MIcroscopic Chemically Reactive Electronic Agents: Summary

MICREAgents is a collaborative project in Unconventional Computing funded by Future Emerging Technologies (FET) in the EU FP7 program. 10 research groups have come together from across Europe (including Israel), together with a research group in New Zealand, with coordination by the Ruhr Universität Bochum to investigate a new kind of embedded computation in which novel artificial entities combine electronic and chemical functionalities.

The central idea of the project is to create an autonomous programmable *microscale electronic chemistry* on suspended particles, approaching the size of mammalian cells. These so-called ***lablets*** (target size 100µm) employ autonomous circuit elements (including power scavenging) and an active microstructured profile to self-assemble in solution in order to communicate with one another and exchange chemicals. The electronic processing should enable them to both direct such association reversibly and to control chemical reactions in the reaction enclosure created by assembly. Pairwise association can then be programmed and electronic signals employed to direct complex microscopic chemical syntheses or analysis tasks. This requires a code, akin to the genetic code.

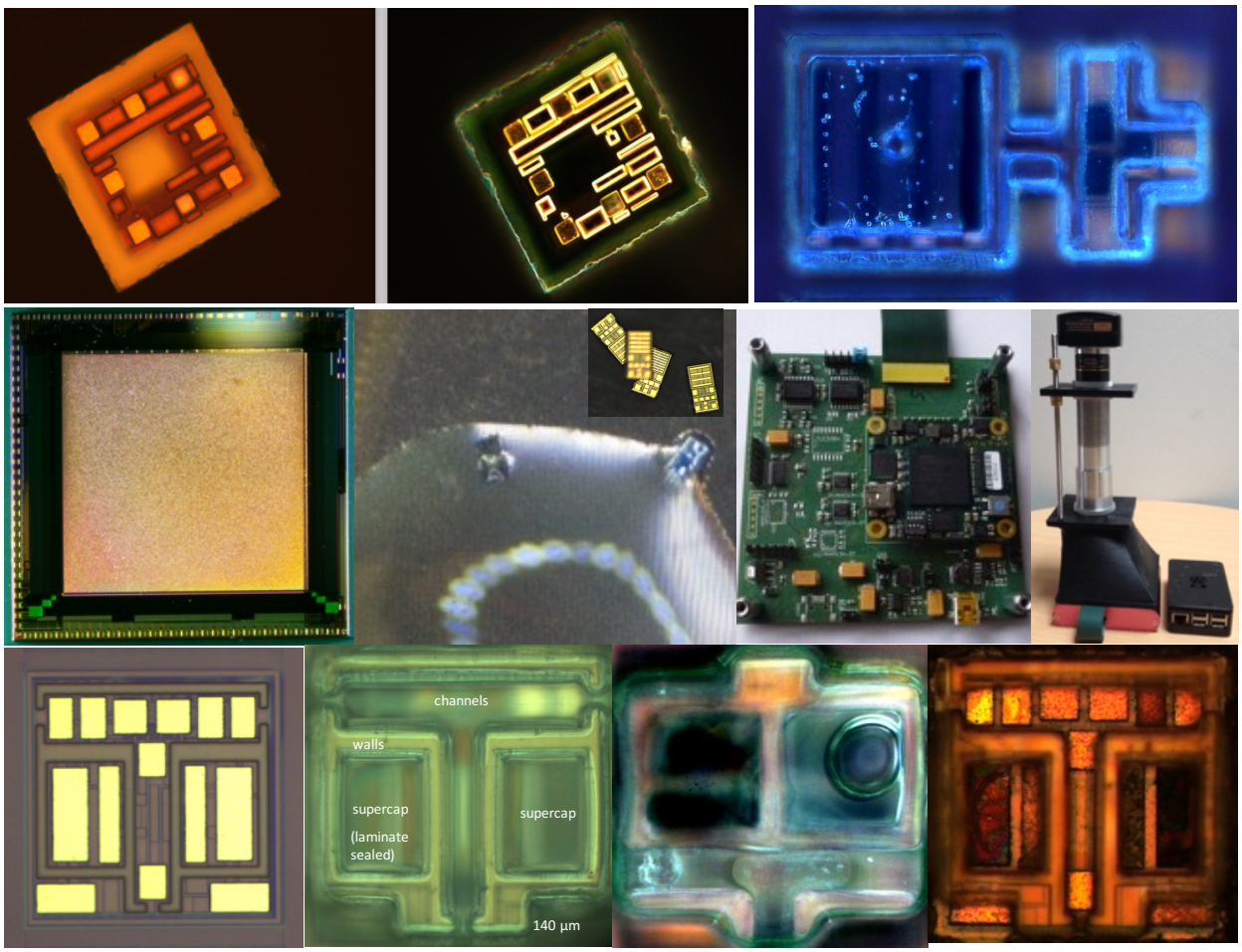

Figure 1: Three generations of lablet and dock design. TL: CMOS1 lablets without power (100x100µm) **TR:** CMOS2 lablets with tandem supercap (100x200 µm) **ML:** Docking chip **MM:** Lablets interacting with docking surface **MR:** Interface board and portable 3D printed system **B:** CMOS3 lablets with integrated supercap (140x140 µm) **BL:** after ENEPIG coating **BM:** with supercap walls and laminate, bubble showing filled electrolyte, **BR:** Singulated CMOS3 lablet with coatings and walls but laminate removed.

This will provide a novel form of computation that microscopically links reaction processing with computation in autonomous mobile smart reactors. This is a next major step towards the integration of computation and reactive chemical processing in electronically programmable systems: it corresponds to a radical integration of autonomous chemical experimentation and represents a novel form of computation. Images of three generations of lablets and their interactions with each other and the dock are shown in fig. 1.

The project makes a radical departure from lab-on-a-chip technology towards "pourable" computers, severing the traditional interfacial bottleneck of lab-on-a-chip experimentation – the complex "umbilical cord" connection the microchips with the external world. This sounds like smart dust technology applied to chemical systems, but the strategy is different. In smart dust, which is now at somewhat larger sub-mm scales, the two factors most affecting miniaturization are the problem of broadcast communication (the antennae for wireless smart dust being required to be larger than the chip) and the problem of autonomous power. Our novel strategy in MICREAgents is to focus on pairwise rather than global communication and to utilize the docking/pairing process also to transfer power between such microelectronic reagents (called lablets). The lablets are not just autonomous microchips in solution however. Traditional CMOS electronic fabrication must be complemented by extensive microscale processing to turn electrical contacts into functional electrodes in the context of specifically interacting autonomous particles with microstructured topography and morphology.

In year one of the project, the first passive and CMOS active lablets and a docking station were created (RUB), an integratable pH sensor was explored (UOG), irreversible and partially reversible DNA directed docking of gel surrogate lablets was achieved (RUG, HUJI), electronically directed DNA mediated processes with DNAzymes established (HUJI), work began on lablet chemical cloning (RUBb), a robust integrable supercapacitor coating in MnO_2 established with 100mF/cm^2 capacitance (UOG), passive and electronically active lablets constructed (RUBa,c), a docking chip and interface for lablet control built (RUBc,a), electronic and physicochemical simulations of lablets developed (RUBa, UOG), connections with smart gel particle applications explored (VSCHT) and computational simulations of lablet swarms performed (SDU).

In years two and three of the project, the functionality of the lablets and dock were extended and a effort concentrated on integrated supercapacitor development and electrochemical power for the lablets as well as reversible docking chemistry. Further developments of polyoxometalate layers for sensing were made (UOG), switchable lateral electrical docking connections between lablets were established (RUG), reversibly electronically switchable DNA processing via ion uptake and release was demonstrated and sensor functionalities for pH, small ions and DNA were developed (HUJI), interdigital lablet supercapacitors were produced and tested (UOG, RUBa), a family of 2nd generation (CMOS2) lablet variants with low power consumption, integrated sensors and other functions were developed (HUJI, UOG), a new general purpose smart docking chip with integrated pH sensor was designed and fabricated (RUBc,a), operating software was extended with full diagnostics for lablets and dock of CMOS1 (RUBa) and physical simulation of communication, electrolocomotion, and other functionalities performed (RUBa, UOG), a magnetic control system for lablets was completed along with a demonstration of controlled interactions with chemical reservoirs (VSCHT) and hierarchical simulations of lablets including their self-replication in swarms were successfully demonstrated (SDU). A key technique in the fabrication was the instrumentation of a programmable galvanic network in CMOS, allowing coating/recoating of specific electrodes on lablets. Bipolar powering of CMOS circuits on microscopic particles using electric fields was investigated (RUBa) and shown to be effective in driving current through active circuit elements in lablets without wired connections.

A highlight of the work in years two and three was the electronically reversible lablet docking (RUG/HUJI) by functionalizing lablets with DNA layers employing rolling circle amplification and reversible DNA hybridization mediated by pH changes. Further key achieve extensions involve (i) pH-switchable and DNAzyme cleavable hydrogels and the activation of enzyme cascades (ii) pH-switchable

aggregation/deaggregation of enzyme cascades. In the final period, the supercap voltage was increased to over 1.4V and capacitance to 850F/m^2 using a Au/MnO_2/PPY system.(RUBa)

Lablet chemistry control (HUJI) advanced the program goals by developing: (i) Means to electrically switch DNA-driven catalytic transformations, programmed transformations and cascaded catalytic processes. (ii) The self-assembly of functional chemical coatings on surface for controlling interfacial electron transfer, dictated synthesis, and programmed catalysis. (iii)Triggered aggregation/deaggregation of microlablets, and methods for the targeted assembly of coatings and catalytic interfaces.

These studies demonstrated innovative means to assemble functional stimuli-responsive hydrogel matrices on patterned domains and to generate metal ion reservoirs on electrode arrays for the electrochemically addressed release of ions and the activation of DNAzymes, DNAzyme cascades and dictated chemical transformations. A model approach for the electronic sensing of DNA on dock or lablet arrays was also developed. The method has several steps shown in Figure 2.

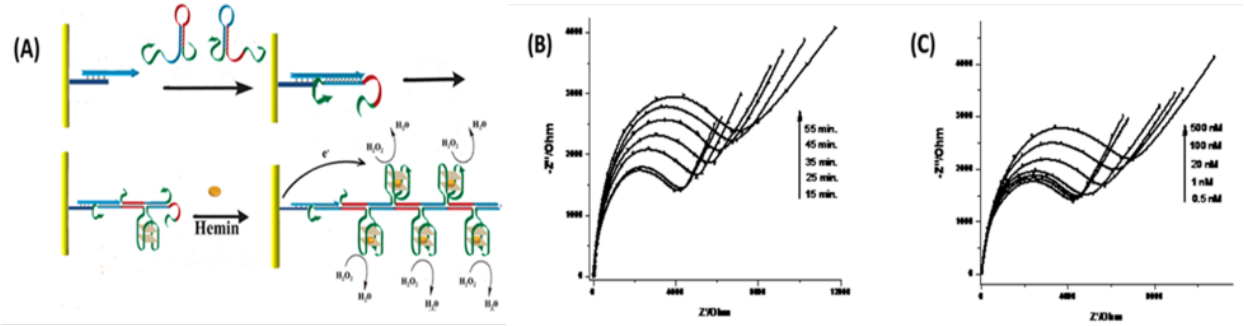

Figure 2 (A) Amplified electrochemical detection of a target gene by the HCR reaction yielding electrocatalytic DNAzyme chains. (B) Time-dependent Faradaic impedance spectra upon the gene-triggered operation of the HCR process on the electrode surface, at a fixed concentration of analyte, 500 nM. (C) Faradaic impedance spectra observed upon sensing different concentrations of the analyte gene, and allowing the HCR process to operate a fixed time-interval of 45 min.

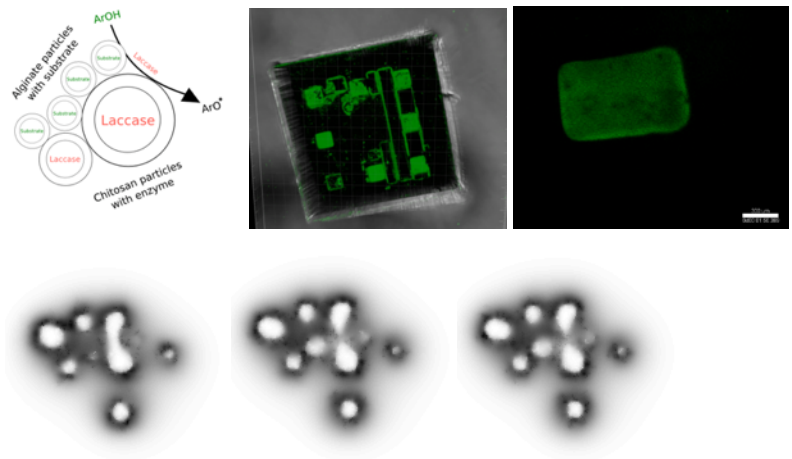

Figure 4 Advanced lablet functionality. **Top:** Development of drug release control mechanism that can be programmed by lablets (left) or the dock (right) to interact with cells. (VSCHT) **Bottom:** Three images of simulations of self-replicating hierarchical structures composed of lablets. (SDU)

Electronically controlled accumulation of micro- and nano-scale vesicles that can store and release biologically active species was achieved by the combination of the docking station above and specifically prepared charged lipid capsules (liposomes) (VSCHT). Thanks to their surface charge, the vesicles can be attracted to, or actively repelled form, certain locations of the docking station by selectively switching on and off individual electrodes or their groups, forming desired spatial patterns. The physiological response of reactive oxygen species (ROS) produced from the liposomes has been demonstrated by the cell death of cancer cells induced by oxidative stress.

Simulations at multiple levels are developed exploring different lablet properties and lablet dynamics. Using density function theory simulations, we have demonstrated that core-shell metal oxide clusters and molecules

are good candidates for metal-oxide-semiconductor (MOS) for electron storage, memory and switching, and are employed in lablet supercaps and sensors. A mesoscopic simulations based on a formal language has clarified how the communication between the lablets and the chemistry could be designed and optimized. A hybrid reaction-diffusion simulation (representing the chemical environment) combined with active local automata (representing the spatially distributed lablets) was developed to explore macroscopic lablet swarm dynamics. Through these simulations, we discovered a novel form for swarm-generated self-replication. Such self-replicating systems demonstrate the potential for evolvability of populations of swarming or self-assembling microcontrollers interacting in a spatial chemical environment. In addition to this work, the problem of encoding chemical information in electronic signals, which represents a generalization of the genetic coding problem, was investigated further (UOA, RUBa) and a relationship with reservoir computing in the NASCENCE fellow UCOMP project established.

In the final period the CMOS3 generation of lablets and dock were designed and fabricated, with integrated supercap and flexible programmability capable of implementing higher order functions such as concentration, docking and locomotion control and a full lablet life cycle. The dock was also improved in sensor and current measurement capabilities. Further developments in docking chemistry integration, sensing capabilities and ion control with the dock were achieved and combinatorial optimization of supercap coatings pixelwise on the dock setup.

One of the major interests in MICREAgents is the problem of establishing an electronic-chemical code and translation machinery, so that the advantages of sharing electronic and chemical information can be explored. This situation is akin to the major problem of the origin of life with the establishment of the genetic code. Like genetic information, electronic information can be readily manipulated and copied, but its translation into functional chemical information useful for embedded construction processing potentially requires significantly complex machinery and orchestration (cf. the ribosome in cell biology). In year two, we moved closer to this goal with more realistic simulations of electronic chemical programmable interactions in lablets (UOA, RUB).

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