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A HIGH PRECISION FLUID HANDLING SYSTEM BASED ON PRESSURE ACTUATION: MULTI-INLETS FLOW-RATE CONTROL

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KEY WORDS

Microfluidic, pressure actuation, flow-rate control, algorithm, regulation, fluid handling system, coupling effects, mass parallel system

ABSTRACT

We present a new algorithm which enables the flow-rate control of a microfluidic system using pressure actuators. The algorithm combines the benefits of pressure flow actuation with the direct flow-rate control of the system. The algorithm can control a complex system with coupling effects or a massively parallel system with independent channels, regardless of the number of channels. We tested the performances of the flow-rate control solution on a coupled microsystem and compared them to the performances of a high precision syringe pump-based solution on the same microsystem. We also present the behavior of a system controlled by the flow-rate control solution and while it was submitted to an external disturbance.

1. INTRODUCTION

Most functions and applications of the microfluidic chips are highly linked to the performances of the flow control device used. The flow control solutions based on displacement-driven flow, such as syringe-pump or peristaltic pump, are widely used. However they lead to poor temporal response [1] and instability in the flow delivery that could limit their relevance in applications where periodic stop-flows or multiple fluid injection are needed [2,3]. The settling time obtained with the syringe pump solutions is highly dependent on the elasticity of the system and the materials used [1,4].

This fluidic behavior could lead to unexpected and unwanted results in many microfluidic applications which highly rely on flow control performances: size variation of droplets at low flow-rates [5], numbers of inconveniences to produce pulsed flow, such as reverse the pumping direction [6] or the need to take into account for the mechanical behavior of the thread screw of the syringe pump [6,7]. New methods have been setting up to decrease the settling time of the syringe pump [4] or increase the stability. They lead to unwanted flow-rate perturbation [4], that can result in destruction of cells [8,9] or in cell detachment of the microchannel [4].

Herein, we present a new method to control the flow-rate(s) in microchannels based on pressure actuatation. This method provides fast settling time and stable flows for a large range of microfluidic applications.

2. PRESSURE ACTUATION

The approach presented here is based on the pneumatic pressurization of the reservoirs containing the liquids which are to be injected into the microsystem. The original pneumatic path combined with a very fast regulation algorithm has been developed to deliver regulated pressure from a pressure source. The principle of pressure actuation in microfluidic systems is shown in Fig.1 and the benefits of this technology are listed in Tab.1. The principle of pressure actuation is described herafter: 1: Pressure values are ordered with a dedicated software. 2: The pressure actuator immediately and automatically provides the requested pressures with very high stability thanks to a feedback loop. 3: By connecting the pressure channels of the pressure actuator to reservoirs the pneumatic pressure provides precise and smooth control of the flow into the microfluidic device.

The patented series of instruments can operate over a wide pressure range (from -800 mbar to 7000 mbar) to control flows from sub nL/min to thousands of mL/min, depending on the hydrodynamic resistance of the microfluidic systems.

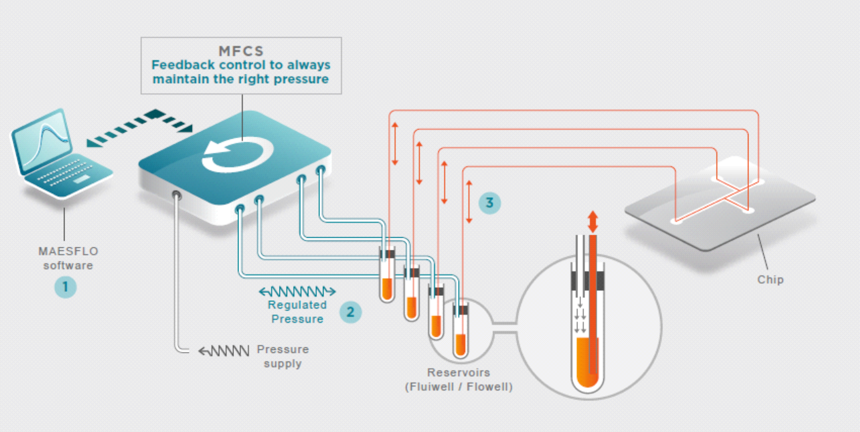

Figure 1: Principle of pressure actuation.

Parameter	Value	Remark
Settling time	< 1s usually between 0.1 to 0.2 s	Output volume dependent. No dependent on the elasticity of the system
Response time	< 16 ms	
Pressure stability	0.1 %	Precision of the flow. No dependent on the elasticity of the system.
Pressure resolution	0.1 % full scale	Down to 25 µbar.
Flexibility	Up to 8 independent channels Adaptable to any kind of pressure source	Ability to control complex fluidic set-up

Table 1: Pressure actuation benefits.

3. FLOW-RATE CONTROL WITH PRESSURE ACTUATION

3.1 Single channel

In some applications, flows need to be controlled by flow-rate. Therefore a flow-rate control tool was developed to maintain the benefits of pressure actuation. To achieve this, a high precision flow sensor is implemented in the fluidic system and a dedicated regulation algorithm was developed and integrated into the software. This algorithm allows for the pressure to be adjusted to achieve the target flow-rate. An autocalibration step is implemented in order to define the characteristics of the system and thereby adapt the algorithm.

This initial algorithm was created to control the flow-rate in a single channel. The results in terms of settling time and stability are shown in Fig.2 and Fig.3 and compared to high precision syringe pump. In the conditions of Fig.2 (channel diameter 50 µm, length 50 cm), the settling time with our system is much shorter: 3 s vs 90 s with the syringe pump. The stability at low flow-rates (Fig.3) is also much higher with the flow-rate control system, 0.2%, and independent of the duration of the experiment (i.e. not volume dependent). With syringe pumps, users have to find a good compromise between the volume to be injected and the precision of the flow. Fig.3 shows that decreasing the syringe volume enables to increase the flow stability. It would then be possible to obtain a flow stability close 0,2% with a smaller syringe to the detriment of experiment duration. With the flow-rate control system using pressure actuation, users do not need to make this compromise as they can have very high stability (around 0.2%) even with high volumes up to 50 mL.

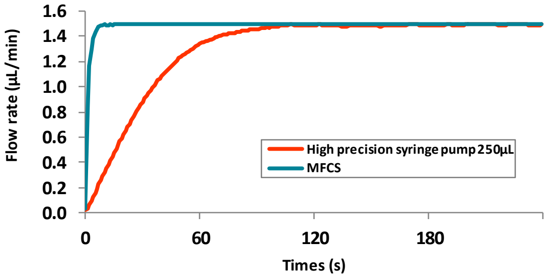

Figure 2: Comparison of the settling time at 1.5 µL/min between high precision syringe pump (~90s) and the first software for single flow-rate control (~3s).

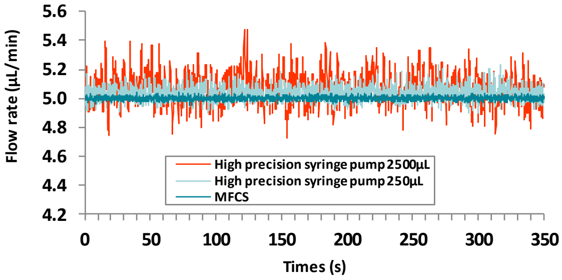

Figure 3: Comparison of the stability at 5 µL/min between high precision syringe pump and the first software for single flow-rate control.

3.2 Expanded algorithm for multiple channels

Typically, researchers need to control the flow-rate of several channels at the same time. Due to coupling effects, characteristic of the microsystem architecture, the flow-rate control of several channels using a pressure actuator would require a deep understanding of the microsystem and the fundamental microfluidic laws. Basically, the user would need to find the right combination of pressure values to obtain the required flow-rates. This combination can be easily determined in basic microsystems, however it is much more difficult to achieve in complex systems with coupled channels and system elasticity (due to material and/or air bubbles).

The algorithm presented here automatically calculates the pressures needed to obtain the desired flow-rate(s) in complex systems. It enables the flow-rate control of any microfluidic system with all the pressure actuation benefits (Tab.1).

The algorithm principle is based on two different steps: an identification step and a regulation mode. The identification step determines the relations between each pressure channel and each flow-rate channel. The relations are dependent on the hydrodynamic resistivity and on the elasticity of the microsystem. This step is reached thanks to Pseudorandom Binary Sequence (PRBS). Identification is critical, especially on coupled microsystem where a modification in one pressure channel could lead to a modification in more than one flow-rate channel. This method enables to identify the fluidic behavior resulting from the internal design and from transitory phenomena such as air bubbles which temporary modify the elasticity of the system.

The regulation mode will then use this result to provide the desired flow-rate(s) using pressure actuator(s). A feedback loop regulation is used to limit the difference between the estimated flow-rate(s) and the measured flow-rate(s). Besides, thanks to the identification step, the method proposed here is able to identify any fluidic behavior modification and to adapt itself during the experiment. The method proposed here can be used for a large range of microsystem designs such as Single Input Single Output (SISO) microsystem, i.e. single flow-rate channel with single pressure channel, or Multiple Input Multiple Output (MIMO) microsystems, i.e. complex microchip with several flow-rate channels and pressure channels. The MIMO microsystems are widely used for biological applications, droplet generation, droplet merging, etc..

The algorithm proposed here is a major improvement compared to the current flow-rate control solutions with pressure actuators or traditional feedback loop regulations, such as a Proportionnal-Integral-Derivative controller (PID controller). This kind of regulation has usually to deal with two major issues: the tuning sensitivity and the stability under disturbances. Even if the tuning can be proceeded with manually or with common method such as Ziegler-Nichols, this step remains complex, especially on MIMO systems, and highly dependent of the system to be controlled. The traditional feedback loop regulation may probably be successful when implemented in basic microsystems such as SISO systems. However as the feedback loop regulation is only based on the difference (error) between order(s) and measure(s), it cannot distinguish the behavior due to transitory phenomena. The regulation will try to match the measure(s) with the order(s), even if it could lead to flow-rate oscillations. In a coupled system, a perturbation may be created by a new flow-rate order on a linked flow-rate channel. It means that on a MIMO system, a traditional feedback loop regulation will lead to unstable behavior even on controllable systems.

3.3 Features and benefits of the new flow-rate algorithm

This new flow-rate algorithm significantly helps the user to precisely control a microfluidic system. The user directly control his system with flow-rates while keeping the pressure actuation benefits, such as very low settling time, high accuracy and stability.

The algorithm proposed here can be used on an undefined system as well, and will help the user to empirically understand the system's behavior. For example, the algorithm is able to point out non-reachable flow-rate requirements to the user, indicating that the system is working at the pressure actuator limits (maximum/minimum pressure reached) or that the fluidic design of the system is incompatible with the requested flow-rate(s).

The algorithm proposed here is able to control a large type and number of microfluidic systems, from a single channel with one pressure input to a massively parallel system with independent channels or a single complex chip with coupling effects between the channels. Only the relevant pressure channels will be activated to reach the desired flow-rate(s). This feature significantly improves the independence of the flow-rate channels even in a complex and coupled system. Thereby, a new flow-rate request on a specific channel will not significantly impact the other channels.

The algorithm also handles positive or negative flow-rates and stop-flows. This feature provides reverse-flow or stop-flow, which are obtained with the responsiveness of pressure actuation.

The new algorithm can handle system perturbations such as atmospheric pressure variation and input fluid level variation, and/or system modifications during the experiment (up to 20% variation of the main fluidic parameters) without consequences for the flow-rate control and accuracy. An example of a system controlled with the algorithm under perturbation is shown in Fig.7.

Finally, the algorithm always knows the pressure(s) and the flow-rate(s) used to control the microsystem. It provides an easy way to determine the microsystem main parameters such as the fluidic resistivity and the fluid viscosity and identify any physical modifications in the device such as clogging or bubbles (volume and localization in the microsystem).

4. ALGORITHM PERFORMANCE

4.1 Comparison to high precision syringe pump on microchip with coupled channels

The new flow-rate algorithm, implemented here, has been tested with an IMT glass chip (ref. ICC-SY05), as shown in Fig.4, and compared to high precision syringe pumps on the same chip.

The following devices were used for the flow-rate algorithm test: one (1) pressure actuator (1000 mbar range), three (3) pressurized reservoirs (2 mL each) and two (2) flow sensors (range of 7 µL/min). The two (2) inlets and the outlet of the chip were connected to the three (3) pressurized reservoirs. The flow sensors are implemented on the two (2) inlets of the microchip. Each inlet of the chip was connected to its dedicated flow sensor and to its dedicated pressurized reservoir with a PEEK tubing (length: 30 cm, inner diameter: 250 µm). The outlet was connected to its dedicated pressurized reservoir with the same PEEK tubing (length: 30 cm, inner diameter: 250 µm).

For the comparative test with the syringe pump solution, the following devices were used: two (2) high precision syringe pumps with 250µL glass syringe each and the two (2) flow sensors (range of 7 µL/min) previously used. The syringe pumps were controlled by the dedicated software recommended by the supplier. Each inlet of the chip was connected to its dedicated flow sensor and to its dedicated syringe pump with a PEEK tubing (length: 30 cm, inner diameter: 250 µm). The outlet was connected to its dedicated reservoir (atmospheric pressure) with the same PEEK tubing (length: 30 cm, inner diameter: 250 µm). All the materials used for the chip (glass), the syringe (glass) and the tubing (PEEK) are known to reduce the settling time when using syringe pump solution for the fluid handling [1,4].

The settling time and the flow-rate behavior of these two experiments were compared when a flow-rate from -4µL/min to 4 µL/min is requested for Q1 while the flow-rate request of Q2 stays constant at 2 µL/min. Fig.5 shows the measured flow-rates Q1 and Q2 in the conditions described above for the two experiments. The solution proposed here leads to a shorter settling time compared to the high precision syringe pumps solution. The settling times are respectively 1.7s compared to 8.5s (Q1).

In addition, the solution proposed here significantly limits the interaction between Q1 and Q2. As shown in Fig.5, the coupling due to the chip design leads to a modification of the flow-rate Q2 when the flow-rate request of Q1 is changed. With the system proposed here, this modification on Q2 stays punctual and limited, leading to an over-dispensed volume of 0.01 µL. The maximal difference for this system between flow-rate request on Q2 (2µL/min) and measured Q2 is +0.49 µL/min. With the syringe pumps the perturbation on Q2 leads to an under-dispensed volume of 0.07 µL. The maximum difference between flow-rate order (2µL/min) and measured Q2 is -0.87 µL/min.

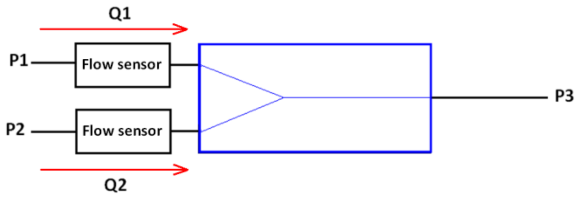

Figure 4: Scheme of the microfluidic system used to test the performance of the new flow-rate control solution.

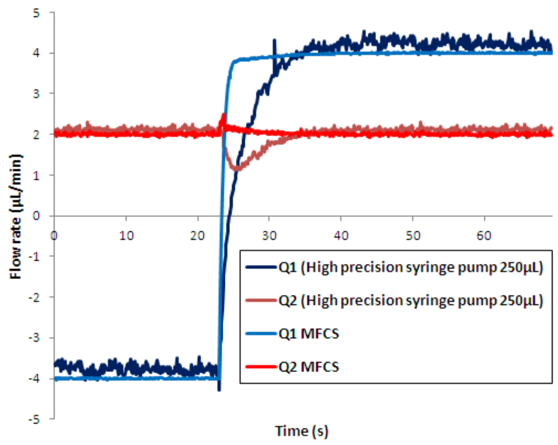

Figure 5: Flow-rates measured during the comparison test between high precision syringe pumps and the solution proposed here on the Y microchip of Fig.4.

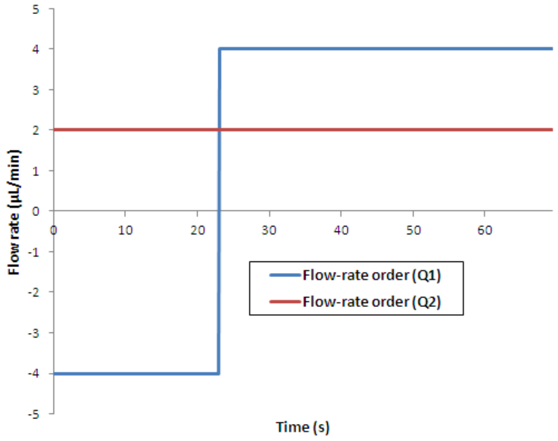

Figure 6: Flow-rate orders during the comparison test between high precision syringe pumps and the solution proposed here on the Y microchip of Fig.4.

4.2 Performance with a system submitted to external disturbance

The set-up used for this test was the same as the one used for the test on coupled channels with the new algorithm control solution (Fig.4).

From 0 min to 3.5 min, flow-rate requests of 2 µL/min for Q1 and -2 µL/min for Q2 were sent to the algorithm presented above to control the system of Fig.4. This first phase is called “before disturbance” in Tab.2. Subsequently, from 3.5 min to 6.5 min, the system was submitted to an external disturbance: the value of the pressure channel P3 was manually decreased and increased, respectively from 200 mbar to 50 mbar and from 50 mbar to 250 mbar. This phase is called “during disturbance” in Tab.2. Then, from 6.5 min to 9.5 min, the external disturbance was stopped and the pressure on P3 remained constant at 250 mbar. This phase is called “after disturbance” in Tab.2.

Fig. 7 shows the flow-rate responses relating to the disturbance in P3. The data in Tab.2 quantifies the performances of the flow-rate control and shows that the algorithm presented here maintains its performance even on a system submitted to external disturbances. The maximal value of the standard deviation is 0.03µL/min.

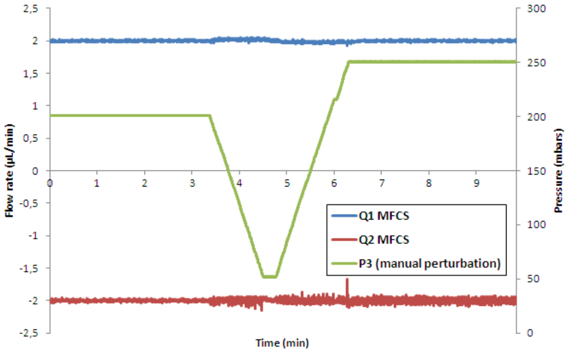

Figure 7: Flow-rates (Q1 and Q2) and output pressure (P3) measured on the Y microchip of Fig.4 with the flow-rate control solution proposed here.

	Flow-rate Q1 (µL/min)	**Flow-rate Q2 (µL/min)**
Before disturbance	2,00 ± 0,01	-2,00 ± 0,01
During disturbance	1,99 ± 0,02	-1,99 ± 0,03
After disturbance	2,00 ± 0,01	-2,00 ± 0,03
Flow-rate order	2	-2

Table 2: Flow-rates measured (Q1 and Q2) during the experiment of the Y microchip of Fig.4 submitted to an external disturbance (variation of P3).

5. CONCLUSIONS

We have presented a new methodology, based on pressure actuation, to control flows in microfluidic systems. As a result of the flow-rate control, we show the ability to control and monitor the relevant parameters of the flow: both pressure and flow-rate with very fast settling times, excellent stability, and repeatability.

With the measurement of both pressure and flow-rate, users are able to characterize their fluidic systems and to detect any modifications (presence of bubble, clogging and/or variation of the viscosity of the system…). This benefit cannot be provided even by a high precision syringe pump due to the fact that the only available parameter to control in the pumps is the flow-rate, and that there is no ability to measure the pressure or the flow-rate.

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REFERENCES AND CITATIONS

[1] J. Goulpeau, V. Taniga and C. A. Kieffer, *Mater. Res. Soc. Symp. Proc.*, 2009, **1191**, 67–72.
[2] H. A. Stone, A. D. Stroock and A. Ajdari, Annu. Rev. *Fluid Mech.*, 2004, **36**, 381–411.
[3] C. Futterer, N. Minc, V. Bormuth, J.-H. Codarbox, P. Laval, J. Rossier and J.-L. Viovy, *Lab Chip*, 2004, **4**, 351–356.
[4] Jianhua Zhou, Kangning Ren, Wen Dai, Yihua Zhao, Declan Ryan and Hongkai Wu, *Lab Chip*, 2011, **11**, 2288-2294
[5] T. Ward, M. Faivre, M. Abkarian and H. A. Stone, *Electrophoresis*, 2005, **26**, 3716–3724.
[6] K. Jo, Y. L. Chen, J. J. de Pablo and D. C. Schwartz, *Lab Chip*, 2009, **9**, 2348–2355.
[7] D. Kim, N. C. Chesler and D. J. Beebe, *Lab Chip*, 2006, **6**, 639–644.
[8] H. Lu, L. Y. Koo, W. M. Wang, D. A. Lauffenburger, L. G. Griffith and K. F. Jensen, *Anal. Chem.*, 2004, **76**, 5257–5264.
[9] H. B. Yin, X. L. Zhang, N. Pattrick, N. Klauke, H. C. Cordingley, S. J. Haswell and J. M. Cooper, *Anal. Chem.*, 2007, **79**, 7139–7144.
[10] www.fluigent.com