Results survey on microfluidics flow control

November 2015

Henne van Heeren, enablingMNT - Netherlands -
Henne@enablingMNT.com
0031 78 6300748

Contents

enablingMNT

enablingMNT has offices in The Netherlands, Germany and the UK with an extensive network of associates and partners worldwide. Whether you need one-off advice, assistance with setting up a production line, a challenging reliability or test problem, impartial support to your business development programs or global marketing and promotional work, **enablingMNT** is available to assist you. We are also available and interested in joining your project teams and can in particular bring vast experience in the areas of project management, dissemination & training, roadmapping, and technical research through our participation in all European programs since ESPRIT3 in the 90's to the recently launched Framework programs.

Henne van Heeren runs the Dutch office of **enablingMNT** and is a specialist in production engineering and supply chain management. He has offered market research and manufacturing related services in the field of MNT since 2003. Henne has a chemistry degree from Utrecht University. His career steps included the responsibility for the transfer and industrialization of the thin film magnetic heads technology from Philips Research to the Business Unit, wafer fab production management, and business development management. He is currently assisting several companies and other organizations in the area of MNT product industrialization using his production expertise and extensive international network.

Short Summary of the MFmanufacturing project

There is a clear need for microfluidics-based or microfluidics-enabled devices in life science applications (pharmaceutical, personalized medicine) and other areas such as environmental, analytical and agro-food. For instance, the costs of an ageing population and the associated increasing costs of healthcare could be controlled by introducing microfluidics based diagnostics devices; on the other hand, microfluidics will enable functionalities otherwise impossible, such as personal DNA sequencing.

Despite several commercial examples of the use of microfluidic technology, its use is not widespread so far. The main reason is a lack of maturity of the market and the technology, especially reflected by the limited availability of mature, cost effective microfluidic components and solutions.

This lack of maturity can be attributed to 2 main causes:

- The lack of an organized industry in which MF manufacturers are mostly specialized in one of the predominant type of basic materials (glass, silicon and polymer) which limits the possibilities, both in terms of equipment and expertise, when integration of complex systems by combination of different devices is necessary.

- The lack of standards (both on a device and on a process integration level), resulting in specific devices for specific applications. Indeed the MF-4 Microfluidic Consortium, a group of stakeholders in Microfluidics from across Europe and the USA investigating the state-of-the-art, recent applications and market dynamics recently, concluded that "general adoption of microfluidics will only be possible with an agreement on standardized interconnects between chips and systems"

The overall ambition of MFManufacturing is therefore to increase the maturity of the microfluidic market and technology, along the lines of the development of the microelectronics field. This will result in new products better fitted technology wise and economically wise to the needs of the users, thereby strengthening the position of the European microfluidic industry. In parallel with the evolution of the microelectronic industry, the project needs to enable the microfluidic industry to go from a "spider assembly" phase to a "PCB"-like phase, for instance by introducing the FCB: Fluidic Circuit Board.

This will enable easier integration and production of MF components across the complete chain of microfluidics actors, both industrial and academic. Next to this, integration of non-microfluidic components such as semiconductor-based sensors, required for integrated microfluidics based solutions, will be facilitated. A prerequisite to this is standardization at different levels.

The two main objectives of the MFManufacturing project are therefore:

- To propose standards for interconnections and process integration in order to respectively enhance interoperability and increase the volume of Microfluidic devices and facilitate the manufacturing flow between partners. The anticipated standardization in the microfluidics field – first of all aimed at strengthening Europe's position – will focus on increasing maturity in:
  - Alignment of microfluidic functions, focusing both on existing and novel functional modules and their interoperability
  - Alignment of microfluidic manufacturing processes, focusing on both hybrid integration processes and on selected de-centralized manufacturing processes
- To organize the European network of Microfluidic SME and RTO manufacturers Distributed Pilot Line (DPL) with distributed manufacturing resources from different manufacturers in order to provide affordable complex MF devices.

Since MFmanufacturing will address the definition and implementation of standards, it will rely on advisory boards which will play an essential role for these activities. These advisory boards will bring together:

- Microfluidic User Groups (MF User Group), representing more widely academic and industrial actors at national and international level on microfluidic technologies. These will provide inputs on the definition of standards and will be first adopters. User groups have already expressed interest in participating to this project: the MF-4 Microfluidic consortium, the GDR Micro et Nanofluidique, the MinacNed network and the ETP-Nanomedicine.
- Standardization institutions, guiding the consortium through the requirement to established standards at international level.

Introduction to the flowcontrol survey

This is the third survey investigating important technical topics in microfluidics. The first survey (2014, about the issue of microfluidic interconnections and chip sizes) was driven by the need for plug and play microfluidics. The results helped us setting up draft standard for microfluidic connections. The second survey (begin 2015) addressed the issue of reliability of microfluidic components and devices and also checked the feasibility of the idea to formulate “operational classes” as a basis for standardised testing. In our view there is a need for such standardized validation tests for microfluidics. Based on the outcome of the second survey and the foregoing one we were able to formulate some “operational classes”, which appropriateness was tested in this third survey. From the second survey we also learned that flow control is seen as a major topic and we decided to dedicate the third survey on microfluidic flow control[1]. It is in the planning to have a fourth survey addressing (bio)sensing in the first half of next year.

The very positive feedback we got from these surveys and the resulting standard initiative, led to discussions with several standardization bodies. After ample consideration we decide to create a standard proposal together with the International Organization for Standardization (ISO). An ISO workshop to discuss microfluidic interconnection standards and classes of application will be held April year.

As said before, the survey is supposed to give us input for / feedback on our microfluidic standardisation initiative. The results of the surveys will be used to fine-tune the standard proposal ensuring a good fit of use and improving the chance of industry wide adaptation.
The whole work plan is sketched in the next figure:

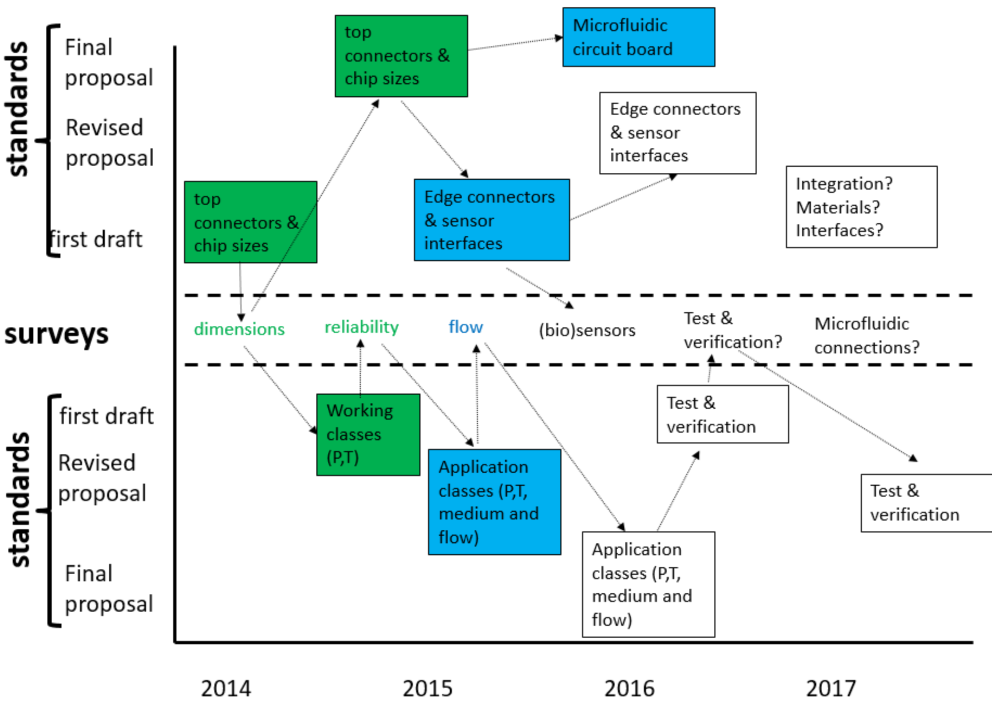


Figure 1: Link between surveys and standardization discussions; green finished, blue on-going activities.

[1] It is in the planning to have a fourth survey addressing (bio)sensing in the first half of next year.

This specific survey had the following major objectives:

1) Can we make the earlier defined microfluidic classes more precise by adding flow parameters to it (media used, viscosity and/or flow rate)?
2) What is the status in controlling the flow; how is the flow brought into motion and how is that flow measured and controlled (pumps and flowsensors)?
3) Can we investigate those issues not just for continuous flow, but also for discontinuous flow?

The survey has been sent to all microfluidic contacts from the enablingMNT database and was promoted on the web by enablingMNT and by the partners in the MFmanufacturing project. The bulk of the received surveys came from the direct mailing, the rest can be contributed for a large part to initiated discussions in relevant LinkedIn discussion groups.

In total we received 266 responses, more than last time. More importantly, the number of respondents that filled in a substantial part of the survey reached a record high: 213 (80%) compared to 154 respectively 141 in earlier surveys. The number of respondents showing an interest in the results of the survey is also much higher than the last time; 150 persons asked for the result of the survey afterwards. (earlier surveys 74 and 114)

The large number of responses will make it possible to divide the responses into groups each representing part of the community. Analysing the answers according to these subgroups will take a little bit more time. The results of this detailed analysis will be discussed with the MFmanufacturing partners and its Advisory Board.

A word of caution is needed: many of the respondents are not limiting themselves to one technology or one application. Some of the individual answers are presumably giving a mixed message.

All the comments of the respondents have been included. As we promised confidentiality, names of the respondents or their organizations will not be given in this report.

Results of the survey

General background of the respondents

Although the survey is anonymously, respondents could indicate if they wanted to receive the results back. From this feedback we learned that the response was not dominated by one country or region, but well spread over the globe. However, a surprising number of respondents used private email addresses, making it not possible to locate the country form all respondents.

The two most often mentioned application area are: research and medical diagnostics/Point of Care; closely followed by lab instrumentation. Although we see a general bias towards research (figure 2), 66 % of the responses are from industry (see figure 3).

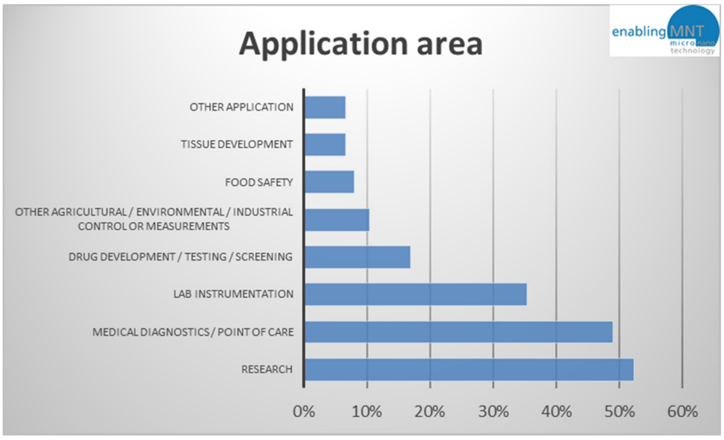


Figure 2: application area (212)[2]

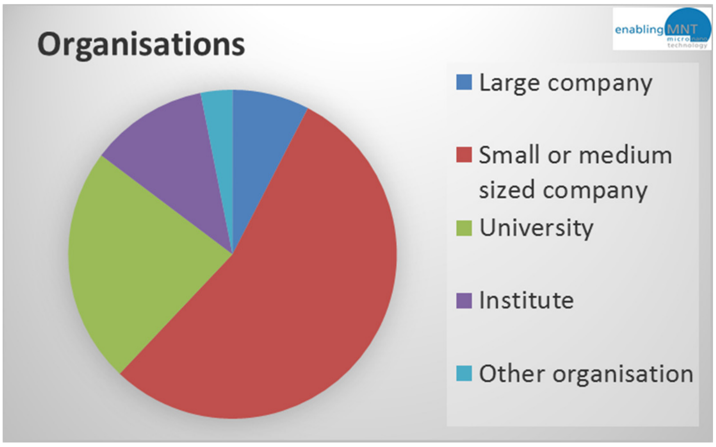


Figure 3: responding organizations (211)

Most of those in the group "other applications" are working in the process industry as shown by the comments:

- Chemical reaction
- Chemical and pharmaceutical synthesis (lab, pilot and production)
- Flow chemistry *(3 times mentioned)*

[2] Number between brackets in the title of the figures refers to the number of answers received to this specific question.

- Biotech
- Embeds point of care monitoring within home medical equipment used to perform activity of daily living
- Process industries, specialty chemicals and pharmaceuticals AI and API
- Gas
- Automotive
- Chemical process development
- We provide technology to make devices
- Consumables for Molecular Diagnostics IVD instruments

Classes of applications

From the results of earlier surveys, we were able to define a number of microfluidic classes, based on the pressure and temperature:

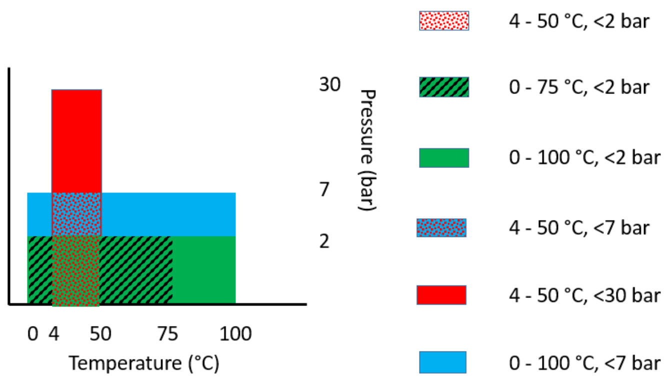


Figure 4: defined microfluidic application classes

The distribution of the respondents over the application classes is similar to the results of earlier surveys, with the majority in the 4-50 °C up till 2 bar range and most of the rest in the other earlier defined classes (see next figure).

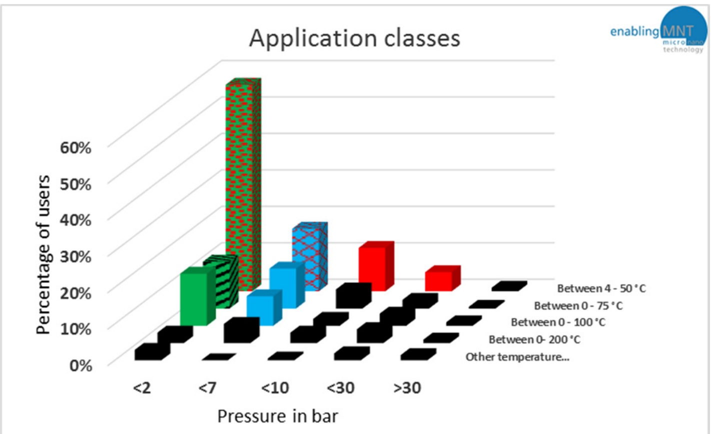


Figure 5: microfluidic application classes (210)

Other pressure / temperature ranges mentioned are:

- Some down to -90 °C, some pressure up to 200 bar, some heated up to 300 °C
- -40 – 10 °C

- Depends on viscosity
- -170 – 400 °C, 0-10 bar, vacuum to 10 bar
- Due to binding to an HPLC, some parts of the instruments are running up to 150 bar.
- <500 bar
- 30 – 50 °C, 90 - 160 bar
- Lack scientific knowledge to answer this question
- Max 100 bar
- Don't exceed 50 °C
- Customer specific. Not sure.
- Some down to -90 °C, some pressure up to 200 bar, some heating up to 300 °C.
- Sometimes cryogenic fluids
- Pressure around 5 bar for valves actuation

The other temperature and pressure ranges mentioned show that several of the ones (particularly those that are not in the area < 200 °C / < 30 bar, are either active in the chemical industry, working with substantial lower or higher temperatures, or with analytical instruments like HPLC, using much higher pressures.

A surprising number of users of microfluidics, nearly 25%, is not restricting itself to liquids (or gasses) only:

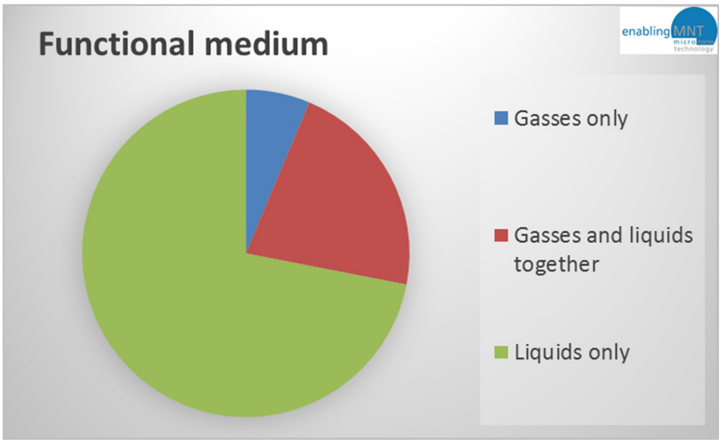


Figure 6: media used.

About 1/3 of the community is working with non-Newtonian Fluids.

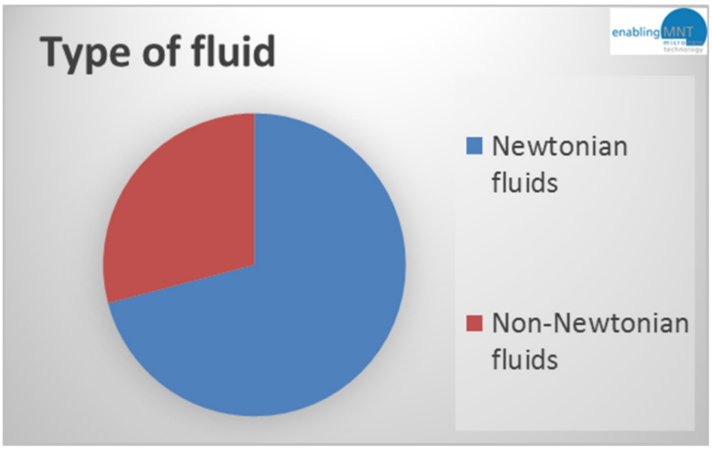


Figure 7: Non Newtonian versus Newtonian fluids used. (141)

A large majority of the users is working with aqueous solutions, with or without biological material, followed by blood, plasma or suspensions. From the “other liquids mentioned” we learn that there is also a substantial group working with organic solvents.

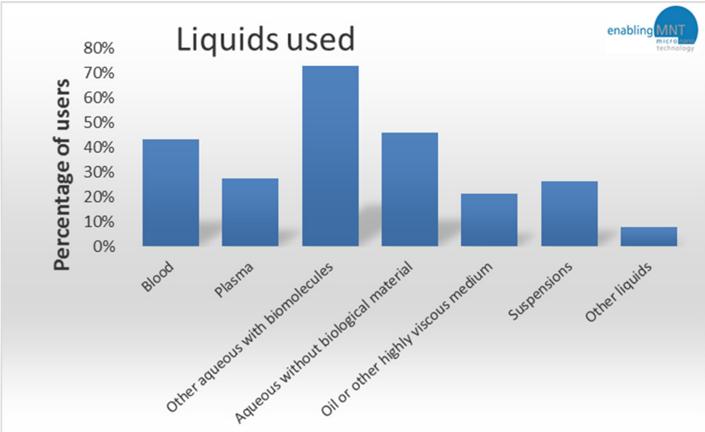


Figure 8: type of liquids used (165)

Other liquids mentioned are:

- Two phase flow, so suspension of one fluid in another
- Supercritical fluids
- Solvents, like acetonitrile, dichloromethane, NMI, THF........
- Solvents (twice mentioned)
- Serum
- Propylene carbonate
- Organic solvents, acids and bases, reactive media, e.g. hydrogen peroxide, pure oxygen
- Organic solvents
- Organic reagent compounds
- Glycerol
- Electrolyte solutions
- Chemicals (organic or water-based solutions)
- Assay reagents
- Acids, bases

The main focus on aqueous liquids is reflected by the high number of users working with viscosities between 1 and 5 cP (see next figure).

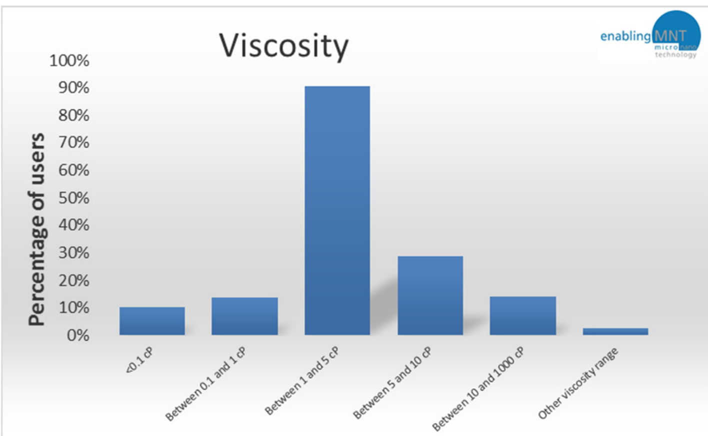


Figure 9: viscosity of the media used (205)

Other viscosity ranges mentioned are:

- Customer specific. Not sure.
- 0.1 and 1000 cP
- Two phase flow so suspension of one fluid in another
- 1000 cP < x < 1000000
- 0.3 – 200 cP
- I do not know
- We have both gasses and water/like liquids in the same system

Although the majority is working with continuous flows, the high number of users working with discontinuous flows (figure 10), cannot be ignored.

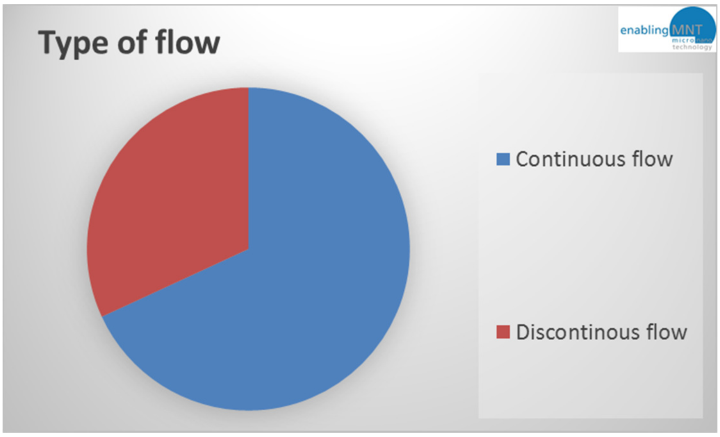


Figure 10: continuous versus discontinuous flow (207)

Of the ones that are using discontinuous flows, nearly half of them are using or supplying dispensing tools:

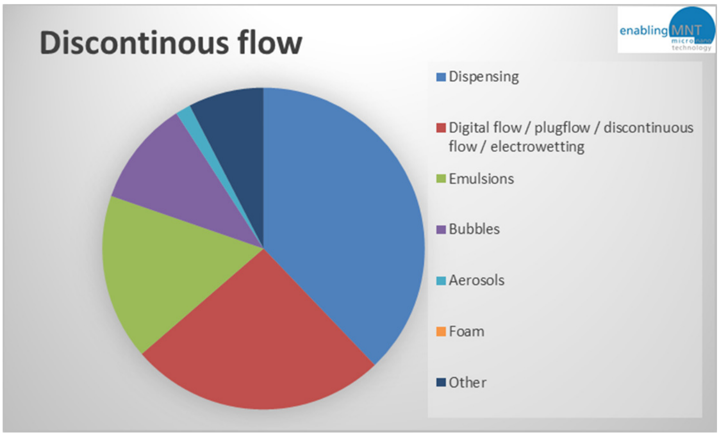


Figure 11: subdivision of discontinuous flow users (66)

The rest of the respondents are involved in creating one or another two phase medium, emulsions, bubbles, aerosols or foam.

Other types of flow mentioned:

- Switching flows
- Customer specific. Not sure.

- Continuous flow and dispensing
- Electro kinetic
- All choice
- Continuous flow or dispensing
- Including two-phase GL and LL flow
- Dispensing of emulsions and bubbles
- A sequence of assay steps requiring flow, then stillness,

One driver of this survey is the wish to defined certain hotspot flow regimes that could become the basis of standardized tests, for instance to qualify microfluidic components and devices like pumps, sensors chips etc. Any hope of finding hotspots in flowrate is shattered by the result of the question what flow rates are being used by the respondents. Although most of the users restrict themselves to a limited flow range, the diversity in total is very high, ranging from below 10 nl/min far into the ml/min range.

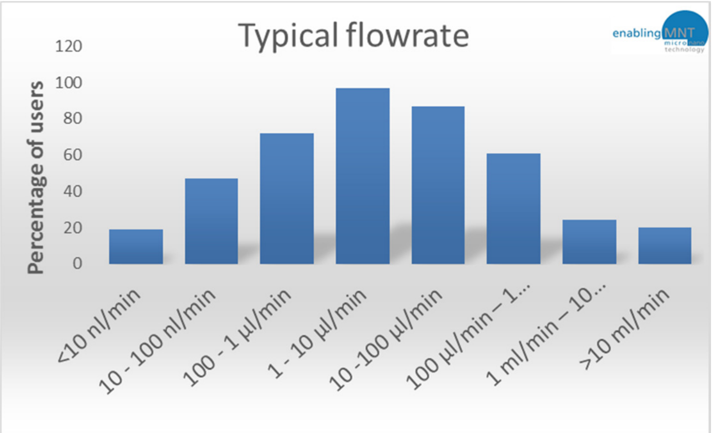


Figure 12: flow rates used (206)

The detailed analysis should show if certain flowrates are linked to certain applications or not.

Pumps

There is no such thing as a leading pump technology in microfluidics, the four most used ones are: syringe pumps, pressurized reservoirs, peristaltic pumps and capillary flow.

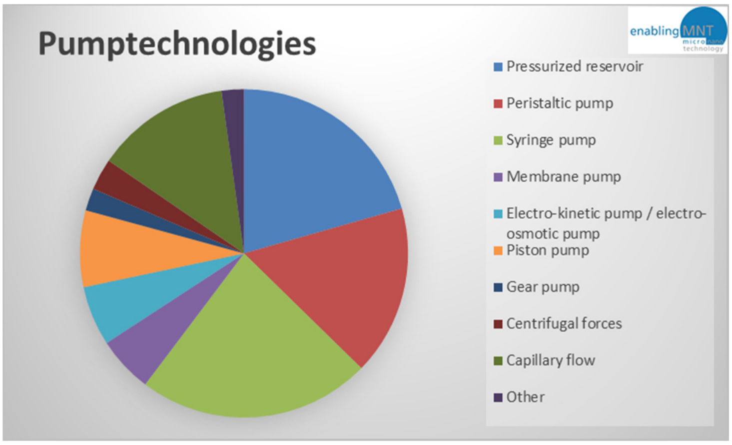


Figure 13: pump technologies used (190)

It still isn’t trivial (due to performance or price requirements) to integrate a pumping function in the disposable and most of the users are using external pumps (see next graph).

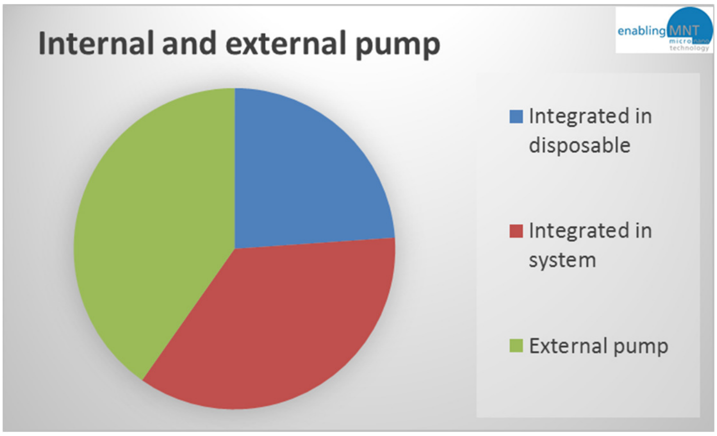


Figure 14: integration level of the pumps used (190)

When it comes to pumps integrated in the disposable, capillary flow is leading followed by, perhaps surprising, pressurized reservoirs (see next figure). For external pumps, syringe pumps are seen by many as the best option, especially by those involved in research activities[3]. Of all the technologies, pressurizing a reservoir is the most versatile.

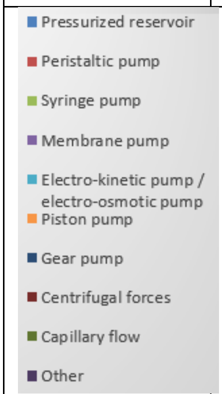
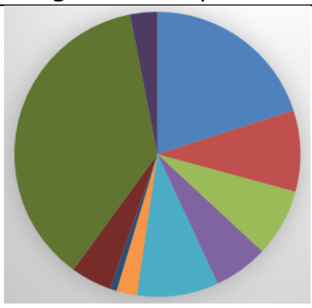
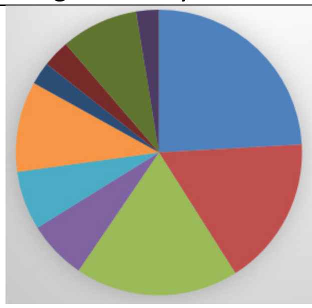
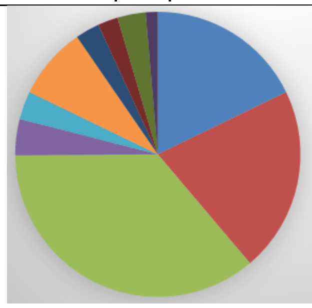
	Integrated in disposable	Integrated in system	External pump
			
Ranking	1) Capillary flow 2) Pressurized reservoir 3) others	1) Pressurized reservoir 2) Syringe pump 3) Peristaltic pump	1) Syringe pump 2) Peristaltic pump 3) Pressurized reservoir

Figure 15: pump technologies used (190)

Other pumping systems mentioned:

- Vacuum source
- Customer specific. Not sure.
- Vacuum pump
- Automotive oil system pressure
- Gravity feed
- Ultrasound
- Not specified. We actually try to model the flows numerically. The way the flow is generated is not important for us.
- Advanced air pressure control system.
- Bellows

[3] As shown by a quick scan of the responses from those involved in research activities.

Measuring and controlling the flow

About half of the population is using flowsensors, slightly more half of those flowsensor users also uses feedback loops to control the flow more accurately.

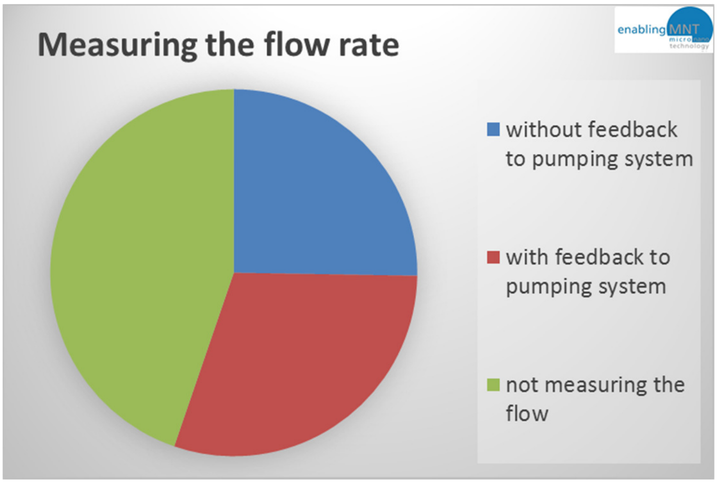


Figure 16: usage of flow sensors (190)

Of those that are measuring the flow, we checked the wanted accuracies of the flow, showing that there is indeed a need to control the flow accurately.

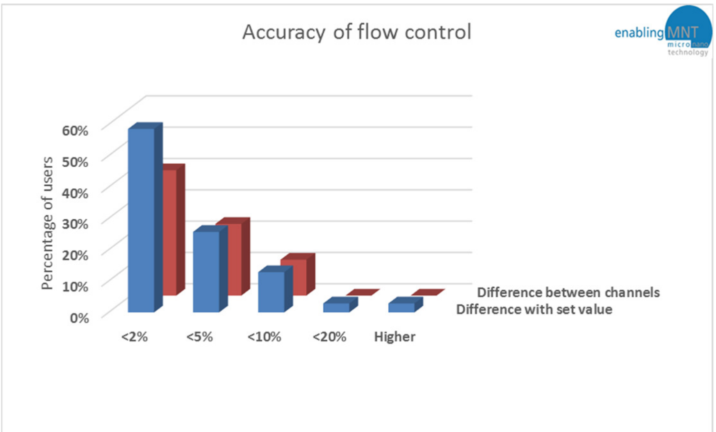


Figure 17: requested accuracy of flow control. (70)

Thermal flow sensors are the most frequently used ones, followed by Coriolis sensors.

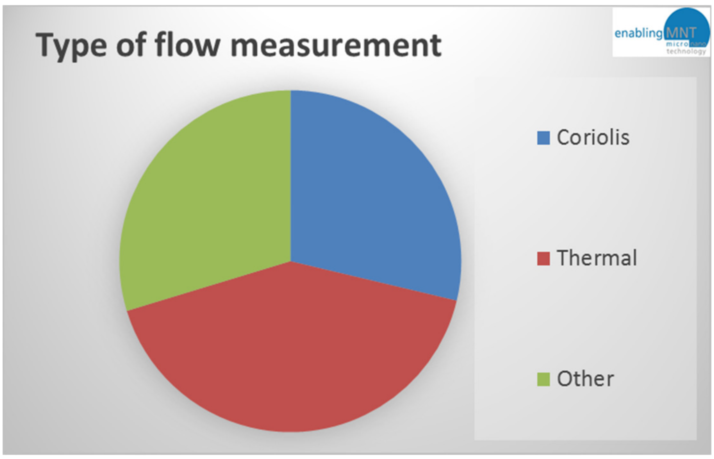


Figure 18: flowsensors used (87)

Seeing the relative large number of other flow sensor technologies used, these two major types doesn't seem to fulfill all the user's requirements. Most of the other flow sensing technologies used are either based on optical methods or using pressure differences over a restriction:

- I don't know
- Pressure drop across restriction
- Optical, capillary front tracking
- Indirectly through current draw and pressure measurement correlations
- Electrochemical, volume measurement
- We are developing electronic flow and pressure sensors.
- Calculated volume of piston
- Pressure drop over a restriction
- Mass
- Camera and/or optical
- Manually
- Sensirion and in-house developed thermal sensor
- Imaging
- Optical, electrical
- Microscope, optical, droplet velocity
- rotameter for gas flow
- Camera
- Optical or electrical (impedance between electrodes)
- Pressure
- Displacement/image analysis
- Volumetric
- Laboratory scale with resolution 1 mg
- PIV[4]
- Simple calculations based on input flow, dimensions, viscosity etc.

Repeatability and accuracy are the main issues for flowsensor users, followed by cost.

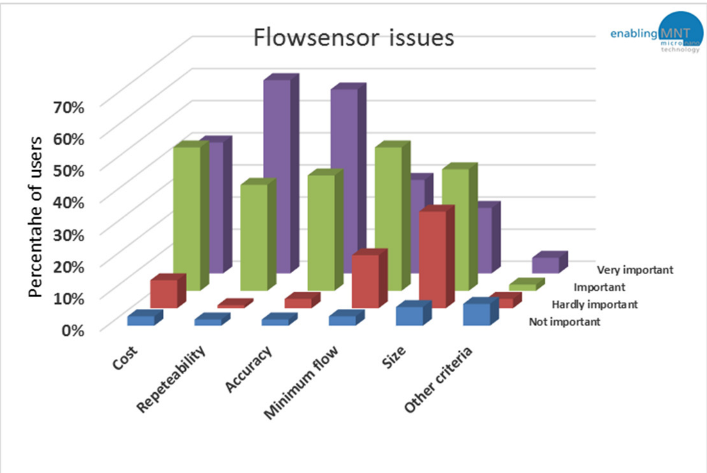


Figure 19: flows sensor issues (103)

[4] PIV measures whole velocity fields by taking two images shortly after each other and calculating the distance individual particles travelled within this time.

Other issues mentioned are:

- Depends on user's case. For example in research can go for big size but not from instrumentation solution which dictates a feedback.
- Reliability, Reliability, and Reliability
- No right answer available
- Range
- Interface to macro-system
- Fast scanning rate
- Data collection via cable to computer

To see what are the most important items in flowcontrol we showed a figure with the most important characteristics of the flow after a step change in the flowrate[5] (see figure 19).

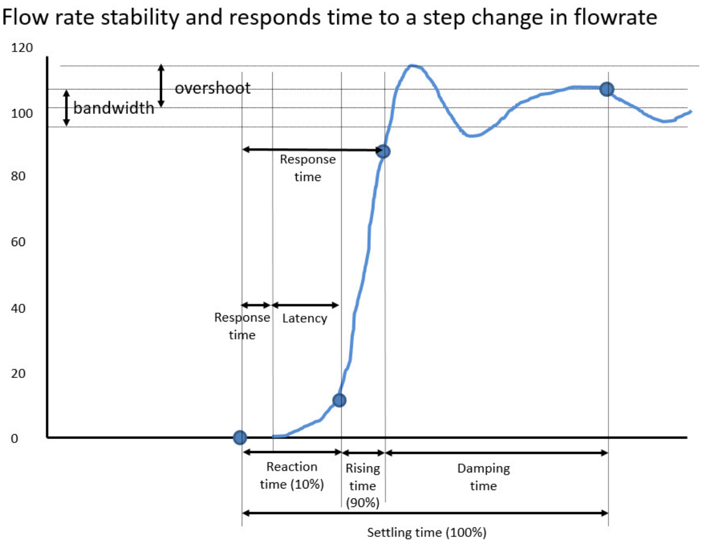


Figure 20: flow control characteristics explained

The most important flow control issue is response time, followed by reaction time. Issues as damping time, rising time and settling time are seen as less important. I.e. the users want their microfluidic flow change fast, not so much reaching a certain set point or bandwidth quickly.

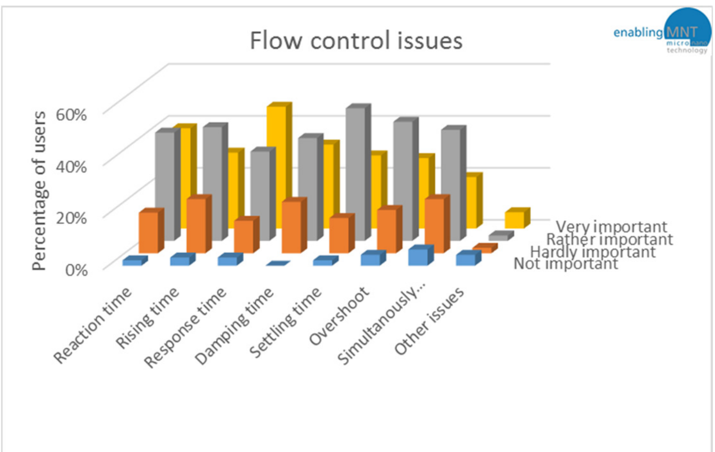


Figure 21: flow control issues (96)

[5] Unfortunately we caused a bit confusion by using the term "response time" twice. Suggestions for better names are welcome.

Other flow control issues mentioned:

- Bandwidth (3* mentioned)
- With the low volumes we deal with the stability of the flow over time is critical.
- Bandwidth, flow stability is critical
- The sensing part is very sensitive to flow
- Equal filling of multiple cavities/symmetry
- I study steady state flow, that's why these parameters are unimportant.

Mixing and valves

Nearly three quarters of the respondents are mixing flows (figure 22) , usually 2-4 flows (figure 23).

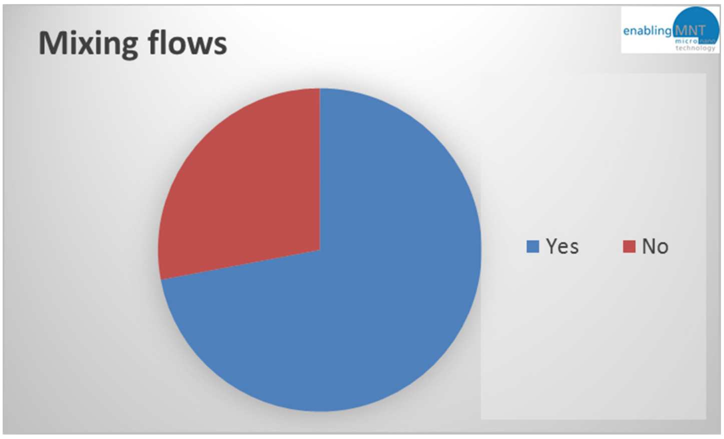


Figure 22: Mixing flows (93)

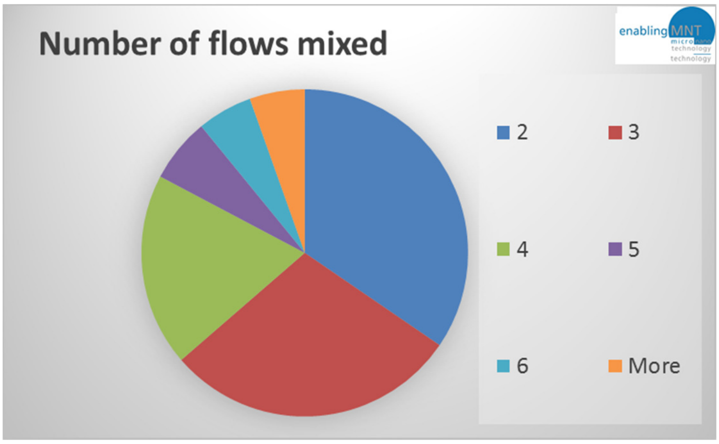


Figure 23: number of flows mixed (70)

Although there are obviously many advantages to integration of valves and technologies are readily available, the majority is still using external valves (see next figure).

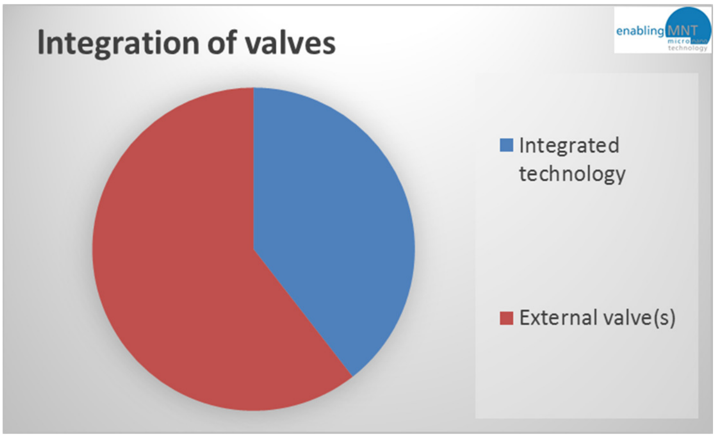


Figure 24: internal or external valves (76)

Pneumatics seems to be the preferred technology for valves in microfluidics (Warning, we received only a few answers).

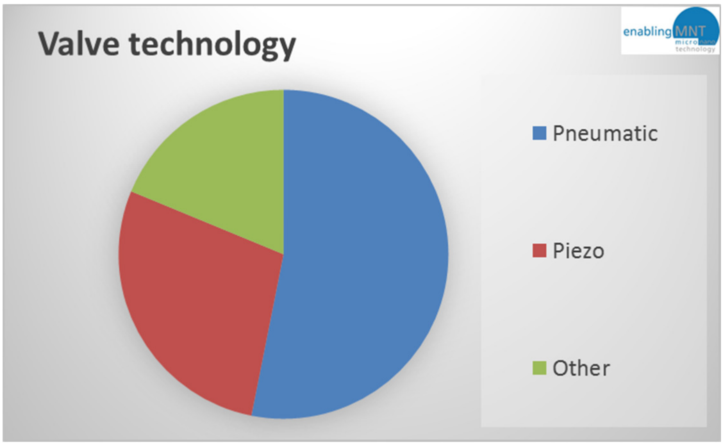


Figure 25: valve technologies used (32)

Other valve technologies mentioned:

- Multiple pumps of course
- Biosensor and nanotechnology
- Not available at the moment.
- Droplet generation system
- Undisclosed
- No valves

Dispensing

The distribution of the users over the range of dispense rates and droplet volumes (figure 26) is rather broad, although in general the community is operating above 10 nl and below 1000 droplets / second, with a peak in the area >100 nl and below 1 droplet second (see next figure).

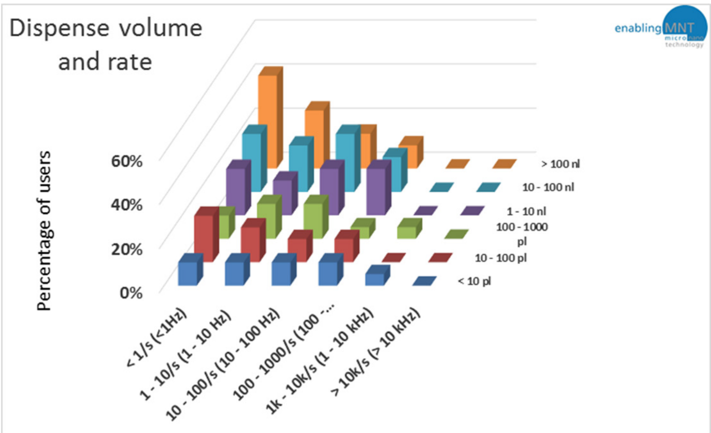


Figure 26: droplet size versus dispense rate (19)

Digital flow/plug flow/discontinuous flow/electro wetting/emulsions/bubbles / aerosols

Although the diversity is again high, the “hotspot” seems to be below 10k/s and between 10 pl and 10 nl , and most of the users stay below 1M droplets / bubbles per second (see next figure).

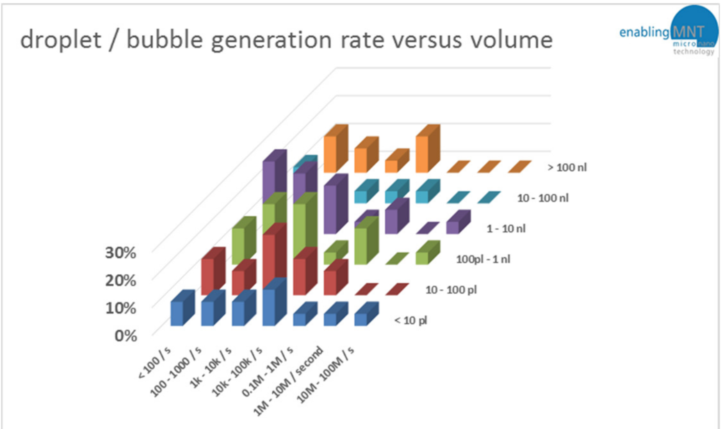


Figure 27: droplet generation rate versus droplet volume (23)

Final comments made by the respondents

- Interfaces with external connections are an important consideration in the design of microfluidics. Also, issues like bubble generation, clogging, what methods are there used to address them?
- We measure pressure continuously and feed back to the pump to control flow. P=QR
- Lot of question depend on use cases.
- Would like to understand how much of market is polymer based vs glass, silicon or silicon/glass.
- Keep up the good work
- I took this survey, unsure as to whether I was qualified to participate. I suspect that I as a platform for a microfluid analytical solution related to urinalysis/fecal analysis, I am NOT eligible. But would still like to see results.
- We have so many different application where we use flow sensors and flow actuators. I tried to give a summary of what we are using and is important to us.
- Nice
- Thanks Henne, I couldn't answer all questions. Best regards
- good survey
- For years, the availability of a reliable, small and affordable flow sensor has been a challenge faced by microfluidics community at large. I hope that this survey results motivate someone to come up with a solution!
- the frequency of generation of droplets: using the diameter of the droplets to replace the volume of the droplets may be more clearly understood without additional conversion.
- the spec's given are a summary of different devices and different applications.
- NA
- Please ask for chemical resistivity, optical transparency and sensor integration in the next round.
- Some of our products are single use, some are re-usable.
- It is quite difficult to answer some of the questions without a specific pumping system and application in mind. In many cases we do most of the things listed, but with different products in different applications.
- Thanks and all the best
- thank you
- I work in hydrodynamic separation.
- Nice survey! interesting graphs of flow rate vs. time.
- Thank you very much. I am looking forward to get the results. Great idea !

Conclusions

The survey was very well received within the community and the responses together create a good overview of the state of the art in microfluidic flow control. 211 Respondents answered at least 5 or more of the questions. As before, the responses came from all over the world, from industry, universities and institutes and from several application areas. A complication factor for analysis is that many of the respondents are not limiting themselves to one specific flowrate, medium or even application.

The distribution of the respondents over the application classes is similar to the results of earlier surveys, with the majority in the 4-50 °C up till 2 bar range and most of the rest in the other earlier defined classes, confirming the appropriateness of these classes. Many of those that does not belong to these application area, are either from the process industry or working with analytical instruments like for instance HPLC and therefore working with a higher range of temperatures and/or higher pressures.

The majority of the users is working with aqueous solutions, with or without biological material, followed by those using blood, plasma, suspensions and organic solvents. A perhaps surprising large number of users, nearly 25%, is not restricting itself to liquids (or gasses) only. In line with this, a third of all users is working with discontinuous flows. Of the ones that are using discontinuous flows, nearly half are using, developing or supplying dispensing tools. The dispense rate is generally below 1000/s; the dispensed volume has a broad distribution range with a peak in the group above 10 nl.

In regards to droplet generation rates and droplet volume for non-dispensing applications, we see that the users are mostly generating droplets above 10 pl and below 10 nl with a generating rate below 1 million droplets / second.

Although most of the users (continuous or discontinuous flows) restrict themselves to a limited flow range, the diversity in total is very high, ranging from below 10 nl/min far into the ml/min range. The detailed analysis should show if certain flowrates are linked to certain application classes or not.

There is no such thing as a leading pump technology in microfluidics, the four most used ones are syringe pumps, pressurized reservoirs, peristaltic pumps and capillary flow. When it comes to pumps integrated in the disposable, capillary flow is leading followed by, perhaps surprising, pressurized reservoirs. For external pumps, syringe pumps are seen by many as the best option, especially by those involved in research activities. Of all the pumping technologies, pressurizing a reservoir is the most versatile, being used often integrated in the disposable or as an external system.

About half of the population is using flowsensors, slightly more than half of those flowsensor users are using feedback loops to control the flow more accurately. A large part of the users want very accurate control of the flows with 5% or even 2% maximal variation of set value or differences between channels. This might be difficult to achieve without feedback loops based on very accurate flow sensors. (Which are being used by only by a minority of the community.) Thermal flow sensors are the most frequently used flowsensors, followed by Coriolis sensors. Most of the other flow sensing technologies mentioned are either optical methods or using pressure differences over a restriction.

The most important flow control issue seems to be response time, followed by reaction time. Issues as damping time, rising time and settling time are seen as less important. I.e. the users want their microfluidic flow to change fast, not so much reaching a certain set point quickly of getting into a certain or bandwidth fast.

Nearly three quarters of the respondents are mixing flows, usually 2-4 flows, often using external valves.

Some respondents made suggestions for other survey topics:

- Interfaces with external connections
- Issues like bubble generation, clogging, what methods are used to address them?
- Would like to understand how much of market is polymer based vs glass, silicon or silicon/glass.
- Please ask for chemical resistivity, optical transparency and sensor integration in the next round.

We can’t honor all these wishers, but the coming survey will be about (bio)sensing.

When it comes to the questions we asked ourselves before creating this survey:

1) Can we make the earlier defined microfluidic classes more precise by adding flow parameters to it (media used, viscosity and/or flow rate)?

The answer is yes, but we need to do a more detailed analysis before we know what are the most appropriate parameters.

2) What is the status in controlling the flow; how is the flow brought into motion and how is that flow measured and controlled (pumps and flowsensors)?

This answer is given in this report.

3) Can we investigate those issues not just for continuous flow, but also for discontinuous flow?

We might be able to make a few statements about state of the art in dispensing, the issue of two phase flow is a bit to diverse for general conclusions

Acknowledgement

The most important contribution to this work has been made by those members of the microfluidic community who took time to answer the large number of question we send them. We are very grateful for their support!

This work was supported by the Microfluidic Consortium and the MFManufacturing project, co-funded by grants from the UK, France and the Netherlands and the ENIAC Joint Undertaking

Appendix: standards for microfluidics.

December 2015 we will launch a whitepaper about our standard proposal: Design Guideline for Microfluidic Device and Component Interfaces. If you like to have this guideline, please send a mail to henne@enablingMMT.com and we put you on the list. In April next year there will be in ISO workshop addressing the issue of standardization of microfluidics. If you are interested to participate, let us know.

Below some samples from the draft Design Guideline for Microfluidic Device and Component Interfaces.

Design for Microfluidic Device and Component Interface Guidelines, version 0.6

Contents

understandable by all and implementable by the product manufacturers as well as by the research labs. These guidelines are considered as a first essential step but certainly not an end point.

Definitions

In order to clarify the discussions, below a few definitions will be given. Also the area where our guidelines apply will be described.

We have considered two parts particularly important for interoperability: the chip and the connector.

The chip is a flat microfluidic device. Important are its format and the position of the fluidic inlets and outlets. Our guidelines will specify at least:

- The chip format
- The inlet /outlet port localization

The connector is defined by two sides; the side connected to the chip and the other side that is left open and can be connected to a tube, an instrument, a fluidic circuit board, another chip, etc...

Although one can easily represent itself a chip, it is much less true for the connector which is important to consider in a very broad way. Indeed in establishing these guidelines, we considered as connector not only typical connectors such as those sold by Dolomite, Micronit and others, but also the possibility to use other types of assembly methods such as adhesives (double face tape, glue..), O rings with a clamping system or even the often used mini-Luers.

Not defining completely the connectors but only the side connected to the chip gives a huge freedom of use, independently of the chip material or the chip to chip assembly method. However, defining only the geometry (port location, and foot print) is still a great achievement since it enables interoperability.

By defining only the chip geometry we avoid all the chip to chip, chip to fluidic circuit board, chip to outer world discussions, simplifying the problem to the chip and to the chip side of the connector. This simplicity enables a large number of users and manufacturers to consider using these guidelines.

In order to better clarify chip topology we have agreed on the following terminologies represented in figure 1:

- Top or Bottom connections (ToB connections)
- Edge connections

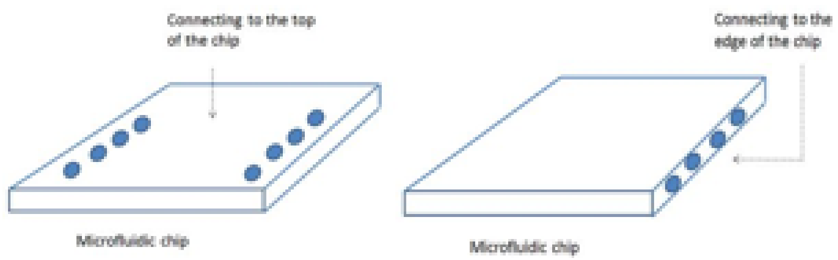


Figure 1: Schematics showing top side (left) and edge (right) connections.

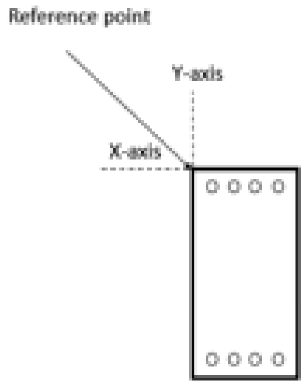


Figure 5: 15*30 mm chip with axes and reference point.

A 30*15 mm chip has the X axis along the 30 mm side. The Y axis is again on the left and the reference point on the top left corner. (See next figure.)

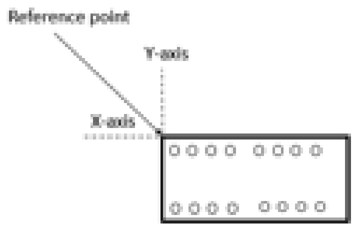


Figure 6: 30*15 mm chip with axes and reference point.

As a preference one should chose the naming (and with that the X axis) in such a way that (most of) the microfluidic connections are on the side of the X axis.

Square chips

For square chips, the positioning of the XY axis is more arbitrary, but again the preference is that (most of) the connections are near the X axis. If that would lead to two different options due to asymmetric placement of the microfluidic ports, one should choose the one with most of the ports near the reference point (See next figures)

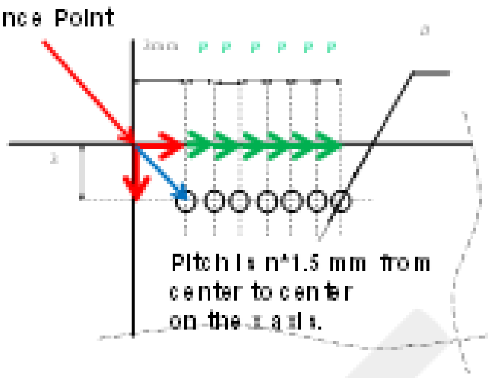


Figure 10: Top view of ToB connections showing the position of the row of hole at a distance of centre to centre of 1.5 mm from each other on the X axis.

There is a preference for a 3.0 mm port pitch (n=2). In the microfluidic field, 3 mm spacing is considered as state of the art for spacing between ports. For the near future chips and connectors with 1.5 mm pitches will likely become available.

4.1. Nominal distance of the first fluidic port from reference point

Nominal distance of the first hole/fluidic port from the reference point is a key guideline (3 mm, 3 mm) (figure 11). The distance is defined from the reference point to the centre of the hole. This 3 mm distance from one side is the minimum distance for all four sides. This 3 mm distance was adopted after discussion with injection moulding manufacturers, assuring that such a distance from the edge ensured a robustness when using injection technologies.

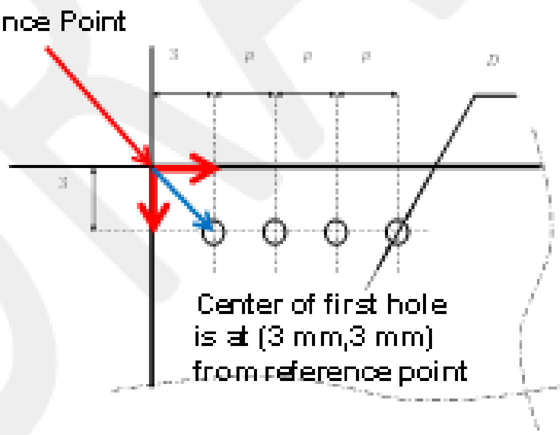


Figure 11: Top view of ToB connections showing the position of the first hole at a distance of 3 mm from each side of the top left corner of the chip.

4.2. Distance between two rows

Distance between two rows is a multiple of 1.5 mm (p*1.5 mm) from centre to centre on the y axis (figure 12). Not all the rows are necessarily present on the chip or connector, but row positions are fixed. This 1.5 mm grid enables several configurations. The row positioning is always established from the reference point, in order to avoid cumulative drifts. The same reasoning was applied to the Y axis as the one used for the X axis. There is a preference for a 3.0 mm row pitch (p=2).

4.6 Summary Table of all the interconnect guideline dimensions and tolerances

Top or bottom standard interconnection dimensions are summarized in the table below:

Parameters	Nominal value	Minimal value	Maximal value	Tolerance
Reference point : Left chip corner				0 mm
Distance of the first hole from the reference point (3 mm, 3mm) (corner edge to hole centre)	(3 mm,3 mm)			+/- 0.15 mm
Minimal distance of any hole from any side of the chip		3 mm		
Distance between holes or Port pitch (centre to centre)	n*1.5 mm	1.5 mm		+/- 0.15 mm
Rows are parallel to the chip's x axis at a distance from ref. point of n*1.5	n*1.5	1.5 mm		+/- 0.15 mm
Hole diameter for 1.5 mm grid		0.4 mm	0,7 mm	
Hole diameter for 3 mm grid		0.4 mm	2.0 mm	
Hole diameter for 4.5 mm grid		0.4 mm	3.5 mm	
Total Chip Thickness	1 mm	0.85 mm	1.15 mm	+/- 0.15 mm
Total Chip Thickness	1.7 mm	1.58 mm	1.92 mm	+/- 0.22 mm
Total Chip Thickness	2 mm	1.80 mm	2.20 mm	+/- 0.20 mm
Total Chip Thickness	4 mm	3.60 mm	4.40 mm	+/- 0.40 mm
Tight Tolerance of outer chip dimension (desired)				+/- 0.05 mm
Lower Tolerance of outer chip dimension (when tight tolerance not achievable)				+ 0.05 / - 0.15 mm

Table 3: Key parameters for top interconnection standardization and tolerances .

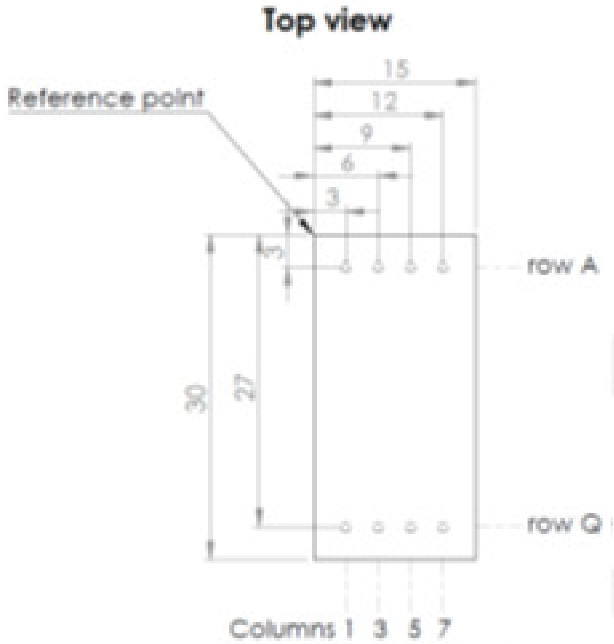
5. Standard guide lines for chip formats

5.1 Microscope slide format standards

The official microscope slide standard[4] allows all sizes in length between 76 and 74 and in width 26 and 24 mm. This will not work for affordable and reliable connectors. The two most commonly used dimensions are 75.6 x 25.4 and 75 x 25. We have chosen the slide format that fits best to the grid of 1.5 mm, which is therefore the 25.0 x 75.0 mm slide format.

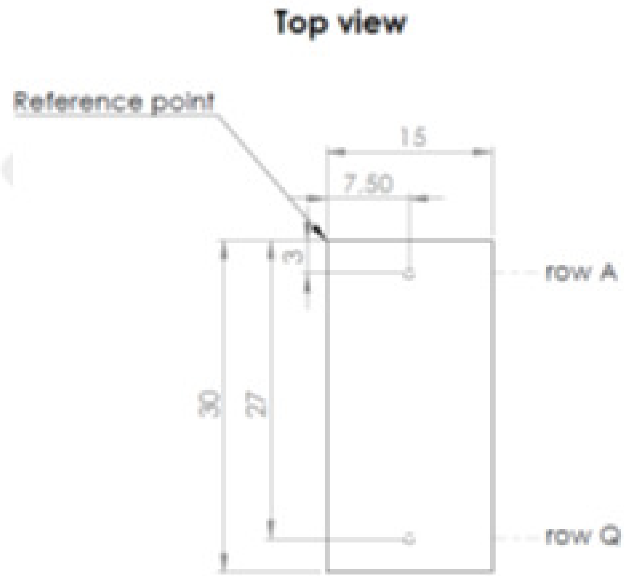
In order to have symmetrical connectors, we have modified the first hole location for this format: the first hole position will be at 3.5 mm from the long edge and 3.0 mm from the short edge. Preferred configuration is with the first row at 6 mm for the starting point in the X axis (long side)

[4] Standard Microscope slide: ISO (International Organization for Standardization) 8037-1:1986



Port designation	Function
A1	Fluid inlet #1
A7	Fluid outlet #1
Row Q	Electrical connections

Figure 21: Top view of a 15*30 mm building block with ports on the short side.



Port designation	Function
A4	Fluid Inlet
Q4	Fluid outlet

Figure 22: Top view of a 15*30 mm building block with centred ports.

7 Edge Connectors

Some outcomes from the top connector discussion can be used for the edge connector specification: distance to edge (3 mm), port pitch (based on a grid of 1.5 mm) and chip sizes (multiples of 15*15 mm). There are however two additional dimensions to be defined: thickness of top layer and thickness of bottom layer. Besides that the specification of the diameter of the port might be different from those of top holes.

Only chip to tube connectors will be discussed, the option of an interposer (for fanning out) is not taken into account.

7.1 Reference lines

All distances are given with reference to two lines:

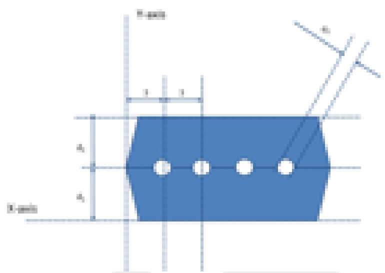


Figure 28: Items to be specified for edge connectors[7].

7.2 Leak free connection with tubing

Often used small polymer tubes have an outer thickness of 0.8 mm. In order to have ample room for tolerances and leak free connection of clamped connectors, a preferred thickness of 2 mm and a minimal thickness of 1.4 mm for the total stack are recommended by experts[8]. Below 1.4 mm gluing the tubes is recommended[9]. In that case the need for standard thicknesses of the layers is less urgent.

7.3 Possible general cases

From the discussion above and table 2 on page 3 we distinguish the following general cases:

	Thickness bottom layer	Thickness top layer	Corresponding tubes[10]	Comment
A	2 +0.2 / -0.2[#]	2 +0.2 / -0.2[#]	0.8 or 1.6	
B	2 +0.2 / -0.2[#]	1.0 +0.15 / -0.15[#]	0.8 or 1.6[†]	
C	2 +0.2 / -0.2[#]	0.7 +0.07 / -0.07	0.8 or 1.6[†]	Includes glass with silicon
D	1.0 +0.15 / -0.15[#]	1.0 +0.15 / -0.15[#]	0.8 or 1.6[†]	
E	1.0 +0.15 / -0.15[#]	0.7 +0.07 / -0.07	0.8 or 1.6[†]	Includes glass with silicon
F	0.7 +0.07 / -0.07	0.7 +0.07 / -0.07	0.8 or 1.6[†]	Includes glass with silicon

[7] To ease the discussion in the rest of the document it is assumed that the thickest layer is at the bottom.
[8] In the future constructions using 0.4 mm chips are foreseen.
[9] An alternative method could be the use of a (bonded) spacer. In that case the spacer thickness can be adapted to the standard for the edge connection.
[10] These are recommended tube sizes, other (smaller) tubes can also be used.