltage module 140 to induce electrophoretic separation in the micro channels. Additionally, the controller module 180 can control the thermal module 120 to maintain a suitable temperature at the second domain 111b during separation, for example, to maintain the temperature for denaturing separation of the DNA fragments.

[0066] The controller module 180 then controls the detection module 150 to detect the labeled DNA fragments. The detection module 150 can emit and direct a laser beam to the micro channels to excite the fluorescent labels to emit fluorescence. Further, the detection module 150 can detect the emitted fluorescence and store detection data in a memory. The detection data can include a detection time, and a detected color (wavelength), along with a detected intensity, such as a relative magnitude of the detected fluorescence. The detection data can be transmitted to the personal computer for storage. Additionally, the controller module 180 can provide control statuses to the personal computer to inform the user. For example, the controller module 180 can send an analysis completed status to the personal computer when the control procedure is completed.

[0067] The DNA analyzer 100 can be suitably configured for various DNA analyses by suitably adjusting the reagents housed by the reagent carrier and the control procedure executed by the controller module 180.

[0068] Fig. 2A shows a swab storage example 212, and Figs. 2B-2C show a side elevation view and a front elevation view of a sample cartridge example 215 according to an embodiment of the disclosure. The swab storage 212 includes a case 203, a seal cap 202 and a swab 205. The seal cap 202 and the swab 205 are attached together. In addition, the swab storage 212 includes an identifier, such as a barcode label 204 that can be attached to the case 203, an RFID tag 201 that can be implanted in the seal cap 202, and the like.

[0069] Before taking DNA sample, the swab 205 is safely stored in the case 203 to avoid contamination. After taking DNA sample, the swab 205 can be placed in the sample cartridge 215.

[0070] The sample cartridge 215 can include a microfluidic chip 211, a sample acceptor 207 and a reagent carrier 206. The sample acceptor 207 includes a plurality of separated wells 207A-207D for taking swabs. Each well includes a liquid phase mixture 214 that is sealed by a membrane 208 at a bottom portion of the well. The liquid phase mixture 214 can conduct enzymatic digestion of all proteins and other cellular interferences, with the exception of DNA, and thus can perform DNA extraction and purification when a swab with DNA sample is inserted in the liquid phase mixture 214.

[0071] While the sample cartridge 215 is described in the context of swabs, it should be understood that the sample cartridge 215 can be suitably adjusted to suit other DNA gathering methods, such as blood stain cards, airborne samples, fingerprints samples, and the like.

[0072] In an embodiment, the seal cap 202 is a stepped seal cap that can seal the well in a first step, and a second step. When the seal cap 202 seals the well in the first step, the swab 205 does not puncture the membrane 208, and can be safely sealed in the well to maintain sample integrity. When the seal cap 202 seals the well in the second step, the swab 205 punctures the membrane 208 and is immersed in the liquid phase mixture 214.

[0073] The reagent carrier 206 houses various solutions for DNA analysis. In an STR typing example, the reagent carrier houses reagents for multiplexed STR amplification. In addition, the reagent carrier houses a coating solution, such as poly-N-hydroxyethylacrylamide, and the like. The coating solution can be used to coat micro channel walls prior to the separation. Further, the reagent carrier houses a dilution solution, such as water, formamide, and the like. The dilution solution can be used to reduce the ionic strength in order to promote better electro-kinetic injection. In an embodiment, the reagent carrier houses an internal lane standard (ILS). The ILS can be used for size measurement.

The reagent carrier also houses a polymer solution for electrophoretic separation in the micro-scale chip environment.

[0074] During operation, for example, a new disposable cartridge 215 is taken from a storage package, and installed in a DNA analyzer, such as the DNA analyzer 100. Then, a swab 205 can be used to take a DNA sample. The swab 205 is then identified and inserted into one of the wells 207A-207D and sealed in the first step. Additional swabs 205 can be used to take DNA samples, and then identified and inserted into the un-used wells 207A-207D. Further, the DNA analyzer 100 can include a mechanism that can push the seal caps 202 to seal the wells 207A-207D in the second step, thus the swabs 205 can puncture the membrane 208, and immerse in the liquid phase mixture 214.

[0075] Fig. 3 shows a schematic diagram of a microfluidic chip example 311 according to an embodiment of the disclosure. The microfluidic chip 311 includes various micro structures, such as inlets 312-314, reaction reservoirs 315-316, channels 317a-317b, electrode reservoirs 318, outlets (not shown), and the like, that are integrated for single-chip DNA analysis. It is noted that the various micro structures can be designed and integrated to suit for various DNA analyses, such as STR typing, sequencing, and the like.

[0076] The inlets 312-314 can be coupled to a pressure module to inject solutions in the microfluidic chip 311. As described above, the connection can be made via a micro-macro interface. In an example, the inlet 312 is for injecting a template DNA solution from a well of the sample acceptor 207, and the inlet 313 is for injecting PCR reagents from the reagent carrier 206. In addition, the inlet 313 can be used for injecting dilution solution and ILS from the reagent carrier 206.

[0077] The reaction reservoirs 315-316 are configured for various purposes. In an example, the reaction reservoir 315 is configured for the PCR amplification, and the reaction reservoir 316 is configured for the post-PCR processes, such as dilution, and the like. More specifically, the reaction reservoir 315 is located in a first domain 311a, which is a thermal control domain. The temperature within the thermal control domain 311a can be precisely controlled. In an example, an infrared heating unit directs heat to the thermal control domain 311a, a cooling fan disperses heat from the thermal control domain 311a, and an infrared sensing unit measures a temperature in the thermal control domain 311a. The infrared heating unit and the cooling fan can be controlled based on the temperature measured by the infrared sensing unit. The infrared heating unit, the cooling fan, and the infrared sensing unit can perform thermal control without contacting the thermal control domain 311a.

[0078] In another example, the temperature in the thermal control domain 311a is measured by a thermal coupling technique. More specifically, the microfluidic chip 311 includes a thermal-coupler reservoir 319 within the first domain 311a. Thus, the solution temperature within the reaction reservoir 315 and the thermal-coupler reservoir 319 can be closely related. The solution temperature within the thermal-coupler reservoir 319 can be measured by any suitable technique. Based on the measured solution temperature within the thermal-coupler reservoir 319, the solution temperature within the reaction reservoir 315 can be determined. Then, the infrared heating unit and the cooling fan can be controlled based on the temperature measured by the thermal coupling technique in order to control the solution temperature in the reaction reservoir 315.

[0079] In an embodiment, after the PCR amplification, the PCR mixture is fluidically directed from the reaction reservoir 315 to a post-PCR clean-up/dilution domain, such as the reaction reservoir 316. In the reaction reservoir 316, the PCR mixture is diluted. In an example, the PCR mixture and a dilutant solution are mixed together according to a ratio from 1:5 to 1:20 (1 part of PCR mixture to 5-20 parts of dilutant). Further, ILS can be added in the reaction reservoir 316 to mix with the PCR mixture.

[0080] The channels 317a-317b are located in a second domain 311b. Electric fields can be suitably applied onto the channels 317a-317b. In an example, the channels 317a-317b are configured according to a cross-T design, having a short channel 317a and a long channel 317b.

[0081] The electrode reservoirs 318 can be used to apply suitable electric fields over the short channel 317a and the long channel 317b. Thus, the short channel 317a is configured for electro-kinetic injection, and the long channel 317b is configured for electrophoretic separation. For example, when a high voltage is applied to the short channel 317a, DNA fragments can be injected from the reaction reservoir 316 into the short channel 317a at the intersection of the short channel 317a and the long channel 317b. The long channel 317b can be filled with sieving matrix. When a high voltage is applied to the long channel 317b, the injected DNA fragments can migrate in the long channel 317b to the positive side of the electric field induced by the high voltage, in the presence of the sieving matrix. In an example, the length of the long channel 317b is about 8.8 cm with detection at about 8 cm from the intersection.

[0082] It should be understood that the microfluidic chip 311 can include other structures to assist DNA analysis. In an example, the microfluidic chip 311 includes an

alignment mark 321. The alignment mark 321 can assist a detection module to align to the long channel 317b.

[0083] During operation, for example, the inlet 312 can input a template DNA into the reaction reservoir 315, and the inlet 313 can input PCR reagents into the reaction reservoir 315. Then, thermal-cycling can be induced at the first domain 311a, and PCR amplification can be conducted in the reaction reservoir 315 to amplify DNA fragments based on the template DNA and the PCR reagents. After the PCR amplification, the DNA amplicons in the reaction reservoir 315 can be mobilized into the reaction reservoir 316 in a liquid flow. In the reaction reservoir 316, a dilution solution and ILS can be input to mix with the DNA fragments. Further, the DNA fragments in the reaction reservoir 316 can be injected across the short channel 317a by electro-kinetic injection. The DNA fragments then migrate in the long channel 317b under the force of electric field applied over the long channel 317b. The speed of migration depends on the sizes of the DNA amplicons, in the presence of the sieving matrix. Thus, the DNA fragments are separated in the long channel 317b according to their sizes.

[0084] Fig. 4 shows an exemplary DNA analyzer 400 according to an embodiment of the disclosure. The DNA analyzer 400 is packaged in a box. The box includes handles, wheels and the like, to facilitate transportation of the DNA analyzer 400. In an implementation, the total weight of the DNA analyzer 400 is less than 70 lb, and is appropriate for two persons to carry.

[0085] The DNA analyzer 400 is implemented in a modular manner. Each module can be individually packaged, and can include an interface for inter-module couplings. Thus, each module can be easily removed and replaced. The modular design can facilitate assembly, troubleshooting, repair, and the like.

[0086] The DNA analyzer 400 includes a user module (UM) 410, an active pressure module (APM) 430, a detection module 450, a power module (PM) 460, a computing module 470, and a controller module (CM) 480. In addition, the DNA analyzer 400 includes a sample cartridge storage 415 and a swab storage 412.

[0087] The UM 410 includes a holder to hold a sample cartridge, such as the sample cartridge 215, at an appropriate position when the sample cartridge is inserted by a user. Further, the UM 410 includes interface components to couple the sample cartridge 215 with, for example, the APM 430, the detection module 450, and the like. The UM 410 includes thermal components, such as resistance heaters 421, a cooling fan 422, an infrared

heating unit 423, and the like. The thermal components can be suitably positioned corresponding to the sample cartridge 215. For example, a resistance heater 421 is situated at a position that can effectively control a temperature of the liquid phase mixture within the plurality of separated wells on the sample cartridge 215. The temperature can be determined to optimize enzyme activities of the liquid phase mixture to conduct enzymatic digestion of all proteins and other cellular interferences, with the exception of DNA. Another resistance heater 421 is at a position that can effectively control a temperature of the separation channel on the microfluidic chip 211. The infrared heating unit is at a position that can direct heat to the thermal control domain of the microfluidic chip 211 on the sample cartridge 215. The cooling fan is at a position that can effectively disperse heat from the thermal control domain. Further, the UM 410 includes a high voltage module that can apply suitable high voltages via the electrode reservoirs of the microfluidic chip 211.

[0088] It is noted that the UM 410 can include other suitable components. In an embodiment, the UM 410 includes a magnetic module that can suitably apply magnetic control over a domain of the microfluidic chip 211.

[0089] The APM 430 includes suitably components, such as pumps, vacuums, and the like, to apply suitable pressures to the microfluidic chip 211 to enable fluid movement.

[0090] The PM 460 receives an input main power, and generates various operation powers, such as 6 V, 12 V, 24 V, 1000V, 2000V, and the like, for various components of the DNA analyzer 400.

[0091] The detection module 450 can include a laser module (LM) 451, a passive optics module (POM) 452, and an active optics module (AOM) 453. The LM 451 can include any suitable device to emit a laser beam. In an embodiment, the LM 451 includes an argon-ion laser. In another example, the LM 451 includes a diode laser. In another embodiment, the LM 451 includes a solid state laser, such as a coherent sapphire optically pumped semiconductor laser. The solid state laser can have a reduced size and weight, and can consume less power than the argon-ion laser. In addition, the solid state laser generates less waste heat, such that fan size can be reduced to reduce footprint of the DNA analyzer 400.

[0092] The AOM 453 includes optical elements that may need to be adjusted with regard to each inserted microfluidic chip. In an example, the AOM 453 includes a plurality of optical fibers that are respectively coupled to a plurality of separation channels on the microfluidic chip. The plurality of optical fibers can respectively provide laser beams to the

plurality of separation channels to excite fluorescence emission. In addition, the plurality of optical fibers can return the emitted fluorescence from the plurality of separation channels.

[0093] The POM 452 includes various optical elements, such as lens, splitters, photo-detectors, and the like, that do not need to be adjusted with regard to each inserted microfluidic chip. In an example, the POM 452 is calibrated and adjusted with regard to the LM 451 and the AOM 453 when the detection module 450 is assembled. Then, the optical elements within the POM 452 are situated at relatively fixed positions, and do not need to be adjusted with regard to each inserted microfluidic chip.

[0094] The controller module 480 is coupled to the various components of the DNA analyzer 400 to provide control signals for DNA analysis. The controller module 480 includes a control procedure that determines sequences and timings of the control signals.

[0095] The computing module 470 is implemented as a personal computer. The personal computer includes a processor, a memory storing suitable software, a keyboard, a display, and a communication interface. The computing module 470 can provide a user interface to ease user control and monitor of the DNA analysis by the DNA analyzer 400.

[0096] Fig. 5 shows a flow chart outlining a process example for using a DNA analyzer, such as the DNA analyzer 400, to perform DNA analysis according to an embodiment of the disclosure. The process starts at S501, and proceeds to S510.

[0097] At S510, a user of the DNA analyzer 400 plugs in a main power supply. In an embodiment, the main power supply can be a 110 V, 50 Hz, AC power supply, or can be a 220V, 60 Hz, AC power supply. The power module 460 can convert the main power supply to a plurality of operation powers, and provide the plurality of operation powers to the various modules of the DNA analyzer 400. Then, the process proceeds to S515.

[0098] At S515, the user starts up a user control interface. For example, the user turns on the personal computer 470, and starts a software package that interacts with the user and the controller module 480. The software package enables the personal computer 470 to provide a user control interface on the display. Further, the software package enables the personal computer 470 to receive user instructions via the keyboard or mouse. The software packages can also enable the personal computer 470 to communicate with the controller module 480. Then, the process proceeds to S520.

[0099] At S520, the user instructs the DNA analyzer 400 to initialize. The user control interface receives the initialization instruction, and the software package enables the personal computer 470 to send the initialization instruction to the controller module 480. The

controller module 480 can then initialize the various components of the DNA analyzer 400. For example, the controller module 480 can power on the various components, check the status and reset the status if needed. Then, the process proceeds to S525.

[0100] At S525, the user inserts a sample cartridge 215 in the UM 410. The sample cartridge 215 can be positioned by a holder. The interface components can suitably couple the sample cartridge 215 to other components of the DNA analyzer 400. Then, the process proceeds to S530.

[0101] At S530, the user takes a swab 205, and lets the DNA analyzer 400 to identify the swab 205. In an example, the DNA analyzer 400 includes a barcode reader that can read the barcode label 204 attached to the case 203 for storing the swab 205. In another example, the DNA analyzer 400 excites the RFID 201 implanted in the seal cap 202 of the swab 205 to obtain a unique serial number of the swab 205. Then, the process proceeds to S535.

[0102] At S535, the user uses the swab 205 to take a DNA sample and inserts the swab 205 into a well of the sample cartridge 215. The user may repeat the steps S530 and S535 to insert multiple swabs 205 into the separated wells of the sample cartridge 215. Then, the process proceeds to S540.

[0103] At S540, the user instructs the DNA analyzer 400 to start a DNA analysis. The user control interface receives the start instruction, and the software package enables the personal computer 470 to send the start instruction to the controller module 480. The controller module 480 can start a control procedure corresponding to the DNA analysis. In an example, the controller module 480 starts an STR typing procedure corresponding to a multiplexed STR typing analysis. In another example, the controller module 480 starts a sequencing procedure corresponding to DNA sequencing analysis. Then, the process proceeds to S545.

[0104] At S545, the user waits and monitors the status of the DNA analysis. The control procedure can specify sequences and timings of control signals to various components of the DNA analyzer 400 corresponding to the DNA analysis. Then, the controller module 480 automatically sends the control signals according to the sequences and the timings specified in the control procedure. In addition, the controller module 480 receives status and feedback signals from the various components, and sends them to the personal computer 470. The personal computer 470 then provides the analysis status for the user to monitor. Then, the process proceeds to S550.

[0105] At S550, the controller module 480 finishes executing the control procedure, and sends an analysis-completed status to the personal computer 470. The personal computer 470 can inform the user of the analysis-completed status via the user control interface. Then, the process proceeds to S555.

[0106] At S555, the user performs post data processing. The user can store the raw data of the DNA analysis, or transmit the raw data to a remote receiver. In addition, the user may start a software package for post data processing. Alternatively, the software package for post data processing can be suitably integrated with the control procedure. Thus, after the control procedure is successfully executed, the software package for post data processing is executed automatically to perform post data processing. The process then proceeds to S599 and terminates.

[0107] It is noted that to perform another DNA analysis, the user may throw away the sample cartridge and repeat S520-S550. It is also noted that the sequence of the DNA analysis steps can be suitably adjusted. For example, S535 and S530 can be swapped, thus a swab can be first used to take a DNA sample, and then identified by the DNA analyzer 400.

[0108] Fig. 6 shows a flow chart outlining a process example 600 for a DNA analyzer to perform multiplexed STR typing according to an embodiment of the disclosure. The process starts at S601 and proceeds to S610.

[0109] At S610, the controller module 480 controls the resistance heater 421 to maintain a temperature for template DNA extraction and purification. More specifically, the resistance heater 421 is positioned corresponding to the plurality of wells on the sample cartridge 215. A well can accept a swab 205. The swab 205 can puncture the membrane that seals the liquid phase mixture at the bottom of the well, thus the swab 205 is immersed into the liquid phase mixture. The liquid phase mixture can extract and purify a template DNA from the swab at the temperature according to enzymatic DNA isolation method. In an embodiment, the liquid phase mixture can achieve a compatible DNA concentration and purity to silica based solid phase extraction method in about 6 minutes. Then, the process proceeds to S620.

[0110] At S620, the controller module 480 controls the APM 430 to flow the extracted template DNA and reagents to a reaction reservoir for the PCR amplification. For example, the reagent carrier 206 houses reagents for multiplexed STR amplification. The controller module 480 sends control signals to the APM 430. In response to the control signals, a pump pumps the liquid phase mixture from the well to the reaction reservoir, and

another pump pumps the reagents from the reagent carrier 206 to the reaction reservoir. Then, the process proceeds to S630.

[0111] At S630, the controller module 480 controls the cooling fan 422 and the infrared heating unit 423 to induce thermal cycling in the reaction reservoir for the multiplexed STR amplification. In addition, the reagents can attach fluorescent labels to the DNA amplicons during the STR amplification process. The process then proceeds to S640.

[0112] At S640, after the PCR amplification, the solution can be diluted. More specifically, the controller module 480 sends control signals to the APM 430 after the PCR amplification. In response to the control signals, the APM 430 flows the DNA amplicons into a dilution reservoir. In addition, the APM 430 flows a dilution solution from the reagent carrier into the dilution reservoir. The process then proceeds to S650.

[0113] At S650, the controller module 480 sends control signals to the high voltage module in the UM 410 to inject the DNA amplicons across the injection arm (the short channel 317a). Then, the process proceeds to S660.

[0114] At S660, the controller module 480 sends control signals to the high voltage module in the UM 410 to apply appropriate high voltage over the separation channel (the long channel 317b) to separate the DNA amplicons based on sizes. The process then proceeds to S670.

[0115] At S670, the controller module 480 sends control signals to the detection module 450 to excite the fluorescent labels to emit fluorescence and detect the emitted fluorescence. The raw detection data can be sent to the personal computer 470 for storage and post-processing. The process then proceeds to S699, and terminates.

[0116] It is noted that some process steps in the process 600 can be executed in parallel. For example, the step S660 and the step S670 can be executed in parallel. The controller module 480 sends control signals to both the high voltage module in the UM 410 and the detection module 450 at about the same time. The control signals to the high voltage module in the UM 410 cause the electrophoretic separation in the separation channel, while the control signals to the detection module 450 cause fluorescence detection.

[0117] It is noted that the process 600 can be suitably adjusted along with reagents adjustments for other DNA analysis, such as qPCR DNA quantitation, sequencing, and the like.

[0118] In a qPCR DNA quantitation example, step S601 to S630 are executed, and step S640 to S670 can be deleted. In addition, in step S630, when thermal cycles are induced

in a qPCR reservoir for PCR amplification, the controller module 480 sends control signals to the detection module 450 to detect fluorescence emitted by the fluorescent labels in the qPCR reservoir.

[0119] It is also noted that a magnetic solid phase purification process step can be suitably added into the process 600 to facilitate further volume reduction, thus the process 600 can be adjusted for DNA sequencing.

[0120] Fig. 7 shows a block diagram of an exemplary detection module 750 coupled with an exemplary sample cartridge 715 having a microfluidic chip 711 according to an embodiment of the disclosure. The detection module 750 can be suitably installed in a DNA analyzer, such as the DNA analyzer 100, or the DNA analyzer 400. Further, the detection module 750 can be coupled with other components, such as a controller module of the DNA analyzer. The controller module can control the detection module 750, and other modules, such as thermal module, pressure module, high voltage module, and the like, to act on the microfluidic chip 711 to perform an integrated single-chip DNA analysis. The detection module 750 includes a laser module 751, a passive optics module 752 and an active optics module 753. These elements can be coupled together as shown in Fig. 7.

[0121] The microfluidic chip 711 can be configured for an integrated single-chip DNA analysis, such as the microfluidic chip 311 shown in Fig. 3. The microfluidic chip 711 includes various domains that can be suitably configured for various purposes. For example, the microfluidic chip 711 includes a first domain configured for PCR amplification and a second domain having a separation channel configured for electrophoretic separation. Additionally, the microfluidic chip 711 includes, for example, purification domain, post-PCR clean-up/dilution domain, and the like.

[0122] The detection module 750 is optically coupled to the microfluidic chip 711. As described above, the microfluidic chip 711 includes a separation channel configured for electrophoretic separation of DNA fragments. The DNA fragments migrate in the separation channel based on their sizes. The DNA fragments can be suitably tagged with fluorescent labels. The fluorescent labels can be optically detected by the detection module 750. Based on the detected fluorescent labels, DNA analyses, such as identification, sequencing, and the like, can be suitably performed.

[0123] More specifically, the detection module 750 directs a laser beam to a location of the separation channel along the migration direction of the DNA fragments. The laser beam can excite the fluorescent labels attached to the DNA fragments to emit

fluorescence when the DNA fragments migrate through the location. The detection module 750 collects the emitted fluorescence and detect properties of the fluorescence, such as intensity, wavelength, timing, and the like. The detected properties can be suitably stored, and analyzed.

[0124] The laser module 751 can include any suitably laser device, such as an argon-ion laser device, a solid state laser, and the like, to generate the laser beam. In an example, the laser module 751 includes a coherent sapphire optically pumped semiconductor laser (OPSL) outputs a laser beam of 488 nm wavelength, and has an output power of 200 mW. The laser module 751 provides the laser beam to the passive optics module 752 via any suitable optical channel, such as an optical fiber, and the like.

[0125] The passive optics module 752 interfaces with the active optics module 753 and the laser module 751. The passive optics module 752 receives the laser beam from the laser module 751 and transmits the laser beam to the active optics module 753. On the other side, the passive optics module 752 receives an optical signal returned by the active optics module 753. Further, the passive optics module 752 converts the optical signal into an electrical signal, and suitably processes the electrical signal.

[0126] The passive optics module 752 includes various optical components, such as a set of optics 790 and a photo-detector 799, that are generally situated at substantially fixed positions. In an example, the optical components within the passive optics module 752 are pre-calibrated and fixed at their calibrated positions by the manufacture. In another example, the optics components are calibrated with regard to the active optics module 753 and the laser module 751 when the detection module 750 is assembled together. Then, the optical components are situated at their calibrated positions, and do not need to be adjusted for every sample cartridge 715. It is noted that the passive optics module 752 may adjust the optical components, for example, during a maintenance procedure.

[0127] The active optics module 753 receives the laser beam from the passive optics module 752, and suitably directs the laser beam to the separation channel on the microfluidic chip 711. On the other hand, the active optics module 753 collects fluorescence emitted by the fluorescent labels into an optical signal, and transmits the optical signal to the passive optics module 752.

[0128] The active optics module 753 includes optical components that may need to be adjusted for each sample cartridge 715. In the Fig. 7 example, the active optics module 753 includes a motor 756 coupled to an objective lens 791. The motor 756 can adjust the

objective lens 791 to focus the laser beam onto a location of the separation channel on the sample cartridge 715.

[0129] The detection module 750 is implemented in a modular manner. Each of the laser module 751, the passive optics module 752 and the active optics module 753 can be individually handled, such as manufactured, purchased, tested, and calibrated. Further, the laser module 751, the passive optics module 752 and the active optics module 753 can be suitably coupled together, and assembled in a DNA analyzer. During operation, the active optics module 753 can be calibrated with regard to the microfluidic chip 711 on the sample cartridge 715. The laser module 751 and the passive optics module 752 do not need to be adjusted for every sample cartridge 715.

[0130] During operation, for example, when a new sample cartridge 715 is installed in a DNA analyzer having the detection module 750, the DNA analyzer can start an initialization process to calibrate the detection module 750 with regard to a microfluidic chip 711 on the sample cartridge 715. During the initialization process, the motor 756 aligns the objective lens 791 to a separation channel on the microfluidic chip 711. In an example, the microfluidic chip 711 includes an alignment mark to assist the active optics module 753 to align the objective lens 791 to a desired location on the separation channel.

[0131] Further, the DNA analyzer starts a control procedure to control the various components of the DNA analyzer to act on the microfluidic chip 711 in order to perform an integrated single-chip DNA analysis. For example, template DNA can be suitably extracted and fluidically directed to the first domain of the microfluidic chip 711; a PCR amplification can be suitably induced in the first domain of the microfluidic chip 711 to amplify DNA fragments; then the amplified DNA fragments are suitably injected into the separation channel of the microfluidic chip 711; and then electrophoretic separation can be suitably induced in the separation channel. In addition, the detection module 750 can be controlled to direct a laser beam to the separation channel to excite fluorescent labels used to tag the DNA fragments. The fluorescent labels emit fluorescence. The detection module 750 collects the fluorescence into an optical signal, returns the optical signal, and detects fluorescence information in the optical signal. The detected fluorescence information can be suitably stored, and further processed by the DNA analyzer, or can be transmitted to other device for further processing.

[0132] Fig. 8 shows a block diagram of an optics module 852 coupled with a microfluidic chip 811 and a laser module 851 according to an embodiment of the disclosure.

The optics module 852 includes an objective lens 891, a dichroic mirror 892, a long pass filter 889, a front surface mirror 893, a pinhole 894, a first acromat lens unit 895, an acousto-optic tunable filter (AOTF) 896, a beam block 897, a second acromat lens unit 898, and a photomultiplier tube (PMT) 899. These elements can be suitably coupled together as shown in Fig. 8.

[0133] The laser module 851 emits a laser beam. The laser beam is directed to a separation channel on the microfluidic chip 811 via a first path P1 formed by the elements of the optics module 852. The laser beam can excite fluorescent labels in the separation channel to emit fluorescence. The emitted fluorescence is collected into an optical signal, and suitably returned to the PMT 899 via a second path P2 formed by the elements of the optics module 852.

[0134] The first path P1 includes the dichroic mirror 892 and the objective lens 891. The dichroic mirror 892 is configured to reflect light or allow light to pass through based on wavelength. In an example, the dichroic mirror 892 is configured to reflect light when the wavelength of the light is about 488 nm, and allow light to pass through when the wavelength of the light is larger than 525 nm. Thus, when the laser module 851 is configured to generate the laser beam having a wavelength of 488 nm and the laser beam is suitably directed to the dichroic mirror 892, the dichroic mirror 892 reflects the laser beam. The reflected laser beam is directed to the objective lens 891. The objective lens 891 focuses the laser beam to the separation channel on the microfluidic chip 811. In an embodiment, the objective lens 891 is coupled with a motor (not shown). The motor is used to adjust the objective lens 891 to focus the laser beam to the separation channel on the microfluidic chip 811.

[0135] The second path P2 includes the objective lens 891, the dichroic mirror 892, the long pass filter 889, the front surface mirror 893, the pinhole 894, the first acromat lens unit 895, the AOTF 896, the beam block 897, the second acromat lens unit 898, and the PMT 899.

[0136] The objective lens 891 collects the fluorescence emitted by the fluorescent labels to form an optical signal, and return the optical signal to the dichroic mirror 892. The fluorescent labels can be suitably selected, such that the wavelength of the emitted fluorescence is larger than 525 nm. Thus, the dichroic mirror 892 allows the fluorescence emitted by the fluorescent labels to pass through, and directs the passed optical signal to the long pass filter 889. The long pass filter 889 further filters the optical signal. More

specifically, the long pass filter 889 can be suitably configured to allow the emitted fluorescence to pass through, and filter out shorter wavelengths from the optical signal.

[0137] The front surface mirror 893 is used to change the direction of the optical signal, and thus directs the optical signal to the pinhole 894. The pinhole 894 is configured to block a scattered portion in the optical signal. In an example, the pinhole 893 has a diameter about 1000 μm . The first acromat lens unit 895 is used to focus the optical signal onto the AOTF 896.

[0138] The AOTF 896 is an electrically tunable optical filter. In an example, the AOTF 896 includes an optically birefringent crystal, such as tellurium dioxide (TeO_2). When the AOTF 896 receives an electrical signal having a frequency, the AOTF 896 generates an acoustic wave having the frequency. Further, the acoustic wave is launched into the crystal, and interacts with the optical signal in the crystal. As a result, a portion of the optical signal is diffracted and exits the crystal at an angle different from the rest of the optical signal. The portion of the optical signal has a wavelength that satisfies a matching condition of the crystal with the frequency of the acoustic wave. In an example, the portion of the optical signal satisfying the matching condition exits the crystal at about $\pm 5^\circ$, and the rest of the optical signal exits the crystal without diffraction. When the frequency of the electrical signal is changed, the AOTF 896 selectively diffracts another wavelength in the optical signal that satisfies the matching condition with the changed frequency.

[0139] The beam block 897 is coupled to the AOTF 896 to filter the optical signal to have the selected wavelength. More specifically, the beam block 897 blocks the undiffracted portion of the optical signal, and allows the diffracted portion of optical signal having the selected wavelength to pass through. Then, the second acromat lens unit 898 focuses filtered optical signal to the PMT 899.

[0140] The PMT 899 receives the filtered optical signal having the selected wavelength, and generates an electrical signal, such as a current signal, a voltage signal, and the like, in response to the filtered optical signal. In an example, an amplitude of the electrical signal corresponds to the intensity of the filtered optical signal.

[0141] In an embodiment, multiple fluorescent labels are used for labeling DNA fragment. The multiple fluorescent labels can emit light of different wavelengths. To detect the different wavelengths, a controller is coupled to the AOTF 896. The controller adjusts a control signal to change the frequency of the electrical signal input to the AOTF 896 in order to select different wavelengths for the filtered optical signal.

[0142] Fig. 9 shows a block diagram of a signal processing path 900 according to an embodiment of the disclosure. The signal processing path includes an AOTF module 910, a PMT detector module 920, a phase sensitive detector (PSD) module 930, a post processor module 940, a radio frequency (RF) spectral tuning module 950, and a low-frequency modulation module 960. These elements can be coupled together as shown in Fig. 9.

[0143] The RF spectral tuning module 950 includes circuits to generate an electrical signal having a tunable radio frequency (RF). In an embodiment, the RF spectral tuning module 950 includes a controller and a synthesizer coupled together. The controller can be implemented as a general controller executing software instructions, or can be implemented as application specific integrated circuit (ASIC). The controller generates a control signal indicating a radio frequency, and provides the control signal to the synthesizer. The synthesizer generates the electrical signal having the radio frequency based on the control signal. In an embodiment, the controller repetitively adjusts the control signal corresponding to multiple radio frequencies. Thus, the electrical signal generated by the synthesizer repeats the multiple radio frequencies.

[0144] It is noted that the RF spectral tuning module 950 can include other components to further process the electrical signal. In an example, the RF spectral tuning module 950 includes an RF amplifier to amplify the electrical signal in the RF domain, and reduce harmonic frequency portions in the electrical signal to clean the electrical signal. Then, the cleaned electrical signal is provided to the AOTF module 910.

[0145] The AOTF module 910 receives the electrical signal having the radio frequency. Further, the AOTF module 910 imposes an acoustic wave having the radio frequency on a crystal, such as an optically birefringent crystal. In an example, the AOTF module 910 includes a transducer, such as a piezoelectric transducer, coupled with the crystal. The transducer converts the electrical signal to the acoustic wave having the radio frequency, and launches the acoustic wave into the crystal.

[0146] In addition, the AOTF module 910 receives an optical signal collective of excited fluorescence. The AOTF module 910 filters the optical signal to select a wavelength based on the electrical signal. The wavelength satisfies a matching condition of the AOTF module 910 with the radio frequency of the electrical signal. More specifically, the acoustic wave having the radio frequency interacts with the optical signal on the crystal. As a result, a portion of the optical signal is diffracted and exits the crystal at an angle different from the rest of the optical signal. The diffracted portion of the optical signal has a wavelength that

satisfies the matching condition of the AOTF module 910 with the radio frequency. In an example, the diffracted portion of the optical signal exits the crystal at about 5-7°, and the rest of the return beam exits the crystal without diffraction.

[0147] According to an embodiment of the disclosure, the AOTF module 910 includes a beam-block to allow the diffracted portion of the optical signal to pass through, and block the un-diffracted portion of the optical signal. The filtered optical signal is suitably directed to the PMT detector 920.

[0148] It is noted that when the electrical signal repeats the multiple radio frequencies, the AOTF module 910 scans the optical signal for multiple wavelengths that respectively satisfy the matching condition of the AOTF module 910 with the multiple radio frequencies. Thus, the filtered optical signal repetitively scans the multiple wavelengths.

[0149] The PMT detector 920 receives the filtered optical signal, and generates an electrical signal corresponding the filtered optical signal. More specifically, the PMT detector 920 includes a tube that emits electrons in response to photons. The electrons can be suitably collected and used to generate the electrical signal. Thus, an amplitude of the electrical signal is proportional to the intensity of the filtered optical signal. The electrical signal is provided to the PSD module 930.

[0150] The PSD module 930 is coupled to the low frequency modulation module 960 for reducing noises in the electrical signal. More specifically, the low-frequency modulation module 960 provides a modulation signal to the AOTF module 910, and a reference signal to the PSD module 930. The modulation signal and the reference signal have a relative low frequency comparing to the radio frequencies generated by the RF spectral tuning module 950. The modulation signal is used by the AOTF module 910 to modulate the filtered optical signal. Thus, the electrical signal generated in response to the filtered optical signal is modulated by the relative low frequency. The reference signal is used by the PSD module 930 to demodulate the electrical signal to obtain a spectrally scanned electrical signal. Thus, influences of noises originated in the PMT detector module 920 can be reduced.

[0151] The spectrally scanned electrical signal can be suitably further processed, such as transferred, stored, digitalized, and the like. In the Fig. 9 example, the spectrally scanned electrical signal is processed by the post processor 940 to obtain spectrally separated signals 970. In an embodiment, the controller adjusts the control signal based on a substantially constant time interval. The post processor 940 can separate the spectrally

scanned electrical signal based on the substantially constant interval to obtain the spectrally separated signal 970. The post processor 940 can be implemented as a general processor executing software instructions for post processing, or can be implemented as ASIC.

[0152] Fig. 10 shows a flow chart outlining a process example 1000 for a controller, such as the controller 180, to control a detection module according to an embodiment of the disclosure. The process starts at S1001 and proceeds to S1010.

[0153] At S1010, the controller sends control signals to the detection module to initialize the detection module. For example, when a new sample cartridge having a microfluidic chip is installed in the DNA analyzer 100, the controller 180 sends control signals to the detection module 150 to initialize the detection module 150. In an example, the detection module 150 aligns its objective lens with regard to a separation channel on the microfluidic chip. Thus, the objective lens can direct a laser beam to a location along the separation channel, and can collect fluorescence excited by the laser beam. The process then proceeds to S1020.

[0154] At S1020, the controller determines multiple wavelengths for detection. In an example, the controller receives information about reagents used in PCR and ILS added after PCR. Based on the information, the controller determines types of fluorescent labels used to label DNA fragments, and determines the multiple wavelengths that can be emitted by the fluorescent labels. The controller may further determine radio frequencies corresponding to the multiple wavelengths, and control values to generate the radio frequencies. The controller may make determinations based on an AOTF module used to filter the fluorescence. For example, each wavelength for detection satisfies a matching condition of the AOTF module with one of the determined radio frequencies. In an example, the controller includes a look-up table to assist the controller to make determinations. The process then proceeds to S1030.

[0155] At S1030, the controller provides a control signal to the detection module. The control signal is indicative of a radio frequency. In an example, the detection module includes a synthesizer. The synthesizer generates an electrical signal having the radio frequency according to the control signal. The electrical signal can be further processed, and provided to the AOTF module. The AOTF module includes a transducer that converts the electrical signal into an acoustic wave and launches the acoustic wave into a crystal. The AOTF module also receives an optical signal. The optical signal includes fluorescence collected by the objective lens from the separation channel. The optical signal interacts the

acoustic wave on the crystal. As a result, a portion of the optical signal having a wavelength satisfying the matching condition with the radio frequency can pass the AOTF module. The process then proceeds to S1040.

[0156] At S1040, the controller maintains the control signal for a time duration. The time duration is enough for the AOTF module to settle and filter the optical signal. The filtered optical signal is converted to an electrical signal by a photo-detector, such as PMT. The electrical signal can be further processed, such as digitalized, stored, and the like.

[0157] At S1050, the controller determines whether the detection process ends. When the detection process ends, the process proceeds to S1099 and terminates; otherwise, the process proceeds to S1060.

[0158] At S1060, the controller adjusts the control signal, and provides the adjusted control signal to the detection module. The adjusted control signal is indicative of another radio frequency that can be used to select another wavelength. Similarly, the synthesizer generates the electrical signal having the other radio frequency based on the adjusted control signal. Then, the transducer in the AOTF module converts the electrical signal into an acoustic wave and launches the acoustic wave into the crystal. The acoustic wave interacts with the optical signal in the crystal. As a result, a portion of the optical signal having the other wavelength can pass the AOTF module. Then, the process returns to S1040.

[0159] While the invention has been described in conjunction with the specific exemplary embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art. Accordingly, exemplary embodiments of the invention as set forth herein are intended to be illustrative, not limiting. There are changes that may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A DNA analyzer, comprising:
 - an interface for coupling a microfluidic chip to the DNA analyzer, wherein the microfluidic chip includes:
 - a first domain configured for polymerase chain reaction (PCR) amplification of DNA fragments, the DNA fragments being tagged with fluorescent labels;
 - and
 - a second domain fluidically coupled to the first domain to receive the DNA fragments, the second domain having a separation channel for electrophoretic separation of the DNA fragments; and
 - a detection module optically coupled with the microfluidic chip that includes:
 - a laser source configured to generate a laser beam;
 - a set of optical elements configured to direct the laser beam to the separation channel to excite the fluorescent labels to emit fluorescence while the DNA fragments migrate in the separation channel, and to collect the emitted fluorescence into an optical signal;
 - a filter module configured to filter the optical signal to allow a first portion of the optical signal having a first wavelength to pass; and
 - a photo-detector configured to generate an electrical detection signal in response to the filtered optical signal.
2. The DNA analyzer of claim 1, wherein the photo-detector further comprises:
 - a photo-multiplier tube configured to generate the electrical detection signal in response to the filtered optical signal.
3. The DNA analyzer of claim 1, wherein the set of optical elements further comprise:
 - an objective lens aligned with the separation channel to direct the laser beam to the separation channel and to collect the emitted fluorescence from the separation channel.
4. The DNA analyzer of claim 3, further comprising
 - a motor configured to align the objective lens to the separation channel.
5. The DNA analyzer of claim 1, wherein the filter module further comprises:
 - an acousto-optic tunable filter (AOTF) configured to filter the optical signal to allow the first portion of the optical signal having the first wavelength to pass based on an

electrical tuning signal having a first tuning frequency, the first wavelength satisfying a matching condition of the AOTF with the first tuning frequency.

6. The DNA analyzer of claim 5, further comprising:
a controller configured to generate a control signal indicative of the first tuning frequency; and
a synthesizer configured to generate the electrical tuning signal having the first tuning frequency based on the control signal.

7. The DNA analyzer of claim 6, wherein
the controller adjusts the control signal to be indicative of a second tuning frequency, and that causes:
the synthesizer generates the electrical tuning signal having the second tuning frequency based on the control signal; and
the AOTF filters the optical signal to allow a second portion of the optical signal having a second wavelength to pass based on the electrical tuning signal, the second wavelength satisfying the matching condition of the AOTF with the second tuning frequency.

8. The DNA analyzer of claim 5, further comprising:
a modulation signal generator configured to generate a modulation signal having a modulation frequency, and a reference signal having the modulation frequency, the modulation signal being used by the AOTF to modulate the filtered optical signal; and
a phase-sensitive detector configured to receive the reference signal and the electrical detection signal corresponding to the modulated filtered optical signal, and demodulate the electrical detection signal based on the reference signal.

9. The DNA analyzer of claim 1, further comprising:
a pressure module configured to flow liquid in the microfluidic chip;
a thermal module configured to induce thermal cycling at the first domain of the microfluidic chip for the PCR amplification;
a power module configured to generate voltages to be applied to the second domain of the microfluidic chip for the electrophoretic separation; and
a controller module configured to control the pressure module, the thermal module, the power module, and the detection module according to a control procedure to act on the microfluidic chip for a single-chip DNA analysis.

10. A method of DNA analysis, comprising:

selecting a first wavelength corresponding to a first fluorescent label used to label DNA fragments during polymerase chain reaction (PCR) amplification in a first domain of a microfluidic chip, the DNA fragments having been fluidically directed from the first domain to a second domain of the microfluidic chip having a separation channel for electrophoretic separation;

exciting at least the first fluorescent label to emit fluorescence in the second domain; and

tuning a detection module to detect the emitted fluorescence having the first wavelength.

11. The method of claim 10, wherein exciting the first fluorescent label to emit the fluorescence in the second domain further comprises:

generating a laser beam; and

directing the laser beam to the separation channel to excite the first fluorescent label to emit the fluorescence while the DNA fragments migrate in the separation channel.

12. The method of claim 11, further comprising:

collecting the emitted fluorescence into an optical signal.

13. The method of claim 12, wherein tuning the detection module to detect the emitted fluorescence having the first wavelength, further comprises:

generating an electrical tuning signal having a first tuning frequency;

providing the electrical tuning signal to an acousto-optic tunable filter (AOTF) in the detection module to filter the optical signal and pass a first portion of the optical signal having the first wavelength, the first wavelength satisfying a matching condition of the AOTF with the first tuning frequency; and

detecting the filtered optical signal.

14. The method of claim 13, further comprising:

selecting a second wavelength corresponding to a second fluorescent label used to label the DNA fragments during the (PCR) amplification in the first domain;

adjusting the electrical tuning signal to have a second tuning frequency; and

causing the AOTF to filter the optical signal and pass a second portion of the optical signal having the second wavelength, the second wavelength satisfying the matching condition of the AOTF with the second tuning frequency.

15. A DNA analyzer, comprising:

an interface for coupling a microfluidic chip to the DNA analyzer, wherein the microfluidic chip includes:

a first domain configured for polymerase chain reaction (PCR) amplification of DNA fragments, the DNA fragments being tagged with fluorescent labels; and

a second domain fluidically coupled to the first domain to receive the DNA fragments, the second domain having a separation channel for electrophoretic separation of the DNA fragments;

a detection module optically coupled with the microfluidic chip that includes:

a laser source configured to generate a laser beam;

a passive optics module including passive units that are pre-configured to receive the laser beam and transmit the laser beam; and

an active optics module including at least an active unit to focus the laser beam to the separation channel to excite the fluorescent labels to emit fluorescence while the DNA fragments migrate in the separation channel, and to collect the emitted fluorescence from the separation channel into an optical signal for return, wherein the passive optics module includes:

a filter module configured to filter the optical signal to allow a first portion of the optical signal having a first wavelength to pass; and

a photo-detector configured to generate an electrical detection signal in response to filtered optical signal.

16. The DNA analyzer of claim 15, wherein the photo-detector further comprises: a photo-multiplier tube configured to generate the electrical detection signal in response to the filtered optical signal.

17. The DNA analyzer of claim 15, wherein the active optics module further comprises:

an objective lens aligned with the separation channel to direct the laser beam to the separation channel and to collect the emitted fluorescence from the separation channel.

18. The DNA analyzer of claim 17, wherein the active optics module further comprises:

a motor configured to align the objective lens to the separation channel.

19. The DNA analyzer of claim 15, wherein the filter module further comprises:

an acousto-optic tunable filter (AOTF) configured to filter the optical signal to allow the first portion of the optical signal having the first wavelength to pass based on an electrical tuning signal having a first tuning frequency, the first wavelength satisfying a matching condition of the AOTF with the first tuning frequency.

20. The DNA analyzer of claim 19, further comprising:

a controller configured to generate a control signal indicative of the first tuning frequency; and

a synthesizer configured to generate the electrical tuning signal having the first tuning frequency based on the control signal.

21. The DNA analyzer of claim 20, wherein

the controller adjusts the control signal to be indicative of a second tuning frequency, and that causes:

the synthesizer generates the electrical tuning signal having the second tuning frequency; and

the AOTF filters the optical signal to allow a second portion of the optical signal having a second wavelength to pass based on the electrical tuning signal, the second wavelength satisfying the matching condition of the AOTF with the second tuning frequency.

22. The DNA analyzer of claim 19, further comprising:

a modulation signal generator configured to generate a modulation signal having a modulation frequency, and a reference signal having the modulation frequency, the modulation signal being used by the AOTF to modulate the filtered optical signal; and

a phase-sensitive detector configured to receive the reference signal and the electrical detection signal corresponding to the modulated filtered optical signal, and demodulate the electrical detection signal based on the reference signal.

23. The DNA analyzer of claim 15, further comprising:

a pressure module configured to flow liquid in the microfluidic chip;

a thermal module configured to induce thermal cycling at the first domain of the microfluidic chip for the PCR amplification;

a power module configured to generate voltages to be applied to the second domain of the microfluidic chip for the electrophoretic separation; and

a controller module configured to control the pressure module, the thermal module, the power module, and the detection module according to a control procedure to act on the microfluidic chip for a single-chip DNA analysis.

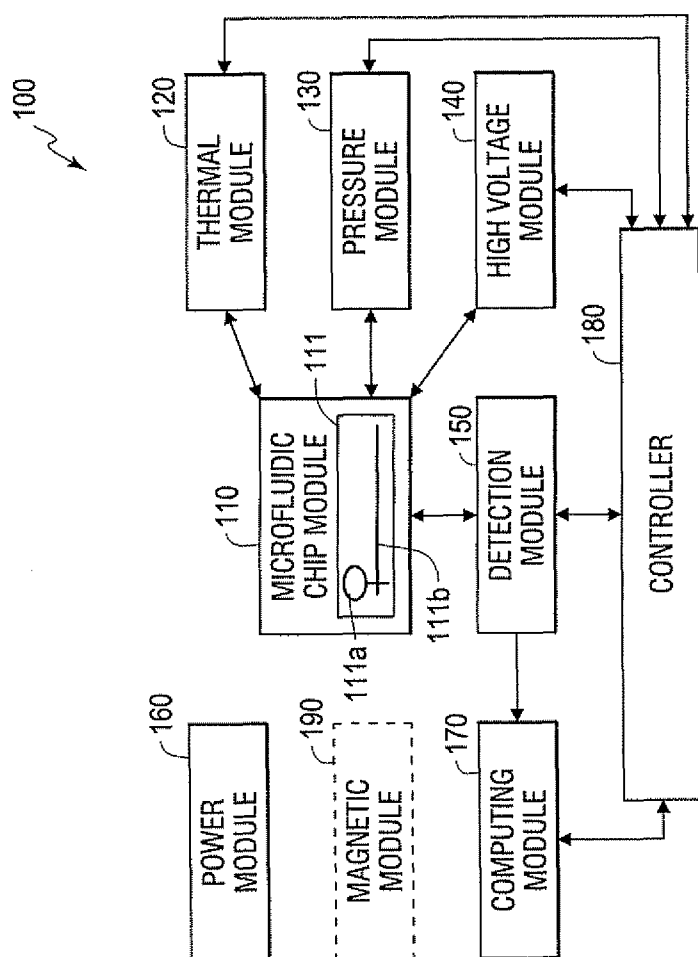


FIG. 1

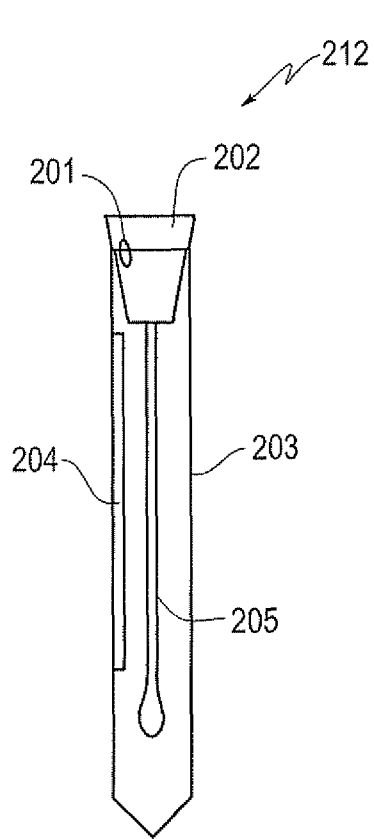


FIG. 2A

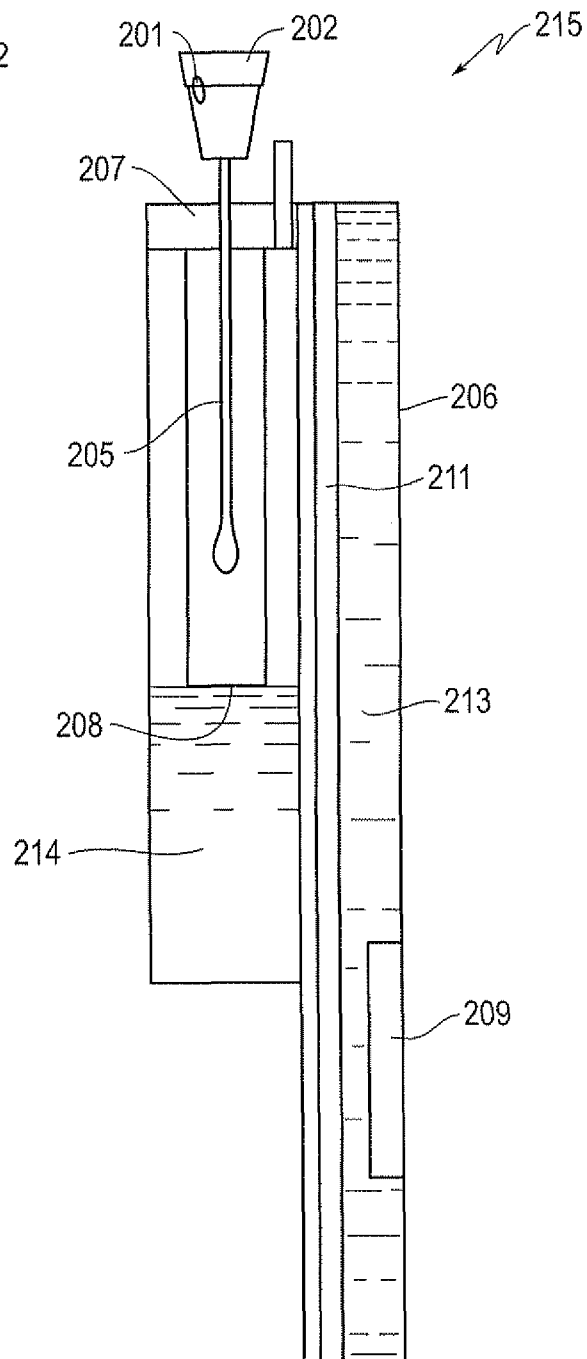


FIG. 2B

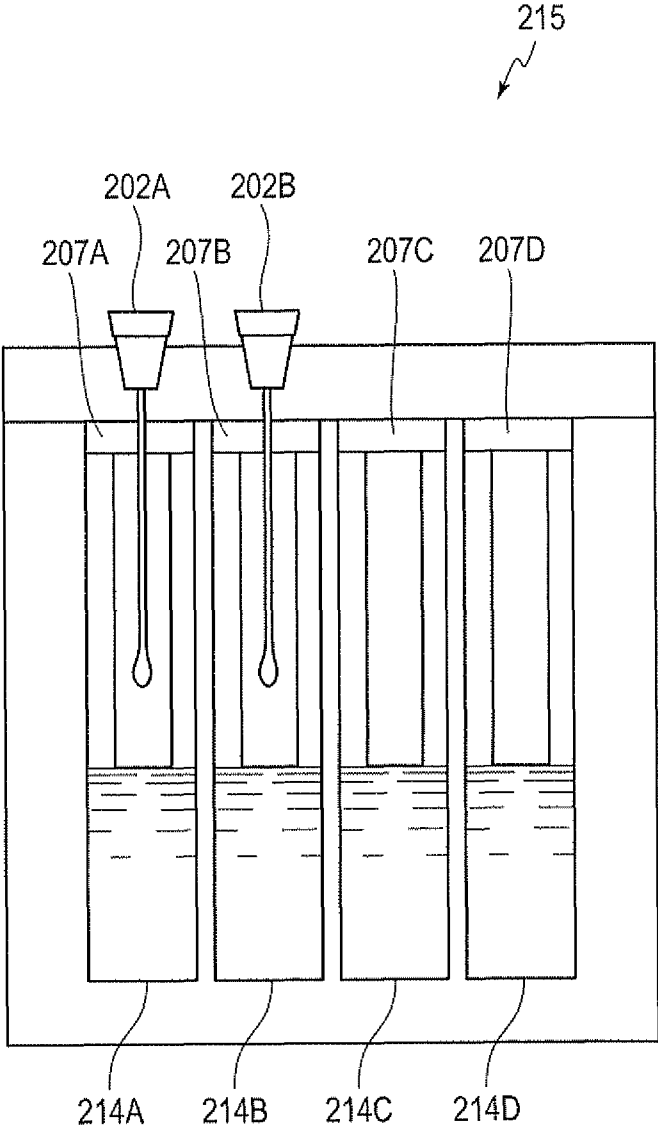


FIG. 2C

4/11

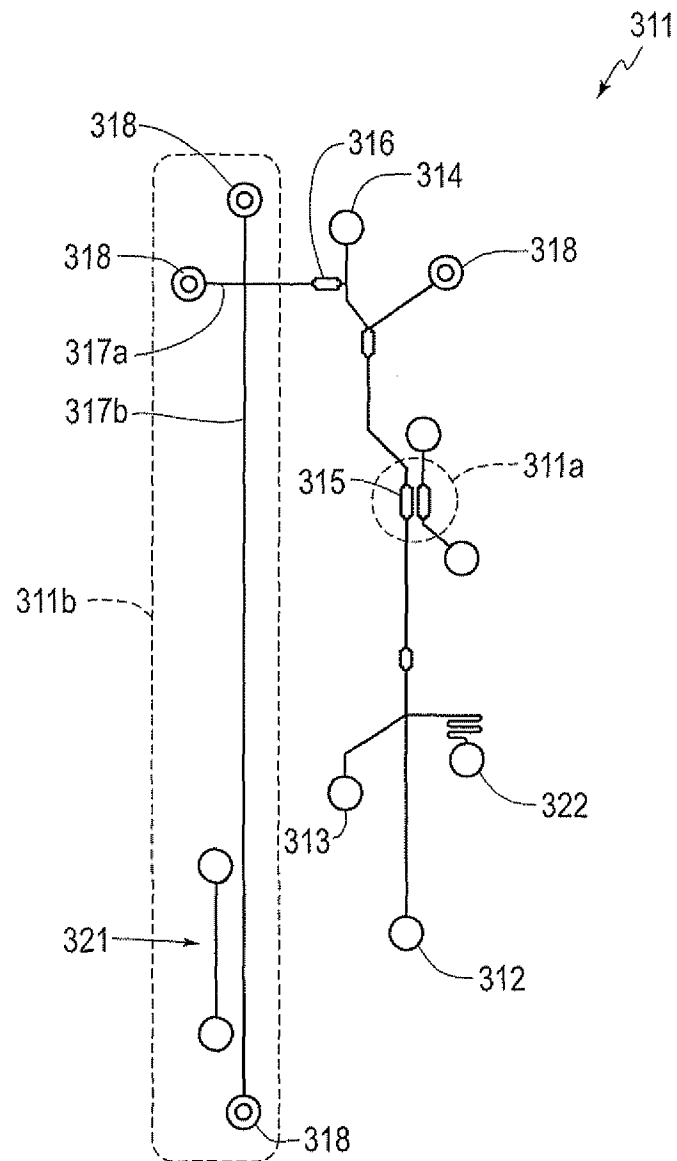


FIG. 3

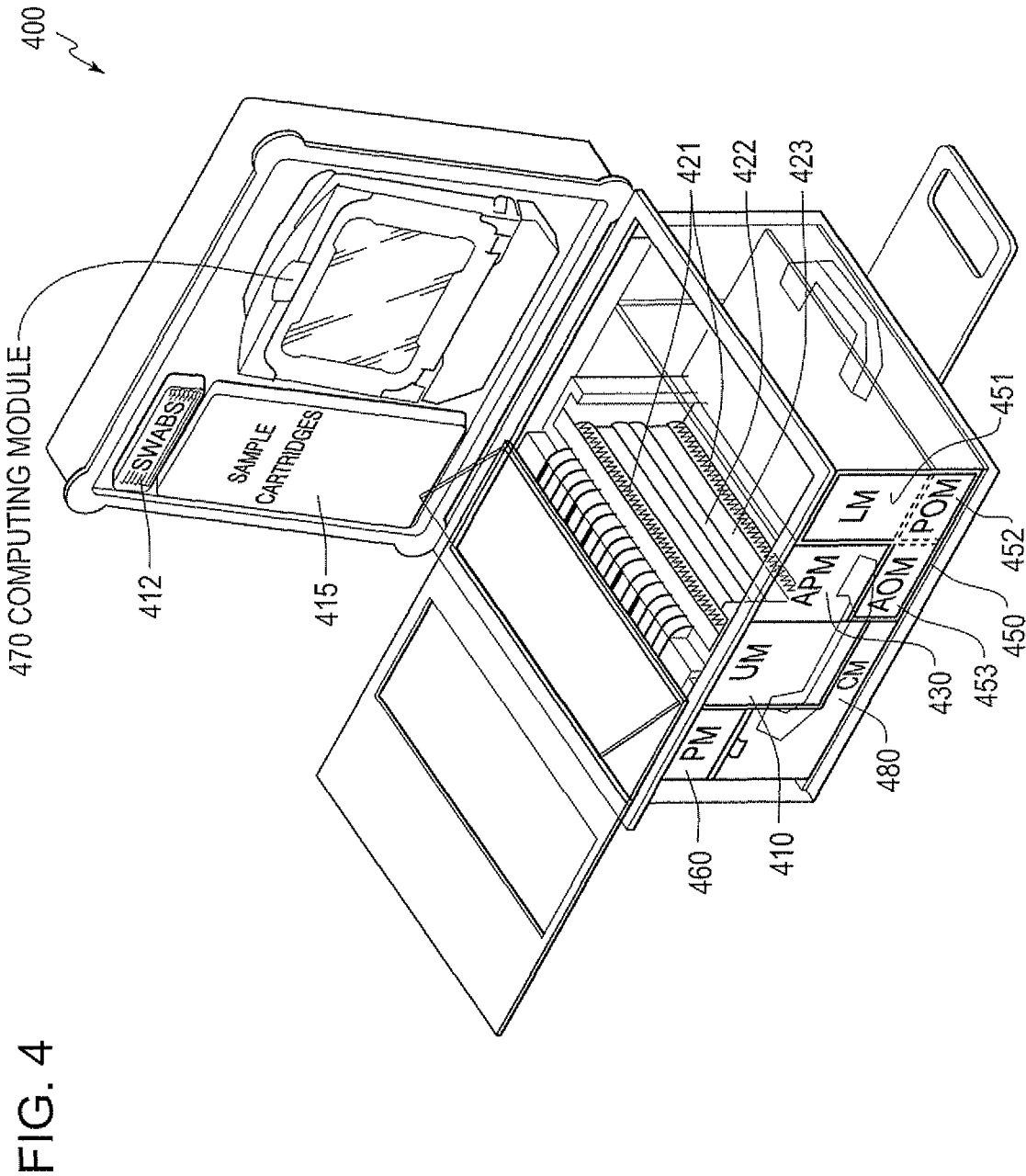
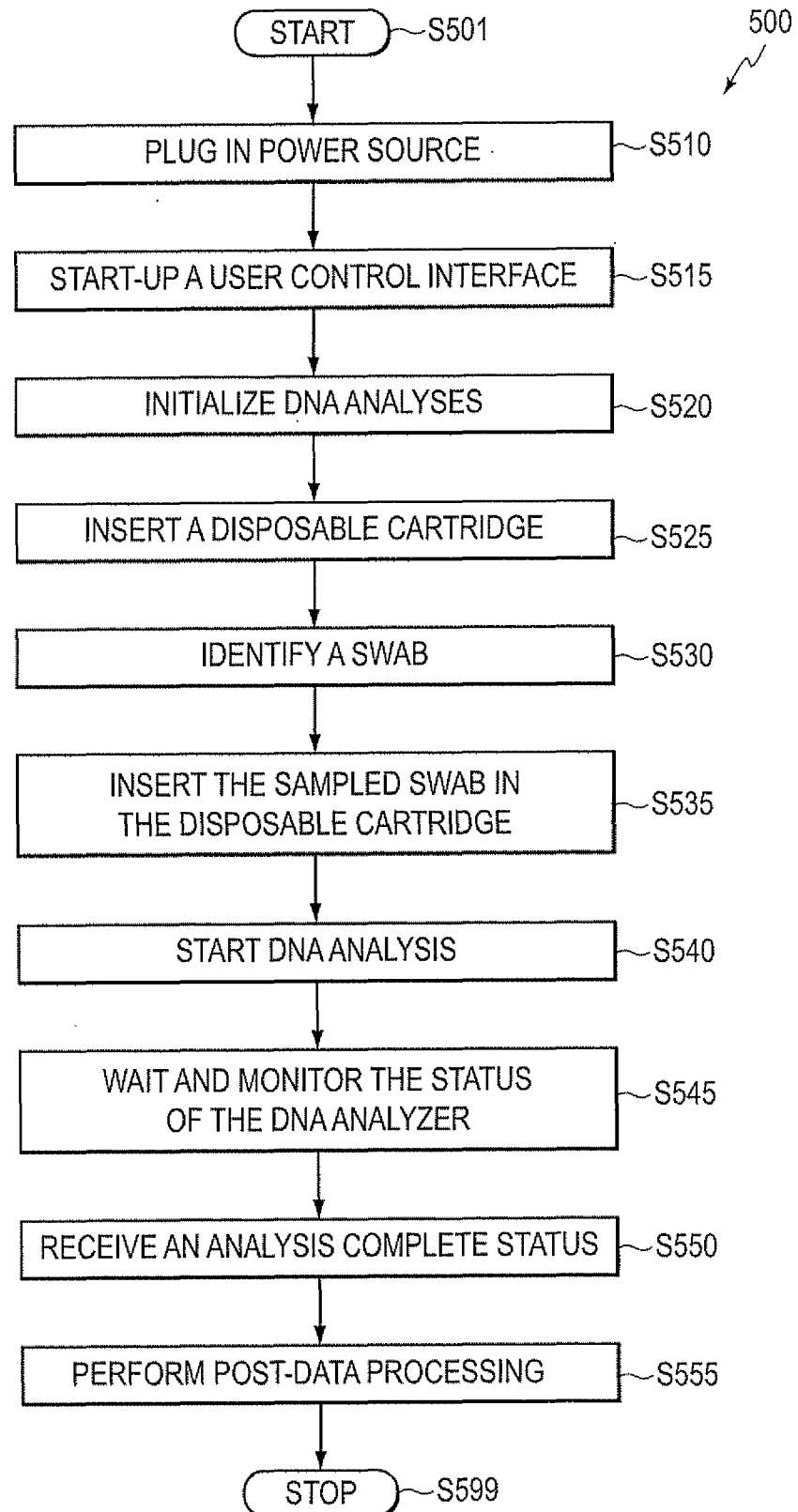


FIG. 5



7/11

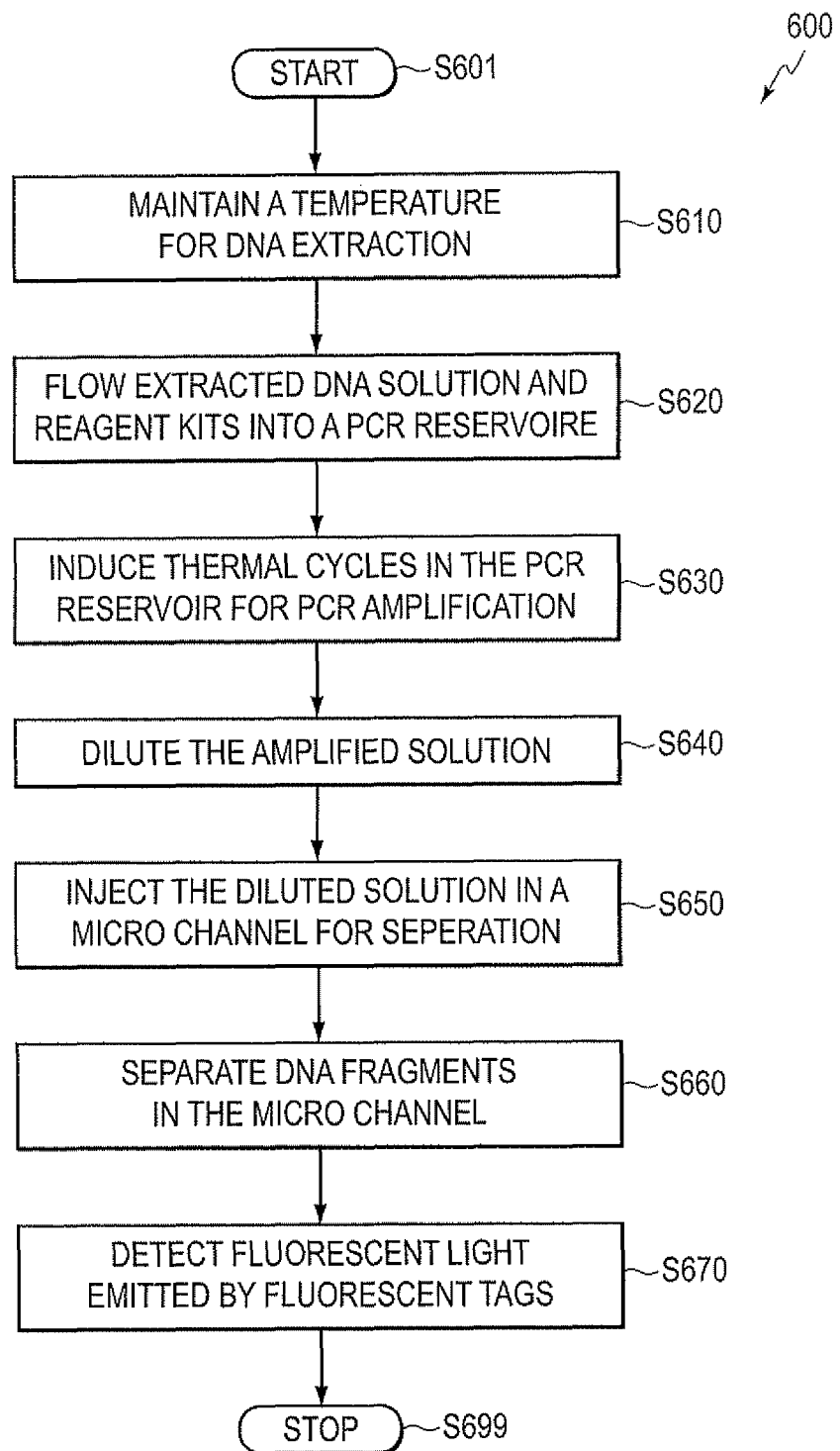


FIG. 6

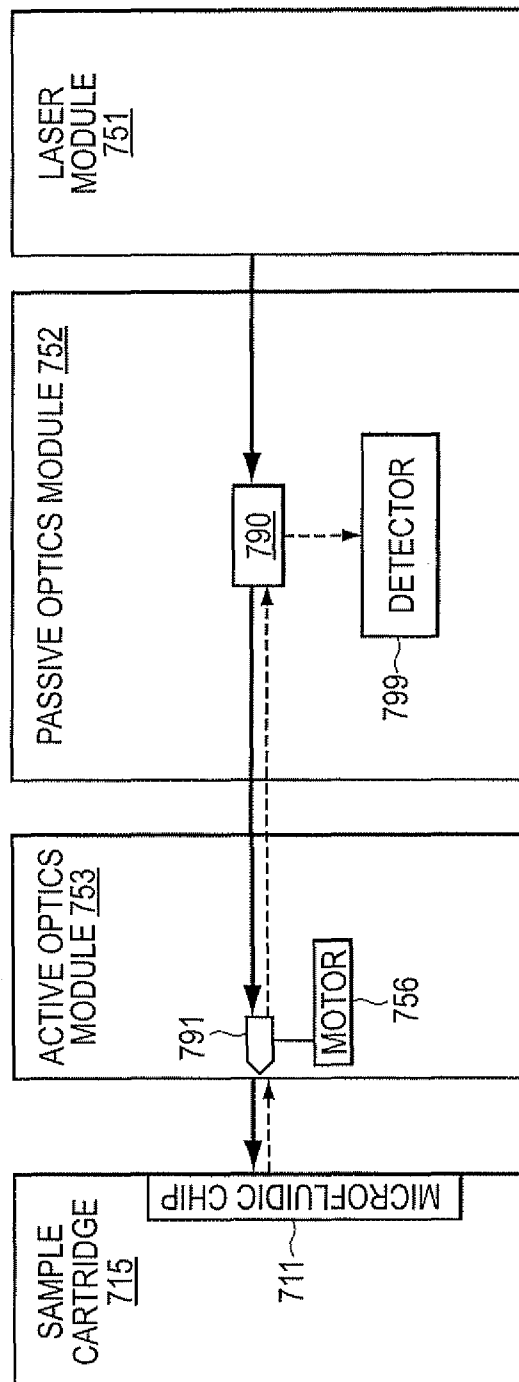


FIG. 7

9/11

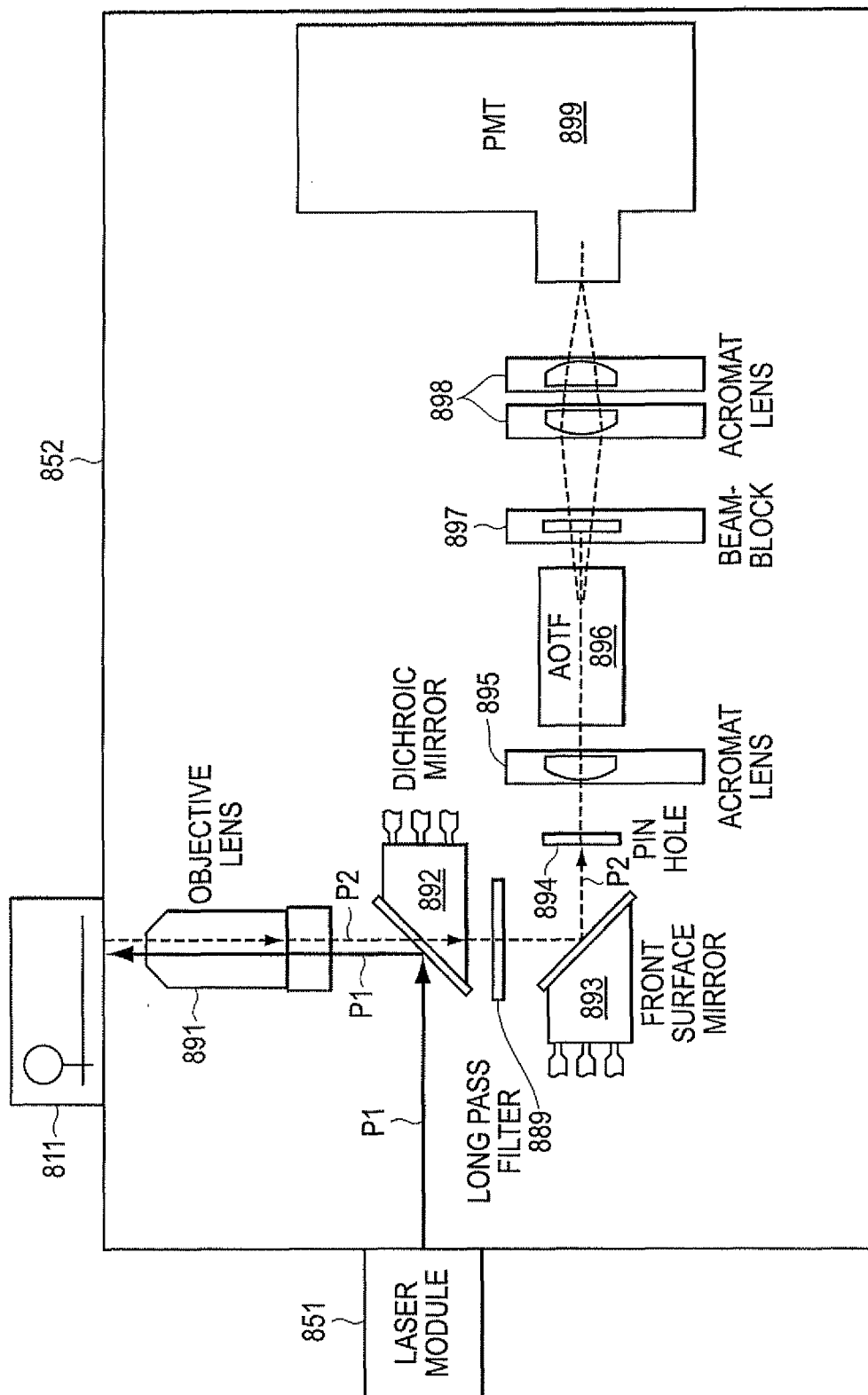


FIG. 8

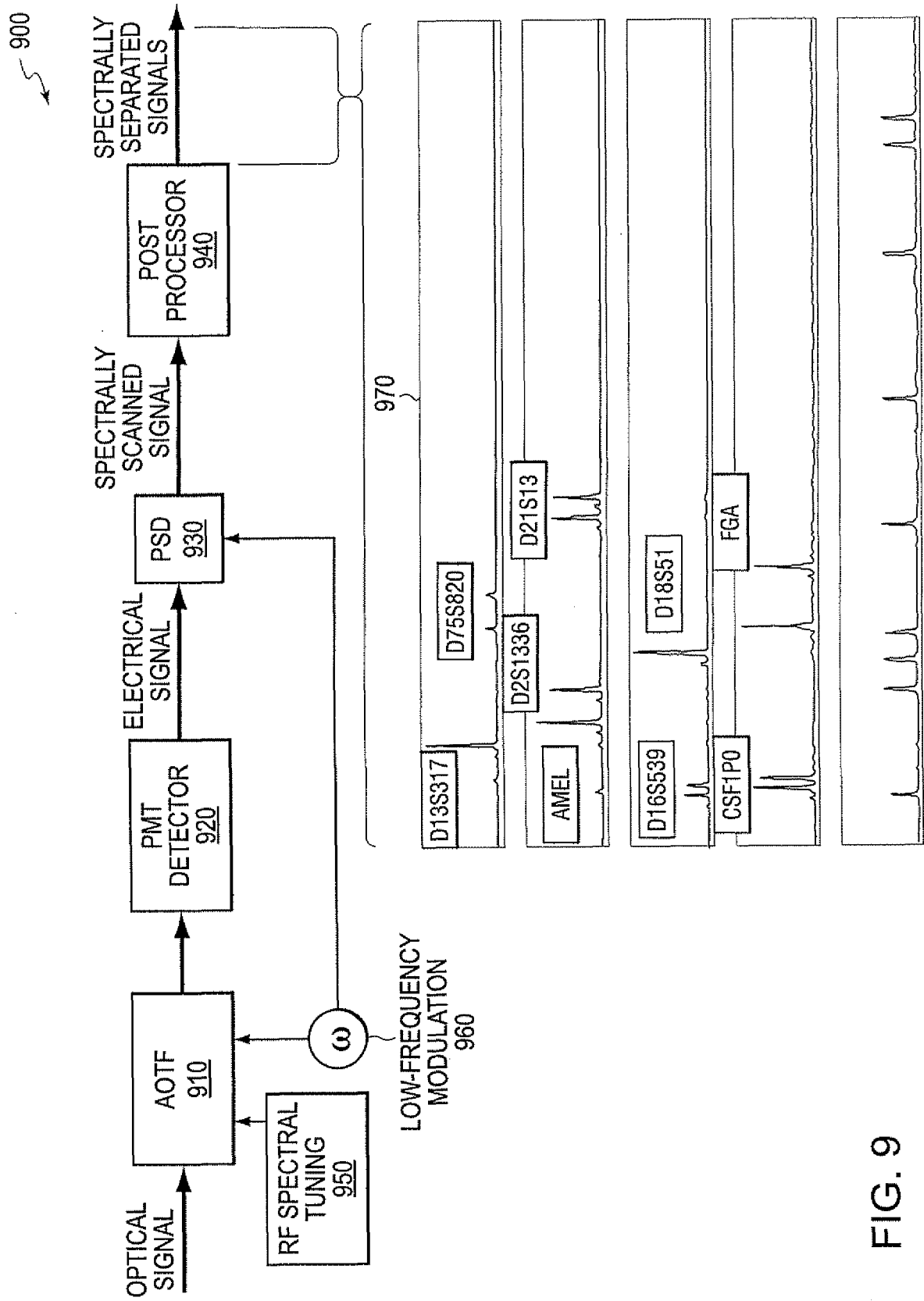


FIG. 9

11/11

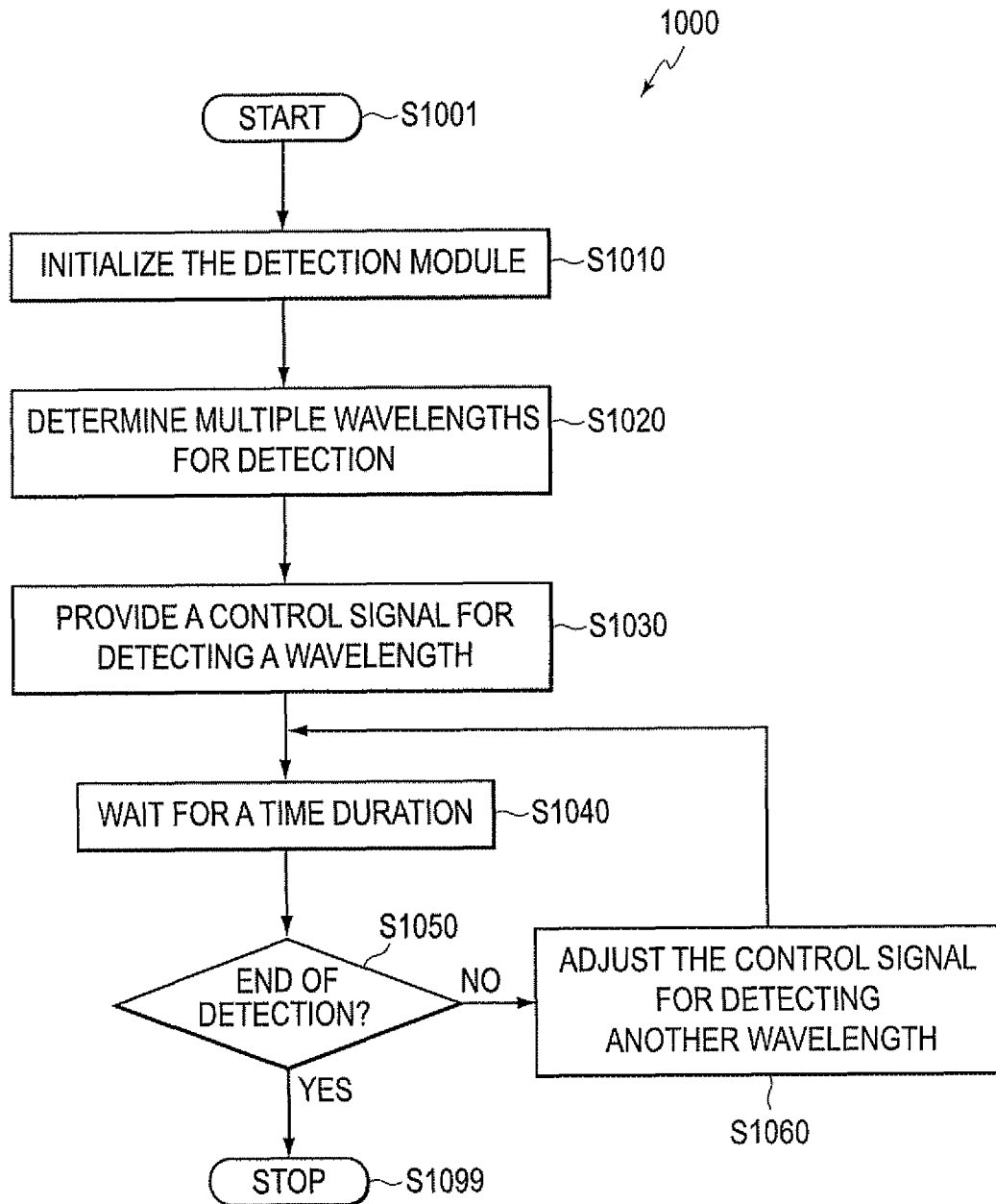


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/026801

A. CLASSIFICATION OF SUBJECT MATTER

ADD. B01L3/00

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)

B01L

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/005248 A2 (CANON U S LIFE SCIENCES INC [US]; HASSON KENTON C [US]; DALE GREGORY A) 10 January 2008 (2008-01-10) paragraphs [0023], [0 24], [0 51] - [0057]; figure 1	1-23
A	WO 2008/143646 A2 (CANON U S LIFE SCIENCES INC [US]; KNIGHT IVOR T [US]; INOUE HIROSHI [U]) 27 November 2008 (2008-11-27) the whole document	1-23
A	EP 1 584 692 A2 (TAIYO YUDEN KK [JP]) 12 October 2005 (2005-10-12) the whole document	1-23
A	US 2003/008308 A1 (ENZELBERGER MARKUS M [DE] ET AL ENZELBERGER MARKUS M [DE] ET AL) 9 January 2003 (2003-01-09) the whole document	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

22 June 2010

Date of mailing of the international search report

30/06/2010

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Skowronski, Maik

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/026801

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008005248	A2	10-01-2008	NONE
WO 2008143646	A2	27-11-2008	CN 101583724 A 18-11-2009 EP 2089542 A2 19-08-2009
EP 1584692	A2	12-10-2005	AT 375406 T 15-10-2007 CN 1680814 A 12-10-2005 CN 101012437 A 08-08-2007 DE 602005002773 T2 24-07-2008 HK 1083355 A1 01-02-2008 JP 2005295877 A 27-10-2005 US 2005266448 A1 01-12-2005 US 2007048777 A1 01-03-2007 US 2008206848 A1 28-08-2008
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