

micro and nanoelectronics
microsystems
ambient intelligence
biology and health

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International Symposium on Research
in Grid/Nano/Bio/Medical Informatics
Madrid-Spain



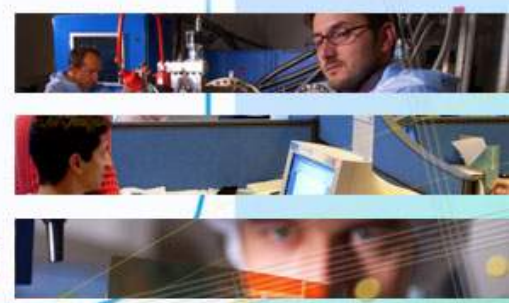
2009



Information processing for biomedical micro-nano technologies

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DTBS/STD/09E-52



Conference highlights

- Molecular profiles
- Micro-nanotechnologies for proteomic analysis coupled with mass spectrometry
- Information processing
- Prospective view towards nanomedicine

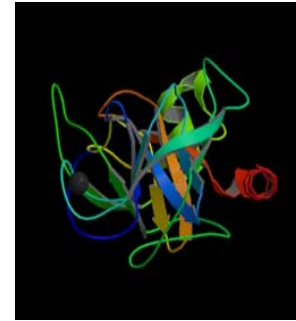
The molecular profiles

- a disease is characterized by a **molecular signature** (cancer, infectious disease, immunological disease,...)
- **multiparametric approach** : a set of genes, proteins, therapeutical molecules, functional relationships
- ➡ ● Need to recognize **signatures** on **molecular profiles**
- **molecular profiles** : a fundamental information for personalized healthcare, risk factor analysis, early detection, therapeutical planning and follow-up, drug development, system biology.

The protein signal to study the cell state

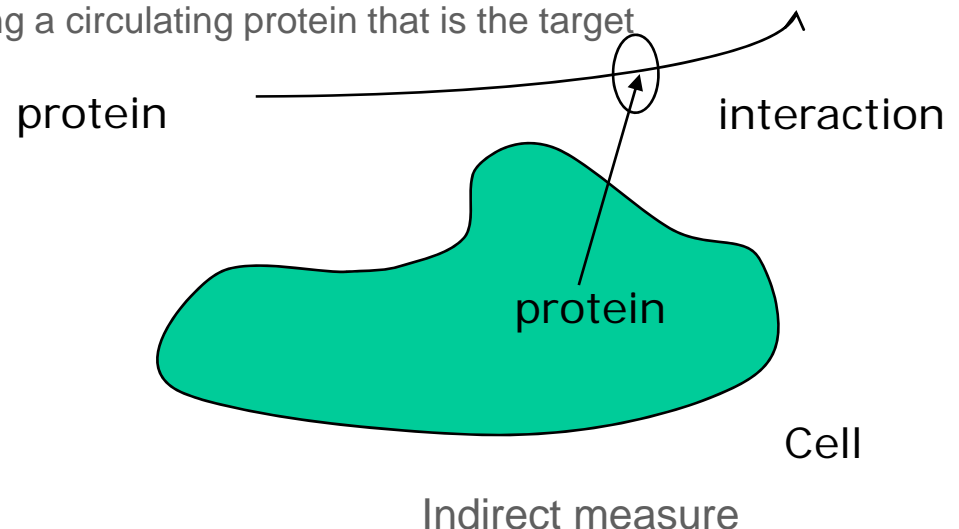
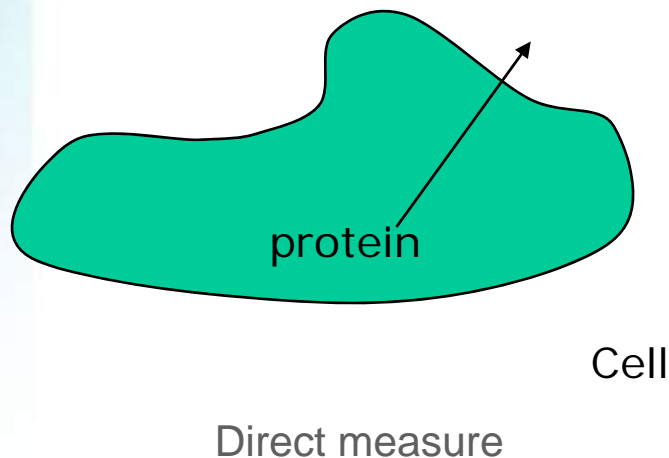
Diagnostic principle based on:

- the proteins
- the modification of protein structure
 - ◆ Translational modifications
 - ◆ Post-translational modifications
- proteomic profiles = a multiparametric approach to be more specific and sensitive

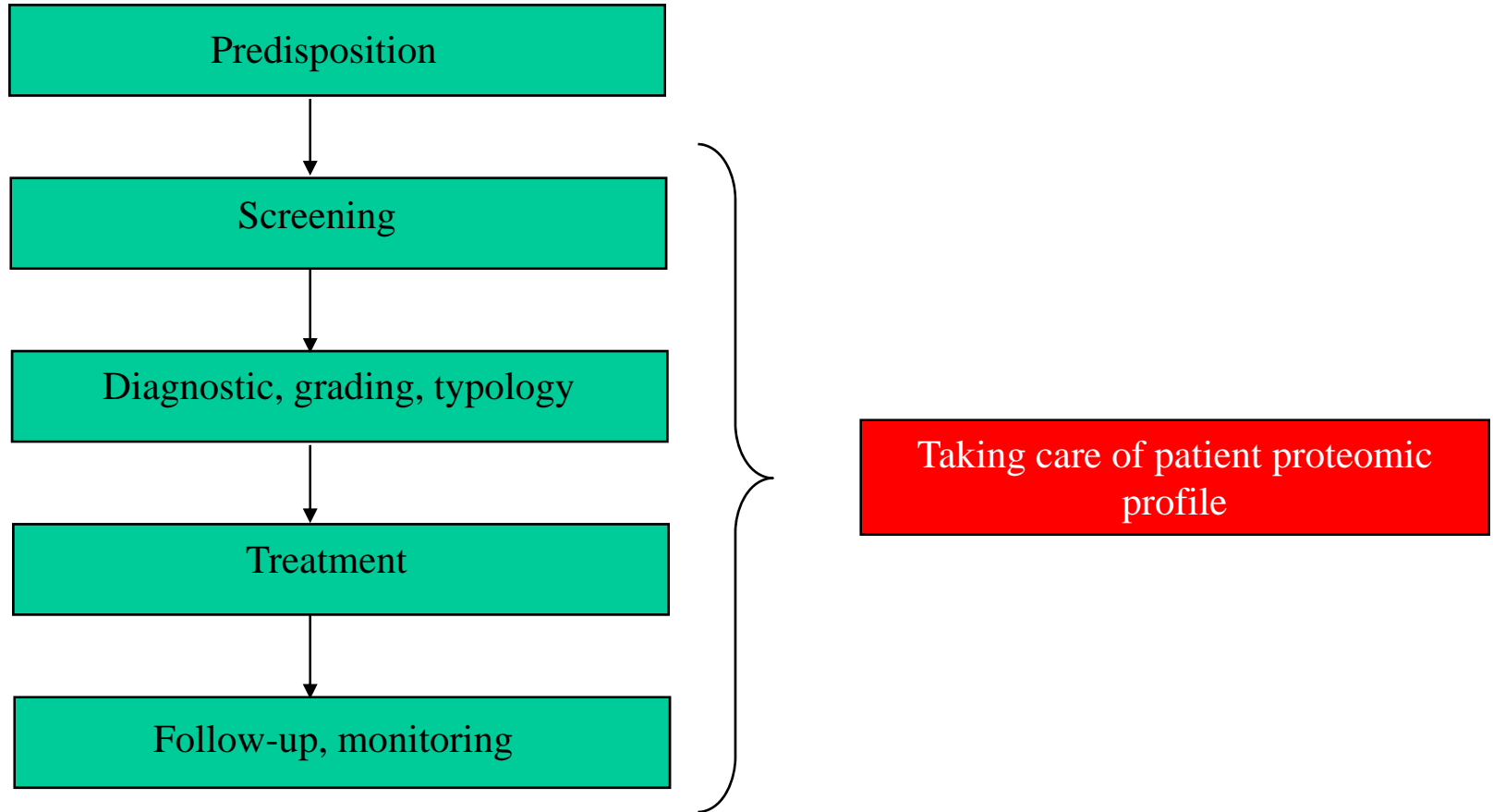


The information can be:

- direct: the target is the emitted protein
- indirect: the protein is cleaving a circulating protein that is the target



Care cycle of a disease like cancer



Lab-on-chip for in-vitro molecular diagnosis

- General trend towards micro-nano bio systems (MNBS) for in vitro diagnosis
- Microfluidics is broadly recognized as a key solution to support molecular diagnostic and point-of-care devices.
- Nanotechnologies for:
 - nanoparticles for in-vitro molecular interaction
 - surface functionalization
 - fluid handling
 - transduction
- Key requirement: to perform better, faster, cheaper and smaller analysis, but still reproducible, sensitive and reliable

Towards nanoparticle based molecular medicine

- Nano particles: vehicles for molecular in-vivo interactions
 - Nanoparticle based molecular recognition
 - Nano carrier
 - Nano harvesting
 - Nano actuators
 - Nano sensors
 - Nano labeling
 - Nano drug delivery

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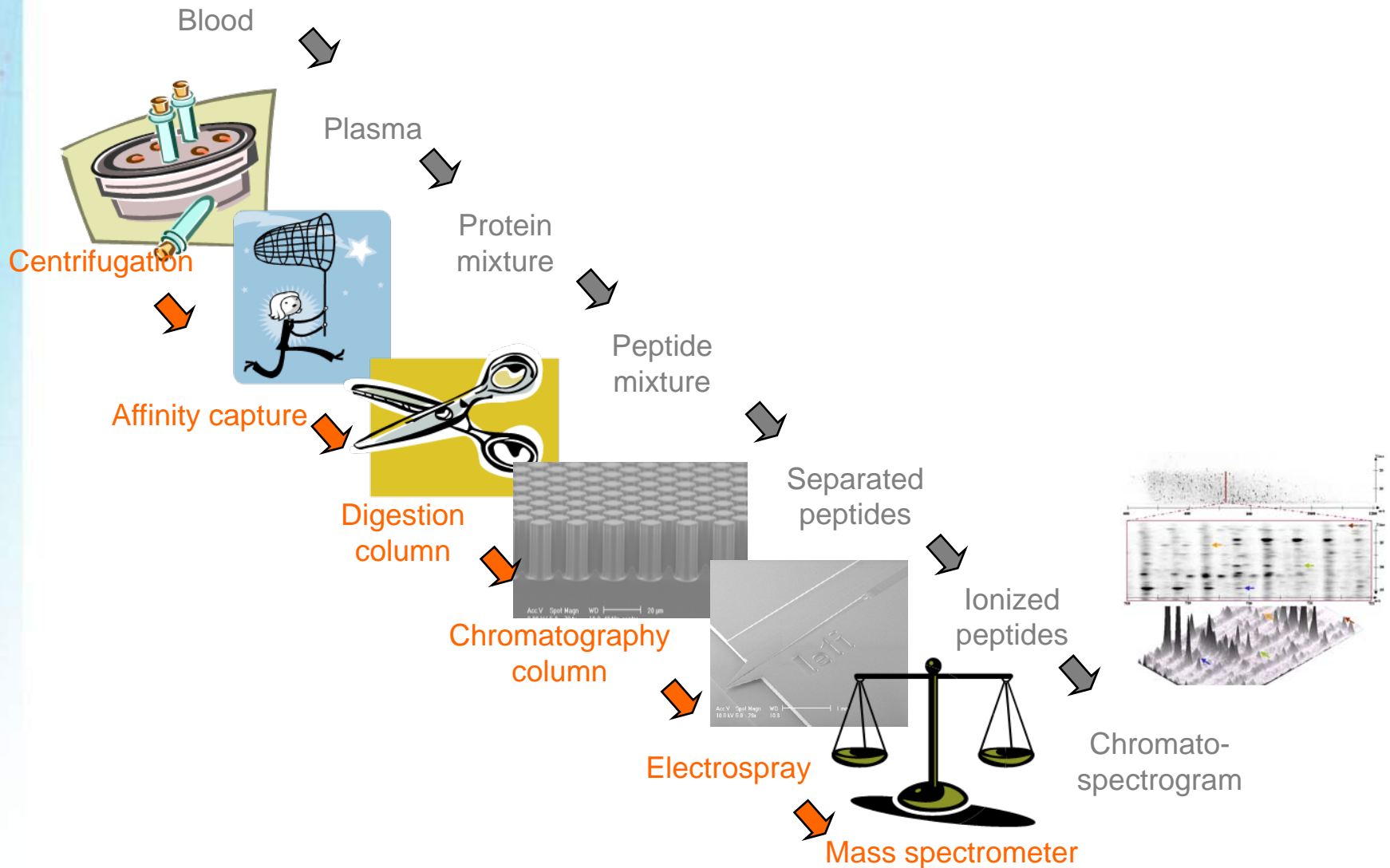
The challenges of protein analysis in plasma

- High sensitivity
 - Our objective: 1 to 1000 ng/ml

- Very large dynamic ratio in protein concentration:
 - Total protein content in plasma: ~100 mg/ml
 - 1 ng/ml corresponds to a ratio of 1 to 10^8 between the targeted proteins and the total protein content

- A large protein content:
 - About 3000 proteins identified in the plasma by the HPPP

The immuno-chromato-ESI-MS analytical chain



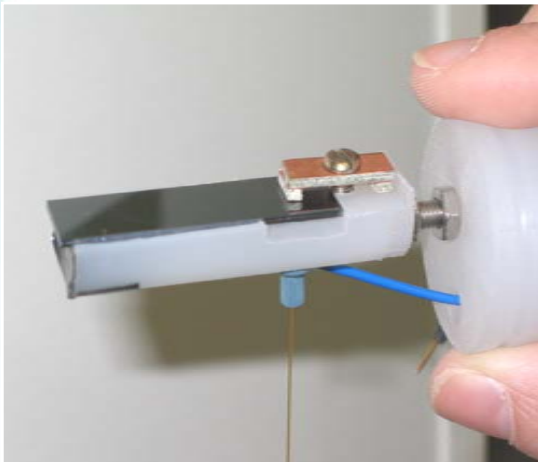
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Micro-nano technology objective: lab-on-chip



■ Point of care :

Full system from blood plasma sample to diagnostic information



■ Lab-on-Chip :

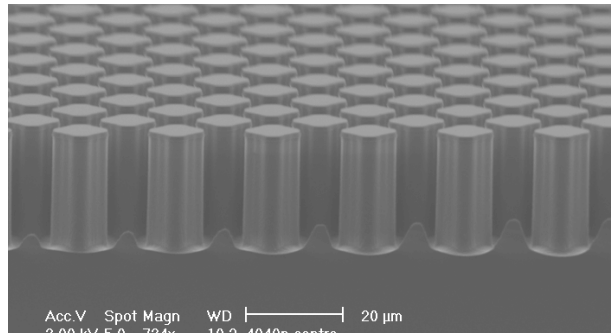
Miniaturized integrated components to increase sensitivity (nano-LC, nano-ESI) and throughput

Why nano-liquid chromatography?

- In chromatography, the detection limit is proportional to the concentration of targeted molecules in elution peak
- The lower is the volume of the elution peak, the higher is the total amount detection limit in the elution peak for a concentration threshold fixed by the mass spectrometer
- Nano-chromatography refers to **columns operating on nanoliter volumes**
- Nano-chromatography columns allow to detect molecular quantity in the **femtomolar range**
- 1 femtomole of molecules (~ 10 pg for a molecule of 10 Kdalton) diluted in 1 mL of plasma correspond to a concentration of 1 picomole/L

Why silicon technology ?

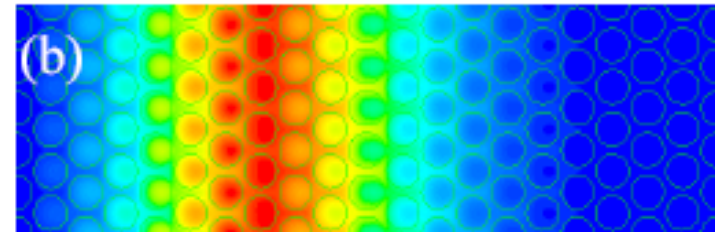
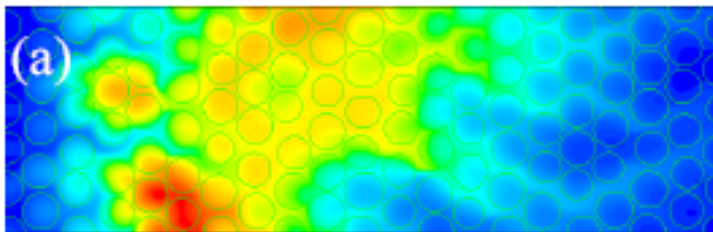
- Reproducible technology with high surface/volume ratio



Micro-pillar structure for large surface / volume ratio

- Optimized hydrodynamic flow

(Computational Fluid Dynamic study from G. Desmet et al, J. Chrom A, 2005)



Hydrodynamic flow simulation in

- a) **Capillary with bead packing**
- b) **Perfectly ordered microstructures**

Towards the integration of the total analytical chain

Objectives:

- To lower the losses and dead volumes at the connection level
- To lower the volume to analyze
- To speed the analytical time length
- To lower the required quantity of solvent and antibodies
- To reduce the costs thanks to mass production

- Full title:
 - high sensitivity multifactor proteomic analytical chain based on integrated components

- Project granted by the Commissariat à l’Energie Atomique (CEA) within the program “Technology for healthcare”

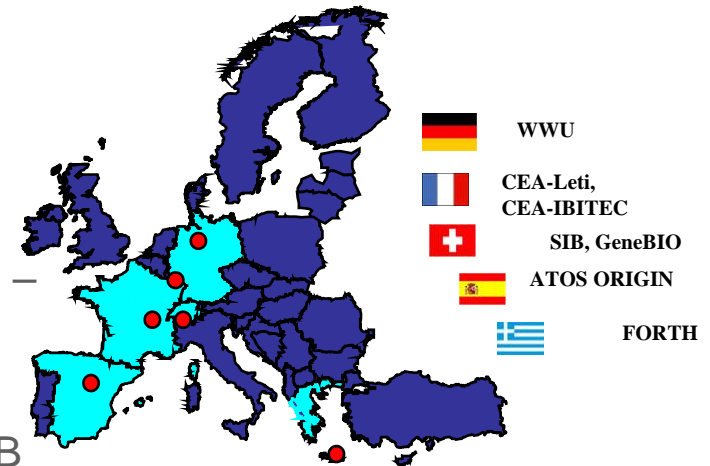
- CAPSI project teams:
 - CEA-LETI
 - CEA-iRTSV-EDyP

FULL TITLE: Lab-On-Chip based protein profiling for CANcer DIAGnosis

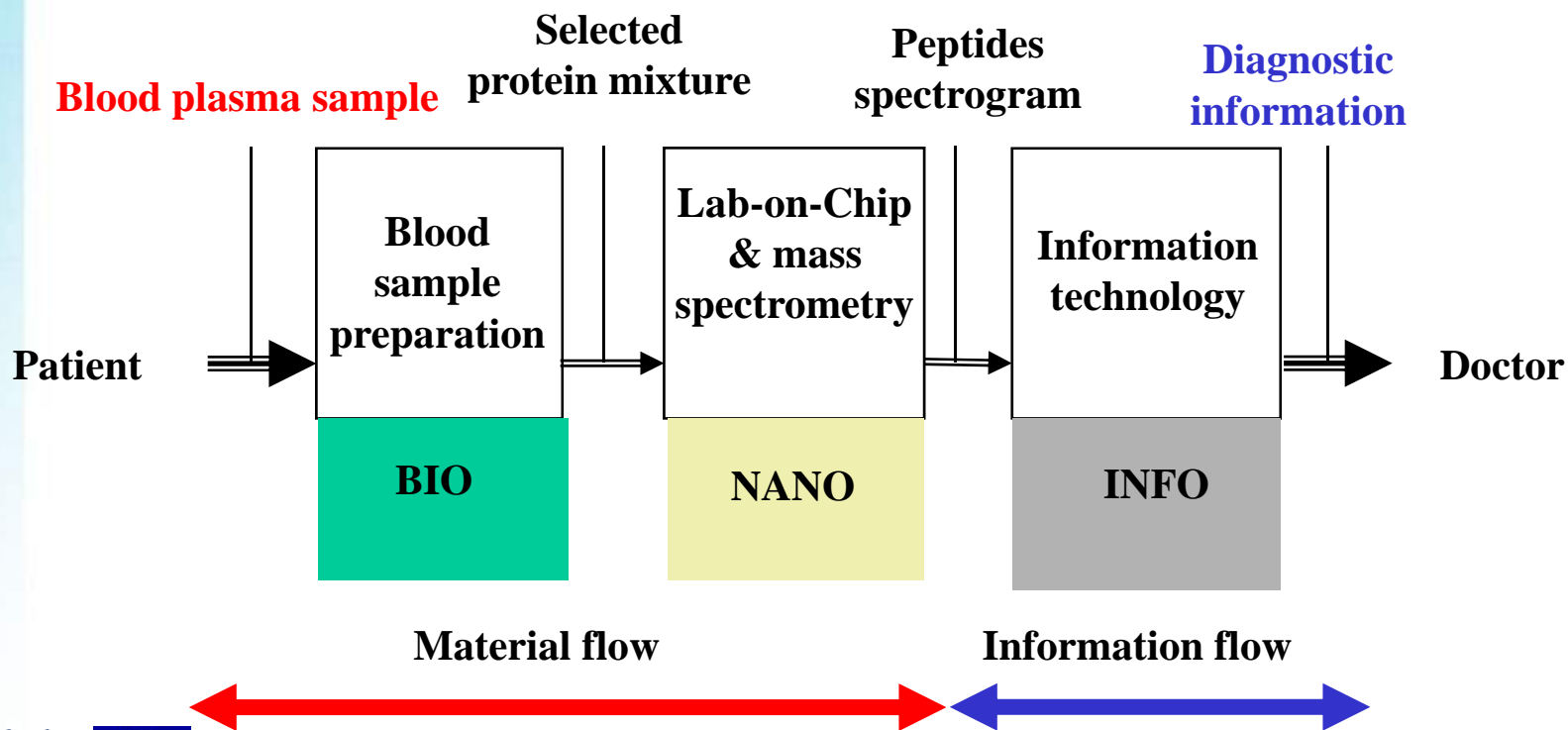
Project granted by the European Commission:
Reference: FP6/2005/IST/5/034202
Call: Priority 2.5.2. Micro/nano based sub-system
Web site: <http://www.loccandia.eu>

List of partners:

- Atos Origin sae, Spain – ATOS
- Commissariat à l’Energie Atomique, France – CEA-LETI, CEA-IBITEC
- Foundation for Research and Technology, Greece – FORTH
- University of Münster, Germany – WWU
- Swiss Institute of Bioinformatics, Switzerland – SIB
- Geneva Bioinformatics, Switzerland - GeneBIO



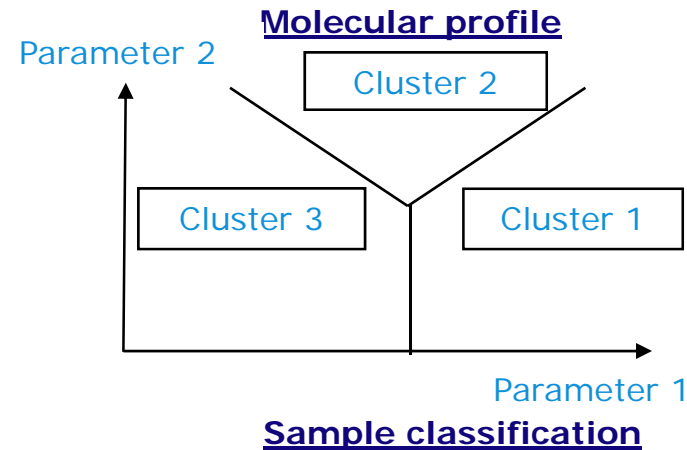
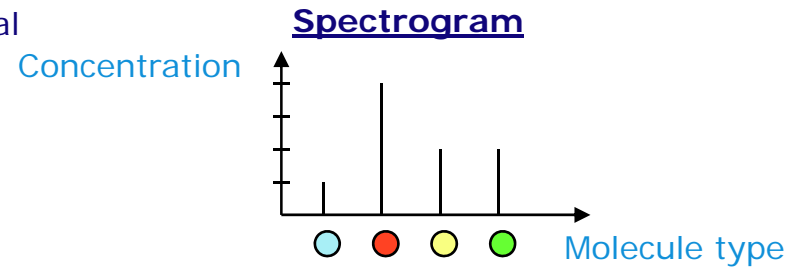
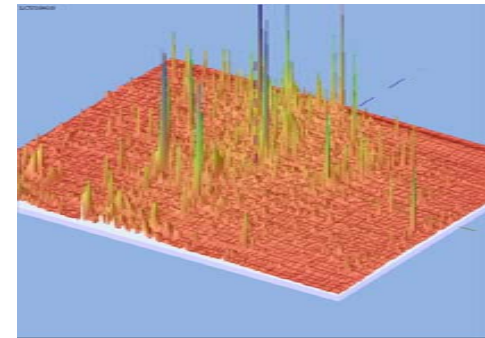
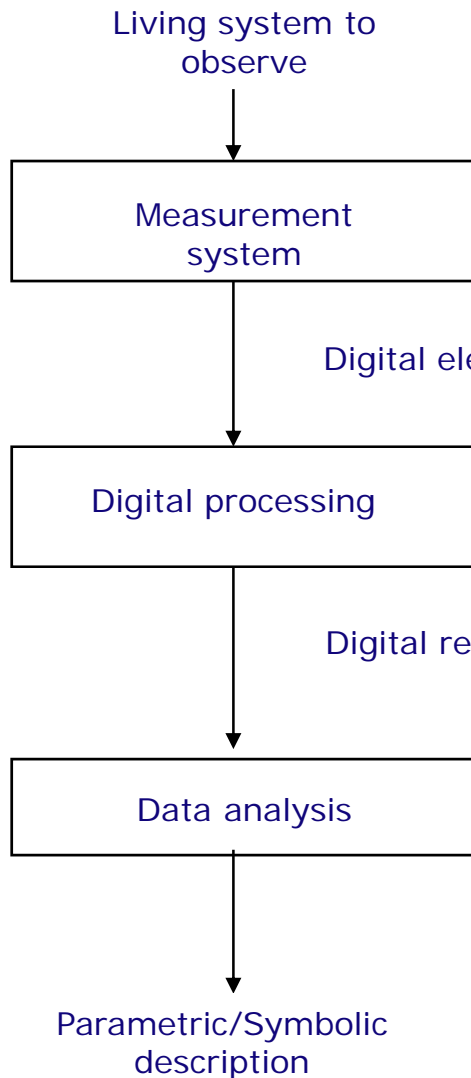
- to integrate a full proteomic analysis chain from blood sample to diagnosis information using innovative nanotechnologies.
- to develop a technology for the detection of low abundant proteins related to pancreatic cancer.



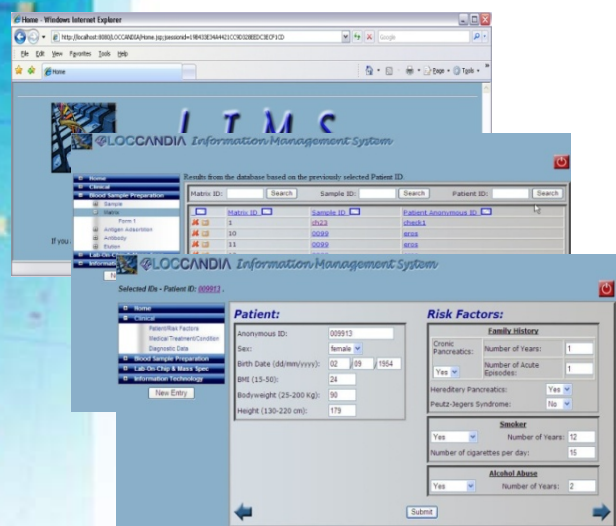
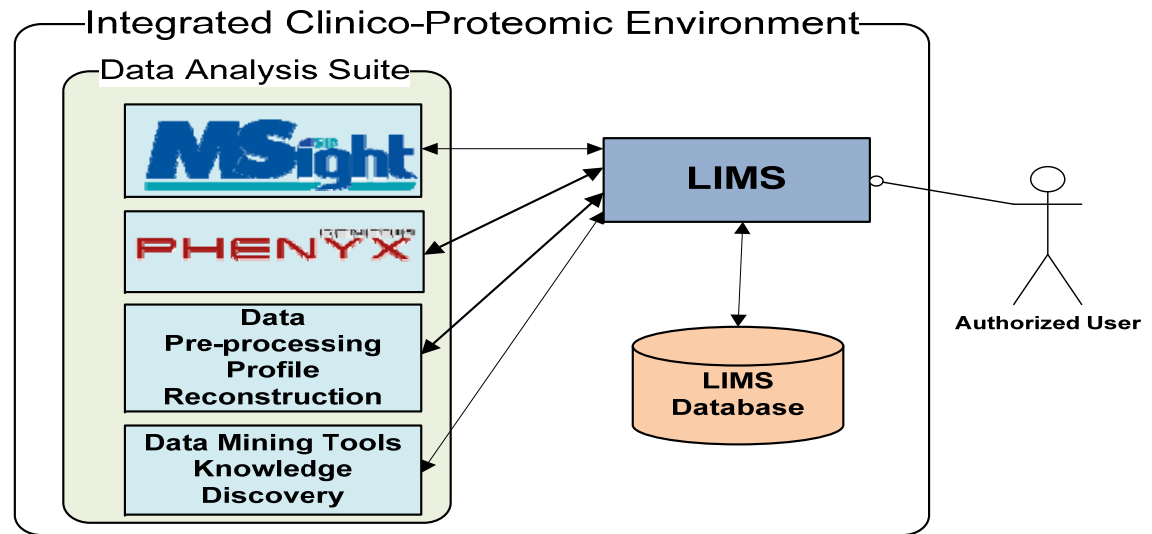
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The main stages in information processing



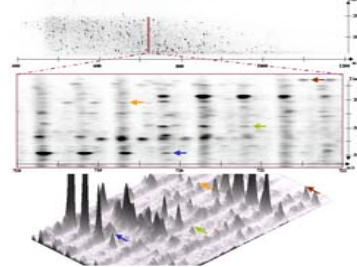
LOCCANDIA information management system (LIMS)



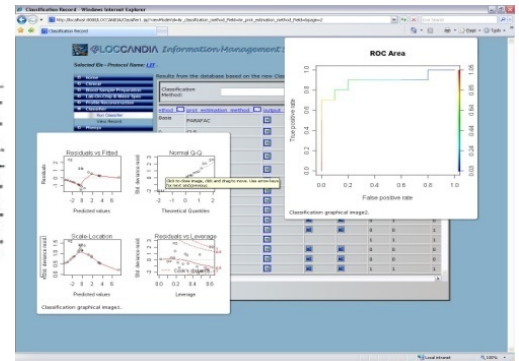
Identification



Molecular Profile Reconstruction



Visualisation



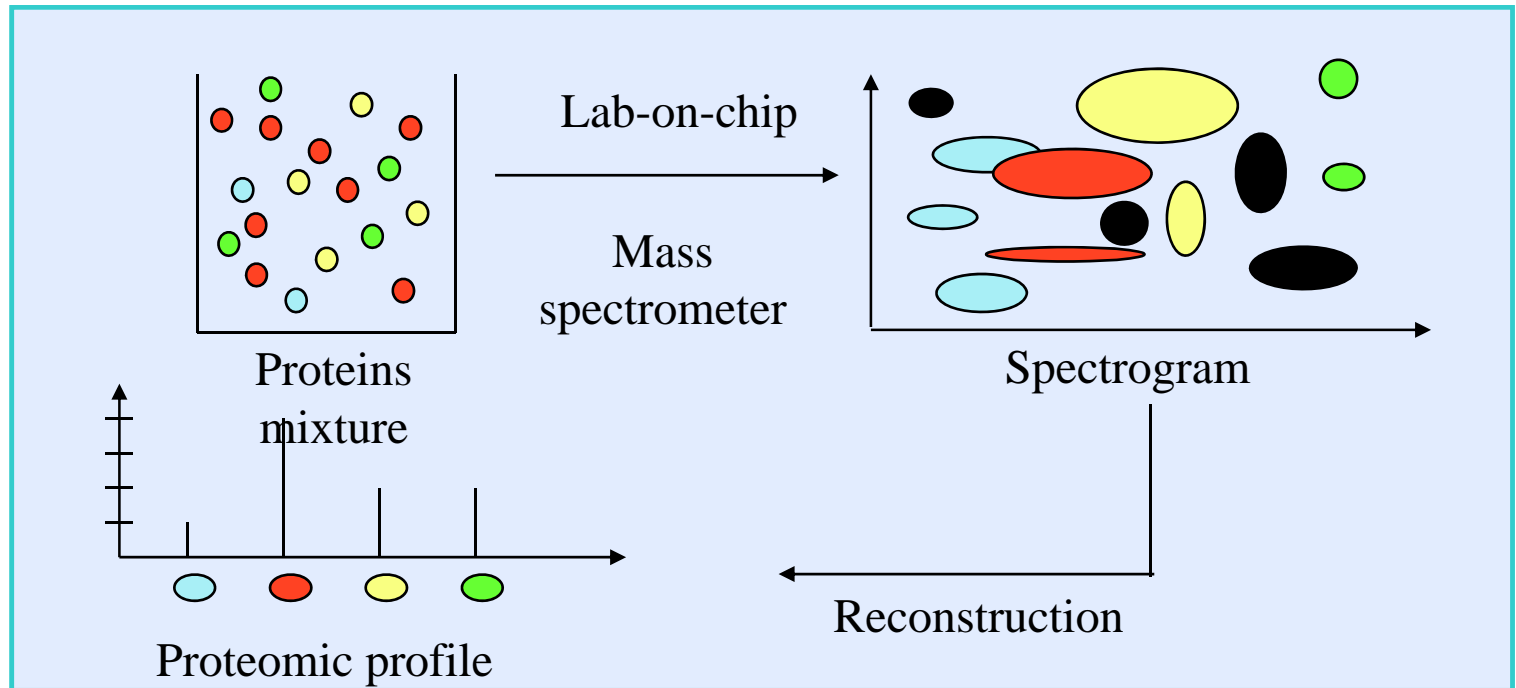
Classification, Diagnostic assistance

Parameter management: Patient, Analytical Chain



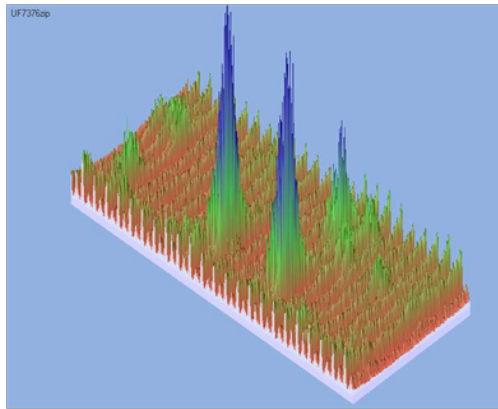
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Molecular Profile reconstruction

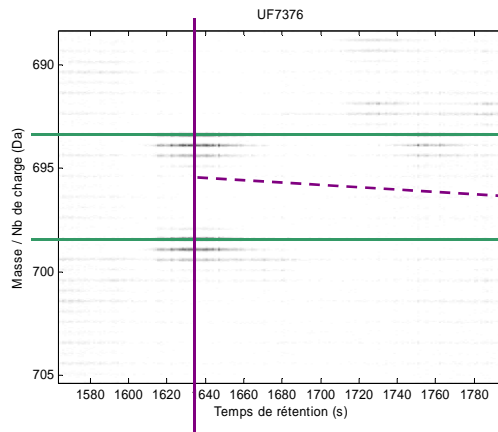


- At CEA/LETI/DTBS, we are currently investigating three main approaches :
 - **chemometrics** processing associated with factorial analysis
 - **statistical signal processing** associated with parametric models
 - **modeling** describing the physico-chemical behavior

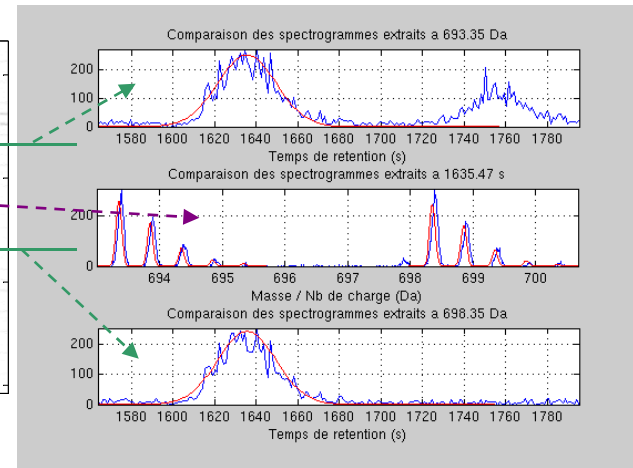
Statistical reconstruction: experimental results



3D display of a zone within the spectrogram around one peptide peak of the targeted protein

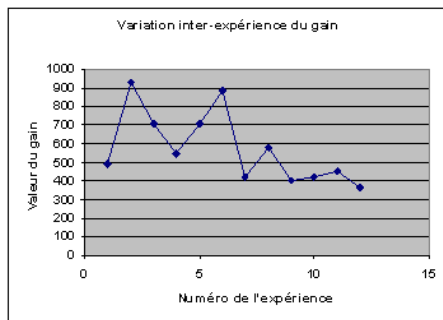


2D display of a spectrogram

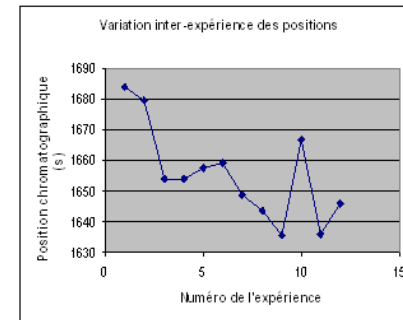


extracted plot

Comparison between adjusted model (red) and measurement (blue)



Gain variation on the set of experiences



Position variation of chromatographic peak on the set of experiences

Ref: Strubel G. (2008) **Reconstruction de profils moléculaires :modélisation et inversion d'une chaîne de mesure protéomique**, INPG Ph. D. thesis

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The Digital Patient

- The Digital Patient for eHealth :
- The combination of complementary multimodal representations
- The bio-profiles = a multiparametric description
 - morphological profiles
 - molecular profiles
 - physiological profiles
- Imaging systems = localisation of the information
- Healthcare objectives = early diagnosis, personalized healthcare, home healthcare monitoring

Key information processing topics at the sensor level for micro-nano-biomedical-systems

- inverse problem
 - profile reconstruction
 - source separation
- statistical signal processing
- model based signal processing
 - system identification
 - functional model
- fluid management
- data analysis:
 - classification
 - decision support
 - signature recognition
 - biostatistics

Complexity

- Complex molecular content of **human samples**
- Sample complexity may be address through **systems biology** and **systems medicine**
- Complex **sample preparation** required combining molecular separation, concentration and transport
- Requirement of **high throughput technologies and data processing**
- Marker identification and validation is a key issue involving large research projects and **bioinformatics resources for data mining**

Sensitivity

- Key parameter for early detection
- Nanotechnologies break sensitivity down up to the molecular level
- Key issue: molecular caption on each elementary nano-sensor
- High sensor parallelization required for efficient detection:
 - Multidimensional signal processing
 - Increase in the computing power requirement
- Quantification requirement:
 - Relative quantification for differential or longitudinal studies
 - Absolute quantification for diagnosis
- Targeted approaches

Specificity

- May be improved by multiparametric analysis to describe the biological variability
- Towards molecular interaction networks
- Find the appropriate parameter space dimension:
 - the more parameters are used, the more complex is the identification phase and the larger should be the size of the cohort for identification and validation
- Try to restrict the field of investigation to specific molecular sub-families (e.g. plasma proteome)
- Improved by the fusion with other information (patient information, complementary measurements)

Robustness

- Technological variation in the analytical chain
- Dispersion on the microsystem characteristics
- Quality and robustness control is mandatory
- High automation is required
- Signal processing has to be robust and adaptive
- From « black box » to « model based » signal processing
- Statistical behavior of the molecular interaction at the nano size

European Technology Platform on Nanomedicine

- Prospective report in November 2006:
Nanotechnology: nanotechnology for Health
strategic research agenda for nanomedicine
<http://cordis.europa.eu/nanotechnology/nanomedicine.htm>
- ETP Nanomedicine web site:
www.etp-nanomedicine.eu
- Secretariat ETP Nanomedicine
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Web site: www.vdivde-it.de

Observatory for Micro-Nano Technologies (OMNT)



- Technological watch expert working groups on:
 - Micro-nano biological instrumentation
 - Nanomedicine
 - Nanosafety

- Contact person:
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