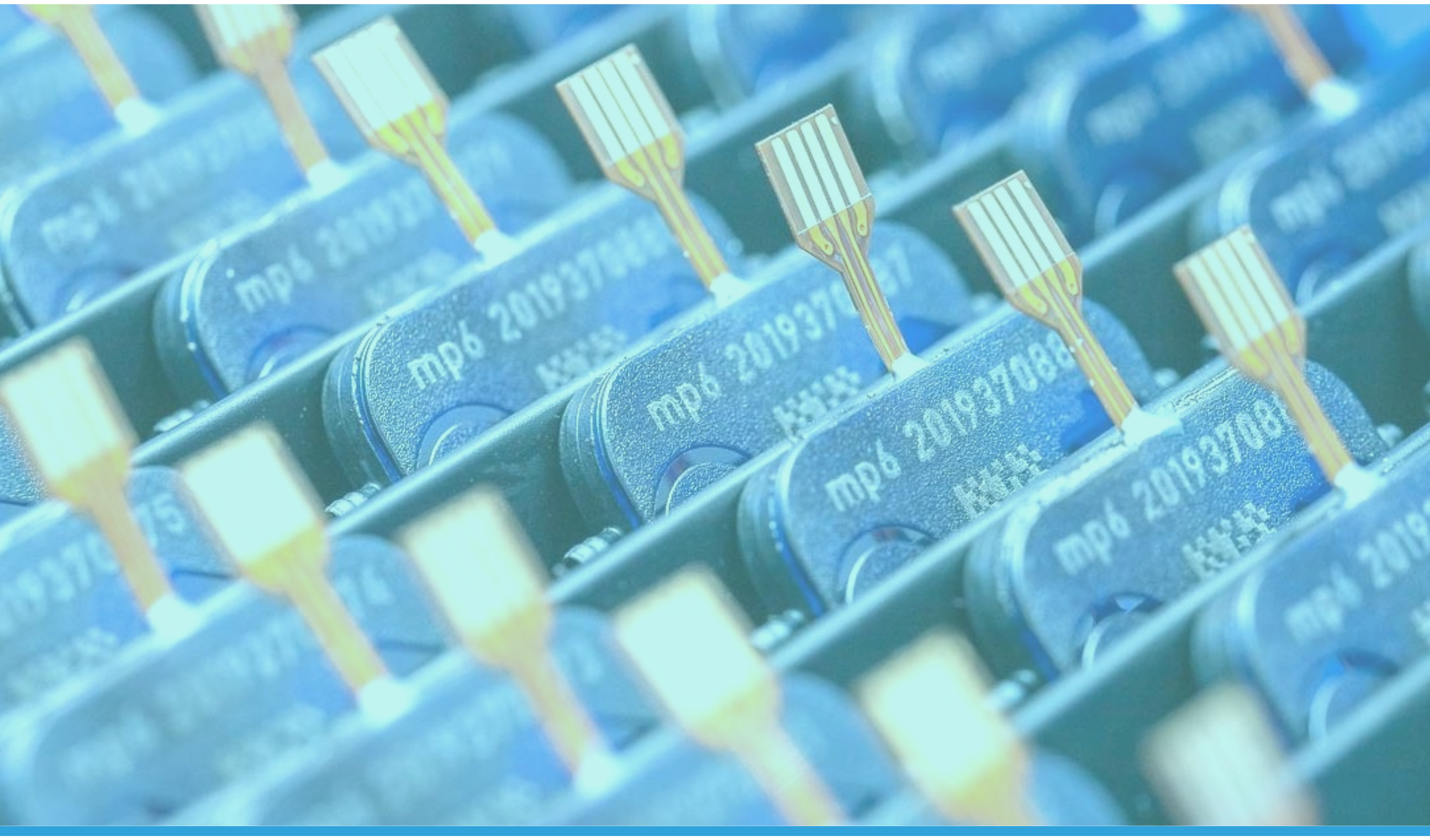
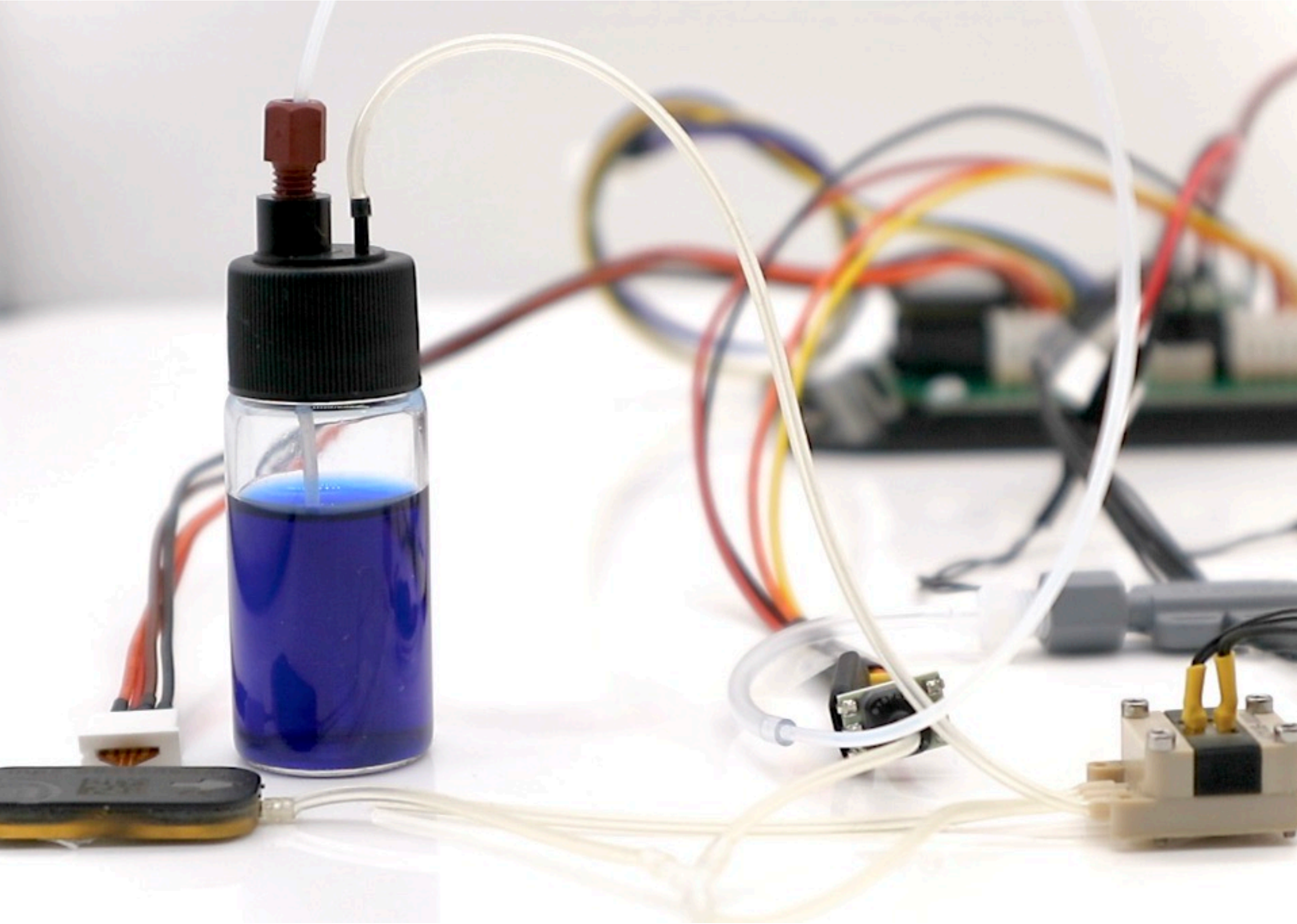
Point-of-Care

CASE STUDY:

SELF-SUSTAINING PRESSURE DRIVEN FLOW IN MICROFLUIDICS



Bartels mikrotechnik memetis



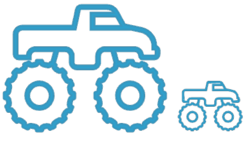
Case Study:

SELF-SUSTAINING PRESSURE DRIVEN FLOW IN MICROFLUIDICS

Focus topics of this case study:

Contamination-free

Accurate dosing even at very low flowrates



Miniature in size, cost, power consumption

Stand-alone/No air pressure line needed

Introduction

Microfluidics - the fine art of creation and manipulation of small portions of fluids, often realized by flow within small, sub-millimeter-scale channels - is coming. What started off in academia and university labs has now fully arrived in industrial labs and commercial applications. Yet, commercial use of microfluidics is evolving every day and there is an ever-increasing number of interesting use cases ahead of us. The interest in microfluidics is tremendous – for several reasons. A high precision flow control is facilitated by the small dimensions. Further, due to the low volumes involved, microfluidics operates with minimal resources such as space, reagents, and energy, which makes it highly attractive for portable applications. Based on these advantageous properties, the implementation of microfluidics in commercially available devices for analysis and diagnostics is highly relevant to the life science industry. Many life science applications today already benefit from microfluidics – yet, in order to fully benefit from this advancement with automated and highly functional devices and equipment, suitable concepts and components are needed. It is these concepts and components that stand in the spotlight of this case study.

The concept of pressure driven flow in microfluidics

Microfluidic dosing is one of these use cases ahead, leading to a lot of novel applications and innovation. Currently, it is widely observed in the modern lab and can, in general, be realized by different approaches to drive a flow. One of them is pressure driven flow, which offers a number of specific advantages, e.g. pulsation-free operation and cost-effectiveness. Another advantage particularly useful for contamination-free dosing is that neither a pressure source nor flow control elements have to come into direct contact with sample fluids, which makes pressure-driven flow a perfect technology for operating disposable fluidic chips and cartridges intended for one-time use.

These advantages specific to pressure driven flow are combined with the general advantages of microfluidics, such as a minimum use of sample fluids and reagents. Building on these advantages, microfluidic dosing turns out to be a perfect match to the rising number of point-of-care (PoC) applications, especially related to testing and diagnostics. However, until today, the field of microfluidics is one of largely passive structures and is therefore fighting with a low level of dosing precision, as active fluid control encounters various challenges in mobile use:

1. How to create a mobile pressure source?
2. How to enable contamination-free fluid handling in a compact system?
3. Are active components energy-efficient enough to be operated by batteries?
4. Can an active fluid control system be small and thus portable enough to be used at the PoC?

More generally speaking, the question is: Can the advantages of microfluidics be leveraged in an active and automated system that can be operated outside of well-equipped labs, directly at the PoC?

Yes it can!

In a first step, it is important to create a clear picture of the overall functionality of the dosing system. Once this is reached, the implementation in a miniaturized format needs to be addressed. The main requirements are:

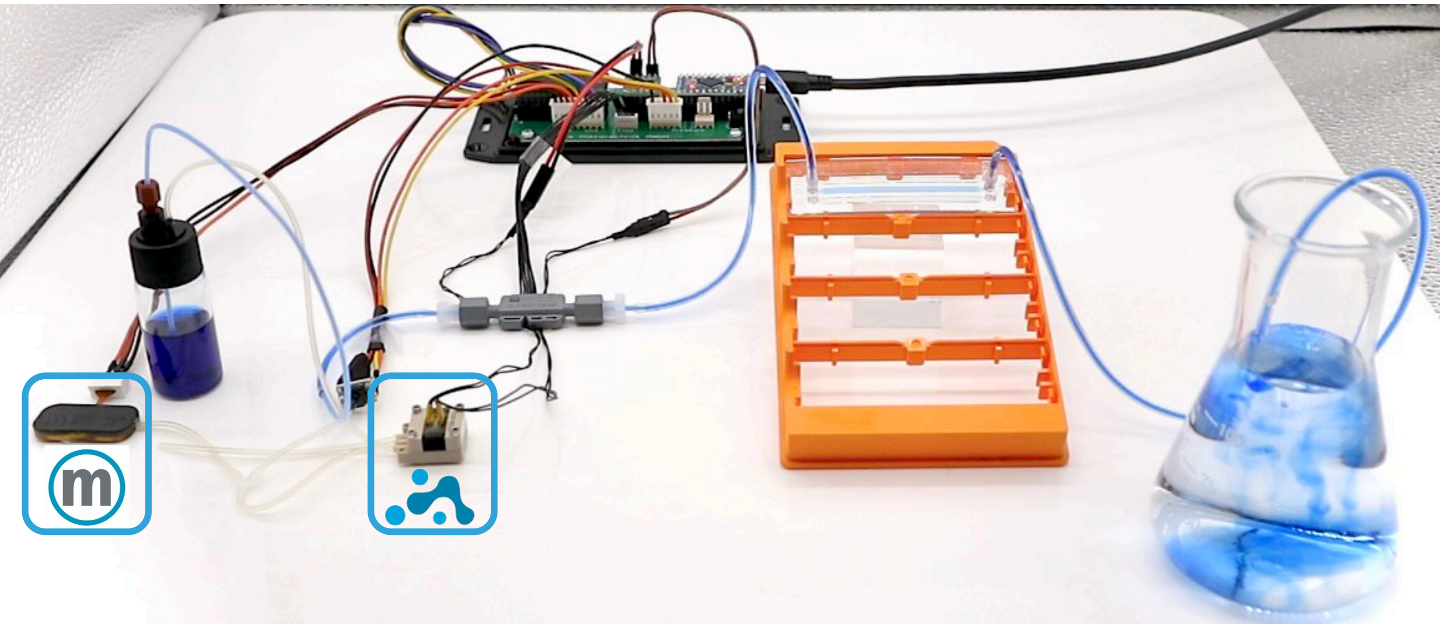
1. The system should have active fluid control capabilities allowing a certain degree of automation to reduce potential errors originating from manual use;
2. The system is intended for use at the Point-of-Care. Therefore it should be a dosing system that is characterized by small dimensions, weight and low energy consumption;
3. The system should consist of two separate parts, one that performs the analysis in direct contact with sample liquids and will therefore be contaminated, but that can be disposed economically after usage. The second part is reusable and contains the active components allowing for active and automated fluid control;
4. Dosing should be relatively precise with 5-10% tolerance, which is difficult to achieve by passive components creating pressure and flow.

A very good fit for these requirements during the ideation and feasibility stage of the development is the principle of pressure driven flow. In a pressure driven flow system, a pressure source is linked to a fixed volume containing the fluid to be dosed. As the pressure source increases the pressure in this fixed volume the fluid will be displaced through an outlet channel. By controlling the pressure precisely, dosing of the fluid can be controlled in a very stable manner. As a consequence, the basic principle of pressure driven flow builds on a controllable pressure source and a fixed volume to be filled with a dosing fluid. The advantage of pressure driven flow becomes clear very quickly. As soon as the pressure is controlled precisely and electronically, the dosing itself can be automated with a high degree of precision. In addition, the control unit (which is the pressure source) is not in contact with the fluid to be displaced. Therefore, this part will be surely contamination-free, whereas the fixed volume containing the fluid and the outlet channels need to be exchanged for each individual experiment or analysis.

Implementing pressure driven flow in an active microfluidic system

In general, the pressure source used is compressed air which is easily available in on-premises systems or centralized labs. Yet, in order to create a mobile system, the pressure source and its control need to become mobile. In order to realize this, the necessary components need to be small, lightweight and ideally highly energy-efficient. As a consequence, we sourced several micro components to realize the overall system, containing

- 1 piezoelectric micropump to provide sufficient pressure (Bartels Mikrotechnik, model: mp6 micropump)
- 1 pressure sensor providing a control parameter for closed-loop control of the pump (Honeywell, ABP series)
- 1 fixed volume (glass cartridge)
- 1 active microvalve to offset pressure in the cartridge and atmospheric pressure in order to reduce dosing volume/ speed (memetis, custom valve based on model: bistable valve BV1101)



The glass cartridge containing the liquid sample is equipped with a special cap having two openings: the first one ends in the cap above the liquid level (later to be connected to the pump and valves); the second opening ends in a tube at the bottom of the cartridge. As soon as a positive pressure is applied to the first opening in this setup, liquid will be pressed into the tube and leave the cartridge through the second opening in a continuous, pulsation-free stream. The cartridge and its cap are the only components that come into direct contact with sample liquid, so that this part of the system can be designed as a disposable, if necessary.

In the next step, a fluidic connection between the sample container (glass cartridge) and the active components (pump and valves) needs to be established. For this purpose, a fluidic manifold is designed and fabricated by 3D-printing from a biocompatible resin. The pump will act as a pressure source to displace sample liquid from the cartridge, whereas two valves will be used to quickly turn on and off the overpressure applied to the cartridge. The connector manifold is designed with a T-shaped channel, one branch being connected to the outlet of the piezo pump in series to a microvalve, the second branch connected to a second microvalve with its outlet open to the ambient, and the third branch connected to the cap of the sample cartridge by a tube. This design can be easily extended to operate multiple cartridges using the same pump, by just adding additional valves and pressure output lines. The operation principle is schematically shown in Fig. 1.

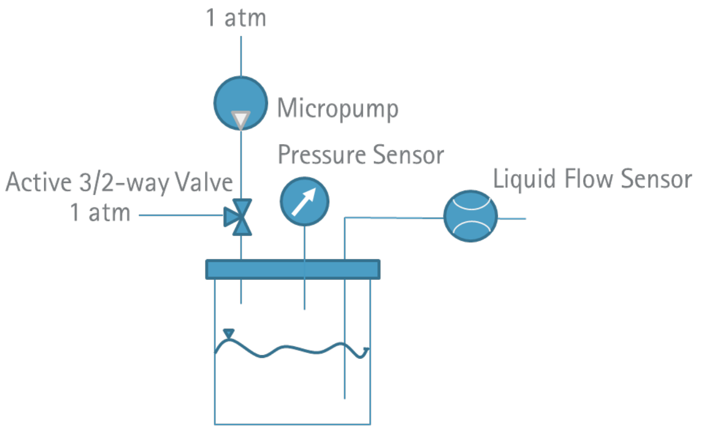


Fig. 1: Operation Principle

With this setup, several requirements defined appear to be sufficiently addressed. Yet, it is important to characterize the system's performance, in particular in terms of dosing accuracy. Thus, a high-resolution flow sensor (Sensirion, SLF3x series) is connected to the outlet tube of the sample cartridge and a pressure sensor (Honeywell, ABP series) is coupled to the tube between fluid control manifold and sample cartridge cap, using an additional T-junction.

Discussion of self-sustaining pressure driven flow system

In order to evaluate the developed self-sustaining pressure driven flow system, the requirements defined above will serve as a guideline.
One key objective defined is to create a system that is composed of active components, thereby allowing for automated operation. The selected fluid control components all classify as active components, whereby a Bartels Mikrotechnik mp6 micropump provides the necessary pressure and memetis microvalves allow for quick start and stop of pumping.
A second key objective is to create a dosing system that is characterized by small dimensions, weight and low energy consumption. In order to achieve a system fulfilling these requirements, the individual components need to stand out in terms of low weight, size and energy consumption. This holds true for all components used within the presented system. Bartels Mikrotechnik mp6 micropump demonstrates a very low energy

consumption of 150 mW, with high performance in a small package (size: 30 x 15 x 3,8 mm³; weight: 2 g).

The bistable microvalves of memetis only require 75mJ per switching. With less than 2 gram and an overall size of a sugar cube, this valve is highly portable. All of the components chosen can be operated by a battery. Therefore, the system's fit to PoC-requirements has successfully been demonstrated.

Third, the system should consist of a disposable part and a reusable unit, thereby allowing contamination free operation. This is achieved by connecting the pump-valve-system to the air inlet of the (cheap and potentially disposable) glass cartridge, so that it never gets in touch with the fluid to be dosed.

Lastly, the most crucial requirement remains to be demonstrated: dosing accuracy with 5-15% tolerance. Based on the setup from Fig. 1 three cases have been investigated:

1. Achieving a defined flow rate by pumping air inside the cartridge utilizing a closed-loop principle between liquid flow sensor and micropump
2. Comparing the changing behavior between flow rates actively forced by active valves and passively without the use of a valve
3. Dosing stop behavior with and without active valves

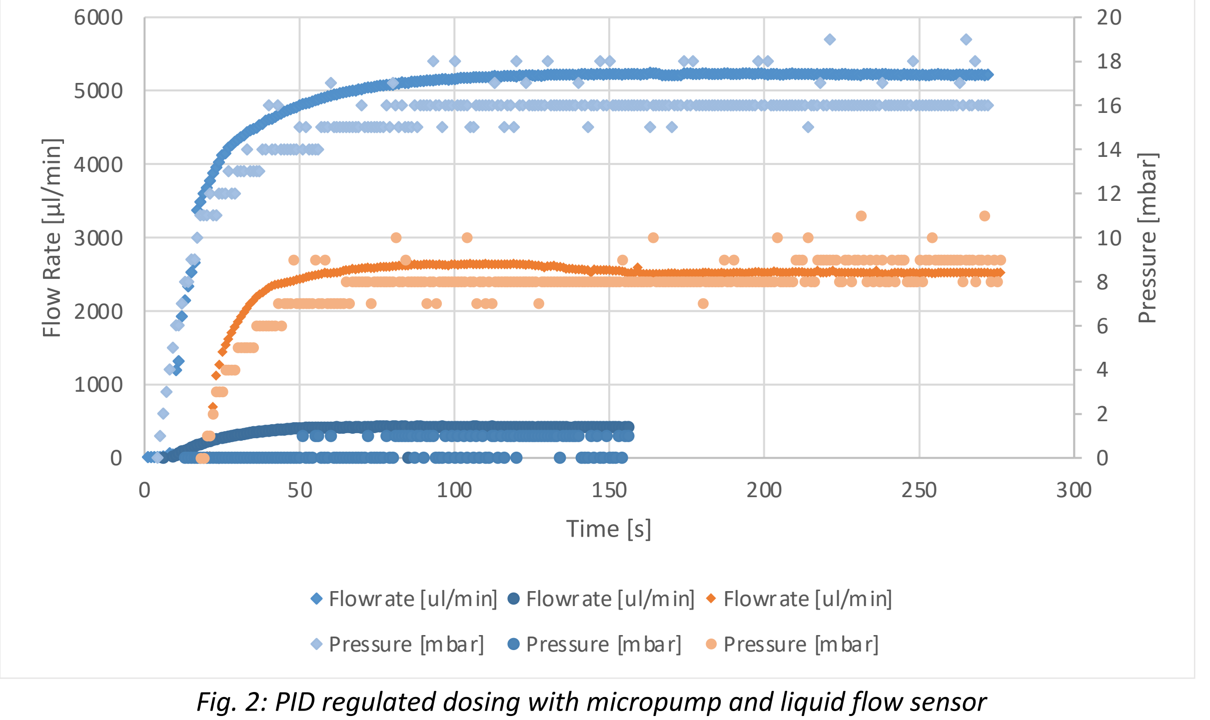


Fig. 2: PID regulated dosing with micropump and liquid flow sensor

According to the first investigation target, Fig. 2 shows the dosing performance of the pressure driven flow system consisting of the micropump and a liquid flow sensor measuring the flow that is dosed out of the cartridge. The flow sensor gives back a feedback to a microcontroller that is able to adjust the parameters of the pump driver aligning the correct performance and generating a very accurate flow rate. So even if the pump does not directly transport the medium that is measured by the liquid flow sensor, it is possible to realize a functioning alignment for the regulation. It is obvious that the measured pressure follows the defined liquid flow rate. This result supports the fact that a pressure regulated system will also be adequate for realizing an indirect dosing system which allows the user to minimize the contaminated components to a minimum.
Next, one needs to consider the question how shifting between flow rates of the pump or even stopping the pump, will influence the dosing process. Fig. 3 and Fig. 4 show the behavior of switching between flow rates of the pump and "waiting" until the system passively and actively (utilizing active valves) reduces the pressure value that fits to the desired flow rate of the overall system. From Fig. 3 it is obvious that changing the flow rate from 5 ml/min down to 3 ml/min roughly takes 50 s which is too much for many applications. Fig. 4 shows a reasonable solution to that problem. Using active valves, the lower flow rate can be adjusted with a much faster response time. In this case the system is able to switch between 5 ml/min and 4 ml/min within 1 s. In addition, using active valves to control a change in pressure, a high precision dosing within the set tolerance range of 5-10% can be achieved.

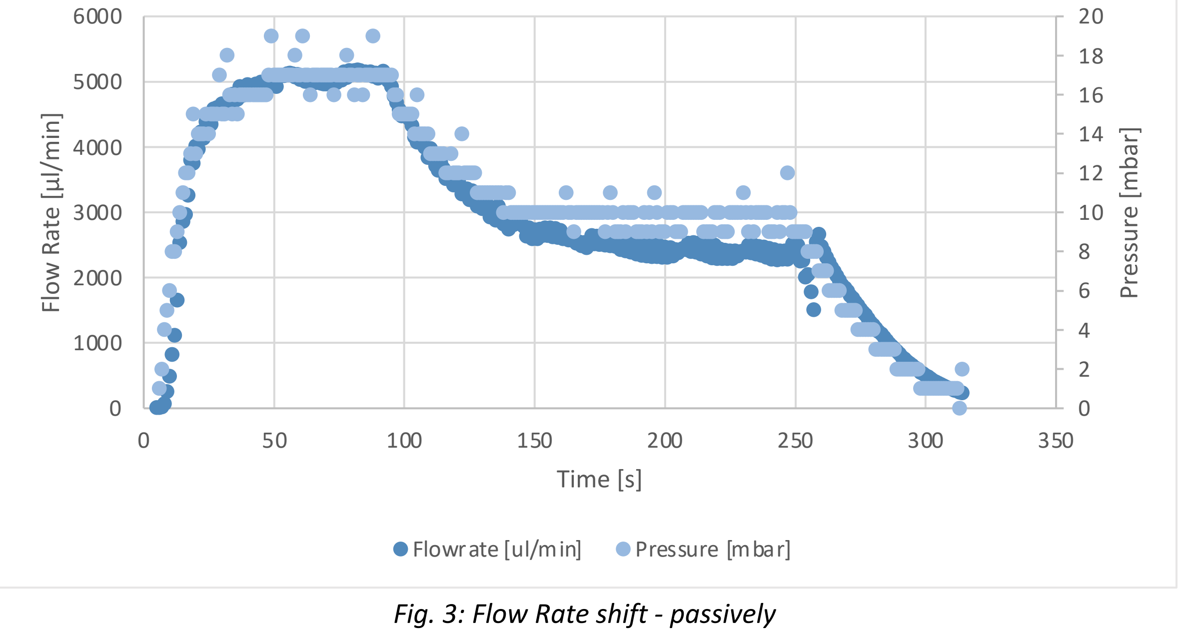


Fig. 3: Flow Rate shift - passively

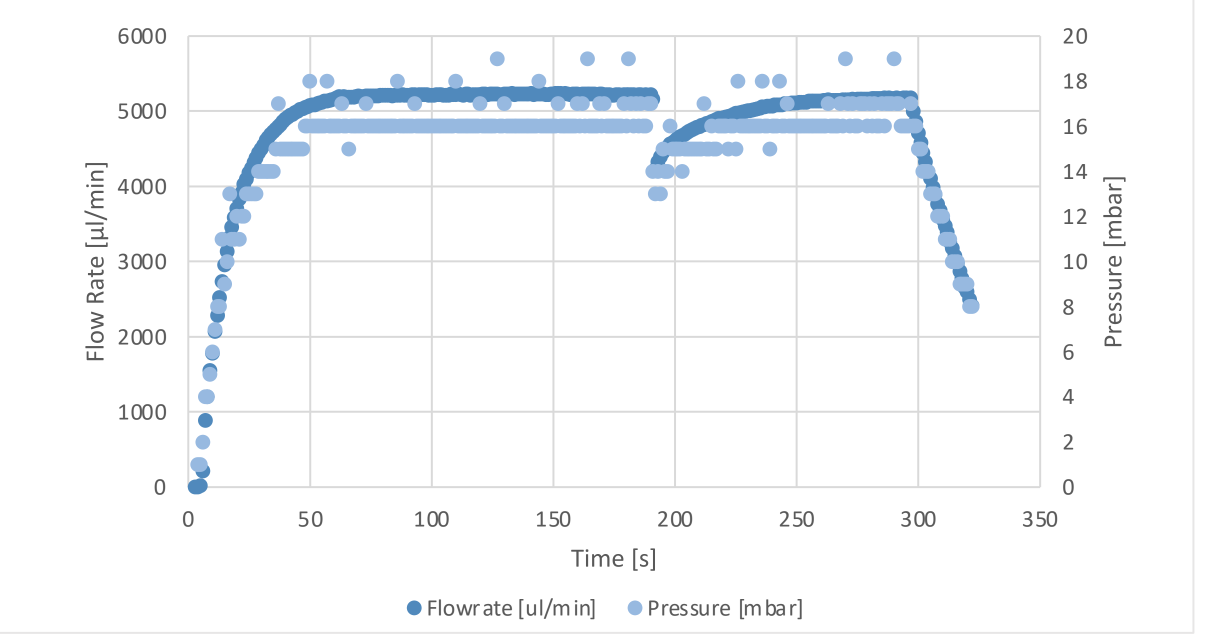


Fig. 4: Flow Rate shift - actively with active valves

This observation becomes even clearer when investigating the stopping behavior. Fig. 5 and Fig. 6 give an impression on how much time it takes to end the dosing process.

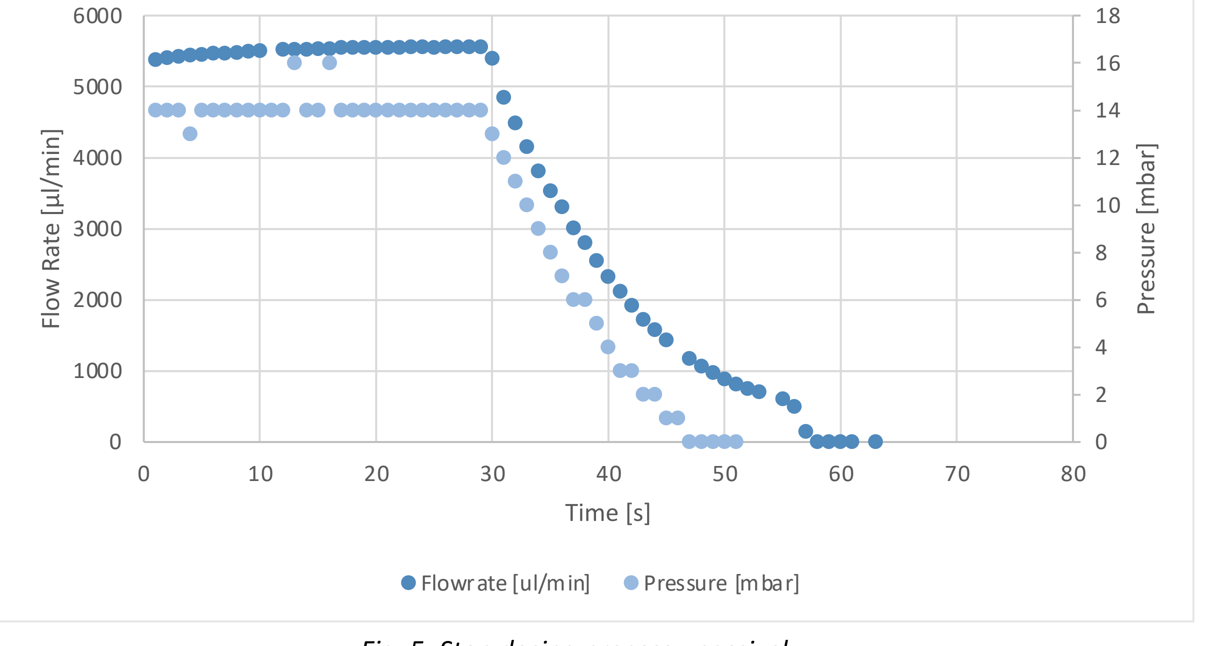


Fig. 5: Stop dosing process - passively

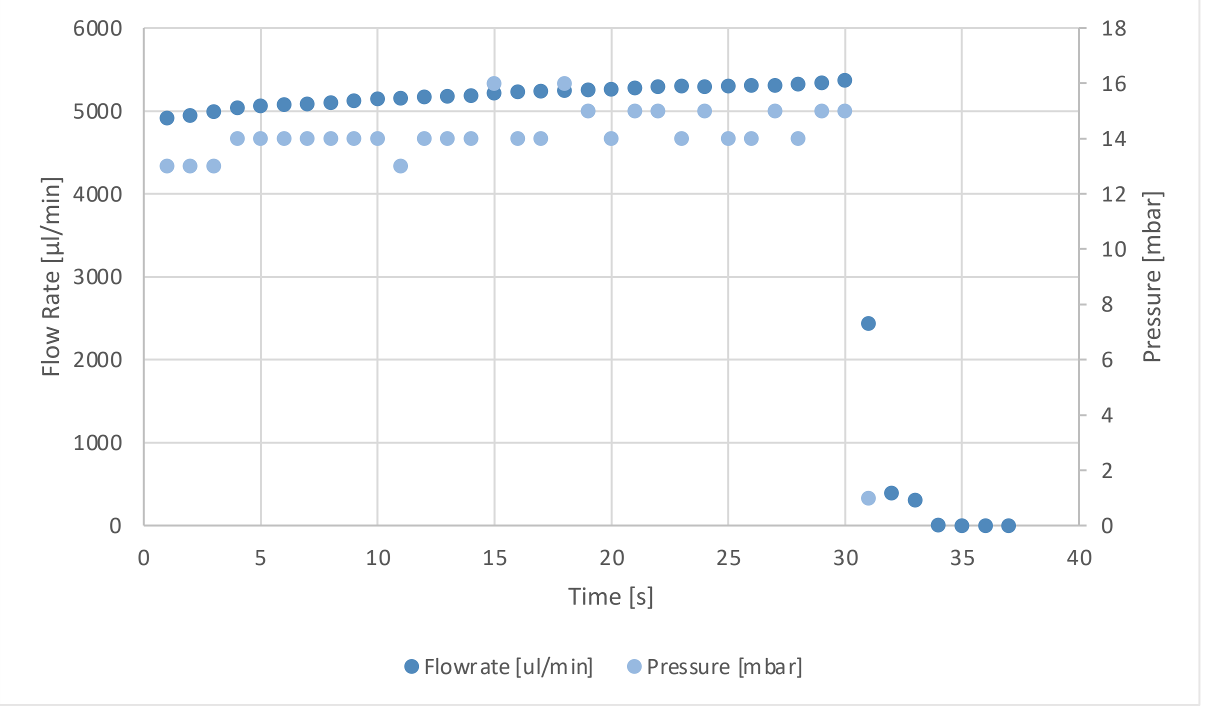


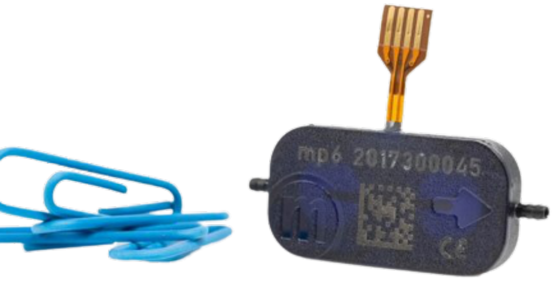
Fig. 6: Stop dosing process - actively

The combination of a micropump as a pressure source and active valves for pressure control appears best suited to address the key objective 4, as it enables precise dosing also in case of a variation in dosing volume.

Conclusion

Using lightweight piezo pumps and shape-memory-driven valves, a self-sustaining pressure driven flow system was built that has the potential to bring microfluidics into mobile applications directly at the point-of-care. The system was carefully designed in a way that omits any contact between sample fluid and the active component, hence it is perfectly suited for operating disposable sample cartridges, e.g. for medical quick tests, food or environmental analyses. Due to their low power consumption, pump and valves can be conveniently powered by battery. The whole microfluidic system can be smaller than a cigarette box and does not produce any disturbing noise nor does it dissipate considerable waste heat. Using a miniaturized pressure driven flow system as presented above, all the advantages of disposable microfluidic cartridges can be combined with an increased level of automatization and intelligence – at a competitive price, since the active fluid control part of the system is reusable.

Components and systems used



mp6 micropump
by Bartels Mikrotechnik

The available, industrialized and commercialized example is the mp6 micropump by Bartels Mikrotechnik GmbH. This micro pump is a positive displacement membrane pump utilizing piezo buzzers. The alternating displacement of the piezo actuators lead to the following typical fluidic values of the pump:

- Liquid flow range (water) = 5 - 8000 µl/min and pressure < 600 mbar
- Gas flow range < 25 ml/min and pressure < 150 mbar

BV 1101 bistable valve
by memetis

The innovative shape memory actuator technology developed by memetis GmbH not only ensures increased miniaturization of fluidic components and systems but also allows for silent switching, very low power consumption and highly flexible customization. The bistable valve “BV1101” is characterized by high lifetime, a broad range of wetted material options and very low energy consumption enabling battery operation.

Acknowledgement

Our Partner, *memetis* from Karlsruhe, Germany, was instrumental in defining our research path, whereby we were able to develop a great solution for contamination free dosing by pressure driven flow. For that, we are extremely grateful, and we are looking forward to our close collaboration. In case you are interested in the above-described microfluidic components or if you are interested in getting in touch with either one of us, *memetis* or Bartels Mikrotechnik, please feel free to contact us. You can find the contact details below. Also, check out the memetis website to learn more about their whole portfolio: https://www.memetis.com/en/

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Bartels Mikrotechnik with passion for microfluidics!

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