Summary

According to a first aspect of the present invention, there is provided, an instrument for biological analysis, comprising: an excitation source producing electromagnetic radiation; a sample holder configured to receive a plurality of biological samples; an optical sensor configured to receive an emission from the biological samples; an excitation optical system disposed along an excitation optical path and configured to direct the electromagnetic radiation from the excitation source to the biological samples; an emission optical system disposed along an emission optical path and configured to direct electromagnetic emissions from the biological samples to the optical sensor; a plurality of filter components configured to be interchangeably located along at least one of the optical paths, the plurality of filter components comprising: a first filter component characterized by a first optical power and a first filter having a first filter function, the first filter function characterized by at least one of a first low-pass wavelength or a first high-pass wavelength; a second filter component characterized by a second optical power and a second filter having a second filter function, the second filter function comprising at least one of a second low-pass wavelength that is different than the first low- pass wavelength or a second high-pass wavelength that is different than the first high-pass wavelength, wherein at least one of the optical powers of the plurality of filter components is greater than zero for electromagnetic radiation transmitted through a corresponding one of the filters.

According to a second aspect of the present invention, there is provided an instrument for biological analysis, comprising: an excitation source producing electromagnetic radiation; a sample holder configured to receive a plurality of biological samples; an optical sensor configured to receive an emission from the biological samples; an excitation optical system disposed along an excitation optical path and configured to direct light from the light source to the biological samples; an emission optical system disposed along an emission optical path and configured to direct light from the biological samples to the optical sensor; a plurality of optical components configured to be interchangeably located along at least one of the optical paths, the plurality of optical components comprising: a first optical component having a primary optical characteristic and a secondary optical characteristic; a second optical component having different values of the primary optical characteristic and of the secondary optical characteristic than first

optical component, wherein at least one of the optical powers of the plurality of optical components is greater than zero for electromagnetic radiation transmitted through a corresponding one of the optical components.

According to a third aspect of the present invention, there is provide an instrument for biological analysis, comprising: a light emitting diode (LED) light source producing light having wavelengths over the entire range from 450 nanometers to 700 nanometers; a sample holder configured to receive an two-dimensional array of biological samples; a two-dimensional optical sensor array; an excitation optical system disposed along an excitation optical path and configured to simultaneously direct light from the light source to the biological samples; an emission optical system disposed along an emission optical path and configured to direct light from at least some of the biological sample to the optical sensor; a first filter component comprising a first filter having a first filter function configured to transmit light over a predetermined range of wavelengths and a first refractive element having a non-zero optical power; a second filter component comprising a second filter function configured to transmit light over a range of wavelengths not included in the predetermined range of the first filter; a first configuration in which the first filter component is located along the emission optical path and the second filter component is located outside the emission optical path; and a second configuration in which the second filter component is located along the emission optical path and the first filter component is located outside the emission optical path, wherein at least one of the optical powers of the first filter and the second filter is greater than zero for electromagnetic radiation transmitted through a corresponding one of the first filter and the second filter.

According to a fourth aspect of the present invention, there is provided an instrument for biological analysis, comprising: an excitation source producing electromagnetic radiation; a sample holder configured to receive a plurality of biological samples; an optical sensor configured to receive an emission from the biological samples; an excitation optical system configured to direct light from the light source to the biological samples; an emission optical system disposed along an emission optical path and configured to form an image of the biological samples at an image plane located on or proximal the optical sensor; a plurality of filters having different transmission wavelength bands, the filters being interchangeably located

along the emission optical path; wherein the image plane of the biological samples have the same location along the emission optical path when any one of the filters is located along the emission optical path, wherein at least one of the optical powers of the plurality of filters is greater than zero for electromagnetic radiation transmitted through a corresponding one of the filters.

According to a fifth aspect of the present invention, there is provided a method for monitoring a plurality of biological samples, comprising: providing an instrument as defined in the first aspect; locating a sample array comprising a plurality of biological samples within the sample holder; locating the first ~~optical~~ filter component along the at least one of the optical paths; using the optical sensor to simultaneously record an image of the plurality of biological samples while the first ~~optical~~ filter component is located along the at least one of the optical paths; locating the first ~~optical~~ filter component away from the at least one of the optical paths and locating the second ~~optical~~ filter component along the at least one of the optical paths; using the optical sensor to simultaneously record an image of the plurality of biological samples while the second ~~optical~~ filter component is located along the at least one of the optical paths.

According to a sixth aspect of the present invention, there is provided an instrument for biological analysis, comprising: an excitation source producing electromagnetic radiation; a sample holder configured to receive a plurality of biological samples, the sample extending over a rectangular area characterized by a first aspect ratio having a first value; an optical sensor configured to receive an emission from the biological samples; an excitation optical system configured to direct the electromagnetic radiation from the excitation source to the biological samples; an emission optical system configured to direct electromagnetic emissions from at least some of the biological samples to the optical sensor; a rectangular emission filter disposed along an optical path between the sample holder and the optical sensor, the rectangular emission filter characterized by a second aspect ratio having a second value; wherein the first value is within twenty percent of the value second value, wherein an optical power of the rectangular emission filter is greater than zero for electromagnetic radiation transmitted through the rectangular emission filter.

WHAT IS CLAIMED IS:

1. An instrument for biological analysis, comprising:

an excitation source producing electromagnetic radiation;

a sample holder configured to receive a plurality of biological samples;

an optical sensor configured to receive an emission from the biological samples;

an excitation optical system disposed along an excitation optical path and configured to direct the electromagnetic radiation from the excitation source to the biological samples;

an emission optical system disposed along an emission optical path and configured to direct electromagnetic emissions from the biological samples to the optical sensor;

a plurality of filter components configured to be interchangeably located along at least one of the optical paths, the plurality of filter components comprising:

a first filter component characterized by a first optical power and a first filter having a first filter function, the first filter function characterized by at least one of a first low-pass wavelength or a first high-pass wavelength;

a second filter component characterized by a second optical power and a second filter having a second filter function, the second filter function comprising at least one of a second low-pass wavelength that is different than the first low-pass wavelength or a second high-pass wavelength that is different than the first high-pass wavelength;

wherein at least one of the optical powers of the plurality of filter components is greater than zero for electromagnetic radiation transmitted through a corresponding one of the filters.

2. The instrument of claim 1, wherein the plurality of filter components includes a third filter component comprising a third optical power and a third filter function.

3. The instrument of claim 2, wherein the third filter function comprise at least one of a third low-pass wavelength that is different than either the first low-pass wavelength or the second low-pass wavelength, or a third high-pass wavelength that is different than either the first high-pass wavelength or the second high-pass wavelength.

4. The instrument of claim 1, wherein at least one of the optical powers is about zero Diopters.

~~5. The instrument of claim 1, wherein the second optical power differs from the first optical power by an amount that is greater than zero.~~

~~6. The instrument of claim 5, wherein the second optical power differs from the first optical power by an amount that is less than or equal to one-third of a Diopter.~~

~~7. The instrument of claim 1, wherein at least one of the optical powers is greater than zero for electromagnetic radiation transmitted through a corresponding one of the filters.~~

~~8~~5. The instrument of claim 1, wherein ~~at least~~the other one of the optical powers is less than zero for electromagnetic radiation transmitted through a corresponding one of the filters.

~~9~~6. The instrument of claim 1, wherein the first optical power is zero and the second optical power is greater than zero ~~or less than zero~~.

~~10~~7. The instrument of claim 1, wherein the plurality of filter components has a first condition in which the first filter component is disposed along the emission optical path and a second condition in which second filter component is disposed along the emission optical path, the second optical power differing from the first optical power by an amount sufficient to at least partially compensate for an aberration introduced by the second filter relative to the first filter.

~~11~~8. The instrument of claim ~~10~~7, wherein the aberration is a chromatic aberration.

~~12~~9. The instrument of claim ~~10~~7, wherein the aberration is a sphero-chromatic aberration.

~~13~~10. The instrument of claim 1, wherein the first filter component comprises a single optical element characterized by the first optical power and a first filter function.

~~14~~11. The instrument of claim 1, wherein the filter components are configured to be interchangeably located along the emission optical path.

~~15~~12. The instrument of claim 1, wherein the plurality of filter components comprises at least two interchangeable optical elements having differing optical powers and at least two interchangeable filters having differing filter functions, the at least two optical elements being selectable independently of the at least two filters.

~~16~~13. The instrument of claim 1, wherein the first filter component comprises a first optical element characterized by the first optical power and a second optical element characterized by the first filter function and an optical power of zero Diopters or about zero Diopters.

~~17~~14. The instrument of claim ~~16~~13, wherein the first optical element is disposed proximal the second optical element.

~~18~~15. The instrument of claim ~~16~~13, wherein the first optical element and the second optical element are attached to a common fixture so that they move together when located in the at least one of the optical paths.

~~19~~16. The instrument of claim ~~16~~13, wherein the first optical element comprises one or more of a refractive lens, a curved mirror, a diffractive optical element, or a holographic optical element.

~~20~~17. The instrument of claim 1, further comprising a first lens element and a second lens element, the lens elements having positive optical power and disposed along the emission optical path, the first lens element disposed between the optical sensor and one of the filter component, the second lens element disposed between the one of the filter components and the sample holder.

~~21~~18. The instrument of claim ~~20~~17, wherein the lens elements comprise one or more of a refractive lens, a Fresnel lens, a curved mirror, a diffractive optical element, a holographic optical element.

~~22~~19. The instrument of claim ~~20~~17, wherein the second lens element is disposed along the excitation optical path.

~~23~~20. The instrument of claim ~~20~~17, further comprising a beamsplitter disposed along the emission optical path, the second lens element and the beamsplitter disposed along the excitation optical path.

~~24~~21. The instrument of claim ~~20~~17, wherein the first lens element comprises a commercially available camera lens and the second lens element comprises a biconvex lens.

~~2522~~. The instrument of claim ~~2017~~, wherein the excitation source comprises an LED light having a spectrum, the spectrum comprising a relative power of at least 10 percent over a wavelength range from 470 nanometers to 660 nanometers.

~~2623~~. The instrument of claim 1, wherein the optical sensor comprises a charge coupled device (CCD) detector array, a complementary metal–oxide–semiconductor (CMOS) detector array, or at least one photomultiplier detector.

~~2724~~. The instrument of claim 1, wherein the optical sensor comprises a charge coupled device CCD detector array or a complementary metal–oxide–semiconductor CMOS detector array comprising at least 4,000,000 pixels.

~~2825~~. The instrument of claim 1, further comprising a sample holder retained by the sample holder containing a plurality of discrete biological samples.

~~2926~~. The instrument of claim ~~2825~~, wherein the biological samples comprise one or more of an oligonucleotide, a DNA molecule, an RNA molecule, a chromosome, or a protein molecule.

~~3027~~. The instrument of claim ~~2825~~, wherein the plurality of discrete biological samples are disposed in a corresponding plurality of containers.

~~3128~~. The instrument of claim ~~3027~~, wherein the plurality of containers comprise one or more of a plurality of vessels, wells, through-holes, tubes, chambers, cavities, compartments, or channel portions.

~~3229~~. The instrument of claim ~~3027~~, wherein the sample holder comprises one or more substrates including the plurality of containers.

~~3330~~. The instrument of claim ~~3229~~, wherein the sample holder comprises one or more substrates retaining the plurality of containers and a mounting block retaining the one or more substrates.

~~3431~~. The instrument of claim ~~3229~~, wherein all of the plurality of containers are simultaneously illuminated by electromagnetic radiation from the excitation source.

~~35~~32. The instrument of claim ~~34~~31, wherein substrate comprises 96 containers or 384 containers.

~~36~~33. The instrument of claim ~~34~~31, wherein the substrate comprises a plate including a plurality of through-holes.

~~37~~34. The instrument of claim ~~34~~31, wherein the substrate comprises a plate including at least 3072 through-holes.

~~38~~35. The instrument of claim ~~28~~25, further comprising an optical element disposed along both the excitation optical path and the emission optical path.

~~39~~36. The instrument of claim ~~38~~35, wherein the optic element comprises one or more of a refractive lens, a window with no optical power, a beamsplitter, a mirror, or a diffractive optical element.

~~40~~37. The instrument of claim ~~38~~35, wherein the optical element comprises one or more of a field lens or lens array including a plurality of lenses corresponding to the plurality of discrete biological samples.

~~41~~38. The instrument of claim ~~38~~35, wherein the excitation optical systems forms a telecentric optical system.

~~42~~39. The instrument of claim ~~28~~25, further comprising a heating block and an electronic controller together configured to control a thermal environment of the discrete biological samples.

~~43~~40. The instrument of claim ~~42~~39, further comprising a heated cover configured to control a thermal environment of the discrete biological samples, at least a portion of the sample holder disposed between heated cover and the heating block.

~~44~~41. The instrument of claim ~~28~~25, further comprising a window disposed along at least one of the excitation optical path or the emission optical path, the window separating a first volume proximal the sample hold and a second volume distal the sample holder, the volumes including the at least one of the excitation optical path or the emission optical path, the window configured to reduce or eliminate convective flow between the distal chamber and the proximal chamber.

~~45~~42. The instrument of claim ~~44~~41, wherein the window is disposed along both the excitation optical path and the emission optical path.

~~46~~43. The instrument of claim ~~44~~41, wherein the window comprises a surface having a normal disposed at an offset angle relative to an optical axis of the at least one of the excitation optical path or the emission optical path.

~~47~~44. The instrument of claim ~~28~~25, wherein the sample holder comprises a sealed case forming a cavity containing the plurality of discrete biological samples, the sealed case comprising a base and a window providing optical access to the discrete biological samples.

~~48~~45. The instrument of claim ~~47~~44, wherein the window comprises a surface having a normal disposed at an offset angle relative to an optical axis of the at least one of the excitation optical path or the emission optical path.

~~49~~46. The instrument of claim ~~28~~25, further comprising an electronic processor comprising an electronic memory and configured to receive an image signal from the optical sensor, wherein the image signal comprises a plurality of discrete sample images produced in response to an amount of a target molecule contained in respective ones of the discrete biological samples.

~~50~~47. The instrument of claim ~~49~~46, wherein the image signal comprises a first image signal having a first magnification when the first filter component is disposed along the emission optical path and the image signal comprises a second image signal having a second magnification when the second filter component is disposed along the emission optical path, the electronic memory comprising instruction for use by the processor to adjust at least one of the first image signal or the second image signal so that at least some of the discrete sample images of each image signal are aligned to one another.

~~51~~48. The instrument of claim ~~49~~46, wherein at least some of the discrete biological samples comprise a fluorescent reporter molecule and at least some of the discrete sample images correspond to emission signals produced when the at least some of the discrete biological samples are illuminated by the excitation source.

~~52~~49. The instrument of claim ~~49~~46, wherein the plurality of filter components has a first condition in which the first filter component is disposed along the emission optical path and a second condition in which second filter component is disposed along the emission optical path, the discrete sample image being isolated from one another under both the first condition and the second condition.

~~53~~50. The instrument of claim ~~49~~46, wherein the instrument is configured to receive and produce the plurality of discrete sample images for each of:

a sample holder comprising a plurality of sample containers have a volume of 33 nanoliters; or

a sample holder comprising a plurality of sample container having a volume of 100 microliters.

~~54~~51. The instrument of claim ~~53~~50, wherein the instrument is configured to receive and produce the plurality of discrete sample images for:

a sample holder comprising a plurality of sample containers having a volume of 1 microliter;

a sample holder comprising a plurality of sample containers having a volume of 5 microliters; or

a sample holder comprising a plurality of sample containers having a volume of 10 microliters.

~~55~~52. The instrument of claim ~~49~~46, wherein the instrument is configured to receive and produce the plurality of discrete sample images for each of:

a sample holder comprising 96 discrete biological samples;

a sample holder comprising 384 discrete biological samples; or

a sample holder comprising at least 12,000 discrete biological samples.

~~56~~53. The instrument of claim ~~55~~52, wherein the sample holder comprising the at least 12,000 discrete biological samples comprises at least 48,000 discrete biological samples.

~~57~~54. The instrument of claim ~~55~~52, wherein the sample holder comprising the at least 12,000 discrete biological samples comprises at least 100,000 discrete biological samples.

5855. The instrument of claim 5552, wherein the sample holder comprising the at least 12,000 discrete biological samples comprises one or more substrates.

5956. The instrument of claim 5552, wherein the sample holder comprising the at least 12,000 discrete biological samples comprises four substrates, each substrate comprising at least 3,072 through-holes.

6057. The instrument of claim 1, wherein the excitation source is selected from the group consisting of a light emitting diode (LED), a halogen lamp, and a laser.

6158. The instrument of claim 1, wherein the excitation source comprises an LED producing at least 5 watts of total output optical power for all emitted wavelengths.

6259. The instrument of claim 1, wherein the excitation source comprises an LED producing at 5 watts of total output optical power for all emitted wavelengths and has a relative power of at least 10 percent over a wavelength range from 470 nanometers to 660 nanometers.

6360. The instrument of claim 1, wherein the instrument is a real-time polymerase chain reaction (qPCR) instrument.

6461. The instrument of claim 1, wherein the instrument is a sequencing instrument.

6562. The instrument of claim 1, further comprising a thermal control unit configured to control the temperature of the biological samples.

6663. The instrument of claim 1, further comprising a thermal control unit configured to cycle the temperature of the biological samples in a manner suitable for performing a polymerase chain reaction on the biological samples.

6764. An instrument for biological analysis, comprising:

an excitation source producing electromagnetic radiation;

a sample holder configured to receive a plurality of biological samples;

an optical sensor configured to receive an emission from the biological samples;

an excitation optical system disposed along an excitation optical path and configured to direct light from the light source to the biological samples;

an emission optical system disposed along an emission optical path and configured to direct light from the biological samples to the optical sensor;

a plurality of optical components configured to be interchangeably located along at least one of the optical paths, the plurality of optical components comprising:

____a first optical component having a primary optical characteristic and a secondary optical characteristic;

____a second optical component having different values of the primary optical characteristic and of the secondary optical characteristic than first optical component;

wherein at least one of the optical powers of the plurality of optical components is greater than zero for electromagnetic radiation transmitted through a corresponding one of the optical components.

~~68~~65. An instrument for biological analysis, comprising:

a light emitting diode (LED) light source producing light having wavelengths over the entire range from 450 nanometers to 700 nanometers;

a sample holder configured to receive an two-dimensional array of biological samples;

a two-dimensional optical sensor array;

an excitation optical system disposed along an excitation optical path and configured to simultaneously direct light from the light source to the biological samples;

an emission optical system disposed along an emission optical path and configured to direct light from at least some of the biological sample to the optical sensor;

a first filter component comprising a first filter having a first filter function configured to transmit light over a predetermined range of wavelengths and a first refractive element having a non-zero optical power;

a second filter component comprising a second filter function configured to transmit light over a range of wavelengths not included in the predetermined range of the first filter;

a first configuration in which the first filter component is located along the emission optical path and the second filter component is located outside the emission optical path; and

a second configuration in which the second filter component is located along the emission optical path and the first filter component is located outside the emission optical path;

wherein at least one of the optical powers of the first filter and the second filter is greater than zero for electromagnetic radiation transmitted through a corresponding one of the first filter and the second filter.

~~69~~66. An instrument for biological analysis, comprising:

an excitation source producing electromagnetic radiation;

a sample holder configured to receive a plurality of biological samples;

an optical sensor configured to receive an emission from the biological samples;

an excitation optical system configured to direct light from the light source to the biological samples;

an emission optical system disposed along an emission optical path and configured to form an image of the biological samples at an image plane located on or proximal the optical sensor;

a plurality of filters having different transmission wavelength bands, the filters being interchangeably located along the emission optical path;

wherein the image plane of the biological samples have the same location along the emission optical path when any one of the filters is located along the emission optical path; and

wherein at least one of the optical powers of the plurality of filters is greater than zero for electromagnetic radiation transmitted through a corresponding one of the filters.

~~70~~67. The instrument of claim ~~69~~66, wherein the image plane is located within 100 micrometers of a surface of the optical sensor

~~71~~68. The instrument of claim ~~69~~66, further comprising a sample array disposed within the sample holder comprising the plurality of biological samples.

~~72~~69. The instrument of claim ~~71~~68, wherein the image of the biological samples comprises a plurality of spots comprising emission light from corresponding ones of biological samples.

~~73~~70. A method for monitoring a plurality of biological samples, comprising:

providing an instrument according to claim 1;

locating a sample array comprising a plurality of biological samples within the sample holder;

locating the first ~~optical~~ filter component along the at least one of the optical paths;

using the optical sensor to simultaneously record an image of the plurality of biological samples while the first ~~optical~~ filter component is located along the at least one of the optical paths;

locating the first ~~optical~~ filter component away from the at least one of the optical paths and locating the second ~~optical~~ filter component along the at least one of the optical paths;

using the optical sensor to simultaneously record an image of the plurality of biological samples while the second ~~optical~~ filter component is located along the at least one of the optical paths.

~~74~~71. The method of claim ~~73~~70, wherein the at least one of the optical paths is the emission optical path

~~75~~72. The method of claim ~~73~~70, further comprising:

providing a third optical power and a third filter having a third filter function, the third filter function comprising at least one of a third low-pass wavelength that is different than either the first low-pass wavelength or the second low-pass wavelength, or a third high-pass wavelength that is different than either the first high-pass wavelength or the second high-pass wavelength;

locating the first and second optical components away from the at least one of the optical paths and locating the third optical component along the at least one of the optical paths;

using the optical sensor to simultaneously record an image of the plurality of biological samples while the third optical component is located along the at least one of the optical paths.

~~76~~73. An instrument for biological analysis, comprising:

an excitation source producing electromagnetic radiation;

a sample holder configured to receive a plurality of biological samples, the sample extending over a rectangular area characterized by a first aspect ratio having a first value;

an optical sensor configured to receive an emission from the biological samples;

an excitation optical system configured to direct the electromagnetic radiation from the excitation source to the biological samples;

an emission optical system configured to direct electromagnetic emissions from at least some of the biological samples to the optical sensor;

a rectangular emission filter disposed along an optical path between the sample holder and the optical sensor, the rectangular emission filter characterized by a second aspect ratio having a second value;

wherein the first value is within twenty percent of the value second value;

wherein an optical power of the rectangular emission filter is greater than zero for electromagnetic radiation transmitted through the rectangular emission filter.

~~77~~74. The instrument of claim ~~76~~73, wherein first value is within five percent of the value second value.

~~78~~75. The instrument of claim ~~76~~73, wherein the first value is the same as the second value.

~~79~~76. The instrument of claim ~~76~~73, further comprising a second rectangular emission filter characterized by a third aspect ratio having a third value, wherein the first value is within twenty percent of the value third value.