4. BIOINFO

- Modeling of human TYRO-3 kinase domain

- Quantitative assessment of myocardial function & perfusion in MRI using nonrigid registration with highdimensional information measures

- Une recherche d'information centrée sur l'utilisateur pour une meilleure exploitation des données biomédicales

- Computer-aided diagnosis and image biomarkers in asthma and COPD

- ICT and biomedical applications: diagnostic of genetic mutations and study of genetic oscillators

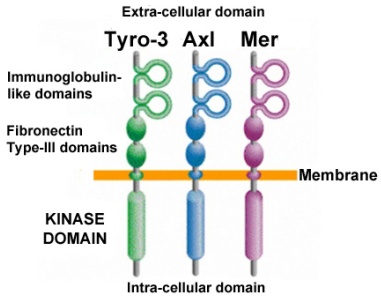
- Computer-assisted diagnosis and follow-up of lung nodulation and idiopathic interstitial pneumonias

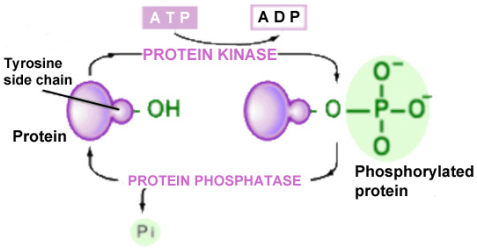
Modeling of human TYRO-3 kinase domain

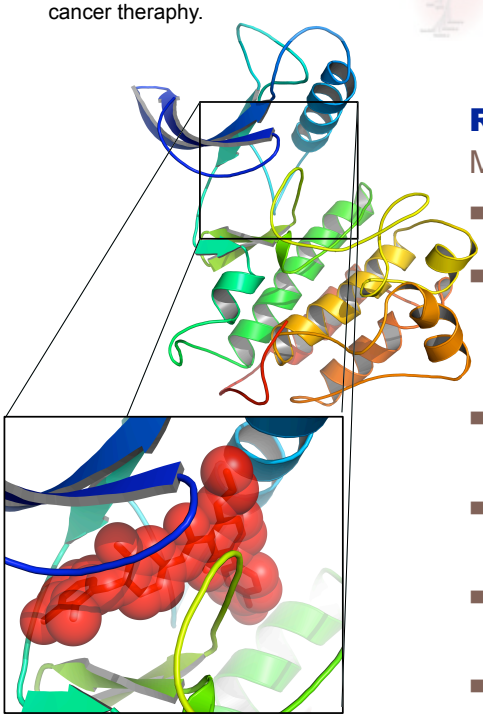
SCIENTIFIC CONTEXT

The role of Tyro-3 | Therapeutic target

- Tyro-3 is a receptor tyrosine kinases (RTKs) that belongs from the TAM subfamily (containing Axl, Mer and Tyro-3) [1].
- The RTKs family play a pyvotal role in the transduction of signals from the extracellular environment to the cytoplasm and nucleus, modulating cell survival, growth, differentiation, adhesion, and motility, highlighting the their role in normal cellular function [2].
- TAM receptors are ectopically or over-expressed in a wide array of human cancers. In particular, Tyro-3 expression has been associated with acute myeloid leukemia (AML), multiple myeloma and bladder cancer [2].
- The full lenght receptor (890 aminoacides) is a trans-membrane protein characterized by the presence of an ecto-domain (N-terminal, aminoacides 41-429), followed by a transmembrane domain (430-450) and an intracellular domain (C-terminal, 451-890) [3].
- Kinases are known targets and 11 inhibitors are already used in the cancer theraphy.







RESULTS

Molecular modeling

- The models were obtained by « homology modeling » methods using the MODELLER© software (University of California San Francisco).
- X-ray emperimental structures of c-Met in complex with « Type II inhibitors » (identity ; similarity with Tryo-3; pdb: 3F82, 3LQ8) and c-KitMet in complex with « Type II inhibitors » (identity; similarity; pdb: 1T46) were used as templates to obtain the 3D structure of Tyro-3 models.
- Sequence alignements between templates and Tyro-3 were performed using BlastP with BLOSUM62 matrix algorithm (NCBI), T-Coffee and Expresso (CRG, Barcelona).
- The modeling process results in the selection of three Tyro-3 models made by different templates selection (3F82 and 1T46 structures as template; 3F82 and 3LQ8; 1T46, 3F82 and 3LQ8).
- The.quality of the models was estimated by analysis of their Ramachandran plots, QMEAN server analyses[4], MolProbity[5] and by visual checking using visualization softwar
- The binding site of « Type-II inhibitor » of Tyro-3 was characterised.

DISCUSSION AND PERSPECTIVES

Looking for inhibitors

- The obtained Tyro-3 models allowed the elucidation of hydrophobic, polar and hydrogen bond interactions, which define the binding properties and profitable peculiarities aimed to select potential inhibitors. Moreover, they represent a basis for further small-molecules docking experiments.
- Will it be possible to find new selective « Type-II inhibitors » by docking virtual screening of compound libraries?
- Will it be possible to design new selective inhibitors by structure-based drug design?

[1] Manning G, et al.: **The protein kinase complement of the human genome.** ***Science 2002, 298:1912-1934.***
[2] Linger RM, et al.: **TAM receptor tyrosine kinases: biologic functions, signaling, and potential therapeutic targeting in human cancer.** ***Adv Cancer Res 2008, 100:35-83.***
[3] Magrane M, Consortium U: **UniProt Knowledgebase: a hub of integrated protein data.** ***Database (Oxford), 2011:bar009.***
[4] Benkert P, Kunzli M, Schwede T: **QMEAN server for protein model quality estimation.** ***Nucleic Acids Res 2009, 37:W510-514***
[5] Richardson DC et al.: **MolProbity: all-atom contacts and structure validation for proteins and nucleic acids.** ***Nucleic Acids Res 2007, 35:W375-383.***

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Colloque Ingénierie et STIC pour la Santé

6 et 7 Mars 2012

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Quantitative assessment of myocardial function & perfusion in MRI using nonrigid registration with high-dimensional information measures

MAP5 UMR 8145

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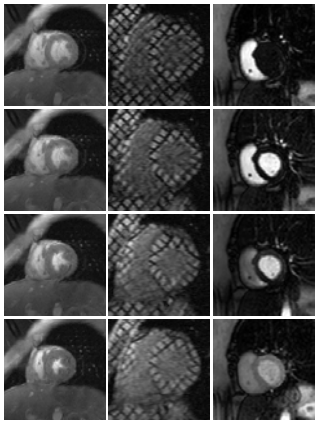
EARLY DIAGNOSIS & FOLLOW-UP OF MYOCARDIAL ISCHEMIA

Cardiac MRI



- A one-stop-shop for dynamically imaging the heart morphology & function
- A valuable investigation tool for assessing myocardial function and perfusion

Challenges

- Bridging the gap from visual inspection to quantitative assessment of ischemic pathologies in clinical routine
- Developing reliable unsupervised Computer-Aided Diagnosis tools based on efficient computational models
  - > Measuring myocardial strain from tagged MRI
  - > Quantifying myocardial blood flow from contrast-enhanced perfusion MRI
- A common image understanding issue: estimating / compensating nonrigid motion in image sequences with nonlinear intensity variations

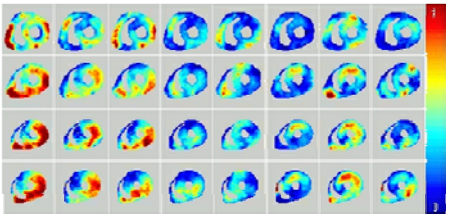
A UNIFIED APPROACH

Multi-feature/view information-theoretic image registration

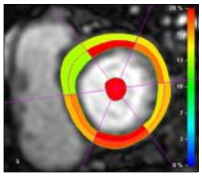
- Multiple local / nonlocal image features as high-dimensional random variables
- State-of-the-art geometric estimators of classical / generalized information measures based on k-nearest neighbor (kNN) statistics
- Sound properties in high dimensions: consistency / asymptotic unbiasedness / well-posedness
- Closed-form optimization over finite / infinite spatial transform spaces
- Efficient implementation: fast approximate kNN search / stochastic gradient descent / GPU acceleration

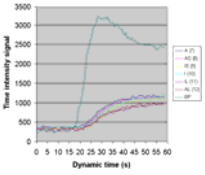
THE CARDIOMETER PLATFORM

Measuring myocardial strain in tagged MRI



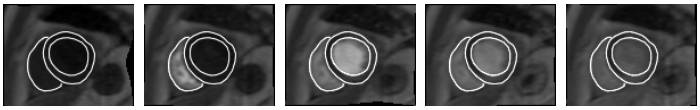
- Motion estimation: frame-to-frame pairwise registration
  - > features: intensity + structure tensor
  - > Tsallis information / C^1-smooth motion
- Radial / circumferential / longitudinal strain maps at pixel & myocardial segment scales





Assessing cardiac perfusion in contrast-enhanced MRI

- Respiratory motion compensation : groupwise registration onto a motionless reference
  - > features: contrast enhancement curves
  - > normalized mutual information / FFD warp
- Segmental first-pass curves & clinical perfusion indices



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6-7 Mars 2012

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Une recherche d'information centrée sur l'utilisateur pour une meilleure exploitation des données biomédicales

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ALÈS • NÎMES • PAU
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Partenaires

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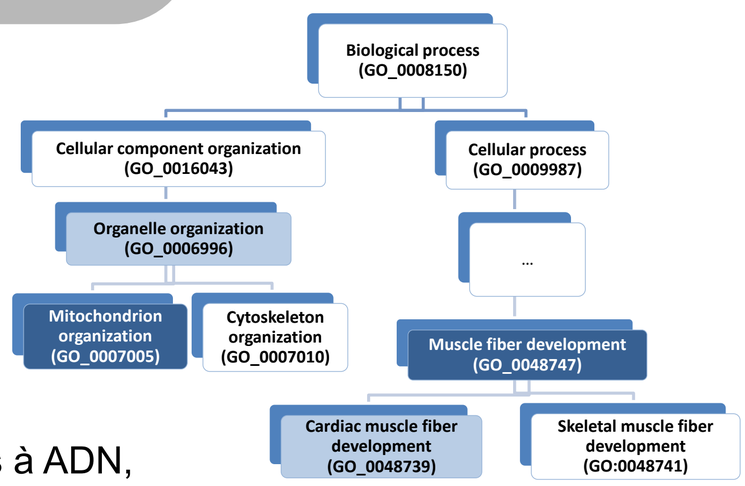
Institut national de la santé et de la recherche médicale

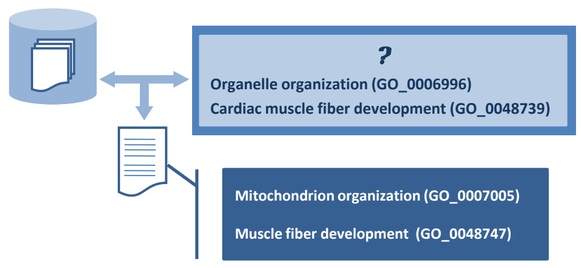
Recherche de gènes

L'ontologie de domaine comme support du calcul de pertinence, …

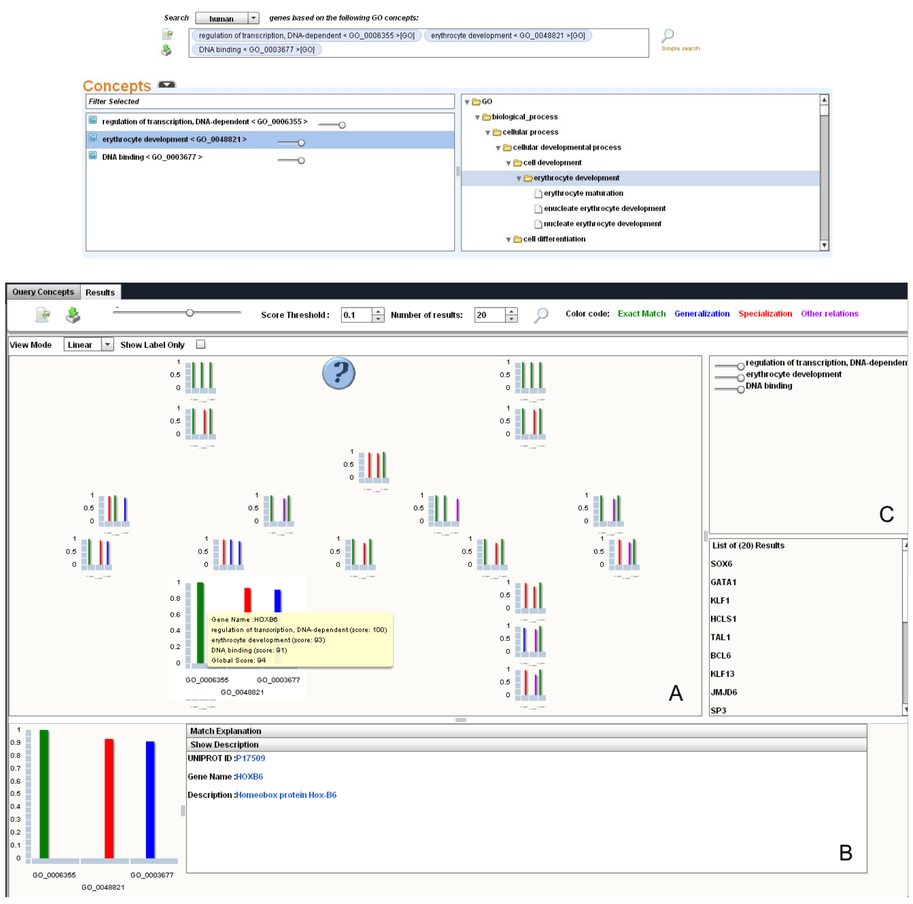


[GeneOntology]

- Croissance exponentielle des ressources disponibles (puces à ADN, séquençage haut débit, …)
- Capacité d'innovation dépendante de la capacité à trouver (rapidement) la bonne information au bon moment
- Croisement entre données biologiques et publications scientifiques



L'équipe KID du centre de recherche LGI2P de l'Ecole des Mines d'Alès, a conçu et développé l'environnement OBIRS (*Ontological Based Information Retrieval System*, http://www.ontotoolkit.mines-ales.fr/ObirsClient/) qui permet d'améliorer la recherche d'information centrée sur l'utilisateur en utilisant une ontologie de domaine (Gene Ontology, MeSH…) et une indexation conceptuelle.



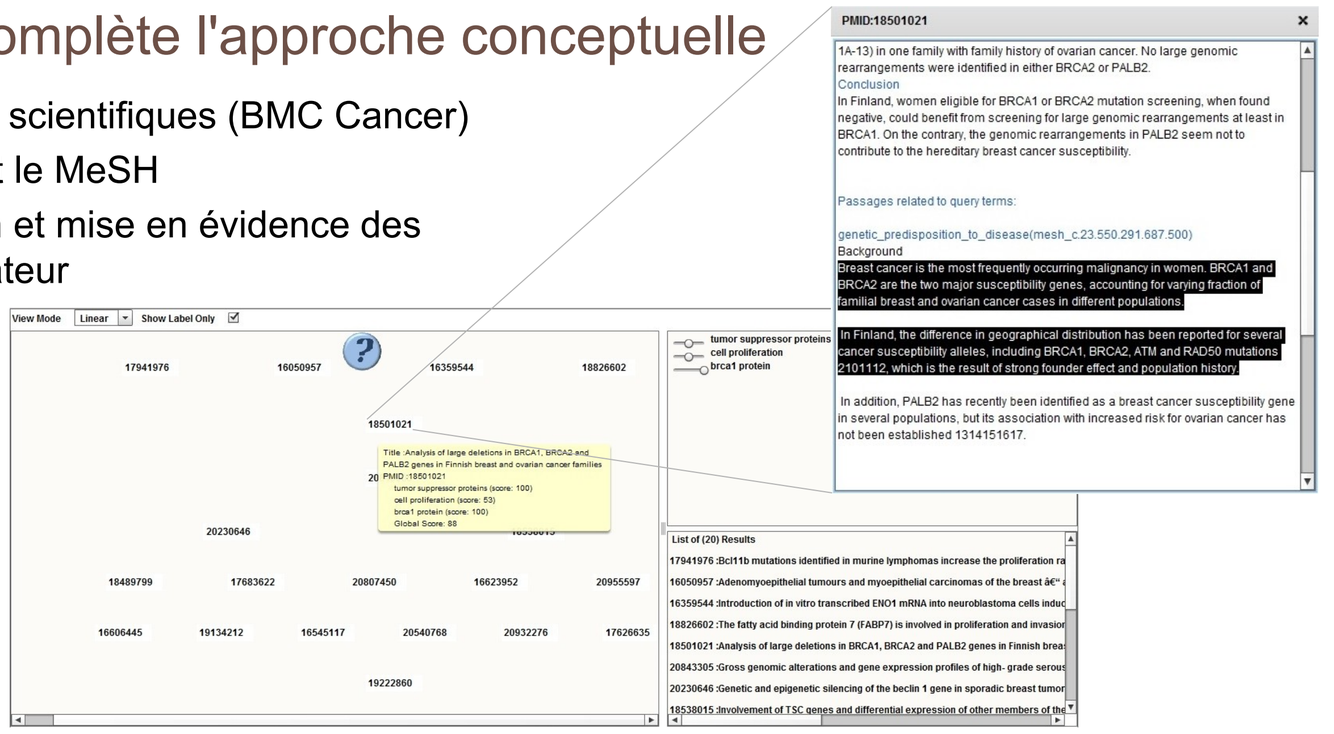
…de la personnalisation et de la justification des résultats

- Vue globale des résultats : carte sémantique où les résultats sont positionnés relativement à leur pertinence par rapport à la requête de l'utilisateur (A)
- Description de chaque gène retrouvé : nom, description, lien (B)
- Paramétrisation : pondération des termes de la requête (C)
- Représentation des gènes avec des histogrammes : une barre est associée à chaque concept de la requête de l'utilisateur :
  - sa hauteur est proportionnelle à sa pertinence
  - sa couleur indique si ce concept
    - annote lui-même un document
    - ou un de ses "fils"
    - ou un de ses "pères"
    - ou un de ses "cousins"

Recherche de publications scientifiques

Où l'approche lexicale complète l'approche conceptuelle

- Application à la fouille de corpus scientifiques (BMC Cancer)
- Recherche d'information utilisant le MeSH
- Analyse de textes, segmentation et mise en évidence des passages pertinents pour l'utilisateur



Publication :
User centered and ontology based information retrieval system for life sciences
Mohameth-François Sy, Sylvie Ranwez, Jacky Montmain, Armelle Regnault, Michel Crampes, Vincent Ranwez
Bioinformatics 2012, 13(Suppl 1):S4
http://www.biomedcentral.com/1471-2105/13/S1/S4

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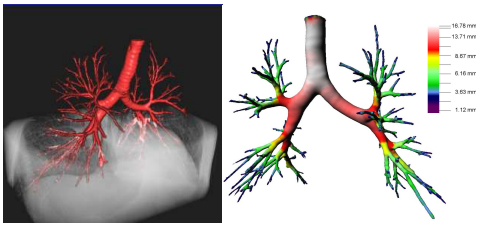
Computer-aided diagnosis and image biomarkers in asthma and COPD

MAP5

Understanding the mechanisms and relationships between airway structure/physiology and the clinical phenotype/genotype in asthma and COPD is the clinical aim behind the concept "image as marker". Capturing the morpho-functional changes of airways using CT imaging provides pathology markers and allows treatment planning, disease progression assessment and therapy outcomes prediction.

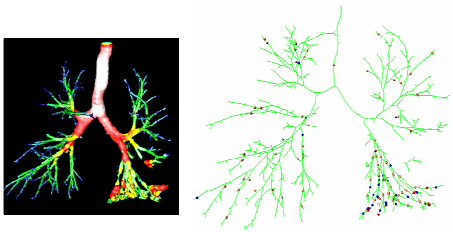
Catalin FETITA

Airway remodeling analysis: qualitative to quantitative…



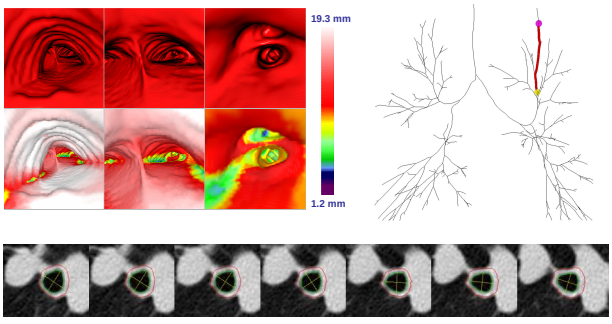
3D airway lumen segmentation from CT and color-coded max-caliber information

- Automated 3D segmentation of airway lumen morphology enables visual feed-back on geometry and topology features.
- Analysis of local shape variation based on max-caliber computation provides semi-quantitative information on airway obstruction.
- A shape variation index derived along the central axis from the min/max-caliber of the airway lumen allows automatic detection and localization of shape abnormalities (stenosis, bronchiectasis).

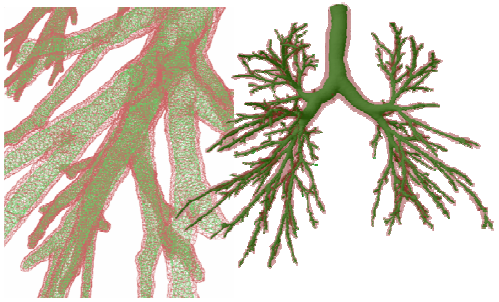


Automatic airway shape analysis: detection and CA mark-up of pathology-related abnormalities (stenosis – orange/red and bronchiectasis – blue)

- Central axis (CA) provides interaction and navigation facilities such as surgical planning in (enhanced) virtual bronchoscopy.
- The assessment of airway wall remodeling based on cross-section quantification of lumen/wall areas is achieved in a high-throughput framework which allows dense sampling measurements in order to capture the disease heterogeneity.
- The fully-3D airway wall segmentation provides complete quantification of wall remodeling (including subdivisions).

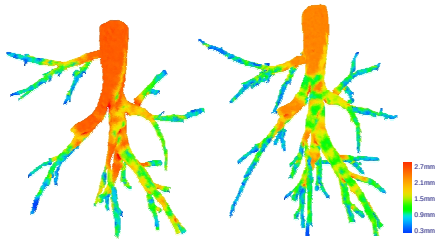


Navigation and planning via virtual (max-caliber enhanced) bronchoscopy, and high-throughput cross-section quantification



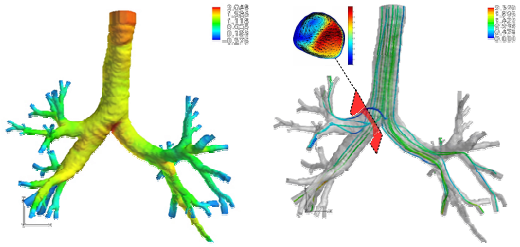
Volumetric segmentation and quantification of the airway wall

… and morphological to functional



Airway wall thickness before / after treatment in a patient with severe asthma

- Quantitative follow-up of airway wall remodeling informs on the disease impact and/or therapy outcome
- Functional behavior can be predicted using computational fluid dynamics simulations (CFD).
- Several large-cohort clinical trials performed in asthma and COPD.



CFD simulations (wall pressure and velocity profiles) in a normal airway geometry (courtesy R-MOD project)

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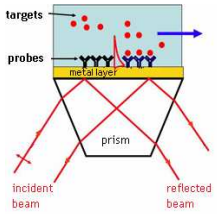
ICT and biomedical applications: diagnostic of genetic mutations and study of genetic oscillators

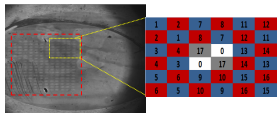
MAP5

New *lab-on-a-chip* technologies dedicated to the study of molecular interactions, genetic diagnosis, but also to the design of controlled biological organisms (synthetic biology) require adapted ICT tools to analyze the image data information acquired. Two applications are presented, one dedicated to the mutation diagnostic with surface plasmon resonance (SPR) biochips, the other one targeting the design of genetic oscillators and their study based on single-cell tracking with epifluorescence microscopy.

Catalin FETITA

Genetic diagnosis based on SPR imaging

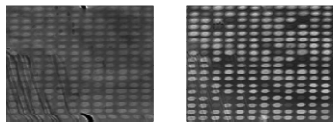




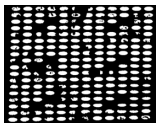
Typical SPR image obtained from the CCD camera, and elementary spotting matrix containing 6 × 6 spotting regions. Red - wild spot (WS), blue - mutated spot (MS), white - empty spot, grey - calibration spot

- Specific calibration steps, both experimental and image-based, were designed to overcome the heterogeneity of the signal at the biochip surface.
- A real-time spatio-temporal classification approach extracts the effective interaction zone of each probe, where the signal is collected.
- The genetic diagnostic is established by monitoring the time-updated evolution of the difference signal WS–MS computed for all wild and mutated probes of the biochip.

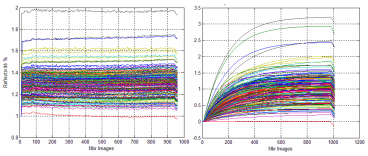
- Providing a lower cost tool for genetic diagnosis based on SPRi requires automatic extraction and calibration of the target-probes interaction signal in a real-time framework.
- The objective is to predict the evolution of the molecular interactions under study and thus formulating a diagnostic (wild / mutated / heterozygote target) before the end of the experiment.



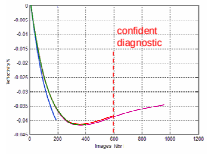
Original (left) and calibrated (right) image data



Effective interaction regions

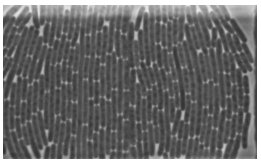


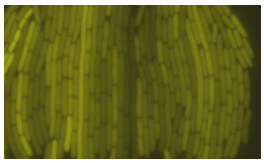
Interaction signals for all biochip probes without (left) and with calibration procedure (right)



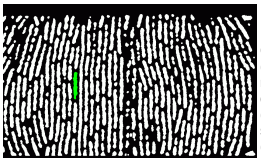
Real-time genetic diagnostic with 30% time saving, the injected target is heterozygote (WS – MS = 0)

Study of genetic oscillators

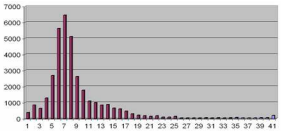




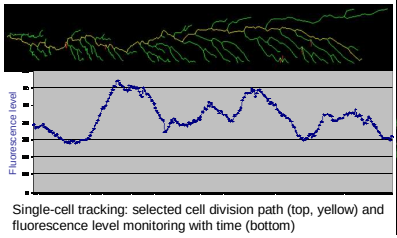
Phase-contrast (left) and fluorescence (right) sequence for *E. coli* single-cell tracking



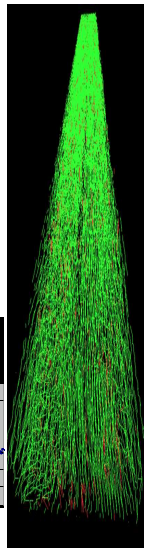
Cell segmentation (left) and cell lineage reconstruction for all cells on the biochip (right), allowing single-cell tracking (*e.g.* green cell)



Cell division time computed from the whole biochip (histogram peak)



Single-cell tracking: selected cell division path (top, yellow) and fluorescence level monitoring with time (bottom)



- Characterize the performance of elementary genetic circuits and parts at the single-cell level.
- Design, build and characterize genetic oscillators as one of the basic parts governing programmed cell behavior.
- Use *E. coli* as model organism, grown in purpose-made microfluidics biochips and monitored with epifluorescence microscopy (phase-contrast and fluorescence image data).
- Design and study novel types of plasmids which repress the replication of their own DNA and are expected to demonstrate oscillations in copy number. The plasmid copy number is reported by the fluorescent protein generation controlled by a constitutive promoter inserted in the same plasmid.
- Fully automatic approach for single-cell segmentation and tracking using the phase-contrast sequence.
- Cell division time computation and fluorescence level monitoring along individual cell lineage paths.
- Efficient framework for analysis and design of genetic oscillators allowing parallel investigation of several “traps” on the microfluidic biochip with different cell growth conditions.

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6-7 février 2012

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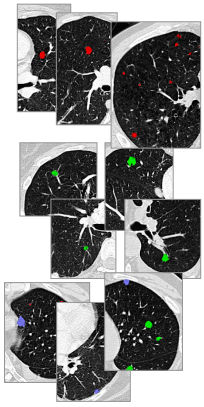
Computer-assisted diagnosis and follow-up of lung nodulation and idiopathic interstitial pneumonias

Catalin FETITA

MAP5

Lung diseases remain a major healthcare concern in terms of efficient therapeutic outcome, early diagnosis and quantitative follow-up. The developed ICT-based solutions presented in the following target both neoplasic and non-neoplasic pathologies.

Targeted pathologies



Lung nodules:

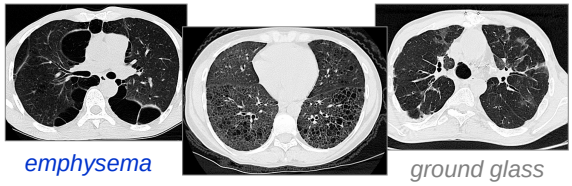
- dense masses of various shapes and sizes (from few mm up to several cm),
- non-uniform textures and good contrast with respect to the lung parenchyma.

According to their spatial location, lung nodules can be classed as:

- **solitary** - no connection to other dense tissue,
- **juxta-vascular** - "touching" at least a blood vessel,
- **sub-pleural** - connected to the thorax cage or mediastinum.

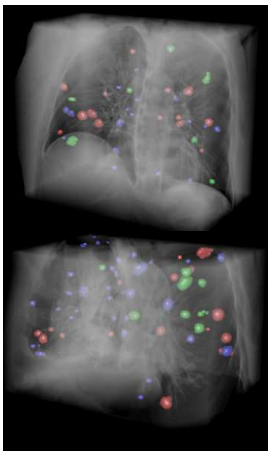
Emphysema and idiopathic interstitial pneumonias:

- non-neoplasic irreversible diseases,
- affect the tissue and space within and around the alveoli and sometimes also the airways, the blood vessels and the pleura, leading to profound impairment in lung physiology.
- to date, no treatment is available for most of IIPs.

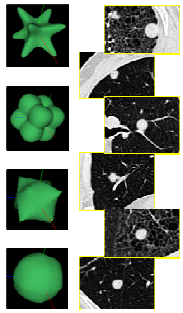


emphysema *ground glass* *fibrosis / honeycombing*

Automated screening of lung nodules



- An original 3D approach based on mathematical morphology and exploiting the grayscale connectivity between dense lung tissues is developed providing automatic segmentation of nodules irrespective to their spatial location and adjacency, of sizes ranging from 2 to 20 mm diameter.
- The performance of such a CAD system in terms of volumetric assessment of lung nodules was evaluated using an objective reference database involving mathematically simulated nodules.

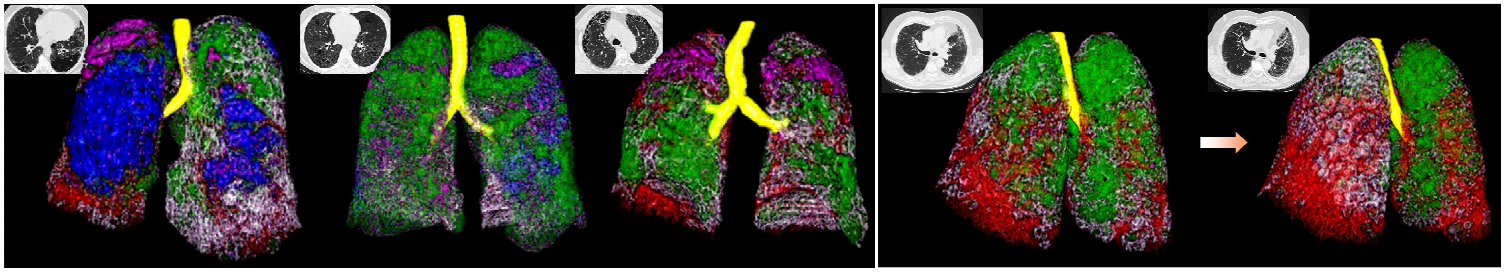


Automated screening of two metastasis of lung carcinoma with discrimination of nodule spatial location.

Simulated nodules (spiculated, lobular, round shapes) and image data for validation

Lung texture analysis in emphysema and IIPs

- Fully automatic volumetric CAD solution.
- Approach combining multiresolution morphological filtering, texture and fuzzy logic analysis.
- Qualitative evaluation performed on clinical routine studies on emphysema and IIPs by experienced radiologists.
- High accuracy in pathology detection with moderate discrimination between some small emphysema and fibrosis/honeycombing patterns.
- Great clinical potential in early pathology detection, longitudinal follow-up and therapy design and evaluation.



Disease patterns detection and quantitative follow-up (15 months): blue=emphysema, violet=fibrosis/honeycombing, white=ground glass, red=high-dense fibrotic tissue, green=normal parenchyma, yellow=large airways

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