μElectronics Components for Lab-On-Chip Instruments in Molecular Diagnostics

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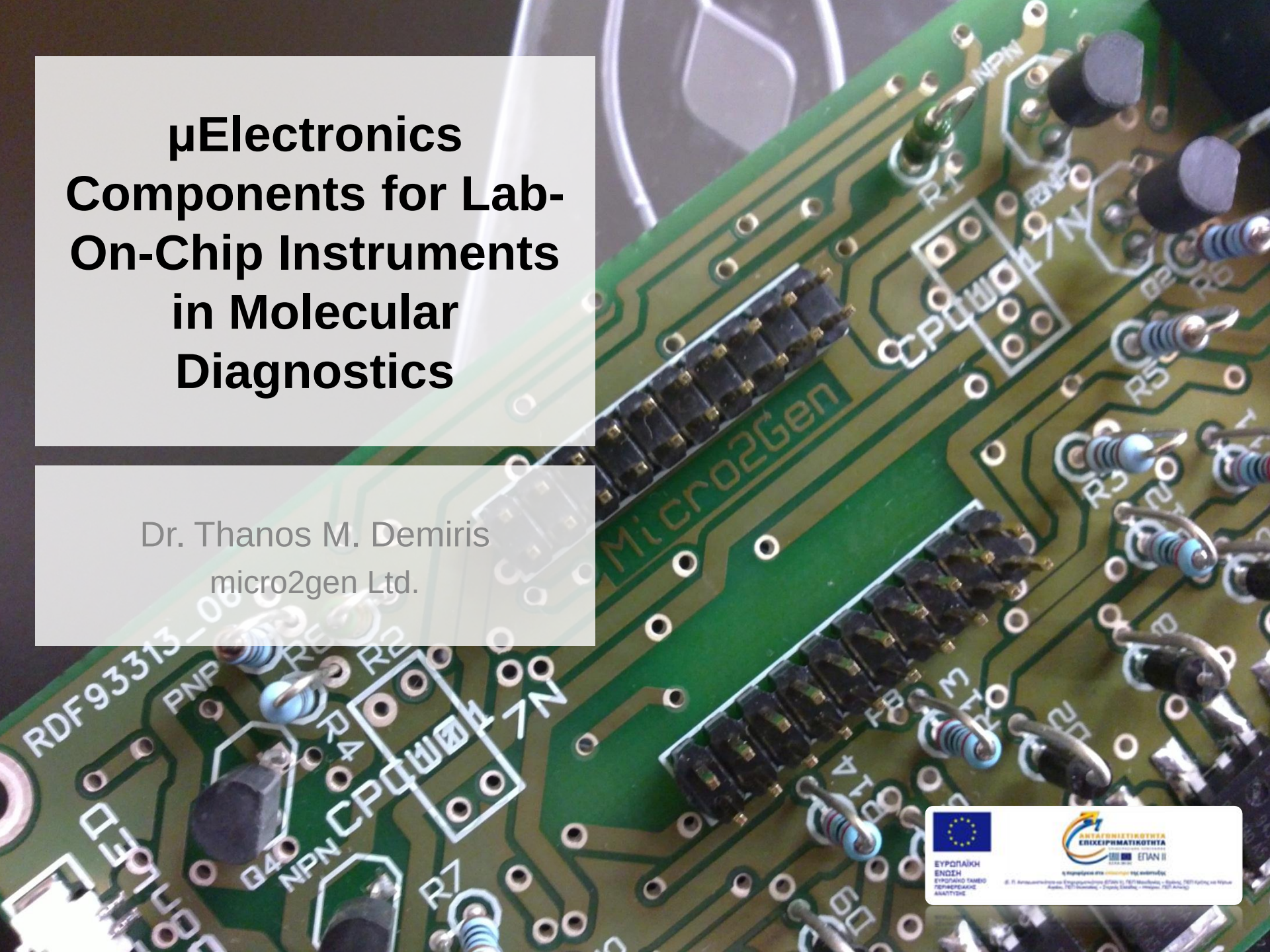
micro2gen Ltd.



Project Motivation

- The Market Value of Biochips and microarrays in molecular diagnostics (Jain Pharma-Biotech Report 2011)
  - was **$2.15 billion** in 2010
  - expected to grow to **$3.5 billion** by the year 2015
  - and **$10.6 billion** by the year 2020
  - About **75%** of biochips are **DNA** chips
  - **15%** are **protein** chips
  - 10% use other technologies
  - By 2015, **20% of the biochip market** is expected to be "**lab-on-a-chip**"
- Involved in this market
  - Large pharmaceutical industry
  - Specialized Enterprises (instrumentation, microfluidics etc.)
  - Numerous research institutions

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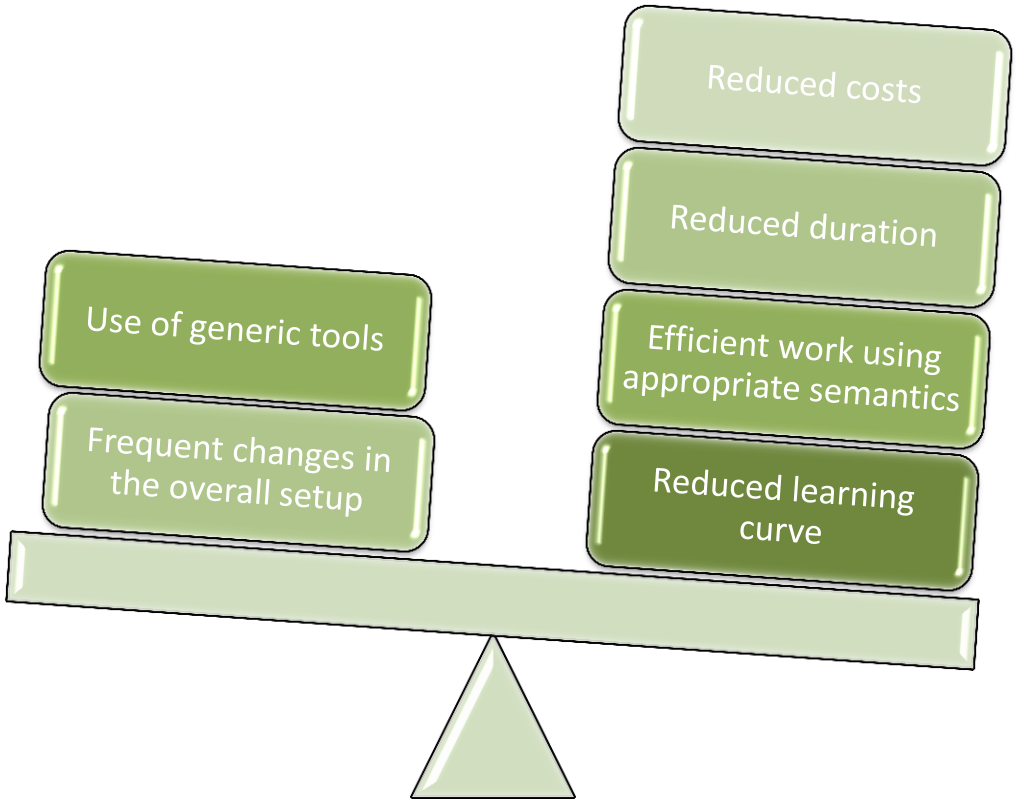
State-of-the-art in Prototyping

Everyday work of Lab-on-a-Chip groups

Domain-specific Tools



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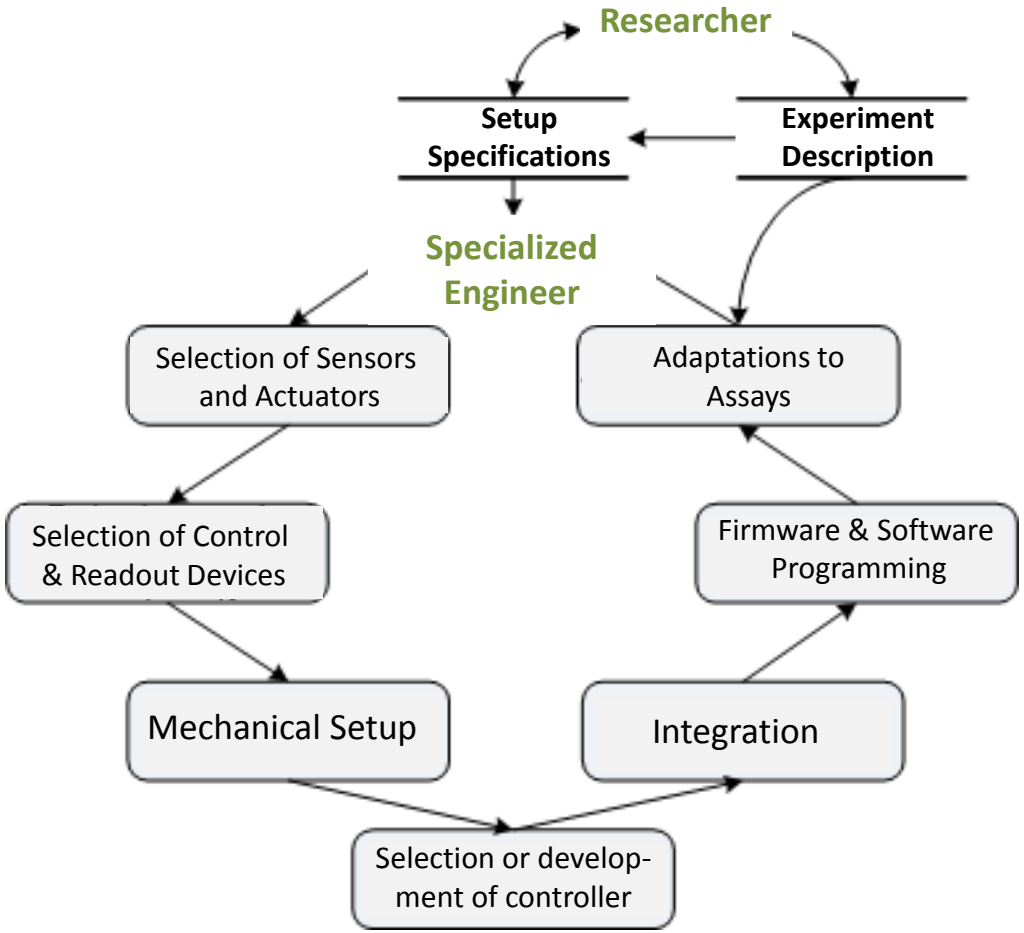
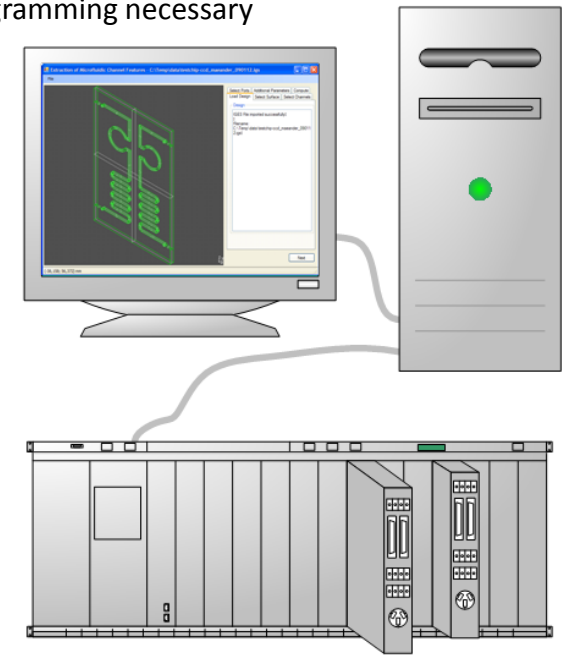
State-of-the-art in Prototyping

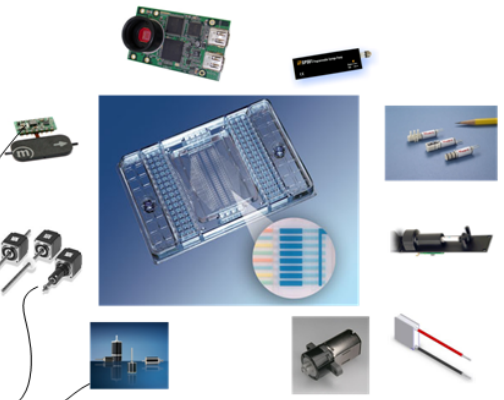


Suggested Structure of the Solution

Flexible Software:
Operation by researchers
No Programming necessary



Support for virtually all typical
sensors and actuators on the market
+ innovative proprietary solutions



Ready to use control and readout hardware
Novel control components (machine vision)
Fully flexible and extensible

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Goals of the project

- Create a comprehensive state-of-the-art in sensors and actuators
- Define a flexible solution architecture
- Introduce specialized control hardware to reduce costs of deployment and introduce new features
  - Machine vision control of fluidic motion
  - Flexible and accurate position determination
  - Speed measurements (not for continuous flow)
  - Volume measurements (not for continuous flow)
- Introduce various novel biosensors and the corresponding readout modules
  - A new generation of capacitive biosensors
- Use existing biochips but also develop a novel and completely different solution within the project
- Validate using an actual PoC genotyping scenario

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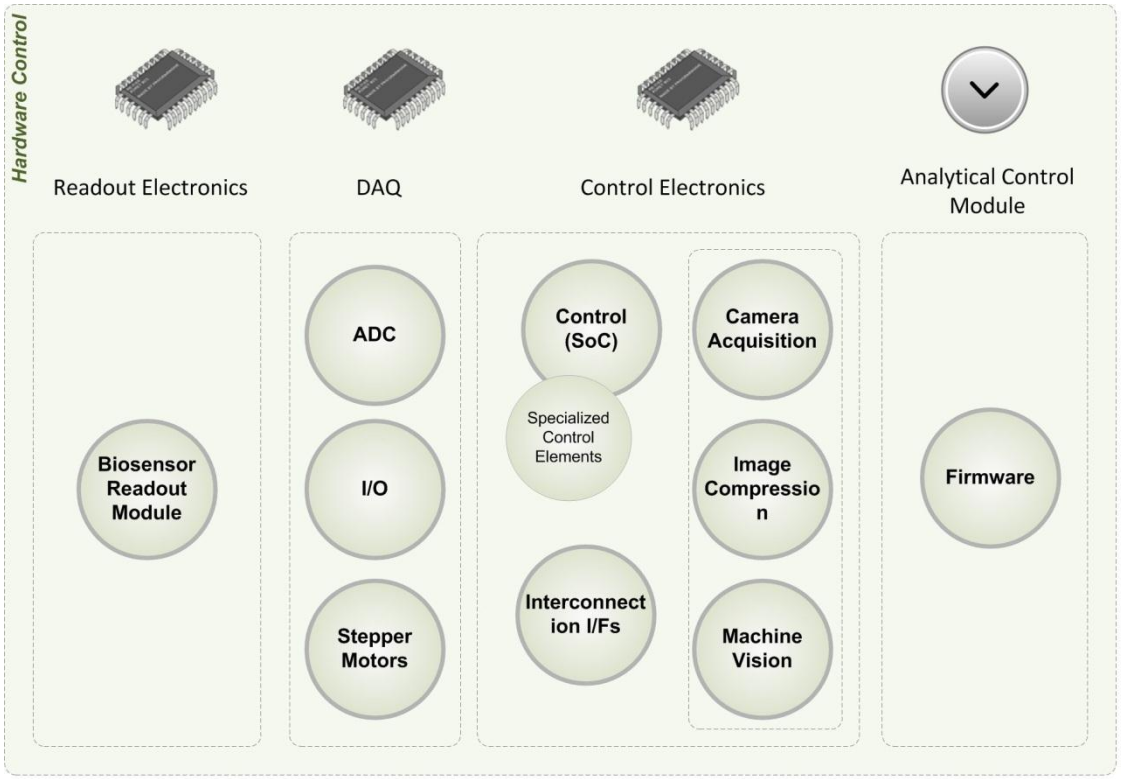
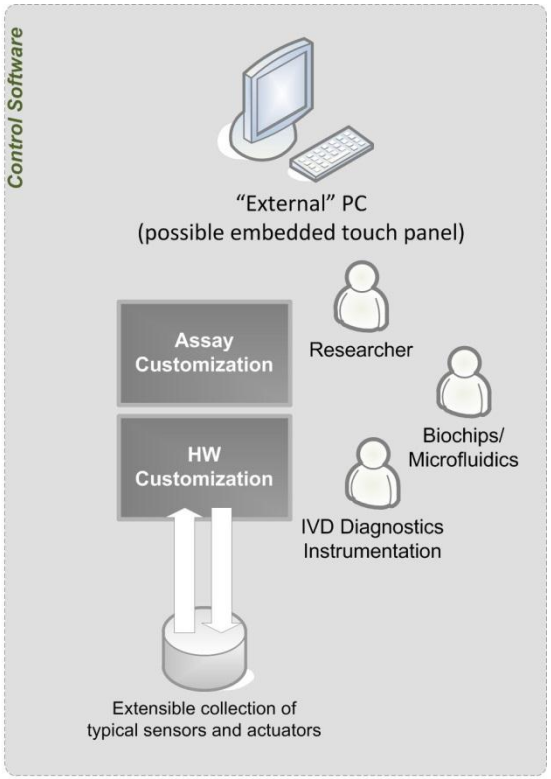
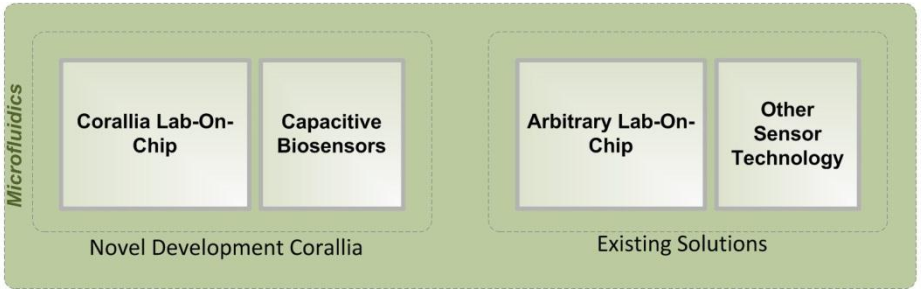
Suggested solution architecture overview







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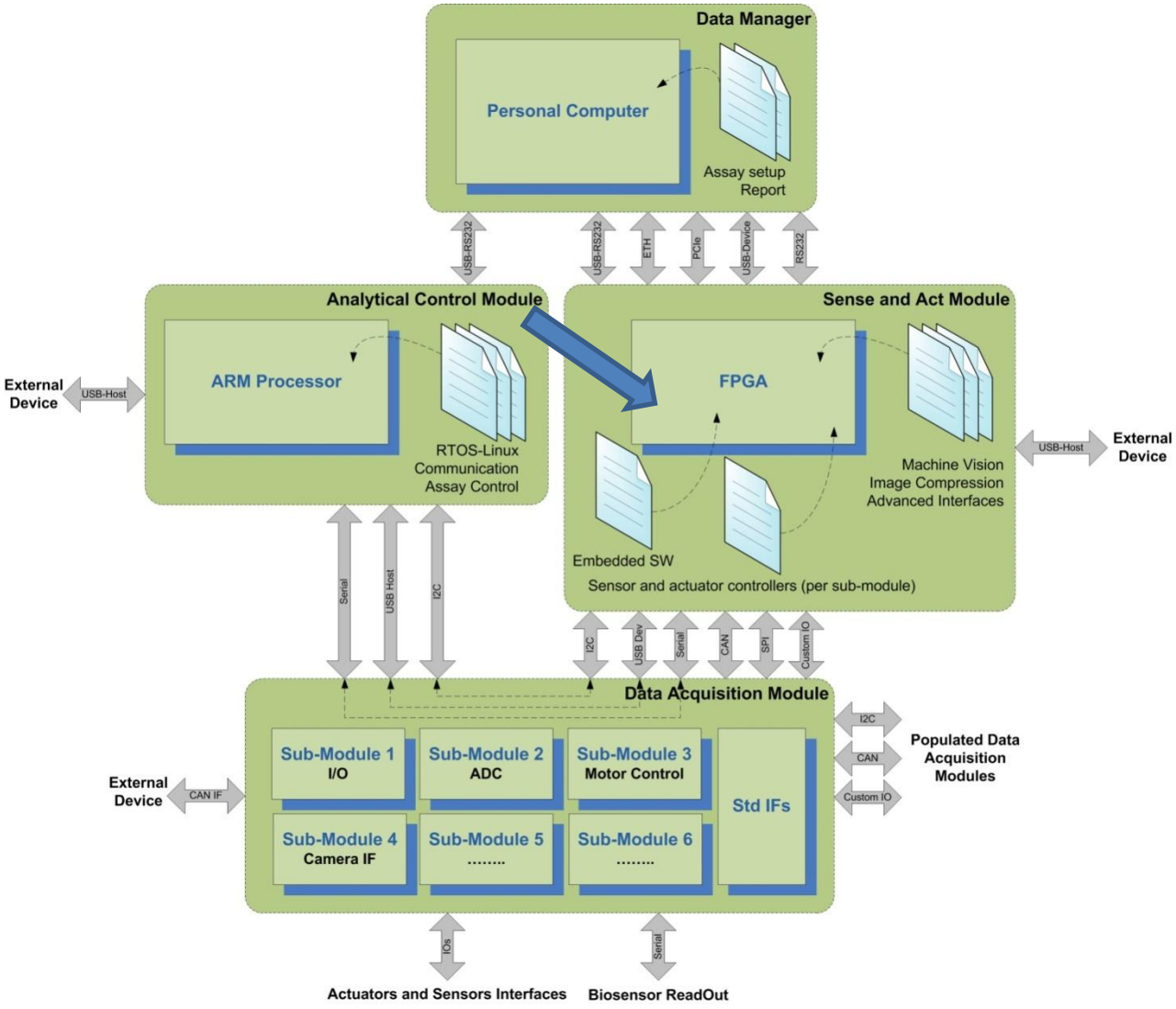
Hardware Deployment Overview



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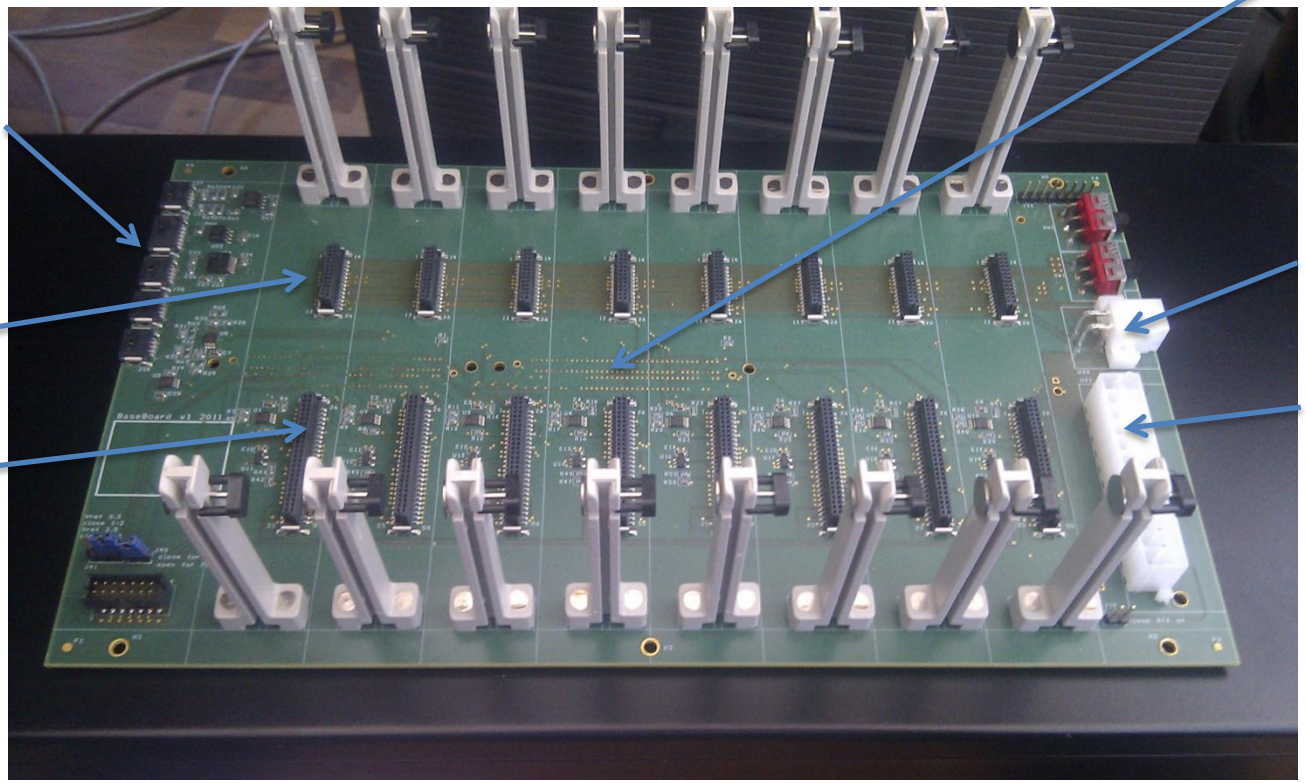

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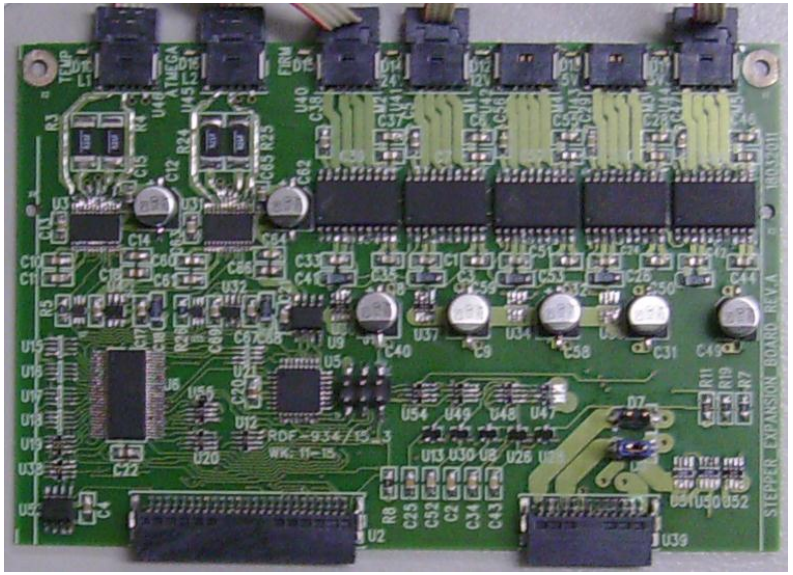
Sample Board: Stepper Control

- Simultaneous Control of
  - 2 medium power motors
  - 5 reduced power motors
- Control of:
  - Syringe pumps
  - Peristaltic pumps
  - Linear Drives
  - Etc.



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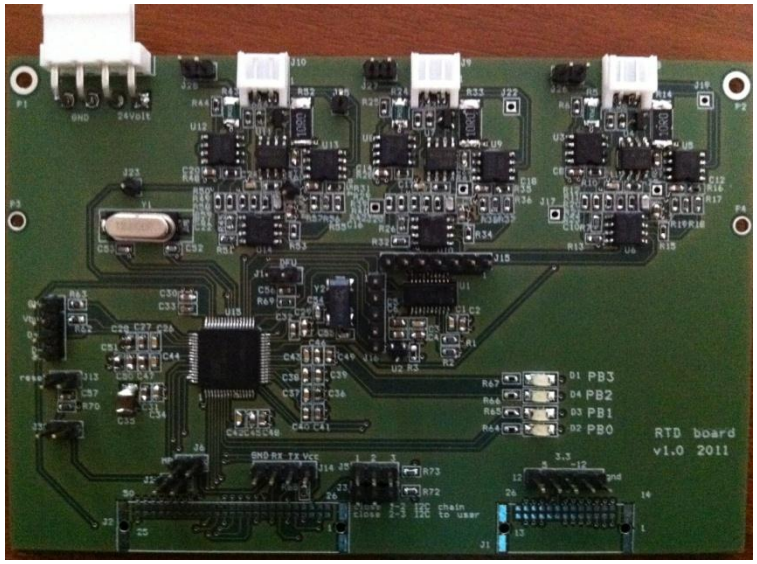
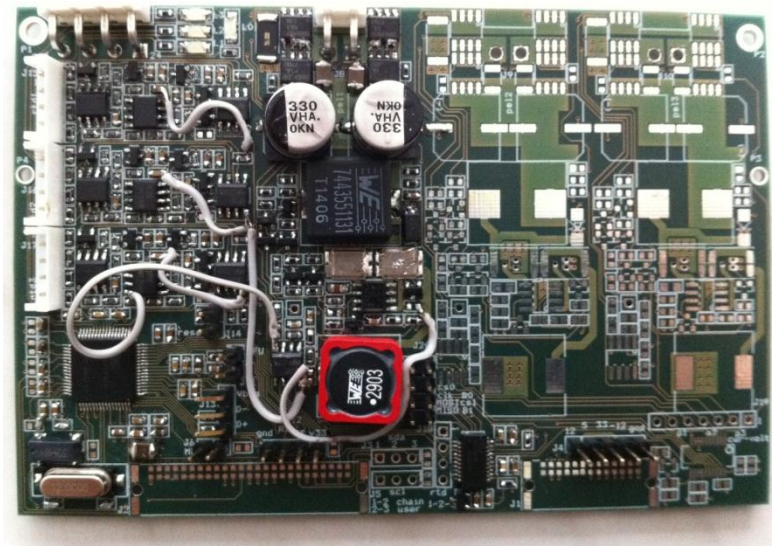
Sample Board(s): Temperature Control

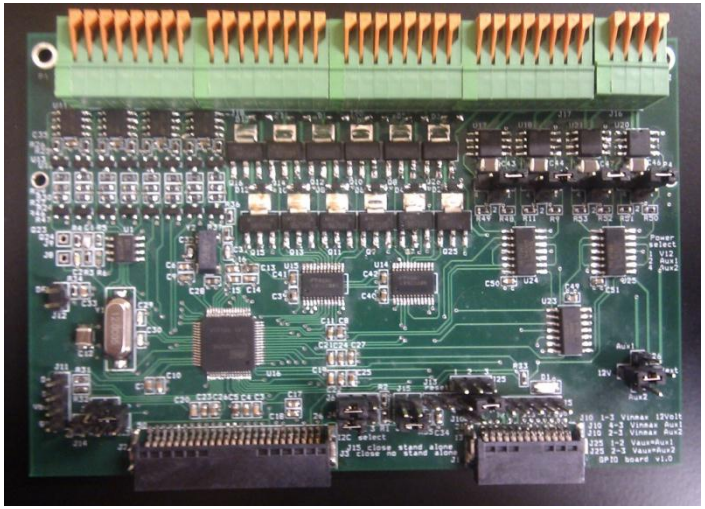
- Resistive heaters
  - Simultaneous control of 3 resistive heaters
  - Closed control loop with temperature checks and PID control for temperature estimation
  - Suitable for microheaters (see Corallia LoC)
- Peltier Elements
  - Simultaneous control of 3 peltier
  - Closed control loop with temperature checks and PID control for temperature estimation





Sample Board: GPIOs

- 8 inputs: voltage up to 24 V, electronically regulated low voltage 0-3.3V
- 16 outputs 1A/24V
  - 6 outputs with PWM
  - 2 out of 6 with electronic reversing of polarity
- Applications:
  - DC motors
  - LEDs for lighting
  - Control signals
  - Etc.



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Machine Vision Control

- Novel Control mechanism
  - Initial concept conceived within the framework of the FP7 CDMEDICS project
  - Replaces distinct pre-selected control points on a biochip, thus enhancing flexibility
  - Reduces mechanical alignment problems
  - Significantly reduces costs (feasible with a low-cost camera and low-cost illumination sources)
  - Introduces new measurements: speed, volume, bubble formation etc.
  - Allows for remote access and technical support while an experiment is running!
  - Requires visible wave-front but is also suitable for two-phase microfluidics (not suitable for continuous flow)

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Machine Vision Control Implementation

- Spartan-6 XC6SLX150TFGG676-3 - 180Hz clock, 1024^2 frame size
  - 11,657 ms for chip detection
  - 1,456 ms for edge detection
  - 44,83 μs for flow detection
- Implementation of a frame-grabber
  - Any Camera-link camera can be attached to the system
- Implementation of an image compression IP on hardware
  - For remote access and frame transfer over an Ethernet connection

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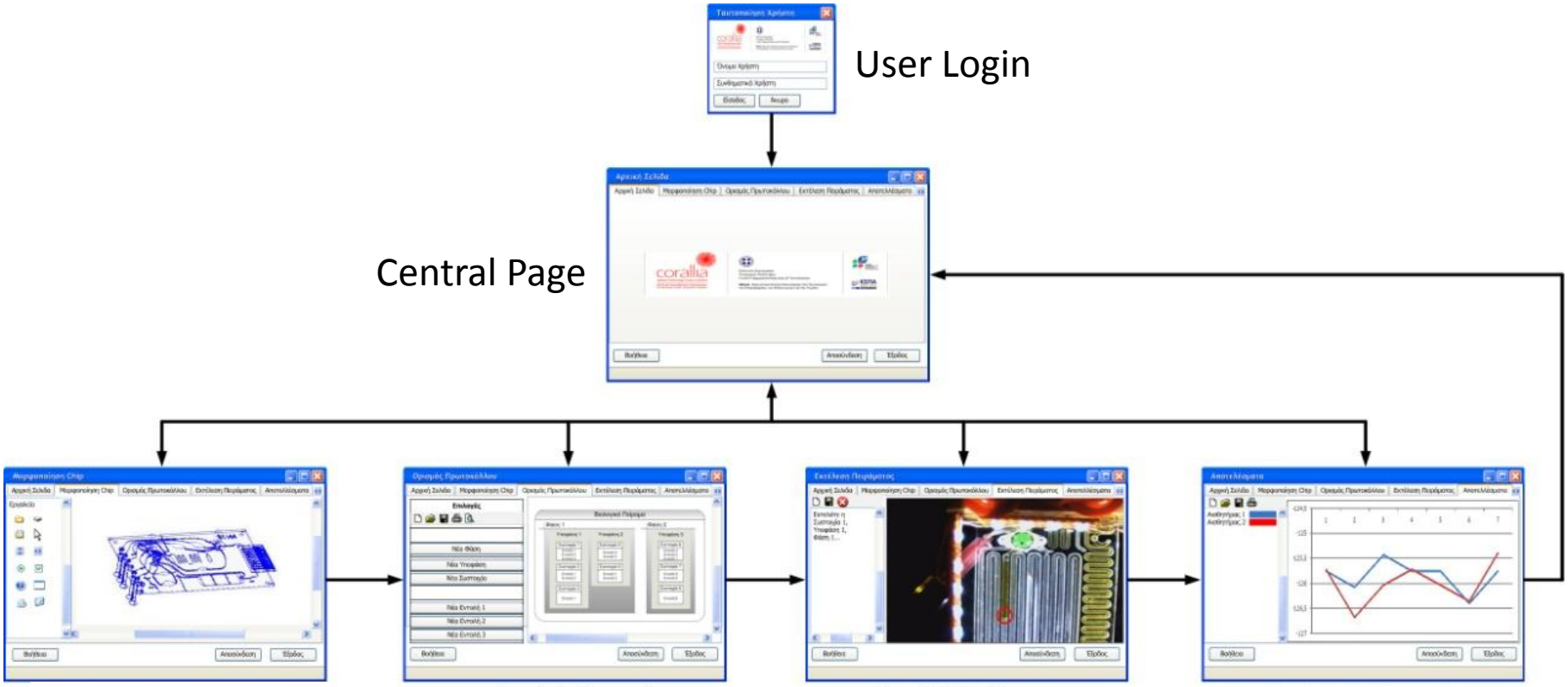
Software Concept



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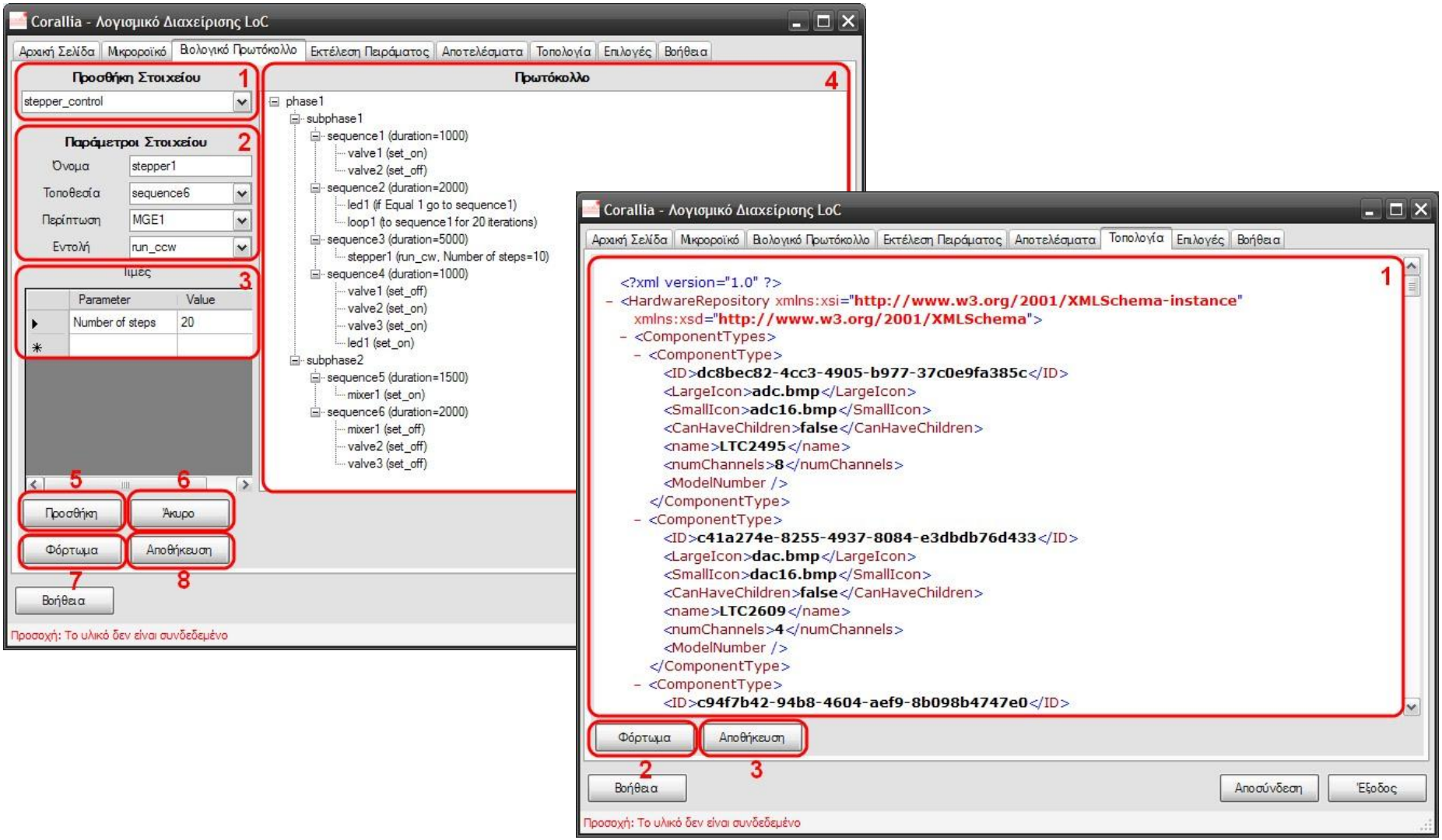
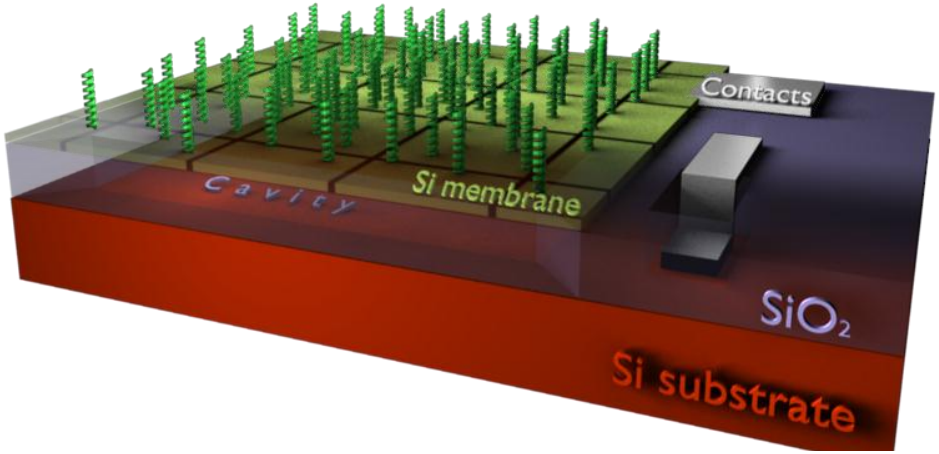
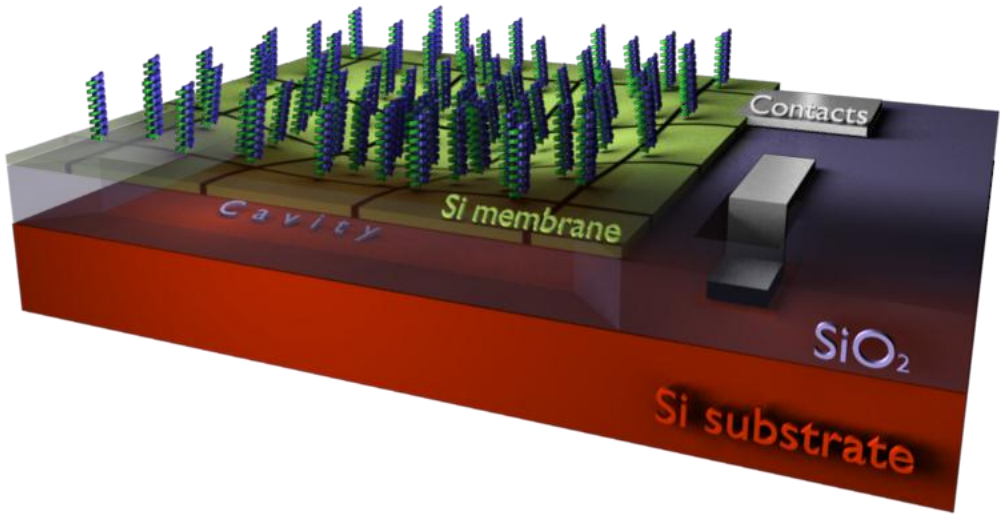
Software Details



Capacitive Biosensors - Concept

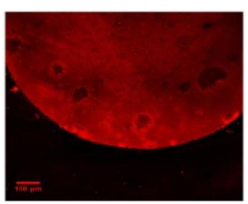


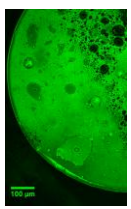


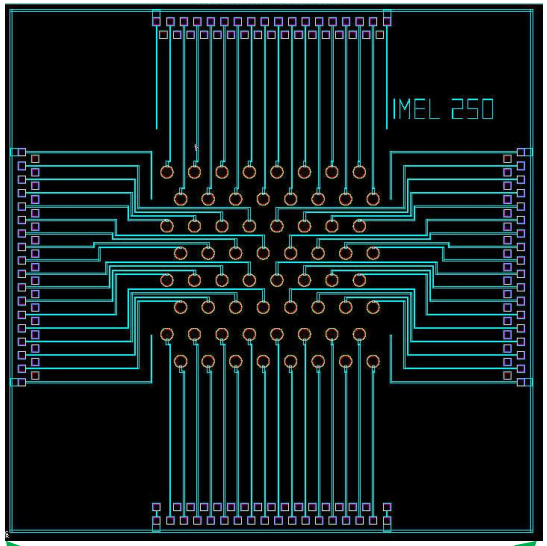
Si Membrane diameter [µm]	125 - 275
Si Membrane thickness [µm]	0.7 - 1.5
Depth of support surface [µm]	0.5 - 1.5
Coverage [$R_{membrane}/R_{biomaterial}$]	70%

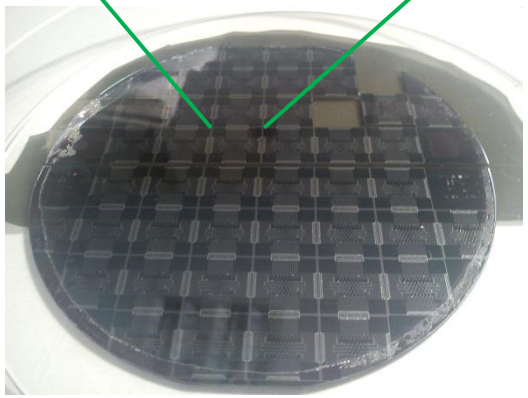
Capacitive Biosensors - Measurements

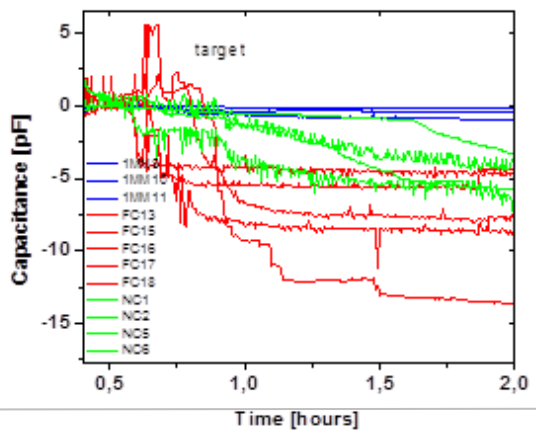
- Construction of a capacitive biosensor array
  - Consists of 64 independent biosensors
  - Each membrane has a diameter of 150-250 μm

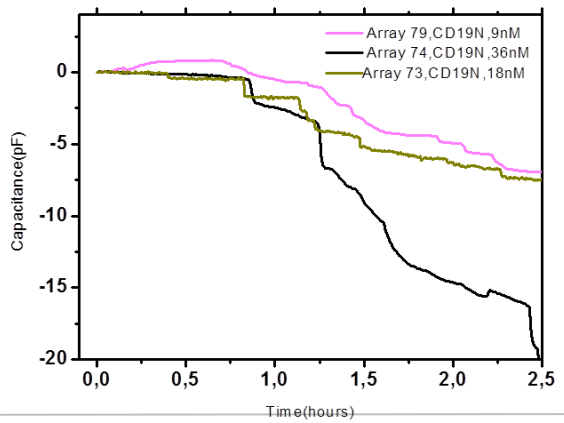












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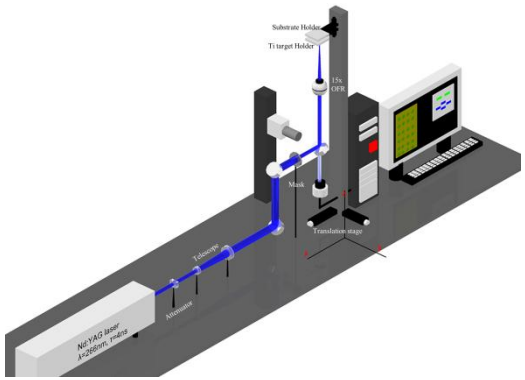
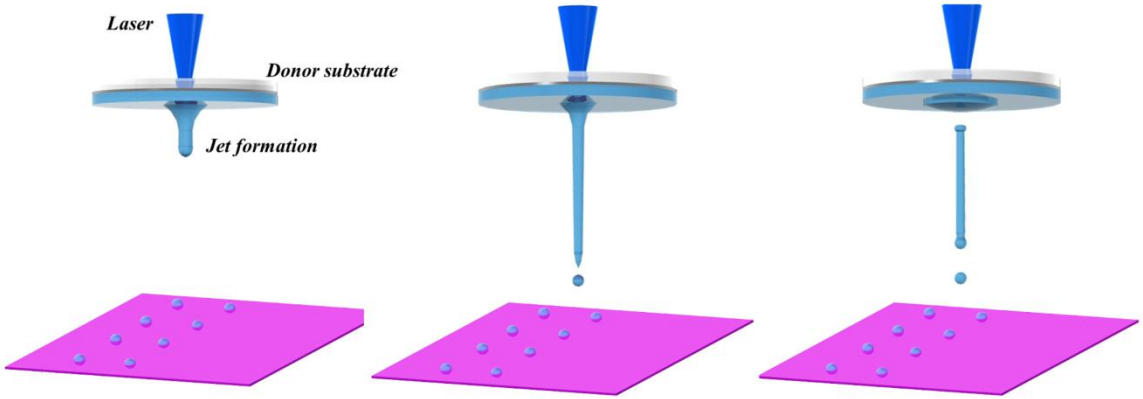
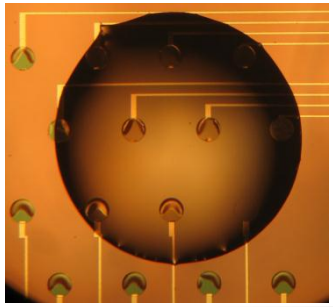
Specialized deposition technology

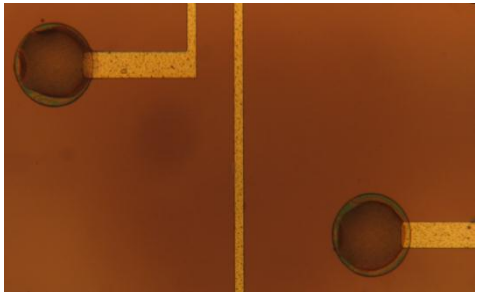




- LIFT (laser induced forward transfer): The laser energy is transferred to a donor substrate with an absorbing layer (40 nm Ti)
- The inner energy of the absorption layer is transferred through a heat wave to the thin film of the fluid and a droplet is formed
- The droplet is expanding and then detached in form of a jet



Pipette deposition
V= 1μL



Laser deposition
V= pL

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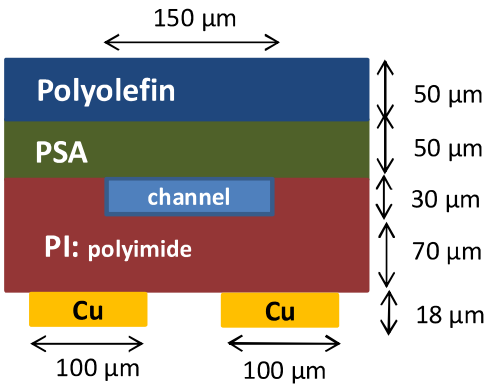
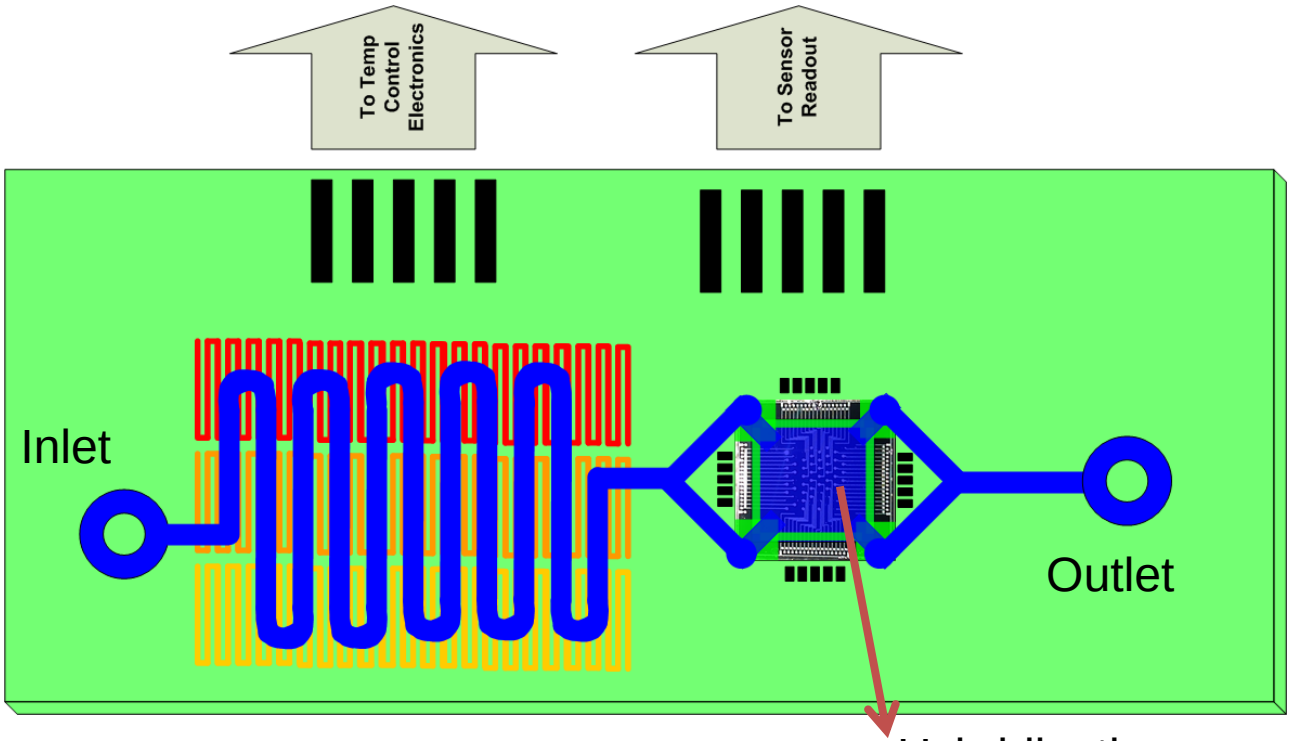
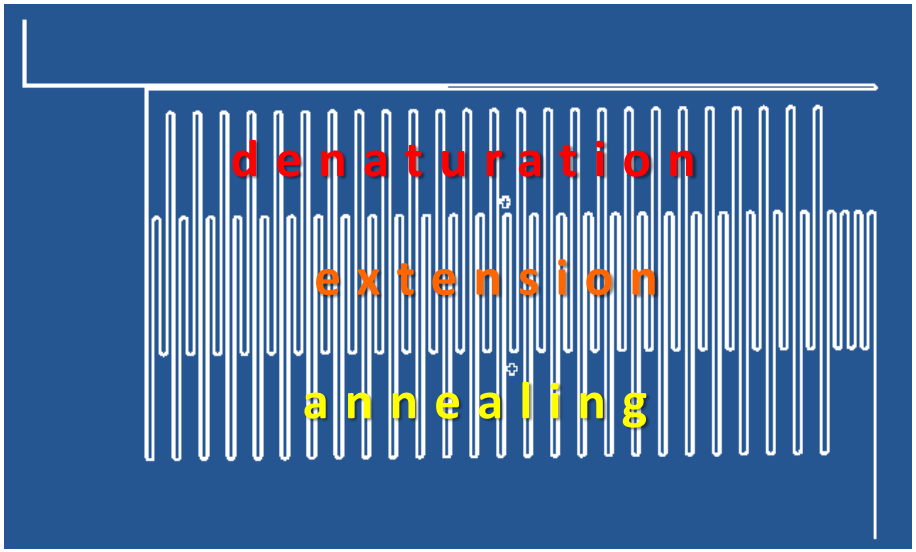
A novel biochip integrating the sensors

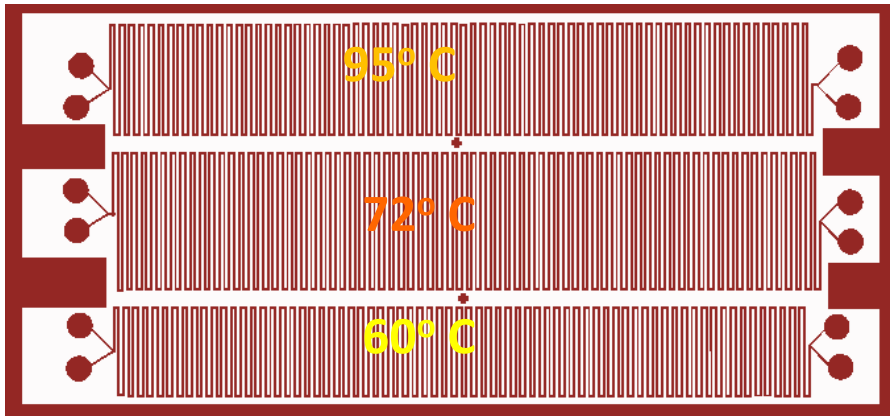


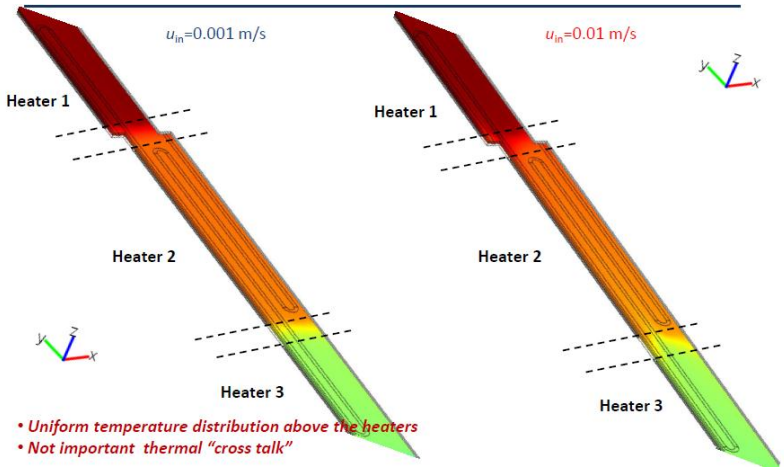


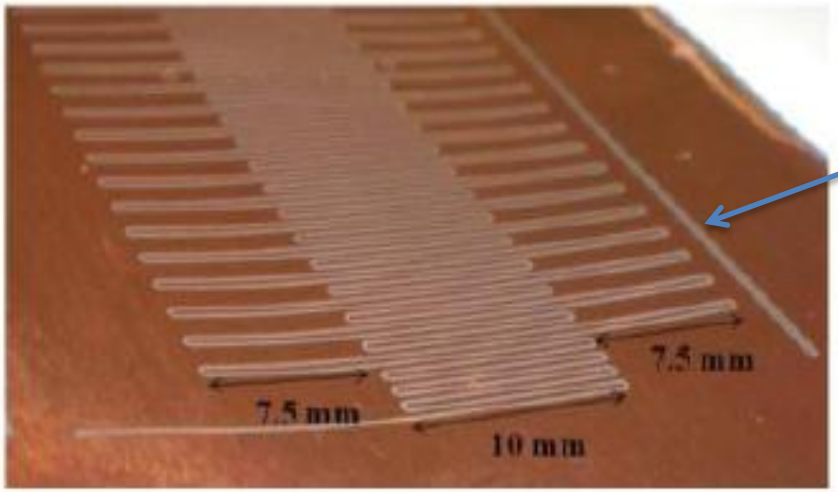
Metalized polymeric material, integrating microchannels and heaters in one disposable microsystem

PCR Zone Description



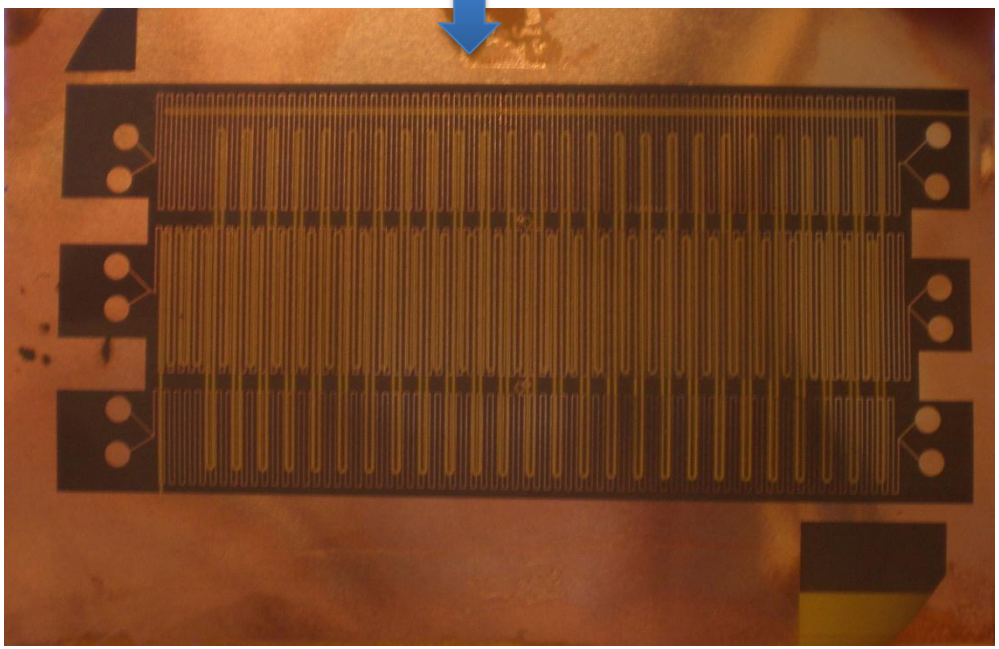


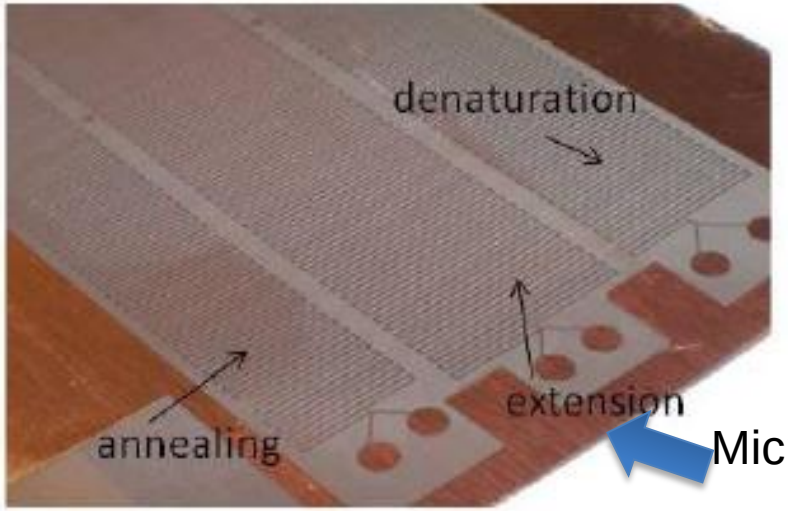




Micro-Channels

Two sided arrangement





Microthermal elements

Validation target

- KRAS is usually tethered to cell membranes
- The protein product of the normal KRAS gene performs an essential function in normal tissue signaling, and the mutation of a KRAS gene is an essential step in the development of many cancers
- The most common mutation appears on G12D
- In the case of colorectal cancer the detection of KRAS mutations is used for treatment evaluation with antibodies against EGFR (40% of all cases)

Conclusions

- Creation of a domain-specific overall solution
  - Featuring specialized hardware
  - Novel controls implemented with hardware acceleration
  - Flexible software to replace programming and reduce experimentation time
- To be used as a rapid prototyping tool or
- To be incorporated as IP components in existing solutions
- Validated using real scenarios and setups
- With ssignificant bioproducts
  - Novel biosensors
  - Novel biochips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MICROSYSTEMS FOR MOLECULAR DIAGNOSTICS
ΑΡΙΣΤΟΤΕΛΕΙΟ
ΠΑΝΕΠΙΣΤΗΜΙΟ
ΘΕΣΣΑΛΟΝΙΚΗΣ
AUTH Electronics Lab
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ΕΝΩΣΗ
ΕΠΑΝ II