Micro- and Nanotechologies for Bio- Medical Applications

IMT-Bucharest, www.imt.ro

CEO and President of the Board:
Prof. Dan Dascalu (dascalu@imt.ro)

The structure of the organisation is displayed on www.imt.ro
(see also the scientific report 2005 in electronic form)

Field of activity of IMT: *micro- and nanotechnologies*.

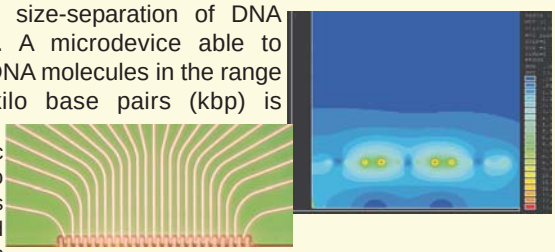
Romania established in 1993 the Institute for Microtechnologies, or IMT (as the first institute from Eastern Europe having this profile), as well as the "microtechnologies" field of research in the National R&D plan (1993). IMT became a national R&D institute in 1996, also including nanotechnologies in its field of activity. Since 2004, the research thematic area was oriented towards **convergent technologies**, i.e. **micro-nano-bio-technologies**.

IMT (**www.imt.ro**) has now a very convincing participation in FP6, covering the whole spectrum of instruments. At the same time IMT took a decisive step in developing infrastructures for technology transfer and innovation (with the support of the national programme INFRATECH). The science and technology park for micro-and nanotechnologies MINATECH-RO, with a second clean room and new equipments (including electron beam lithography and RIE) open in spring 2006.

The **NanoBioLab**, developed in IMT for the network **RO-NANOMED** (**www.imt.ro/ronanomed**), see below, is part of the new technological area. IMT is **the national contact point for the European technological platform of nanomedicine** (contact address: **nanomedicine@imt.ro**).

Microsystem for DNA macromolecule separation

Achievements: Design and fabrication of a dielectrophoretic device for size-separation of DNA molecules. A microdevice able to separate DNA molecules in the range of tens kilo base pairs (kbp) is proposed.



Metallic microelectrodes deposited on a glass plate

Simulated electric field for 6 successive gold electrodes, 3mm wide and 3mm space deposited on oxidised silicon (++-- ++).

The DNA molecules separation is obtained using a travelling electric wave, created by a line of metallic microelectrodes, successive polarized; microelectrodes of few microns wide were realised by microlitographic techniques.

MATNANTECH project (2004-2006);

Contact person: Florea Craciunoiu (floreac@imt.ro)

(see other examples on the following pages)

IMT: Main areas of interest in FP7 (selection related to "bio" applications)

A. Information and Communication Technologies (ICT) - Development of mixed-technology for micro/nano systems (e.g.microfluidic/ICT/micro-nano, bio/chemical) - Development of innovative microstructures and systems for prevention, diagnostics and treatment processes: micro-fluidics and lab-on-a-chip; bio-photonics chips (biosensor with microphotonics components and systems); silicon biochips; controlled drug delivery systems; bioMEMS (bio microsensors). - Development of microsensors, bio-sensors, bio-photonic sensors and arrays of sensors for an optimised environmental control and monitoring, for food quality control, and for home applications - Teraherz environmental monitoring systems on a chip(SoCs)

B. Nanosciences, Nanotechnologies, Materials and new Production Technologies (NMP) - Nanomaterials: new nanostructured semiconductor, organic, organic/anorganic hybrids materials with controlled properties, new functionalities and improved performances for industrial applications; biomaterials and hybrid materials; carbon nanotubes and fullerenes based materials. - Integration of nanomaterials and nanostructures for microsystems; - New advanced characterization techniques development for nanomaterials and nanostructures; Nano-bio-tehnologies - New approaches for interfacing biological and non- biological components; - Self- assembly nanostructures on micro/ nanoprocessed silicon surfaces, with biomedical applications; - Integration of the nano- bio- technologies with information technologie, social, cognitive and neurosciences in order to find to alleviate the effect of disabilities and to create new types of nanotransducers

Strategy

The strategic objectives of the institute on medium term are the following:

a. The institute intends to become an excellence centre in research and development related to the integration/ convergence of technologies (micro-nano-biotechnologies)

b. The institute will function as a "technological pole", by using the facilities such as "clean room" spaces and the whole complex of equipments and computing technique to provide a platform of interaction of the Romanian research with industry and education. In Romania, IMT has a unique position through the activities carried out until now, but this role will be further developed and strengthen.

Details about participation of IMT in European projects related to the "bio" field

• Multi-domain platforms for integrated micro-nano technology systems – Service Action (**INTERGRAMplus**), IP, Priority 2 -IST, Contract no.: 027540 (2005-2007), Coordinator: QinetiQ Ltd, UK. IMT position: partner; Contact person for IMT: PhD. Carmen Moldovan (cmoldovan@imt.ro).

• Development of a toxin screening multi-parameter on-line biochip system (**ToxiChip**), STREP, Priority 2 -IST, Contract Number: 027900 (2006-2009), Coordinator: Dr. Terri Wood, University College Cork - National University of Ireland. IMT position: partner; Contact person for IMT: PhD. Carmen Moldovan (cmoldovan@imt.ro).

• Lab-On-A-Chip Implementation of Production Processes for New Molecular Imaging Agents (**MI-lab-on-chip**), STREP, Priority 3 -NMP, Contract no: 516984 (2005-2007). Coordinator: Dr. Jean-Luc MorelleTRASIS SA, Liege, Belgium; 5 partners involved. IMT position: partner;

Contact person for IMT: PhD. Student Oana Nedelcu (oanan@imt.ro).

• A network for bringing NANOtechnologies TO LIFE (**Nano2Life**), NoE, (2003-2007), Priority 3 -NMP, Coordinator: Dr. Patrick Boisseau, CEA France. IMT position: Associated Partner; Contact person for IMT: Prof. Dan Dascalu (dascalu@imt.ro).

• MIcro-NanOSystems EUROpean NETwork pursuing the integration of NMS and ACC in ERA (**MINOS-EURONET**), SSA, Priority 2 -IST, Contract no: 015704 (2005-2007), Coordinator: National Institute for R&D in Microtechnologies (IMT-Bucharest); 17 partners. Coordonator: Prof. Dan Dascalu (dascalu@imt.ro).

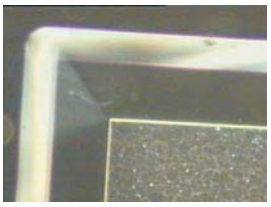
• Advanced Handling and Assembly in Microtechnology (**ASSEMIC**), Marie Curie Research Training Network, Contract: 504826 (2004-2007), Coordinator: Prof. Dr. Werner Brenner from Institute of Sensors and Actuators Systems, Vienna Univesity of Technology-ISAS; IMT position: partner; Contact person for IMT: PhD. Raluca Muller (ralucam@imt.ro).

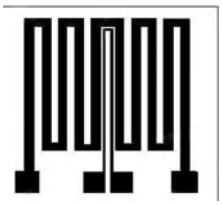
Application of micro- and nanotechnologies in the „bio" domain (including medical and environmental)

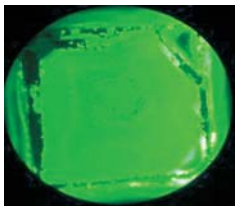
Silicon-Chip-Based Bioanalytical Microdevices

A silicon microchip with a microreactor and a heater for oligonucleotide amplification by polymerase chain reaction - PCR and rapid analysis of the DNA samples is realized. Achievements: •silicon array microfabrication; •reactor surface functionalisation and DNA immobilization; • PCR cycling and on-chip DNA microarray hybridization.•DNA microarray (after washing) scanned with a confocal fluorescent scanner.

PCR microdevice 4x4 mm2 chip structure: (a) microreactor; (b) temperature sensor; (c) Fluorescent primer immobilisation, 10 pmols / µl on the reservoir surface functionalized with poly (lysine)



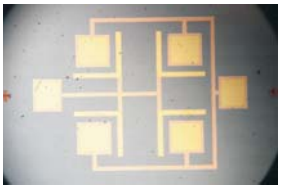


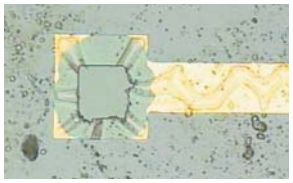


MATNANTECH Project (2003-2005) Co-ordinator : IMT-Bucharest, (Project Manager: Monica Simion: monicas@imt.ro); Partners: IMT Bucharest, Center of Nanotechnologies; Faculty of Biology, University of Bucharest, Dextercom. SRL

Microsystem for controlled drug delivery

Achievements: (i) design and fabrication of a Si microchip with a microreservoir array; (ii) calibration of microchip to deliver programmed drug doses over a prolonged period, at specific time intervals. The dissolution of gold cap to release the desired drugs (encapsulated in microreservoirs) occurs by a chemical redox reaction.





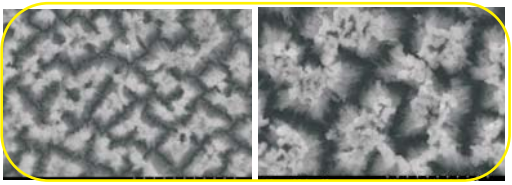
MATNANTECH Project (2003-2005) Co-ordinator: IMT-Bucharest, (Project Manager: Mihaela Miu: mihaelam@imt.ro); Partners: Institute for Chemical-Pharmaceutical Research; Oncological Institute "Al. I. Treistoreanu"

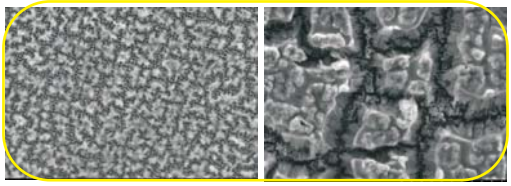
Gold electrodes (300x300 mm2,) on the back-side of the microstructure 4x4 mm2 chip structure

Nanostructurated silicon membrane technology for pharmaceutical microdevices

Monolith porous silicon (PS) devices as well as PS membranes are resorbable by the body, so the rate of the released substance will be related directly to the dissolved rate of the silicon material. Achievements: •design and fabrication of pharmaceutical microdevices on silicon;•silicon nanostructured membrane impregnation with Mg, K, Fe;•study of mesoporous silicon implant for pharmaceutical substances release; •study of the surface of PS layers modifications related to different exposure times in SBF (simulated body fluids). In the first day, a strong release of Fe and K was observed due to the dissolution of the iron/potassium salt from the PS pores. After that the iron release takes place in the same time with the degradation of the PS matrix in SBF solution.

Bioresorbable Fe/ Si nanostructured matrix exposed 1 day (a) and 5 days (b) in SBF





Bioresorbable K/ Si nanostructured matrix exposed 5 day (a) and 15 days (b) in SBF

MATNANTECH Project (2003-2005) Co-ordinator : IMT-Bucharest, Project Manager Anca Angelescu: ancaa@imt.ro); Partners: Institute for Chemical-Pharmaceutical Research; Center for Organic Chemistry

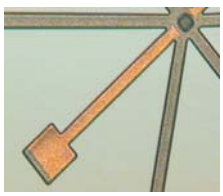
Lab-on-a-chip: Silicon multifunctional test structures with biomedical applications

Achievements: Design of a test bio-chip structure containing a two-steps microreactor, many microreservoires and micro-channels between them, and a cap with micro-pipes was proposed. All these structures were realized by silicon micromachining. The central reservoir was porosified in order to obtain a porous membrane.

This membrane is biocompatible with human tissue/ biological cells and can be impregnated with drugs or can be immersed in a drug solution; the influence of the drug on the ill cells can be investigated.

MINASIST project (2004-2005);

Contact person: Anca Angelescu: **ancaa@imt.ro**



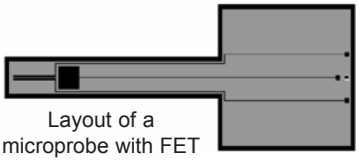
Microfluidic Biochip for Biomedical Application (a - x20; b - x10)

Technology for obtaining biosensors for bioterrorism toxin detection

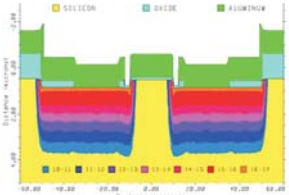
Achievements: The project aims to develop the technology for manufacturing a microsystem to monitor and detect toxins from natural environments (water, air, food). The integrated microsystem will include the biosensor that permits electrical measurements of several toxins and electronic circuits for signal processing. Field effect gas sensors are based on metal-insulator-semiconductor structures in which the enzyme deposited on the gate is detecting the toxins presence. ISFET sensors use the field effect transistors to detect very small quantities (10-3 g). Examples are biological and medical applications. The ISFET is essentially an extended gate field effect transistor with the surface of the transistor and the reference electrode.

Results obtained within the SECURITY project "Technology for obtaining biosensors for bioterrorism toxins detection" TOXISISTEM.

Project manager: Dr. Carmen Moldovan, IMT-Bucharest.



Layout of a microprobe with FET sensor on the tip

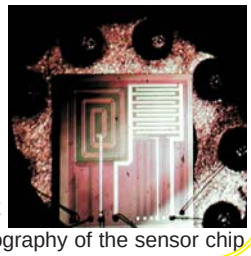


Simulation of the ISFET sensor

Application of micro- and nanotechnologies in the „bio" domain (including medical and environmental)

Biosensors for neurotoxic substances detection

Achievements: The biosensors for neurotoxic substances will be developed as ISFET-type biosensors. The ISFET structure is represented by a concentration-potential transducer, with a biosensitive layer deposited on the gate (acetylcholinesterases, immobilised on chitosane), which generates an interface potential on the gate. The enzymatic ISFET structure is developed in CMOS technology and the sensor's response characteristics depend mainly on the AChE enzyme immobilisation mode.



Optical photography of the sensor chip

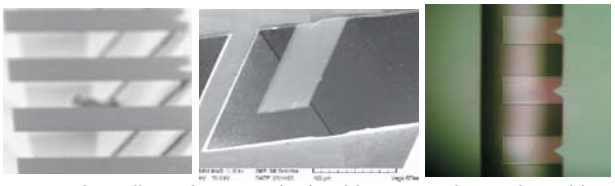
Results obtained within the MATNANTECH project "Biosensors for food neurotoxic substances detection" – SENBIONET. Project manager: Chem. Rodica [illegible], IMT.

Cantilever arrays used as biosensor in biochemical applications

Microcantilevers are highly sensitive to mechanical stress, which is largely caused by surface tension of layers deposited onto a cantilever. A thin bio-molecular layer, with the potential to bind biochemical samples to the cantilever surface, will change the deflection of the cantilever in the presence of a biochemical specimen. The cantilever arrays where obtained in 1.5 mm thick SiO_2 by wet anisotropic etching of <100> Si wafers.

Simulations using COVENTORWARE 2004 were carried out systematically in order to investigate cantilever deflection. Using the numerical calculations the cantilever parameters were optimised in order to increase its sensitivity.

MATNANTECH Project (2004-2006), Microtechnologies for multifunctional cantilevers , integrable on silicon substrate for microsensors and microactuators, Coordinator: IMT Bucharest, Project manager: Raluca Muller (ralucam@imt.ro).



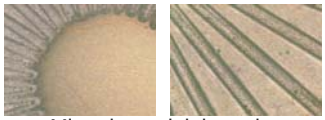
Array of cantilever beams, obtained by wet anisotropic etching: a) SEM image of the entire area; b) SEM image of a single beam; c) Optical microphotograph of a set of beams.

Technology to obtain microfluidic devices by silicon microprocessing having applications in thermal transfer and biology.

The project aims to realize a silicon surface, or other substrates microprocessing to obtain microfluidic devices based on microchannels, having applications in thermal transfer and biology. The resist is used as a sacrificial layer. Achievements:

• Technology for microfluidic devices microprocessing; • Non – standard lithography onto various substrates; • Thermal and mass transfer modelling and simulation in microfluidic devices; • Measurement and characterization techniques of the device, the microprocessed micro-heat sink.

MATNANTECH Project (2004 – 2006). Co – ordinator IMT – Bucharest, (Project Manager: Antonie Coraci: antoniec@imt.ro). Partners: UVT – Targoviste, and ROMES SA – Bucharest.

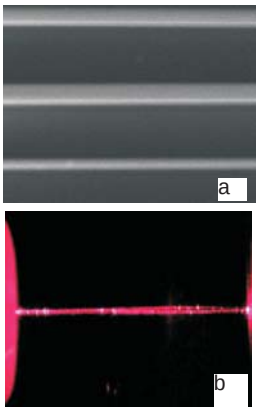


Micro-heat sink based on silicon surface microprocessed Au

Surface microprocessed silicon monoxide structure realized on glass substrate having a microchannel and a microcavity.

Optical biosensor based on integrated interferometer using polymeric waveguides

The biosensor consists of SU-8 polymer waveguides integrated on silicon substrate and is based on the evanescent interaction of light with an immobilized bio-sample on a waveguide. Changing the specimen causes a variation of the refractive index of the cladding layer, which can be observed through the phase shift between light of both interferometer branches. The interferometer comprises of two branches: a reference and a sensing waveguide. The latter of which is in direct contact with a bio-sensitive layer and can bind biological specimens. This layer serves as cladding for the sensing waveguide. Changing the specimen causes a variation of the refractive index of the cladding layer, which can be observed through the phase shift between light of both interferometer branches.

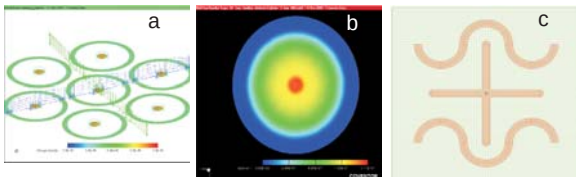


Images of SU-8 waveguide profiles: a – SEM image of several waveguides with different width; b – AFM image o the edge of a single waveguide; c- light propagation in a single MZ interferometer coupled to a fibered light source.

MATNANTECH Project (2004-2005), Integrated photonic microstructures for chemical and biological analyses; Coordinator: IMT Bucharest, Project manager: Raluca Muller (ralucam@imt.ro);

MI Lab-on-Chip - Implementation of Production Processes for New Molecular Imaging Agents

Acronym: MI-lab-on-chip, STREP-FP6, Priority 3 NMP, 2005-2007, Contract No. 221105. Objective: Developing multiple steps radio-pharmaceutical chemistry processes at the micro molar scale. IMT Team is carrying out the simulation for Lab-on chip components: mecanical, electrostatic, microfluidic, thermal, electrokinetic, chemical, fluid-structure interaction analysis. Contact IMT Bucharest: Oana Nedelcu, oanan@imt.ro.



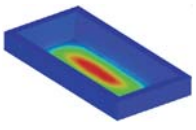
Electrostatic and electrokinetic simulation results: a) Electric field distribution;b) Distribution of ions concentration in elementar cell; c) Masks design

Biomicrocaps fabricated on silicon

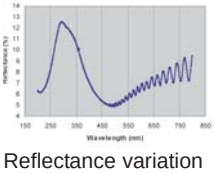
Microprocessed microcavities having porous silicon membrane used in drug delivery by a new implant technique. Achievements:

• Porous nanostructured membrane microfabrication by auto-stop etching on p+ silicon; • Coventor ware device simulation; • Microdevice design; • Porous silicon membrane mechanical simulation.

PN. Project (2003 – 2005) Co-ordinator IMT – Bucharest (Manager Cecilia Podaru: ceciliap@imt.ro). Technology to obtain microfluidic devices by silicon microprocessing having applications in thermal transfer and biology.



Conventor Ware simulation on the whole device



Reflectance variation of the porous silicon versus wavelength

"Integrated Research Network Devoted to Nanobiotechnology for Health - Romanian Nanomedicine Network" RO-NANOMED , http://www.imt.ro/ro-nanomed

The RO-NANOMED project is devoted to the creation and development of an integrated research network in the field of nanobiotechnology for health. This network is targeting integration into the European Technology Platform (ETP) "NanoMedicine". IMT-Bucharest (Prof. Dan Dascalu) was nominated as contact point of the mirror group for the European Technology Platform (ETP) "NanoMedicine" (each country may have a national representative, acting as a contact point). IMT has created an interest group - "Nanomedicine" Romania - with 71 participants: 25 participants from 10 National R&D Institutes, 5 participants from 3 R&D Institutes of the Romanian Academy, 3 participants from 3 R&D Institutes, 28 participants from 15 Universities, 6 participants from 6 SMEs, 4 participants from 4 Hospitals. The contact address is nanobio@imt.ro. OBJECTIVES: 1. Creating a Romanian research network in nano-biotechnology for health, which is continuing and amplifying the previous activity of the CENOBITE network (2002-2004). 2. Focusing the research on the domains targeted by the ETP Nanomedicine. This will be achieved by financing 14 "research mini-projects", devoted precisely to the three domains of the ETP NanoMedicine (i.e. regenerative medicine, targeted drug-delivery, nano-diagnostics). 3. Creating a physical platform of research integration through NANOBIOLAB, a laboratory implemented in the technological area of IMT-Bucharest, part of MINATECH-RO (The Scientific and Technological Park in Micro and Nanotechnologies). 4. Providing intensive networking at national level, by extending the network with new partners (including companies, NGOs etc.) 5. Promoting durable integration of national activities in the European Technology Platform. The previous experience of the common work, as well as the focus on the main scientific topics in Nanomedicine will facilitate European cooperation. Services offered by RO-NANOMED partners inside the network. IMT-Bucharest offer access to- equipments - facilities for micro-nanofabrication: the only clean room class 100 in Romania, offering conditions for controlled temperature and humidity; services for silicon, glass and quartz micromachining. - laboratories for simulation and computer aided design for Microsystems and micro-nanostructures (COVENTOR and CADENCE and Mentor Graphics) - characterization equipment - education and training through the International Centre for Education and Training in Micro and Nanotechnology (ICETMNT) Institute of Macromolecular Chemistry "Petru Poni", Iasi: - Training activities on specific equipments, training during different courses and summer schools. Dissemination during various events - Access to equipments - Consultancy Institute of Biochemistry of the Romanian Academy: - Access to equipments - Consultancy: for biocompatibility tests of different materials; for evaluating the nanomaterials applications R&D National Institute for Nonferrous and Rare Metals: w Access to equipments - Assistance for the following activities: Functionalized nanoparticles synthesis by sol-gel and hydrothermal processes; Thin films obtaining by hydrothermal-electro-chemical and electrophoresis techniques; Obtaining of compact sintered layers; Methods for complete chemical analysis; - Training and educational activities . Dissemination and protection of property rights, promotion participation to international and European projects by collaborating with CTT AVANMAT and CTT Baneasa "Victor-Babes" University of Medicine and Pharmacy Timisoara: w Offers educational program at European level to Romanian or foreign PhD students. - Will develop a program for biomedical research, according to European standards and educational and research programs, assuring also competent clinical services.

Contact: **Prof. Dan Dascalu** (dascalu@imt.ro); **Eng. Claudia Roman** (claudiae@imt.ro), IMT-Bucharest, Romania

NANOBIOLAB, a new laboratory within the clean room of IMT-Bucharest

The **NANOBIOLAB** has been developed in the100-class clean room built at IMT-Bucharest, with the support of the **Integrated Research Network Devoted to Nanobiotechnology for Health – Romanian Nanomedicine Network" RO-NANOMED and is used in common by the 13 partners in the project.**

NANOBIOLAB is devoted to technological research (new materials, structures, particles, devices etc.) involving biological materials.

Available equipments:

- **"GeneMachines OmniGrid Micro"** - Nano-Plotter, allowing bio-chips development; dispersing of adhesives and liquid crystals; analysis of adherent cells or tissue slices, for nanobiotechnology projects as lab on chip, biochips

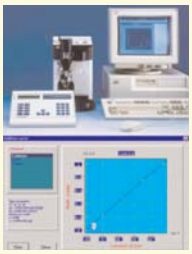
GeneMachines OmniGrid Micro- Nano-Plotter

- **"GeneTAC UC4 Microarray Scanner"** – this equipment is used for reading the chips, acting as a pair of the nano-plotter, for DNA detecting and deposition.

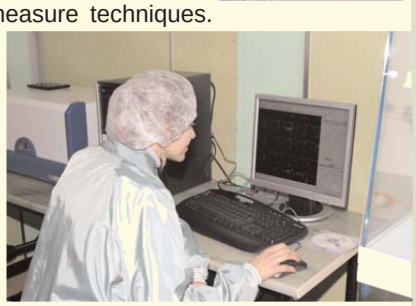
This two-color system includes green (532nm) and red (635nm) lasers coupled with high performance optics optimized to maximize collection of fluorescence signal while minimizing the damage caused by photobleaching. The scanner includes hardware and powerful and easy-to-use microarray analysis software for fast and reliable imaging, collection and storage of very large data sets and consolidates these data with experimental information.

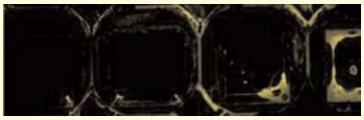
GeneTAC UC4 Microarray Scanner

- ***Chemical bench*** for surfaces cleaning and functionalizing, together with a dedicated software
- ***Voltametric techniques equipment*** - TRACELAB 50, electrochemical device with TRACE MASTER 5 software, from RADIOMETER ANALYTICAL. The polarographic analyzer is controlled by an microprocessor used for polarographics and voltametrics analyses. POL150 needs a 200 Hz voltage. The device can be used for all the polarographic, and differential pulse measure techniques.

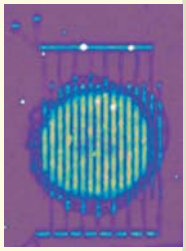


The software controls all process parameters and can recognize some polarographic picks or it can be calibrated to recognize all the interested picks. This system is used for the research activity, being important for elements analysis and also for organic molecules.





Details of silicon micro-reservoirs plotted with fluoresceine one time



Enzyme based biosensor (fluorescence)

Contacts: **Prof. Dan Dascalu** (dascalu@imt.ro)
Dr. Irina Kleps (irinak@imt.ro)
Dr. Carmen Moldovan (cmoldovan@imt.ro)