System-Level Design Automation Tools for Digital Microfluidic Biochips*

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ABSTRACT
Biochips based on digital microfluidics offer a powerful platform for massively parallel biochemical analysis such as clinical diagnosis and DNA sequencing. Current full-custom design techniques for digital microfluidic biochips do not scale well for increasing levels of system integration. Analogous to classical VLSI synthesis, a top-down system-level design automation approach can shorten the biochip design cycle and reduce human effort. We present here an overview of a system-level design methodology that includes architectural synthesis and physical design. The proposed design automation approach is expected to relieve biochip users from the burden of manual optimization of bioassays, time-consuming hardware design, and costly testing and maintenance procedures.

Categories and Subject Descriptors
B.7.2 [**Integrated Circuits**]: Design Aids.

General Terms
Algorithms, Performance, Design, Reliability

Keywords: Synthesis, physical design, microfluidics, biochip

1. INTRODUCTION
Microfluidics-based biochips are rapidly emerging as a key enabling technology for biochemical analysis. These composite microsystems are also referred to as lab-on-a-chip or bio-MEMS interchangeably in the literature [1, 2, 3]. In contrast to conventional biochemical analyzers, they automate highly repetitive laboratory tasks by replacing cumbersome equipments with miniaturized and integrated systems, and they enable the handling of small amounts, e.g., micro- and nano-liters, of fluids. Thus they are able to provide ultra-sensitive detection at significantly lower costs per assay than traditional methods, and in a significantly smaller amount of laboratory space.

Recently a promising microfluidics technology has been proposed that manipulates liquids as discrete droplets [4]. Following the analogy of microelectronics, this novel approach is referred to as "digital microfluidics". In contrast to continuous-flow biochips, digital microfluidics-based biochips offer scalable system architecture based on a two-dimensional microfluidic array of identical basic cells. Moreover, because each droplet can be controlled independently, these "digital" systems also have dynamic reconfigurability, whereby groups of cells in a microfluidic array can be reconfigured to change their functionality during the concurrent execution of a set of bioassays. This property can be utilized to achieve longer system lifetime through on-line reconfiguration to avoid operational faults. It can also be used to increase yield through production-time reconfiguration to bypass manufacturing faults.

Over the next few years, digital microfluidic biochips are expected to pave the way for complex systems for massively parallel bioassays and chemical analysis. As a result, system integration and design complexity will emerge as major challenges. Consequently, current full-custom design techniques will not scale well for larger designs. There is a pressing need to deliver the same level of computer-aided design (CAD) support to the biochip designer that the semiconductor industry now takes for granted. Moreover, it is expected that these microfluidic biochips will be integrated with microelectronic components in next-generation system-on-chip (SOC) designs. The 2003 International Technology Roadmap for Semiconductors (ITRS) clearly identifies the integration of electrochemical and electro-biological techniques as one of the system-level design challenges that will be faced beyond 2009, when feature sizes shrink below 50 nm [5].

In this paper, we present an overview of a system-level design methodology that addresses key issues in the architectural and physical designs of digital microfluidic biochips. Analogous to classical VLSI synthesis, a top-down design automation approach can be used to relieve biochip users from the burden of manual optimization of assays and time-consuming hardware design. Users will be able to describe bioassays at a sufficiently high level of abstraction; synthesis tools will then map the behavioral description to a microfluidic biochip and generate an optimized schedule of bioassay operations, the binding of assay operations to resources, and a layout of the microfluidic biochip. Moreover, these system-level design automation tools can also be utilized to ensure high system dependability during the biochip operation. Once some cells are detected to be defective, dynamic reconfiguration techniques, incorporated in the design automation tools, will then be used to easily bypass faulty cells and remap bioassays operations to other fault-free resources. Thus the biochip user can concentrate on the development of the nano- and micro-scale bioassays, leaving implementation details to the design automation tools.

The organization of the remainder of the paper is as follows. Section 2 reviews microfluidic biochip technology. We focus here on digital microfluidic biochips based on electrowetting. Typical design methodologies of today are also reviewed and discussed. Next, Section 3 proposes a novel top-down system-level design

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methodology for digital microfluidic biochips. Challenges in the proposed design automation flow are also identified and analyzed. Finally, conclusions are drawn in Section 4.

2. DIGITAL MICROFLUIDICS

2.1. Microfluidic biochips

The basic idea of microfluidic biochips is to integrate all necessary functions for biochemical analysis onto one chip using microfluidics technology. These micro-total-analysis-systems (μTAS) are more versatile and complex than DNA microarrays, which are representative of early biochips. Integrated functions include microfluidic assay operations and detection, as well as sample pre-treatment and preparation.

So far there are two different generations of microfluidic biochips. The so-called *first generation* microfluidic biochips were based on continuous liquid flow through fabricated microchannels, and actuation of liquid flow is implemented either by external pressure sources, integrated mechanical micropumps, or by electrokinetic mechanisms (e.g., electro-osmosis) [2, 3, 6]. The continuous-flow systems are adequate for many well-defined and simple biochemical applications, but they are unsuitable for more complex tasks requiring a high degree of flexibility or complicated fluid manipulations [2, 3]. Permanently-etched microstructures lead to limited reconfigurability and poor fault tolerance capability. Therefore, the fabrication of complex yet reliable continuous-flow biochips remains a major technical challenge.

Alternatives to the above closed-channel continuous-flow systems include novel open structures, where the liquid is divided into discrete, independently controllable droplets, and these droplets can be manipulated to move on a substrate. Due to the inherent properties of dynamic reconfigurability and architectural scalability, this *second-generation* microfluidic paradigm can be used to implement programmable "microfluidic processors". A number of methods for manipulating microfluidic droplets have been proposed in the literature [7 – 15]. These techniques can be classified as chemical, thermal, acoustical and electrical methods, among which electrical actuation methods have received considerable attention in recent years.

Dielectrophoresis (DEP) and electrowetting-on-dielectric (EWOD) are the two most common electrical methods [4, 11 – 15]. DEP relies on the application of high-frequency AC voltages [12, 13], while EWOD is based on DC (or low-frequency AC) voltages [4]. Both these techniques take advantage of electrohydrodynamic forces, and they can provide high droplet speeds with relative simple geometries. Liquid DEP actuation, defined as the attraction of polarizable liquid masses into the regions of higher electric field intensity, relies on coplanar electrodes patterned on a substrate, coated with a thin dielectric layer, and energized with AC voltage (200-300 V-rms at 50-200 kHz). Rapid dispensing of large numbers of picoliter-volume droplets and a voltage-controlled array mixer have been demonstrated using DEP [12, 13]. However, excessive Joule heating may be a problem for DEP actuation, even though it can be reduced using materials of higher thermal conductivity or by reducing structure size [12, 14]. EWOD uses DC (or low-frequency AC) electric fields to directly control the interfacial energy between a solid and liquid phase. In contrast to DEP actuation, Joule heating is virtually eliminated in EWOD because the dielectric layer covering the electrodes blocks DC electric current [14]. The EWOD technique for digital microfluidic biochips forms the basis of the work reported in this paper; we describe it in more detail in the next section. Note that even though the system-level design automation methodology described herein is applied to EWOD-based biochips, it can easily be extended for DEP-based digital microfluidic biochips.

2.2. Structure of Digital Microfluidic biochips

Electrowetting-on-dielectric (EWOD) refers to the modulation of the interfacial tension between a conductive fluid and a solid electrode coated with a dielectric layer by applying an electric field between them. An imbalance of surface tension is created if an electric field is applied to only one side of the droplet; this interfacial tension gradient forces the droplet to move.

The basic cell of a EWOD-based digital microfluidic biochip consists of two parallel glass plates, as shown in Figure 1(a). The bottom plate contains a patterned array of individually controllable electrodes, and the top plate is coated with a continuous ground electrode. All electrodes are formed by indium tin oxide (ITO). A dielectric insulator, e.g., parylene C, coated with a hydrophobic film of Teflon AF, is added to the plates to decrease the wettability of the surface and to add capacitance between the droplet and the control electrode. The detailed fabrication process is described in [15]. The droplet containing biochemical samples and the filler medium, such as the silicone oil, are sandwiched between the plates; the droplets travel inside the filler medium. In order to move a droplet, a control voltage is applied to an electrode adjacent to the droplet and at the same time the electrode just under the droplet is deactivated. The EWOD effect causes an accumulation of charge in the droplet/insulator interface, resulting in an interfacial tension gradient across the gap between the adjacent electrodes, which consequently causes droplet transport. By varying the electrical potential along a linear array of electrodes, electrowetting can be used to move nanoliter volume liquid droplets along this line of electrodes. The velocity of the droplet can be controlled by adjusting the control voltage (0 ~ 90 V), and droplets can be moved at speeds of up to 20 cm/s [15]. Droplets can also be transported, in user-defined patterns and under clocked-voltage control, over a two-dimensional array of electrodes without the need for micropumps and microvalves.

Colorimetric enzyme-kinetic assays such as glucose and lactate assays have been recently demonstrated in lab experiments on a digital microfluidic biochip [16]. This biochip uses a microfluidic array, which moves and mixes droplets containing biochemical samples and reagents, and an integrated optical detection system consisting of a LED and a photodiode; see Figure 1 [16]. Furthermore, these assays can be integrated to form a set of multiplexed bioassays that are performed concurrently on a microfluidic platform. Figure 2 illustrates a fabricated microfluidic system used for multiplexed bioassays [16]. Note that to demonstrate multiplexed assays, only cells and electrodes used for the bioassay have been fabricated.

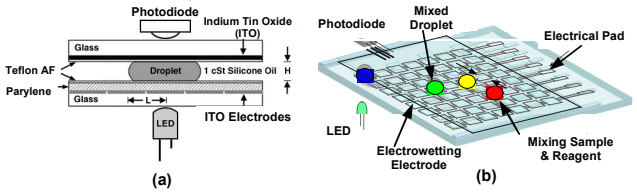

Figure 1: Schematic of a digital microfluidic biochip: (a) basic cell; (b) Top view of microfluidic array.

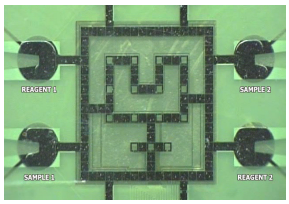

Figure 2: Mcrofluidic array used for multiplexed bioassays.

2.3. Typical Design Methodology

Current design methodologies for digital microfluidic biochips are typically full-custom and bottom-up in nature. Since much microfluidics work to date has been focused on device development, most design automation research for microfluidic biochips has been limited to device-level physical modeling of components [17, 18]. There are also some available commercial computational fluid dynamics (CFD) tools, such as CFD-ACE+ from CFD.

Once the devices are optimized using detailed physical simulation, they can be used to assemble a complete microfluidic biochip. Therefore, a bottom-up development approach is rather natural, which involves the development of each block from the device to system level. Microfluidic devices (e.g., electrodes and glass plates) are combined to form microfluidic modules (e.g., mixers or storage units), which are then combined to obtain the complete system (e.g., microfluidics-based glucose detectors). Since the system behavior can only be verified at this stage, costly and time-consuming redesign effort is required at the circuit level if the system does not satisfy design constraints.

Although these full-custom and bottom-up methodologies have been employed successfully in the past, they are clearly insufficient for the design of complex microfluidics biochips. As developments in microfluidics continue, it is likely that future digital microfluidic biochips will contain a large number of basic components. Thus, an efficient design methodology and system framework are required. While top-down system-level design tools are now commonplace in IC design, few such efforts have been reported for digital microfluidic biochips. A recent release of CoventorWare from Coventor, Inc. includes microfluidic behavioral models to allow top-down system-level design. However, this CAD tool is only able to deal with continuous flow systems, and it is therefore inadequate for the design of digital microfluidic biochips. In this paper, we outline a system design methodology that attempts to apply classical design automation techniques to the digital microfluidic biochip design, and thus speed up the design cycle and reduce human effort.

3. SYSTEM-LEVEL DESIGN METHODOLOGY

3.1. Proposed Top-Down Design Method

Motivated by the analogy between digital microfluidic biochips and digital integrated circuits, we aim to leverage advances in classical integrated circuit CAD techniques to address the design challenges associated with large-scale biochemical applications. The proposed system-level top-down design methodology is not only used to reduce biochip design complexity and time-to-market with the aid of design automation tools, but it can also be extended to enhance the yield and reliability of biochips in manufacturing and operational phases, respectively.

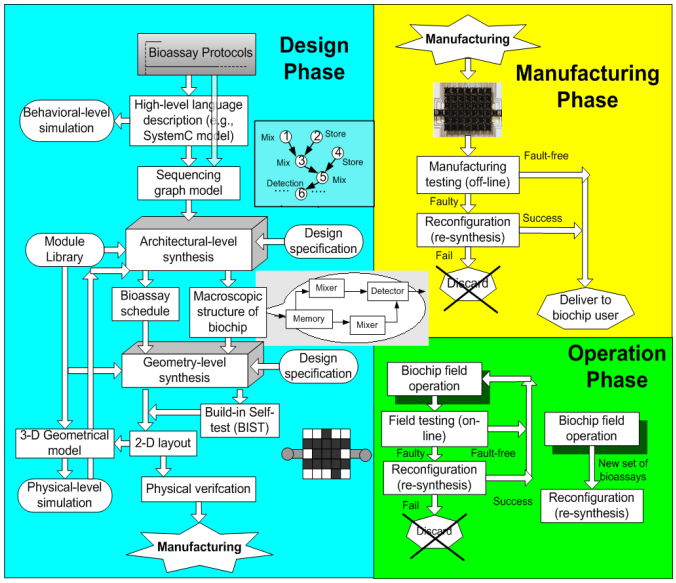

Figure 3: Overview of top-down design methodology.

The framework of this design methodology is illustrated in Figure 3. First biochip users, e.g., biochemists, provide the protocol for nano- and micro-scale bioassays. We anticipate that advances in micro-scale chemistry will lead to such well-defined protocols. A sequencing graph $G(V, E)$ can directly be applied to describe this assay protocol, where vertex set $V = \{v_i: i = 0, 1,\ldots, k\}$ in one-to-one correspondence with the set of assay operations and edge set $E = \{(v_i, v_j): i, j = 0, 1,\ldots, k\}$ represents dependencies between assay operations. We can also use a high-level description language such as SystemC to model the protocol, and then derive a sequencing graph model from it. Moreover, this model can be used to perform behavioral-level simulation to verify the assay functionality at the high level [1].

Next, a synthesis tool is applied to generate detailed implementations of digital microfluidic biochips from the sequencing graph model [19]. A microfluidic module library is also provided as an input of the synthesis procedure. This module library, analogous to a standard/ custom cell library used in cell-based VLSI design, includes different microfluidic functional modules, such as mixers and storage units. Each module is characterized by its function (mixing, storing, detection, etc.) and parameters such as width, length and operation duration. The microfluidic modules can be characterized through experiments, and their parameters can be stored for use by CAD tools that support large-scale biochip design. In addition, some design specifications are also given *a priori*, e.g., an upper limit on the completion time, an upper limit on the size of microfluidic array, and the set of non-reconfigurable resources such as on-chip reservoirs/ dispensing ports and integrated optical detectors.

The proposed synthesis tool performs both architectural-level synthesis (e.g., scheduling and resource binding) and geometry-level synthesis (e.g., module placement and routing) [19, 20]. The output of the synthesis tools includes the mapping of assay operation to on-chip resources, a schedule for the assay operations, and a 2-D biochip physical design (e.g., the placement of the modules). The synthesis procedure attempts to find a desirable design point that satisfies the input specifications and also optimizes some figures of merit, such as performance and area; its details will be discussed later. Moreover, since digital microfluidic biochips need to be tested adequately not only after

fabrication, but also continuously during in-field operation, self-testing has played an important role in the enhancement of biochip yield and reliability. Thus design-for-test (DFT) is also incorporated in the proposed synthesis procedure, whereby a test plan and a set of test hardware (e.g., test droplet sources/sinks and capacitive detection circuits) associated with the synthesized assay operation and biochip physical design are generated [21, 22]. After synthesis, the 2-D physical design of biochip (i.e., module placement and routing) can be coupled with detailed physical information from a module library (associated with some fabrication technology) to obtain a 3-D geometrical model. This model can be used to perform physical-level simulation and design verification at the low level. After physical verification, a digital microfluidic biochip design can be sent for manufacturing.

Digital microfluidic biochips are fabricated using standard microfabrication techniques. Due to the underlying mixed technology and multiple energy domains, they exhibit unique failure mechanisms and defects. A manufactured microfluidic array may contain several defective components. We have observed defects such as dielectric breakdown, shorts between adjacent electrodes, and electrode degradation [22]. Reconfiguration techniques can be used to bypass faulty components to tolerate manufacturing defects. Bioassay operations bound to these faulty resources in the original design need to be remapped to other fault-free resources. Due to the strict resource constraints in the fabricated biochip, alterations in the resource binding operation, schedule and physical design must be carried out carefully. Our proposed system-level synthesis tool can be easily modified to deal with the reconfiguration issue to support defect tolerance. Using the enhanced synthesis tool, a set of bioassays can be easily mapped to a biochip with a few defective cells. Thus we do not need to discard the defective biochip, thereby leading to a higher yield of biochips.

As digital microfluidics-based biochips are widely deployed in safety-critical applications, the field testing is also required to ensure the high reliability of biochips. Once the testing procedure determines the faulty status of biochips, the operation of the normal bioassay is stopped. Then the reconfiguration techniques are applied to tolerate the operational faults through redesigning the biochip with the aid of proposed system-level design automation tools. In addition, the similar reconfiguration and design automation techniques can also be applied to remap a new set of bioassays to a fabricated microfluidic biochip, thereby increasing the biochip utilization and reducing the manufacturing cost.

Compared to the full custom and bottom-up design methods, this top-down system-level design methodology not only reduces the design cycle time and time-consuming redesign efforts, but it can also deal with design-for-test (DFT) and design-for-reliability (DFR) issues efficiently.

3.2. Synthesis Techniques

Synthesis research for digital microfluidic biochips can benefit from classical CAD techniques, which is a well-studied problem and advances in synthesis techniques for integrated circuits continue even today.

As stated before, we envisage that the synthesis of a digital microfluidic biochip can be divided into two major phases, referred to as architectural-level synthesis (i.e., high-level synthesis) and geometry-level synthesis (i.e., physical design) [19, 20]. Architectural-level synthesis is used to generate a macroscopic structure of the biochip from the behavioral model of assay protocols; this structure is analogous to a structural RTL model in electronic CAD. The biochip macroscopic model provides an assignment of assay functions to biochip resources, as well as a mapping of assay functions to time-steps, based in part on the dependencies between them. On the other hand, geometry-level synthesis creates a physical representation at the geometrical level, i.e., the final layout of the biochip consisting of the configuration of the microfluidic array, locations of reservoirs and dispensing ports, and other geometric details.

The goal of a synthesis procedure is to select a design that minimizes a certain cost function under resource constraints. For example, architectural-level synthesis for microfluidic biochips can be viewed as the problem of scheduling assay functions and binding them to a given number of resources so as to maximize parallelism, thereby decreasing response time. Geometry-level synthesis addresses the placement of resources and the routing of droplets to satisfy objectives such as area or throughput. Defect/fault tolerance can also be included as a critical objective in the proposed synthesis method.

In architectural-level synthesis, both resource binding problem and scheduling problem are addressed to generate a structural view of biochip design. As in the case of high-level synthesis for integrated circuits, resource binding in the biochip synthesis flow refers to the mapping from bioassay operations to available functional resources. Note that there may be several types of resources for any given bioassay operation. For example, a 2×2-array mixer, a 2×3-array mixer and a 2×4-array mixer can be used for a droplet mixing operation. In such cases, a resource selection procedure must be used. On the other hand, due to the resource constraints, a resource binding may associate one functional resource with several assay operations; this necessitates resource sharing. Once resource binding is carried out, the time duration for each bioassay operation can be easily determined. Scheduling determines the start times and stop times of all assay operations, subject to the precedence constraints imposed by the sequencing graph. In a valid schedule, assay operations that share a microfluidic module cannot execute concurrently. We have developed an optimal strategy based on integer linear programming for scheduling assay operations under resource constraints [19]. Since the scheduling problem is NP-complete, we have also developed two heuristic techniques that scale well for large problem instances. While the heuristic based on *list scheduling* is computationally more efficient, the second heuristic based on *genetic algorithms* yields lower completion times for bioassays. In addition, the heuristic based on *genetic algorithms* is also able to handle resource binding. Experiments show that the results obtained from the heuristics are close to provable lower bound for a bioassay of large size [19].

A key problem in the geometry-level synthesis of biochips is the placement of microfluidic modules such as different types of mixers and storage units. Based on the results obtained from architectural-level synthesis, placement determines the locations of each module on the microfluidic array in order to optimize some design metrics. Since digital microfluidic biochips enable dynamic reconfiguration of the microfluidic array during run-time, they allow the placement of different modules on the same location during different time intervals. Thus, the placement of modules on the microfluidic array can be modeled as a 3-D packing problem. Each microfluidic module is represented by a 3-D box, the base of which denotes the rectangular area of the module and the height denotes the time-span of its operation. The microfluidic biochip placement can now be viewed as the problem

of packing these boxes to minimize the total base area, while avoiding overlaps. Since the placement problem is known to be NP-complete [20], a simulated annealing-based heuristic approach

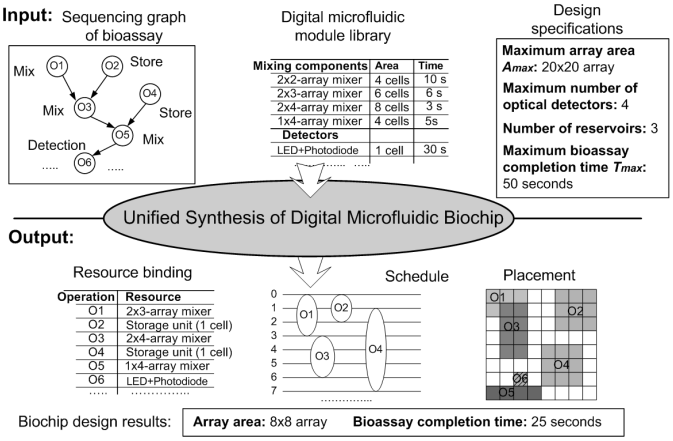

Figure 4: An example illustrating unified system-level synthesis.

has been developed to solve the problem in a computationally efficient manner [20]. Solutions for the placement problem can provide the designer with guidelines on the size of the array to be manufactured. If module placement is carried out for a fabricated array, area minimization frees up more unit cells for sample collection and preparation.

Moreover, we can further enhance the synthesis methodology by unifying operation scheduling, resource binding, and module placement together; Figure 4 illustrates the design flow for the proposed synthesis method. A combinational optimization method, such as parallel recombinative simulated annealing (PRSA), can be used for this integrated synthesis method [23]. All three tasks, i.e., resource binding, scheduling, and placement, are carried out at each step of the algorithm. Thus, exact placement information, instead of a crude area estimate, is used to judge the quality of architectural-level synthesis. This information is utilized by the annealing process to select resources and schedule bioassay operations to produce a high-quality design. This method allows architectural design and physical design decisions to be made simultaneously. Moreover, defect tolerance can be easily incorporated during synthesis, whereby resources for bioassay functions are carefully selected and placed in the array to bypass defective cells; in this way, the bioassay functionality is not compromised.

3.3. Challenges

Several challenges are encountered in the development of the proposed top-down system-level design methodology. First, we note that, following the geometry-level synthesis, the automatically-generated layout of digital microfluidic biochips need to be coupled with more detailed geometrical data for 3-D physical simulation. Although this detailed simulation-based approach can be used for physical verification, it is time-consuming and highly dependent on the accuracy of the geometrical model. We can speed up and automate the physical verification procedure for biochip designs by leveraging classical integrated circuit verification techniques (e.g., design rule checking). As in circuit design, the layered microfabrication process information can be encapsulated in a layout design rule file. The synthesized layout of microfluidic biochip is verified to satisfy an abstraction of geometric design constraints, which consequently ensures robust manufacturing. However, the design rules that need to be checked in the microfluidic biochips are significantly different from those in circuit area. They are also unlike classical MEMS due to the fluidic domain [24]. The determination of accurate and efficient design rules for physical verification of digital microfluidic biochips remains a critical technical challenge.

Coupling of energy domains also affect the synthesis and performance optimizations of biochips. Due to coupling effect between different energy domains (e.g., electrical, fluidic and thermal domains) [1], multiple-objective optimization problems must be solved during synthesis. For example, we should not only aim to minimize the assay operation time, but we should also keep the power consumption low to avoid fluid overheating. Such optimization problems that span several energy domains appear to be extremely difficult. Efficient solutions to such optimization problem are nevertheless essential to ensure the quality of biochips designed using automated synthesis techniques.

4. CONCLUSION

We have presented a new system-level design automation methodology for droplet-based microfluidic biochips. In this proposed method, synthesis tools are used to map the behavioral description of bioassays to a microfluidic biochip and generate an optimized schedule of bioassay operations, the binding of assay operations to resources, and a layout of the microfluidic biochip. Compared to the current full custom and bottom-up design methods, this top-down system-level design methodology can significantly reduce the design cycle time and time-consuming redesign efforts. This work is expected to enable high-volume productions and applications of microfluidics-based biochips, thereby paving the way for the integration of biochip components in the next generation of SOC designs, as envisaged by the 2003 ITRS document.

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