

One aspect of the present invention involves incorporation of various components of a sample separation system or instrument into a common cartridge, cassette, or case that may be advantageously loaded into the system or instrument in a way that simplifies set up for performing a sample separation assay, process, test, or experiment. Another aspect of the present invention involves a sample separation cartridge, cassette, or case having an optical section that, upon loading into a sample separation system or instrument, can be aligned to an optical system and/or detector in a manner that is advantageously simple, accurate, and stable. In yet another aspect of the present invention, involves a sample separation system or instrument comprising an illumination optical configuration that advantageously reduces optical noise, for example, optical noise created by Raman scattering by water molecules within a sample solution contained in one or more capillaries used during, or in preparation for, a sample separation assay, process, test, or experiment.

In one example, a system for separating biological molecules includes a plurality of capillaries configured to separate biological molecules in a sample, each capillary comprising a detection portion configured to pass electromagnetic radiation into the capillary; a capillary mount, the plurality of capillaries coupled to the capillary mount such that the detection portions are fixedly located relative to one another; a plurality of optical fibers corresponding to the plurality of capillaries, each optical fiber comprising a receiving end configured to receive emissions from a respective one of the detection portions; a fiber mount, the optical fibers being coupled to the fiber mount such that the receiving ends of the optical fibers are fixedly located relative to one another; an emission optical system configured to direct emissions from the detection portions into the receiving ends of the optical fibers; an optical detector configured to produce an alignment signal when emissions from at least one of the plurality of capillaries is transmitted through a respective at least one of the optical fibers and onto the optical detector; and a motion stage configured to move to a plurality of locations, one or more of the capillary mount, the fiber mount, or at least a portion of the emission optical system. The motion stage is configured to align the receiving ends of the optical fibers to the detection portions based on values of the alignment signal at the plurality of locations.

In another example, a method of separating biological molecules includes providing a plurality of capillaries, each capillary comprising an detection portion, the capillaries coupled to a capillary mount such that detection portions are fixedly located relative to one another; providing a plurality of optical fibers corresponding to respective ones of the plurality of capillaries, each optical fiber comprising a receiving end configured to receive emissions from

a respective one of the detection portions, the optical fibers being coupled to a fiber mount such that the receiving ends are fixedly located relative to one another; producing values of an alignment signal from an optical detector by transferring emissions within the detection portion of at least one of the capillaries through a respective at least one of the optical fiber and to the optical detector; moving, one or more times to one or more different locations, the capillary mount or the fiber mount; at each of the one or more locations, producing a respective value of the alignment signal from the optical detector by transferring emissions within the detection portion of the at least one capillary through the at least one optical fiber to the optical detector; and aligning the capillaries to the receiving ends of the plurality of optical fibers based on the values of the alignment signals.

Detailed Description of the Drawings

The following description provides embodiments of the present invention, which are generally directed to systems, instruments, devices, and methods for preparing, observing, testing, and/or analyzing biological samples. Such description is not intended to limit the scope of the present invention, but merely to provide a description of embodiments.

Exemplary systems and methods related to the various embodiments described in this document include those described in following applications:

- U.S. patent application number 15/124,013, filed on March 7, 2014;
- U.S. patent application number 15/124,129, filed on March 7, 2014;
- U.S. patent application number 15/124,168, filed on March 7, 2014;
- U.S. design patent application number 29/591,445, filed on January 19, 2017;
- U.S. design patent application number 29/591,865, filed on January 24, 2017;
- U.S. design patent application number 29/591,867, filed on January 24, 2017;
- U.S. provisional patent application number 62/460,700, filed on February 17, 2017;
- U.S. provisional patent application number 62/463,467, filed on February 24, 2017;
- U.S. provisional patent application number 62/463,551, filed on February 24, 2017;
- U.S. provisional patent application number 62/463,528, filed on February 24, 2017.

WHAT IS CLAIMED IS:

1. A system for separating biological molecules, the system comprising:

a plurality of capillaries configured to separate biological molecules in a sample, each capillary comprising a detection portion configured to pass electromagnetic radiation into the
5 capillary;

a capillary mount, the plurality of capillaries coupled to the capillary mount such that the detection portions are fixedly located relative to one another;

a plurality of optical fibers corresponding to the plurality of capillaries, each optical fiber comprising a receiving end configured to receive emissions from a respective one of the
10 detection portions;

a fiber mount, the optical fibers being coupled to the fiber mount such that the receiving ends of the optical fibers are fixedly located relative to one another;

an emission optical system configured to direct emissions from the detection portions into the receiving ends of the optical fibers;

15 an optical detector configured to produce an alignment signal when emissions from at least one of the plurality of capillaries is transmitted through a respective at least one of the optical fibers and onto the optical detector; and

a motion stage configured to move to a plurality of locations, one or more of the capillary mount, the fiber mount, or at least a portion of the emission optical system;

20 wherein the motion stage is configured to align the receiving ends of the optical fibers to the detection portions based on values of the alignment signal at the plurality of locations.

2. The system of claim 1, wherein the emission optical system comprises one or more lenses disposed along an optical path between the detection portions and the receiving ends.

3. The system of claims 1 or 2, wherein the motion stage comprises a translation stage
25 configured to translate the motion stage within a plane parallel to the receiving ends of the optical fibers and/or parallel to a plane passing through the detection portions.

4. The system of any one of claims 1-3, further comprising:

a processor; and

a memory encoded with instructions for:

moving the motion stage to the plurality of locations;
for each location, capturing one or more respective values of the alignment
signal from the optical detector;
determining an alignment position based on the respective values;
5 moving the motion stage to the alignment position so that the detection portions
are aligned to the receiving ends of the optical fibers.

5. The system of claim 4, wherein each of the values of the alignment signal comprises one or more of:

an average signal from the optical detector for at least two of the capillaries;
10 a mean signal from the optical detector for at least three of the capillaries;
a signal from the optical detector corresponding to a highest emission from between at least two of the capillaries.

6. The system of claim 4, wherein the memory is further encoded to evaluate whether a signal from the optical detector corresponding to emissions from one or more of the capillaries is a
15 noise signal and/or a signal not produced by Raman scattering from water molecules.

7. The system of any one of claims 1-6, further comprising a first electrode and a second electrode, the electrodes configured to produce an electric potential across the capillaries.

8. The system of any one of claims 1-7, wherein each capillary comprises an outer coating surrounding a capillary core, the outer coating of the capillary configured to reflect and/or
20 absorb light from emission signal, wherein the outer coating is not present within the detection portion of each capillary.

9. The system of any one of claims 1-8, wherein the capillaries are coupled to the capillary mount such that each capillary touches an adjacent capillary of the plurality of capillaries along a portion outside the detection portion.

25 10. A method of separating biological molecules, comprising:
providing a plurality of capillaries, each capillary comprising an detection portion, the capillaries coupled to a capillary mount such that detection portions are fixedly located relative to one another;

providing a plurality of optical fibers corresponding to respective ones of the plurality of capillaries, each optical fiber comprising a receiving end configured to receive emissions from a respective one of the detection portions, the optical fibers being coupled to a fiber mount such that the receiving ends are fixedly located relative to one another;

5 producing values of an alignment signal from an optical detector by transferring emissions within the detection portion of at least one of the capillaries through a respective at least one of the optical fiber and to the optical detector;

moving, one or more times to one or more different locations, the capillary mount or the fiber mount;

10 at each of the one or more locations, producing a respective value of the alignment signal from the optical detector by transferring emissions within the detection portion of the at least one capillary through the at least one optical fiber to the optical detector; and

aligning the capillaries to the receiving ends of the plurality of optical fibers based on the values of the alignment signals.

15 11. The method of claim 10, further comprising:

providing an emission optical system configured to direct emissions from each of the detection portions into the receiving end of the respective optical fiber; and

moving, one or more times to one or more locations, at least one of: the capillary mount or the fiber mount, or the emission optical system.

20 12. The method of any one of claims 10-11, wherein the values of the alignment signal are produced by Raman scattering emission from water molecules within a polymer solution contained in the capillaries.

13. The method of any one of claims 10-12, wherein the values of the alignment signal comprise emissions from a single one the capillaries.

25 14. The method of any one of claims 10-13, wherein the values of the alignment signal comprise an average of the emissions from more than one of the capillaries.

15. The method of any one of claims 10-14, further comprising:

loading one or more samples containing a fluorescent molecule into the plurality of capillaries;

propagating the one or more samples through the capillaries by producing an electric potential across the capillaries;

illuminating each detection portion with a source beam of electromagnetic radiation to produce a plurality of emitted signals from the each of the detection portions;

- 5 determining a nucleotide sequence of a molecule based on the plurality of emitted signals.