"Lab-on-a-Chip Foundry Service": A Systematic Approach to the Development of Centrifugal Microfluidic Technologies

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Abstract:
This contribution provides a novel approach to a time and cost-efficient development of polymeric lab-on-a-chip applications. Rather than starting from scratch, new designs are derived from a library of validated laboratory unit operations (LUOs) and prototyped by standard operating procedures (SOPs). LUOs as well as SOPs are systematically documented and retrieved from a "BlueBook".
The essential ingredients for the development of lab-on-a-chip applications are liquid handling technologies and fabrication technologies as well as test and development tools. This paper outlines a streamlined approach based on a microfluidic platform concept to reduce the cost, time and risks for the development of lab-on-a-chip technologies. As an example illustrating the platform concept, we describe our centrifugal microfluidic "Lab-on-a-Disk" platform.
The paradigm of the platform concept is to establish a library of LUOs such as metering, mixing and routing which are validated by experiments and accompanying simulations for a certain parameter range. The concatenation of these LUOs allows to realize complex applications. The layout is then transferred into hardware according to SOPs and afterwards measured at a designated test and development stand. Design rules for the LUOs, procedures (SOPs) and other relevant information such as materials or device components are documented and retrieved from a wiki-based software-based knowledge management portal called "BlueBook".

Keywords: Lab-on-a-Chip Foundry Service, centrifugal microfluidic platform, standard operating procedures, laboratory unit operations, knowledge management system

Introduction

Currently, the field of microfluidic lab-on-a-chip devices can be characterized by a great variety of components and fabrication schemes [1,2]. This includes a wide range of components such as pumps, valves, mixers, and heaters as well as many concepts for liquid handling, e.g. pressure driven, peristaltic, electroosmotic and centrifugal systems as well as concepts such as surface acoustic waves and electrowetting. Furthermore, many different materials are in use, among them glass, silicon, ceramics and plastics. Due to this large diversity, collaborations and supply chains of different companies forming new products by just combining off-the-shelf products are still out of reach. This lack of standards and defined interfaces is at least one bottleneck for the commercial proliferation of microfluidic technologies. FlowMap [1], a market study, was carried out to identify benefits and bottlenecks of microfluidic applications for the life sciences. While microfluidics offers unique selling points such as high-level system integration, automation, miniaturization, and parallelization, it turned out that several bottlenecks impede the anticipated commercial success story. High development risks due to high-level system integration and unacceptable risks caused by often starting from scratch again cause a long time-to-market. As the industry lacks standards and defined interfaces, there are no reliable commercial supply chains. Also the high costs for the purchase and operation of equipment and infrastructure as well as the fragmented patent situation and complex regulatory issues are not beneficial. To deal with most of these bottlenecks, standards and microfluidic technology platforms were requested by key players.

Lab-on-a-Chip Foundry Service

HSG-IMIT has recently launched a "Lab-on-a-Chip Foundry Service" which is slated to be fully operational in fall 2008. The central idea is to offer the development of a customer specific microfluidic device in less than a month and at reasonable costs by concatenating standardized and validated procedures in design, prototyping, testing, and fabrication. The service and its components will be described here in detail.
With a structured customer interface and ready-for-mass-production prototypes, the service comprises the complete prototyping chain.

After identification of the specific requirements of the customer, a first layout is generated by special design rules consisting of parameterized and validated laboratory unit operations (LUOs), such as mixing, metering or routing. A customized assay is laid out by concatenating these LUOs and prototyped using validated standard operating procedures (SOPs) in selected materials.
Standardized components and their systematic integration also support short development cycles. The whole prototyping is supported by several development tools. Software for use in layout with a library of LUOs and SOPs helps to shorten the number of design iterations. Simulation software assists to find ideal parameters for new LUOs. A designated test and development stand enables device and system tests.
The business infrastructure features selected suppliers and service providers able to adapt to our standards and to collaborate in their further enhancement. Several unit operations are covered by own IPR.
Microfluidic platforms are established by more and more companies and institutes [2]. For example, IMM and thinXXS each operate a pressure driven platform while Advalytix uses surface acoustic waves for liquid handling. HSG-IMIT's full Lab-on-a-Chip Foundry Service including the parameterized fluidic design rules is based on its centrifugal microfluidic platform. However, the polymer prototyping itself can, of course, also be provided for other liquid handling concepts.

Development Cycle

To build a microfluidic, customer specific assay within our Lab-on-a-Chip Foundry Service, we gather information from the customer via a standardized protocol exhibiting a general questionnaire and a detailed description of the system to be designed. This information is used to plan a raw design. It is then refined by concatenation of LUOs (i.e. mixing, metering or routing) to form a complete biochemical assay (see Fig. 1). To build a prototype out of the resulting layout, we resort to the SOPs (such as sealing, surface modification or mastering technologies), which are referenced in the LUOs. After the prototype is ready, it is tested at our stroboscopic test and development stand. When functional tests reveal insufficient quality, feedback is given to design a modified layout or to change production methods. The number of iterations is lowered due to the parameterized and validated character of our LUOs and SOPs, shortening future development times to less than one month. When all tests are passed, the prototype is ready for mass production.

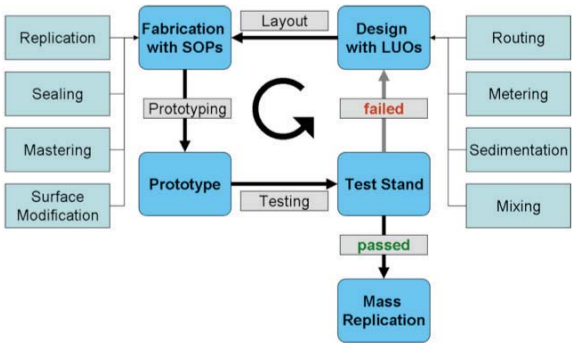

Fig. 1: *Development Cycle*

Knowledge Management System

Obviously, the gathering, use and management of knowledge are crucial for success. If no knowledge management system is established, information about proper prototyping of microfluidic devices is only available from journal publications, PhD theses, and patents, or as knowledge stored in the head of employees. This implicit knowledge is often neither easily accessible nor suitable to provide a detailed ready-to-work description, thus resulting in often starting from scratch.
A knowledge management system stores all kinds of data and consists of two parts. The first one is a database which contains all information. To ensure the completeness of datasets, we use templates to generate new entries (in the form of "articles"), comprising structured headlines which have to be filled with appropriate information by the editor. Our hierarchical structure and a searchable full text index allow immediate access to the desired article via a web browser.
The other major part of a knowledge management system is the data management, ensuring contextual sense, quality and timeliness of an article. To guarantee a proper quality of our article, a revision by an internal expert is required. The editor sends a new article or changes on an existing article to be checked for sense and quality standards to him. Either the article is rejected with recommended changes or it is accepted and thus given clearance for use in the development cycle. In addition, we have established a proper version management for articles, templates and the revision process itself.
Currently, we use a MediaWiki to store all our SOPs and LUOs. This knowledge management system is internally referred to as "BlueBook". MediaWiki is well known as the backend of Wikipedia. In MediaWiki, content is separated from layout; it can easily be filled by everyone using templates and Wiki text instead of by far more complicated HTML

source code. In addition, MediaWiki enables cross linking of articles, e.g. of SOPs with LUOs. This reduces the amount of data in an article by simply referencing other articles instead of repeated typing.

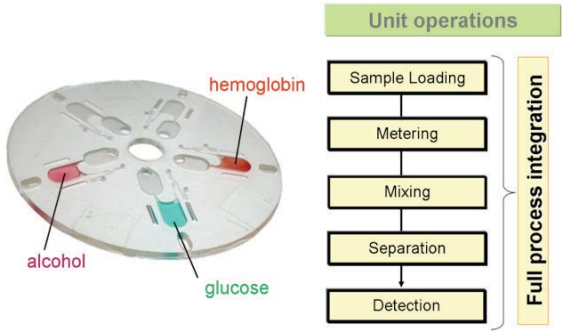

Fig. 2: *Assay on a centrifugal microfluidic "Bio-Disk" and associated LUOs*

Example Bio-Disk

HSG-IMIT's microfluidic centrifugal platform is demonstrated by our Bio-Disk technology [3,6]. It monolithically integrates an entire lab on a single disk. The Bio-Disk (see Fig. 2) is an IVD device that consists of a disposable disk exhibiting all the LUOs for liquid handling and of a base instrument, holding a motor, a liquid dispenser, and a laser-based detection system. These components are controlled by an integrated Linux PC with a touch screen at the front of the device.
To analyse blood parameters, e.g. concentrations of glucose, alcohol or haemoglobin in whole blood, the LUOs sample loading, metering, mixing, separation and detection are concatenated. Each reaction channel features reagents specific to the particular assay (see Fig.2). The process flow is controlled by a designated frequency protocol of the spinning drive. Direction, speed and acceleration of rotation are key factors to control the opening of valves, the intensity of mixing, and the process of sedimentation.

Fabrication Chain

Our disks are fabricated according to standard operating procedures (SOPs). These procedures are developed and applied at HSG-IMIT and at IMTEK of the University of Freiburg. Currently HSG-IMIT's Lab-on-a-Chip Foundry Service is mainly focussed on its centrifugal microfluidic platform based on polymer substrates [4]. Thus, the typical production chain (see Fig. 3) starts with a customer specific layout from the design team. Prototypes are milled out of a CD shaped polymer substrate. For production of more than a few disks, soft embossing and injection moulding technologies are typically used. Therefore, masters are required, which are commonly precision milled out of plastic substrates and out of aluminium blocks, and then possibly cast into an elastomeric stamper. These masters then allow rapid and cheap replication in mass production. Subsequently, surface modification technologies, such as mask based spray coating, plasma treatment, and dip coating, are used to change the wetting and adsorption behavior. Stationary phases can be integrated by filters or aggregated particles. If onboard reagent storage is required, dry or lyophilized reagents can be placed on the disk, while liquids are currently stored in the base instrument.
After that, the disk is sealed with a foil using thermal diffusion bonding or self adhesive bonding. To separate objects, contour writing (e.g. laser cutting) is used.

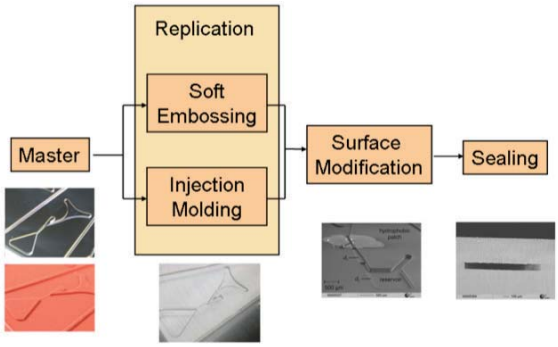

Fig. 3: *Fabrication Chain*

Designated Test and Development Stand

Functional tests are conducted on a stroboscopic test stand comprising a microscope with an interconnected camera and stroboscopic light source. When the rotating disk and the stroboscopic light source are synchronized in frequency and phase, the flash lightens up the area on the disk to be investigated. The camera takes high resolution images each time the observed segment enters the microscope's focus. These images can be combined to a movie to examine time-dependent behaviour [5].
The development is supported by simulation tools such as computational fluid dynamics (CFD). These tools help to verify theoretical models and to quickly arrive at optimal layout parameters. Such tools are especially used in the development of new LUOs.

Summary and Conclusion

We have presented our systematic approach to the development of microfluidic technologies in our Lab-on-a-Chip Foundry Service. We demonstrated the principle on our centrifugal microfluidic

platform. The presented approach provides many advantages. The customer specifies its demands for his new microfluidic device via a structured template that ensures the transfer of all relevant information. This saves time which would otherwise be lost in additional communication and delayed development. Validated LUOs, which are used to design a layout, reduce the development time by concatenating well established and validated microfluidic unit operations instead of starting the design each time from scratch. As each LUO also displays validated information (SOPs) about its own fabrication, these SOPs also reduce development time for production methods.
Both LUOs and SOPs are collected and managed in a knowledge management system. This ensures the conservation, quality, and timeliness of knowledge. Further, the completeness and contextual sense of datasets is guaranteed by templates and by the mandatory revision of experts. We anticipate that, on the long run, time savings in design and prototyping will overweigh the time and costs to establish and manage such a system.
Our test and development stand is designated to observe microfluidic behaviour. It helps to observe the movement of liquids in real-time and at high resolution. This allows detecting possible problems by simple observation even in rotating systems. The alternative would be to acquire and interpret functional results and draw conclusions about microfluidic malfunctions. Simulation tools support the verification of microfluidic models. Both the test stand and the simulation tools reduce time for device and system tests thus revealing malfunctions or otherwise guaranteeing match of quality standards.
Thus this approach saves time, costs and risks in development of prototypes and fabrication methods in the field of lab-on-a-chip systems.

Future Prospects

The future tasks comprise the successful launch of the full Lab-on-a-Chip Foundry Service and the expansion of available LUOs and SOPs well as their validation and parameterization. Long term goals are the use of layout data files in simulation, a virtual assembly, system level consistency checks, and an automated generation of fabrication protocols.

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