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ScienceDirect

Procedia Technology 20 (2015) 54 – 59

Procedia Technology

The International Design Technology Conference, DesTech2015, 29th of June – 1st of July 2015, Geelong, Australia

Lab-on-a-chip or Chip-in-a-lab: Challenges of commercialization lost in translation

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Abstract

Lab-on-a-chip technology has been long envisaged to have tremendous commercial potential, owing to the ability of such devices to encapsulate a full range of laboratory processes in a single instrument and operate in a portable manner, rapidly and at low cost. Devices are believed to have potential in fields ranging across medical diagnostics, environmental sampling and a range of consumer products, however, to date very few devices have attained commercial success. This review examines the challenges relating to the commercialization of lab-on-a-chip technology from fundamental research to mass manufacturing and aims to provide insight to both academics and product development specialists the perceived hindrances to commercialization and a strategy by which future work could be translated into commercial success.

Peer-review under responsibility of School of Engineering, Faculty of Science Engineering & Built Environment, Deakin University

Keywords: lab-on-a-chip, commercilization, microfluidics, translation

1.0 Introduction

In the recent decades technologies evolving from the translation of microsystems and microelectronics manufacturing techniques have led to the creation of a variety of novel devices with the ability to encapsulate a variety

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Peer-review under responsibility of School of Engineering, Faculty of Science Engineering & Built Environment, Deakin University
doi:10.1016/j.protcy.2015.07.010

of laboratory processes into a singular miniaturized platform, the so called, lab-on-a-chip. The field of lab-on-a-chip, and its related microsystems counterpart technologies (microfluidics, MEMS/NEMS, μTAS, etc) have now developed into truly multidisciplinary fields, requiring equal contributions from fields ranging across biology, chemistry, software development, physics and material science, in addition to the traditional skills of microfabrication and engineering used in their original inception and development. It is worth perhaps re-iterating at this point what is generally understood as lab-on-a-chip or microfluidics technology, which in itself highlights a confusion in technology translation, that there is no one single definition or indeed terminology by which all facets of this technology can be neatly expressed or pigeonholed. Lab-on-a-chip technology essential comprises devices which have an element that is millimeter to centimeter sizes which encapsulate more than one laboratory processes into a singular device. Such devices typically comprise microfluidic elements for fluid handling and additional components for fluid control, processing and some detection capability. Though here we make reference to lab-on-a-chip, this same definition could hold true for μTAS, etc and so these technologies should not be considered as mutually exclusive but belong to the same technological family.

Lab-on-a-chip, enabled by the complimentary use of microfluidics and biosensing has long been speculated to be one of, if not the definitive, methods by which laboratory based chemical and biological techniques can be integrated into miniaturized, low-cost analytical devices for portable diagnostics in a range of sampling scenarios (medicine, environmental, etc). The market for microfluidic devices has been estimated to have a net value of $1.6 billion and is forecast to rise to $3.6-5.7 billion by 2018 [1], representing a significantly large commercial opportunity for this sector. Despite the promise and maturity of the technology, which has spanned several decades since the landmark first generation work by Terry et al 1979 [2] and later by Manz et al 1990 [3], the vast majority of systems have yet to be realized into commercial products or as ubiquitous tools used routinely as research grade instrumentation outside of specialist laboratories. The reason for the lack of immediate uptake of lab-on-a-chip technology despite it abundant advantages in sample processing have been somewhat of an enigma and have been the subject of debate by many of the prominent members of the scientific community [4]. Where lab-on-a-chip technology has been more successful has arguable been less as fully integrated devices for a bespoke purpose, over use as enabling tools for research endeavor or specialize fluid processing applications, with several companies worldwide offering such services (Dolomite, Microfluidic ChipShop, Minifab, etc).

There are however notable exceptions to this trend and a handful of lab-on-a-chip devices have successfully made it to the market and are ubiquitous in our daily lives, the most obvious examples being the humble inkjet printer cartridges and the home pregnancy test kit (although not traditionally perceived as but satisfying the technological specifications of lab-on-a-chip). More niche examples can also be found, such as microarrays and specialist medical diagnostics devices such as the Triage® cardiac panel (BiositeInc, USA) [5] and the i-Stat (Abbott Laboratories, USA). It is somewhat unclear why these devices have been more successful than their more modern and more integrated functionality modern counterparts, but it is believed we are converging closer to the answers. With respect to devices such as the Triage® cardiac panel and i-Stat, despite their well-developed technology, proven functionality and aesthetically pleasing designs, their uptake as the benchmark device/technique of preference in their intended utility within a clinical capacity, has been limited. The reason for this are multi-fold, but primarily are attributed to cost constraints for a given hospital/clinic and issues relating to user training/clear route for information relay, which ultimately don't provide clinicians an added value which far exceeds current practices. This point is echoed in a recent commentary on microfluidic commercialization by Volpatti et al 2014, where they stress the importance to the community to strive forward with research into the pressing needs where microfluidics is not only the best, but the only solution for a given challenge [1]. Holger Becker in an article series for the journal Lab-on-a-chip, based around the theme of commercialization of microfluidics, very eloquently and insightfully addresses many of the key challenges and factors relating to the slow uptake of such technology [7-12]. This series provided valuable insights into the perception of the technology and how due to a complex interplay of the economy of scale in mass manufacturing, IP issues, lack of standardization, early inflated technological expectations that failed to materialize and several other crucial factors, the microfluidics industry has yet to flourish to its full potential. He also raises thought provoking debate as to whether there is such a thing as the 'killer application' in microfluidics, a comment mirrored in an earlier industry focus of microfluidics by Carsten Haber in 2006 [13]. In terms of commercialization of microfluidics the 'killer application' factor has likely played a major role in the reluctant uptake of the wealth of promising research based lab-on-a-chip technology, as investors are likely opting for alternative technologies with

higher profit margins and a more well defined route to market [1]. So what is the solution?

2. Unresolved challenges

Lab on a chip technology has reached a staggering level of maturity, with a multitude of ingenious devices and individual components allowing for a variety of complex chemical and biological assays to be performed in a single device, rapidly and with matching sensitivity to their traditional lab based counterparts. In the pursuit of engineering excellence in areas such as added device functionality, increased endpoint detection sensitivities and lower resolution manufacturing processes from the micro to the nanoscale, many academic researchers are found guilty of leaving the challenge of technology transfer into a commercially viable product as an afterthought over being a critical consideration of the overall engineering process chain. It is therefore believed that researchers in the lab-on-a-chip community need to focus less on further demonstrations of advanced functionality, but more on the challenge of integration, standardization, economy of scale for mass market appeal and, perhaps more importantly, the added value to the application the device is aimed towards.

2.1 Systems integration

The untold reality of many lab-on-a-chip devices are that such devices require the use of ancillary equipment such as fluidic pumps, high current power supplies, signal acquisition devices (microscopes, spectrometers, etc), with which to operate. Most of these devices are significantly larger than the lab-on-a-chip systems themselves, typically taking up a significant volume of space on a laboratory bench, negating many of benefits related to device miniaturization. This has led to the commonly heard pun and inspiration for the title of the article 'it's not a lab-on-a-chip but a chip-in-a-lab'. If we consider the implementation of such systems into practical, usable areas, such as the point of care or even within specialist laboratories, such instrumentation would generally require the use of a skilled user. This introduces complications pertaining to user training and standardization protocols for use, a lack of portability, and the hiring of a skilled technician for operation and device maintenance, all of which hinder the uptake of the technology in the mainstream. Over the last two decades, individual lab-on-a-chip components have been comprehensively demonstrated and so to some degree it is considered trivial combining these into a singular, integrated device, be it on occasion at the expense of portability, usability, simplicity of manufacturing or cost. What must be recognized is that for commercial applications, technologies that do not readily allow a device to overcome the 'chip in a lab' bottleneck must sadly be disregarded over what may be more simplistic but crucially more practical technology with usability and seamless integration of components as its core attributes. With respect to fluidic processing, the difficulty can generally lie in the so called 'chip-to-world' interface by which the sample is introduced, the fluidic handling system and the actuation method to deliver and control fluids within a chip. For the vast majority of cases fluids are introduced though the use of a micro port and tubing, where flow is achieved through a mechanical pumping mechanism (e.g syringe pumps). Researchers have realized the use of on-chip pumps and valves for flow control, however, the issue of the chip to world interface still remains, in addition to the added fabrication complexity which may not readily translate to mass manufacturing. Commentators on the commercialization of microfluidics have been discussing the importance of world-to-chip interface for nearly a decade now [13] and only more recently are we seeing this issue being addressed. With respect to greater commercialization potential and as with the issue of the chip-in-a-lab conundrum, the chip-to-world interface must be addressed from the initial design phase with the aim of making the device as 'user friendly' as possible. Looking again at commercially successful examples this is readily demonstrated in the case of inkjet cartridges being simple plug and play systems and in the home pregnancy test kit which simply requires the loading of a sample onto the lateral flow membrane. Another less exploited area of integration, is to tailor devices to operate within existing systems where fluidic sample handling is already taking place, such as within livestock milking stations and chemical processing plants. In these examples there is an integrated infrastructure for fluid handling that could suit the addition of modular based components that could be integrated into the existing supply lines within the process chain. It is speculated that such instrumentation may depart from the traditional notion of 'chip' based devices but share all the same technology of current counterparts. Advantageously, such devices would likely complement existing technology in the target market, requiring the minimal of technology investment and alteration of existing practices, thus potentially allowing a greater level of

market acceptance and uptake. Finally a more interesting area of integration which is becoming more prevalent in the research community is the synergistic use of current ubiquitous technologies with their own innovations, such as replacing the use of a bespoke photodetector and data analysis system with the use of a camera and the computation ability of a mobile phone [14]. The elegance of this methodology is that not only is the overall design simplified and the cost reduced through reduction of the components required, but consideration is made to simplify the user interface (generally an intuitive app) and the management of data (processing and transmission through the phones connectivity). Such innovations may potentially increase the accessibility of lab-on-a-chip devices into the mainstream through complimentary use of ubiquitous devices, which added to the reduction in componentry for the overall device, enhances the commercial potential and market acceptance. It is anticipated that such dual use functionality and interconnectivity of devices will become more prevalent in the future for not only lab-on-a-chip, but most consumer devices, and should be a consideration academics should take note of.

2.2 Economies of Scale

Researchers generally aim to prove a hypothesis and do so in a single minded manner without worrying about issues such as economies of scale, with the field of lab-on-a-chip being no exception. Many innovations can be guilty of high degrees of complexity in the fabrication of individual components, and the complete device may require several highly specialized and labor intensive manufacturing techniques. Fabricating such devices generally draws more on the skill and experience of an individual user, across several interactive process, rather than being something which can be streamlined into a single manufacturing process. Examples of such high complexity systems are those which comprise components such as micro actuation systems (valves, pumps, etc) and fluid storage reservoirs coupled with microfluidics, while the device can also require complex surface modifications (e.g bonding, bio-fouling coatings, etc) and the binding of organic biorecognition elements on a single chip. Many traditional fabrication methods used to create micro and nano scale structures, such as lithographical techniques, do not translate well into large scale production. Additionally, backend processes (assembly, bonding, surface modifications, etc) and quality control at large scales volumes can contribute up to 80% of total production costs [8]. Therefore high complexity research based methodologies are generally at odds with what production and manufacturing personnel would see as satisfactory, where it is more desirable to reduce complexity to the bare minimum. It is therefore envisaged that for a system with a perceived commercial application, researchers from the design phase should opt for fabrication techniques that are readily up-scaleable, using designs which minimize the complexity and process stages required for backend processing. In addition to the design and fabrication, the choice of materials becomes crucial, particularly with respect to the cost and the desirable intrinsic material properties for the application in question. Currently the predominant material used by research groups for the fabrication of microfluidic systems in the poly (dimethylsiloxane) (PDMS) [15] despite the wealth of alternative fabrication materials, such as polymers, paper, silicon, etc. Processes using PDMS have been significantly refined since their original introduction to the lab on a chip community, with a wealth of demonstrated fabrication techniques and generic components found in the literature. However, PDMS is limited in its commercial application owing to the difficulty in up scaling of mass manufacturing and the relatively high cost compared to alternatives such as polymers. More critically, the intrinsic material properties of native PDMS can lead to affects such as evaporation, leeching and absorption of a flowed liquid sample [14] which perhaps makes it unsuitable for repeatable, robust microfluidic biological and chemical analysis applications. These limitations can be overcome through post processing of the material, but adds an additional backend processing stage and therefore makes it more undesirable for commercial manufacturing. This therefore begs the question to the research community over its continued prevalence in microfluidic applications and research efforts must either focus on the up-scaled manufacturing of PDMS or shift to a more intensive evaluation of alternative fabrication materials of choice for lab-on-a-chip application, such as low-cost polymers.

2.3 Standardization

The issue of standardization overlaps with several of the previous point surrounding the issue of fabrication, device functionality and materials using the manufacturing of a given lab-on-a-chip device. More specifically, there is no one standard/preferred material or fabrication technique both research and commercial efforts are geared towards.

Microfluidic solutions companies are found offering devices made from substrates such as glass, metals, polymers and elastomers, all of which require their own material specific fabrication techniques. This is in stark contrast to many successful large scale manufacturing processes, such as the microelectronics industry, where arguably silicon is the material of choice and fabrication techniques and backend processes have been refined and standardized to this substrate. There is a subtle irony in this example given that the initial techniques for lab-on-a-chip fabrication had been derived from the microelectronics processes. Whist the great diversity in material and fabrication selection allows for greater flexibility and innovation in terms of research endeavor, it greatly limits a standard material and technique reaching the mainstream for lab-on-a-chip manufacturing and is likely a contributing factor the slow commercial uptake of the technology. The other conflict of interest between academia and the commercial methodology is the tendency of academics to strive primarily to prove a given hypothesis, the so called proof-of-concept in a 'single-chip' experiment, before their attention is moved to the next hypothesis to prove [10]. This attitude has led to a failure of many investigations in the field failing to cite the reproducibility and chip-to-chip variability for a given material and fabrication method [1]. This tendency is at odds with production personnel who strive to achieve the greatest degree of batch-to-batch or chip-to-chip repeatability in terms of fabrication tolerances and performance, to give the end user the most standardized instrumentation possible. Indeed without this benchmark, many devices will be unsuccessful in the commercial arena, despite incorporating high levels of academic innovation, particularly in application of critical result endpoints such as in medical diagnostics. What is required is for academics to perhaps examine more closely the chip-to-chip variability and repeatability of use, to provide more statistically relevant results of not only their own work to support the ever increasingly popular claims of a devices potential for use in the real world, but to also aid manufacturers in determining the feasibility of producing a product using a particular design, fabrication technique or material.

2.4 The Added value

For a new lab-on-a-chip innovation to have high potential for commercialization and uptake as a routinely used instrumentation, the device must not only surpass the existing methodologies/devices in terms of performance, cost and usability, but in many instances must do so by at least one or two orders of magnitude in providing a solution of value to the end user. If the proposed device only offers more minor, incremental improvements for a particular applications, then the end users may be reluctant to uptake the technology over more tried and tested methods, where training and routes for data management are well defined. In many instances within the literature there appears to be a conflict of understanding between classical research based goals and the true added value a constructed device is providing within the context of the problem it is aimed at addressing. For example, the research community traditionally holds the ability to perform a test rapidly, or in the case of biosensors, with an increased sensitivity as the pinnacle benchmarks required to validate their systems superiority over existing methodologies. However, in some applications a device is aimed towards, there is no added value if a test was performed rapidly or not. For example in the case of genetic testing for disease there is no advantage to having the result within an hour as opposed to within several days as the outcome for the patient with ultimately be the same. Equally, the pursuit, of lower limits of detection (LLD) from a biosensor may be technologically impressive, but adds no value to a system if the target measurement range is generally significantly above that of the LLD. This conflict is further exemplified through some of the claims made by academics regarding the translational potential of lab-on-a-chip devices, where publications readily boast about the 'low-cost' and the 'portability' of their innovations in the context of a real world scenario, but there is a sense researchers don't fully appreciate the true associated costs or value should such devices be considered commercially. Generally, in such work, while demonstrating high levels of innovation either operate under the 'chip-in-a-lab' paradigm or the upscaling costs that include backend processes are not fully appreciated. Additionally, some devices may be guilty of engineering a capability which would not otherwise be required, for instance portable 'in-field' measuring of environmental samples may not provide any advantage over simply analysing a sample in the laboratory as time is not critical to the measurement outcome. For the greatest degree of commercial success and added value of the technology, researchers should ideally focus their efforts into technologies which are only possible given the use of lab-on-a-chip. In other applications researchers must have a greater awareness in the initial engineering phases to create a lab-on-a-chip solution that address a 'true' market need and which draws upon the technology's intrinsic advantages by which to provide a strategic advantage over existing methods. For instance,

medical scenarios where time has a critical impact on a patients wellbeing (cardiac biomarker detection) would benefit from a lab-on-a-chip platform to provide a result rapidly and in a portable manner, whereas the same would not be true for genetic testing of disease.

3. Conclusion

It is now increasingly obvious that research into lab-on-a-chip technology has reached a critical mass, where the abundant demonstrations of innovations need to move into the next phase of development into usable consumer products. This challenge will require a shift in the mind-set of researchers in the field to engage more with their industrial counterparts to realize a greater appreciation for the delicate balance of functionality, cost, sensitivity and device complexity with how this will translate to the economies of scale for mass manufacturing. This in itself is a non-trivial hurdle in the transferal of technology to the market. Ironically, it is believed that the reductionist approach may be required in stripping back lab-on-a-chip technology to its bare essentials for not only ease of manufacturing, but reducing chip-to-chip variations by minimizing the number of variables that negatively impact the efficacy of the final device. This approach is perhaps at odds with modern advancements in the field where researchers strive to demonstrate innovative functionalities at the trade-off of increased complexity, and ultimately, a reduced capacity for mass manufacturing. It is debatable whether there is such a thing as a single 'killer application' in lab-on-a-chip/microfluidic technology but it seems abundantly apparent that through careful consideration by researchers to the challenges involved in commercialization, an appreciation of the end-user needs and the added value the technology provides for a particular application, such technology is likely to find greater prevalence and market penetration in the near future.

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