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RESEARCH PAPER

Microfluidic devices: a road forward by standardization of interconnects and classification

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Abstract Over the past decade, the issue of standardization in the microfluidics arena has been brought up several times, but its exact role remains largely unclear. A recent initiative has been launched to identify items that are in need of standardization. This paper represents the outputs from discussions with industrial and academic experts and results from an online survey. The results show the need to address standard interconnects and to develop a classification system for microfluidic devices. Here, we propose to standardize pitch spacing dimension that will enable complex high-density world-to-chip microfluidic interconnections. We also present a first attempt to classify existing microfluidic devices. It is envisaged that a system of classification will be pivotal in the development of standard documents, which details testing guidelines for the purpose of reliability assessment of microfluidic devices. The proposed standards to be developed are currently being supported by several industrial organizations and have the advantage that they do not depend on proprietary interests relating to any organization.

1 Introduction

In recent years, the issue of standardization in microfluidics has been raised by several authors (Stavis 2012; van Heeren 2012). Of particular, focus has been the standardization of interconnects; interconnects here are defined as those connections that are made to/from microfluidic devices (Fredrickson and Fan 2004). In 2012, van Heeren highlighted the importance of standardizing interconnects, as being cost-effective in the design and manufacturing of microfluidic devices. Although the need to standardize interconnects is clear, several specific issues have not yet been resolved. The issue in relation as to what aspects of interconnections should (and can be) standardized has been an issue for the past decade, in which much discussion has taken place but with very little progress was made. In the last decade, several proposals have been put forward. For example, Gartner et al. (2004) stated that the microfluidics community should take into account existing infrastructures and standards already in use, as this coincided with the fact that many companies are already making microfluidic products for use in established industries. In particular, Becker proposed a stronger link between microfluidic interconnects with the existing standards found in life science and existing laboratory equipment. Subsequently, he proposed the need to make interconnections to the microscope slides or microtiter plate possibly with (mini)Luer connectors. Indeed, such formats have an added advantage in that they are already in use by the microfluidic community (van Heeren 2012). Microscope slides, for example, have been used as a substrate for etching channels or creating polymeric structures (Nanassy et al. 2007; Tantra et al. 2014). Likewise, microtiter plates have been employed as the construction material for microfluidic devices (Harink et al. 2014).

Although such formats have the advantage to fit with existing user's infrastructure, several limitations exist. In the case of microscope slides, the substrate material usually employs glass substrates and glass substrates, which can be more expensive when compared to polymer-based

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substrates (Becker 2009). As a result, there is a tendency for manufacturers to employ glass slides of smaller chip dimensions, such as 15 × 15, 30 × 15 and 45 × 15 mm, rather than the standard microscope slides of about 75 × 25 mm. Furthermore, connections to glass using (mini)Luer connectors cannot be made without substantial additional cost, which is in contrast to corresponding polymeric processing. As a result, connectors to glass chips often involve the use of clamped connectors or having reusable chipholders.

So far, our discussion has focused "physical standards", i.e. standardizing interconnections. In addition to such physical standards, standardization activities can also include development and publication of standard documents. According to International Organization for Standardization (ISO), these standard documents are important as they publish "*requirements, specifications, guidelines or characteristics that can be used consistently to ensure that materials, products, processes and services are fit for their purpose*" (http://www.iso.org/iso/home/standards.htm). The importance of such standard documents is to provide a route towards harmonization, which will result in achieving an agreed, repeatable and reliable way of doing something. It plays a very important role in the device industry because it encourages consistency, enhances safety, improves efficiency and companies often employ them to their advantage.

Up to now, several attempts have been made to publish document standards in the microfluidics arena. This ultimately led to the creation of a working group in ISO, CEN/TC 332 (WG 7 micro process engineering), and subsequently the publication of an ISO document entitle "Micro process engineering—vocabulary", which give terms and definitions for micro process engineering applied in chemistry, pharmacy, biotechnology and food technology (ISO 10991 2009). In addition to this, a DIN standardization group on microreaction technology has also been established. This group is currently active and working on standard characterization processes for microreactors. Although not technically a "standards" body, there are also interest groups that produce standard documents. SEMI, for example, is a trade body with interest in microelectromechanical (MEMS) and microsystems. In the past, they have proposed standards for microfluidic interconnections, but these did not link well with existing markets or established pro forma standards. An important point to highlight is that the development of internationally recognized standards usually takes a long time to realize, with large amount of effort involved (Bradley and Ieee 1992). Because of this, it is important that the microfluidic community identifies those items that are in immediate need of standardization, in order that the process will be driven by needs of different stakeholders such as end-user and manufacturers. Having sufficient demand for the standard is required not only for the purpose of developing the standard document but also for the eventual successful uptake. In order to establish whether a standard is required or not, there is a need to have a clearer idea of the market segments and to understand requirements in each of these segments in relation to standard documents.

This paper will attempt to answer several questions related to standardization. First, the paper will focus on the much discussed topic of standardizing interconnects. Although the need to standardize interconnections has already been echoed by several past workers, the question remains as to what part of the interconnections should be standardized. Second, another issue that also needs resolving is to establish what other key items (in addition to interconnections) to consider for standardization.

The first port of call in attempting to answer these questions is to have fruitful discussion with key stakeholders. The output from such a discussion will then be used to formulate a set of important questions of relevance, for further consideration before scripting survey questions. A subsequent online survey will then be conducted and output analysed. The results will have implications, which will be further explored and potential solutions presented.

2 Method

A discussion was held to exchange ideas and information with stakeholders, mainly with ad hoc groups such as the Microfluidics Consortium.[1] Productive discussions were also held between consortium partners in a project called MFmanufacturing.[2] The MFmanufacturing project is a recently launched pan European project whose goal is towards the standardization of interconnects. This discussion is subsequently extended to other organizations, for instance with Dutch and German microfluidic interest groups and the SEMI. This not only ensures input from a wide range of users but also helps in disseminating the results of the discussion. It is good to mention that although academics are involved in the discussion, the majority of the involved parties are from the industry.

The initial discussion phase resulted in the identification of a set of questions, which was subsequently filtered and developed to form part of a questionnaire. The purpose of the questionnaire was twofold: "test the waters" in relation to standardization and identify the requirements in relation to standardizing interconnects. "Testing the waters" involved trying to: identify the different market segments

1 http://www.microfluidicsinfo.com.

2 http://mf-manufacturing.eu.

associated with the use of microfluidic devices, establish key issues and check initial assumptions. The questionnaire was sent via an online survey tool, Survey Monkey during July and August 2014, after which the results of the survey were compiled for analysis.

The respondents for the survey were chosen from a list of contacts from a network database compiled by enablingMNT, through its role as a consultant within the microfluidics arena for the past 12 years. One hundred and thirty-four responded and filled in the survey, with the majority coming from the industry. Half of those that responded were small-medium enterprises (SMEs) and close to a quarter being research laboratories at universities. The remainder was made up of large enterprises and other research organizations. A substantial proportion of respondents were involved in medical diagnostics and point of care. The remainder had interest in laboratory instrumentation, drug development/testing/screening, food safety, agricultural, environmental control or research.

3 Interconnections: what to standardize?

The survey identified four most common types of connectors used by the respondents. The four types involved the use of glue (e.g. of plastic tubes), Luer connectors, clamped connectors and chipholders. The use of glue can be considered as one of earliest methods to create a connector. Such connectors were made in early 1990s, which involved the gluing of plastic tubes on to holes in a coverplate of microfluidic device (Fredrickson and Fan 2004). In its most primitive form, these plastic tubes were cut from disposable pipette tips, resulting in the formation of wells in which samples or reagents can be dispensed into. Such connectors are often made manually. An advantage in the application of an adhesive, such as the gluing of tubes with UV-cured adhesives, is to achieve strength and permanent interface. However, a disadvantage is that the final connector may not be suitable with commercial tubings and fittings. In this instance, Luer connectors can be attractive as they are considered to be an industry standard. However, a common difficulty with such connectors is the large dead volume normally associated with them. In addition, the shapes of such connectors are bulky, which means they are not small enough to allow for high-density connections. Lastly, although Luer connectors can be easily integrated in polymer chips, fixing them onto glass substrates may be cumbersome in that it may require a gluing step. In a situation that requires high-density connections, it is necessary to ensure that there is sufficient fixation of the connectors and overall protection to the microfluidic device. In such a scenario, a clamped connector or chipholder system may be ideal. In this context, clamped connectors are attractive and especially useful when several tubes must be connected to a chip. As clamped connectors use force to press tubes to a chip surface, usually using an interface layer, they are constructed to prevent leakage, which is another ideal feature for a connector. Another advantage of clamped connectors is that they can be reusable. A chipholder enables microfluidic connection in a similar fashion as the connector described above, but it also provides mechanical fixation and protection, similar to a package in electronics. Furthermore, they can have additional functionalities such as facilitating electrical or optical connections. Overall, the ultimate choice as to what connectors are suitable will boil down to end-user's requirements for the specific application.

Table 1 aims to present a simplified overview of the advantages and disadvantages of the four types of connectors. Obviously, in reality the list in Table 2 is more exhaustive, as there are other types of connectors available; these have been described elsewhere (Temiz et al. 2015).

Although a snapshot picture of state of the art has now been presented, the question yet to be answered is: What part of the interconnections should be standardized and for whom? The outcome of the survey and the discussion with other stakeholders has highlighted several key points. First, the respondents indicated that an ideal standard interconnection is one that is easy to plug, be removable and

Table 1 Summary of four main connectors: main advantages/disadvantages

	Luer	Glued	Clamped	Chipholder
Suitability for glass and silicon chips	–	+	++	++
Ease of use for multiple interconnects	0	–	+	++
Relative cost	++	+	–	–
Medium resistance	–	++	++	++
Dead volume	–	–	++	++
Reusable	++	–	++	++

Table 2 Microfluidic device classification proposed

Classes	Minimum temperature (°C)	Maximum temperature (°C)	Maximum pressure (bar)
A	4	50	2
B	0	75	2
C	0	100	2
D	4	50	7
E	0	100	7
F	4	50	30

reusable. Having said this, the concept of "re-usability" will undoubtedly be of interest to certain segments of the market, such as those end-users requiring high pressures/temperatures and those requiring more than four ports. However, it will be of little importance to those who are interested in developing disposable chips, such as designers of medical diagnostic products. In this sense, the drive to have reusable connectors is not of general concern. A second interesting find from the survey is that that there is substantial interest to combine microfluidic interconnections with other types of connectors such as for electrical or optical interconnections. Subsequently, this will mean the need to cater for more complex level of integrations between the different types of connectors. In fact, ~30 % of respondents indicated the preference to combine electrical and microfluidic interconnections, while 25 % preferred to combine optical and microfluidic interconnections. In addition to this, higher-level complexity (as opposed to only have microfluidic connections) is the need to cater for high-density connections. From the survey, the need to have complex and high-density connections is not surprising, as this issue message has been previously echoed by past workers. Jensen et al. (2013) highlighted that there is a growing trend for further miniaturization, especially in instances when there is a need to integrate microfluidics connectors with other types of connectors such as electrical or optical. The implication from our finding is clear: there is a need to find smaller components and subsequently smaller pitch spacing dimensions.

The need for smaller pitch spacing dimensions has been further discussed amongst consortium partners within the MFmanufacturing project. Our discussion started with looking as to what has been done with regard to pitch connections and was followed by estimating from the survey what future implications must be taking into account. The output from the discussion resulted in a proposal for standard pitch spacing based on a 0.75-mm grid and using multiples of 0.75, such as 1.5 mm; this is a lot smaller than the currently frequently used 3–9 mm pitches. This small pitch dimensions will open a route towards further miniaturization, for instance when very small chips and tubes are preferred. It is good to mention that this proposal prescribes only the position of the ports and is therefore supplier independent and the final choice on how the connections are made up will be left entirely to the user.

4 Other items requiring standardization?

In addition to standardization of pitch connections, another goal of the survey is to collect information to understand other key issues in microfluidics, so as to identify priority items for standardization. One notable outcome was the rather unexpected high number of users that showed an interest in edge connectors. However, the most outstanding issue surrounds the topic of reliability, in particular how to ensure that devices are reliable. This result is not surprising, as the issue of reliability has been previously highlighted by Tantra et al. (2013). According to Tantra, the need to have reliable, robust microfluidic device is key and can potentially be seen as barrier to commercialization. The importance of reliability is not only a requirement for product qualification but often a necessity for the purpose of regulation.

The need to have reliable devices will mean the need to develop suitable testing schemes. However, hundreds of microfluidic prototype devices exist, which ultimately will require different testing schemes. Under such circumstances, the development of ad hoc method for testing may be appropriate. Having said this, it was highlighted by Tantra and van Heeren (2013) that there is a need and a way to speed up the process of testing. This can only be achieved by developing a common testing strategy and publishing appropriate standard documents. This will not only minimize duplication efforts but will enhance harmonization of activity on a global scale.

The first step towards improved harmonization especially for testing is the need to develop a generic classification system independent of specific applications. This has not been previously attempted. One potential route to establish a classification system is to group existing microfluidic devices in relation to certain similarities, for example in accordance with their working conditions such as temperature range, in which the device can operate under. From the survey, the different microfluidic devices currently in use and the typical working conditions ranges associated with such devices have been identified. Subsequently, taking into account the results of the survey, a first attempt to identify classes was made, based on the different working conditions, e.g. certain range of pressure/temperature. The results are given in Table 2. As indicated by the survey, most of the users are operating their device below 100 °C and 10 bar. Furthermore, most of the suppliers of microfluidic pumps and sensors specified the working range of their products for temperatures between 4 and 50 °C. For applications based on polymerase chain reaction (PCR) in microchip devices, a maximum working temperature of 100 °C is often needed. As 100 °C is too much for several often used materials, 75 °C is also considered as the upper temperature limit. The specifications of 2 and 7 bars in Table 2 are pro forma standard maximum pressures.

Table 2 presents only a starting point in relation to classification. Undoubtedly, a more comprehensive classification scheme is envisaged, once other distinctive features like flow and media used have been taken into account. It is therefore likely that other classes and sub-classes will be introduced into the scheme of things, which will be explored in the next survey. For example, we will explore whether this classification system can be extended to take into account the different media or flow ranges. In addition, the classification system will need to take into account special devices, such as those that operate at higher pressures/temperatures than those listed in the table. For example, the classification system will need to be extended to take into account special cases such as HPLC-Chip technology (Ehlert et al. 2010), where pressures are significantly higher than those listed.

5 Conclusions

There is a pressing need for more standardization work to be infused into the microfluidics arena. Although much has been written on this topic, remarkably little progress has been made to date. For example, there has been much discussion on the standardization of connectors, but a great deal of uncertainty as to what exactly should be standardized exists. In this paper, we attempt to answer this question, as well as trying to identify other priority items requiring standardization. The method we used is to involve a wide range of (industrial) stakeholders and concentrate on standards that are not dependent on proprietary technologies. An online survey was used to investigate issues around standardization. The implications from the survey findings are twofold. First, there is a need to standardize pitch spacing dimensions. In the standardizing of pitch spacing dimensions, there is a need to have smaller pitch spacing; the drive here stems from the need to cater for more complex microfluidic devices and to consist of different types of connections as well as high-density connections. Second, the survey indicated the need to develop a classification system; this would be advantageous from the need to have a common testing strategy for the purpose of reliability. From the survey, we have identified the microfluidic devices currently in use, and as a result a classification scheme has been proposed on the basis of grouping devices on the basis of their working operating conditions. Six different classes have been presented here for further consideration. It is envisaged that such a classification scheme will be revisited, in order to take into other devices in other applications areas not identified in the survey.

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Compliance with ethical standards

Conflict of interest Part of the work has been performed in the project MFmanufacturing, co-funded by grants from the UK, France and the Netherlands and the ENIAC Joint Undertaking. Henne van Heeren (from enablingMNT) and Ratna Tantra (from NPL) are project partners within the MFmanufacturing project.

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