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(54) LOOP-TYPE MICROFLUIDIC SYSTEM

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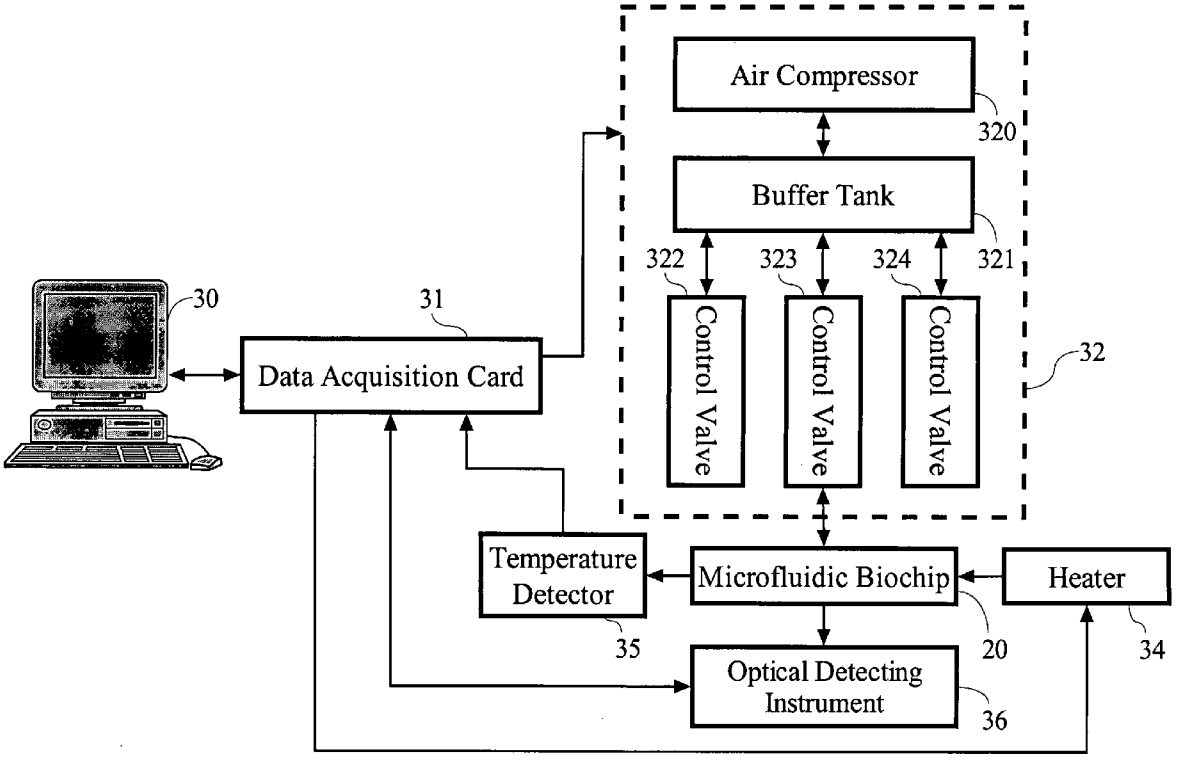
(57) **ABSTRACT**

The present invention provides a loop-type microfluidic system, and the microfluid therein could be driven to move around the loop-channel repeatedly by the air comes from the air holes and through the driving conduits. In order to process the polymerase chain reaction (PCR), the microfluid should bear the temperature changes for three times. Hence, plural temperature controllers are utilized to adjust the temperatures of the sections constituting the loop-channel. Moreover, the times of cycles may be determined based on the desired times of reactions. The present invention could also increase or decrease the number of the air holes, the driving conduits and the temperature controllers to adjust the times of temperature changes according to the demands of various biochemical reactions.



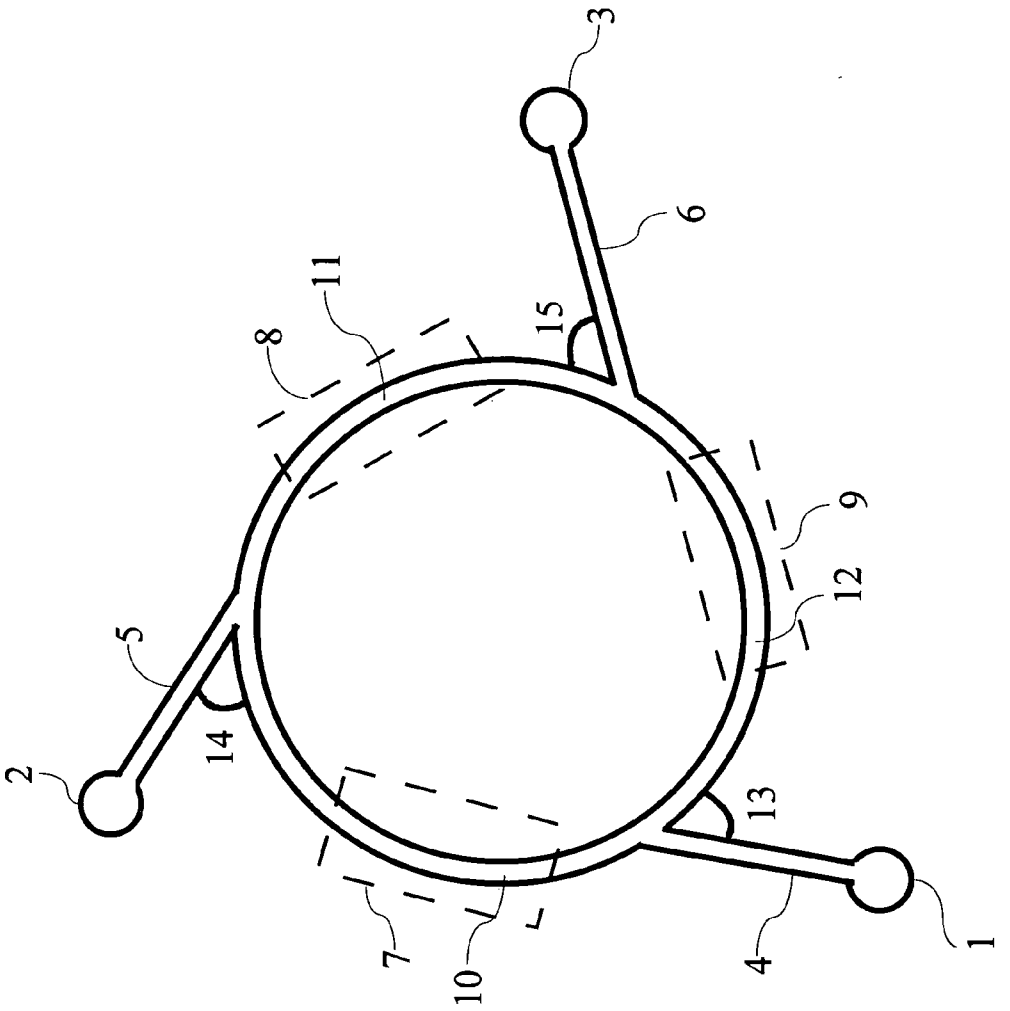


Fig. 1

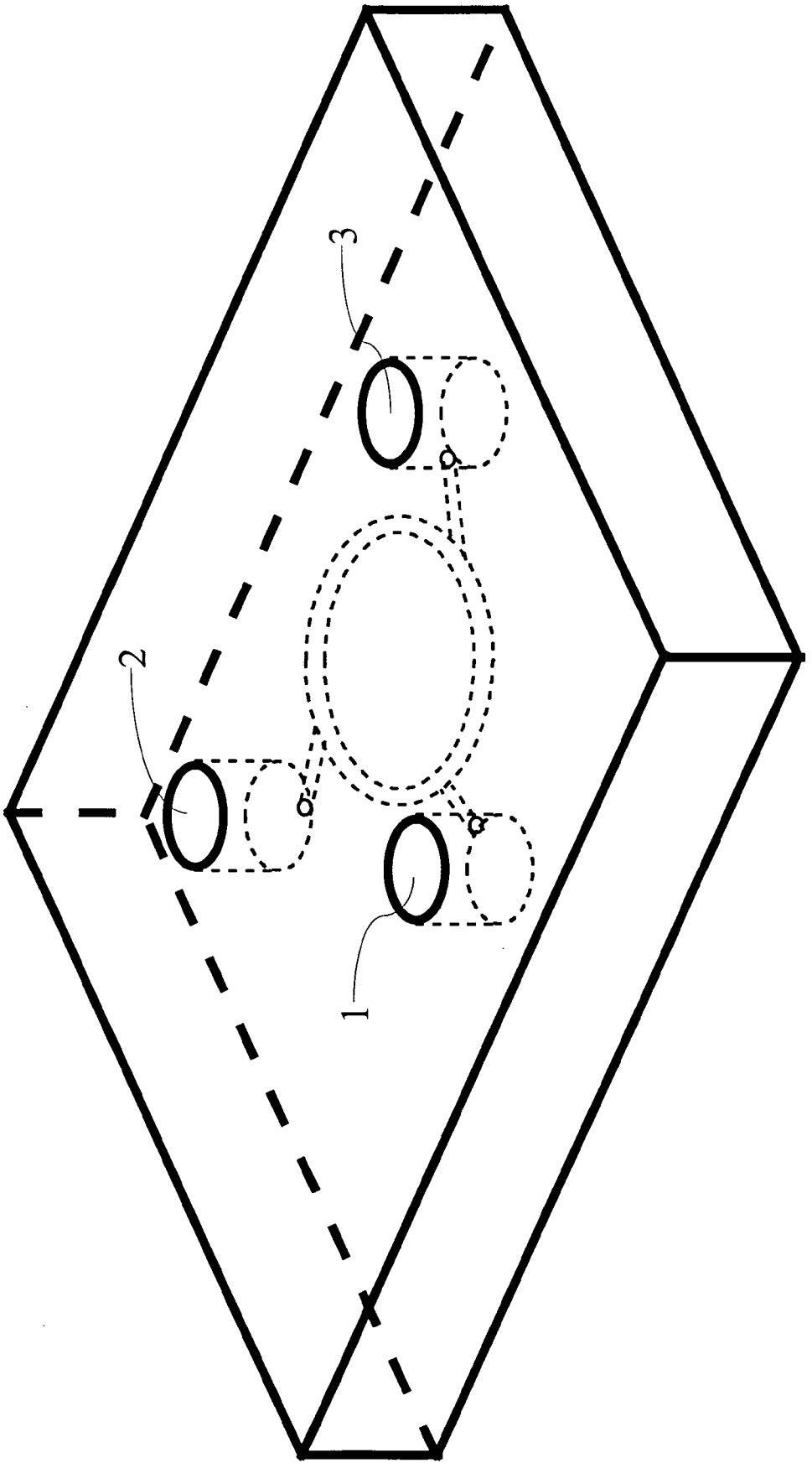


Fig. 2

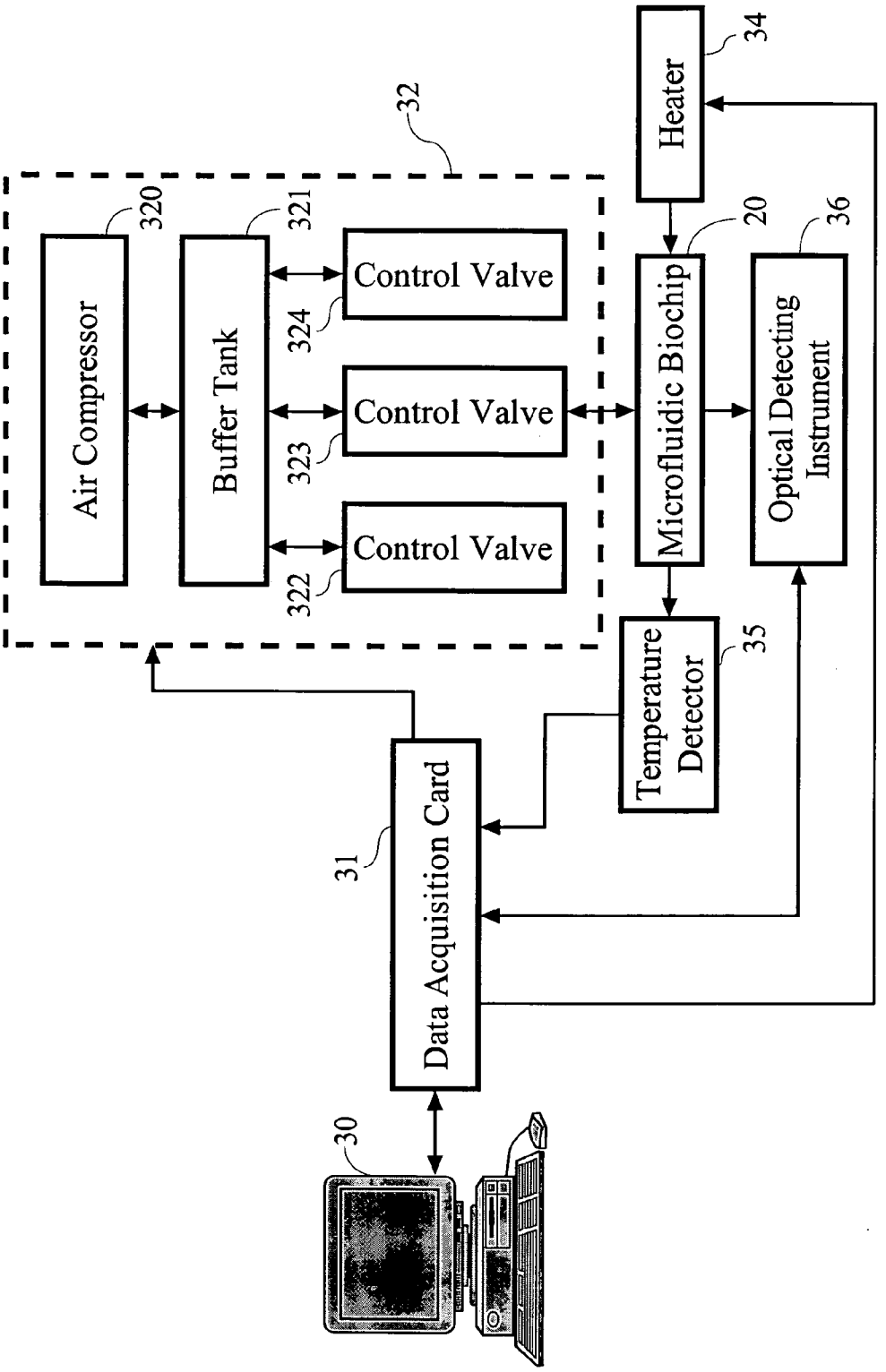

Heater
34
32
320
321
Air Compressor
Buffer Tank
Control Valve
Control Valve
Control Valve
324
323
322
20
36
Microfluidic Biochip
Optical Detecting Instrument
Temperature Detector
35
31
Data Acquisition Card
30

Fig. 3

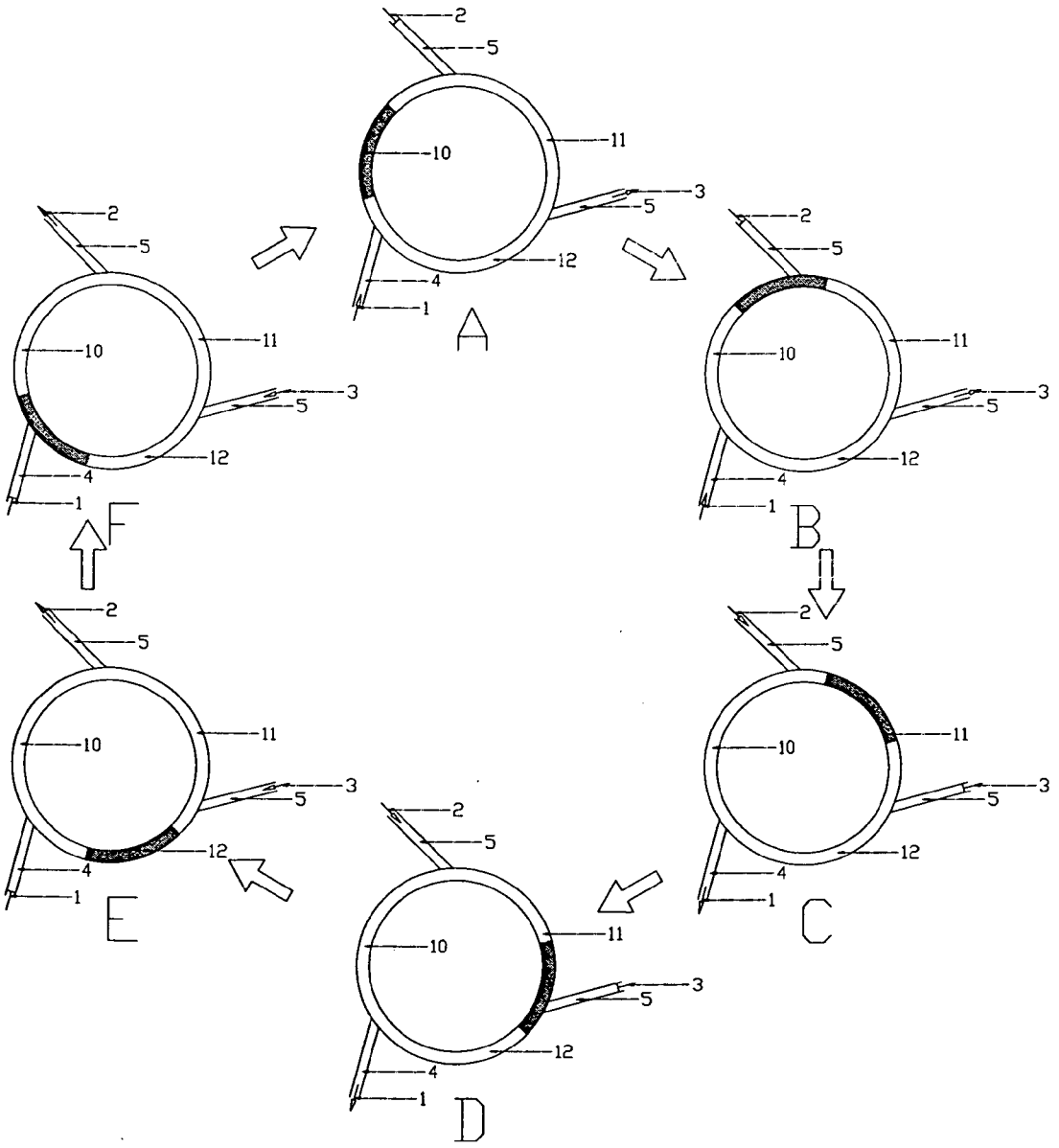


Fig. 4

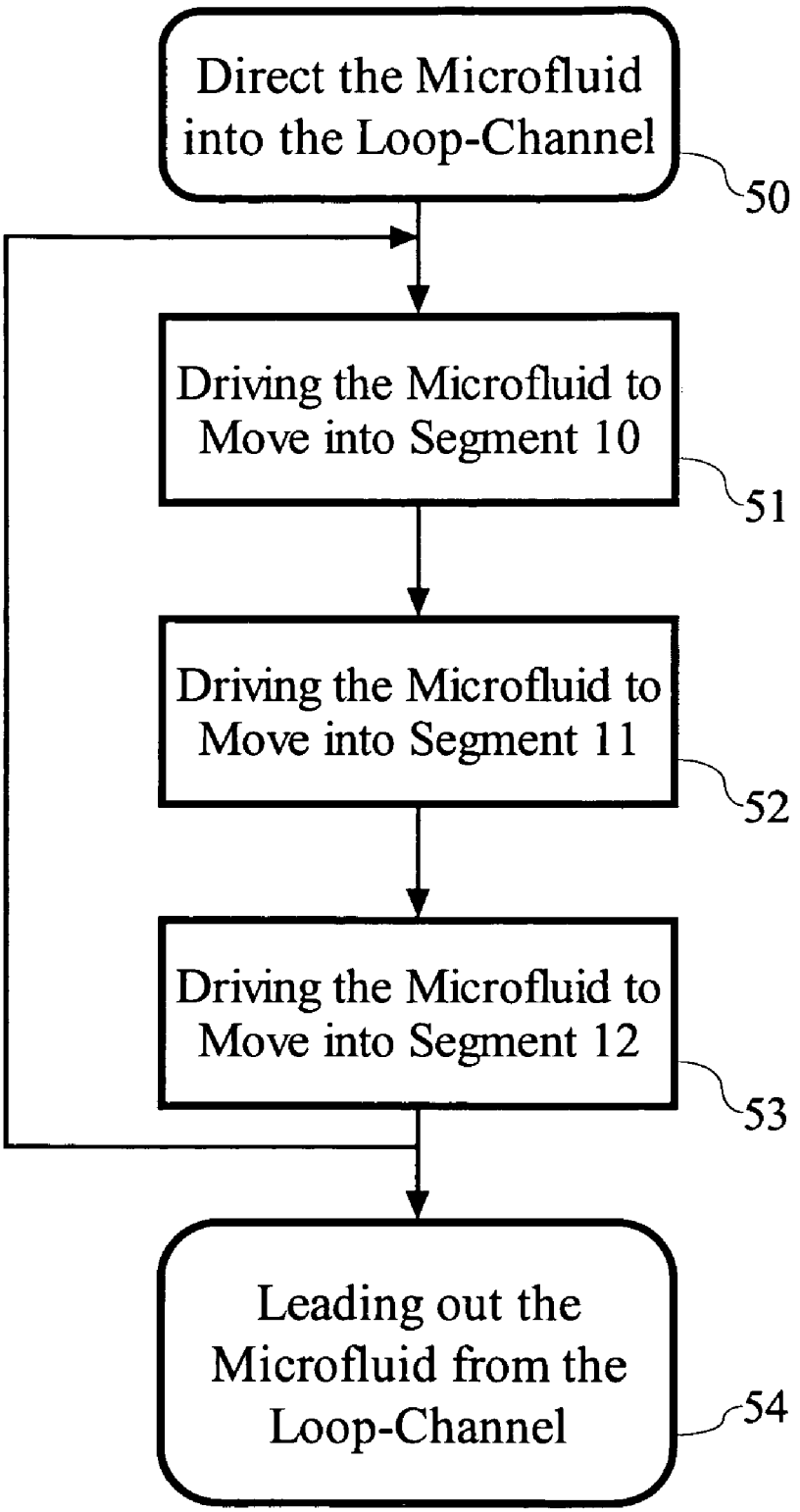

Direct the Microfluid into the Loop-Channel
50
Driving the Microfluid to Move into Segment 10
51
Driving the Microfluid to Move into Segment 11
52
Driving the Microfluid to Move into Segment 12
53
Leading out the Microfluid from the Loop-Channel
54

Fig. 5

LOOP-TYPE MICROFLUIDIC SYSTEM

FIELD OF THE INVENTION

[0001] The present invention is related to a microfluidic system, particularly to a loop-type microfluidic system utilizing a micro loop-channel.

BACKGROUND OF THE INVENTION

[0002] With the development of technology, the biochip controlled by the computer could implement various biochemical reactions conventionally operated by hands. Such biochip may even handle the complicated microfluidic operation.

[0003] Generally, the microfluidic operation may be applied to the polymerase chain reaction (PCR). It could exactly find out specific base sequence with hundreds of base pairs from the nucleic acid molecule with millions of base pairs, and reproduce this sequence for more than one million times. The process of PCR mainly comprises three steps which repeat sequentially. First, in the step of denature, the temperature is raised to 95° C. so that the double strand structure of the DNA template would be opened. Next, in the step of annealing, the temperature is declined to 50-60° C. so that a pair of primers would enter the DNA molecule to mount in the position of the base pair. Finally, in the step of extension, the temperature is raised to 65-75° C. to activate the polymerase and form a new double strand nucleic acid molecular sequence.

[0004] By repeating the above three steps, the polymerase chain reaction is performed for DNA amplification. Usually, the PCR performed by conventional machine would cost about three hours. However, with the development of the micro machining processes, the substrate could be etched to form the microfluidic channels thereon. In addition, the copper piece with constant temperature could be applied as the thermal source to form a biochip for biochemical reaction. This kind of biochip has small size, fast cycle speed and tiny requirement of specimen. The biochip could further coupled to the electrophoresis chip to form a DNA analysis system.

[0005] Recent researches mainly focus on the improvement of the heating material, the size of the micro channel, the material of the substrate or the cycle times of the PCR chip. The main principles are similar and only the unidirectional movement is applied. This kind of design should modify the length of the channel according to the reaction times. Generally, about thirty times of reaction are preferably required, and therefore the longer micro-channel is necessary. Besides, the times of reaction could not be adjusted at one's own choice to obtain the best result.

[0006] Conventionally, the microfluidic movement device merely utilizes linear direction. For example, TW Patent No. 499302 filed on Nov. 5, 2001, entitled "A system and method for driving microfluid by air," disclosed the manipulation of the air pressure to make the microfluid move forward and backward repeatedly. TW Patent No. 528836 filed on Jun. 9, 1999, entitled "Method and device for driving microfluid," disclosed the air-driven microfluidic reciprocation system and temperature controller for biochemical reaction. Such techniques could merely be applied to simple biochemical reaction, rather than complicated biochemical or chain reaction. Especially for PCR, the temperature of the microfluid should be changed repeatedly and quickly. Consequentially, if the aforementioned conventional techniques are applied to PCR, the difficult temperature change control would be necessary, and then the experiment or reaction may become much more complicated.

[0007] Additionally, referring B. C. Giordano, J. Ferrance, S. Swedberg, A. F. R. Huhmer, and J. P. Landers, "Polymerase Chain Reaction in Polymeric Microchips: DNA Amplification in Less Than 240 Seconds," Anal Biochemistry 291, PP. 124-132, 2001, the specimen is placed in the chamber of the biochip, and the temperature controller would modify the temperature to obtain the cycles of three-level temperature change. Although the times of reaction could be determined on one's demand, the fast temperature control is complex and difficult.

[0008] The prior art also provides the microfluidic thermal cycle system which enables the microfluid moving forward and backward. However, the fast temperature change is still required, even though the length of channel is shortened and the reaction times can be adjusted by the user.

[0009] Followings are other related reference: (1) Capillary electrophoresis (CE) chip, developed by Harrison et al. who proposed a complex manifold of capillary channels fabricated in glass substrate using micromachining techniques, see Harrison, D. J., Manz, A., Fan, Z., Ludi, H. and Widmers, H. M., Anal. Chem. 64, 1926 (1992)); (2) Polymerase chain reaction (PCR) microchip, designed by Kopp et al., on which the sample was controlled to flow continuously in an unidirectional channel through three thermostated temperature zones to complete a total of 20-cycle PCR amplification, see Kopp, M. U., Mello, A. J. and Manz, A., Science. 280, 1046 (1998); (3) Flow switch, investigated by Lee et al., for continuous 1×N sample switching and injection based on microfluidic phenomena of hydrodynamic focusing and valveless flow switching, see Lee, G. B., Hung, C. I., Ke, B. J., Huang, G. R. and Hwei, B. H., J. Micromech. Microeng. 11, 567 (2001); (4) Integrated microfluidic devices, for example, Bums et al. developed a microfabricated device having the fluidic channels, heaters, temperature sensors, and fluorescence detectors for DNA analysis, see Bums, M. A., Johnson, B. N., Brahmasandra, S. N., Handique, K., et al., Science. 282, 484 (1998); Yokoyama et al. investigated thermal-bubble type micropump with loop-type micro channel for cooling purpose, see Yokoyama, Y., Takeda, M., Umemoto, T. and Ogushi, T., Sensors and Actuators, A111, 123 (2004). Kang et al. developed a radial grooved micro heat pipes allowing separation of the liquid and vapor flow in a three-layer structure which was fabricated on silicon wafer using bulk micromachining, see Kang, S. W., Tsai, S. H. and Chen, H. C., Applied Thermal Engineering, 22, 1559 (2002). The most common and evolved techniques for microfluid driving include on-chip micropump and external driving source. Zengerle et al. developed a micropump actuated by electrostatic for bidirectional driving, see Zengerle, R., Ulrich, J., Kluge, S., Richter, M. and Richter, A., Sensors and Actuators A50, 81 (1995); Hartly patented his invention on peristaltic micropump, see Hartley, F. T., U.S. Pat. No. 5,705,018 (1998); Piezoelectric valveless micropump was designed by Olsson et al., see Olssen, A., Stemme G. and Stemme, E., Sensors and Actuator A47, 549 (1995); Jen et al investigated a bidirectional microfluid driving system by suction and

exclusion controlled from external servo system, see Jen, C. P. and Lin, Y. C., J. Micromech, Microeng, 12, 115 (2002).

[0010] In conclusion, the conventional microfluidic driving and movement devices merely allow the microfluid move in linear direction. If one-way movement is adopted, longer micro-channel would be required. Thus, the frequency of malfunction is highly raised, and the reaction times are unchanged. Micro-chamber and reciprocation PCR chip may modify the number of cycles, but the necessary temperature change control would also complicate the manipulation of chain reaction.

SUMMARY OF THE INVENTION

[0011] In view of the aforementioned problems, the present invention therefore provides a loop-type microfluidic system and device. The microfluid within the loop-channel could be driven to circle around repeatedly, and the temperature controllers may control the temperature of each segment of the loop-channel so that the microfluid would undergo one time of three-level temperature change in each circle. With the control of the circling times, the preferred times of reactions would be performed to obtain accurate result.

[0012] One purpose of the present invention is proving a loop-type microfluidic system which comprises a loop-channel for allowing the microfluid moving therein, plural air holes for allowing the entrance or the drain of the air or the microfluid, and plural driving conduits for allowing the air or the microfluid passing through. One end of each driving conduit is connected to the loop-channel and the other end is connected to one of the air holes. The air supply is coupled to the air holes for enabling the entrance or drain of the air so as to drive the microfluid within the loop-channel. At least one temperature controller is coupled to the loop-channel to control the temperature of the microfluid within the loop-channel.

[0013] Another purpose of the present invention is providing a loop-type microfluidic device, which comprises a loop-channel for allowing the microfluid moving therein, plural air holes for allowing the entrance or the drain of the air or the microfluid, and plural driving conduits for allowing the air or the microfluid passing through. One end of each diving conduit is connected to the loop-channel and the other end is connected to one of the air holes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIG. 1** is the schematic structure diagram illustrating the loop-type microfluidic device according to the preferred embodiment of the present invention.

[0015] **FIG. 2** is the three-dimensional schematic diagram of the loop-type microfluidic biochip.

[0016] **FIG. 3** is a system block diagram illustrating the loop-type microfluidic system, according to the preferred embodiment of the present invention.

[0017] **FIG. 4** illustrates the process for driving the microfluid in the loop-channel.

[0018] **FIG. 5** is the flow chart of the process for driving the microfluid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0019] The present invention is described with the preferred embodiments and accompanying drawings. It should be appreciated that all the embodiments are merely used for illustration. Although the present invention has been described in terms of various preferred embodiments, the invention is not limited to these embodiments. The scope of the invention is defined by the claims. Modifications within the spirit of the invention will be apparent to the person having ordinary skill in the art.

[0020] Referring to **FIG. 1**, the structure of the microfluidic biochip according to the preferred embodiment of the present invention is provided. The biochip comprises a loop-channel **10-12**, driving conduits **4-6** and air holes **1-3**. It should be appreciated that although merely three driving conduits and corresponding air holes are illustrated in **FIG. 1**, the drawing only exemplifies the preferred embodiment of the present invention, namely the application of PCR which requires three-level of temperature changes. To phase in other words, the present invention may also be applied to other embodiments, instead limited in the three-level-temperature reaction. Besides, the number of the driving conduits and the air holes may be modified on the user's demand. The number of the air holes is preferably identical to that of the driving conduits, and furthermore the driving conduits connect to the air holes one by one. The present invention is mainly applied for the microfluidic specimen, so the diameters of the driving conduits and the loop-channel are preferably about 100 micron.

[0021] The following embodiments illustrate the application to the PCR, but the present invention is not limited to be used in PCR. Generally, since the specimen of PCR should bear three-level temperature changes, the present embodiment would identify the loop-channel into three segments **10-12** by associated driving conduits **4-6**. Three temperature controllers **7-9** are utilized to control the temperature of each segment. Because the microfluidic channel of the present invention is loop type, the microfluid could circle around therein and pass through segments **10-12** with different temperatures sequentially. Thus, the effect of three-level temperature changes could simply be obtained. Temperature controllers **7-9** may use various heating means, such as heating by metal contact or infrared rays. Moreover, because of the loop type of the present invention, each temperature controller could simply maintain in respect fixed temperature to achieve the purpose of three-level temperature changes. The complicated fast temperature change control is no longer required.

[0022] Since the microfluidic specimen circles around in the loop-channel in clockwise or anticlockwise direction, the times of reaction would depend on the times of circling. Therefore, no matter how many times of the reaction is required, even up to tens or thousands, the enlargement or the extension of the loop-channel is unnecessary. In conclusion, the present invention could simplify the structure, save a lot of space and reduce the frequency of malfunction. Besides, in the drawings, the shape of the loop-channel is a circle, but the present invention could still adopt other suitable closed loop-channels in various shapes, such as an ellipse or a polygon.

[0023] **FIG. 2** illustrates the three-dimensional diagram of the loop-type microfluidic biochip according to the present invention. The dimension of the biochip is about 3 to 4 centimeters and the thickness is about 0.1 centimeter. As shown in **FIG. 2**, loop-channel **21** (namely segments **10-12**

in **FIG. 1**) and driving conduits **4-6** are included in substrate **20**. Air holes **1-3** are used as inlets or outlets for allowing the entrance or the drain of the microfluid and the compressed air. In one embodiment of the present invention, the forming of the microfluidic biochip may be implemented by etching the channels (including **1-6** and **21**) on a lower substrate and covering the etched lower substrate with an upper substrate or other materials. It should be noted that manufacturing method of the biochip is not significant for the present invention, so various known techniques could be applied to produce the biochip. The present invention should not be constrained in any embodiments. Since the loop-type design is adopted, the microfluidic biochip could be formed in extremely small size, no matter how many times of biochemical reactions are desired to perform.

[**0024**] **FIG. 3** illustrates the block diagram of the microfluidic system. The system mainly applies the air to drive the microfluid within the biochip to perform the loop movement, such as movement in clockwise orientation or anticlockwise orientation. Air supply **32** works as the air source and comprises air compressor **320**, buffer tank **321** and plural control valves **322-324**. The number of the valves is at least the same as that of the air holes of biochip **20**. Three valves **322-324** in the preferred embodiment illustrated in **FIG. 3** are respectively coupled to three air holes **1-3** of biochip **20**.

[**0025**] First, air compressor **320** compresses the air to required air pressure and then stores the compressed air in buffer tank **321**. After that, buffer tank **321** provides the compressed air to valves **322-324**, respectively. Besides allowing the compressed air entering the loop-channel though the air holes and the driving conduits, the valves could also drain the air or the microfluid from the loop-channel.

[**0026**] The system in **FIG. 3** may be controlled by computer **30**. Computer **30** may coupled to or installed with a data acquisition card **31**. Data acquisition card **31** could provide driving signals to air supply **32** to drive the movement of the microfluid within the loop-channel of the biochip by the entrance or the drain of the compressed air. As this system is applied to the biochemical reaction, a heater **34** and a temperature detector **35** would be coupled to biochip **20**. Heater **34** is controlled by the signals from computer **30** through data acquisition card **31** to provide heat in order to raise the temperatures of segments **10-12** to required levels. Temperature detector **35** could detect the temperatures within the biochip during biochemical reaction, and provide the detected temperatures to computer **30** via data acquisition card **31** for feedback control. In the situation of PCR, the system may further comprise an additional Optical Detecting Instrument **36**, which could directly detect the specimen reacting within the loop-channel to monitor the reproduction efficiency of the DNA. Such monitored information is also provided to computer **30** via data acquisition card **31**, and the required reaction times as well as the timing for stopping the reaction are determined accordingly. It should be noted that the structure of air supply **32** is merely illustrated for exemplification, instead of limitation. Any suitable devices with the ability to provide the air with enough pressure into the air holes and drain the air or the microfluid from biochip **20** could be applied to the present invention.

[**0027**] Moreover, the present invention drives the microfluid within the loop-channel to move in circle by means of the air coming from the air holes of biochip **20**. As shown in **FIG. 1**, there are three included angles **13-15** between the loop-channel and driving conduits **4-6**. The level of included angles **13-15** would determine the moving direction of the microfluid within the loop-channel, and the arrangement in **FIG. 1** could let the microfluid move clockwise. Nevertheless, the present invention is not limited to the configuration of **FIG. 1**, and included angles **13-15** may still be modified to let the microfluid move anticlockwise. Included angles **13-15** are preferably falls among 0 to 45 degrees. The smaller the included angles are, the greater the driven force would be. It may become more difficult to manipulate the movement. However, too large included angles may disperse the air so as to produce insufficient driven force. Besides, the present invention uses the control valve to control the entrance or the drain of the air or the microfluid, so the gate or valve is not required between driving conduits **4-6** and the loop-channel. This simplifies the structure of the biochip so as to save the cost and reduce the frequency of malfunction.

[**0028**] Referring **FIG. 4** and **FIG. 5**, **FIG. 4** illustrates the driving process of the microfluid within the loop-channel according to one embodiment of the present invention, and six stages A-F are included. **FIG. 5** is the flow chart of the driving process. First, in step **50**, the microfluidic specimen is directed into segment **10**, as shown in stage A. In one embodiment of the present invention, the air supply utilizes the air to push the specimen into segment **10** via air hole **1** and driving conduit **4**. Next, in step **51**, the specimen is driven to move into segment **11**, as shown in stage B. In this process, the control valve corresponding to air hole **1** would allow the air with suitable pressure entering into the loop-channel via driving conduit **4** while the control valve corresponding to air hole **3** would allow the drain of the air. Thus, the clockwise push force would be formed in segment **46** to drive the microfluid therein to move to segment **11**, as shown in stage C.

[**0029**] After that, in step **52**, the specimen would be driven to segment **12** by the air. As shown in stage D, air hole **3** is closed, and the compressed air would come from air hole **2** and then exit via air hole **1**. In this way, a driving force would be generated to push the specimen moving from segment **11** to segment **12**, as shown in step E.

[**0030**] Following that the specimen enters segment **12**, the specimen would move to segment **10** in step **53** to complete a round of clockwise circling movement. As shown in stage F, air hole **1** is closed, and the compressed air would come from air hole **3** and then exit via air hole **2**. Thus, similar to the above operation, a driving force would be generated to push the specimen moving from segment **12** to segment **10**, as shown in step A.

[**0031**] Since the embodiment is applied to PCR, the temperature controller would adjust the temperature of each segment for reaction in advance. For instance, the temperature of segment **46** is set at 94° C., that of segment **47** is set at 50° C. and that of segment **48** is set at 70° C. Accordingly, for every round of circling around the loop-channel, the specimen could undergo one cycle of three-level temperature change. By repeating above operation, the specimen could go through desired cycles of three-level temperature change. Before the desired cycles are finished, step **53** would

be followed by step **51** to perform another clockwise movement. As the desired cycles are reached, the specimen would be led out to obtain the accurate result of reaction, as shown in step **54**.

[**0032**] The prior art merely applies linear unidirectional or reciprocation movement. The biochip utilizing unidirectional movement does not need the complex thermal change control, but the times of reaction is limited. Bedsides, for this kind of biochip, the size would be extended and the structure would be complicated. The biochip utilizing reciprocation movement may maintain better size, but the complex thermal change control is necessary and therefore the accurate result of reaction would be difficult to obtain. The loop-design of the present invention can solve all of the problems mentioned above as well as preserve every advantages of prior art. The efficiency of the reaction would therefore be highly raised. In addition, the present invention adopts valve-less design in the channel or conduits, so the manufacture of the biochip could be simplified to reduce the cost.

[**0033**] As is understood by a person skilled in the art, the foregoing preferred embodiments of the present invention are illustrated of the present invention rather than limiting of the present invention. It is intended to cover various modifications and similar arrangements included within the spirit and scope of the appended claims, and the scope of which should be accorded the broadest interpretation so as to encompass all such modifications and similar structure. While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

We claim:

1. A loop-type microfluidic system, comprises:

a substrate having:

a loop-channel for allowing the microfluid moving therein,

air holes for allowing the entrance or the drain of air or the microfluid, and

driving conduits for allowing the air or the microfluid passing therethrough, wherein one end of each said driving conduits connected to said loop-channel and the other end connected to one of said air holes;

an air supply coupled to said air holes for enabling the entrance or drain of the air through said air holes and said driving conduits to drive the microfluid within said loop-channel; and

one or more temperature controllers coupled to said loop-channel for controlling the temperature of the microfluid within said loop-channel.

2. The loop-type microfluidic system as set forth in claim 1, wherein the diameter of said driving conduits and said loop-channel is about 100 micron.

3. The loop-type microfluidic system as set forth in claim 1, wherein an included angle between said loop-channel and each said driving conduit controls the moving direction of the microfluid within said loop-channel.

4. The loop-type microfluidic system as set forth in claim 3, wherein the moving direction includes clockwise orientation and anticlockwise orientation.

5. The loop-type microfluidic system as set forth in claim 3, wherein the included angle falls among 0 to 45 degrees.

6. The loop-type microfluidic system as set forth in claim 1, wherein the shape of said loop-channel includes a circle, an ellipse or a polygon.

7. The loop-type microfluidic system as set forth in claim 1, wherein the number of said air holes is identical to that of said driving conduits, and said driving conduits connect to said air holes one by one.

8. The loop-type microfluidic system as set forth in claim 7, wherein said air supply enables the entrance or the drain of the air through said air holes to drive the microfluid within said loop-channel move toward a direction.

9. The loop-type microfluidic system as set forth in claim 8, wherein said air supply enables the entrance of the air in one of said air holes while enabling the drain of the air in another one of said air holes.

10. The loop-type microfluidic system as set forth in claim 1, which further comprises:

an Optical Detecting Instrument coupled to said loop-channel for detecting the microfluid within said loop-channel.

11. The loop-type microfluidic system as set forth in claim 1, wherein said temperature controller controls every segment of said loop-channel respectively.

12. The loop-type microfluidic system as set forth in claim 11, wherein the temperature of at least one segment of said loop-channel is different from those of other segments.

13. A loop-type microfluidic device, comprises:

a substrate a substrate having:

a loop-channel allowing the microfluid moving therein,

air holes allowing the entrance or the drain of air or the microfluid, and

driving conduits allowing the air or the microfluid pass therethrough;

wherein one end of each said driving conduits connected to said loop-channel and the other end connected to one of said air holes.

14. The loop-type microfluidic system as set forth in claim 13, wherein the diameter of said driving conduits and said loop-channel is about 100 micron.

15. The loop-type microfluidic system as set forth in claim 13, wherein an included angle between said loop-channel and each said driving conduit controls the moving direction of the microfluid within said loop-channel.

16. The loop-type microfluidic system as set forth in claim 15, wherein the moving direction includes clockwise orientation and anticlockwise orientation.

17. The loop-type microfluidic system as set forth in claim 15, wherein the included angle falls among 0 to 45 degrees.

18. The loop-type microfluidic system as set forth in claim 13, wherein the shape of said loop-channel includes a circle, an ellipse or a polygon.

19. The loop-type microfluidic system as set forth in claim 13, wherein said air supply enables the entrance or the drain

of the air through said air holes to drive the microfluid within said loop-channel move toward a direction.

20. The loop-type microfluidic system as set forth in claim 19, wherein said air supply enables the entrance of the air in one of said air holes while enabling the drain of the air in another one of said air holes.

21. The loop-type microfluidic system as set forth in claim 13, wherein said temperature controller controls every segment of said loop-channel respectively.

22. The loop-type microfluidic system as set forth in claim 21, wherein the temperature of at least one segment of said loop-channel is different from those of other segments.

* * * * *