Automatic Design of Microfluidic Devices
An Overview of Platforms and Corresponding Design Tasks
(Tutorial Summary)

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***Abstract*—This overview paper summarizes the content of a tutorial given at the 2018 edition of the Forum on specification & Design Languages. The aim of the tutorial was to introduce the technology of microfluidic devices, which gained significant interest in the recent past, as well as corresponding design challenges to a community focused on design automation and corresponding specification/design languages. By this, the overview presents a starting point for researchers and engineers interested in getting involved in this area.**

I. Introduction

Microfluidic devices provide a more convenient and cost-effective way to conduct biochemical, biological, or medical experiments [1], [2]. Instead of conducting tests manually in a fully equipped lab using expensive lab equipment and human resources, these devices allow to conduct biochemical and medical experiments on a small chip – yielding so-called *Labs-on-Chips* (LoCs). This requires much smaller sample/reagent volumes and leads to a significantly higher throughput. Examples in which microfluidic devices have successfully been applied include e.g. PCR [3], protein crystallization [4], sample preparation [5], nanoparticle synthesis [6], drug screening [7], or encapsulation [8], [9]).

However, designing the corresponding chips has become a considerably complex task. Depending on the respective platform thousands – or even tens of thousands – of entities and features have to be put together and/or dedicated physical characteristics (e.g. the flow of fluids or the resistance of channels) have to be considered. Despite these challenges, most of the microfluidic devices are still designed manually thus far. This frequently leads to designs that often do not perfectly work as desired after the first try, but require frequent (costly and time-consuming) iterations.

At the same time, several methods and solutions for design automation of microfluidic devices have been proposed in the past years. Although they are not that heavily used by the actual stakeholders yet, they provide a starting point for introducing and exploiting EDA methods in the microfluidic domain. However, in order to truly introduce design automation to the microfluidic community, the respective methods need to be much more focused on the actual needs of these stakeholders. Besides other issues, this also requires the resulting tools to be much more accessible and significantly simpler to use.

This requires experts from the design automation community to be familiar with the respective platforms as well as the corresponding design challenges. In this tutorial, we aim for providing an introduction to both issues. To this end, we provide an overview on different microfluidic platforms (including devices based on electrowetting and continuous flows as well as solutions based on a passive routing concept) and the corresponding design tasks. Afterwards, we sketch how to automatically address these design tasks. References are provided to equip the interested reader with comprehensive descriptions for a more in-depth treatment. Overall, this shall provide a starting point for researchers and engineers interested in getting involved in this area.

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II. Electrowetting-based Microfluidic Devices

The first platform considered in this tutorial relies on a discretization of the considered fluids into so-called *droplets* of picoliter or nanoliter size. This is accomplished by a technique called electrowetting [1], [10] and eventually yields microfluidic devices usually referred to as *Digital Microfluidic Biochips* (DMFBs).

A. The Platform

A DMFB is a two-dimensional electrical *grid* controlled by underlying electrodes and their electrical actuations. Using those, an electric field is generated which allows to "hold" discretized portions of fluids, the *droplets*, on a particular cell within the grid. By assigning time-varying voltage values to turn electrodes on and off, droplets can be moved around the grid. This technique, called *electrowetting-on-dielectric* [11], eventually provides a platform on which droplets derived from laboratory fluids such as blood, urine, or corresponding reagents can be exposed to several *operations* such as mixing, heating, or analyzing.

These operations are realized by so-called *modules* which may be physically built onto the chip or are virtually realized through electrowetting. More precisely, *physical modules* include:

- *Dispensers*: Fluids to be used in the experiment are kept in so-called *reservoirs*. Whenever required, a sample, i.e. a droplet of the corresponding fluids, is taken from this reservoir and placed onto the grid. For this purpose, *dispensers* for each fluid are physically added next to the outer cells of the grid. For each *type* of fluid considered in the experiment (e.g. blood, urine, reagents), a separate reservoir and, hence, a separate dispenser has to be provided.
- *Sinks*: If droplets are not needed anymore during the execution of an experiment, they shall be removed from the grid (e.g. in order to make room for other droplets and/or operations). For this purpose, similar to dispensers, sinks are added to the outer cells of the grid. Since sinks are used for waste disposal only, no differentiation between types is necessary.
- *Heaters*: Heating samples may be an integral part of an experiment. To provide this operation, heaters can be added to the chip. For this purpose, heating devices are placed below selective cells. Then, droplets occupying this cell can be heated if desired.
- *Detectors*: At the end of an experiment, the properties of the resulting droplet shall usually be examined. For this purpose, respective sensor devices are placed below selective cells. Then, droplets occupying this cell can be analyzed with respect to different characteristics such as color, volume, etc.

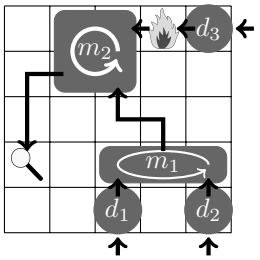
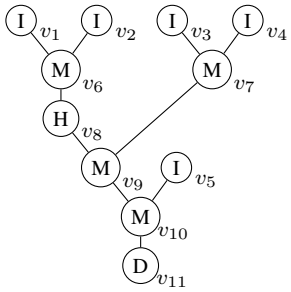


Fig. 1: An experiment conducted on a DMFB.



(a) Sequencing graph.

RESOURCE	AREA	TIME
Dispenser (I)	–	1
Mixer_1	2×3	7
Mixer_2	3×3	5
Heater	1×1	10
Detector	1×1	15

(b) Module library.

AREA	TIME
5×5	50

(c) Constraints.

Fig. 2: Specification of an experiment.

While physical modules always require corresponding devices built-in onto the chip, some of the operations can implicitly be realized by the movements of droplets (which in turn is realized through electrowetting as described above). In the following, these modules are called *virtual modules*. Examples include:

- *Mixers*: Mixing fluids (represented by droplets) is an integral part of almost every experiment. Using electrowetting, this can be realized by simply routing the respective droplets to be mixed to the same cell. In order to accelerate diffusion, the newly formed droplet is moved back and forth between several cells.
- *Splitters*: Droplets resulting from mixing operations have twice the size than the input droplets. To reduce them to normal size, they are split up. This can be realized by simultaneously activating cells of the grid that are on the opposite sides of the droplet. Then, the resulting forces split the droplet into two parts.

Overall, modules allow for the realization of various operations to be performed in laboratory experiments. Some of them are available in different fashions with respect to the number of occupied cells and the number of time steps required for their execution. A list of all available modules (including their implementations) is provided in a *module library*.

Example 1. *Fig. 1 illustrates the realization of an experiment on a 5×5-grid. In the first timestep, the droplets d_1, d_2, and d_3 are dispensed onto the chip. While the droplets d_1 and d_2 are mixed for 4 timesteps in mixer m_1, droplet d_3 is heated to its desired temperature for 3 timesteps. The heated droplet d_3 and the result of the mixing operation are then mixed for another 7 timesteps. The resulting droplet is eventually analyzed by the detector in timesteps 15-21. As can be seen, different fashions of modules are applied for the mixing operation. The first mixer required a 2×2-subgrid and 5 timesteps, while the second one occupied a 1×3-subgrid over 7 timesteps.*

B. The Design Process

To design DMFBs, several automatic synthesis methods have been proposed in the recent past. These methods require a specification of the experiment to be realized as well as the resources available for this purpose. More precisely, the following input is usually provided:

- A *sequencing graph* which specifies the experiment to be realized by the involved fluids (in terms of droplets) as well as the respective steps (in terms of operations) and their dependencies of execution,
- a *module library* providing the available modules which can be used in order to realize the respective operations given in the sequencing graph, and
- additional *constraints* e.g. on the size of the grid on which the experiment shall be conducted or the maximal duration of the experiment.

Example 2. *Fig. 2 provides a specification of an experiment to be realized on a DMFB. The sequencing graph in Fig. 2a defines the dispensing operations (v_1 to v_5) and their successors. The module library in Fig. 2b lists the modules available to realize those operations. Additionally, constraints as shown in Fig. 2c state that the entire experiment is to be conducted onto a 5×5-grid taking at most 50 timesteps.*

Having these inputs, the following design questions need to be addressed:

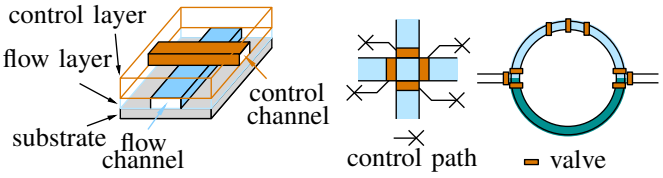
- Which modules shall be applied in order to realize an operation?
- When (at what timesteps) shall each operation be conducted?
- Where (on which cells or sub-grid) shall each operation be conducted?
- How shall the respective droplets be routed towards their destination?
- What pins/cells need to be actuated in order to realize the respective operations and routings onto the grid?

All these question eventually represent typical system design tasks such as *binding*, *scheduling* [12], [13], *placement* [14]–[17], and *routing* [18]–[22], respectively, for which dedicated DMFB-related solutions have been proposed as given in the references. In addition, the pin-actuation problem is addressed in works such as [23], [24]. Finally, initial approaches for a *one-pass design flow* have been introduced in [25], [26] – aiming for conducting all these tasks in a single and integrated process.

Recently, also extensions of DMFBs are considered in which droplets are not actuated by single electrodes but a sea-of-micro-electrodes – yielding so-called *micro-electrode-dot-array biochips* (MEDA biochips, see e.g. [27]–[29]). This additionally allows for a much greater flexibility e.g. through allowing droplets of rather arbitrary sizes, diagonal movements, etc. With the emerge of this extended platform, also correspondingly adjusted design methods have been proposed e.g. in [30]–[32].

III. FLOW-BASED MICROFLUIDIC DEVICES

The second platform covered by this tutorial is composed of microchannels and microvalves, which are respectively called channels and valves for simplicity. A channel is etched on a substrate to conduct fluid samples between devices. The movement of fluid samples is coordinated by valves, whose states are controlled by air pressure patterns [33]–[35]. Since fluid segments instead of droplets are manipulated on such a platform, it is thus referred to as *flow-based microfluidic biochips*.



(a) Valve structure. (b) Switch. (c) Mixer.

Fig. 3: Components in flow-based microfluidic devices.

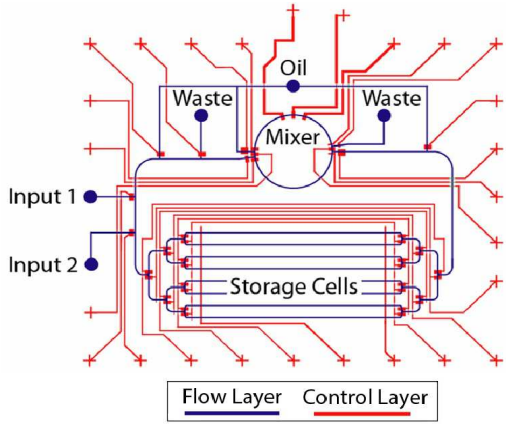


Fig. 4: Flow-based biochip w/ mixer and storage unit [37].

A. The Platform

A flow-based microfluidic biochip has a structure with two layers. Flow channels are itched on silicon/glass substrates or made from dimethylsiloxane using soft lithography [36] to transport fluid samples and reagents between devices. Above flow channels, control channels are used to deliver air pressure to the crossing points between flow channels and control channels. Both, flow and control channels, are made from elastic materials, so that air pressure in a control channel extends it and, thus, squeezes the flow channel underneath. Consequently, the movement of the fluid sample or reagent in the flow channel is blocked. After the pressure in the control channel is removed, fluid transportation in the flow channel can be resumed. Consequently, valves are constructed at these crossing points, as illustrated in Fig. 3a.

Valves are the basic flow control components in a flow-based microfluidic biochip. When multiple transportation channels intersect with each other, only one channel can be used simultaneously. To avoid fluid contamination, valves need to be built at the intersections of flow channels to direct the flow transportation, in fact forming switching as shown in Fig. 3b. At a given moment, only two of the four valves in the switch open to allow fluid to pass. This transportation control can be configured dynamically by changing the states of these valves with respect to the requirements of the application, so that complex biochemical assays can be executed by simple biochips with time multiplexing.

Using valves, more complex devices such as mixers can also be implemented. For example, in Fig. 3c, three valves are constructed along a circular channel at the top. If these valves are switched alternately with a pattern 101, 100, 110, 010, 011, 001, where 1 means the valve is open and 0 means the valve is closed, a flow along the circular channel can be generated – emulating the peristaltic effect for mixing fluid samples and reagents [36].

In a flow-based biochip, channels are used to transport fluid samples. If a fluid sample resides in a channel segment instead of being moved, this sample can be considered as stored inside this channel segment. This feature is very useful since it is easy to implement the storage function anywhere inside a flow-based biochip. When multiple channels are arranged side-by-side and multiplexing is implemented at the input and the output of these channels, a dedicated storage unit can also be implemented.

Example 3. *Fig. 4 shows a flow-based microfluidic biochip with a mixer at the top and a dedicated storage unit at the bottom. At a given moment, the valves at the input and the output of the storage unit only allow one fluid sample to be moved into or out of the storage unit – similar to memory blocks in electronic systems. The mixer can be used to mix fluid samples entering the chip from the two input ports. Intermediate results can be saved in the storage unit temporarily and fetched later for further processing. Through the oil port, a flow path can be constructed to push fluid samples between devices. The waste ports are used to discard fluid samples that are of no use anymore.*

Similar to DMFBs, further dedicated devices such as heaters, filters and detectors can also be constructed in a flow-based biochip to provide specific functions. As a result, a flow-based biochip can be considered as a channel network connecting dedicated devices. Unlike in DMFBs, all these devices are dedicated and operations must be executed by the corresponding devices at given locations. Intermediate result must be transported between these devices through the channel network to execute complex biochemical applications.

B. The Design Process

Designing flow-based microfluidic biochips is similar to designing DMFBs. A sequencing graph describing the experiment protocol as shown in Fig. 2a is used to define what operations need to be executed and how their results need to be transported. Furthermore, the devices available to a flow-based biochip can also be described as a module library, similar to Fig. 2b. The difference is that the areas of these devices do not matter so much as in DMFBs, because these devices are pre-built on the chip instead of being formed on the chip on-the-fly.

Since devices in flow-based biochips are fixed at given locations, the results from these devices should be moved between them through the channel network that connects the devices. This is the major difference between a flow-based biochip and a DMFBs, because the latter allows the locations of devices to be moved so that fluid transportation is more flexible. When multiple fluid samples are moved across a channel network in a flow-based biochip, fluid transportation needs to be arranged carefully to avoid conflicts. In addition, washing operations need to be performed to remove residue of fluid samples to avoid contamination. Consequently, designing a flow-based biochip is more transportation-centered compared to designing a DMFBs.

The major challenges of designing flow-based microfluidic biochips are listed as follows:

- When should a fluid transportation be conducted and when should it be stopped to avoid conflicts with other fluid samples?
- Where should storage units be implemented and how large should they be?
- When and how should flow channels and devices be washed?
- How should flow and control channels be developed together to reduce design complexity.

In the recent years, synthesis methods for flow-based microfluidic biochips have started to be introduced. For high-level synthesis, the work flows in [38], [39] minimize the execution time of bioassays and valve switching activities, respectively. In addition, a distributed storage system is proposed in [40], [41] to improve transportation efficiency. Moreover,

washing is implemented in [42], [43] to avoid contamination. For physical design, the placement of devices and routing of channels in flow-based biochips are dealt with simultaneously in [44] and formulated as a SAT problem in [45] to achieve a close-to-optimal result.

Control logic synthesis is investigated in [46] and the method in [47] minimizes pressure propagation delay to reduce the response time of valves. Switching patterns of valves are examined in [48], [49] to reduce the largest number of valve switching activities to improve the reliability of valves, and length-matching is incorporated in control channel routing in [50]. Flow-layer, control-layer and valve switching are considered together in [51], [52] to simplify overall design complexity.

Fault models and an ATPG-based test strategy for flow-based biochips are proposed in [53], [54] to deal with manufacturing defects. Design-for-testability and defect diagnosis are further addressed in [55]–[57].

To provide better reliability and flexibility, *Programmable Microfluidic Devices* (PMDs) [58] have been explored in [59], [60]. Channel crossing on a general array architecture is avoided in [61] and valve control sequences are arranged carefully for such a chip in [62]. Test generation is introduced in [63] to improve test efficiency.

IV. Passive Routing Concepts for Microfluidic Devices

Both platforms reviewed above rely on an *active* control method realized either by actuations of electrodes or dedicated valves – resulting in rather costly and error-prone solutions. As an alternative to that, another platform recently got investigated which entirely relies on a *passive routing concept*. This concept has been applied e.g. in *Networked Labs-on-Chips* [64] and *Hydrodynamic Controlled Microfluidic Networks* [65].

A. The Platform

Passive routing concepts can be realized on top of two-phase flow microfluidics, where the respectively considered droplets flow in an immiscible continuous flow inside closed channels. Pumps generating the continuous flow eventually distribute this flow among the network, which may consists of a set of modules executing unit operations. By this, the respectively injected droplets will be passed through a particular path of modules – executing operations such as mixing, splitting, delaying, incubating, detecting, or heating [66]–[70] and, hence, realizing the desired medical/biochemical experiment.

In order to explicitly route droplets along the desired paths (without using active controls based on electrodes or valves), so-called bifurcations and corresponding hydrodynamic forces are exploited. More precisely, a *bifurcation* as shown in Fig. 5 yields different volumetric flow rates in its successor channels which depend on the respective geometries of those channels. For example, the smaller the diameter and/or the longer the channel, the higher the resistance and viscosity of the continuous phase[1]. Because of that, a *single* droplet arriving at a bifurcation will always flow along the successor with the lower fluidic resistance (called the *default* successor) [71], [72]. However, since droplets themselves increase the resistance of a channel (e.g. through their viscosities, droplet size, and geometry as studied e.g. in [73]–[75]), they temporarily block the default successor for following droplets – allowing a following droplet to take a different path (as observed and/or simulated e.g. in [64], [65], [76]–[79]).

[1]Note that a *bypass* channel [71] connects the endpoints of the two successor channels. This bypass cannot be entered by any droplet and is used to make the droplet routing only dependent on the resistances of the successors (and not the entire network).

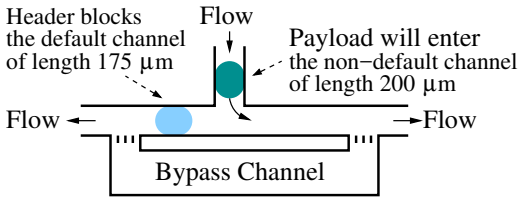


Fig. 5: Bifurcation.

These concepts of default successors at bifurcations and the possibility to block them with other droplets allow to realize arbitrary paths through a microfluidic network. More precisely, if the actually considered droplet (called *payload* droplet) is supposed to take a non-default successor at any bifurcation in the network, it has to make sure that another droplet (called *header* droplet) arrives before and blocks the default successor. This is accordingly sketched in Fig. 5, where the blue droplet (the header) blocks the path so that the green droplet (the payload) takes the intended path. Overall, this allows to *passively* route payloads through different paths and, hence, different sequences of modules can be executed without any additional hardware or control logic on the device.

Example 4. *Consider the network shown in Fig. 6. Here, a pump produces a continuous flow in which payload and header droplets are injected. Then, the droplets can take different paths and, by this, realize different experiments. For example, if just a single payload droplet is injected, only default paths are taken, i.e. the modules mixing, heating, and incubating are executed. If additionally a header is injected at a particular time so that the channel c_4 is blocked when the payload arrives at the second bifurcation, a path of the payload is realized in which the heating step is skipped.*

In order to avoid that operations of modules are executed on headers, the modules are shielded by a droplet by size sorter [80]. A sorter steers payloads towards the module and forwards headers. Therefore, the sorter uses the different droplet sizes (i.e. droplet volumes) of headers and payloads. Finally, the network contains bifurcations allowing droplets to take multiple paths and, by this, to realize different experiments on a payload. Whether a path is implemented by the default- or by the non-default successor channel, is also defined by the network.

B. The Design Process

Exploiting this routing concept requires a very dedicated and sensitive design as just small differences e.g. in some channel lengths may change the hydrodynamic forces within the network and, hence, change the behavior of the microfluidic device. Accordingly, the following steps shall be conducted in order to guarantee a correct design.

First, a proper architecture needs to be defined. This strongly depends on the given set of operations to be executed and their corresponding order. In order to allow for a cost-effective architecture, operations can be re-used for different experiments. For example, the experiments shown in Figs. 7a–7c can all be realized by an architecture sketched in Fig. 7d. A method automatically determining a suitable method has been proposed in [81].

The resulting architecture can directly been mapped to a structure as shown before in Fig. 6. However, it remains to be defined how to properly dimension the used channels. This constitutes a significant challenge since the dimensions of the channels significantly affect the flow of the droplets. In order to aid designers in this task, methods proposed in [82] allow for automatically determining and validating corresponding dimensions.

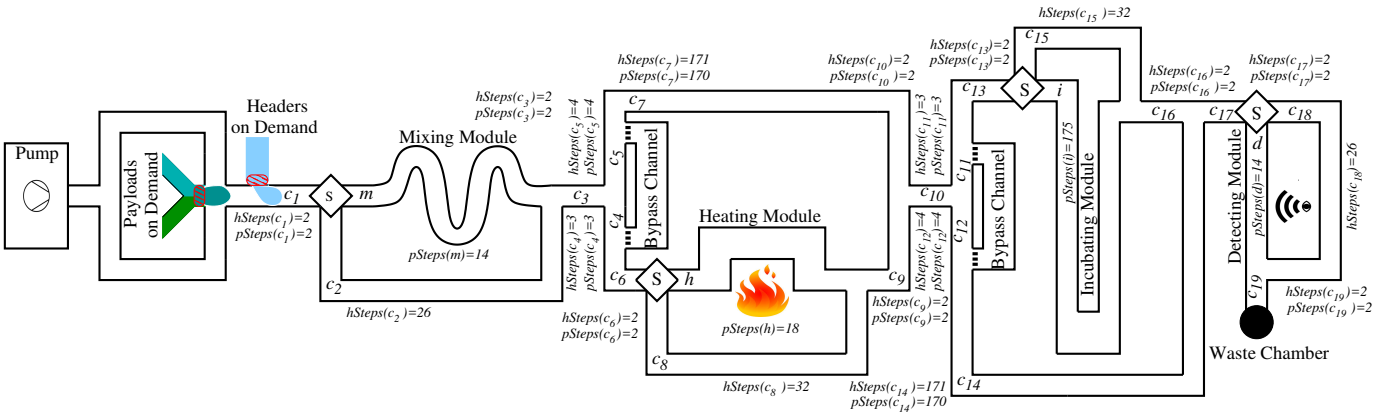
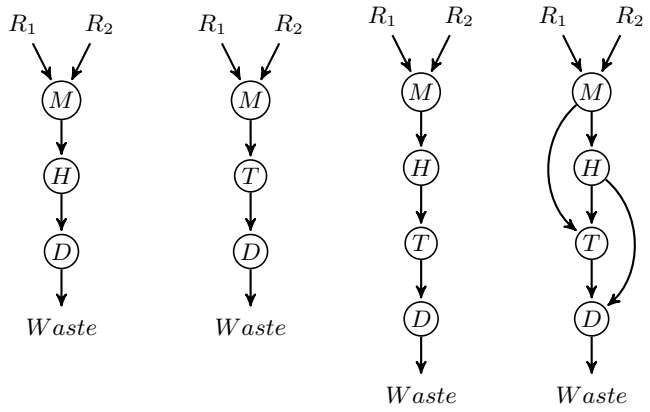


Fig. 6: Microfluidic network supporting passive droplet routing.



(a) Experiment 1. (b) Experiment 2. (c) Experiment 3. (d) Res. Arch.

Fig. 7: Given experiments and resulting architecture.

Then, payload and header droplets need to be injected into the network at dedicated times. This requires the determination of dedicated droplet injection sequences which make sure that the header droplets arrive in bifurcations at exactly the time when they are supposed to block a default channel. For ring networks as e.g. proposed in [65], [76], [77], [83], [84], the injection time of the header and payload droplets can be calculated by a formula. However, if dedicated architectures are employed as shown in Fig. 7d, more elaborated methods are required. To this end, a discrete model as proposed in [85] as well as corresponding automatic search methods as proposed in [86] can be utilized. This may even unveil that a corresponding droplet sequences cannot be determined for a given architecture and dimensioning which makes verification of the corresponding devices an important design step [86].

Finally, the resulting design as well as the determined droplet sequences shall be simulated prior to its fabrication. This allows to validate the correct execution of the design and pin-points designers to possible problems before physically realizing the obtained designs. To this end, initial methods for simulation are available e.g. in [87], [88].

V. Conclusions

This tutorial summary provided an overview on different microfluidic devices as well as corresponding challenges researchers and engineers have to tackle when designing them. This shall provide a starting point for researchers and engineers interested in getting involved in this area. For a more in-depth treatment of the respective issues, we are referring to the references provided below.

VI. Acknowledgments

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