TOWARDS DESIGN AUTOMATION FOR MICROFLUIDIC DEVICES

G. Fink[1], *M. Hamidović*[2], *W. Haselmayr*[2] and *R. Wille*[1]
[1] Johannes Kepler University, Institute for Integrated Circuits, Linz, Austria
[2] Johannes Kepler University, Institute for Communications Engineering and RF-Systems, Linz, Austria

ABSTRACT

Microfluidics is a prospective field which provides technological advances to the life sciences and is an enabling technology when it comes to, e.g., biological cell studies, high throughput drug development, and diagnostic screenings. However, the design process of microfluidic devices is still in its infancy and usually accomplished entirely by hand so far–frequently resulting in a "trial-and-error" scheme. In order to overcome this "trial-and-error" approach, we provide a selection of design automation tools as well as simulation methods in this work, which allow for deriving the design, for validating the functionality of the design, and for exploring alternative designs, without the need of an actual fabricated and costly prototype.

KEYWORDS

microfluidics, design automation, simulation

INTRODUCTION

Microfluidics deals with the control and manipulation of small amounts of fluids (in the order of few micro- to pico-liters) and provides technological advances to the life sciences. It is an enabling technology when it comes to, e.g., biological cell studies, high throughput drug development, and diagnostic screenings. Corresponding devices are called Lab-on-a-Chip (LoC), which minimize, integrate, automate, and parallelize typical laboratory operations such as mixing heating, incubation, etc. on a single chip. This has several advantages compared to conventional methods, since it requires significantly less reagent and sample volumes (e.g. relevant for restricted samples or costly reagents), facilitates shorter reaction times and, hence, higher throughput of numerous laboratory activities. This eventually provides affordable, accessible, sensitive, specific, easy-to-use, and robust healthcare for both developed and developing countries.

Despite these promises, the design and layout process of such microfluidic devices is still in its infancy and far away from the standards, which e.g. is taken for granted in the "traditional" chip/semiconductor industry. In fact, the current design process is usually accomplished entirely by hand so far, which is particularly critical, since the design process is a rather complex task where a huge number of physical parameters need to be considered, e.g., the dimensions of the channels, flow rates, the applied liquids, etc., which all depend and affect each other. As a result, designers often rely on their expert knowledge and derive the design based on manual calculations, simplifications, as well as assumptions. However, such a design process can be very error-prone and frequently results in a "trial-and-error" scheme, as sketched in Fig. 1. That is, a prototype of the current design gets fabricated and, then, physical experiments are conducted to test its functionality. If the prototype does not show the intended behavior (which frequently is the case, particularly in first iterations), the designer has to revise the design, repeat the production and test its functionality again. Even for simple microfluidic devices, this can lead to multiple iteration loops, yielding a time-consuming and rather costly design and production process. In order to overcome this "trial-and-error" approach, design automation tools as well as simulation methods (utilizing different abstraction levels to cope with complexity) can be employed (cf. Fig. 1). These tools and simulation methods allow for deriving the design, for validating the functionality of the design, and for exploring alternative designs, without the need of an actual fabricated and costly prototype. Furthermore, these tools can help to make microfluidics more accessible, in particularly for end-users, i.e., biologists, chemists, or medical experts, which usually have no expertise in designing mi-

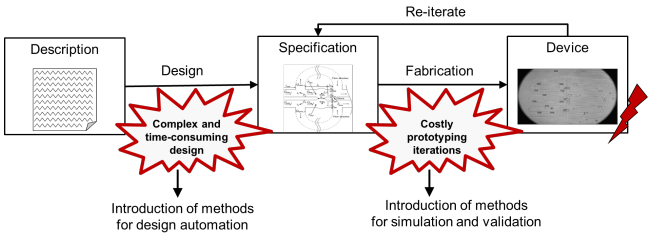

Figure 1: Thus far, microfluidic devices are often designed manually – a complex and time-consuming task. This frequently results in designs which, once fabricated, do not work as intended and, hence, have to be revised in re-iterations. Methods for design automation as well as simulation and validation can help here.

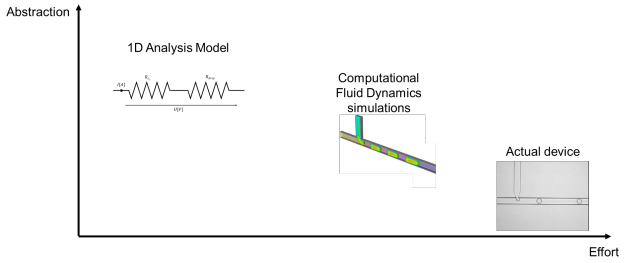

Figure 2: Design automation tasks can be conducted on different abstraction levels. If more physical details are needed, CFD simulations provide a good abstraction level, but also require more setup and computational efforts. In contrast, many design tasks can also be conducted on the more abstract 1D analysis model, which is easier to set up and fast to execute.

crofluidic devices. In this work, we provide a selection of corresponding design automation methods.

ABSTRACTION LEVELS

In order to develop corresponding design automation tools and simulation methods, a physical model which describes the behavior of microfluidics is needed. Here several physical models can be utilized, where each model can be seen as a different abstraction level (sketched in Fig. 2).

These levels can be categorized by their abstraction (plotted on the y-axis) and the respectively required effort/costs (plotted on the x-axis). Lower abstractions (e.g., CFD simulations [2]) consider more physical details and, hence, allow, e.g., more precise simulations. But they also result in higher costs with respect to setup and computation time. In contrast, higher abstractions (e.g., the one-dimensional (1D) analysis model [7]), need fewer requirements and, hence, can be applied early in the design process for deriving the specification of the design, for initially validating the functionality by using simulation, and also for design exploration.

SIMULATOR

One example of a corresponding method is the simulator proposed in [5], which utilizes the 1D analysis model and can be used to simulate droplet-based microfluidic devices. In such droplet-based devices, small amounts of fluids, so-called droplets, flow through closed micro-channels inside a second immiscible fluid which acts as a carrier for the droplets. These droplets usually contain biological or medical samples which can then be mixed, reacted, heated, incubated, etc. and found great applications, e.g., for DNA sequencing, cell analysis, organism analysis, and drug screening.

The simulator captures the behavior of a microfluidic network in five steps:

1. *Initialization:* In order to simulate a droplet-based microfluidic network, the designer has to initialize the simulation first. This means, the designer has to provide the following specifications:
   - Dimensions of all channels (i.e. their length, width, and height)
   - Structure of the network (i.e. how the channels/pumps are connected with each other)
   - Pressure or volumetric flow rate of the supply pumps
   - Properties of the continuous and dispersed phase (viscosity, density, interfacial-tension)
   - Droplet volumes and their injection times

   After passing these specifications to the simulator, the actual simulation process can start and the following steps are performed in a loop.
2. *Compute flow state:* The simulator converts the channels and droplets into their equivalent hydrodynamic resistances and derives a linear equation system that captures the physical behavior. This equation system is then used to determine the instantaneous flow state (i.e. pressure drops and flow rates in all channels) inside the microfluidic network. With the obtained flow rates, it is possible to determine the droplet velocities, which are required for the next step.
3. *Compute next event-time:* An event is basically an incident, which changes the current flow state of the microfluidic network and can be triggered by
   - injecting a droplet into the network,
   - a droplet flowing into another channel, or
   - a droplet leaving the network.

   Therefore, the simulator computes the time when the next event gets triggered, which is achieved by using the previously computed droplet velocities.
4. *Update system state:* The simulator updates the system state (i.e. droplet positions and their resistances in the channels) accordingly to the occurred events and droplet velocities.
5. *Termination condition:* If a termination condition is reached (e.g. all droplets left the network), the simulation stops, otherwise, the simulator continues with Step 2 and computes the flow state again. Because the simulator stores each system state at every time step, the paths of the droplets as well as the flow states of all time steps can be easily obtained.

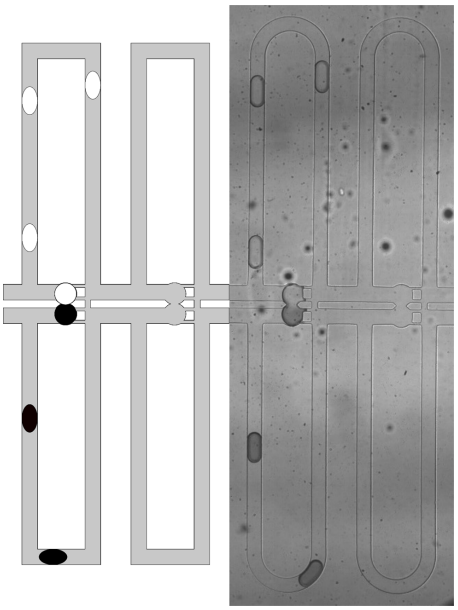

Figure 3: Comparison of the simulation output (left-hand side) to the actual physical realization (right-hand side) of the microfluidic device proposed in [1]. Even at this high abstraction (the 1D analysis model is employed), rather precise simulations can be conducted. The simulator is freely available at http://iic.jku.at/eda/research/microfluidics_simulation/.

Overall, after initializing the simulator, it always recalculates the flow state of the network, when the old one becomes invalid due to an occurrence of an event. A huge advantage of such an event-based simulation compared to CFD-Simulations tools like COMSOL Multiphysics, Ansys, or OpenFOAM (such as proposed in [2, 8]) is that the computational time is much lower and, therefore, allows to simulate even large microfluidic networks in negligible runtime.

With the help of this simulator, it was possible, e.g., to significantly improve the design of a device which is able to screen drug compounds that inhibit the tau-peptide aggregation [1] (cf. Fig. 3). The original design of this device took a whole month, required six different prototypes, and produced costs of about $1200. Using simulations (rather than a "trial-and-error" approach), these efforts could be reduced to a single day, one prototype, and costs of $200 only [3].

DESIGN AUTOMATION

When designing a microfluidic device, designers often have to conduct tasks entirely by hand–resulting in time consuming and labor-intensive processes. Design automation tools for microfluidic devices address this problem, by providing the designer with methods and means to automatically generate proper designs.

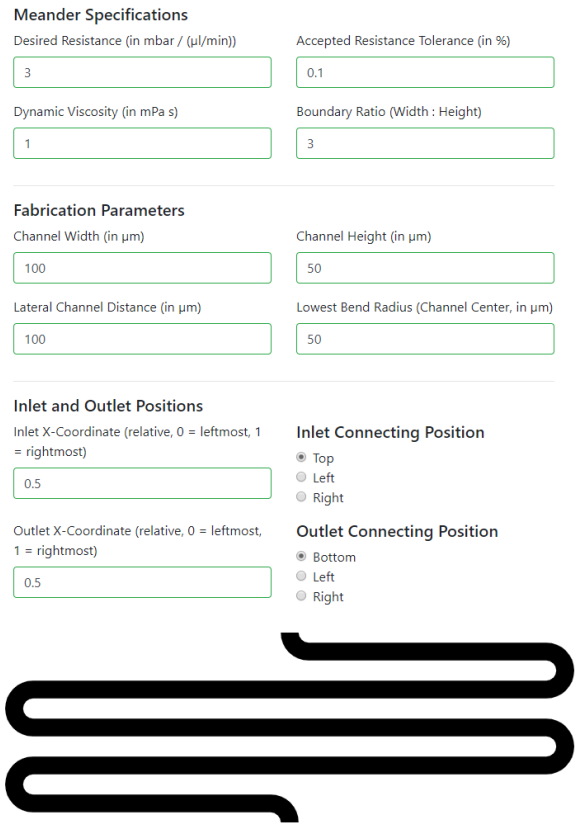

Figure 4: Once corresponding parameters such as the desired fluidic resistance, fabrication parameters, as well as the positions of the inlets and outlets are provided (see top part of the figure), a meander design satisfying these parameters is automatically generated (see bottom part of the figure). The tool is freely available at http://iic.jku.at/eda/research/meander_designer/.

Meander-Designer

Meander channels are a central microfluidic component which are often integrated in many different platforms such as pressure driven, droplet-based, and paper-based microfluidics. However, even for this frequently re-occurring component, designers still have to manually draw the meander channel for their respective application and design rules. The online-tool *Meander-Designer* (proposed in [4] and found under the link http://iic.jku.at/eda/research/meander_designer/) addresses this issue and automates this tedious task, while still retaining the full control over the design. More precisely, the designer only has to provide corresponding parameters such as the desired hydrodynamic resistance, fabrication parameters, as well as the positions of the inlets and outlets (cf. the input mask shown in Fig. 4). Based on that, a design satisfying these parameters is automatically generated, as shown in the bottom of Fig. 4.

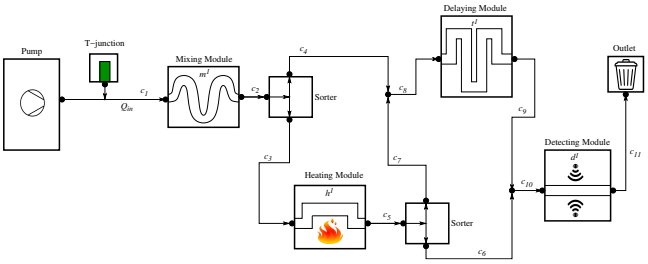

Figure 5: In order to design a droplet microfluidic network, all used components have to be properly chosen, such as the pumps, modules, sorters, and channels. Especially the dimensioning of the channels between the components constitutes a significant challenge. A corresponding method is proposed in [6].

Dimensioning of channels

In order to design a droplet microfluidic network as shown in Fig. 5, all used components have to be properly chosen, such as the pumps, modules, sorters, and channels. The specifications of all components and how they are connected determine the flow of droplets. Especially the specification of channels (i.e. their resistances) can be varied in a broad bandwidth and, by this, their dimensioning constitutes a significant challenge. In fact, improper specifications can cause

- the flow in channels/modules to be in the wrong direction or
- the time a droplet requires to pass a channel/module to be too long/short.

However, for dimensioning a microfluidic network, a huge number of constraints and dependencies have to be considered and already slightly changing e.g. the resistance of a single channel may change the behavior of the entire microfluidic system.

In the work proposed in [6], these problems are addressed by introducing automatic methods that aid designers in the specification of droplet microfluidic networks—especially in the dimensioning of channels. More precisely, methods are proposed which automatically allow to (1) validate whether a manually derived specification indeed works as intended, i.e. fulfills certain objectives as well as (2) conduct the dimensioning to obtain a proper specification.

CONCLUSIONS

This work provided a brief selection of automatic methods for important tasks in the design of microfluidic devices. We strongly believe those may provide the basis for comprehensive and elaborated design automation flows to be established in the near future.

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