Design and Optimization for Digital Microfluidic Biochips

Competition Category: Undergraduate
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1 Problem and Motivation

Microfluidic-based biochips are soon revolutionizing clinical diagnostics and many biochemical laboratory procedures due to their advantages of automation, cost reduction, portability, and efficiency [18]. Conventional technology depends on the manipulation of continuous liquid flow through microfabricated channels. However, actuation of flow is implemented with external assistance of micro-pump and micro-valve, which are complex and cumbersome. Moreover, permanently-etched channels greatly restrict the feasibility and versatility. Regarding this, microfluidic research is witnessing a paradigm shift from the continuous-flow-based architecture to *droplet*-based architecture or, in particular, the so-called *digital microfluidic biochip* (DMFB) [1, 4, 5, 11, 14].

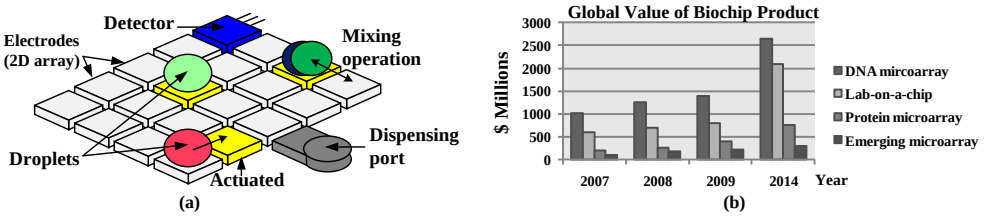

Figure 1: (a) Schematic view of a DMFB. (b) Global-value estimation of the biochip product.

Generally, a DMFB consists of a two-dimensional (2D) electrode array and peripheral devices (e.g., optical detector, dispensing port, etc.), as schematically shown in Figure 1(a) [11, 18]. The sample carriers on DMFBs, *droplets*, being miniaturized and *discretized* liquids, are controlled by underlying electrodes using electrical actuations (i.e., a principle called electrowetting-on-dielectric or EWOD) [15]. By assigning time-varying voltage values to turn on/off electrodes, droplets can be moved around the entire 2D array to perform fundamental operations (e.g., dispensing and mixing) [7, 16]. These operations are carried out in a *reconfigurable* manner due to their flexibility in area and time domain [4]. Compared with continuous-flow-based biochips, DMFBs offer various advantages including more flexible control mechanism and higher throughput and sensitivity as well as lower sample/reagent volume consumption.

Due to these advantages, DMFBs have attracted much effort devoted to serving the need from marketplace such as healthcare, environmental, and toxin monitoring applications. As reported in Figure 1(b) [2], the global market value for biochip products is an estimated $2.6 billion in 2009, but is expected to increase to nearly $6 billion in 2014, for a 5-year high compound-annual-growth-rate (CAGR) of 17.7%. Continuing growth of various applications have dramatically complicated the chip/system integration and design complexity [5, 11], making traditional *manual* designs not suitable enough especially under the time-to-market circumstance. For purpose of efficiency and effectiveness, it is necessary to develop high-quality computer-aided-design (CAD) tools for design automation. About this concern, lots of combinatorial and geometric optimization problems arising along the CAD flow of DMFBs are needed to be solved. As a consequence, in this research we shall discuss our CAD algorithms to approach several primary optimization problems appearing along the flow. **Regarding these CAD algorithms, we have published three works in top conferences, ACM/IEEE DAC and ACM/IEEE ICCAD [31, 33, 36]; two works in top journals, IEEE TCAD [34, 35]; one work in ACM ISPD [32]; one work in IEEE ICCD [29]; one work in IWBDA [30].**

2 Background and Related Work

A regular CAD flow of designing DMFBs consists of two stages, *fluidic-level synthesis* and *chip-level design* [11]. As illustrated in Figure 2(a)-(c), in fluidic-level synthesis, a given assay (e.g., in-vitro, PCR, etc.) with its operations (e.g., dispensing, mixing, etc.) as well as their mutual dependences is first abstracted as a sequencing graph. Next, scheduling algorithms concerning parallelism assign time-multiplexed steps to these operations and bind them to a given number of fluidic devices from a standard library [17]. Based on the scheduled result, device-placement algorithms are applied to generate a suitable layout [20, 26], followed by conducting droplet-routing algorithms to build droplet behaviors in a *reconfigurable* manner [19, 27]. On the other hand, chip-level design determines the control-signal plan for the underlying electrodes to execute the synthesized result. As illustrated in Figure 2(d)-(f), required/used electrodes for executing droplet controls are obtained.

Then, these electrodes should be addressed by control pins to identify the input signals. Finally, conduction wires must be routed to establish correspondence between control pins and the external controller [8, 11]. Although several novel algorithms have been proposed along the design flow, there are still many insufficiencies as identified as follows:

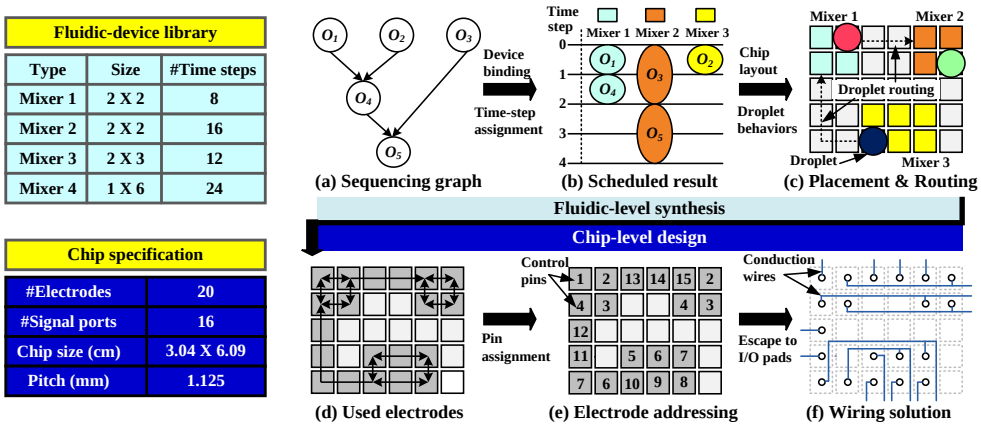

Figure 2: Computer-aided-design (CAD) flow of DMFBs.

- Droplet routing plays the most dominating factor in measuring the assay performance realized on DMFBs. It determines each droplet's moving/routing path from one site to another for performing the specified operation. Constraints posed by maintaining minimum spacing between different droplets bring about significant difficulties in solving the droplet-routing problem. Nevertheless, existing droplet-routing algorithms confront a severe routability problem as they typically conduct a simple shortest-path algorithm without good plan [3, 6, 10, 19, 27]. To resolve this problem, we incorporate the idea motivated from traffic control into droplet routing. With appropriately considering the congestion issue, our router provides higher performance and routability over existing ones [29].
- On the other hand, the cross-contamination problem between different droplets has emerged as a weakness of current droplet-routing algorithms [21]. To avoid this problem, additional scheduling effort of washing operations should be incorporated into droplet routing. Existing algorithms suffer from timing overhead of assay execution as they separate the washing operations and droplet routing, which degrades the ability of real-time response [28]. To avoid this problem, we propose the *first* droplet routing algorithm with *simultaneous* droplet routing and washing scheduling to make assays be correctly executed without any contamination problem [30, 31, 34].
- In electrode addressing, pin-count/signal-bandwidth minimization is a crucial issue as its large impact on chip fabrication, packaging, and cost. Existing algorithms simply post-processing pin-count minimization after droplet routing, whereas the solution quality is inevitably limited by the droplet-routing result [22]. Hence, we propose the *first* droplet-routing algorithm that integrates pin-count reduction techniques into droplet routing thereby achieving greater solution quality [32, 35].
- Existing electrode-addressing algorithms focus on minimally grouping electrodes with compatible control signals [13, 22, 23, 25]; yet they neglect the potentially induced power-consumption problem resulted from control-signal sharing [18, 24]. This issue is especially critical for battery-driven devices developed for healthcare applications. To overcome this problem, we propose the *first* power-aware addressing algorithm that simultaneously minimizes the pin count and power consumption [36].
- Unfortunately, it appears that *no* research findings are yet available concerning the chip-level wiring problem. Most of them are still worked out by manual methods, which are critically inefficient [11]. As wiring feasibility is highly related to the electrode-addressing result, we propose the *first* CAD algorithm that unifies the two design stages to achieve high solution quality and design integration [33].

3 Approach and Uniqueness

In this section, we discuss the proposed CAD algorithms for solving practical problems of droplet routing, contamination avoidance, pin-constrained designs, electrode addressing, and wire routing.

3.1 Droplet-Routing Algorithms

As modern droplet routing problems contain hundreds of droplets being concurrently moved, the congestion issue has become a significant issue in dominating routability. However, most previous works ignore this issue thereby suffering from severe routability problems [3, 6, 10, 19, 27]. To remedy this deficiency, we proposed a routability-driven routing algorithm [29] with the idea of constructing global routing tracks on the microfluidic array to make droplets route on specific tracks orderly. The intuition behind our global-routing-track construction is similar to traffic control, as each droplet can be regarded as a car. If most of the cars have common driving direction (from source to target) on the global routing track, we will assign the track to the preferred driving direction, which is beneficial to the traffic control. As shown in Figure 3(a), we sequentially route each droplet orderly along these tracks by adopting A* maze searching technique. Next, we propose a dynamic-programming

(DP)-based routing compaction that transforms the sequential routing result (2D) into concurrent manner (i.e., 3D, time involved). Our DP-based compaction decodes each 2D routing path into an 1D string and then model the compaction process into a LCS-like (i.e., longest common subsequence) recursion, as shown in Figure 3(b). After this compaction process, the entire parallelism of droplet movements can be maximized. That is, the latest arrival time among droplets can be minimized to achieve fast assay execution time and enhance real-time response.

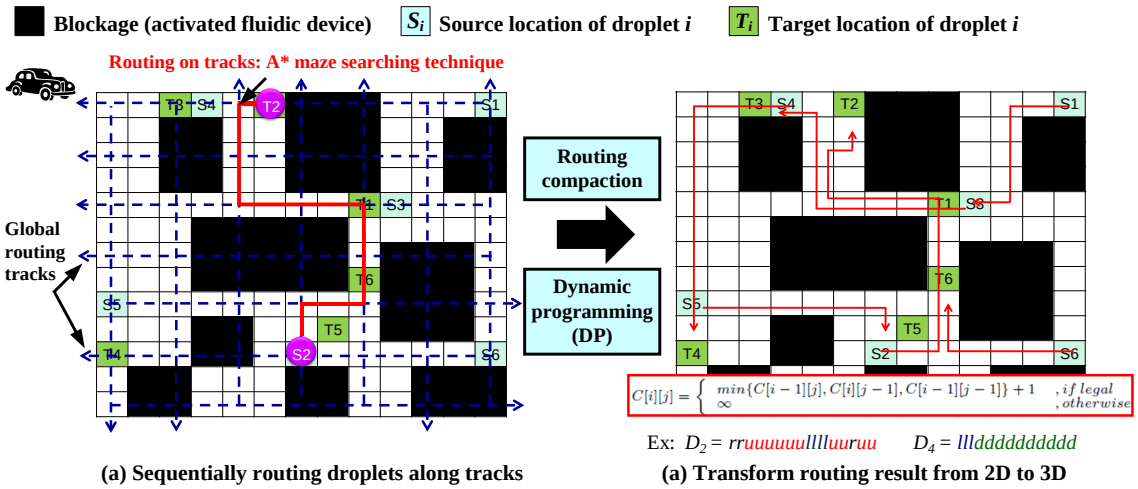

Figure 3: The proposed algorithm of routability-driven droplet routing.

For some protein-related assays, molecules and substances inside the droplets have the potential to leave behind the surface on microfluidic array, which leads to a contamination problem [21]. As shown in Figure 4(a)-(b), when two droplets successively pass through the same location, the residue left behind by the first droplet can contaminate the second droplet and may lead to erroneous assay outcomes. Previous works conduct the disjoint-route algorithm to avoid the overlap between different droplet routes thereby avoiding the contamination problem, as shown in Figure 4(c). However, increasing complexity of DMFBs has made it impossible to guarantee the existence of disjoint routes for each case. To resolve this problem, wash droplets are introduced and scheduled between successive droplet visits to clean up the residues on the surface, as shown in Figure 4(d). Prior works utilize this scheme by dividing the original droplet-routing problem into a series of stages, where washing operations are scheduled between successive stages; yet this separate design consideration may incur timing overhead as washing operations usually take a long time [28].

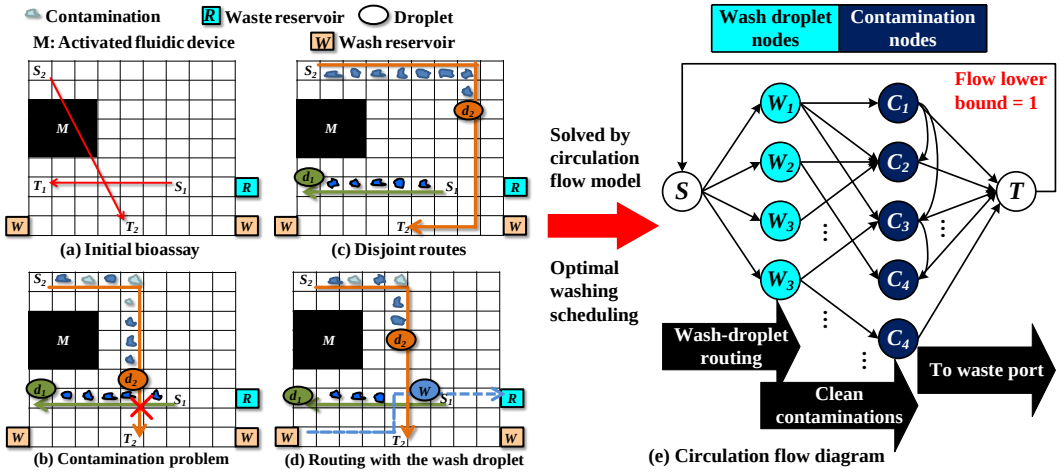

Figure 4: The proposed droplet-routing algorithm with contamination avoidance.

To remedy such insufficiencies, we propose a circulation-flow model to formulate simultaneous droplet routing and washing operations [30, 31, 34]. We first adopt the proposed routability-driven droplet-routing algorithm to generate an initial routing result. Based on this result, we can obtain timing and spacing occurrences of induced contaminated spots. As shown in 4(e), all required elements for scheduling washing operations are formulated into a flow network, where wash droplets and contaminated spots are modeled as nodes. And edge connections represent their correlations and preserve the timing and spacing topologies of contaminated spots. With appropriately setting the lower-bound value of the back flow to be one, at least one flow can pass through a wash-droplet node, contamination nodes, and then to the sink node. In other words, at least one wash droplet can be enabled to clean all contaminations and collect them to the waste-reservoir port. Required objective such as the timing requirement can be modeled to the flow cost. Finally by solving the circulation-flow network, the scheduling problem for washing operations can be optimized, while generating a correct droplet-routing result without any contamination problem.

3.2 Pin-Constrained Design, Electrode Addressing, and Wiring for Chip Realization

To correctly drive the electrodes for controlling droplets, *electrode addressing* is introduced as a method through which electrodes are assigned and controlled by pins to identify input signals. Early addressing designs relied on *direct addressing*, where each electrode is directly and *independently* assigned by a dedicated control pin [9]. This addressing maximizes the flexibility of electrode controls. However, for large arrays, the high pin-count demand greatly increases the fabrication cost. Recently, *pin-constrained* design has been raised as a promising solution to this problem. One of the major approaches, *broadcast addressing*, reduces the number of control pins by assigning a single control pin to multiple electrodes with mutually-compatible control signals [22]. In other words, multiple electrodes can share a single control signal/pin and are thus driven simultaneously.

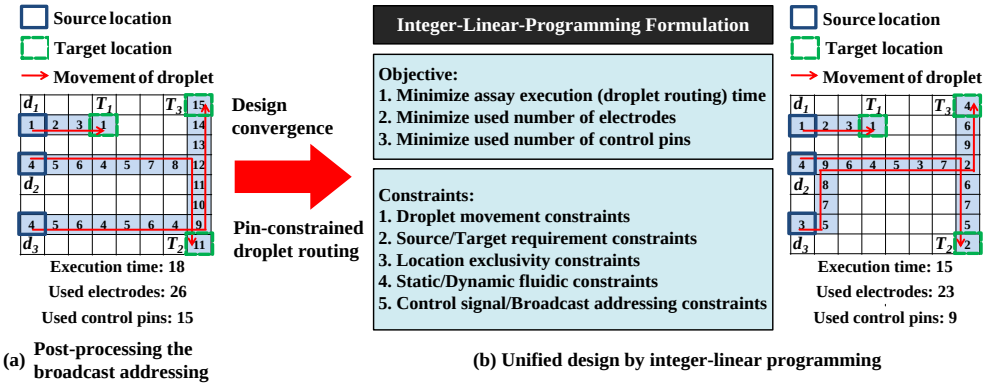

Figure 5: The proposed pin-constrained droplet-routing algorithm.

Most previous works deal with the pin-constrained design by simply post-applying the broadcast addressing to a droplet-routing result [22, 23, 25]. Nevertheless, their solution quality of pin-count reduction is quite limited by the given routing result. To overcome the limitation, we proposed a pin-constrained droplet-routing algorithm that simultaneously considers the droplet routing and pin-count reduction [32, 35]. We adopt an integer-linear-programming (ILP) formulation to formulate all required objectives and constraints. The proposed ILP formulation manages to search a feasible droplet-routing result while *simultaneously* minimizing assay completion time and the number of used electrodes and control pins. All necessary constraints posed by fluidic property and control-signal sharing are faithfully formulated as well. Take Figure 5 for example. (a) shows the typical design method that post-applies the broadcast addressing to a droplet-routing result. Compared with (a), our unified design algorithm, based on ILP formulation, outperforms the result of (a) in terms of assay completion time and used numbers of electrodes and control pins. In this way, our design method can achieve high performance of droplet behaviors and low-cost chip fabrication.

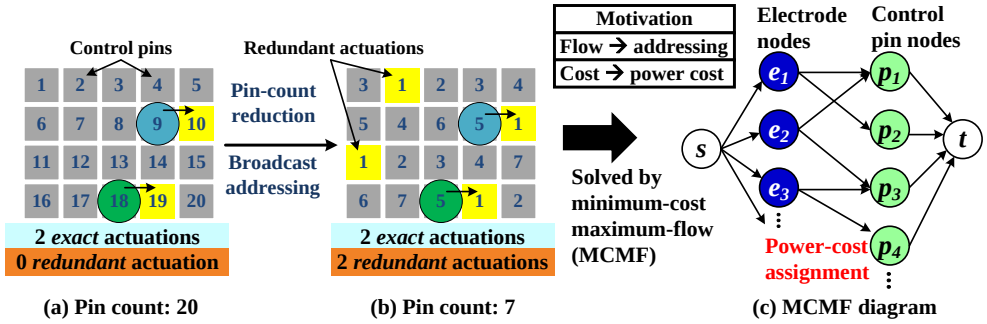

Figure 6: The proposed algorithm for power-aware broadcast addressing.

Although broadcast addressing serves as a promising solution to pin-constrained designs, yet the induced redundant actuations during signal merging have the potential to cause a power-consumption problem [18]. For example, in Figure 6(a), the direct-addressing result needs two *exact* actuations for moving the two droplets at this time step. In Figure 6(b), after applying the broadcast addressing, the pin count is greatly reduced from 20 to 7. Nevertheless, the addressing result potentially introduces two *redundant* actuations for moving the two droplets. As electrodes are controlled in a series of time steps, if control pins are not carefully assigned to electrodes, the addressing result will introduce a great number of redundant actuations thereby leading to high power consumption. Regarding this concern, performance of battery-driven applications is inevitably limited. Unfortunately, at present researches focusing on this issue are still critically lacking. Consequently, we propose the *first* power-aware addressing algorithm in the literature that incorporates the power-consumption minimization into broadcast addressing [36]. As shown in Figure 6(c), we propose a minimum-cost maximum-flow (MCMF) network to solve the addressing problem, where electrode addressing and power consumption are modeled as flow distribution and flow cost, respectively. By solving the MCMF network, the addressability can be maximized (i.e., maximum flow value) with minimum power consumption (i.e., minimum flow cost).

To actually realize the DMFB, electrical connections must be established on control pins. More specifically, conduction

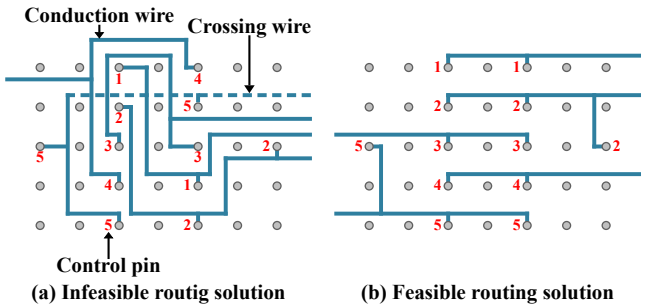

Figure 7: Comparison of two different design methods for performing the same fluidic controls. (a) Considers electrode addressing and routing separately. (b) Considers electrode addressing and routing simultaneously.

wires must be routed between electrodes and external control circuits[1]. Unfortunately, it appears that *no* research findings are yet available concerning the chip-level wiring problem. Most of them are still worked out manually, which are critically inefficient especially under the circumstance that modern DMFBs have high-density electrodes to be routed. Even so, solving such a routing problem is non-trivial. The most biggest challenge comes from multiple broadcast-addressing results corresponding to different wiring connections. If broadcast addressing and routing cannot be converged to an integrated design, the feasibility and quality of the routing solution may be inevitably limited. This concern can be illustrated in Figure 7. In (a), the separate consideration of broadcast addressing and routing confronts many back detours and thus degrades the routability. In contrast, in (b), if the routability issues can be incorporated into broadcast addressing, the resulted routing solution has higher feasibility and quality. To this end, we propose the *first* routing algorithm that simultaneously considers the broadcast addressing and routing [33]. We apply the MCMF network with the motivation that "*maximizing routability*" is formulated to "*maximum flow value*" and "*minimizing routing cost*" is formulated to "*minimum flow cost*". By solving the MCMF network, the entire routing problem can be effectively and efficiently solved.

4 Results and Contributions

Several real-life assays such as in-vitro diagnosis, DNA sequencing, protein sequencing, multiplexed immunoassay, etc. [1, 12, 18, 19, 20, 22], are used to evaluate our algorithms. In [29], our routing algorithm achieves 100% routability and fast assay completion time over prior works. Hence we enable the real-time response and high reliability that are needed to be addressed in healthcare applications. In [30, 31, 34], we can correctly complete droplet routing without any contamination problem while maintaining fast assay execution time rather than timing overhead as prior works usually suffer from. This achievement is especially helpful for many protein-related applications as they require an efficient router to avoid the inherent contamination problem. In [32, 35], we outperform prior works in terms of assay completion time, numbers of used electrodes and control pins, which leads to high routing performance and low-cost fabrication. In [36], the proposed addressing algorithm significantly reduces the power consumption incurred from broadcast addressing, which greatly facilitates the development of battery-driven applications such as hand-held portable devices. In [33], we provides a solution to replace manually-wiring manner with an automated design. Our algorithm achieves high success rate of routability on signal connections with small CPU runtime, which is very effective and efficient over the manual design. As a whole, these experimental results demonstrate the effectiveness, efficiency, and robustness of our algorithms as well as justifying the capability of handling several crucial and practical issues arising along the CAD flow of DMFBs. With the CAD tools realized by our algorithms, we summarize three major contributions as follows:

- We have utilized the knowledge brought from computer science to optimize several practical design problems of DMFBs. Our works have inspired more research interests and discussions devoted to this emerging field recently.
- We have formulated several design problems into classic computational problems that have well-studied theoretical foundations in computer science. Through computer programs, these design problems can be effectively and efficiently solved. Hence, our CAD tools yield high solution quality over existing ones that usually realized by simple heuristics.
- With the aid of our CAD tools, DMFB researchers can concentrate on the high-level abstraction of assay functionality, leaving optimization and implementation details to CAD tools.

As the design complexity of DMFBs continuously increases, CAD has become a necessary trend to establish an efficient development path from technology to commercialization. It is expected that the automated design flow will transform the DMFB research and use, in the same way as electronic design automation (EDA) revolutionized the very-large-scale-integration (VLSI) design in 1980s and 1990s. We believe the our CAD tools will facilitate the transformation and assist DMFB users and designers in adapting more easily to this emerging technology.

[1] In this paragraph, routing refers to the chip-level wiring condition, which is different from the droplet routing in fluidic-level synthesis.

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[2]Note that in the research field of electronic design automation (EDA) and computer-aided design (CAD), proceedings of ACM/IEEE Design Automation Conference (DAC) and ACM/IEEE International Conference on Computer-Aided Design (ICCAD) are recognized as two *top conferences*; IEEE Transaction on Computer-Aided Design of Integrated Circuits and Systems (TCAD) is recognized as the *top journal*.