

form an electrode; and a plurality of fluidic channels 118, comprising a first fluidic channel 118a and a second fluidic channel 118b, provided in the substrate 110, each of the plurality of fluidic channels 118 being configured to form a fluid pathway for allowing a fluid sample to flow through and at least one of the first and second fluidic channels 118a/118b comprising a cell manipulation portion 120, the cell manipulation portion 120 comprising a plurality of constriction portions ~~120~~124. The first and second electrode channels 114a/114b are each coupled to the first fluidic channel 118a and the electrodes (e.g., which may be referred to herein as first and second electrodes) of the first and second electrode channels 114a/114b are configured to measure an electrical impedance therebetween via the first fluidic channel 118a. The third and fourth electrode channels 114c/114d are each coupled to the second fluidic channel 118b and the electrodes (e.g., which may be referred to herein as third and fourth electrodes) of the third and fourth electrode channels 114c/114d are configured to measure an electrical impedance therebetween via the second fluidic channel 118b.

[0014] It can be understood by a person skilled in the art that for illustration purpose only and without limitation, FIG. 1A illustrates an example configuration (e.g., first example configuration) of the microfluidic device 100 whereby the first fluidic channel 118a comprises the cell manipulation portion 120. That is, the first fluidic channel 118a is the above-mentioned one of the first and second fluidic channels 118a/118b comprising the cell manipulation portion 120. It will be appreciated by a person skilled in the art that the microfluidic device 100 is not limited to the first fluidic channel 118a comprising the cell manipulation portion 120, and in another example configuration (e.g., second example configuration (not shown)), the second fluidic channel 118b may instead comprise the cell manipulation portion 120. That is, the second fluidic channel 118b is the above-mentioned one of the first and second fluidic channels 118a/118b comprising the cell manipulation portion 120. Furthermore, in yet another example configuration (e.g., third example configuration), the first and second fluidic channels 118a/118b may each comprise a respective cell manipulation portion, such as shown in FIG. 1B.

[0015] FIG. 1B depicts a schematic drawing of a microfluidic device 150 for single cell processing according to various embodiments of the present invention, which is the same as the microfluidic device 100, except that the first and second fluidic channels

CLAIMS

What is claimed is:

5 1. A microfluidic device for single cell processing, the microfluidic device comprising:

a substrate;

10 a plurality of electrode channels, comprising a first electrode channel, a second electrode channel, a third electrode channel and a fourth electrode channel, provided in the substrate, each of the plurality of electrode channels containing an electrode material to form an electrode; and

15 a plurality of fluidic channels, comprising a first fluidic channel and a second fluidic channel, provided in the substrate, each of the plurality of fluidic channels being configured to form a fluid pathway for allowing a fluid sample to flow through and at least one of the first and second fluidic channels comprising a cell manipulation portion, the cell manipulation portion comprising a plurality of constriction portions, wherein

20 the first and second electrode channels are each coupled to the first fluidic channel and the electrodes of the first and second electrode channels are configured to measure an electrical impedance therebetween via the first fluidic channel, ~~and~~

25 the third and fourth electrode channels are each coupled to the second fluidic channel and the electrodes of the third and fourth electrode channels are configured to measure an electrical impedance therebetween via the second fluidic channel, and

30 the cell manipulation portion of said at least one of the first and second fluidic channels is provided in the corresponding fluidic channel such that the electrodes of the corresponding electrode channels of the plurality of electrode channels are configured to measure the electrical impedance therebetween based on an electrical conduction path formed therebetween through the cell manipulation portion of the corresponding fluidic channel.

2. The microfluidic device according to claim 1, wherein the cell manipulation portion further comprises a plurality of relaxation portions, the plurality of relaxation portions and the plurality of constriction portions in the cell manipulation portion being arranged alternately along the fluidic channel.
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3. The microfluidic device according to claim 2, wherein in the cell manipulation portion, each adjacent pair of constriction portions of the plurality of constriction portions is interspaced by a corresponding relaxation portion of the plurality of relaxation portions.
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4. The microfluidic device according to claim 2 or 3, wherein said at least one of the first and second fluidic channels comprises a linear portion, the linear portion comprising the cell manipulation portion.
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5. The microfluidic device according to any one of claims 2 to 4, wherein in the cell manipulation portion, each of the plurality of constriction portions has a cross-sectional dimension that is less than a cross-sectional dimension of a non-cell manipulation portion of the fluidic channel, and each of the plurality of relaxation portions has a cross-sectional dimension that is equal to or greater than the cross-sectional dimension of the non-cell manipulation portion of the fluidic channel.
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6. The microfluidic device according to claim 5, wherein
said each of the plurality of constriction portions is configured to compress a single cell flowing therethrough,
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said each of the plurality of relaxation portions is configured to decompress the single cell flowing therethrough, and
said single cell has a size that the microfluidic device is configured to process.
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7. The microfluidic device according to claim 5 or 6, wherein

said each of the plurality of constriction portions has an elongated shape extending in a direction of the fluid pathway, and

said each of the plurality of constriction portions has dimensions which are the same.

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8. The microfluidic device according to any one of claims 1 to 7, wherein

the first and second electrode channels are coupled to the first fluidic channel at coupling portions, including a first coupling portion and a second coupling portion, of the first fluidic channel, respectively,

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the third and fourth electrode channels are coupled to the second fluidic channel at coupling portions, including a third coupling portion and a fourth coupling portion, of the second fluidic channel, respectively,

the cell manipulation portion of said at least one of the first and second fluidic channels is provided between the coupling portions of the corresponding fluidic channel such that the electrodes of the corresponding electrode channels of the plurality of electrode channels are configured to measure the electrical impedance therebetween ~~via~~ based on the electrical conduction path formed therebetween through the cell manipulation portion of the corresponding fluidic channel.

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9. The microfluidic device according to any one of claims 1 to 8, wherein

the first and second electrode channels are coupled to the first fluidic channel via a first coupling channel and a second coupling channel, respectively, each of the first and second coupling channels being configured to form a fluid pathway for allowing the fluid sample to flow so as to expose the electrodes of the first and second electrode channels for direct contact with the fluid sample when the fluid sample is being flowed in the first fluidic channel, and

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the third and fourth electrode channels are coupled to the second fluidic channel via a third coupling channel and a fourth coupling channel, respectively, each of the third and fourth coupling channels being configured to form a fluid pathway for allowing the fluid sample to flow so as to expose the electrodes of the

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third and fourth electrode channels for direct contact with the fluid sample when the fluid sample is being flowed in the second fluidic channel.

10. The microfluidic device according to any one of claims 1 to 9, wherein the cell
5 manipulation portion comprises three or more constriction portions.

11. The microfluidic device according to any one of claims 1 to 10, wherein
the first fluidic channel and the second fluidic channel are parallel to each
other,

10 the first and second electrode channels each comprises an aligned portion
configured to be adjacent the first fluidic channel and to be aligned with the first
fluidic channel so as to extend in a parallel manner thereto; and

the third and fourth electrode channels each comprises an aligned portion
configured to be adjacent the second fluidic channel and to be aligned with the
15 second fluidic channel so as to extend in a parallel manner thereto.

12. A method of manufacturing a microfluidic device for single cell processing, the
method comprising:

providing a substrate;

20 forming a plurality of electrode channels, comprising a first electrode
channel, a second electrode channel, a third electrode channel and a fourth
electrode channel, in the substrate, each of the plurality of electrode channels
containing an electrode material to form an electrode; and

25 forming a plurality of fluidic channels, comprising a first fluidic channel
and a second fluidic channel, in the substrate, each of the plurality of fluidic
channels being configured to form a fluid pathway for allowing a fluid sample to
flow through and at least one of the first and second fluidic channels comprising a
cell manipulation portion, the cell manipulation portion comprising a plurality of
constriction portions, wherein

30 the first and second electrode channels are each coupled to the first fluidic
channel and the electrodes of the first and second electrode channels are

configured to measure an electrical impedance therebetween via the first fluidic channel, ~~and~~

the third and fourth electrode channels are each coupled to the second fluidic channel and the electrodes of the third and fourth electrode channels are configured to measure an electrical impedance therebetween via the second fluidic channel, and

the cell manipulation portion of said at least one of the first and second fluidic channels is provided in the corresponding fluidic channel such that the electrodes of the corresponding electrode channels of the plurality of electrode channels are configured to measure the electrical impedance therebetween based on an electrical conduction path formed therebetween through the cell manipulation portion of the corresponding fluidic channel.

13. The method according to claim 12, wherein the cell manipulation portion further comprises a plurality of relaxation portions, the plurality of relaxation portions and the plurality of constriction portions in the cell manipulation portion being arranged alternately along the fluidic channel.

14. The method according to claim 13, wherein in the cell manipulation portion, each adjacent pair of constriction portions of the plurality of constriction portions is interspaced by a corresponding relaxation portion of the plurality of relaxation portions.

15. The method according to claim 13 or 14, wherein said at least one of the first and second fluidic channels comprises a linear portion, the linear portion comprising the cell manipulation portion.

16. The method according to any one of claims 13 to 15, wherein in the cell manipulation portion, each of the plurality of constriction portions has a cross-sectional dimension that is less than a cross-sectional dimension of a non-cell manipulation portion of the fluidic channel, and each of the plurality of relaxation

portions has a cross-sectional dimension that is equal to or greater than the cross-sectional dimension of the non-cell manipulation portion of the fluidic channel.

17. The method according to claim 16, wherein

5 said each of the plurality of constriction portions is configured to compress a single cell flowing therethrough,

 said each of the plurality of relaxation portions is configured to decompress the single cell flowing therethrough, and

10 said single cell has a size that the microfluidic device is configured to process.

18. The method according to claim 16 or 17, wherein

 said each of the plurality of constriction portions has an elongated shape extending in a direction of the fluid pathway, and

15 said each of the plurality of constriction portions has dimensions which are the same.

19. The method according to any one of claims 12 to 18, wherein

20 the first and second electrode channels are coupled to the first fluidic channel at coupling portions, including a first coupling portion and a second coupling portion, of the first fluidic channel, respectively,

 the third and fourth electrode channels are coupled to the second fluidic channel at coupling portions, including a third coupling portion and a fourth coupling portion of the second fluidic channel, respectively,

25 the cell manipulation portion of said at least one of the first and second fluidic channels is provided between the coupling portions of the corresponding fluidic channel such that the electrodes of the corresponding electrode channels of the plurality of electrode channels are configured to measure the electrical impedance therebetween ~~via~~ based on the electrical conduction path formed therebetween through the cell manipulation portion of the corresponding fluidic channel.

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20. The method according to any one of claims 12 to 19, wherein
the first and second electrode channels are coupled to the first fluidic
channel via a first coupling channel and a second coupling channel, respectively,
5 each of the first and second coupling channels being configured to form a fluid
pathway for allowing the fluid sample to flow so as to expose the electrodes of the
first and second electrode channels for direct contact with the fluid sample when
the fluid sample is being flowed in the first fluidic channel, and
the third and fourth electrode channels are coupled to the second fluidic
10 channel via a third coupling channel and a fourth coupling channel, respectively,
each of the third and fourth coupling channels being configured to form a fluid
pathway for allowing the fluid sample to flow so as to expose the electrodes of the
third and fourth electrode channels for direct contact with the fluid sample when
the fluid sample is being flowed in the second fluidic channel.
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21. The method according to any one of claims 12 to 20, wherein the cell
manipulation portion comprises three or more constriction portions.
22. The method according to any one of claims 12 to 21, wherein
20 the first fluidic channel and the second fluidic channel are parallel to each
other,
the first and second electrode channels each comprises an aligned portion
configured to be adjacent the first fluidic channel and to be aligned with the first
fluidic channel so as to extend in a parallel manner thereto, and
25 the third and fourth electrode channels each comprises an aligned portion
configured to be adjacent the second fluidic channel and to be aligned with the
second fluidic channel so as to extend in a parallel manner thereto.
23. A method of single cell biophysical phenotyping using the microfluidic device for
30 single cell processing according to any one of claims 1 to 11, the method
comprising:

obtaining a first impedance measurement based on the electrodes of the first and second electrode channels with the first fluidic channel having a fluid sample flowing therein;

5 obtaining a second impedance measurement based on the electrodes of the third and fourth electrode channels with the second fluidic channel having a fluid sample flowing therein;

obtaining a differential impedance measurement based on the first impedance measurement and the second impedance measurement, the differential impedance measurement comprising a differential impedance signal; and

10 determining one or more biophysical properties of a single cell in the fluid sample that flowed in one of the first and second fluidic channels comprising the cell manipulation portion based on the differential impedance signal.

15 24. The method according to claim 23, wherein the one or more biophysical properties of the single cell is determined based on the differential impedance signal obtained at least over a time period where the single cell flowed through the cell manipulation portion of said one of the first and second fluidic channels.

20 25. The method according to claim 24, wherein over said time period, no cell flowed through a corresponding portion of the other one of the first and second fluidic channels.

25 26. The method according to claim 24 or 25, wherein the differential impedance signal obtained over said time period comprises a plurality of impedance peaks corresponding to instances where the single cell flowed through the plurality of constriction portions, respectively, of the cell manipulation portion of said one of the first and second fluidic channels.

30 27. The method according to claim 26, wherein said determining one or more biophysical properties of the single cell comprises determining one or more of a deformability property, an electrical property and a relaxation property of the

single cell in the fluid sample that flowed in said one of the first and second fluidic channels based on the plurality of impedance peaks of the differential impedance signal obtained over said time period.

- 5 28. The method according to claim 27, wherein the deformability property of the single cell is determined based on a width of each of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
- 10 29. The method according to claim 27 or 28, wherein the electrical property of the single cell is determined based on a magnitude of each of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
- 15 30. The method according to any one of claims 27 to 29, wherein the relaxation property of the single cell is determined based on a comparison between a width of a first impedance peak of the plurality of impedance peaks and a width of a subsequent impedance peak of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
- 20 31. The method according to claim 30, wherein the subsequent impedance peak is a last impedance peak of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
- 25 32. A system for single cell biophysical phenotyping, the system comprising:
 - the microfluidic device for single cell processing according to any one of claims 1 to 11; and
 - a computing system comprising:
 - a memory; and
 - at least one processor communicatively coupled to the memory and
- 30 the microfluidic device, and configured to:

obtain a first impedance measurement based on the electrodes of the first and second electrode channels with the first fluidic channel having a fluid sample flowing therein;

5 obtain a second impedance measurement based on the electrodes of the third and fourth electrode channels with the second fluidic channel having a fluid sample flowing therein;

10 obtain a differential impedance measurement based on the first impedance measurement and the second impedance measurement, the differential impedance measurement comprising a differential impedance signal; and

15 determine one or more biophysical properties of a single cell in the fluid sample that flowed in one of the first and second fluidic channels comprising the cell manipulation portion based on the differential impedance signal.

33. The system according to claim 32, wherein the one or more biophysical properties of the single cell is determined based on the differential impedance signal obtained at least over a time period where the single cell flowed through the cell manipulation portion of said one of the first and second fluidic channels.

20 34. The system according to claim 33, wherein over said time period, no cell flowed through a corresponding portion of the other one of the first and second fluidic channels.

25 35. The system according to claim 33 or 34, wherein the differential impedance signal obtained over said time period comprises a plurality of impedance peaks corresponding to instances where the single cell flowed through the plurality of constriction portions, respectively, of the cell manipulation portion of said one of the first and second fluidic channels.

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36. The system according to claim 35, wherein said determining one or more biophysical properties of the single cell comprises determining one or more of a deformability property, an electrical property and a relaxation property of the single cell in the fluid sample that flowed in said one of the first and second fluidic channels based on the plurality of impedance peaks of the differential impedance signal obtained over said time period.
37. The system according to claim 36, wherein the deformability property of the single cell is determined based on a width of each of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
38. The system according to claim 36 or 37, wherein the electrical property of the single cell is determined based on a magnitude of each of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
39. The system according to any one of claims 36 to 38, wherein the relaxation property of the single cell is determined based on a comparison between a width of a first impedance peak of the plurality of impedance peaks and a width of a subsequent impedance peak of the plurality of impedance peaks of the differential impedance signal obtained over said time period.
40. The system according to claim 39, wherein the subsequent impedance peak is a last impedance peak of the plurality of impedance peaks of the differential impedance signal obtained over said time period.