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(54) **Mixing junction**

(57) The invention is directed to a process for mixing two or more streams in a microfluidic device and to a microfluidic device for carrying out said process.

The process involves providing at least a first fluid stream in a first channel having a width and length which define a plane, providing at least a second fluid stream in a second channel lying out of said plane, and combining said first fluid stream and second fluid stream in a junction, which junction joins at least said first and second channel, wherein said first channel has a height which is smaller than the width of said first channel and which

height is smaller than at least one dimension of said second channel, said dimension lying in said plane.

The microfluidic device of the invention comprises a junction, which junction joins two or more channels, wherein the width and length of a first of said two or more channels define a plane and at least a second of said three or more channels lies out of said plane, said first channel having a height being smaller than the width of said first channel and which height is smaller than at least one dimension of said second channel, said dimension lying in said plane.

Figure 1B

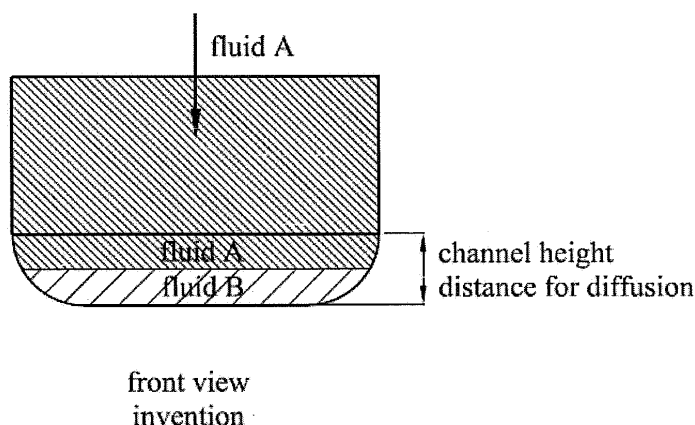
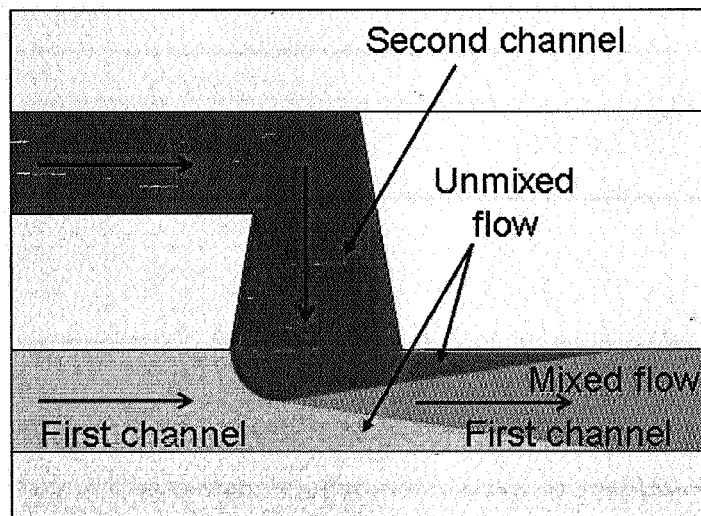


Figure 5



Description

[0001] The invention is directed to a process for mixing two or more streams in a microfluidic device and to a microfluidic mixer for carrying out said process, and to a microfluidic device comprising said microfluidic mixer.

[0002] Microfluidics deals with the behaviour, precise control and manipulation of microliter to picoliter volumes of fluids. It is a multidisciplinary field intersecting engineering, physics, chemistry, microtechnology and biotechnology. Microfluidics is a relatively new field of technology and is used *e.g.* in the development of lab-on-a-chip technology. Microfluidics can be applied to a variety of technical areas including biochemical analysis, medical diagnostics, chemical synthesis, and environmental monitoring. For example, use of microfluidic systems for acquiring chemical and biological information presents certain advantages. In particular, microfluidic systems increase the response time of reactions and reduce reagent consumption. Furthermore, when conducted in microfluidic volumes, a large number of complicated biochemical reactions and/or processes may be carried out in a small area, such as in a single integrated device. Examples of desirable applications for microfluidic technology include analytical chemistry, chemical and biological synthesis, DNA amplification, and screening of chemical and biological agents *i.a.* for activity.

[0003] In particular, microfluidic technology is of interest for microreactor chip technology. Microreactor chips are chips which are designed for the production of chemical substances. Such microreactor chips can be used, for instance, for the synthesis of chemical products which, for whatever reason, is impossible or unfavourable when using conventional batch technology. Examples thereof include very exothermic chemical reactions for which temperature control is very important.

[0004] The behaviour of fluids at the microscale can differ from "macrofluidic" behaviour in that factors such as surface tension, energy dissipation, and fluidic resistance start to dominate the system. When working with fluids in conventional macroscopic volumes, achieving effective mixing between two or more fluid streams is a relatively straightforward task. Various conventional strategies may be employed to induce turbulent regions that cause fluid streams to mix rapidly. For example, active stirring or mixing elements (*e.g.* mechanically or magnetically driving) may be employed. Alternatively special geometries may be employed in flow channels to promote mixing without the use of moving elements.

[0005] Applying conventional mixing strategies to microfluidic volumes is generally ineffective and/or impractical, because at the small scales of microfluidic channels some interesting and unintuitive properties appear. To begin with, microfluidic systems are characterised by extremely high surface-to-volume ratios and correspondingly the Reynolds number, which characterises the presence of turbulent flow, is extremely low (typically less than 2 000) for most achievable fluid flow rates. At such

low Reynolds numbers, fluid flow within most microfluidic systems is surely within the laminar regime, and mixing between fluid streams is motivated primarily by diffusion. In the laminar regime, using conventional geometric modifications such as baffles is generally ineffective for promoting mixing. Moreover, the task of integrating moveable stirring elements and/or their drive means in microfluidic systems using conventional methods is extremely difficult due to volumetric and/or cost constraints, in addition to concerns regarding their complexity and reliability.

[0006] In the prior art, a number of attempts have been made in order to solve this microfluidic mixing problem.

[0007] WO-A-03/059498, for instance, describes a microfluidic device, which combines two fluid streams of reagents in a mixing channel. Subsequently, the combined stream is passed over a contraction/expansion region, which is said to promote mixing, in particular at high fluid flow rates and multiple contraction/expansion regions. Effective mixing according to this system only starts after the junction of the two fluid streams at the contraction/expansion region. In addition, effective mixing requires multiple contraction/expansion regions which considerably increase costs and volume on the microfluidic chip.

[0008] WO-A-03/059499 describes a microfluidic device in which a first fluid stream of reagent flows from a first wide channel through a multiple of small apertures into a second wide channel to join a second fluid stream of reagent. By virtue of flowing through the multiple small apertures, the first fluid is divided into several substreams that appear as "streaks" in the second fluid, which are said to provide a large interfacial contact area between the two fluids and promote mixing. Apart from the fact that it is technically difficult and expensive to construct this system (in particular when a large number of apertures is applied with a very small distance between the apertures), the diffusion distance of the first fluid in the direction perpendicular to the second fluid is relatively long. Moreover, the first fluid also needs to diffuse in the direction parallel to the second fluid stream for complete mixing. This can be a rather slow process.

[0009] There remains a strong need for improved mixing of fluid streams in a microfluidic system or device. Such improved mixing should not be accompanied with technically complicated or costly structures, but should be accomplished through a simple and effective design.

[0010] Object of the invention is to fulfil this need in the art.

[0011] The inventors surprisingly found that this object can be met by a process in which the different fluid streams are joined in a junction having a specific three-dimensional design, such that the distance for diffusion of the separate reactants is significantly reduced.

[0012] Accordingly, in a first aspect the invention is directed to a process for mixing two or more fluid streams in a microfluidic device, comprising

- providing at least a first fluid stream in a first channel having a width and length which define a plane,
- providing at least a second fluid stream,
- combining said first fluid stream and second fluid stream in a junction, which junction joins at least said first and a second channel lying out of said plane,

wherein said first channel has a height which is smaller than the width of said first channel and which height is smaller than at least one dimension of said second channel, said dimension lying in said plane.

[0013] In a further aspect, the invention is directed to a microfluidic mixer for carrying out the process of the invention, said mixer comprising a junction, which junction joins two or more channels, wherein the width and length of a first of said two or more channels define a plane and at least a second of said two or more channels lies out of said plane, said first channel having a height being smaller than the width of said first channel and which height is smaller than at least one dimension of said second channel, said dimension lying in said plane.

[0014] In yet another aspect, the invention is directed to a microfluidic device comprising said microfluidic mixer.

[0015] Current fabrication processes for microfluidic devices allow the production of devices with multiple layers and hence three-dimensional designs. The present invention advantageously uses this relatively new field of technology to provide a highly effective way of mixing streams of fluids in a microfluidic device.

[0016] The term "microfluidic" as used in this application is meant to refer to structures or devices through which fluid(s) are capable of being passed or directed, wherein one or more of the dimensions is less than 500 μm .

[0017] The term "length of a channel" as used in this application is meant to refer to the largest dimension of the channel. Normally, the length of the channel is the direction of the channel in which fluid flows.

[0018] The term "width of a channel" as used in this application is meant to refer to the largest dimension of the channel perpendicular to the length of the channel.

[0019] The term "height of a channel" as used in this application is meant to refer to the dimension perpendicular to the length of the channel and perpendicular to the width of the channel.

[0020] The invention involves a process for mixing two or more fluid streams in a microfluidic device. The microfluidic device can be any microfluidic device in which two or more fluid streams require effective mixing. In particular, the invention is advantageous when applied in a microreactor chip in which multiple reactants are mixed in order to react with each other. Depending on the reaction to be performed quick and effective mixing may be essential to achieve a satisfactory reaction and high through-put. Also chemical and biological analysis systems can benefit of the invention, where *e.g.* pH-buffers, markers or reagents need to be mixed with the chemical

sample to achieve proper analysis.

[0021] A very convenient and relatively cheap method of manufacturing microfluidic devices is by wet etching a specific channel structure in a wafer, such as a glass wafer, and subsequently covering the wet-etched glass with a cover wafer. This results in a microfluidic device having a two-dimensional channel structure. Wet-etching normally yields channels that have a width (in the plane of the wafer) which is at least two times the height (perpendicular to the plane of the wafer) of the channel. In practice, the width of the channels is often approximately at least five times the height of the channel.

[0022] Different methods can be used to achieve microfluidic devices where the microfluidic channels are divided over two or more planes, *i.e.* where three or more wafers, or other materials, are stacked, *e.g.* wafer bonding, wafer clamping, and wafers sealed with membranes. Though, due to the aggressive property of many reagents used in microreactors, glass and stainless steel are the preferred materials for microfluidic devices for microreactor technology. Due to better chemical properties, the transparency and the smaller sizes of glass microfluidic devices over stainless steel microfluidic devices, glass is much more popular for fabrication of microfluidic devices. To avoid risk of leakage and to resist high pressures, multistack bonding technology is used to achieve multistack glass microfluidic devices.

[0023] Multistack bonding technology (described for instance by Pigeon et al. in Electronics Letters 1995, 31 (10), 792-793) allows bonding more than two wafers (such as glass wafers). This allows for the manufacture of microfluidic devices having multiple floors with channel structures. Three-dimensional structures can be designed in which for instance channels run above each other. This enables the process in the microfluidic device to be parallelised, which is highly advantageous for instance to scale up synthetic reactions performed in a microfluidic device. At the same time such a three-dimensional channel design allows for a junction across different layers. Such a junction can be utilised for carrying out the invention.

[0024] In accordance with the process of the invention at least two fluid streams are provided. These streams can be gaseous or liquid. Typically, the streams can be reagents of a reaction (such as a synthetic reaction) to be performed in the microfluidic device. Such reagents can all be provided separately, but it is also possible that two or more reagents are provided as a mixture in one stream and another reagent is provided separately in another stream. The streams can be introduced in the microfluidic device through a number of inlets.

[0025] In the microfluidic device the different streams are guided through different channels. The channels can have any shape. The cross-section of the channels can for instance be circular or semicircular, ellipsoidal or semi ellipsoidal, square, rectangular, or mixtures thereof. In practice, many microfluidic channels are prepared by wet etching of glass. This process has an isotropic character,

giving rise to channels of which the cross-section always has a characteristic shape: two quarter circles at the edges and rectangular in the middle. The two quarter circles are a result of the etching agent (such as HF or BHF), which also causes channels prepared in this way to have a width which is at least twice the height of the channel.

[0026] At least a first channel has a length and a width that define a plane. This plane is usually the plane of the microfluidic device defined by the (multi)layer wafer structure. The first channel has a height (perpendicular to the plane defined by the length and width of the channel) which is smaller than the width of the channel. Such channels are easy and relatively cheap to produce according to the above described wet etching technique. The aspect ratio, defined as the ratio between the width of the channel and the height of the channel, of the first channel is preferably at least 2, more preferably at least 5, and even more preferably at least 10. From a technical point of view the aspect ratio is normally not more than 500, preferably not more than 100.

[0027] The first channel enters a junction wherein the stream flowing through said first channel is joined with at least a second stream entering the junction. The junction can join two or more channels, such as 2, 3, 4, 5, 6, 7 or 8 channels. Junctions that join more than 8 channels are technically more difficult to produce, but are not excluded from the invention. A very convenient junction is a three-way junction such as an Y-junction or a T-junction, wherein one of the channels lies out of the plane defined by the length and the width of the first channel. In practice, the fabrication of T-junctions is less involved and these junctions are therefore preferred.

[0028] Apart from the first channel, also a second channel enters the junction. This channel lies out of the plane defined by the length and the width of the first channel described above. Normally, this channel will also lie out of the plane of the microfluidic device (defined by the multilayer wafer structure). The angle between the second channel and the plane defined by the length and width of the first channel is not of particular importance and can for instance range from 10-170°. The angle of incidence of the second channel does not influence the diffusion length, because the angle does not determine the flow distribution of the combined stream in the mixing channel, where the actual mixing takes place. In practice it is technically more convenient to manufacture microfluidic devices having a T-junction than microfluidic devices having an Y-junction. Therefore, in a preferred embodiment the second channel lying out of the plane is essentially perpendicular to the plane defined by the length and the width of the first channel.

[0029] The second channel can be used to introduce a fluid stream (such as the second fluid stream) into the junction, but it can also be used as a mixing channel to carry off the combined stream of at least the first and the second fluid from the junction. Thus, it is possible to guide the first fluid stream and the second fluid stream through channels both lying in the plane defined by the length

and width of the first channel and carry off the combined fluid stream through the second channel lying out of the plane.

[0030] In accordance with the invention the height of the first channel is smaller than the width of the first channel. In addition, the height of the first channel is smaller than at least one dimension of said second channel, wherein said dimension lies in the plane defined by the length and the width of the first channel. Preferably, said at least one dimension is the width or height of said second channel. This combination of features has the advantageous effect that the diffusion distance of the different streams for mixing becomes relatively small. This is for instance illustrated in the embodiment shown in Figure 1b. Figure 1 compares a prior art two-dimensional junction (front view shown in Figure 1a) with a junction utilised in the invention (front view shown in Figure 1b). In a conventional junction of channels having a width to height aspect ratio of at least two the distance for diffusion for the different streams to mix is mainly determined by the width of the channel. This diffusion distance is relatively long compared to the junction utilised in the invention shown in Figure 1b. This embodiment shows a first channel having an aspect ratio similar to the channels shown in Figure 1a (thus the height of the first channel is smaller than the width of the first channel), which is joined with a second channel lying out of the plane defined by the length and width of the first channel. In the embodiment of Figure 1b the height of the first channel is smaller than the width of the second channel. The distance for diffusion for the different streams to mix is in this way mainly determined by the height of the first channel. As a result the distance for diffusion is much smaller than in the case of the conventional junction shown in Figure 1a. The effect of the invention is even more pronounced because the diffusion time increases quadratically with the diffusion distance.

[0031] It is preferred that said second channel joins the first channel at the junction over at least the full width of the first channel, preferably over the full width. This has the effect that during mixing of the fluid streams, diffusion only has to take place in one dimension. In contrast, when the second channel joins the first channel at the junction over less than the full width of the first channel, diffusion must take place in two dimensions. In an embodiment, the dimension of the second channel in the direction of the width of the first channel corresponds to the width of the first channel.

[0032] Since mixing of the different fluid streams in the process and in the microfluidic device of the invention is very fast, the need for additional mixers is at least significantly reduced, if not entirely removed.

[0033] In practice, the channels lying in the plane defined by the length and width of the first channel will normally be manufactured by wet etching. However, also other manufacturing methods are possible. Examples thereof include dry-etching such as (Deep) Reactive Ion Etching ((D)RIE), powder blasting, milling, drilling, and

photon enhanced etching. For glass structures wet-chemical etching and powder blasting are the common techniques due to economical reasons. Powder blasting gives the possibility for a fast and cheap way of etching glass structures, also with high aspect ratios. Though, due to the aggressive and demolishing character of powder blasting it is not suitable for etching channels with high accuracy. Therefore, when good control over the etching process is needed, wet-chemical etching is the standard.

[0034] Channels lying out of the plane defined by the length and width of the first channel will normally be manufactured by powder blasting. Other examples of fabrication processes include dry-etching such as (Deep) Reactive Ion Etching ((D)RIE), milling, drilling, and photon enhanced etching. A disadvantage of using (D)RIE is that for instance glass is not easily processed with (D)RIE. It is a slow and costly process. In addition, it is believed that multiple runs are required for deep channels, due to deposits on the substrate during the process. This process (also known as the BOSCH-process) is therefore not commonly used for glass substrates. Photon etching is in principle also possible, but is rather costly. Furthermore, the manufacture of microchannels by milling or drilling can be technically difficult, in particular when the channels have very small dimensions.

[0035] The invention will now be illustrated by the following examples, which are not intended to limit the invention in any way.

Example

[0036] The invention was successfully implemented in the parallel microreactor chip depicted in Figure 2. This parallel microreactor chip was fabricated out of three fused silica wafers. The channels were wet-etched, the second channel in the mixer was powder-blasted and the three fused silica wafers were bonded together. The different channels and regions in the microreactor chip are indicated using dyed fluids. The microreactor chip has inlets on the left side, a set of meanders which are part of a flow splitter, where two channels are located above each other, a set of meanders on the right side which serve as microreactors and in the middle eight mixers where the two fluid streams are mixed. Two of these mixers are indicated by the circle. The used microreactor chip, with integrated invention, is schematically shown in Figure 3, which is a schematic side view of the microreactor used and Figure 4, which is a schematic top view of the microreactor used. A detailed schematic drawing of the used mixer is shown in Figure 5.

[0037] The 8-parallel microreactor chip was used to perform a Michael addition reaction for the synthesis of 4-(diethylamino)butan-2-one from methyl vinyl ketone and diethylamine. Figure 6 shows the obtained conversion results. CDue to the use of the invented mixer no additional mixers were necessary to obtain a conversion of 96 % can be achieved in a microreactor with a cross

section of $60\text{ }\mu\text{m} \times 300\text{ }\mu\text{m}$ without additional mixers within a total retention time (including mixing time) of only 7.2 seconds. Using conventional mixers this would not have been possible. Calculation of the diffusion time was done by using the equation for the diffusion time for a diffusion along a single axis: $t_{diff} = x^2/2D$. Based on an estimated diffusion coefficient of the used reagents in anhydrous acetonitrile (MeCN) of $3 \times 10^{-5}\text{ cm}^2/\text{s}$ and a channel height of $60\text{ }\mu\text{m}$ we find a diffusion time of 0.6 s with our mixer. We estimate that proper mixing is achieved after $3 \times t_{diff}$, thus after 1.8 s, which is short enough for our reaction with a total retention time of 7.2 s. Conventional mixing with a Y- or T-mixer with the same channel geometries would have given a $t_{diff} = 15\text{ s}$, and $3 \times t_{diff} = 45\text{ s}$, which is far too long for use in the microreactor chip. Therefore, this example clearly shows the benefits of the invention.

Claims

1. Process for mixing two or more fluid streams in a microfluidic device, comprising

- providing at least a first fluid stream in a first channel having a width and length which define a plane,
- providing at least a second fluid stream,
- combining said first fluid stream and second fluid stream in a junction, which junction joins at least said first and a second channel lying out of said plane,

wherein said first channel has a height which is smaller than the width of said first channel and which height is smaller than at least one dimension of said second channel, said dimension lying in said plane.

2. Process according to claim 1, wherein said second channel joins the first channel at the junction over at least the full width of the first channel.

3. Process according to claim 1 or 2, wherein said at least one dimension is the width or height of said second channel.

4. Process according to any one of the preceding claims, wherein said second fluid stream enters said junction through said second channel.

5. Process according to any one of claims 1-3, wherein said first fluid stream and said second fluid stream enter said junction through a channel lying in said plane and a combined stream of said first and second fluid streams leaves said junction through said second channel.

6. Process according to any one of the preceding

claims, wherein said junction is a three-way junction, preferably a T-junction.

7. Microfluidic mixer for carrying out a process according to any one of the preceding claims, said mixer comprising a junction, which junction joins two or more channels, wherein the width and length of a first of said two or more channels define a plane and at least a second of said two or more channels lies out of said plane, said first channel having a height being smaller than the width of said first channel and which height is smaller than at least one dimension of said second channel, said dimension lying in said plane. 5 10 15
8. Microfluidic mixer according to claim 7, wherein said second channel joins the first channel at the junction over at least the full width of the first channel.
9. Microfluidic mixer according to claim 7 or 8, wherein said at least one dimension is the width or height of said second channel. 20
10. Microfluidic mixer according to any one of claims 7-9, wherein said first channel has a width to height aspect ratio of at least 2, preferably at least 5, more preferably at least 10. 25
11. Microfluidic mixer according to any one of claims 7-10, wherein said junction is a three-way junction, preferably a T-junction. 30
12. Microfluidic device comprising a microfluidic mixer according to any one of claims 7-11. 35
13. Microfluidic device according to claims 12 in the form of a microreactor chip. 40 45 50 55

Figure 1A

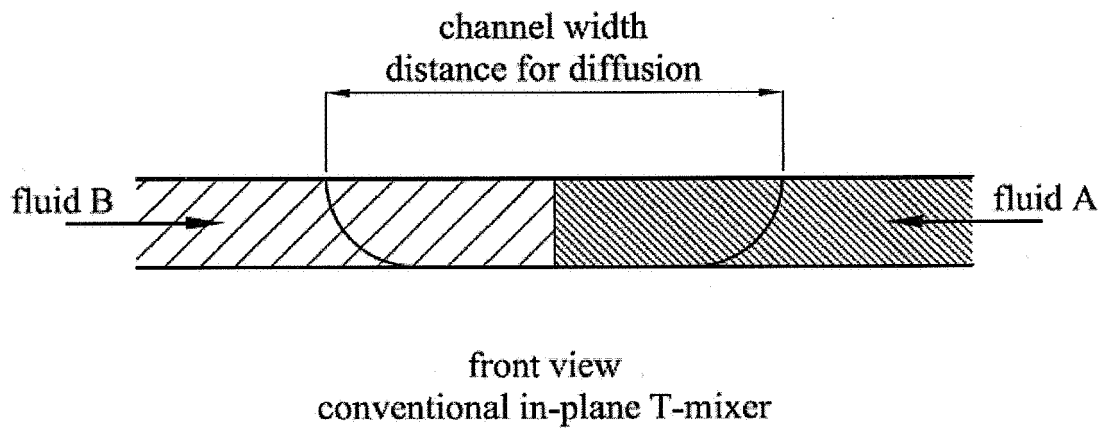


Figure 1B

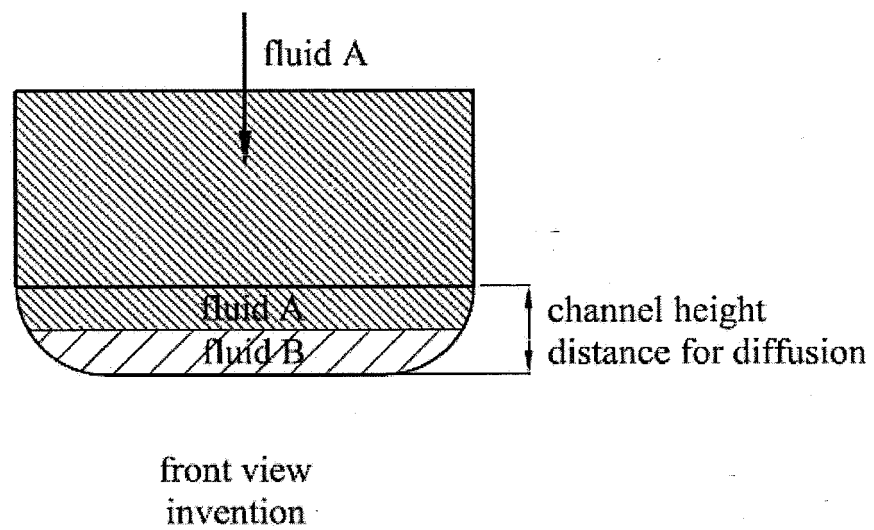


Figure 2

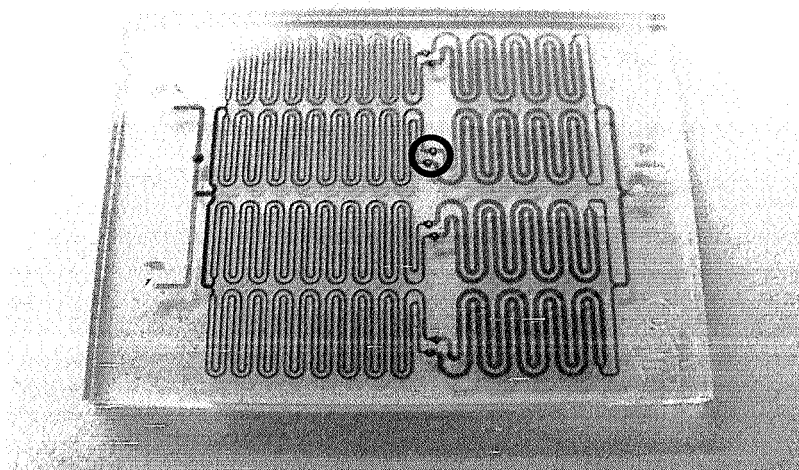


Figure 3

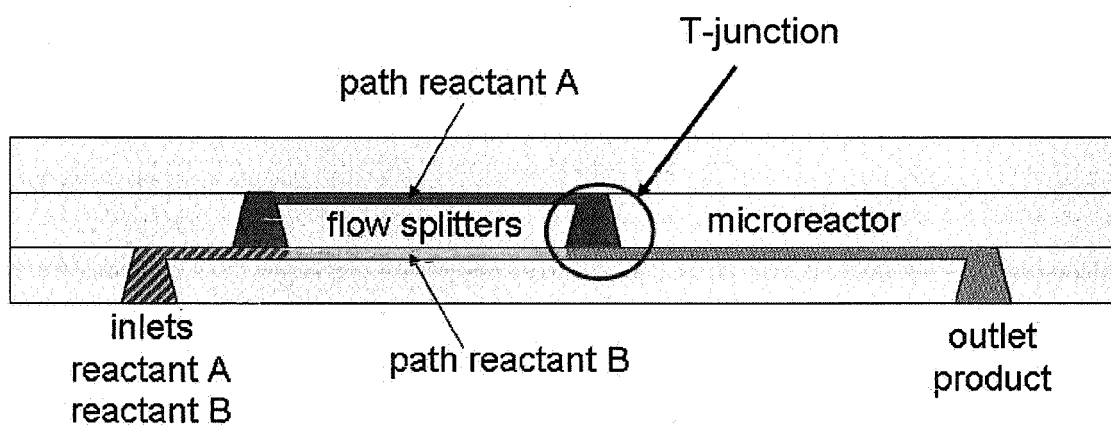


Figure 4

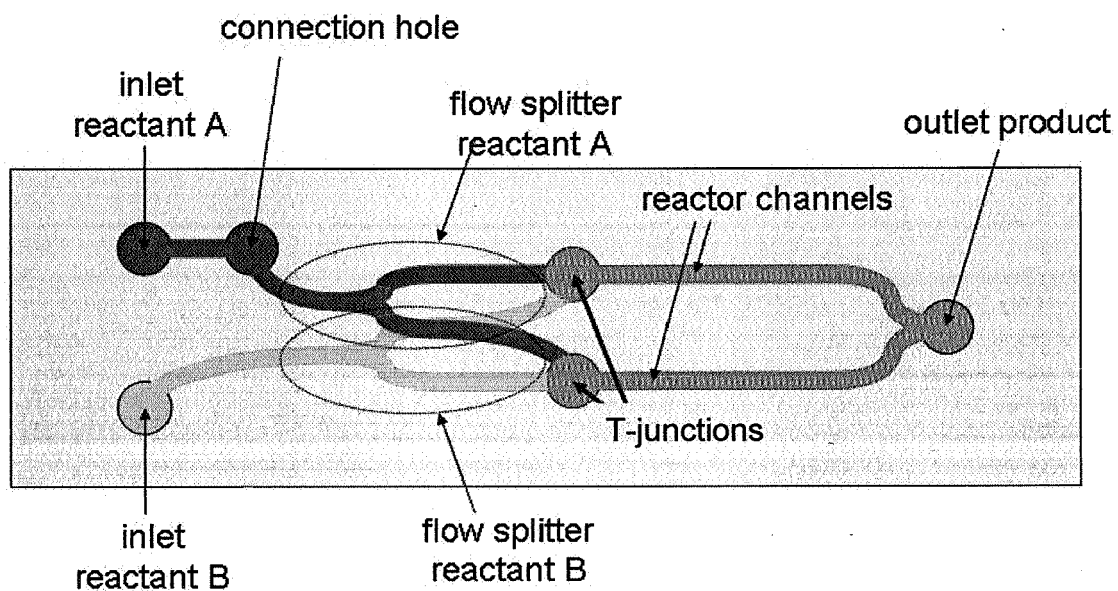


Figure 5

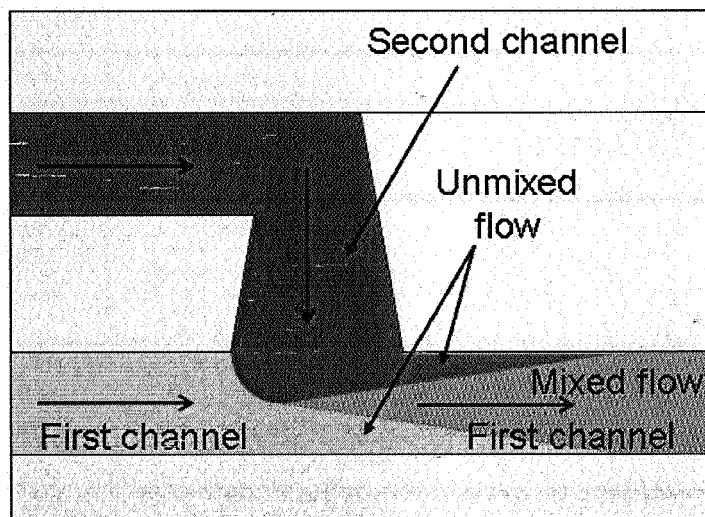
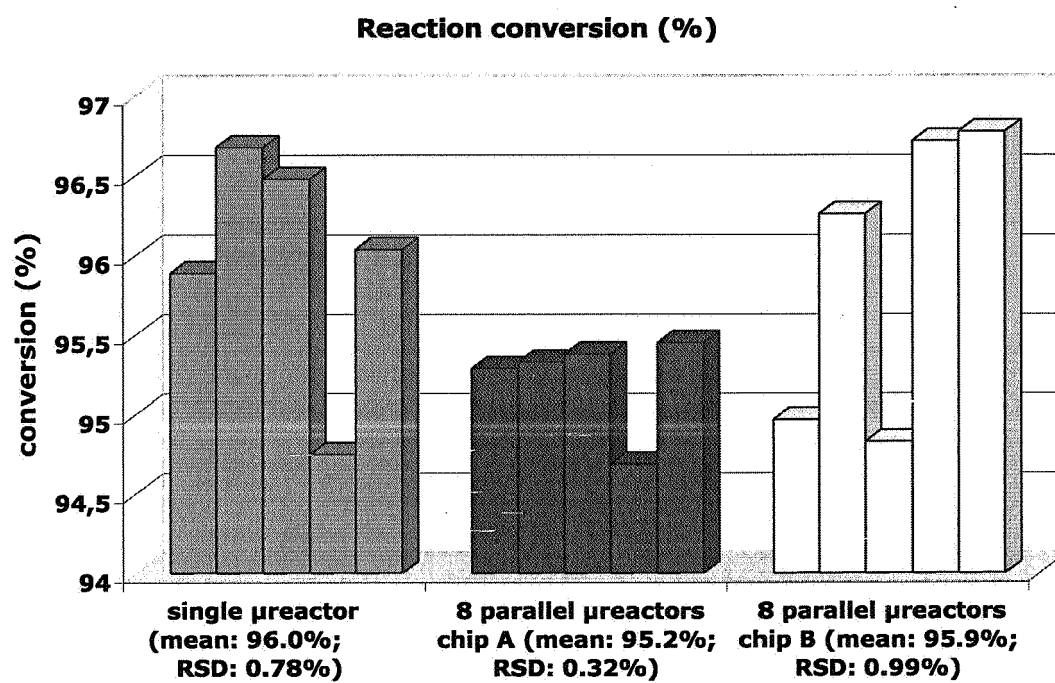


Figure 6





European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 08 15 4104

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2003/133358 A1 (KARP CHRISTOPH D [US]) 17 July 2003 (2003-07-17) * paragraph [0015] - paragraph [0016] * * paragraph [0018] * * paragraph [0061] - paragraph [0062] * * paragraph [0064] * * paragraph [0067] - paragraph [0070] * * paragraph [0079] * * paragraph [0081] * * figures 1A,1B,8A-9B,14A-14C * -----	1-13	INV. B01F13/00 B01F5/04 B01F5/06
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A		5	TECHNICAL FIELDS SEARCHED (IPC) B01F
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 3 September 2008	Examiner Real Cabrera, Rafael
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EPO FORM 1503 03/82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 08 15 4104

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003133358 A1	17-07-2003	NONE	

US 6136272 A	24-10-2000	NONE	

REFERENCES CITED IN THE DESCRIPTION

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