Title: MICROFLUIDIC HEAT EXCHANGER FOR LOCALIZED TEMPERATURE CONTROL

Abstract: Microfluidic devices are a promising new tool for studying and optimizing (bio-) chemical reactions and analyses. Many (bio-) chemical reactions require accurate temperature control, as for example thermocycling for PCR. Here, a new integrated 
temperature control system for microfluidic devices is presented, using chemical reactions to locally regulate temperature. In an embodiment, the evaporation of acetone was used as an endothermic reaction to cool a microchannel. Alternatively, heating of a microchannel can be achieved by dissolution of concentrated sulphuric acid in water as an exothermic reaction. Localization of the contact area of two flows in a microfluidic channel enables control of the position of the temperature effect, while the flow rate ratio influences the magnitude of the thermal effect.
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
Microfluidic heat exchanger for localized temperature control

Field of the invention

The present invention relates to microfluidic devices. More specifically, it relates to spatially localized control of temperatures in microfluidic or micro-electronic devices.

State of the Art

Since the introduction of the miniaturized total analysis system (μTAS) concept in 1990 [1], the development of so-called ‘lab-on-chip’ devices has been an area of exponential growth. Miniaturization of chemical systems allows faster chemical reactions, due to reduced diffusional transport times, and improved chemical analysis with, e.g. faster and more efficient separations. Working on a small scale reduces the risks involved in manipulation of explosive and unstable mixtures required for chemical reactions. Additionally, working with a microchip format dramatically reduces the consumption of sample and reagents, and allows the performance of multiple analyses in parallel, thereby lowering the price per analysis. Large surface-to-volume ratios also make better thermal control possible. Heating and cooling of small liquid volumes can be accomplished in much shorter periods of time. The small thermal mass of the chips themselves also contributes to increased heating and cooling rates. Enhanced heat transfer introduces the potential for improved control of chemical process conditions in microreactors. Certainly the excessive heat build-up which often leads to runaway reactions in conventional reactors can be avoided [2]. Precise temperature control is also required in certain (bio)chemical reactions, such as DNA amplification using the polymerase chain reaction (PCR) [3], and the investigation of reaction kinetics. PCR is a biochemical reaction requiring rapid and precise thermocycling of reagents at three different temperatures between 50°C and 100°C. The potential of faster temperature ramping and more precise temperature control has been the impetus for the integration of PCR into microfabricated devices. The earliest examples of this development were presented by Northrup et al. in 1993 [4] and Wilding et al. in 1994 [5]. More recently, efforts in a number of groups have resulted in several examples of PCR on chip.
In the devices described in [6, 7, 8] external heating elements were used, whereas in [4, 9, 10] heating elements were incorporated in the device through integration of resistive layers heated by the Joule effect. Temperature control of exothermic reactions in micromachined chemical reactors has also been presented using integrated heaters in microreaction chambers [2].

Cooling of microfluidic devices can for example be done with external components or by convection. It has been achieved by clamping [5] or gluing the microfluidic device to an external Peltier element [8], or by contacting the microdevice with a copper block, passively cooled by contact with cooling fins [6]. The convection technique primarily consists of using the heat exchange between the device and ambient air, an effect which may be enhanced by blowing compressed air or nitrogen gas over the microdevice [7, 11]. Integrated cooling techniques have also been presented. In one case, an integrated cooling system utilizing a microchannel in a printed circuit board was described. Either water or methoxy-nonfluorobutane were used as coolants and pumped through the microchannel, removing heat from the electronics [9]. The heat was dissipated in a heat exchanger, positioned elsewhere on the circuit board. A comparable system using microfluidics in combination with a heat exchanger for cooling electronics has been described elsewhere [10]. In the second case, integrated cooling of microelectronic devices took the form of the “fridge-on-a-chip” [12]. Here, microPeltier elements were integrated during the microfabrication process onto the back of micro-electronic devices during the microfabrication process.

Most of the cooling systems described above require external and often bulky components, hereby limiting the possibilities of integration in a microfluidic device. Even a microfluidic cooling system integrated on a printed circuit board [9] requires a heat exchanger elsewhere on the device, complicating the microfabrication process and increasing the footprint of the device and fabrication costs. Similarly, heating small volumes on chip involves the use of external elements, or additional fabrication steps for integration of heating elements.

Summary of the invention

It is an object of the present invention to provide an microfluidic temperature control circuit for locally controlling the temperature of a microfluidic or micro-electronic
component without the need for extra external heat dissipation elements. Therefore, the present invention relates to a microfluidic heat exchanger comprising:
- a first microfluidic channel for providing a first reagent;
- a second microfluidic channel for providing a second reagent;
- a temperature control channel for exchanging heat with a thermally connected component, the temperature control channel being connected to at least the first and the second microfluidic channel, to allow the first and the second reagent to cause either an endothermic or exothermic reaction in the temperature control channel.

This microfluidic heat exchanger enables a new integrated method for spatially localized cooling and/or heating in microfluidic devices using endothermic and exothermic reactions, respectively. The thermal effect can be initiated by mixing two or more reagents by application of a vacuum to the temperature control channel. The invention makes heating or cooling elements obsolete, which results in less complicated devices. Besides, by avoiding electrically powered heating or cooling elements, no extra electrical input is needed for the temperature control.

In a preferred embodiment, an operating temperature is set by fixing one or more of the following parameters:
- area of cross-section of the microfluidic channels and of the temperature control channel;
- geometry of cross-section of the microfluidic channels and of the temperature control channel;
- a ratio L1/L2, where L1 is a length of the first microfluidic channel and L2 is a length of the second microfluidic channel, the lengths (L1, L2) being measured from an inlet (11, 21) along the microfluidic channels, to a connection with the temperature control channel.

Also, the present invention relates to an electronic apparatus comprising:
- a printed circuit board; and
- an electronic device arranged on the printed circuit board;
- a microfluidic heat exchanger as described above;
- a pumping device for causing the first and the second reagents to flow through the temperature control channel,
wherein the temperature control channel is in thermal contact with at least one electronic device and wherein the microfluidic heat exchanger is integrated in the
printed circuit board. In this way, electronic devices can be cooled using the heat exchanger according to the invention. No extra heat dissipation device is required on the printer circuit board, which saves energy consumption and also space on the circuit board.

Furthermore, the invention relates to a microfluidic device comprising
- a microfluidic integrated circuit with at least one microfluidic component; and
- at least one microfluidic heat exchanger as described above,
wherein the temperature control channel is in thermal contact with at least a part of at least one microfluidic component and wherein the microfluidic heat exchanger is integrated in the microfluidic integrated circuit.
Integration of the temperature control system in microfluidic devices is simple, and does not necessarily require additional microfabrication steps. Since the endothermic or exothermic chemical reaction takes place in a microchannel, integration of a temperature control system does not dramatically increase the footprint of a microfluidic device.

In a preferred embodiment, the microfluidic device comprises sets of heat exchangers, which are positioned at different positions along a microfluidic component, each set of the two heat exchangers being arranged to produce a specific temperature in the part of the at least one microfluidic component. Integrated heat exchangers along a microfluidic component, such as a single reaction channel, allow thermocycling of compounds migrating or being pumped through the reaction channel. The small feature size of the heat exchanger also allows multiple temperature control units on a microdevice where multiple reactions occur in parallel.

Finally, the present invention relates to method according to claim 14.

**Brief description of the drawings**

Below, the invention will be explained with reference to some drawings, which are intended for illustration purposes only and not to limit the scope of protection as defined in the accompanying claims.

Fig. 1 shows a laminar flow of two fluids coming from two reactant channels.
Fig. 2 shows a microfluidic circuit according to an embodiment of the invention.
Fig. 3 is a cross sectional view of the circuitry of figure 2 at the line III-III.
Fig. 4 shows a part of a printed circuit board of an electronic apparatus with a heat exchanger according to the invention.

Fig. 5 shows an embodiment of the invention for the use in a flowing PCR system. Fig. 6 shows an embodiment of the invention for use as a "freeze valve".

**Detailed description of the invention**

The approach for chip-based temperature modification according to the invention is based on the exploitation of endothermic or exothermic reactions in microchannels to respectively cool or heat solutions in an adjacent microchannel or other micro-component. In an embodiment, temperature control channels (TCCs) are directly integrated in the chip together with the microfluidic circuits. Localization of the cooling or heating effect is controlled by positioning the chemical reaction at the reactant flow interface where the two reagent streams are in contact with one another.

Under the usual operating conditions for microfluidic devices, fluid flows are laminar. That is, the velocity at any one point in a channel is predictable and unchanging, and streamlines are well defined.

In figure 1 two fluids coming from two different reagent channels (RC) 1, 2 are merged together into a single temperature control channel 3. The two fluids generally follow laminar streamlines and flow side-by-side, as indicated in figure 1.

Figure 2 shows an embodiment of the invention, in which the temperature control channel 3 (TCC) is in thermal contact with a central channel 4. The central channel 4 is part of a separate microfluidic circuit, the temperature of which has to be controlled. Fluid enters the central channel 4 via an inlet 41 and leaves the central channel 4 via an outlet 42. A first reagent enters RC 1 via inlet 11, and a second reagent enters RC 2 via inlet 21. Inlet 11, 21 may be connected to respective reagent reservoirs via inlet channels (not shown in figure 2). As can be seen from figures 1 and 2, the stream from RC 2 flows along the side of the TCC closest to the central channel 4. After the reaction the flow leaves the temperature control channel 3 via outlet 32. Figure 2 shows a mirrored circuit at the other side of the central channel 4, comprising a similar circuitry 1', 2', 3' and 4.

Figure 3 is a cross sectional view of the circuitry of figure 2 at the line III-III. In figure 3, the two TCCs 3, 3' are shown together with the central channel 4. The channels 3, 3' and 4 are formed in a substrate 5, and are covered by a layer 6, which may for example
be made of glass. Typical values for the widths of the TCCs are 108 µm, and for the width of central channel 54 µm. The depths of the channels may be different for all three channels and may e.g. vary between 2 µm and 500 µm. The widths of the channels may vary between 2 µm and 1000 µm, while the length of the part of the channels where they thermally connect, may vary between e.g. 1 mm and 100 mm. The relative widths of the reagent flows in the TCC 3, 3' are determined by their flow rate ratio. At an interface 10, shown in figure 1, reactions can occur. In the example presented here, two-reagent reactions are used. For cooling, the evaporation of acetone can be used as an endothermic reaction. In the TCC 3, 3', air flows from RC 1 alongside acetone from the RC 2, cooling down the nearby central channel 4, and thus cooling a fluid present in this channel. For heating, for example the violent exothermic dissolution of concentrated H₂SO₄ in water can be used, with water in RC 1 and H₂SO₄ in RC 2.

The microfluidic structure shown in figure 2 and 3, can be etched into a glass substrate using conventional photolithography techniques and wet chemical etching [13]. Other substrate materials using conventional microfabrication techniques as well as imprinting techniques could be used. Sealed microchannels can be formed by bonding to another glass substrate, by forming a hybrid with another material, or by bonding 2 Si wafers etc.

Vacuum at the outlet 32 of the TCC can be used to draw in the reagents from RC 1 and RC 2 into the TCC 3, 3', initializing the chemical reaction, and thus inducing a thermal effect. In an embodiment TCCs 3, 3' are integrated along both sides of the central channel, see Figure 2, to obtain a temperature effect. Different temperature effects and temperature gradients could be obtained. First, a temperature gradient could be obtained along the central channel 4. This could result because, the extent to which a chemical reaction occurs changes as reagents are consumed or depleted, and/or because a reaction is kinetically slow and requires more time to occur. Temperature changes in the TCC 3, 3' themselves could also affect the rates at which reactions occur at different locations along the TCC 3, 3'. Depending on the width of the central channel 4, a temperature gradient can be obtained across the central channel 4. This gradient could be symmetrical, if the reagent channels 1, 1', 2, 2' are identically shaped and the two reagents are the same for both sides of the central channel 4. Non-symmetric gradients
across the central channel 4 could be obtained if different reactions, or the same reaction at different flow rate ratios occurs at both sides of the central channel.

To measure the temperature achieved in the central channel 4, an adequate temperature measurement system is required. Such a system is outside the scope of the present invention.

The extent to which a fluid may be cooled in the central channel 4 depends on the relative volumes of the different reagents, and can be influenced by varying relative flow rates from RC 1 and RC 2. These latter parameters can be controlled by varying the flow resistance of the channels involved. Flow resistance depends on channel cross-section and length as well as fluid viscosity. If a certain pressure $P$ is applied to a channel $i$, the flow $Q_i$ induced through the channel $i$ is given by:

$$Q_i = 2A_i \cdot D_i^2 \cdot P_i / C_i \cdot \eta_i \cdot L_i$$  \hspace{1cm} (1)

where:

$A$ = area of channel cross-section

$D$ = hydraulic diameter (dependent on channel cross-section)

$C$ = geometric constant (dependent on cross-section shape)

$\eta$ = viscosity of the fluid in the channel

$L$ = length of the channel

In the embodiment shown in figure 2, the vacuum applied to the outlet 32 (i.e. the waste reservoir) simultaneously creates the same negative pressure at the ends of RC 1 and RC 2. They also both have the same cross-sectional area and therefore, using equation 1, the flow rate ratio between RC 1 and RC 2 becomes:

$$Q_1/Q_2 = \eta_2 L_2 / \eta_1 L_1$$  \hspace{1cm} (2)

$Q_1/Q_2$ depends only on channel lengths and viscosities of the fluids used, providing some flexibility in setting the flow rate ratio in the two channels.

Two different structures were tested to verify the difference in the cooling effect induced by varying the flow ratio in the reagent channels RC 1, RC 2, as presented in table 1. Using equation 2, the air-to-acetone flow ratios 0.3:1 and 7:1 are obtained. Temperatures in the central channel 4 are estimated at respectively 5 °C and -3 °C, demonstrating the influence of the flow ratio on the cooling effect.
<table>
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<tr>
<th>Reagent1-Reagent2</th>
<th>L_{RC1}: L_{RC2} (mm)</th>
<th>Flow rate ratio</th>
<th>T (°C)</th>
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<tr>
<td>Air-acetone (COOL)</td>
<td>766:12, 30:12</td>
<td>0.3:1, 7:1</td>
<td>5, -3</td>
</tr>
<tr>
<td>Water-H₂SO₄ (HEAT)</td>
<td>766:12, 30:12</td>
<td>0.4:1, 11:1</td>
<td>76, 36</td>
</tr>
</tbody>
</table>

Table 1

Cooling in glass-glass devices is shown to be less efficient than in the glass-PDMS hybrids. This may be because acetone vapour also escapes through the gas-permeable PDMS, thereby driving the acetone evaporation process more strongly and augmenting the cooling effect. This implies that a larger air-acetone contact surface would be required for efficient cooling in a fully glass device.

Heating the central channel 4 can be performed in glass-glass devices, with a layout and operating procedure identical to the devices used for the cooling experiments (figure 1). In an embodiment, concentrated H₂SO₄ from RC 2 and water from RC 1 come together in the TCC, where the exothermic dissolution reaction takes place. In a test, devices identical to the ones used for the cooling tests, were used to investigate the effect of flow ratio on heating. Since the viscosities of the fluids used in this case are different, the flow ratios change as indicated in Table 1. For the 0.4:1 water-to-H₂SO₄ a temperature of 76°C could be estimated, whereas for the 11:1 ratio heating up to 36°C was estimated. These results are summarized in Table 1.

In figure 4, a part of a printed circuit board 100 of an electronic apparatus is shown. According to an embodiment of the present invention, an electrical device 101, see figure 4, is cooled by a microfluidic heat exchanger as described above. The heat exchanger comprises a temperature control channel 3, which is in thermal contact with the electrical device 101. First and second reagents are delivered via a first and second inlet 1, 2 to the TCC 3. In the TCC an endothermic (or exothermic) reaction is caused, which cools (or heats) the electrical device 101, which is in close contact with the TCC 3. At the end of the TCC 3, the reactant is transferred to, for example, a waste via an outlet 32. Preferably the microfluidic heat exchanger is integrated in the printed circuit board 101. In figure 4 only one electrical device is shown, but the invention can be used to cool more than one device with one heat exchanger, or alternatively, several heat exchangers can cool (or heat) several electrical devices.
Figure 5 shows an embodiment of the invention for the use in a flowing PCR system. A microchannel 51 serpintines along nine sets of heat exchangers 52, 53, 54, 55, 56, 57, 58, 59, 60. Each set of heat exchangers is configured as described above. To obtain specific temperatures in the microchannel 51, each set of heat exchangers 52, 53, 54, 55, 56, 57, 58, 59, 60 is supplied by specific reagents. Furthermore, the reagent channels RC 1 and RC 2 of the individual heat exchangers have predetermined lengths, in order to bias the correct flow ratios in the different temperature control channels. In the example of figure 5, three different temperatures T1, T2, T3 are used to amplify DNA strands flowing through the microchannel 51. Thanks to the arrangement of figure 5, the DNA substance is repeatedly exposed to three different temperatures T1, T2, T3, while flowing through the microchannel. To date, PCR in a flowing system has been demonstrated in [6]. Alternatively, PCR can be done in a stagnant system, by variation of a local temperature. Of course, the present invention can also be used in stagnant systems.

Many other biochemical reactions, such as enzyme assays, immunological assays and hybridisation of DNA without non-specific binding are optimal at 37 °C. Additionally, non biochemical reactions, for example used for phosphate analysis [15] and the Berthelot reaction, see ref [16], can be accelerated when performed at elevated temperatures. To control the temperatures at these reactions, a heat exchanger according to the invention can be used. Temperatures can be set by varying the type of reaction, type of reagents, length of reagent channels, cross-section and geometry of the reagent channels 1, 1′, 2, 2′ and TCC 3, 3′, viscosity of the reagents, number of TCCs 3, 3′, or pressure of a pump connected to the inlets 21, 41 and/or outlet 32. It is further noted that reactions in the central channel 4 can be performed either in a continuous flow system, or in a stopped-flow mode where a fluid is brought in and then stopped in the channel.

Figure 6 shows another embodiment of the present invention. By applying the adequate reagents, an endothermic reaction can be causes in the TCC 3, 3′. If the temperature in the TCC 3, 3′ is below the freezing point of a substance, which is pumped through a central channel 65, the substance 70 will locally freeze, blocking the flow in the central channel 65. This application can be used to avoid the substance from entering in, for example, a reaction chamber 66, see figure 6. In this way, the heat exchanger will function as a so-called “freeze valve".
Preferably, the driving force of the microfluidic heat exchanger discussed above is vacuum, resulting in low-power consumption during cooling or heating. Another option is to use pumps, connected to each reagent reservoir for reagent delivery.

In the heat exchanger described above, two reagent channels are used. It is noted that the invention is in no way limited to the use of only two reagent channels nor to two reagents. More reagent channels are conceivable. If, for example, three reagent channels are connected to the TCC 3, 3', it might be possible to create two interfaces. This may enhance the reaction and thus the thermal effect. Moreover, the invention is not restricted to two reagents causing either an endothermic or exothermic reaction. That reaction may, alternatively, be caused by three or more reagents.

Furthermore, the term "Temperature Control Channel" should be broadly interpreted as referring to a cavity in which different reagents react. The channel may well be very short, or may have a very different form, such as a circle or an ellipse. In that case, the term "reaction chamber" would apply. This remark also applies to the central channel 4. It is noted that in the description above, the heat exchanger is either used in a microfluidic device or in a printed circuit board provided with micro-electronic devices. This separation into two different applications (i.e. microfluidics and microelectronics) may vanish if the invention is used inside a micro-electronic device (i.e. inside an electronic integrated circuit "IC"). It is assumed that such an integrated device with both microfluidic heat exchangers and integrated electronic circuitry can be referred to as "microfluidic device".
References
16. Daridon, A. Sequeira, M., Pennarun-Thomas, G., Dirac, H., Krog, J.P.,
Claims

1. A microfluidic heat exchanger comprising:
   - a first microfluidic channel (1; 1') for providing a first reagent;
   - a second microfluidic channel (2; 2') for providing a second reagent;
   - a temperature control channel (3; 3') for exchanging heat with a thermally connected component (4), said temperature control channel (3; 3') being connected to at least said first and said second microfluidic channel (1, 2; 1', 2'), to allow said first and said second reagent to cause either an endothermic or exothermic reaction in said temperature control channel (3; 3').

2. A microfluidic heat exchanger according to claim 1, wherein an operating temperature in said temperature control channel (3; 3') is set by fixing at least one of the following parameters:
   - area of cross-section of said microfluidic channels (1, 2; 1', 2') and of said temperature control channel (3; 3');
   - geometry of cross-section of said microfluidic channels (1, 2; 1', 2') and of said temperature control channel (3; 3');
   - a ratio L1/L2, where L1 is a length of said first microfluidic channel (1; 1') and L2 is a length of said second microfluidic channel (2, 2'), the lengths (L1, L2) being measured from an inlet (11, 21) along said microfluidic channels (1, 2; 1', 2'), to a connection with said temperature control channel (3; 3');

3. A microfluidic heat exchanger according to claim 1 or 2, wherein an operating temperature in said temperature control channel (3; 3') is set by varying at least one of the following parameters:
   - a viscosity of at least said first and said second reagent;
   - a pressure in said microfluidic channels (1, 2; 1', 2') and in said temperature control channel (3; 3').

4. A microfluidic heat exchanger according to any of the preceding claims, wherein said first reagents is air and said second reagent is acetone.
5. A microfluidic heat exchanger according to any of the preceding claims, wherein said first reagents is water and said second reagent is H₂SO₄.

6. An electronic apparatus comprising:
   - a printed circuit board (100); and
   - an electronic device (101) arranged on said printed circuit board (100);
   - a microfluidic heat exchanger (1, 2, 3) according to any of the claims 1-5;
   - a pumping device for causing said first and said second reagents to flow through said temperature control channel (3),
   wherein said temperature control channel (3) is in thermal contact with said at least one electronic device (101).

7. An electronic apparatus according to claim 6, wherein said microfluidic heat exchanger (1, 2, 3) is integrated in said printed circuit board (100).

8. A microfluidic device comprising:
   - a microfluidic integrated circuit with at least one microfluidic component (51); and
   - at least one microfluidic heat exchanger according to any of the claims 1-5,
   wherein said temperature control channel is in thermal contact with at least a part of said at least one microfluidic component (51; 65).

9. A microfluidic device according to claim 8, wherein said microfluidic heat exchanger is integrated in said microfluidic integrated circuit.

10. A microfluidic device according to claim 9, wherein said microfluidic device comprises sets of two of said heat exchangers (52, 53, 54, 55, 56, 57, 58, 59, 60), each of said two heat exchangers (52, 53, 54, 55, 56, 57, 58, 59, 60) being arranged on opposite sites of said at least one microfluidic component (51; 65).

11. A microfluidic device according to any of the claims 8-10, wherein said microfluidic component (51) is arranged for polymerase chain reaction.
12. A microfluidic device according to claim 10 or 11, wherein each of said sets of said two heat exchangers is positioned at a different position along said at least one microchannel, each of said set of said two heat exchangers (52, 53, 54, 55, 56, 57, 58, 59, 60) being arranged to produce a specific temperature in said part of said at least one microfluidic component (51).

13. A microfluidic device according to any of the claims 8-10, wherein said microfluidic heat exchanger is arranged to cause an endothermic reaction, causing a fluid flowing through said microfluidic component (65) to locally freeze.

14. A method for spatially localized temperature control of an integrated device, the method comprising:
   - providing at least one microfluidic heat exchanger, said microfluidic heat exchanger comprising:
     - a first microfluidic channel (1; 1');
     - a second microfluidic channel (2; 2');
     - a temperature control channel (3), said temperature control channel (3; 3') being connected to at least said first and said second channel (1, 2; 1', 2');
     - leading a first reagent through said first microfluidic channel (1; 1') and a second reagent through said second microfluidic channel (2; 2'), to allow said first and second reagent to cause either an endothermic or exothermic reaction in said temperature control channel (3; 3').

15. A method according to claim 14, wherein said first reagents is water and said second reagent is H₂SO₄.

16. A method according to claim 14, wherein said first reagents is air and said second reagent is acetone.

17. A method according to any of claims 14-16, wherein the method comprises:
   - positioning said at least one microfluidic heat exchanger in thermal contact with an electronic integrated device (101).
18. A method according to any of claims 14-16, wherein the method comprises:
   • positioning sets of two of said at least one microfluidic heat exchangers (52, 53, 54, 55, 56, 57, 58, 59, 60) in thermal contact with different parts of a microfluidic component (51) of a microfluidic device.

19. A method according to claim 18, wherein the method comprises:
   • operating said sets of two of said at least one microfluidic heat exchangers (52, 53, 54, 55, 56, 57, 58, 59, 60) at specific temperatures.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7: H01L23/46, H01L23/473, B01J19/00, H05K7/20, B01L7/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7: H01L, B01J, H05K, B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 99 22858 A (BRITISH NUCLEAR FUELS PLC; RAMSHAW COLIN (GB); BURNS JOHN (GB); HA)</td>
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<td>A</td>
<td>14 May 1999 (1999-05-14) page 3, line 6 - line 9; figure 1</td>
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<td>A</td>
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**Date of the actual completion of the international search**

4 February 2004

**Date of mailing of the international search report**

12/02/2004

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