Microfluidic valve

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Abstract: A microfluidic valve and a microfluidic inverter comprising the valve is disclosed. The microfluidic valve comprising a first rigid layer having a first side; a second rigid layer having a second side facing the first side of the first rigid layer; a flexible layer being arranged between the first side of the first rigid layer and the second side of the second rigid layer, in a first state the flexible layer prevents fluid connection between a first input channel and a first output channel, in a second state the flexible layer protrudes into a first indentation providing fluid connection between the first input channel and the first output channel; and a first control gate channel configured to receive a first fluidic control pressure.
MICROFLUIDIC VALVE

The present disclosure relates to a membrane valve, e.g. for microfluidics, such as a monolithic membrane valve, such as a three layer monolithic membrane valve. The disclosure furthermore relates to complementary pneumatic digital logic, such as a complementary pneumatic NOT gate.

BACKGROUND

Microfluidics-based biochips integrate different biochemical analysis functionalities on-chip, miniaturizing the macroscopic biochemical processes to a sub-millimeter scale. These microsystems offer several advantages over the conventional biochemical analyzers, e.g., reduced sample and reagent volumes, faster biochemical reactions, ultra-sensitive detection and higher system throughput, with several assays being integrated on the same chip.

Biochips are used in many application areas like in vitro diagnostics, drug discovery, biotechnology and ecology. There are several types of biochip platforms, each having advantages and limitations.

Although the technology used for fabricating flow-based biochips has advanced fast, allowing increasing miniaturization, the off-chip pressure actuators and pumps are bulky, thereby limiting them to laboratory environments. To address this issue, recent work focuses on reducing the number of off-chip pressure sources, using on-chip pneumatic control logic circuits.

These on-chip pneumatic control logic gates are constructed with valves and pull-up resistors. The pull-up resistors are much larger than the valves themselves, thereby making these gates very huge in area. Thus, the large size of on-chip control gates is a major bottleneck in the practical scaling of flow based microfluidic biochips. In addition to their large size, these gates have poor noise margin due to the large pull-up pneumatic resistor inside each of them, which make dimensioning and optimization very difficult.

SUMMARY

Despite the known solutions there is a need for improved microfluidic valves and microfluidic-based chips, e.g. biochips.
Accordingly, a microfluidic valve is provided comprising: a first rigid layer, a second rigid layer, a flexible layer being arranged between a first side of the first rigid layer and a second side of the second rigid layer, and a first control gate channel.

The first rigid layer has the first side comprising a first primary recess and a first secondary recess. The first primary recess forms a first input channel. The first secondary recess forms a first output channel. The first primary recess and the first secondary recess are separated by a first bridge of material of the first rigid layer.

The second rigid layer has a second side facing the first side of the first rigid layer. The second side comprises a first indentation overlaying a part of the first primary recess and a part of the first secondary recess and the first bridge.

The flexible layer is arranged between the first side of the first rigid layer and the second side of the second rigid layer. In a first state the flexible layer prevents fluid connection between the first input channel and the first output channel. In a second state the flexible layer protrudes into the first indentation providing fluid connection between the first input channel and the first output channel.

The first control gate channel is not forming part of the first primary recess and the first secondary recess, and the first control gate channel is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold the flexible layer is in the first state. When the first fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state.

Also disclosed is a microfluidic inverter comprising a first microfluidic valve, such as the microfluidic valve as disclosed above, and a second microfluidic valve.

The second microfluidic valve comprises a first rigid layer, a second rigid layer, a flexible layer being arranged between a first side of the first rigid layer and a second side of the second rigid layer, and a second control gate channel.

The first rigid layer of the second microfluidic valve has the first side comprising a second primary recess and a second secondary recess. The second primary recess forms a second input channel and the second secondary recess forms a second output channel. The second primary recess and the second secondary recess are separated by a second bridge of material of the first rigid layer.

The second rigid layer of the second microfluidic valve has the second side facing the first side of the first rigid layer, the second side comprises a second indentation
overlaying a part of the second primary recess and a part of the second secondary recess and the second bridge.

The flexible layer of the second microfluidic valve is arranged between the first side of the first rigid layer and the second side of the second rigid layer. In a first state the flexible layer protrudes into the second indentation providing a fluid connection between the second input channel and the second output channel. In a second state the flexible layer prevents fluid connection between the second input channel and the second output channel.

The second control gate channel is not forming part of the second primary recess and the second secondary recess, and the second control gate channel is configured to receive a second fluidic control pressure. When the second fluidic control pressure is lower than the pressure threshold the flexible layer is in the first state. When the second fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state.

The first output channel is in fluid connection with the second output channel forming a common output channel.

It is an advantage of the present disclosure that a microfluidic valve and a microfluidic inverter are provided that increases accuracy, e.g. in eliminating or at least reducing the need for pull-up resistors.

It is a further advantage of the present disclosure that a microfluidic valve and a microfluidic inverter are provided that decreases the area needed for certain parts of the microfluidic chips.

It is an even further advantage of the present disclosure that the need for off-chip pressure sources may be reduced, i.e. facilitating less bulky microfluidic chips setups, thereby facilitating a wider range of uses for the microfluidic chips.

The first control gate channel may be in fluid connection with the second control gate channel. The first control gate channel and the second control gate channel being in fluid connection may form a common control gate channel.

Pressure threshold for the flexible layer of the first microfluidic valve to be in the first state and/or second state, and pressure threshold for the flexible layer of the second microfluidic valve to be in the first state and/or second may be the same.
The first microfluidic valve and the second microfluidic valve may be integrally formed, and/or one or more parts of the first microfluidic valve and the second microfluidic valve may be integrally formed. For example, the first rigid layer of the first microfluidic valve may be integrally formed with the first rigid layer of the second microfluidic valve.

Alternatively or additionally, the second rigid layer of the first microfluidic valve may be integrally formed with the second rigid layer of the second microfluidic valve.

Alternatively or additionally, the flexible layer of the first microfluidic valve may be integrally formed with the flexible layer of the second microfluidic valve.

In the following reference to the first rigid layer, the second rigid layer, and/or the flexible layer may refer to the first rigid layer, the second rigid layer, and/or the flexible layer of either or both of the first microfluidic valve and/or the second microfluidic valve.

The control gate channels may be comprised in the rigid layers. For example, the first control gate channel may be comprised in the first rigid layer. Alternatively or additionally, the second control gate channel may be comprised in the second rigid layer.

The first control gate channel may also be comprised in the second rigid layer, and alternatively or additionally, the second control gate channel may be comprised in the first rigid layer.

The first control gate channel and/or the second control gate channel may comprise a bend, such as a 90 deg. bend. For example, the first control gate channel and/or the second control gate channel may have an L-shaped form. Such shape may provide that the control gate channel, such as the first control gate channel and/or the second control gate channel, terminates on a side of the microfluidic chip rather than on the top/bottom. The control gate channel, such as the first control gate channel and/or the second control gate channel may terminate parallel to the first input port and/or the second input port and/or the first output port and/or the second output port and/or the common output port.

The first control gate channel may be in fluid connection with the first input channel and/or the first output channel, e.g. when the flexible layer is in a state, such as the second state, providing fluid connection between the first input channel and the first output channel.

The first control gate channel may comprise a structure. The structure may be configured to mechanically manipulate the flexible layer. For example, when the first
fluidic control pressure is higher than the pressure threshold the structure is extending and the flexible layer is manipulated by the structure to the second state. Additionally or alternatively, when the first fluidic control pressure is lower than the pressure threshold the structure is retracting and the flexible layer may be manipulated by the structure to the first state.

The structure may be attached to the flexible layer, such as fastened to the flexible layer. For example, the structure may be glued to the structure. Alternatively, the structure may be loosely positioned in the first control gate channel, and about the flexible layer at least when the first fluidic control pressure is higher than the pressure threshold.

The structure may be integrally formed with the flexible layer. For example, the flexible layer may be manufactured with the structure for fitting with the first control gate channel.

The first rigid layer and/or the second rigid layer may be made of acrylic glass, such as polymethyl methacrylate (PMMA), or glass.

The flexible layer may be made of Polydimethylsiloxane (PDMS).

The structure may be made of Polydimethylsiloxane (PDMS). The structure and the flexible layer may be made of the same material.

The input channels, such as the first input channel and/or the second input channel may receive respective fluidic input pressures. For example, the first input channel may be configured to receive a first fluidic input pressure. The second input channel may be configured to receive a second fluidic input pressure. The first fluidic input pressure may be lower than the second fluidic input pressure. The second fluidic input pressure may be between 0 kPa and 20 kPa, such as 5 kPa and/or 10 kPa and/or 15 kPa. The first fluidic input pressure may be between -20 kPa and 0 kPa, such as -5 kPa and/or -10 kPa and/or -15 kPa. Alternatively, the second fluidic input pressure may be between 0 kPa and 50 kPa, such as 5 kPa and/or 10 kPa and/or 15 kPa and/or 20 kPa and/or 25 kPa and/or 30 kPa and/or 35 kPa and/or 40 kPa and/or 45 kPa and/or 50 kPa. The first fluidic input pressure may be between -80 kPa and 0 kPa, such as -10 kPa and/or -20 kPa and/or -30 kPa and/or -40 kPa and/or -50 kPa and/or -60 kPa and/or -70 kPa and/or -80 kPa. However, the first input channel may alternatively be configured to receive the second fluidic input pressure and vice versa.
The pressure threshold may be between the first fluidic input pressure and the second fluidic input pressure. For example, the pressure threshold may be 0 kPa.

For example, the flexible layer may be in the first state when the first fluidic control pressure and/or the second fluidic control pressure and/or the common fluidic control pressure is lower than the pressure threshold, e.g. lower than 0 kPa.

The flexible layer may be in the first state when the first fluidic control pressure and/or the second fluidic control pressure and/or the common fluidic control pressure is equal to the second fluidic input pressure.

For example, the flexible layer may be in the second state when the first fluidic control pressure and/or the second fluidic control pressure and/or the common fluidic control pressure is higher than the pressure threshold, e.g. higher than 0 kPa.

The flexible layer may be in the second state when the first fluidic control pressure and/or the second fluidic control pressure and/or the common fluidic control pressure is equal to the first fluidic input pressure.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other features and advantages of the present invention will become readily apparent to those skilled in the art by the following detailed description of exemplary embodiments thereof with reference to the attached drawings, in which:

Fig. 1 schematically illustrates a side view of an exemplary first microfluidic valve,

Fig. 2 schematically illustrates a side view of an exemplary first microfluidic valve,

Fig. 3 schematically illustrates a side view of an exemplary second microfluidic valve,

Fig. 4 schematically illustrates a side view of an exemplary microfluidic inverter,

Fig. 5 schematically illustrates a side view of an exemplary first microfluidic valve,

Fig. 6 schematically illustrates a side view of an exemplary second microfluidic valve,

Fig. 7 schematically illustrates a side view of an exemplary microfluidic inverter,

Fig. 8 schematically illustrates a top view of an exemplary first or second microfluidic valve,

Fig. 9 schematically illustrates a top view of an exemplary microfluidic inverter,
Fig. 10 schematically illustrates a top view of an exemplary microfluidic inverter wherein the first control gate channel is in fluid connect with the second control gate channel forming a common control gate channel.

5 DETAILED DESCRIPTION

Various embodiments are described hereinafter with reference to the figures. Like reference numerals refer to like elements throughout. Like elements will, thus, not be described in detail with respect to the description of each figure. It should also be noted that the figures are only intended to facilitate the description of the embodiments. They are not intended as an exhaustive description of the claimed invention or as a limitation on the scope of the claimed invention. In addition, an illustrated embodiment needs not have all the aspects or advantages shown. An aspect or an advantage described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced in any other embodiments even if not so illustrated, or if not so explicitly described.

Throughout, the same reference numerals are used for identical or corresponding parts.

Fig. 1 schematically illustrates a side view of an exemplary first microfluidic valve 2. The first microfluidic valve 2 comprises a first rigid layer 4, a second rigid layer 18, and a flexible layer 24.

The first rigid layer 4 has a first side 6. The first side 6 comprises a first primary recess 8 and a first secondary recess 10. The first primary recess 8 forms a first input channel 12. The first secondary recess 10 forms a first output channel 14. The first primary recess 8 and the first secondary recess 10 are separated by a first bridge of material 16 of the first rigid layer 4.

The second rigid layer 18 has a second side 20 facing the first side 6 of the first rigid layer 4. The second side 20 comprises a first indentation 22. The first indentation 22 overlays a part of the first primary recess 8 and a part of the first secondary 10 recess and the first bridge 16.

The flexible layer 24 is arranged between the first side 6 of the first rigid layer 4 and the second side 20 of the second rigid layer 18. In a first state (Fig. 1a) the flexible layer 24 prevents fluid connection between the first input channel 12 and the first output channel 14. In a second state (Fig. 1b) the flexible layer 24 protrudes into the first indentation...
22 providing fluid connection between the first input channel 12 and the first output channel 14.

The first microfluidic valve 2 comprises a first control gate channel 26. The first control gate channel 26 is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold the flexible layer 24 is in the first state (Fig. 1a). When the first fluidic control pressure is higher than the pressure threshold the flexible layer 24 is in the second state (Fig. 1b).

In the illustrated example, the first control gate channel 26 is comprised in the first rigid layer 4, and has an L-shape providing that the first control gate channel 26 terminates parallel to the first input channel 12 and the first output channel 14. However, in an alternative example, the first control gate channel 26 may be a straight channel, such as a straight channel terminating in the top of the first rigid layer 4.

Fig. 2 schematically illustrates a side view of an exemplary first microfluidic valve 2'. The first microfluidic valve 2' comprises a first rigid layer 4, a second rigid layer 18, and a flexible layer 24.

The first rigid layer 4, the second rigid layer 18, and the flexible layer 24 is as described in relation to Fig. 1.

The first microfluidic valve 2' comprises a first control gate channel 26'. The first control gate channel 26' is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold the flexible layer 24 is in the first state (Fig. 2a). When the first fluidic control pressure is higher than the pressure threshold the flexible layer 24 is in the second state (Fig. 2b).

In the illustrated example, the first control gate channel 26' is comprised in the first rigid layer 4, and has an L-shape providing that the first control gate channel 26' terminates parallel to the first input channel 12 and the first output channel 14. However, in an alternative example, the first control gate channel 26' may be a straight channel, such as a straight channel terminating in the top of the first rigid layer 4.

The first control gate channel 26' comprises a structure 28. The structure 28 is configured to mechanically manipulate the flexible layer 24. When the first fluidic control pressure is higher than the pressure threshold the structure is extending and the flexible layer is manipulated by the structure to the second state (Fig. 2b). When the first fluidic control pressure is lower than the pressure threshold the structure is retracted (Fig. 2a). When the structure retracts, the flexible layer 24 is able to return to
the first state, thereby preventing fluid connection between the first input channel 12 and the first output channel 14 (Fig. 2a).

The structure 28 provides for fluidic flow around it, i.e. it does not block the fluidic connection between the input channel 12 and the output channel 14.

The structure 28 may be attached to the flexible layer 24, such as fastened to the flexible layer 24. The structure 28 may be integrally formed with the flexible layer 24. The structure 28 being attached to the flexible layer 24 and/or the structure 28 being integrally formed with the flexible layer 24 may provide that the flexible layer 24 can be manipulated by the structure 28 to the first state (Fig. 2a).

Alternatively, the structure 28 may be positioned in the first control gate channel 26' without fastening to the flexible layer 24.

The length of the structure 28 may be adapted such that at least a part of the structure 28 remains in the first control gate channel 26' when the flexible layer 24 is in the second state (Fig. 2b).

Fig. 3 schematically illustrates a side view of an exemplary second microfluidic valve 32. The second microfluidic valve 32 comprises a first rigid layer 4', a second rigid layer 18', and a flexible layer 24'.

The first rigid layer 4' has a first side 6'. The first side 6' comprises a second primary recess 34 and a second secondary recess 36. The second primary recess 34 forms a second input channel 38. The second secondary recess 36 forms a second output channel 40. The secondary primary recess 36 and the second secondary recess 38 are separated by a second bridge of material 42 of the first rigid layer 4'.

The second rigid layer 18' has a second side 20' facing the first side 6' of the first rigid layer 4'. The second side 20' comprises a second indentation 44. The second indentation 44 overlays a part of the second primary recess 34 and a part of the second secondary 36 recess and the second bridge 42.

The flexible layer 24' is arranged between the first side 6' of the first rigid layer 4' and the second side 20' of the second rigid layer 18'. In a first state (Fig. 3a) the flexible layer 24' protrudes into the second indentation 44 providing a fluid connection between the second input channel 38 and the second output channel 40. In a second state (Fig. 3b) the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.
The second microfluidic valve 32 comprises a second control gate channel 46. The second control gate channel 46 is configured to receive a second fluidic control pressure. When the second fluidic control pressure is lower than a pressure threshold, the flexible layer 24' is in the first state (Fig. 3a). When the second fluidic control pressure is higher than the pressure threshold, the flexible layer 24' is in the second state (Fig. 3b).

In the illustrated example, the second control gate channel 46 is comprised in the second rigid layer 18', and has an L-shape providing that the second control gate channel 46 terminates parallel to the second input channel 38 and the second output channel 40. However, in another alternative example, the second control gate channel 46 may be a straight channel, such as a straight channel terminating in the bottom of the second rigid layer 18'.

Fig. 4 schematically illustrates a side view of an exemplary first microfluidic inverter 30. The first microfluidic inverter 30 comprises a first microfluidic valve 2, as explained in relation to Fig. 1, and a second microfluidic valve 32, as explained in relation to Fig. 3.

In another example (not shown), the first microfluidic inverter 30 comprises a first microfluidic valve 2', as explained in relation to Fig. 2, and a second microfluidic valve 32, as explained in relation to Fig. 3.

The first output channel 14 is in fluid connection with the second output channel 40. The first output channel 14 and the second output channel 40 forms a common output channel 48.

The first microfluidic valve 2 and the second microfluidic valve 32 may be separate valves. However, as also illustrated, they may be formed from the same elements.

The first rigid layer 4 of the first microfluidic valve 2 is integrally formed with the first rigid layer 4' of the second microfluidic valve 32. The first rigid layer 4 of the first microfluidic valve 2 may be the first rigid layer 4' of the second microfluidic valve 32, and vice versa.

The second rigid layer 18 of the first microfluidic valve 2 is integrally formed with the second rigid layer 18' of the second microfluidic valve 32. The second rigid layer 18 of the first microfluidic valve 2 may be the second rigid layer 18' of the second microfluidic valve 32, and vice versa.

The flexible layer 24 of the first microfluidic valve 2 is integrally formed with the flexible layer 24' of the second microfluidic valve 32. The flexible layer 24 of the first
microfluidic valve 2 may be the flexible layer 24' of the second microfluidic valve 32, and vice versa.

Fig. 4a shows the flexible layer 24 of the first microfluidic valve 2 being in the first state, wherein the flexible layer 24 prevents fluid connection between the first input channel 12 and the first output channel 14, and the flexible layer 24' of the second microfluidic valve 32 being in the second state, wherein the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.

Fig. 4b shows the flexible layer 24 of the first microfluidic valve 2 being in the first state, wherein the flexible layer 24 prevents fluid connection between the first input channel 12 and the first output channel 14, and the flexible layer 24' of the second microfluidic valve 32 being in the first state, wherein the flexible layer 24' provides fluid connection between the second input channel 38 and the second output channel 40.

Fig. 4c shows the flexible layer 24 of the first microfluidic valve 2 being in the second state, wherein the flexible layer 24 provides fluid connection between the first input channel 12 and the first output channel 14, and the flexible layer 24' of the second microfluidic valve 32 being in the second state, wherein the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.

Although not illustrated, the first control gate channel 26 may be in fluid connection with the second control gate channel 46. The first control gate channel 26 and the second control gate channel 46 may form a common control gate channel. This may be advantageous as it reduces the complexity.

Pressure threshold for the flexible layer of the first microfluidic valve to be in the first state and/or second state, and pressure threshold for the flexible layer of the second microfluidic valve to be in the first state and/or second may be the same.

The first microfluidic inverter 30 may be configured to receive a first fluidic input pressure on the first input channel 12 and a second fluidic input pressure on the second channel 38. The output pressure in the common output channel 48 is determined by the state of the flexible layer 24, 24'.

When the flexible layer 24 of the first microfluidic valve 2 is in the first state and the flexible layer 24' of the second microfluidic valve 32 is in the first state (Fig. 4b), fluid connection is prevented between the first input channel 12 and the common output channel 48, but fluid connection is provided between the second input channel 38 and
the common output channel 48. Therefore, in this situation, the output pressure in the common output channel 48 will be the pressure in the second input channel 38, e.g. the second fluidic input pressure.

When the flexible layer 24 of the first microfluidic valve 2 is in the second state and the flexible layer 24' of the second microfluidic valve 32 is in the second state (Fig. 4c), fluid connection is provided between the first input channel 12 and the common output channel 48, but fluid connection is prevented between the second input channel 38 and the common output channel 48. Therefore, in this situation, the output pressure in the common output channel 48 will be the pressure in the first input channel 12, e.g. the first fluidic input pressure.

In an example, the first fluidic input pressure may be a negative pressure, such as -20 kPa, and the second fluidic input pressure may be a positive pressure, such as 20 kPa. The pressure threshold of the flexible layer 24, 24' of the first microfluidic valve 2 and the second microfluidic valve 32 may be between the first fluidic input pressure and the second fluidic input pressure, such as 0 kPa.

The control gate channels 26, 46 may be coupled to pressure of the first fluidic pressure and/or the second fluidic pressure. If the control gate channels 26, 46 receive the first fluidic pressure, e.g. -20 kPa, the situation as illustrated in Fig. 4b will arise and the output pressure in the common output channel 48 will be the pressure in the second input channel 38, e.g. the second fluidic pressure, e.g. 20 kPa. If the control gate channels 26, 46 receive the second fluidic pressure, e.g. 20 kPa, the situation as illustrated in Fig. 4c will arise and the output pressure in the common output channel 48 will be the pressure in the first input channel 12, e.g. the first fluidic pressure, e.g. -20 kPa.

Fig. 5 schematically illustrates a side view of an exemplary first microfluidic valve 2". The first microfluidic valve 2" comprises a first rigid layer 4", a second rigid layer 18, and a flexible layer 24.

The first rigid layer 4" has a first side 6". The first side 6" comprises a first primary recess 8' and a first secondary recess 10'. The first primary recess 8' forms a first input channel 12'. The first secondary recess 10' forms a first output channel 14'. The first primary recess 8' and the first secondary recess 10' are separated by a first bridge of material 16' of the first rigid layer 4".
The second rigid layer 18 has a second side 20 facing the first side 6" of the first rigid layer 4". The second side 20 comprises a first indentation 22. The first indentation 22 overlays a part of the first primary recess 8' and a part of the first secondary recess 10' recess and the first bridge 16'.

The flexible layer 24 is arranged between the first side 6" of the first rigid layer 4" and the second side 20 of the second rigid layer 18. In a first state (Fig. 5a) the flexible layer 24 prevents fluid connection between the first input channel 12' and the first output channel 14'. In a second state (Fig. 5b) the flexible layer 24 protrudes into the first indentation 22 providing fluid connection between the first input channel 12' and the first output channel 14'.

The first microfluidic valve 2" comprises a first control gate channel 26". The first control gate channel 26" is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold the flexible layer 24 is in the first state (Fig. 5a). When the first fluidic control pressure is higher than the pressure threshold the flexible layer 24 is in the second state (Fig. 5b).

In the illustrated example, the first control gate channel 26" is comprised in the first rigid layer 4", and the first control gate channel 26" is directed towards another side than the first input channel 12' and the first output channel 14', such as e.g. the first control gate channel 26" is perpendicular to the first input channel 12' and the first output channel 14'. However, in an alternative example, the first control gate channel 26" may be a straight channel, such as a straight channel terminating in the top of the first rigid layer 4".

Fig. 6 schematically illustrates a side view of an exemplary second microfluidic valve 32'. The second microfluidic valve 32' comprises a first rigid layer 4', a second rigid layer 18", and a flexible layer 24'.

The first rigid layer 4' has a first side 6'. The first side 6' comprises a second primary recess 34 and a second secondary recess 36. The second primary recess 34 forms a second input channel 38. The second secondary recess 36 forms a second output channel 40. The secondary primary recess 36 and the second secondary recess 38 are separated by a second bridge of material 42 of the first rigid layer 4'.

The second rigid layer 18" has a second side 20" facing the first side 6' of the first rigid layer 4'. The second side 20" comprises a second indentation 44'. The second
indentation 44' overlays a part of the second primary recess 34 and a part of the second secondary recess 36 and the second bridge 42.

The flexible layer 24' is arranged between the first side 6' of the first rigid layer 4' and the second side 20'' of the second rigid layer 18''. In a first state (Fig. 6a) the flexible layer 24' protrudes into the second indentation 44' providing a fluid connection between the second input channel 38 and the second output channel 40. In a second state (Fig. 6b) the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.

The second microfluidic valve 32' comprises a second control gate channel 46'. The second control gate channel 46' is configured to receive a second fluidic control pressure. When the second fluidic control pressure is lower than a pressure threshold the flexible layer 24' is in the first state (Fig. 6a). When the second fluidic control pressure is higher than the pressure threshold the flexible layer 24' is in the second state (Fig. 6b).

In the illustrated example, the second control gate channel 46' is comprised in the second rigid layer 18'', and the second control gate channel 46' is directed towards another side than the second input channel 38 and the second output channel 40 such as e.g. the second control gate channel 46' is perpendicular to the second input channel 38 and the second output channel 40. However, in an alternative example, the second control gate channel 46' may be a straight channel, such as a straight channel terminating in the bottom of the second rigid layer 18''.

Fig. 7 schematically illustrates a side view of an exemplary microfluidic inverter 30'. The microfluidic inverter 30' comprises a first microfluidic valve 2'', as explained in relation to Fig. 5, and a second microfluidic valve 32'', as explained in relation to Fig. 6.

In another example (not shown), the microfluidic inverter 30' comprises a first microfluidic valve 2'', as explained in relation to Fig. 2, and a second microfluidic valve 32'', as explained in relation to Fig. 6.

The first output channel 14' is in fluid connection with the second output channel 40. The first output channel 14' and the second output channel 40 forms a common output channel 48'.

The first microfluidic valve 2'' and the second microfluidic valve 32'' may be separate valves. However, as also illustrated, they may be formed from the same elements.
The first rigid layer 4" of the first microfluidic valve 2" is integrally formed with the first rigid layer 4' of the second microfluidic valve 32'. The first rigid layer 4" of the first microfluidic valve 2" may be the first rigid layer 4' of the forth microfluidic valve 32', and vice versa.

The second rigid layer 18 of the first microfluidic valve 2" is integrally formed with the second rigid layer 18" of the second microfluidic valve 32'. The second rigid layer 18 of the first microfluidic valve 2" may be the second rigid layer 18" of the second microfluidic valve 32', and vice versa.

The flexible layer 24 of the first microfluidic valve 2" is integrally formed with the flexible layer 24' of the second microfluidic valve 32'. The flexible layer 24 of the first microfluidic valve 2" may be the flexible layer 24' of the second microfluidic valve 32', and vice versa.

Fig. 7a shows the flexible layer 24 of the first microfluidic valve 2" being in the first state, wherein the flexible layer 24 prevents fluid connection between the first input channel 12' and the first output channel 14', and the flexible layer 24' of the second microfluidic valve 32' being in the second state, wherein the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.

Fig. 7b shows the flexible layer 24 of the first microfluidic valve 2" being in the first state, wherein the flexible layer 24 prevents fluid connection between the first input channel 12' and the first output channel 14', and the flexible layer 24' of the second microfluidic valve 32' being in the first state, wherein the flexible layer 24' provides fluid connection between the second input channel 38 and the second output channel 40.

Fig. 7c shows the flexible layer 24 of the first microfluidic valve 2" being in the second state, wherein the flexible layer 24 provides fluid connection between the first input channel 12' and the first output channel 14', and the flexible layer 24' of the second microfluidic valve 32' being in the second state, wherein the flexible layer 24' prevents fluid connection between the second input channel 38 and the second output channel 40.

Although not illustrated, the first control gate channel 26" may be in fluid connection with the second control gate channel 46'. The first control gate channel 26" and the second control gate channel 46' may form a common control gate channel.
Pressure threshold for the flexible layer of the first microfluidic valve to be in the first state and/or second state, and pressure threshold for the flexible layer of the second microfluidic valve to be in the first state and/or second may be the same.

The microfluidic inverter 30' may be configured to receive a first fluidic input pressure on the first input channel 12' and a second fluidic input pressure on the second channel 38. The output pressure in the common output channel 48' is determined by the state of the flexible layer 24, 24'.

When the flexible layer 24 of the first microfluidic valve 2" is in the first state and the flexible layer 24' of the second microfluidic valve 32' is in the first state (Fig. 7b), fluid connection is prevented between the first input channel 12' and the common output channel 48', but fluid connection is provided between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the second input channel 38, e.g. the second fluidic input pressure.

When the flexible layer 24 of the first microfluidic valve 2" is in the second state and the flexible layer 24' of the second microfluidic valve 32' is in the second state (Fig. 7c), fluid connection is provided between the first input channel 12' and the common output channel 48', but fluid connection is prevented between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the first input channel 12', e.g. the first fluidic input pressure.

In an example, the first fluidic input pressure may be a negative pressure, such as -20 kPa, and the second fluidic input pressure may be a positive pressure, such as 20 kPa. The pressure threshold of the flexible layer 24, 24' of the first microfluidic valve 2" and the second microfluidic valve 32' may be between the first fluidic input pressure and the second fluidic input pressure, such as 0 kPa.

The control gate channels 26", 46' may be coupled to pressure of the first fluidic pressure and/or the second fluidic pressure. If the control gate channels 26", 46' receive the first fluidic pressure, e.g. -20 kPa, the situation as illustrated in Fig. 7b will arise and the output pressure in the common output channel 48' will be the pressure in the second input channel 38, e.g. the second fluidic pressure, e.g. 20 kPa. If the control gate channels 26", 46' receive the second fluidic pressure, e.g. 20 kPa, the situation as illustrated in Fig. 7c will arise and the output pressure in the common output channel...
48' will be the pressure in the first input channel 12', e.g. the first fluidic pressure, e.g. -20 kPa.

Fig. 8 schematically illustrates a top view of an exemplary first microfluidic system comprising one microfluidic valve 2", as explained in relation to Fig. 1. For a more clear view the shading has been removed from Fig. 8. The schematically illustration is viewed from the top, and part of the microfluidic system is see-through to get an easy overview of the microfluidic channels.

The microfluidic system comprises a first input channel 12', 38 formed by a first primary recess as shown in e.g. Fig. 1, and a first output channel 14' formed by a first secondary recess as shown in e.g. Fig. 1.

The microfluidic system further comprises a first control gate channel 26", 46', as illustrated in e.g. Fig. 5 or 6. The first control gate channel 26", 46' is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold a flexible layer in the microfluidic valve is in the first state. When the first fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state.

In the illustrated example, the first control gate channel 26", 46' is perpendicular to the first input channel 12' and the first output channel 14'. However, in an alternative example, the first control gate channel 26", 46' may have other angels in relation to the first input channel 12' and the first output channel 14', such as 45 degree angle or 60 degree angle.

Fig. 9 schematically illustrates a top view of an exemplary third microfluidic system comprising two microfluidic valves 2" and 32' creating a microfluidic inverter 30'. The microfluidic inverter 30' is only an inverter when it is configured to receive a first fluidic input pressure on the first input channel 12' and a second fluidic input pressure on the second channel and the first input pressure is equal to the second input pressure. For a more clear view the shading has been removed from Fig. 9. The schematically illustration is viewed from the top, and part of the microfluidic system is see-through to get an easy overview of the microfluidic channels.

The microfluidic system comprises a first input channel 12' formed by a first primary recess as shown in e.g. Fig. 7, and a first output channel 14' formed by a first secondary recess as shown in e.g. Fig. 7. The microfluidic system further comprises a second input channel 38 formed by a secondary primary recess as shown in e.g. Fig.
7, and a second output channel 40 formed by a second secondary recess as shown in e.g. Fig 7.

The first output channel 14' is in fluid connection with the second output channel 40. The first output channel 14' and the second output channel 40 forms a common output channel 48'.

The microfluidic system further comprises a first control gate channel 26", as illustrated in Fig 7, and a second control gate channel 46', as illustrated in Fig 7. The first control gate channel 26" is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold, a flexible layer in the first microfluidic valve 2", the flexible layer is in the first state (see e.g. Fig. 5a). When the first fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state (see e.g. Fig. 5b). The second control gate channel 46' is configured to receive a second fluidic control pressure. When the second fluidic control pressure is lower than a pressure threshold of the flexible layer in the second microfluidic valve 32', the flexible layer is in the first state (see e.g. Fig. 6a). When the second fluidic control pressure is higher than the pressure threshold, the flexible layer is in the second state (see e.g. Fig. 6b).

Pressure threshold for the flexible layer of the first microfluidic valve 2" to be in the first state and/or second state, and pressure threshold for the flexible layer of the second microfluidic valve 32' to be in the first state and/or second may be the same.

The microfluidic inverter 30' may be configured to receive a first fluidic input pressure on the first input channel 12' and a second fluidic input pressure on the second channel 38. The output pressure in the common output channel 48' is determined by the state of the flexible layers in the microfluidic valves 2" and 32'.

When the flexible layer of the first microfluidic valve 2" is in the first state and the flexible layer of the second microfluidic valve 32' is in the first state (see e.g. Fig. 7b), fluid connection is prevented between the first input channel 12' and the common output channel 48', but fluid connection is provided between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the second input channel 38, e.g. the second fluidic input pressure.

When the flexible layer of the first microfluidic valve 2" is in the second state and the flexible layer of the second microfluidic valve 32' is in the second state (see e.g. Fig.
7c), fluid connection is provided between the first input channel 12' and the common output channel 48', but fluid connection is prevented between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the first input channel 12', e.g. the first fluidic input pressure.

In the illustrated example, the first control gate channel 26" and the second control gate channel 46' are perpendicular to the input channels and the output channels. However, in an alternative example, the control gate channels 26" and 46' may have other angels in relation to the input channels and the output channels, such as 45 degree angle or 60 degree angle.

Fig. 10 schematically illustrates a top view of an exemplary second microfluidic system comprising two microfluidic valves 2" and 32' creating a microfluidic inverter 30", as explained in relation to Fig. 7. For a more clear view the shading has been removed from Fig. 10. The schematically illustration is viewed from the top, and part of the microfluidic system is see-through to get an easy overview of the microfluidic channels.

The microfluidic system comprises a first input channel 12' formed by a first primary recess as shown in e.g. Fig. 7, and a first output channel 14' formed by a first secondary recess as shown in e.g. Fig 7. The microfluidic system further comprises a second input channel 38 formed by a secondary primary recess as shown in e.g. Fig. 7, and a second output channel 40 formed by a second secondary recess as shown in e.g. Fig 7.

The first output channel 14' is in fluid connection with the second output channel 40. The first output channel 14' and the second output channel 40 forms a common output channel 48'.

The microfluidic system further comprises a first control gate channel 26", as illustrated in Fig 7, and a second control gate channel 46', as illustrated in Fig 7. The first control gate channel 26" is configured to receive a first fluidic control pressure. When the first fluidic control pressure is lower than a pressure threshold a flexible layer in the first microfluidic valve 2", the flexible layer is in the first state (see e.g. Fig. 5a). When the first fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state (see e.g. Fig. 5b). The second control gate channel 46' is configured to receive a second fluidic control pressure. When the second fluidic control pressure is lower than a pressure threshold of the flexible layer in the second microfluidic valve 32', the flexible layer is in the first state (see e.g. Fig. 6a). When the second fluidic control
pressure is higher than the pressure threshold, the flexible layer is in the second state (see e.g. Fig. 6b).

The first control gate channel 26" is in fluid connection with the second control gate channel 46'. The first control gate channel 26" and the second control gate channel 46' hereby form a common control gate channel.

Pressure threshold for the flexible layer of the first microfluidic valve to be in the first state and/or second state, and pressure threshold for the flexible layer of the second microfluidic valve to be in the first state and/or second may be the same.

The microfluidic inverter 30' may be configured to receive a first fluidic input pressure on the first input channel 12' and a second fluidic input pressure on the second channel 38. The output pressure in the common output channel 48' is determined by the state of the flexible layers in the microfluidic valves 2" and 32'.

When the flexible layer of the first microfluidic valve 2" is in the first state and the flexible layer of the second microfluidic valve 32' is in the first state (see e.g. Fig. 7b), fluid connection is prevented between the first input channel 12' and the common output channel 48', but fluid connection is provided between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the second input channel 38, e.g. the second fluidic input pressure.

When the flexible layer of the first microfluidic valve 2" is in the second state and the flexible layer of the second microfluidic valve 32' is in the second state (see e.g. Fig. 7c), fluid connection is provided between the first input channel 12' and the common output channel 48', but fluid connection is prevented between the second input channel 38 and the common output channel 48'. Therefore, in this situation, the output pressure in the common output channel 48' will be the pressure in the first input channel 12', e.g. the first fluidic input pressure.

In an example, the first fluidic input pressure may be a negative pressure, such as -20 kPa, and the second fluidic input pressure may be a positive pressure, such as 20 kPa. The pressure threshold of the flexible layer of the first microfluidic valve 2" and the second microfluidic valve 32' may be between the first fluidic input pressure and the second fluidic input pressure, such as 0 kPa.

The common control gate channel, created by the first control gate channel 26" being in fluid connection with the second control gate channel 46', may be coupled to
pressure of the first fluidic pressure and/or the second fluidic pressure. If the common control gate channel receives the first fluidic pressure, e.g. -20 kPa, the situation as illustrated in Fig. 7b will arise and the output pressure in the common output channel 48' will be the pressure in the second input channel 38, e.g. the second fluidic pressure, e.g. 20 kPa. If the common control gate channel receives the second fluidic pressure, e.g. 20 kPa, the situation as illustrated in Fig. 7c will arise and the output pressure in the common output channel 48' will be the pressure in the first input channel 12', e.g. the first fluidic pressure, e.g. -20 kPa.

In the illustrated example, the first control gate channel 26" and the second control gate channel 46' are perpendicular to the input channels and the output channels. However, in an alternative example, the control gate channels 26" and 46' may have other angles in relation to the input channels and the output channels, such as 45 degree angle or 60 degree angle.

Although particular features have been shown and described, it will be understood that they are not intended to limit the claimed invention, and it will be made obvious to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the claimed invention. The specification and drawings are, accordingly to be regarded in an illustrative rather than restrictive sense. The claimed invention is intended to cover all alternatives, modifications and equivalents.
LIST OF REFERENCES

2, 2', 2"  first microfluidic valve
4, A', A"  first rigid layer
6, 6', 6"  first side
8, 8'  first primary recess
10, 10'  first secondary recess
12, 12'  first input channel
14, 14'  first output channel
16, 16'  first bridge
18, 18', 18"  second rigid layer
20, 20', 20"  second side
22  first indentation
24, 24'  flexible layer
26, 26', 26"  first control gate channel
28  structure
30, 30'  microfluidic inverter
32, 32'  second microfluidic valve
34  second primary recess
36  second secondary recess
38  second input channel
40  second output channel
42  second bridge
44, 44'  second indentation
46, 46'  second control gate channel
48, 48'  common output channel
CLAIMS

1. A microfluidic valve comprising:
   - a first rigid layer having a first side comprising a first primary recess and a
     first secondary recess, the first primary recess forming a first input channel
     and the first secondary recess forming a first output channel, the first
     primary recess and the first secondary recess being separated by a first
     bridge of material of the first rigid layer;
   - a second rigid layer having a second side facing the first side of the first
     rigid layer, the second side comprising a first indentation overlaying a part of
     the first primary recess and a part of the first secondary recess and the first
     bridge;
   - a flexible layer being arranged between the first side of the first rigid layer
     and the second side of the second rigid layer, in a first state the flexible
     layer prevents fluid connection between the first input channel and the first
     output channel, in a second state the flexible layer protrudes into the first
     indentation providing fluid connection between the first input channel and
     the first output channel; and
   - a first control gate channel not forming part of the first primary recesses and
     the first secondary recess, wherein the first control gate channel is
     configured to receive a first fluidic control pressure, and wherein when the
     first fluidic control pressure is lower than a pressure threshold the flexible
     layer is in the first state, and wherein when the first fluidic control pressure is
     higher than the pressure threshold the flexible layer is in the second state.

2. The microfluidic valve according to claim 1, wherein the first control gate
   channel is comprised in the first rigid layer or the second rigid layer.

3. The microfluidic valve according to claim 1 or 2, wherein the first control gate
   channel is comprised in the first bridge or the first indentation.
4. The microfluidic valve according to any of the preceding claims, wherein the first control gate channel comprises a structure, configured to mechanically manipulate the flexible layer, wherein when the first fluidic control pressure is higher than the pressure threshold the structure is extending and the flexible layer is manipulated by the structure to the second state.

5. The microfluidic valve according to claim 4, wherein the structure is attached to the flexible layer.

6. The microfluidic valve according to any of claims 4 or 5, wherein the structure is integrally formed with the flexible layer.

7. The microfluidic valve according to any of the preceding claims, wherein the first rigid layer and the second rigid layer is made of PMMA or glass.

8. The microfluidic valve according to any of the preceding claims, wherein the flexible layer is made of PDMS.

9. The microfluidic valve according to any of the preceding claims, wherein the first input channel is configured to receive a first fluidic input pressure.

10. The microfluidic valve according to any of the preceding claims, wherein the pressure threshold is 0 kPa.

11. A microfluidic inverter comprising a first microfluidic valve according to any of the preceding claims and a second microfluidic valve, the second microfluidic valve comprising:
   - a first rigid layer having a first side comprising a second primary recess and a second secondary recess, the second primary recess forming a second input channel and the second secondary recess forming a second output.
channel, the secondary primary recess and the second secondary recess being separated by a second bridge of material of the first rigid layer;

- a second rigid layer having a second side facing the first side of the first rigid layer, the second side comprising a second indentation overlaying a part of the second primary recess and a part of the second secondary recess and the second bridge;

- a flexible layer being arranged between the first side of the first rigid layer and the second side of the second rigid layer, in a first state the flexible layer protrudes into the second indentation providing a fluid connection between the second input channel and the second output channel, in a second state the flexible layer prevents fluid connection between the second input channel and the second output channel; and

- a second control gate channel not forming part of the second primary recess and the second secondary recess, wherein the second control gate channel is configured to receive a second fluidic control pressure, and wherein when the second fluidic control pressure is lower than the pressure threshold the flexible layer is in the first state, and wherein when the second fluidic control pressure is higher than the pressure threshold the flexible layer is in the second state,

the first output channel being in fluid connection with the second output channel forming a common output channel.

12. The microfluidic inverter according to claim 11, wherein the second control gate channel is comprised in the first rigid layer or the second rigid layer.

13. The microfluidic valve according to claim 11 or 12, wherein the second control gate channel is comprised in the second bridge or the second indentation.

14. The microfluidic inverter according to any of claims 11-13, wherein the first control gate channel is in fluid connection with the second control gate channel forming a common control gate channel.
15. The microfluidic inverter according to any of claims 11-13 wherein the first rigid layer of the first microfluidic valve is integrally formed with the first rigid layer of the second microfluidic valve, and/or wherein the second rigid layer of the first microfluidic valve is integrally formed with the second rigid layer of the second microfluidic valve, and/or wherein the flexible layer of the first microfluidic valve is integrally formed with the flexible layer of the second microfluidic valve.

16. The microfluidic inverter according to any of claims 11-14, wherein the second input channel is configured to receive a second fluidic input pressure.

17. The microfluidic inverter according to claim 15 as dependent on claim 9, wherein the first fluidic input pressure is lower than the second fluidic input pressure, and/or wherein the pressure threshold is between the first fluidic input pressure and the second fluidic input pressure.
Fig. 3
A. CLASSIFICATION OF SUBJECT MATTER
INV. F16K99/00 B01L3/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
F16K B01L3/00

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) one of which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search
24 January 2018

Date of mailing of the international search report
31/01/2018

Authorized officer
Rui z-Echarri Rueda
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2016/121328 A1 (CHARLES RAYMOND [FR]) 5 May 2016 (2016-05-05) paragraphs [0068] - [0092]; figures 1-5</td>
<td>1-17</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>US 2015093815 AI 02-04-2015</td>
<td>CN 105636697 A</td>
<td>01-06-2016</td>
</tr>
<tr>
<td></td>
<td>EP 3052236 A</td>
<td>10-08-2016</td>
</tr>
<tr>
<td></td>
<td>HK 1223062 A</td>
<td>21-07-2017</td>
</tr>
<tr>
<td></td>
<td>US 2015093815 A</td>
<td>02-04-2015</td>
</tr>
<tr>
<td></td>
<td>US 2017151567 A</td>
<td>01-06-2017</td>
</tr>
<tr>
<td></td>
<td>WO 2015048798 A</td>
<td>02-04-2015</td>
</tr>
<tr>
<td>US 2009060797 AI 05-03-2009</td>
<td>AU 2003303594 A</td>
<td>29-07-2004</td>
</tr>
<tr>
<td></td>
<td>CA 2512071 A</td>
<td>22-07-2004</td>
</tr>
<tr>
<td></td>
<td>EP 1594694 A2</td>
<td>16-11-2005</td>
</tr>
<tr>
<td></td>
<td>EP 2404676 A</td>
<td>11-01-2012</td>
</tr>
<tr>
<td></td>
<td>JP 5250669 B2</td>
<td>31-07-2013</td>
</tr>
<tr>
<td></td>
<td>JP 2006512092 A</td>
<td>13-04-2006</td>
</tr>
<tr>
<td></td>
<td>JP 2011234728 A</td>
<td>24-11-2011</td>
</tr>
<tr>
<td></td>
<td>KR 2005088476 A</td>
<td>06-09-2005</td>
</tr>
<tr>
<td></td>
<td>KR 2011009734 A</td>
<td>31-08-2011</td>
</tr>
<tr>
<td></td>
<td>US 2004209354 A</td>
<td>21-10-2004</td>
</tr>
<tr>
<td></td>
<td>US 2006073484 A</td>
<td>06-04-2006</td>
</tr>
<tr>
<td></td>
<td>US 2009060797 A</td>
<td>05-03-2009</td>
</tr>
<tr>
<td></td>
<td>US 2010224255 A</td>
<td>09-09-2010</td>
</tr>
<tr>
<td></td>
<td>WO 2004061085 A</td>
<td>22-07-2004</td>
</tr>
<tr>
<td>US 2011240127 AI 06-10-2011</td>
<td>EP 2553423 A</td>
<td>06-02-2013</td>
</tr>
<tr>
<td></td>
<td>US 2011240127 A</td>
<td>06-10-2011</td>
</tr>
<tr>
<td></td>
<td>WO 2011123801 A</td>
<td>06-10-2011</td>
</tr>
<tr>
<td></td>
<td>CA 2777445 A</td>
<td>28-04-2011</td>
</tr>
<tr>
<td></td>
<td>CN 102665915 A</td>
<td>12-09-2012</td>
</tr>
<tr>
<td></td>
<td>EP 2490812 A</td>
<td>29-08-2012</td>
</tr>
<tr>
<td></td>
<td>EP 3050626 A</td>
<td>03-08-2016</td>
</tr>
<tr>
<td></td>
<td>ES 2578778 T3</td>
<td>01-08-2016</td>
</tr>
<tr>
<td></td>
<td>JP 5456904 B2</td>
<td>02-04-2014</td>
</tr>
<tr>
<td></td>
<td>JP 2013508715 A</td>
<td>07-03-2013</td>
</tr>
<tr>
<td></td>
<td>KR 20130058654 A</td>
<td>04-06-2013</td>
</tr>
<tr>
<td></td>
<td>RU 2012120796 A</td>
<td>27-11-2013</td>
</tr>
<tr>
<td></td>
<td>US 2012266986 A</td>
<td>25-10-2012</td>
</tr>
<tr>
<td></td>
<td>WO 2011048521 A</td>
<td>28-04-2011</td>
</tr>
<tr>
<td></td>
<td>ZA 201202864 B</td>
<td>27-12-2012</td>
</tr>
<tr>
<td></td>
<td>AU 2001297572 A</td>
<td>21-10-2002</td>
</tr>
<tr>
<td></td>
<td>DE 60120230 T2</td>
<td>29-03-2007</td>
</tr>
<tr>
<td></td>
<td>EP 1386087 A2</td>
<td>04-02-2004</td>
</tr>
<tr>
<td></td>
<td>US 2002195152 A</td>
<td>26-12-2002</td>
</tr>
<tr>
<td></td>
<td>US 2005022889 A</td>
<td>03-02-2005</td>
</tr>
<tr>
<td></td>
<td>US 2006000513 A</td>
<td>05-01-2006</td>
</tr>
<tr>
<td></td>
<td>US 2008257437 A</td>
<td>23-10-2008</td>
</tr>
<tr>
<td></td>
<td>US 2010283757 A</td>
<td>21-10-2010</td>
</tr>
<tr>
<td></td>
<td>US 201300765 A</td>
<td>03-01-2013</td>
</tr>
<tr>
<td></td>
<td>US 2014130920 A</td>
<td>15-05-2014</td>
</tr>
<tr>
<td></td>
<td>WO 02081935 A2</td>
<td>17-10-2002</td>
</tr>
<tr>
<td></td>
<td>FR 3006207 A</td>
<td>05-12-2014</td>
</tr>
<tr>
<td></td>
<td>US 2016121328 A</td>
<td>05-05-2016</td>
</tr>
<tr>
<td></td>
<td>WO 2014191519 A</td>
<td>04-12-2014</td>
</tr>
</tbody>
</table>