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Smartphone-based biosensing platform evolution: implementation of electrochemical analysis capabilities.

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Abstract—**Lab-on-Chip technologies offer great opportunities for the democratization of in-vitro medical diagnostics to the consumer-market. Despite the limitations set by the strict instrumentation and control requirements of certain families of these devices, new solutions are emerging. Smartphones now routinely demonstrate their potential as an interface of choice for operating complex, instrumented Lab-on-Chips. The sporadic nature of home-based in-vitro medical diagnostics testing calls for the development of systems capable of evolving with new applications or new technologies for Lab-on-Chip devices. We present in this work how we evolved the first generation of a smartphone/Lab-on-Chip platform designed for evolvability. We demonstrate how reengineering efforts can be confined to the mobile-software layer and illustrate some of the benefits of building evolvable systems. We implement electrochemical capabilities on our platform prototype and carry out cyclic voltammetry to measure dopamine concentrations over several orders of magnitude.**

Keywords-**Lab-on-Chip; Smartphone; Point-of-Care; In-Vitro Medical Diagnostics; System Evolvability; Platform-Based Design;**

I. INTRODUCTION

Recent advances in Lab-on-Chip (LoC) technologies have raised hope in the ability to better diagnose and monitor disease at the Point-of-Care (PoC). The wide panel of analytical functionalities and ever-increasing performances of LoCs have made them critical vectors for the democratization of In-Vitro Medical Diagnostics (IVMD) in the consumer-market. A certain number of limitations have so far prevented the large-scale development and adoption of direct-to-consumer LoC-based technologies. One is the increasing need for instrumentation and control: as LoCs capabilities increase, so is the complexity of their operation (e.g. optical readout instrumentation, control of digital microfluidics biochips [1], [2], etc.). Smartphone-based systems have a transformative potential in that respect [3]. Many examples already illustrate possible benefits of interfacing LoCs to smartphones, leveraging the computational power, peripherals and usability of the latter to avoid the need for developing complex instruments or controllers [3]. Nevertheless, as we argued in a recent publication, the predictable sporadic nature of home-based IVMD testing questions the justifiability of developing application-specific or non-evolvable systems [4]. So does the fast-pace evolution of the technologies underlying LoC systems (e.g. biosensing, microfluidics). We therefore advocate design for evolvability in smartphone/LoC systems and recently introduced the first generation of a platform implemented in that perspective [4]. We follow up on these initial results and present in this work how we evolved our initial design to allow the execution of electrochemical measurements. We demonstrate the operation of the latter functionality by carrying out the detection of dopamine (DA) using cyclic voltammetry (CV).

II. MATERIALS AND METHODS

A. Platform evolution by functional composition

We relied on a Platform-Based Design (PBD) methodology to develop our initial concept [5] and worked under the guidance of engineering design principles for changeability on which we further elaborate in this paper [6], [7]. PBD enables the mapping of specified system *functions* onto a *target architecture* [5]. This materializes in our case with the possibility to specify LoC operations (i.e. functions) at the high-abstraction mobile-software layer, for varied LoC architectures [4]. An iOS Application Programming Interface (API) gives the LoC application designer access to a set of customizable tasks (figure 1). Among them, we call *elementary tasks* the physical or computational functions realized at the Hardware Accessory (HWA) or LoC level. These tasks were specified according to the *ideality/simplicity* principle: in an attempt to maintain low system complexity while maximizing functionality [6]: we specified the original functional requirements for our platform so as to allow the recovery of low- AC-currents, such as those exhibited by silicon-nanowire field effect transistor biosensors [8], [9]. Among potential means to offer this capability, we decided to rely on the lock-in amplification technique [4], [10]. We then derived the set of *elementary tasks* satisfying the aforementioned *ideality* principle. These are illustrated in figure 2a. Their definition is critical, as it requires the careful evaluation
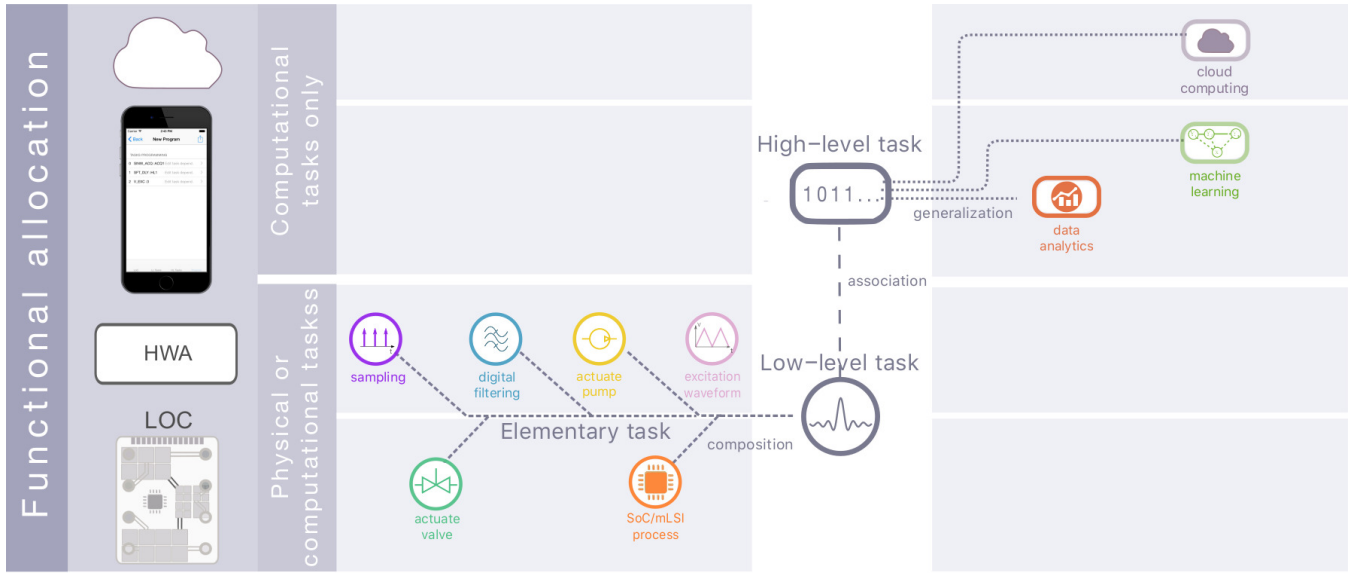
Figure 1. Platform functionality abstractions. *Elementary tasks* are defined as physical or computational functions performed at the low-abstraction HWA or LoC level. They can be composed at the mobile-software layer to form *Low-level tasks*. These *low-level tasks* can be associated to *high-level tasks*, defined as computational-only, mobile-software level or cloud-computing tasks. This abstraction and ontology enables the non-hierarchical manipulation of *low-* and *high-level tasks* at the mobile-software API level, facilitating the specification of new LoC operations

of complexity/flexibility tradeoffs: When low abstraction levels provide great flexibility, implementation complexity may be burdening (e.g. mobile-software control of every HWA CPU register), whereas high abstraction levels will limit changeability but promote simplicity.

These *elementary tasks* were also defined in search of *modularity*: modular architectures should support the reuse of modular elements or aggregation of modules and their interfaces. This property permits the modular *composition* of *elementary tasks* at the high-abstraction mobile-software layer. We refer to these compositions as *low-level tasks*. The composition of the lock-in amplification acquisition function is presented in figure 2a.

Our *elementary tasks* are also *independent*: they should alone provide useful function (e.g. voltage waveform generation for LoC applications requiring specific electric fields patterns).

Finally they are integrated *non-hierarchically* with *high-level tasks* i.e. the computational-only functions associated with LoC operation and realized in mobile-software or in the cloud: the API provides a way to associate *elementary tasks* to *high-level tasks* at the same abstraction layer, allowing for instance for cloud-computing queries to be leveraged at run-time to define succeeding LoC operations.

Our prototype implementation and API rely on a HWA enabling the interfacing of an iPhone 6 (Apple Inc. CA, USA) to passive LoCs embedding current-based biosensors [4]. We built upon available *elementary tasks* to foster electrochemical capabilities to our platform: We imple-

mented the software blocks enabling the execution of cyclic voltammetry from the composition of a voltage waveform generation and current acquisition.

B. Electrochemical measurements

Following implementation, we made use of the available CV acquisition capabilities and proceeded to the electrochemical quantitation of dopamine (DA) solutions obtained from dopamine hydrochloride (Sigma-Aldrich, MO, USA). A stock solution at 0.1 mol/L and successive dilutions were prepared to obtain DA concentrations down to 5.9 nmol/L. We used distilled water (Millipore Milli-Q, Bedford, MA, USA) as a solvent. CV was performed using a scan rate of 100mV/s for potentials ranging from E=-1V to E=1V. Current sensitivities (i.e. reciprocal of the front-end current amplifier gain) were specified programmatically (via the API) so as to maximize the signal-to-noise ratio for a given DA dilution. Each calibration point was obtained by averaging results from three measurements, obtained using a new electrode each time (screen-printed gold-electrodes C223AT, DropSens, Spain) .

III. RESULTS

A. Implementation of cyclic-voltammetry analysis functions

The functional decomposition of CV acquisitions is provided in table 1. The design variables over which the application designer should have control could be mapped to the settings of the available *elementary tasks*. CV acquisitions were thus implemented by the composition of a triangular voltage waveform generation with a synchronous current
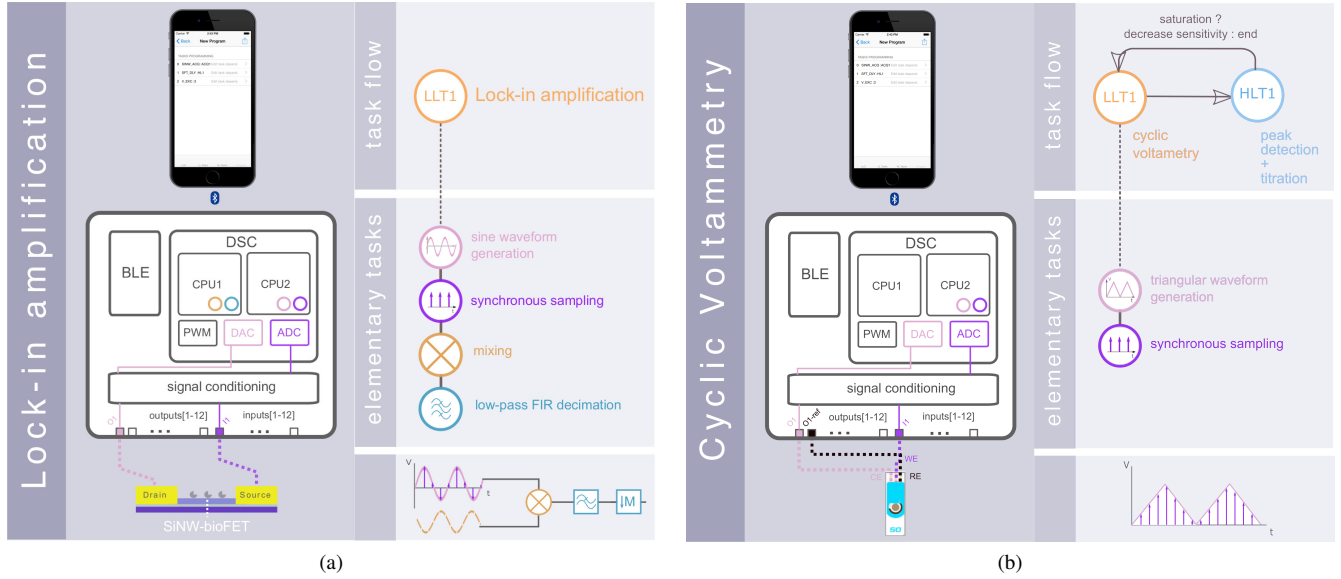
Figure 2. a - Lock in amplification function performed for the recovery of the impedance magnitude and phase from a high-impedance Silicon Nanowire (SiNW) sensor [4]. Lock-in amplification is carried out by applying a sinusoidal voltage waveform between the source and drain of the sensor, amplifying the resulting current running between source and drain and perform phase sensitive detection. (PSD). PSD itself is composed of a mixing step using the excitation reference signal and of a low-pass filtering step, both function been made available in embedded software b - LoC program execution diagram for CV acquisitions. CVs executed successively at decreasing sensitivities if current saturation is detected within the potential range where calibration is carried out. This conditional branching is realized at the mobile-software layer. Cyclic voltammetry LLT1 is composed of two synchronous elementary tasks: a triangular waveform generation and synchronous sampling. CV design variables must therefore translate into settings for the required elementary tasks.
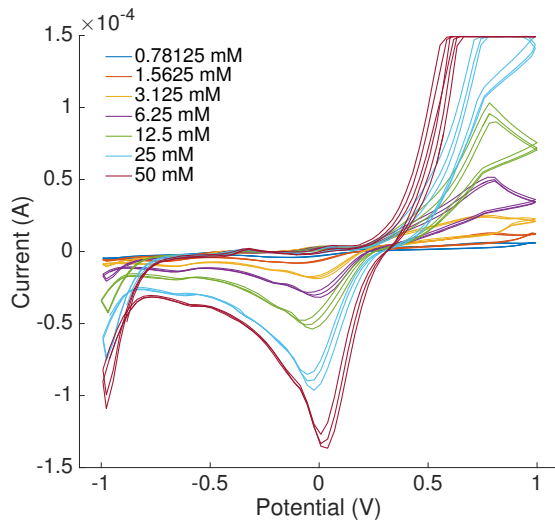

Figure 3. Mobile-phone acquisition data: Cyclic voltammograms. Saturated acquisitions are only discarded when saturation occurs within the potential range of interest.

Figure 4. DA calibration curve. Calibration points are obtained from retrieving local minima around E = 0V;

with a decreased amplifier sensitivity so as to be able to recover the reduction peak current signal (figure 2b).

B. Electrochemical detection of dopamine

After having validated the correct execution of CV acquisitions, DA quantitation was carried out. An illustration of the acquisition data retrieved at the mobile-software layer is given in figure 3. For each acquisition, a calibration point was retrieved from the identification of the local current

acquisition. Both these functions could then be mapped to one of the two available hardware potentiostatic channels (figure 2b). A peak-detection algorithm (i.e. *high-level task*) was inserted in the LoC operation program: starting at high-sensitivity, CV acquisitions are retrieved in iOS and probed for saturation. If a saturation is detected, the CV is repeated
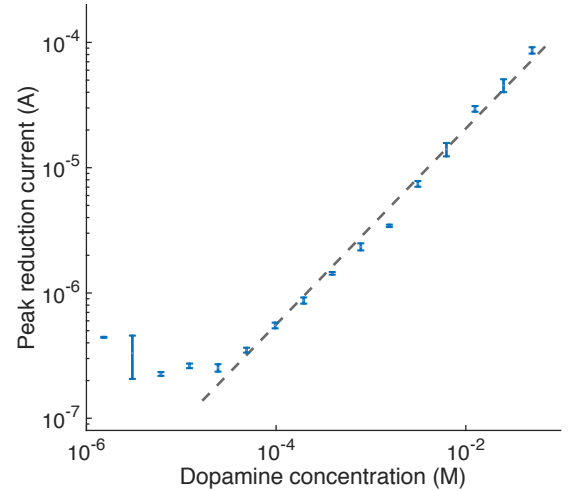
		Initialisation potential	Initialisation duration	Waveform {sine,square,triangle}	Offset potential	Frequency	Amplitude	Number of excitation periods	Ramp start/stop potentials	Duty cycle	Sampling rate	Number of acq. points	Amplifier sensitivity	Sample averaging	Sampling window	FIR LPF	Decimation	Phase Sensitive Detection
Cyclic Voltammetry	Startup potential	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Startup time	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Low potential	—	—	—	X	X	X	—	—	—	—	—	—	—	—	—	—	—
	High potential	—	—	—	X	X	X	—	—	—	—	—	—	—	—	—	—	—
	Scan rate	—	—	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—
	Number of cycles	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—	—	—
	Acq. points/cycle	—	—	—	—	—	—	—	—	—	X	X	—	—	—	—	—	—
	Sensitivity	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—	—
	Filtering	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—
		Voltage Waveform Generation									Current Acquisition					DSP		

minimum at DA's reduction potential. From these points we could derive the calibration curve presented in figure 4b. Our calibration curve spans over several orders of magnitude of DA concentrations with a solid regression coefficients of 0.996, benefiting from the *scalability* of the input current amplifiers combined with a smart algorithm implemented at the iOS software layer.

IV. DISCUSSION

The methodology and results presented in this work illustrate the benefits of PBD coupled with the adoption of appropriate engineering design principles for the implementation of evolvable systems. The development of electrochemical capabilities for our platform required the sole functional composition of existing *elementary tasks* and did not require change to any other system components. This was made possible mainly because of the careful consideration of functional *modularity*. The experimental results provided in section III-B demonstrate the operability of the evolved platform and illustrate the potential benefit of the *non-hierarchical* integration of *high-level* analytics (here a peak-detection algorithm) with LoC operations (here CV acquisitions).

This specific evolution towards electrochemical instrumentation represents of course a special case: The development of other physical functions (e.g. instrumentation at the HWA level or microfluidic actuation at the LoC level) may require more drastic system changes. In such a case, the reengineering effort and cost will depend upon how change propagates throughout the entire system architecture. We are currently addressing this matter using Change Propagation Analysis (CPA) [11].

V. CONCLUSION

We demonstrated in this work how PBD and design for evolvability can result in low re-engineering efforts for the adoption of new LoC architectures or operations. More specifically we demonstrated how to develop electrochemical capabilities for our system by the composition of existing functional block available at the API level. Our endeavour acknowledges that change is the predominant paradigm in engineering complex systems. It finally provides evidence as to the potential benefits of design for evolvability for direct-to-consumer PoC systems.

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