When Embedded Systems meet Life Sciences: Microfluidic Biochips for Real-Time Healthcare

Mirela Alistar
Hasso-Plattner Institute
mirela.alistar@hpi.de

Jan Madsen
Technical University of Denmark
jama@dtu.dk

Tsung-Yi Ho
National Tsing Hua University
tyho@cs.nthu.edu.tw

Robert Wille
Johannes Kepler University
robert.wille@jku.at

ABSTRACT

Biochips are cyber-physical system with realistic potential to improve the healthcare process, e.g., by providing faster disease diagnosis and at-home direct treatment. We review the area of biochips on its way to becoming a strong research field. However, for the real breakthrough to happen, a stronger collaboration among disciplines is needed. Thus, we organized this tutorial at Embedded Systems Week, to inform researchers about the potential of biochips. We presented the vision, the research challenges and an overview of the design automation as well as of the fabrication work. We show how the conventional methods in embedded systems can be applied to biochips to optimize their execution and design. Besides that, we conducted a hands-on lab that allowed the participants to get in direct contact with biochips. The participants were highly inspired and we hope their interest will result in fruitful collaborations.

Keywords: biochips, real-time healthcare, design automation, routing, microfluidics, genetics

VISION: BIOCHIPS FOR REAL-TIME HEALTH

The conventional approach to healthcare (Figure 1) takes a significant time from the installment of disease to the patient being cured. In many cases, this delay may lead to the death of the patient. It is sound to affirm that receiving healthcare in time is critical.

That is the main reason behind the many phone applications developed for healthcare monitoring. A future cyber-physical system based on biochips, will enable (i) a faster disease diagnosis and (ii) at-home direct treatment.

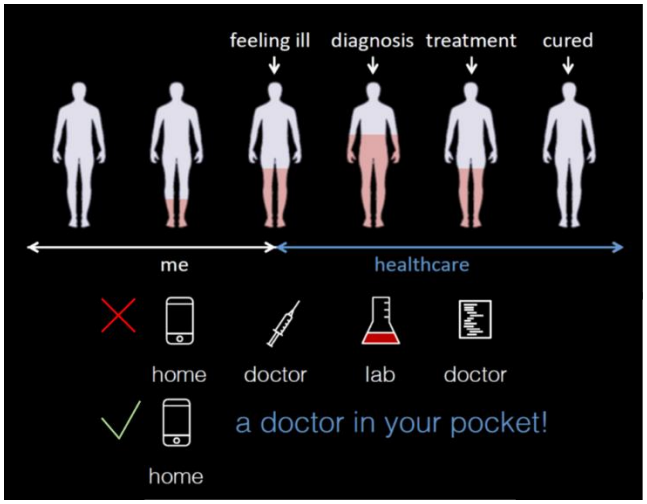

Figure 1: A biochip-based system can shorten the delay from the installment of the disease to the patient being cured.

The main advantage of our system is accessibility: more people will have access to healthcare. Another important advantage is a faster healthcare process, by reducing the delay from the installment of the disease to the cure.

Figure 2: The main advantage of the system is accessibility: more people will have access to healthcare.

HIGH-LEVEL SYSTEM

Figure 3 presents the envisioned system for on-patient real-time detection of biomarkers. A phone controls the system and collects the results. The data is stored in the cloud for further analysis. The patients are later informed on the decision of the experts ('e-doctors') regarding their treatment.

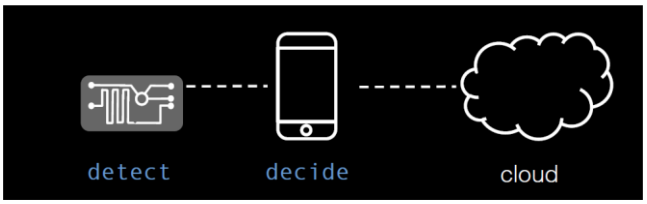

Figure 3: Envisioned system for biomarkers detection.

Droplet-based biochips were introduced in the late 2000s as a promising solution to a 'lab-on-a-chip' that can automate, miniaturize and integrate complex biochemical applications [4]. Figure 4 shows a prototype for the envisioned system.

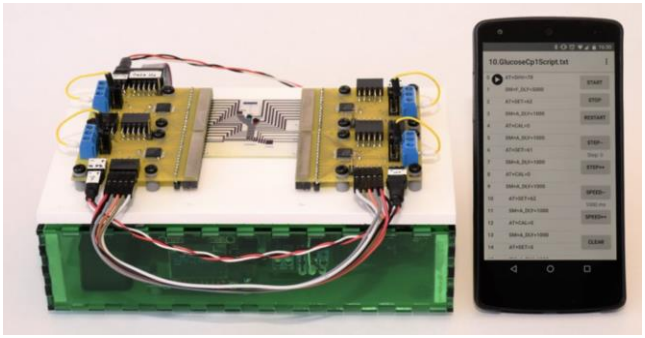

Figure 4: A paper-based biochip controlled by the software running on a phone. The communication is wireless and thus, can be done at distance. A small prototype was demonstrated for in-vitro diagnosis.

TECHNOLOGY

Biochips are electronic devices that can perform the tasks traditionally performed by a human wet lab technician with a pipette, such as in-vitro diagnosis.

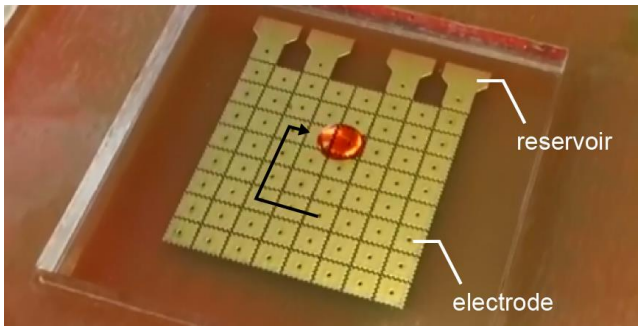

Figure 5: The OpenDrop biochip has four reservoirs and 8x8 electrodes holding a single droplet. The biochip can move the droplet by applying a voltage to a neighboring electrode.

As shown in Figure 5, biochips consist of electrodes, with each electrode capable of holding a droplet. To move a droplet, biochips apply electrical voltage on a neighbor electrode. The voltage attracts the droplet and the droplet moves. In such way, biochips can run biochemical processes ('bio-protocols'), i.e., sequences of operations on droplets, including dispensing, splitting and mixing (Figure 6).

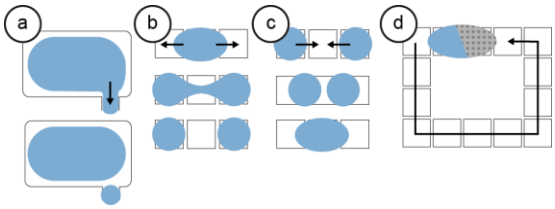

Figure 6: To execute biochemical processes or *bio-protocols*, biochips (a) dispense, (b) split, (c) merge and (d) mix droplets.

CHEAP FABRICATION

Significant research efforts have been directed towards fabricating a cheap and reliable biochip. The most successful fabrication techniques so far are based on chromium electrodes on a glass substrate (Figure 7), gold electrodes on a printed circuit board, as in Figure 5, and silver electrodes printed on photographic paper.

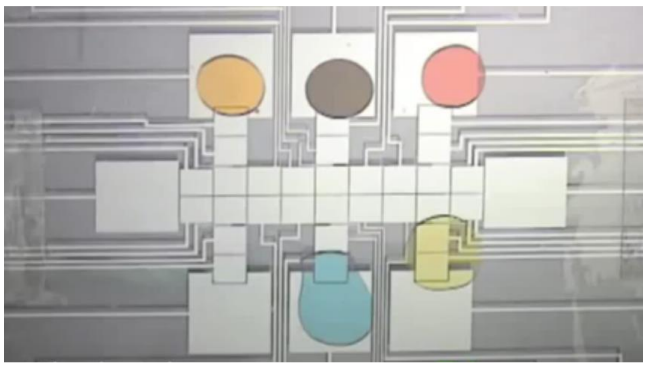

Figure 7: Dropbot is built using vapor deposition of chrome on a glass substrate. This fabrication method is the most expensive, but the glass substrate can be easily sterilized and thus reused multiple times [1].

The recent development of paper-based biochips (Figure 8) is a significant step towards our vision. These biochips are printed on gloss photographic paper using a home inkjet printer that was previously loaded with conductive ink. Paper-based biochips are very cheap, and thus disposable. Consequently, contamination can be avoided in a simple manner (i.e., by disposing the biochips after each use), without the need of sterilization.

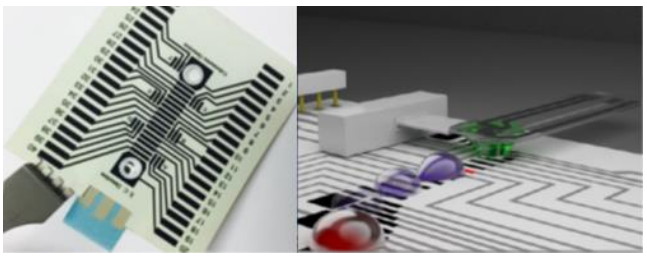

Figure 8: Paper-based biochips have ink-jet printed electrodes. This biochip uses a cheap ink based on carbon-nanotubes for conductivity [3]. These biochips are disposable, making them highly suitable for point-of-care diagnosis.

However, there are several limitations to paper-based biochips: (i) short shelf life and (ii) limited number of electrodes, because, unlike PCB, multiple layering is not possible on paper.

SYNTHESIS SOFTWARE

To synthesize a bio-protocol means translating it into droplet movements. The synthesis of bio-protocols is a NP-complete problem, very similar to the conventional embedded systems problem of scheduling a task graph on a given architecture with a defined set of resources. Traditionally the synthesis is divided in a series of four steps: (1) binding of the droplets (tasks) to the electrode modules (resources), (2) scheduling of the droplets, (3) placement of electrode modules on the biochip grid and (4) routing the droplets from one module to another.

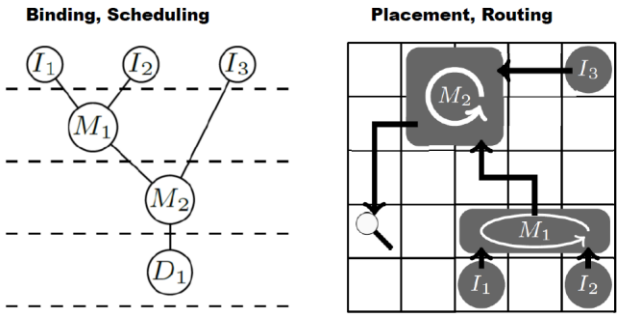

Figure 9: The traditional synthesis problem consists of binding and scheduling the tasks (here, droplets) on the given resources (here, electrodes) that need to be placed on the architecture (here, biochip). Droplets also act as data (messages) that need to be routed from one resource to another.

We review a novel approach that synthesizes in one-step, using Boolean satisfiability [2]. Thus we formulate the synthesis problem as a sequence of decision problems. The proposed SAT encoding proved to provide better results than the traditional approach.

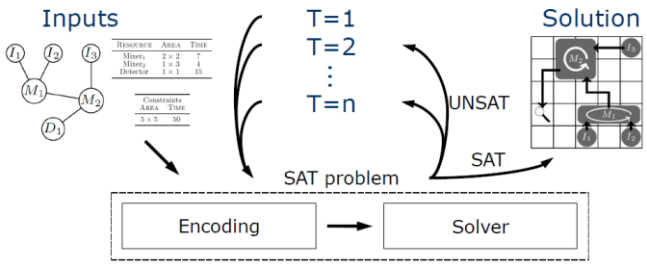

Figure 10: One-step synthesis using Boolean satisfiability [2].

SOLVING THE ROUTING CONFLICTS

Determining the routes of the droplets is NP-complete. Routing of droplets has to be done such that (i) there is no undesired droplet merging and (ii) the bio-protocol completes in time. We call (i) the fluidic constraint and (ii) the timing constraint. Figure 11 depicts the fluidic constraint.

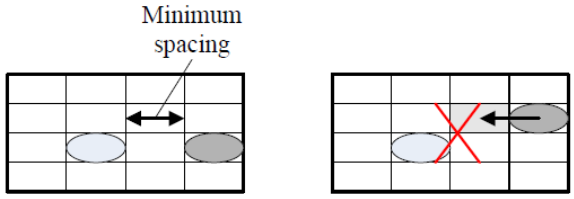

Figure 11: When two droplets are too close they merge instantly together by default. A minimum spacing of one electrode is required for both stationary and moving droplets.

The routing problem can be summarized as follows:

Given as **input**: a netlist of n droplets $D = \{d_1, d_2, \ldots, d_n\}$, the locations of m, the blockages $B = \{b_1, b_2, \ldots, b_m\}$, and the timing constraint T_{max}, we have as **objective** to route all droplets from their sources to their targets, satisfying the fluidic and timing **constraints**. Figure 12 further shows the example of dynamic control interference between droplets and control lines on paper-based biochips.

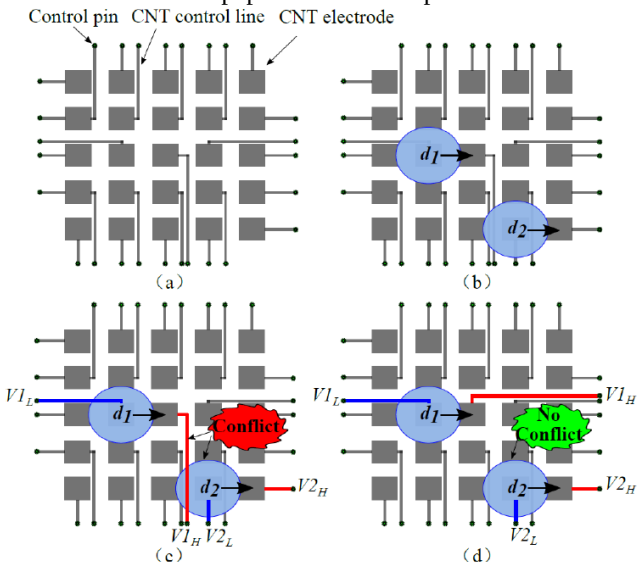

Figure 12: (a) Routed control lines (b) Droplets and are scheduled to move rightward at the same time (c) The control line of d_1 adversely affects the movement of droplet d_2 due to the voltage interference (d) The control line of is rerouted to resolve the conflict [5].

The problem is solved by modeling the biochip as a network-flow graph with specific minimum cost flow formulation. After we determine an escape route, we re-route the droplets using A* search. Researchers have also proposed a co-design routing that adjusts the cost function depending on the current routing scenario.

HANDS-ON LAB

The participants (including 2 female researchers) were involved in a series of practical tasks meant to consolidate the knowledge presented so far. All tasks were executed in teams of two, facilitating collaboration and networking.

First, the participants were challenged to search around for the combination of fluid and substrate that would give the highest contact angle. We tested diluted soap, coffee, milk and water on the following substrates: phone cover, conference badge, disposable waxed cup and tea bag envelope. The participants learnt the importance of the contact angle (and its properties) for biochips.

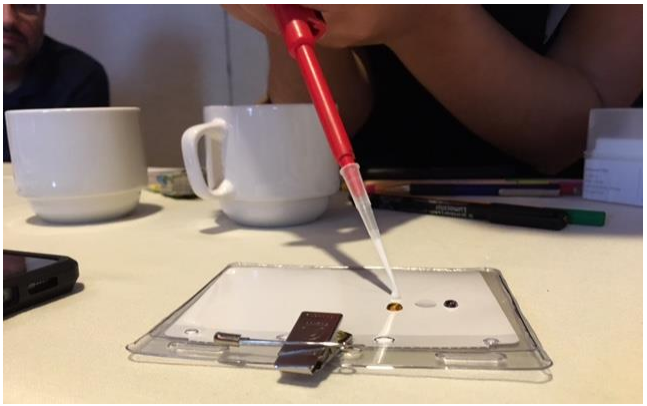

Figure 13: Coffee, soap, milk and water droplets on the back of a conference badge.

The second task for the participants was a series dilution of flavored droplets to achieve the ideal concentration for a contact angle of 120 degrees.

Figure 14: Participants perform a series dilution on several fluids.

Then, the participants were exposed to a live demonstration of a biochip moving and mixing droplets. As a third task, each team had to develop their own bio-protocol for a sleep enhancer, a Pennsylvania aroma, cloth detergent flavor and insect repellent. For this task, the teams were given 8 fluids of different aromas that had to be combined to define the bio-

protocol. The participants also determined the routes and the scheduling of their own bio-protocol.

Figure 15: Side view of the real-biochip moving a droplet.

DISCUSSIONS AND FUTURE WORK

The participants reported that the tutorial was **informative**, and that the information load was not too heavy. Five participants would have liked even more technical details and they all reported that the **hands-on lab was easy** to understand and perform: 'although I have never ever done anything like that before I still got a feeling I learnt it'. All participants found the tutorial **inspiring** and when asked about collaboration interest, one suggested that he could use his techniques (in Matlab, Simulink) to model and verify fluids. One participant found the **team work** very inspiring and it allowed her to interact and learn more from the others. Another participant suggested to split the tutorial over two days, with a break in between, giving them the chance to sleep over the knowledge and get more ideas.

Overall, the participants were extremely enthusiastic and interested in the topic.

As future work, we presented potential applications in synthetic biology, a living pill (Figure 16) and cancer cures.

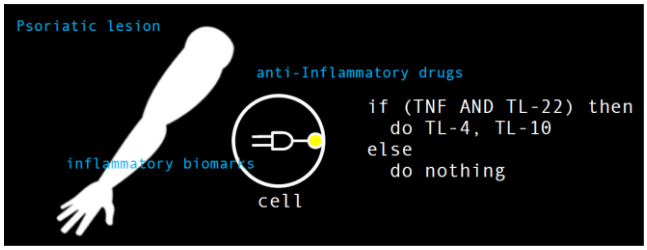

Figure 16: The living pill analyzes the biomarkers and produces the cure [6].

CONCLUSIONS

We believe that the area of biochips is becoming a strong field that require strong interdisciplinary collaborations. A lot of the classical methods in embedded systems can be applied to biochips to optimize their execution and design. Moreover, existing embedded systems can be integrated with biochips to form advanced cyber-physical systems.

Since the field is just emerging, any research contribution has significant impact. **Thus, we strongly encourage engagement of embedded systems researchers in addressing the current problems concerning biochips.**

Through running such tutorial, we aim at informing the researchers about the potential of biochips. The participants were interested and we hope their interest will result in research collaboration as we aim at expanding the field.

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