DEVICES AND METHODS FOR SAMPLE PARTITIONING

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/131,513, filed December 29, 2020, the contents of which are hereby incorporated by reference in their entirety.

BACKGROUND

[0002] Microfluidic devices are devices that contain structures that handle fluids on a small scale, such as microliters, nanoliters, or smaller quantities of fluids. One application of microfluidic structures is in digital polymerase chain reaction (dPCR). For example, a microfluidic structure with multiple partitions may be used to partition a nucleic acid sample for dPCR. For genomic researchers and clinicians, dPCR is particularly powerful in rare mutation detection, quantifying copy number variants, and Next Gen Sequencing library quantification. The potential use in clinical settings for liquid biopsy with cell free DNA and viral load quantification further increases the value of dPCR technology.

SUMMARY

[0003] Provided herein are methods and devices that may be useful for partitioning and analysis of a sample (i.e. a biological sample), for example, amplifying and quantifying nucleic acids. The present disclosure provides methods, systems, and devices that may enable sample preparation, sample amplification, and sample analysis. Sample analysis may be performed through the use of digital polymerase chain reaction (dPCR). Samples may be partitioned into chambers of differing sizes and volumes as to assist with analyte detection and assay dynamic range. This may enable sample analysis, for example nucleic acid amplification and quantification, at a reduced cost and complexity as compared to other systems and methods.

[0004] In an aspect, the present disclosure provides a device for partitioning a sample, comprising: a channel having at least two branches; a first plurality of chambers, the first plurality of chambers including a first chamber disposed along a first branch of the at least two branches; and a second plurality of chambers, the second plurality of chambers including a second chamber disposed along a second branch of the at least two branches.

[0005] In some embodiments, the first volume is at least twice as large as the second volume. In some embodiments, the first volume is at least five times as large as the second volume. In some embodiments, the device does not include any moving parts. In some embodiments, the device further comprises a channel in fluid communication with the first plurality of chambers and the second plurality of chambers. In some embodiments, the device further comprises a cover

configured to seal the first plurality of chambers, the second plurality of chambers, and the channel. In some embodiments, the device further comprises a body comprising the channel, the first plurality of chambers, and the second plurality of chambers, and wherein the cover is fixed to the body.

[0006] In some embodiments, the second plurality of chambers is in fluid communication with the channel upstream of the first plurality of chambers. In some embodiments, the channel comprises at least two branches, and wherein the first plurality of chambers is disposed along a first branch of the at least two branches and the second plurality of chambers is disposed along a second branch of the at least two branches.

[0007] In some embodiments, the first plurality of chambers comprises at least about 1,000 first chambers and the second plurality of chamber comprises at least about 1,000 second chambers. In some embodiments, the first plurality of chambers comprises at least about 5,000 first chambers and the second plurality of chamber comprises at least about 5,000 second chambers. In some embodiments, a total volume of the first plurality of chambers is less than about 10 microliters (μL). In some embodiments, a total first volume of the first plurality of chambers is greater than or equal to about 10 μL. In some embodiments, a total second volume of the second plurality of chambers is less than about 1 μL. In some embodiments, a total volume of the second plurality of chambers is greater than or equal to about 1 μL. In some embodiments, a total first volume of the first plurality of chambers is at least five times as large as a total second volume of the second plurality of chambers. In some embodiments, the total first volume is at least ten times as large as the total second volume.

[0008] In some embodiments, the first chambers of the first plurality of chambers comprise substantially similar volumes. In some embodiments, the second chambers of the second plurality of chambers comprise substantially similar volumes. In some embodiments, the first volume is greater than or equal to about 100 picoliters (pL). In some embodiments, wherein the first volume is less than or equal to about 1000 pL. In some embodiments, the second volume is less than or equal to about 250 pL.

[0009] In some embodiments, the second volume is greater than or equal to about 25 pL. In some embodiments, a first depth of the first chamber is substantially similar to a second depth of the second chamber. In some embodiments, a first cross-sectional area of the first chamber is substantially different than a second cross-sectional area of the second chamber. In some embodiments the device is a microfluidic device

[0010] In a further aspect, the present disclosure provides a method of analyzing an analyte, comprising: directing a fluidic sample including said analyte from a channel of a fluidic device to a first chamber of the fluidic device via a first branch of the channel, and a second chamber of the fluidic device via a second branch of the channel, wherein the fluidic device further includes (i) a first plurality of chambers including the first chamber, and (ii) a second plurality of chambers including the second chamber; and detecting said analyte in said first chamber and said second chamber.

[0011] In some embodiments, the first volume provides a first lower limit of detection of the analyte in the first chamber that is lower than a second lower limit of detection of the analyte in the second chamber provided by the second volume. In some embodiments, the first volume provides a first upper limit of detection of the analyte in the first chamber that is lower than a second upper limit of detection of the analyte in the second chamber provided by the second volume of the second chamber. In some embodiments, the method further comprises detecting the analyte at a concentration at or above the first lower limit of detection and below the second lower limit of detection. In some embodiments, the method further comprises detecting the analyte at a concentration above the first upper detection limit and below the second upper detection limit. In some embodiments, the first volume provides a first working range of detection of the analyte in the first chamber that is different than a second working range of detection of the analyte in the second chamber provided by the second volume. In some embodiments, the first volume permits analysis of a first analyte concentration and the second volume permits analysis of a second analyte concentration, and wherein the first analyte concentration and the second analyte concentration are different.

[0012] In some embodiments, the first volume is at least twice as large as the second volume. In some embodiments, the first volume is at least five times as large as the second volume. In some embodiments, the fluidic device does not include any moving parts.

[0013] In some embodiments, the fluidic device further comprises a channel in fluid communication with the first plurality of chambers and the second plurality of chambers, and wherein, in (b), the fluidic sample is directed from the channel to the first chamber and the second chamber. In some embodiments, the method further comprises a cover configured to seal the first plurality of chambers, the second plurality of chambers, and the channel. In some embodiments, the fluidic device comprises a body comprising the channel, the first plurality of chambers, and the second plurality of chambers, and wherein the cover is fixed to the body. In some embodiments, the second plurality of chambers are in fluid communication with the channel upstream of the first plurality of chambers. In some embodiments, the channel comprises at least two branches, and wherein the first plurality of chambers is disposed along a first branch

CLAIMS

WHAT IS CLAIMED IS:

1. A device for partitioning a sample, comprising:

a channel having at least two branches;

a first plurality of chambers, the first plurality of chambers including a first chamber disposed along a first branch of the at least two branches; and

a second plurality of chambers, the second plurality of chambers including a second chamber disposed along a second branch of the at least two branches.

2. The device of claim 1, wherein

the first plurality of chambers includes at least 100 first chambers,

the second plurality of chambers includes at least 100 second chambers,

the first chambers has a first volume different from a second volume of the second chamber, and

said first volume is at least twice as large as said second volume.

3. The device of claim 2, wherein said first volume is at least five times as large as said second volume.

4. The device of claim 2, wherein said device does not include any moving parts.

5. The device of claim 1, wherein the channel is in fluid communication with said first plurality of chambers and said second plurality of chambers.

6. The device of claim 5, further comprising a cover configured to seal said first plurality of chambers, said second plurality of chambers, and said channel.

7. The device of claim 6, further comprising a body defining said channel, said first plurality of chambers, and said second plurality of chambers, and wherein said cover is fixed to said body.

8. The device of claim 5, wherein said second plurality of chambers is in fluid communication with said channel upstream of said first plurality of chambers.

9. The device of claim 1, wherein said first plurality of chambers comprises at least 1,000 first chambers and wherein said second plurality of chambers comprises at least 1,000 second chambers.

10. The device of claim 9, wherein said first plurality of chambers comprises at least 5,000 first chambers and wherein said second plurality of chambers comprises at least 5,000 second chambers.

11. The device of claim 1, wherein a total volume of said first plurality of chambers is less than 10 microliters (μL).

12. The device of claim 1, wherein a total first volume of said first plurality of chambers is greater than or equal to 10 μL.

13. The device of claim 1, wherein a total second volume of said second plurality of chambers is less than 1 μL.

14. The device of claim 1, wherein a total volume of said second plurality of chambers is greater than or equal to 1 μL.

15. The device of claim 1, wherein a total first volume of said first plurality of chambers is at least five times as large as a total second volume of said second plurality of chambers.

16. The device of claim 15, wherein said total first volume is at least ten times as large as said total second volume.

17. The device of claim 1, wherein first chambers of said first plurality of chambers comprise substantially similar volumes.

18. The device of claim 1, wherein second chambers of said second plurality of chambers comprise substantially similar volumes.

19. The device of claim 1, wherein said first volume is greater than or equal to 100 picoliters (pL).

20. The device of claim 19, wherein said first volume is less than or equal to 1000 pL.

21. The device of claim 1, wherein said second volume is less than or equal to 250 pL.

22. The device of claim 21, wherein said second volume is greater than or equal to 25 pL.

23. The device of claim 1, wherein a first depth of said first chamber is substantially similar to a second depth of said second chamber.

24. The device of claim 23, wherein a first cross-sectional area of said first chamber is substantially different than a second cross-sectional area of said second chamber.

25. The device of claim 1, wherein said device is a microfluidic device.

26. A method of analyzing an analyte, comprising:

directing a fluidic sample including said analyte from a channel of a fluidic device to a first chamber of the fluidic device via a first branch of the channel, and a second chamber of the fluidic device via a second branch of the channel,

wherein the fluidic device further includes (i) a first plurality of chambers including the first chamber, and (ii) a second plurality of chambers including the second chamber; and

detecting said analyte in said first chamber and said second chamber.

27. The method of claim 26, wherein

the first plurality of chambers includes at least 100 first chambers,

the second plurality of chambers includes at least 100 second chambers,

the first chamber has a first volume different from a second volume of the second chamber, and

said first volume provides a first lower limit of detection of said analyte in said first chamber that is lower than a second lower limit of detection of said analyte in said second chamber provided by said second volume.

28. The method of claim 27, wherein said first volume provides a first upper limit of detection of said analyte in said first chamber that is lower than a second upper limit of detection of said analyte in said second chamber provided by said second volume of said second chamber.

29. The method of claim 27, further comprising detecting said analyte at a concentration at or above said first lower limit of detection and below said second lower limit of detection.

30. The method of claim 29, further comprising detecting said analyte at a concentration above said first upper detection limit and below said second upper detection limit.

31. The method of claim 26, wherein said first volume provides a first working range of detection of said analyte in said first chamber that is different than a second working range of detection of said analyte in said second chamber provided by said second volume.

32. The method of claim 26, wherein said first volume permits analysis of a first analyte concentration and said second volume permits analysis of a second analyte concentration, and wherein said first analyte concentration and said second analyte concentration are different.

33. The method of claim 26, wherein said first volume is at least twice as large as said second volume.

34. The method of claim 33, wherein said first volume is at least five times as large as said second volume.

35. The method of claim 26, wherein said fluidic device does not include any moving parts.

36. The method of claim 26, further comprising a cover configured to seal said first plurality of chambers, said second plurality of chambers, and said channel.

37. The method of claim 36, wherein said fluidic device comprises a body defining said channel, said first plurality of chambers, and said second plurality of chambers, and said cover is fixed to said body.

38. The method of claim 26, wherein said second plurality of chambers are in fluid communication with said channel upstream of said first plurality of chambers.

39. The method of claim 26, wherein said first plurality of chambers comprises at least 1,000 first chambers and said second plurality of chamber comprises at least 1,000 second chambers.

40. The method of claim 39, wherein said first plurality of chambers comprises at least 5,000 first chambers and said second plurality of chamber comprises at least 5,000 second chambers.

41. The method of claim 26, wherein a total volume of said first plurality of chambers is less than 10 microliters (μL).

42. The method of claim 26, wherein a total volume of said first plurality of chambers is greater than or equal to 10 μL.

43. The method of claim 26, wherein a total volume of said second plurality of chambers is less than 1 μL.

44. The method of claim 26, wherein a total volume of said second plurality of chambers is greater than or equal to 1 μL.

45. The method of claim 26, wherein a total first volume of said first plurality of chambers is at least five times as large as a total second volume of said second plurality of chambers.

46. The method of claim 45, wherein said total first volume is at least ten times as large as said total second volume.

47. The method of claim 26, wherein first chambers of said first plurality of chambers comprise substantially similar volumes.

48. The method of claim 26, wherein second chambers of said second plurality of chambers comprise substantially similar volumes.

49. The method of claim 26, wherein said first volume is greater than or equal to 100 picoliters (pL).

50. The method of claim 49, wherein said first volume is less than or equal to 1000 pL.

51. The method of claim 26, wherein said second volume is less than or equal to 250 pL.

52. The method of claim 51, wherein said second volume is greater than or equal to 25 pL.

53. The method of claim 26, wherein a depth of said first chamber is substantially similar to a depth of said second chamber.

54. The method of claim 53, wherein a cross-sectional area of said first chamber is substantially different than a cross-sectional area of said second chamber