Reconfigurable Microfluidic Device for Drug Synthesis

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The drug development industry is facing an increase in development costs and lower approval rates. Microfluidic technology offers promising results for its usage in several processes in this field. This project aims to develop a reconfigurable microfluidic chip which could be used in drug synthesis optimization. The proposed device is capable of redefining its fluidic channel using a large array of microvalves, thus, various tasks could be performed using a single device. To achieve such a goal, a highly scalable microvalve with a fast response time is needed to be designed. A Peltier actuated microvalve has been proposed, using a bidirectional heat pump, the valve is expected to perform a fast closing and opening action. The valve is fabricated using 3D printed and CNC metal parts, avoiding microfabrication complications and minimising the cost and production time. An electronic circuit capable of controlling a large array of the valve is also proposed. The cost of the fabricated valve is less than £30 per valve, it can be closed in 1.11 seconds and opened in 1.85 seconds. Further development could reduce the response time of the valve and the integration of the valve to form an array is highly feasible.

1. Introduction

The increase in the cost and time of the development of new drugs[1] together with more strict regulations applied to the safety of the new drugs[2] have caused the decrease of approved new drugs. the pharmaceutical industry's continually reduced efficiency and rising costs are caused by the high risk in the drug development process. Almost half of the drugs candidate fail in phase III clinical trials where 80% of the cost is already incurred, while only a tiny fraction of 10% successfully enter the market[3]. Reduction in time and expense at each stage of the drug development process may be achieved with the help of microfluidics.

Microfluidic is the study of manipulating fluids and particles in a very small space, down to the micron and submicron scale, as well as the development of techniques and technology to do so. Compared to conventional laboratory equipment, microfluidic devices drastically reduce the amount of time and materials needed to complete tasks[4]. There are many applications of the microfluidic platform in the drug synthesis process, for example, concentration manipulation[5,6], sample preparation[7,8], bioseparations[9,10], and preclinic evaluation[11,12].

This project focuses on drug synthesis optimization, a reconfigurable microfluidic device is proposed to be used in this process. Unlike, traditional static microfluidic devices which are built for specific purposes, reconfigurable microfluidic devices can be reconfigured to perform various functions without the need to redesign and refabricate the new devices[13]. The ultimate goal of this work is to fabricate a device which is capable of various tasks essential for drug synthesis, including mixing reagents, separating, and controlling temperature. Anyhow, given limited time, this project will only focus on the microfluidic channel redefining function and the peristaltic pumping function. Peristaltic pumping, which is analogous to the movement of the gastrointestinal tract, involves regularly compressing some parts of the fluid duct to force fluid to travel in a specific direction. The proposed design of the device consists of an array of microfluidic valves which are used to define the desired microfluidic path. The valve must be independently controllable and can be opened and closed fast enough to perform peristaltic pumping. The conceptual design is shown in figure 1.

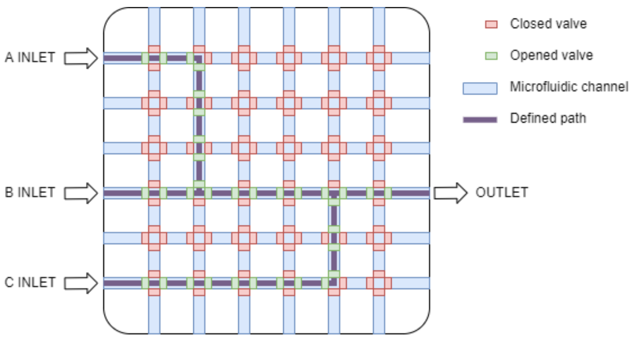

Figure 1 Reconfigurable microfluidic device concept example consists of six vertical and six horizontal microfluidic paths. At each junction are located four microfluidic valves. The valves shown in green are opened to form a path as illustrated by dark grey lines. The current part allowed a mixture of chemicals A and B then chemical C is added later. The mixture exited the device on the right side.

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One of the most critical parts of the proposed design is the valve. A microfluidic valve must be specifically designed to fit the purpose of this device. Thus, the valve will be designed regarding the following design specification.

- The valve can be fabricated at a sensible cost, considering hundreds of valves are needed for a single device.

- Each valve has its own actuator which can be opened and closed in less than a second, to perform peristaltic action.

- The valve controlling mechanism is scalable, meaning that hundreds of valves can be easily fabricated and controlled.

- The valves can be placed close to each other on a scale that is sensible for the overall size of the device.

- All components that will come in contact with the liquid in the fluidic channel must have high chemical resistance, in order to operate with a variety of solvents.

In order to achieve such a design, the design of microfluidic valves that have been proposed before is investigated. Some reconfigurable array of valves in the microfluidic device have been proposed before[14], by using the addressing method, a large number of valves can be controlled with less actuator, however, the speed is reduced, and the valves are also required to operate in a specific order, thus, the flexible channel defining, and peristaltic action is hard to achieve. There is also a software-programmable microfluidic device which uses pneumatic actuation to control valve array and be able to perform a peristaltic action[15], as shown in figure 2, however, the multiplexer system, that is used to control the numbers of valves by less actuator, is still large, compared to the working area of the device, thus, by scaling up the system to hundreds or thousands of valves, the overall size of the device will be unreasonable large. The usage of one actuator for each valve could overcome the issue mentioned before, thus, some of those designs will be discussed.

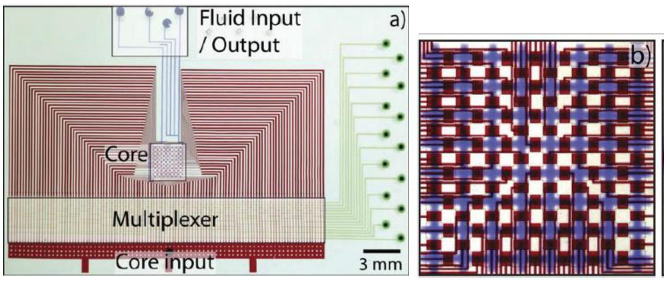

Figure 2 (a) the array of pneumatically actuated valves in the core area controlled by multiple pipelines applying pressure through a 7-bit microfluidic multiplexer. (b) micrograph of the core area, independently actuated valves surrounding each node providing control over their connectivity[15].

Ice valve which uses a cooling element to freeze and block the liquid inside the channel is a considerable choice because of the simple structure of the channel which allows chemical resist material to be used easily[16]. However, this type of valve may not be able to operate on reagents which have a very low freezing point, Thus, not practical for a chemical synthesis platform. The diagram of the device is shown in figure 3.

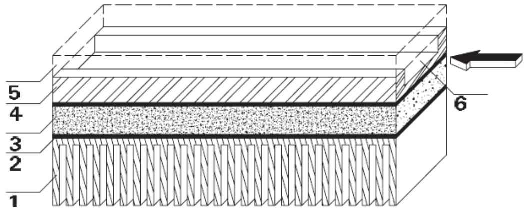

Figure 3 Schematic diagram of an ice valve, the valve uses a Thermoelectric cooling device (TECD) to freeze and block the liquid in the channel consisting of 1. fin-like heat exchanger, 2. heat conducting and insulated layer, 3. TECD, 4. working channel, 5. electric heater, 6. working fluid[16].

Another interesting actuation method is using solenoid actuators. It can be used to push a valve membrane to deflect and block the microchannel, resulting in a fast-operating valve design which is easy to fabricate[17], as shown in figure 4. However, the size of the typical solenoid actuator is relatively large about several centimetres, hence, integrating thousands of valves in a single chip is impractical. The other actuation method is a piezoelectric device, an actuator which uses the property of some material which deforms after the voltage is applied. A large array of piezoelectric actuated valves is reported[18], each valve can be accessed easily and independently in this design, which offers simple control of the device as shown in figure 5. Yet, the custom-made multi-head piezoelectric actuator used in this study is very complicated and expensive.

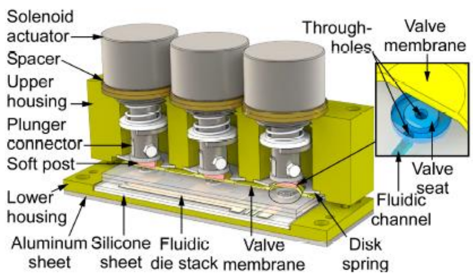

Figure 4 The solenoid actuated microvalve module which transmit the displacement from solenoid actuators to valve membranes. The valve membrane will then be pushed on the valve seat and seal the through holes[17].

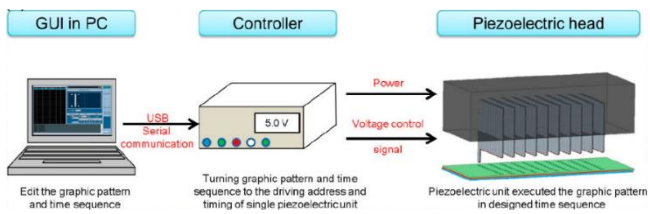

Figure 5 The array of piezoelectric heads being independently controlled by a controller unit. Each head is responsible for pushing the membrane of each microfluidic valve membrane in the array of valves[18].

A thermally actuated valve is considered a good choice for this project as it has been reported to be made at a low cost and can be scaled up easily, due to the simplicity of the heating method[19]. As shown in figure 6, this type of valve utilizes the thermal expansion of an expansion medium (Paraffin wax for this example) while being heated to push the membrane and block the flow channel. In this study, the operation time of the wax valve is still long because of the cooling of the expansion medium, it might be able to improve this design by replacing the resistance heater with the Peltier device, an electrically driven solid-state heat pump which capable of transferring the between two sides. By using this, the expansion medium can be heated and cooled at command. There already have been some studies that utilize the thermoelectric heat pump in microfluidic valves [20], but the fabrication process of the valve is complicated, and a microfabrication facility is needed. When applied in a large microfluidic array, the cost of a valve impact the work significantly. Hence, this project will investigate the Peltier actuated microvalve, which can be fabricated at a low cost without microfabrication equipment.

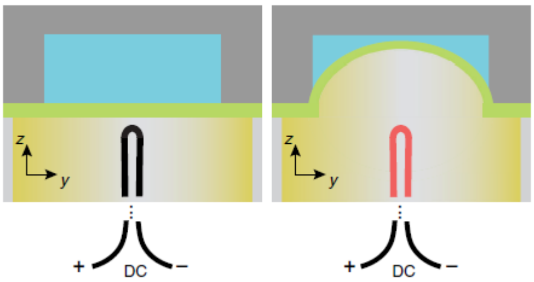

Figure 6 Thermally actuated valve using an electric heater to heat the expansion medium (wax), which then inflates and blocks the flow channel[19].

2. Methodology

2.1 Prototype Designing

The idea of this prototype is to test whether the usage of a Peltier device instead of a common resistance heater could enhance the performance of the thermal-actuated microfluidic valve. This prototype of a normally open valve is aimed to have two main advantages over traditional microfluidic valves. First, the valve can be opened as quickly as closed, and second, the valve can be effortlessly assembled at low cost. The conceptual design of this prototype is illustrated in figure 7.

The common concept in the traditional thermal actuated microfluidic valve[19] is that the expansion medium is stored in a sealed chamber. When heated, it expands and pushes a thin membrane to deflect and block the fluidic channel, therefore, the valve is closed. To reopen the valve, the user must wait for the expansion medium to passively cool down. However, in this design, with the usage of the miniature Peltier device as a heater, the valve can actively pump the heat out of the medium and cool it down. Therefore, this design of the valve is expected to be opened at a comparable speed and controllability of the valve closing action.

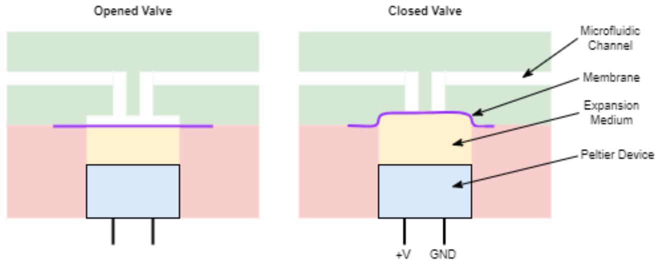

Figure 7 Conceptual design of Thermoelectrically Driven Thermal Actuated Microfluidic Valve Prototype. The figure on the left is the opened valve, and the figure on the right is the closed valve. The Peltier device is used to heat the expansion medium to expand and push the membrane to close the valve. Reversing the voltage applied to the Peltier result in the valve opening.

In this design, the other main goal apart from the valve performance is to reduce the cost and simplify the manufacturing process as much as possible. Thus, the valve is designed in such a way that it can be built using only basic engineering tools such as a 3D printer and a milling machine. Considering the conceptual design and the manufacturing technique available, the detailed design of this prototype has been proposed as shown in figure 8. The topmost part of the prototype is the microfluidic channel and connectors. The features on both sides of this part are designed to connect with Luer-lock syringes which are the inlet and outlet of the valve module. The membrane located underneath the middle part of the microfluidic channel can be deflected when the expansion medium expands. Without the expansion of the medium, the membrane does not block the channel, therefore, the valve is normally open. The membrane is made from 50 µm thick PEEK (Polyether ether ketone) due to its high chemical resistance. The expansion medium is stored inside an O-ring between the membrane and the Peltier device. The expansion medium is olive oil which has been used before in previous studies of thermal actuated microfluidic valves[19]. The O-ring is made from Nitrile rubber which is flexible and thus can prevent the leakage of the expansion medium. Under the O-ring, the Peltier device shown in blue is placed on a custom-made Aluminium piece, which was machined to have a pocket the size of the Peltier device. This base part is responsible for dissipating away the heat that the Peltier device draws out from the expansion medium. Therefore, Aluminium is the chosen material for this part because of its high thermal conductivity.

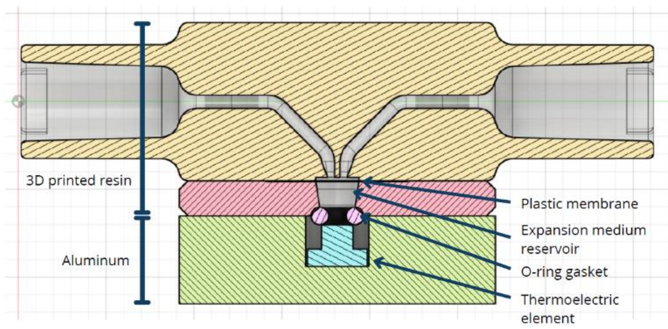

Figure 8 detailed design of Peltier Driven Thermal Actuated Microfluidic Valve Prototype.

2.2 Hardware Fabrication

The 3D printer Formlab Form 3B+ is used to print the microfluidic channel and syringe connector part. The round 750 µm diameter microfluidic channel integrated with two Luer-lock syringe connectors attached to both ends has been printed. The material used for this part is Formlab standard clear-coloured resin which is recommended by the manufacturer for fabricating the microfluidic device, due to its transparency, which simplifies the observation of the channel features inside the device[21]. A previous study suggested that using this printer and material, the 500 µm round channel is the smallest size that can be printed without any complication[22]. However, from the test prints, the 750 µm round channel is the smallest size that can be printed successfully every time, thus, it has been selected. The valve area is shown in figure 9.

The base aluminium part is made using the CNC machine. The Peltier device chosen for this prototype is CP0734-238, it is the smallest Peltier module available from a major supplier with a size of 3.4 mm by 3.4 mm. It is operated by a 0.5 V power supply and consumes a current of a maximum of 3 A. The size of the Peltier determines the size of the valve. The Luer-lock syringe, PEEK membrane, Nitrile rubber O-ring, and the Peltier device are bought from Mouser. All the parts are then assembled using four M3 Screws which go through each corner of the 3D printed part and lock in the tapped holes in the aluminium part. The assembled unit of the valve is shown in figure 10.

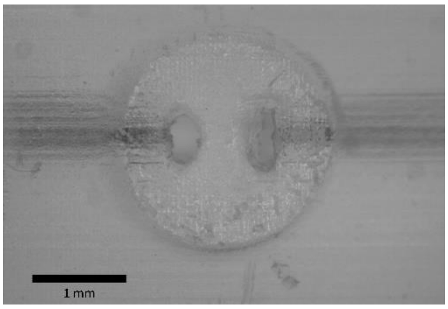

Figure 9 Microscopic image of the bottom view of 3D printed microfluidic channel. The circle is the valve area which the membrane is located. The opening of left channel and right channel will be blocked when the expansion medium expand and deflect the membrane, hence the liquid could not travel pass through the valve.

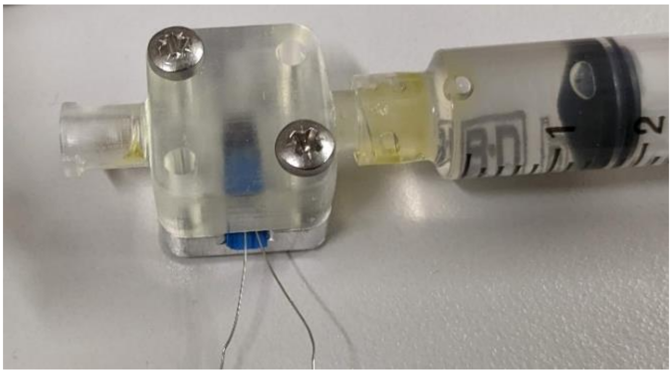

Figure 10 The assembly of the Peltier-driven thermal actuated valve. The syringe is connected to the right side of the valve as an inlet for the liquid.

2.3 Control Circuit

The microfluidic valve, which uses a Peltier device as an actuator, needs an electronic circuit to control the voltage supplied to the element. Therefore, a custom-made PCB (printed circuit board) has been designed for this purpose. The specification of the PCB is as follows.

- The PCB can supply an invertible voltage of 0.5 V to the Peltier device to force the heat to flow both ways (Into the expansion medium to close the valve and out of the expansion medium to open the valve)

- The PCB can generate a signal to open and close multiple microfluidic valves independently at the same time. Thus, the PCB can be used for future experiments with multiple valves.

- The PCB can supply enough electric current for every connected Peltier device, which is a maximum of 0.7 A per element.

- The PCB can be controlled using serial communication from the computer.

After the PCB specification is defined, the schematic and layout of the PCB are designed, respectively. After iterations of the design, the PCB layout is concluded as shown in figure 11. This PCB is capable of controlling 4 microfluidic valves at the same time. The PCB manufacturing process is outsourced by JLCPCB company.

The first section is the array of LEDs that display the valves' status. There are four sets of LEDs, each set is responsible for displaying the status of each valve. One set is consisting of two LEDs, red and blue. Red LED is lit when the Peltier device pumps heat toward the medium, and the blue LED is lit when the heat is drawn in the opposite direction. In the other words, when the valve is signalled to close the red LED is lit, and when the valve is signalled to open the blue LED is lit. If the valve is in the idle state, the channel is open, and the two LEDs for the valve are both off.

The second section is the output channels. Four pairs of through holes are located here. Each pair of through holes is designed to connect to a Peltier device located in the microfluidic valve. Next to each pair located an H-bridge driver chip. This chip provides invertible voltage to the Peltier devices.

The third section is the power management unit. The barrel connector on the leftmost side of the PCB receives power from the 5V power supply.

The selected power supply, AC-DC power supply SMI36-5 can provide maximum power of 25W. The voltage from the barrel connector is used to power the microcontroller directly and is used as a logical voltage reference for the signal processing unit and drivers. The Linear regulator chip is used to convert the

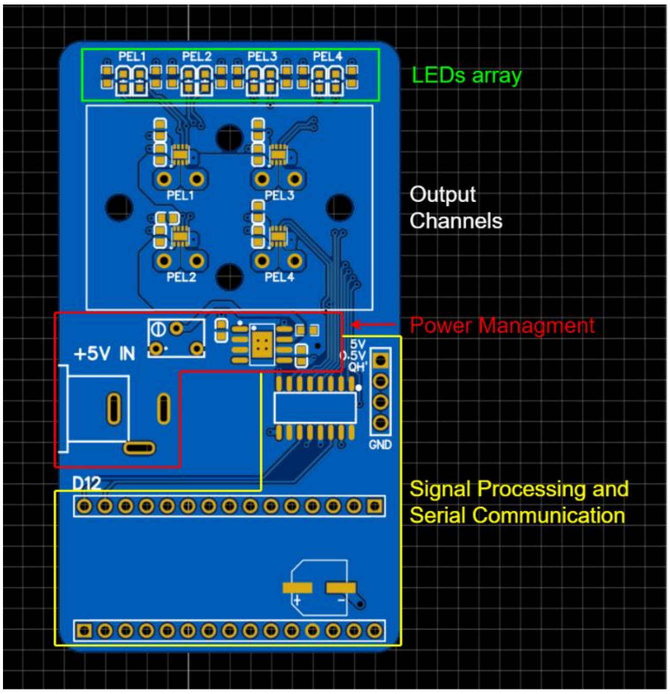

Figure 11 The PCB layout. The PCB consists of four main parts which are indicated by four different colour squares.

voltage of 5V down to 0.5V and provide the converted voltage to the drivers.

The fourth section is the signal processing and serial communication unit. The two rows of pin header at the bottommost of the PCB are used to connect with a microcontroller Arduino Nano. The Arduino communicates with the user's computer via serial communication by the USB cable. When an input is received from the computer, the Arduino commands the 8-bit shift register chip to signal the drivers corresponding to the input. The shift register chip is used because the signal can be cascaded. Using a signal from only a few pins of the Arduino, the command for a large number of valves can be generated. However, in this project, the shift registers chip signals only four onboard drivers.

Theoretically, using the shift register chip, this PCB can be used as a control centre for multiple responder PCBs. Responder PCBs have no onboard microcontroller, but they can control their valve corresponding to the signal given from the control centre. Responder PCBs haven't been designed or used in this project, but the current PCB has pin headers made for connection to these responders for usage in future development. These pin headers are located on the right side of the PCB. The completed PCB is shown in figure 12.

2.4 Firmware

The firmware for this PCB is written in C++ and is installed on the Arduino nano. The expected input is a string of numbers "1","2","3" or "4" received through the Arduino's serial port. After the signal is received the PCB will switch the state of the valve whose number corresponds to the input string. Multiple numbers can be sent in one string. For example, if all valves are open and the PCB receive the input string "13", valve number 1

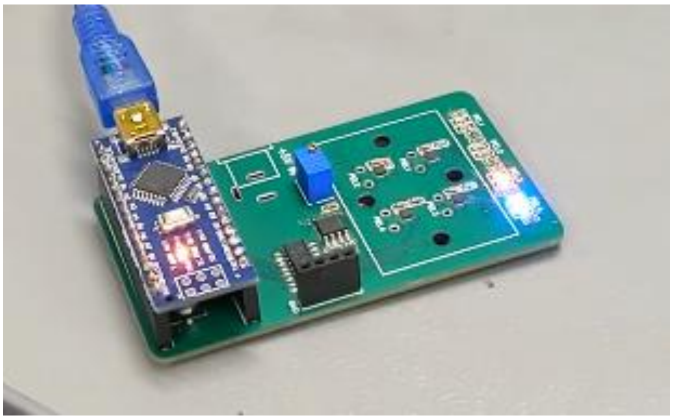

Figure 12 Fully assembled PCB. The PCB is connected to the computer via a USB cable. In this picture, the LEDs array state that the PCB is signalled to close valve number 3 (red light), and open valve number 4 (blue light).

and number 3 will be closed at the same time. Then, if the string "1" is received, valve number 1 will be opened, but valve number "3" will remain closed.

For usage in experiments, the firmware can be easily modified. The valve opening action can be chosen between inverting the voltage supplied to the Peltier device to force heat out of the medium and simply cutting off the heating and letting the medium cool down.

2.5 Testing

As mentioned before, this prototype is aimed to have superiority over traditional microfluidic valves in two main aspects, the simplicity of the fabrication process and the valve opening speed. The proposed design, which needed only a 3D printer and common engineering tools to fabricate, already satisfied the first aspect. Therefore, an experiment has been set up to assess the valve opening speed of the prototype. The null hypothesis is that: there is no statistically significant difference between the opening time of the thermoelectrically driven microfluidic valve and the traditional thermal actuated microfluidic valve.

To test the hypothesis, the evaluation must be run on two setups, firstly, the microfluidic valve that is closed by a heater and opened by natural dissipation of heat, secondly, the microfluidic valve that is closed and opened by a Peltier device. However, the other variables such as microfluidic channel properties, valve size, and fluid pressure must be controlled. Therefore, the experiment on two setups should be conducted on the same hardware configuration with different controlling firmware.

The hardware setup is shown in figure 13. A syringe loaded with food colouring-infused water is mounted on the inlet of the fully assembled microfluidic valve unit, while the fluid viewing tube is mounted to the outlet. The syringe is fixed at an angle with a c-clamp. The microfluidic valve unit is electrically connected to the controller PCB. A fixed load is applied to the syringe plunger using a bottle of water placed on a 70° angled plate. Thus, the force applied to the syringe is always constant. The reason that the water-filled bottle is used is that the force from its weight can be fine-tuned so that the fluid inside the microfluidic chip is

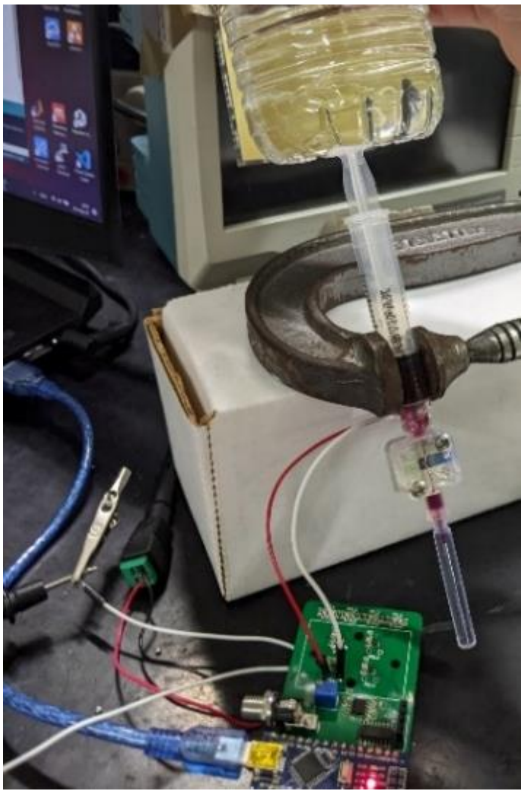

Figure 13 The experiment setup. The water bottle is about to be released on the syringe plunger. The PCB is connected to the valve unit via 2 wires, red and white and connected to the computer via the blue USB cable

moving at the observable speed. The weight used in the experiment is 537.4 g, therefore, the total force applied to the syringe is 4.95 N.

Using the same hardware configuration, the experiments have been executed on two firmware. In the first firmware, when the button on the computer's keyboard is pressed, the command string will be sent to the PCB. The PCB will then power the Peltier device to pump the heat toward the expansion medium and close the valve. When the button is pressed again, the PCB will stop applying voltage to the Peltier device. Therefore, the valve is opened because the heat dissipates away from the medium. In the second firmware, as same as the first firmware, when the button is pressed, the valve close. However, when the button is pressed again, the PCB inverted the voltage applied to the Peltier device. The heat is forced to flow out of the medium and dissipate away in the aluminium block underneath the Peltier device.

The first firmware represents a traditional thermal actuated microfluidic valve, which opens after the heat dissipated away naturally from the medium. The second firmware represents the prototype that has been developed in this project, in which the flow of heat is controlled by a Peltier device.

The experiment is started by carefully applying the weight to the syringe. The food colouring-infused water moves down slowly from the syringe through the microfluidic valve unit. While it is moving down through the observation tube, the button is pressed then the valve is closed. After the liquid completely stopped, the button is pressed again to open the valve, after the valve opened, the liquid started to move down through the observation tube again. The whole experiment is filmed. The video frames include the observation tube and the valve status displaying LEDs array on the PCB as shown in figure 14. The experiment is executed 15 times on each firmware using the same hardware configuration.

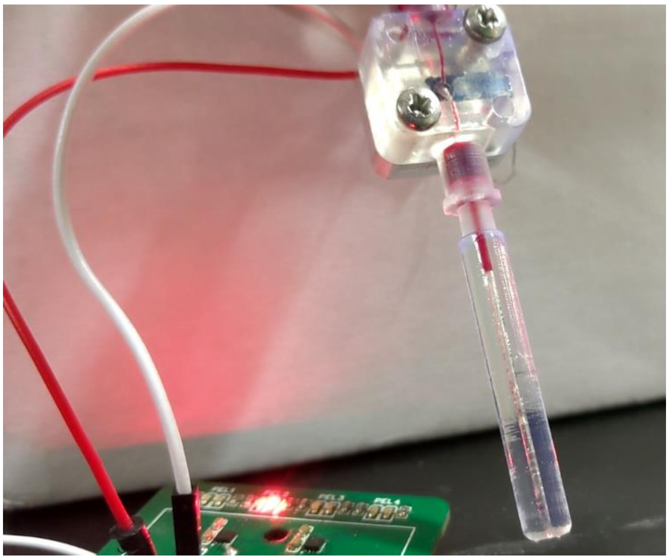

Figure 14 Example frame from the video. The level of the red liquid inside the observation tube can be seen together with the LED on the PCB. At this time frame, the red LED is lit, which means the Peltier device is heating the medium, thus the valve is in the closed state.

After all, the videos of the experiments on both firmware are obtained, and there are two pieces of information which are needed to extract from the videos. First, the time between the start of heating and the closure of the valve. Second, the time between the opening signal and the opening of the valve.

The time point in the video when the heating start is easily obtained by finding the frame in which the red light on the PCB is lit. The time point of the opening signal can also be observed from the fade of the red LED for the first firmware and the light of the blue LED for the second firmware. Next, the time point where the valve is open and closed can be determined by the movement of the liquid in the observation tube.

The motion detection feature of the software VLC media player is used to find the last frame that the liquid moves before it stops and the first frame that the liquid move after it stops. These two frames determine the time point at which the valve is fully closed and fully opened respectively. All the time points are attained in the resolution of 100 milliseconds. Therefore, the required time points from the video are obtained, and the closing and opening time required for each firmware in each experiment can be calculated. These raw data are shown in supplementary information section.

3. Results and Discussion

The single unit of the Peltier-driven microfluidic valve successfully achieves control over the fluidic channel. The valve can be closed completely and reopened again. The time required to close and open the valve in two firmware is obtained. The first firmware represents the traditional thermal actuated valve, and the second firmware represents the Peltier-driven valve. Each firmware has been tested 15 times. The mean and standard deviation of the data is shown in the bar plot as in figure 15.

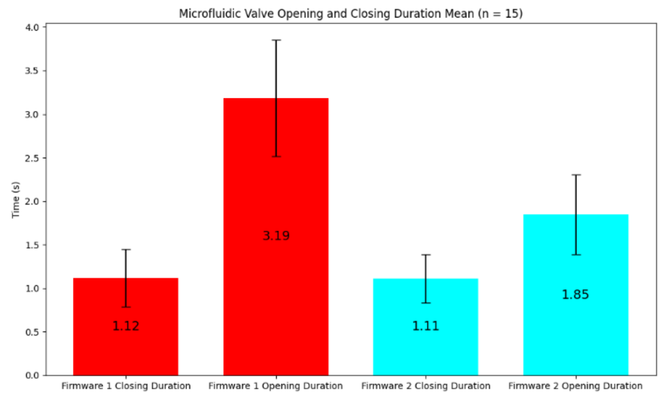

Figure 15 The mean of the time required to open and close the valve for the first firmware (red) and the second firmware (cyan) from the experiment is represented by the height of the bars. It is calculated from 15 data points. The standard deviation of each data is illustrated by the error bars.

To confirm that the control variable, such as fluidic channel properties, the power sent to the valve, and the shape of the valve is the same for the two groups of the experiments, the closing duration between the two setups must be statistically tested. The null hypothesis is that there is no statistically significant difference between the closing duration of the two groups. The python code is used to obtain the P-value between the first and the second firmware closing duration. The code is shown in figure 16. The P-value is 0.95, hence, the null hypothesis is not rejected at the threshold value α = 0.01 level. Therefore, it is likely that the control variable is well controlled and there is no difference occurring in the hardware between the experiment of the two groups.

Then, to confirm that the usage of the Peltier element can open the microfluidic valve faster than the traditional method, the opening time between the two firmware must be analysed. The null hypothesis is that: there is no statistically significant difference between the opening time of the experiment in the first and the second firmware. And the alternative hypothesis is that: The first firmware valve opening time is statistically significantly greater than the valve opening time of the second firmware.

The mean opening time of the Peltier version is 1.34 seconds slower than the traditional version, which is 42.05% lower. By performing the one-tail null hypothesis significance testing, the p-value of 5.49 x 10-7 is obtained. Using the threshold value α = 0.01, the null hypothesis can be rejected. Therefore, it is likely that using the Peltier as an actuation device, the valve opening time can be significantly reduced, compared to the traditional thermal actuated valve.

It is important to note that in the Peltier-driven microfluidic valve, the valve opening time is still slightly higher than the valve closing time. This might occur because of the natural behaviour of the Peltier device. When the heat is transferred from one side to the other, the amount of heat accumulated on the hot side is higher than the amount of heat drawn from the cold side. The additional heat is generated by the internal resistance of the Peltier device. Thus, Peltier's efficiency of heating is higher than cooling. Therefore, given the same amount of electrical power, the valve closing action, which requires pumping the heat into the valve, can be performed faster than the valve opening action, which requires pumping the heat out of the valve.

The other critical aspect of this valve is the overall cycle time of closing and opening the valve. In some designs of the traditional thermal actuated microfluidic valve, the operating time of the valve is on the scale of microseconds[23]. Nevertheless, the proposed Peltier valve operating time is on the scale of seconds, this can be explained by the scaling law. The size of the proposed valve, which is roughly 2 mm, is significantly larger than the other microfluidic valves which are in the scale of submillimetre[23]. When the diameter or length of the valve increase, the volume of the expansion medium increase in the magnitude of the power of three. Hence, an exponentially greater amount of heat is needed for the expansion medium to reach a certain temperature.

Given the limited time and resources, the design of the valve in this project the smallest feasible valve size is limited. There are several possible approaches to minimizing the size of this valve design, for example, ordering the extra small custom-made

```
import pandas as pd
from scipy.stats import ttest_ind

Raw = pd.read_excel("/content/drive/MyDrive/Microfluidic result/Experiment data.xlsx")
Data = Raw.loc[0:14,["Heater Close Duration","Heater Open Duration","Thermoelectric Close Duration","Thermoelectric Open Duration"]]

Result1 = ttest_ind(Data["Heater Close Duration"],Data["Thermoelectric Close Duration"], equal_var=False)
Result2 = ttest_ind(Data["Heater Open Duration"],Data["Thermoelectric Open Duration"], equal_var=False, alternative="greater")
print(Result1)
print(Result2)

Ttest_indResult(statistic=0.05989911217338344, pvalue=0.9526739543621074)
Ttest_indResult(statistic=6.403928155723322, pvalue=5.488444387581623e-07)
```

Figure 16 Python code used for calculating P-values. First, the four groups of data consist of 15 data point each are imported from an excel file. Then, the P-test is run on the first two groups of data which are Valve closing duration of firmware 1 and 2 which result in P-value of 0.95. Next, the P-value from the valve opening time between firmware 1 and 2 is obtained, which is 5.49 x 10^{-7}.

Peltier device from a capable company, and using microfabrication facilities to fabricate the expansion medium storage of the valve.
The current price per valve for this design is less than £30. Most of the price is the cost of the Peltier device which is around £23 per module. In large-scale integration, the price per unit will be lower as the Peltier device can be bought as a large order. Moreover, this valve can be fabricated without the cost of operating the microfabrication facility.
Although the 3D printed resin which is used to create the microfluidic channel does not have a chemical resistance property. The valve membrane is made from a chemical-resistant polymer, PEEK. In future improvement, only the channel is needed to be replaced with a chemical-resistance material such as glass. Thus, based on the current design, the goal of the chemical resistance microfluidic chip is relatively easy to achieve.

4. Conclusion

The new design of thermoelectrically driven thermal actuated microfluidic valve has been proposed and fabricated. The design is based on the concept of a thermal actuated valve, which utilizes the expansion of heated olive oil to push the membrane and block the microfluidic channel. Using the Peltier device as an actuator, its capability of transferring heat in two ways allows the valve to be opened almost as fast as the closed, within approximately 1.85 and 1.11 seconds respectively. Additionally, using this actuation method together with the proposed controlling circuit, a large number of the valve can be operated in a single microfluidic chip.
The valve is currently partially chemical resistant; however, the relatively simple replacement of the channel's material could render the valve completely chemical resistant. The fabrication cost per valve is less than £30 without the hidden cost of microfabrication equipment operation.
Even though the overall operation time of the valve rendered it impractical in the real microfluidic application, the minimal ratio of the closing and opening time of the valve together with its scalability still defines this design as a potentially valuable candidate for usage in the reconfigurable microfluidic device. Further study on this design might reduce the operation time of the valve, and improve its chemical inertness, thus, allowing its practical usage as a crucial component of the drug synthesis platform in the future.

5. Bibliography

1 M. Dickson and J. P. Gagnon, Nat Rev Drug Discov, 2004, **3**, 417–429.

2 D. Jones, Nat Rev Drug Discov, 2007, **6**, 855+.

3 S. Y. F. Wong Hawkes, M. J. V. Chapela and M. Montembault, QSAR Comb Sci, 2005, **24**, 712–721.

4 L. Y. Yeo, H. C. Chang, P. P. Y. Chan and J. R. Friend, Small, 2011, 7, 12–48.

5 V. v. Abhyankar, M. A. Lokuta, A. Huttenlocher and D. J. Beebe, Lab Chip, 2006, **6**, 389.

6 L. Chen, F. Azizi and C. H. Mastrangelo, Lab Chip, 2007, **7**, 850.

7 L. A. Legendre, J. M. Bienvenue, M. G. Roper, J. P. Ferrance and J. P. Landers, Anal Chem, 2006, **78**, 1444–1451.

8 B. Jung, R. Bharadwaj and J. G. Santiago, Anal Chem, 2006, **78**, 2319–2327.

9 R. J. Meagher, Y. K. Light and A. K. Singh, Lab Chip, 2008, **8**, 527.

10 C. A. Emrich, I. L. Medintz, W. K. Chu and R. A. Mathies, Anal Chem, 2007, **79**, 7360–7366.

11 C.-W. Wei, J.-Y. Cheng and T.-H. Young, Biomed Microdevices, 2006, **8**, 65–71.

12 N. Ye, J. Qin, W. Shi, X. Liu and B. Lin, Lab Chip, 2007, **7**, 1696.

13 F. Paratore, V. Bacheva, M. Bercovici and G. v. Kaigala, Nat Rev Chem, 2022, 6, 70–80.

14 T. Thorsen, S. J. Maerkl and S. R. Quake, Science (1979), 2002, **298**, 580–584.

15 L. M. Fidalgo and S. J. Maerkl, Lab Chip, 2011, **11**, 1612–1619.

16 L. Gui and J. Liu, Journal of Micromechanics and Microengineering, 2004, **14**, 242–246.

17 H.-T. Lu, Y. Qin and Y. Gianchandani, , DOI:10.3390/s2102.

18 Y. Yalikun and Y. Tanaka, Micromachines (Basel), 2016, **7**, 83.

19 M. Sesen and C. J. Rowlands, Microsyst Nanoeng, 2021, **7**, 48.

20 T. Huesgen, G. Lenk, T. Lemke and P. Woias, in 2010 IEEE 23rd International Conference on Micro Electro Mechanical Systems (MEMS), IEEE, 2010, pp. 1159–1162.

21 https://formlabs.com/uk/blog/microfluidics-millifluidics-lab-on-a-chip-manufacturing/.

22 B. Carnero, C. Bao-Varela, A. I. Gómez-Varela, E. Álvarez and M. T. Flores-Arias, Materials Science and Engineering: C, 2021, **129**, 112388.

23 P. Selvaganapathy, E. T. Carlen and C. H. Mastrangelo, Sens Actuators A Phys, 2003, **104**, 275–282.

Supplementary Information

Raw data of the valve closing and opening time of firmware 1 (Heater only) and 2 (Peltier).

Firmware 1 (Heater only)		Firmware 2 (Peltier)	
Closing time (s)	Opening time (s)	Closing time (s)	Opening time (s)
0.9	2.2	1.1	2
0.8	3.8	1	1.9
1.2	2.8	0.8	1.9
0.8	4	1.7	1.4
1.2	2.5	1	1.6
0.8	3.2	1.4	1.4
0.8	4	1	1.8
1.6	2.4	0.8	3
1.2	3.6	1.1	1.6
1.7	2.4	0.7	1.9
1.3	3.2	1	2
0.9	3.6	1.5	1.3
0.9	4.2	1	2.4
1.7	2.6	1.3	2.2
1	3.3	1.3	1.3