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On the complexity of design tasks for Digital Microfluidic Biochips

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A R T I C L E I N F O

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A B S T R A C T

Digital Microfluidic Biochips (DMFBs) is an emerging technology aiming at the automatic processing of biological assays. Experiments are conducted by routing droplets of liquids on a grid. Determining a routing is the first step in the design process. A particular routing is carried out by actuating the cells of the DMFB grid in a certain manner. These actuations are controlled by microcontrollers having a limited number of output pins. Thus, it is usually not possible to control each cell separately, but multiple cells have to share a common control pin leading to the pin assignment problem.

In recent years, a wide range of heuristic as well as exact approaches has been proposed to solve these problems. While the NP-completeness of routing and pin assignment has already been conjectured in the literature, we present the first actual proofs. Thus, the use of general-purpose approaches like SAT solvers is indeed justified. We additionally prove the NP-completeness for variants of the routing problem.

1. Introduction

Recent advances in microfluidic technologies have enabled the emergence of a new paradigm in automating laboratory procedures in biochemistry and molecular biology: *Digital Microfluidic Biochips* (DMFBs) [1]. These devices provide a platform in which liquids (in terms of discrete *droplets* of nanoliter to picoliter volumes) can be moved around and typical laboratory operations such as mixing, heating, analyzing, etc. can be conducted. More precisely, a DMFB usually offers a 2-dimensional grid of cells (*positions*) onto which droplets can be placed. The movements of droplets between different positions is realized through electrodes beneath all positions. These can be turned on or off, thereby realizing electrical actuations that move droplets using the *electrowetting-on-dielectric* principle [2,3]. Compared to conventional experiments conducted by laboratory technicians, this leads to significant advantages such as high throughput, low reagent consumption, and minimal to no manual intervention. As a result, DMFBs have widely been used for various biochemical applications, such as point-of-care clinical diagnostics, large-scale immunoassays, high-throughput DNA sequencing, and protein crystallization for drug discovery [4,5].

With the increase in the size of DMFBs and the complexity of experiments to be realized, it is expected that the design of such biochips will require automation to the same extent as conventional VLSI design does. In the past decade, noticeable research has been conducted in this regard. Several approaches have been introduced which aid engineers in the task of realizing particular laboratory experiments onto given DMBFs [6–10]. They basically follow the same well-known steps as in the design of conventional systems (e.g., allocation, binding, scheduling, placement, and routing), but additionally consider the intrinsic properties and constraints of DMFBs. Within this design flow, the problem of routing is of particular importance. Droplet routing determines routing paths for all droplets from their initial positions to the desired positions, such that unintended droplet mixing is avoided and on-going fluidic operations are bypassed.

Determining routing solutions that do not exceed a certain route length is of utmost importance as liquids often degenerate over time (e.g. denaturation of proteins, general evaporation). Furthermore, every single droplet movement leaves some residue, eventually completely dispersing the droplet.

In addition to these hard constraints that ensure the feasibility of the resulting routes, corresponding routing approaches aim to minimize the time required to actually move all droplets to their target positions as to optimize the overall throughput of the device.

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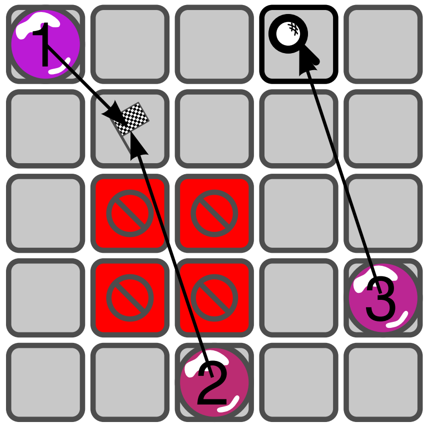
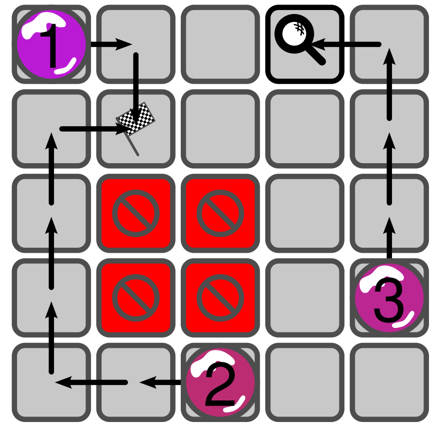


(a) Routing problem consisting of three droplets.



(b) Exemplary routing solution using 6 steps.

Fig. 1. Sample routing problem and a possible solution.

Example 1. *Consider the situation depicted in* Fig. 1(a). *On a biochip of size* 5×5, *three droplets are to be routed. Droplet 3 should be moved from its starting position in the right-most column to a detecting device in the top row while the other two droplets are to be routed to their common target without passing the blocked* 2×2*-region highlighted in red. One possible solution of this routing problem that requires the minimal number of six steps is shown in* Fig. 1(b).

There has been a considerable amount of work on droplet routing for DMFBs [11–15]. Instead of explicitly enumerating and validating all possible routings (which quickly becomes infeasible due to an exploding search space), the proposed approaches either apply *heuristics* in order to construct a solution or formulate the particular routing problem symbolically as a sequence of decision problems ("Can the routing be conducted in at most k time steps?"). Passing these problems to solving engines for Boolean Satisfiability (SAT) or SAT Modulo Theories (SMT), the solver either determines a precise *exact* routing (i.e., the routing is performed within the smallest possible number of time steps) or proves that no valid routing does exist under the given constraints.

As solving satisfiability problems is well-known to be NP-complete, the corresponding exact approaches don't scale as well as the heuristic ones which, in turn, provide solutions which can not be guaranteed to be even close-to-optimal. So far, however, it was not clear whether the complexity of the routing problem indeed justifies the use of heuristic approaches or exact approaches with an exponential run-time at all—or whether at some point an algorithm could possibly be developed that is able to find minimal solutions in polynomial-time.

Although it was already conjectured in the literature that droplet routing on DMFBs is an NP-complete problem, in this paper we present the first actual Proof for this claim. Moreover, we show that this result does not only hold for conventional DMFB architectures using square-shaped cells, but also for other cell shapes that have been proposed recently (like, e.g., hexagons and triangles [16,17]) as well as for *micro-electrode-dot-array* architectures (MEDA, see e.g. Ref. [18]).

In addition, we also consider another important task that is to be addressed in order to actually realize the routing on the DMFB: pin assignment. To this end, recall that droplets are moved by actuating the electrodes underneath the cells. As a consequence, biochips with hundreds of cells, as e.g. in Ref. [19], pose a serious problem for the physical realization of the connection between the cells and the corresponding control logic. In fact, already for biochips with only around 250 cells, wire routing using only a single PCB layer becomes almost infeasible. Adding more PCB layer relaxes the problem but, at the same time, increases manufacturing cost. Even if the wire routing problem was solved satisfactorily, one would need a micro-controller with an appropriate amount of output pins. Alternatively, shift registers could be used. Both approaches increase the manufacturing costs even further.

To overcome this problem, the idea is to drive multiple electrodes by the same control signal. The process of assigning control signals to electrodes is known as pin assignment and, again, several heuristic as well as exact approaches have been proposed in the past (see, e.g. [15,20]). Different authors already noted that there is a close relationship between the pin assignment problem and other (NP-complete) problems such as *graph coloring* [20] or *partitioning into cliques* [21–23]. In this paper, however, we provide the first formal Proof of the NP-completeness of pin assignment.

Before analyzing the complexity of the routing problem and the pin assignment problem in Sections 3 and 4, respectively, the next section precisely defines these problems and introduces the formal model allowing to actually conduct the complexity proofs.

2. DMFB model and design problems

In general, all physical aspects such as the voltage needed to drive droplets or the precise movement speed are necessary for understanding the DMFB technology as such. However, when trying to perform computer-aided design for these chips, such level of detail is actually a hindrance and a high-level view that abstracts away implementation details that are not of primary importance for the design of biological assays is employed instead.

In the following such a model, that allows to formulate the considered design problems in a formal way as well as to prove its complexity, is introduced.

2.1. Geometry of the biochip

The physical layout of the cells, called *grid*, is described by means of an undirected graph $G = (\mathcal{P}, E)$. The vertices from $\mathcal{P}$ represent the cells (*positions*) and the edges E model the possible droplet movements between adjacent cells. The positions are identified by Cartesian coordinates with the origin $(1, 1)$ in the lower left corner of the biochip, i.e. $\mathcal{P} \subset \mathbb{N} \times \mathbb{N}$. Denoting the set of adjacent positions that is reachable in one step from a given position p by $N(p)$ (also called *neighbourhood* of p), the set of edges E can then be described as $E = \{\{p, p'\} \mid p, p' \in \mathcal{P} \wedge p \in N(p')\}$. In order to model that a droplet can wait on a position, $N(p)$ always contains p itself. For convenience, we use the notation $p + M := \{p + m \mid m \in M\} \cap \mathcal{P}$ to describe the neighbourhoods where $M \subset \mathbb{Z} \times \mathbb{Z}$ summarizes all possible directions of movement. The