MECHANICAL ENGINEERING | PHYSICS | PRESERVATION OF THE ARCHITECTURAL HERITAGE | SPATIAL PLANNING AND URBAN DEVELOPMENT | STRUCTURAL SEISMIC AND GEOTECHNICAL ENGINEERING | TECHNOLOGY AND DESIGN FOR ENVIRONMENT AND BUILDING | TERRITORIAL DESIGN AND GOVERNMENT | AEROSPACE ENGINEERING | ARCHITECTURAL AND URBAN DESIGN | ARCHITECTURAL COMPOSITION | ARCHITECTURE, URBAN DESIGN, CONSERVATION OF HOUSING AND LANDSCAPE | **BIOENGINEERING** | BUILDING ENGINEERING | DESIGN | DESIGN AND TECHNOLOGIES FOR CULTURAL HERITAGE | ELECTRICAL ENGINEERING | ENERGY AND NUCLEAR SCIENCE AND TECHNOLOGY | ENVIRONMENTAL AND INFRASTRUCTURES ENGINEERING | INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING | INFORMATION TECHNOLOGY | INTERIOR ARCHITECTURE AND EXHIBITION DESIGN | MANAGEMENT, ECONOMICS AND INDUSTRIAL ENGINEERING | MATERIALS ENGINEERING | MATHEMATICAL MODELS AND METHODS IN ENGINEERING

PhD Yearbook | 2016

Chair:
Prof. Andrea Aliverti

# DOCTORAL PROGRAM IN BIOENGINEERING

The main objective of the PhD Programme in Bioengineering is to prepare the PhD candidates to develop high level engineering problem-solving abilities in biomedical, healthcare and life sciences, inside research groups or in private/public industrial contexts, through a strong interdisciplinary training bridging engineering and medical/biological knowledge.
During the PhD, the candidates develop a scientific research project dealing with a complex problem which can be at different scales, from the molecular and the cellular levels to living organisms up to biomedical systems. They investigate original methods, devices, and systems with different purposes: increasing knowledge, proposing innovative methods for diagnosis and therapy as well as improving healthcare and daily life structures and services. At the end of the PhD programme, the candidate are expected to be able to carry out innovative projects and research and development in the field of Bioengineering, by proposing new methodological and technological solutions and properly evaluating the technology impact in healthcare, life science and biomedical industry.
During the three years of the program, PhD candidates perform their research through theoretical and experimental activities in four major areas: biomimetic engineering and micro-nano technologies; rehabilitation engineering and technology; technologies for therapy; physiological modelling and non-invasive diagnostics.
More specific areas include but are not limited to: molecular and cellular engineering, biomaterials, tissue engineering, bio-artificial interfaces and devices, neuro-prostheses, movement analysis, cardiovascular and respiratory system bioengineering, central nervous system signal and image processing for rehabilitation, biomechanics, computational fluid-dynamics, computer assisted surgery and radiotherapy, robotics, artificial organs, implantable devices, biomedical signal and image processing, E-Health, bioinformatics, functional genomics and molecular medicine.
The PhD Program in Bioengineering is organized with an inter-departmental structure. Faculty members of the PhD Advisory Board belong to two Departments of the Politecnico di Milano, namely DEIB (Department of Electronics, Information and Bioengineering) and CMIC (Department of Chemistry, Materials and Chemical Engineering "G. Natta").
PhD candidates (who are, in average, 20 per year) develop their PhD research programs within experimental laboratories located at the Politecnico di Milano or outside it, typically biomedical research centers, hospitals or industries.
When the research is performed within the Politecnico, PhD candidates are usually assigned to one of the following laboratories belonging to the DEIB and CMIC: Laboratory of Biological Structure Mechanics (LaBS, CMIC), Laboratory of movement analysis "Luigi Divieti" (DEIB), Medical Informatics laboratory (DEIB), Neuroengineering and medical robotics Laboratory (NearLab, DEIB), Biosignals, Bioimaging and Bioinformatics Lab (B3 lab, DEIB), Biomaterials laboratory (CMIC), Biomedical Technology Lab (TBMLab, DEIB), Experimental Micro and Biofluid dynamics (μBS Lab, DEIB), Computational Biomechanics Lab (DEIB), Biocompatibility and Cell culture Lab (BioCell, CMIC), Bioreactors Laboratory (CMIC). The Istituto di Elettronica, Ingegneria dell'Informazione e delle Telecomunicazioni (IEIIT) of the Consiglio Nazionale delle Ricerche (CNR), which is located at DEIB, represents another possible option.
Stage periods in distinguished research institutes in Italy and abroad are an essential feature of the PhD candidate training.
The candidates are encouraged to carry out part of their research activities in contact with other research groups, preferably abroad through periods of at least three months spent in laboratories where the candidate can acquire further skills to develop his/her research work and thesis.
Collaborations that may involve the PhD students are presently active with several national and international research and academic Institutions. Very often, the involvement of companies and clinical partners facilitates the technological transfer of applied research into industry and clinical applications.
The educational offer includes *ad hoc* advanced courses specifically designed for the PhD in Bioengineering. The offer includes also the school of the National Bioengineering Group, which is held yearly for one week in Bressanone (Bz). Every year, the School is focused on different topics. As examples, the themes of the last years have been: Neuroscience, robotics and intelligent machines (2006), Computational Genomics and Proteomics (2007), Wearable Intelligent Devices for Human Health (2008), Bioengineering for Cognitive Neurosciences (2009), Synthetic biology (2010), Neuro-informatics (2011), Biomedical devices from research to market (2012), Regenerative medicine (2013), From functional recovery to artificial organs (2014), Experimental models for development methods for 3R (2015).
The PhD Board of professors ('PhD Board') is composed by highly qualified and active researchers in Bioengineering, belonging to DEIB and CMIC. The PhD Board is responsible of all the candidate's activities. The competencies of Faculty members cover a wide spectrum of research fields. This allows a continuous updating of the PhD program and ensures that the PhD candidates are involved in innovative work.

## COMPOSITION OF THE PHD BOARD

| | |
|---|---|
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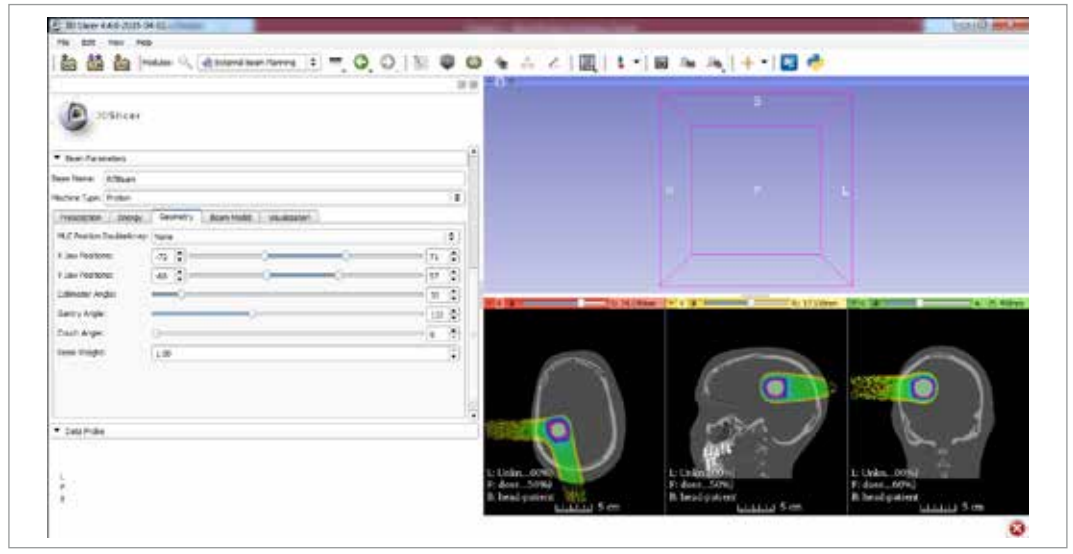
The PhD Programme in Bioengineering relies also on an Advisory Board Member, formed by distinguished experts coming from R&D industries, research and clinical centers, in order to ensure that that the goals of the PhD Program are in line also with the needs of non-academic world.

# AN OPEN SOURCE SOFTWARE FOR PROTON TREATMENT PLANNING

**Maxime Desplanques** - Advisor: Prof. Guido Baroni
Co-Advisor: Assist. Prof. Gregory C. Sharp

This report describes in three sections the complete method for the creation of an open-source, multi-platform Treatment Planning System (TPS) dedicated to proton beam lines.
The first part outlines the implementation of a proton Dose Calculation Engine (DCE) based on pencil beam algorithms in Plastimatch, an open-source software for medical image computation. The DCE was decomposed into two types of algorithms: the model of the beam line elements and the dose summation algorithms in the input CT-images. An accurate analysis of the proton pencil beam deformation due to beam line elements was performed. Three pencil beam dose summation algorithms were developed, in addition to the reference well-known Hong's algorithm, and compared with dose distributions computed by Monte Carlo simulations. The second part illustrates how the proton pencil beam model was upgraded with respect to Hong's reference algorithms, providing a better description of the lateral scattering of protons in both the range compensator and in the patient heterogeneities. The last part describes the creation of a user-friendly interface, implemented in the open-source software for medical image computation and visualization 3D Slicer. The interface, connected to the dose DCE developed in Plastimatch, simulates a commercial TPS: it allows the setting of the parameters required for both the beam line characterization and the definition of a specific treatment plan.
The entire beam line model implemented in Plastimatch was based on the Hong's method, known as the reference method for proton pencil beam dose calculations and dedicated to passively scattered beam line. The approach was validated by Monte Carlo simulations and compared to the three alternative dose summation models developed in this project: the Ray Tracer (RT), the Cartesian Geometry dose Summation algorithm (CGS) and the Divergent Geometry dose Summation algorithm (DGS).
In particular conditions, such as heterogeneous media, the reference algorithm is known to compute inaccurately the proton beamlet spread. We proposed to upgrade it in two ways: at first, by building a new model that described the lateral scattering of proton pencil beamlets in range compensators. The study evaluated multiple analytical models of beamlet spreads that are customized for a PMMA range compensator. Four different models were chosen and their accuracies were tested by Monte Carlo measurements in the particle therapy energy range.
At a later stage, a differential method accounting for the patient heterogeneities was developed with the help of the proton scattering power theory and implemented as an alternative algorithm in Plastimatch. Finally, the TPS developed in this project proposed to automatically conform the dose distribution around a target volume. To reach this objective, three algorithms were achieved: a collimator shaper based on the projection of the target volume in the beam frame, a range compensator creator considering the lack of material upward the target volume, and a Spread Out Bragg Peak (SOBP) designer.
The four dose summation algorithms were tested in broad beam conditions. The CGS, DGS and HGS were in good agreement with Monte Carlo simulations (2.5%-2.5 mm gamma-index scores > 95%).
The Hong's algorithm describing the beamlet spread in the patient was assessed to be accurate only in homogeneous water equivalent media. In heterogeneous phantoms involving air gaps, the Hong's model led to 60% errors on the Full Width at Half Maximum (FWHM) of the beamlet lateral spread when compared to Monte Carlo simulations. Once the differential method based on the scattering power theory was applied in the same conditions, this error was reduced to 6%. Improvements were also found in cortical bone-water heterogeneities, reducing the error on the FWHM from 30% with the Hong's approach to 2.5% with the differential approach. Regarding the PMMA-range compensator analytical models, the most significant input parameters proved to be the distance from the effective origin of the scattering inside the range compensator, the particle energy and the range compensator thickness. The study showed that two models considering the effective origin of scattering were more accurate than simpler models that did not contemplate such factor, and they provided estimations of beamlet spread induced by PMMA range compensators in the order of 0.2 % ± 3.1 % (mean ± standard deviation, compared to MC simulations) when the reference Hong's model provided discrepancies in the order of -6.7% ± 7.7%. Ultimately, the report proposes an overview of the complete interface including the presentation of the modules for the beam line characterization and the treatment plan definition. Two different treatment plans are presented as examples, which have been successfully created from the SlicerRt interface connected to the Plastimatch DCE (Figure 1).
The study showed that a basic TPS dedicated to passively scattered proton beam line could be contrived with accuracy. The dosimetric study validated two new dose summations algorithms (CGS and DGS) in addition to the reference HGS algorithm, the CGS being slightly faster than the HGS. We also proposed a differential approach describing the pencil beamlet spread with a higher accuracy than the reference method, especially in heterogeneous media. The Plastimatch DCE achieved acceptable accuracy (2.5%-2.5 mm gamma-index scores > 95%) in both homogeneous and heterogeneous phantoms in a satisfying computation time (<5 min) on a common laptop or computer. These different improvements in the pencil beam definition allowed to create a complete basic TPS, calling the Plastimatch DCE, which was demonstrated to be more accurate than the reference Hong's method. We hope that the open-source TPS developed during this PhD project will contribute to a better understanding and estimation of the delivered dose in particle therapy, especially for pencil beam dose calculation methods, and will help the research groups that couldn't afford a commercial TPS.



**1. Software interface overview for the example of a brain treatment plan. The ODV is shown on a colorwash scale and overlapped on the input CT-images. The target volume is represented in white.**

# ELECTROMAGNETIC FIELDS EXPOSURE ASSESSMENT IN THE EARLY LIFE: FROM PRENATAL STAGE TO INFANCY

**Ilaria Liorni** - Advisor: Dr. Marta Parazzini
Co-Advisor: Dr. Paolo Ravazzani

In the last decades there has been an increasing public concern relative to the growing diffusion of man-made EMF sources working at several frequencies and to the health effects they could generate. The attention has been mainly focused on fetuses and very young children, supposed to be more susceptible to EMF, because exposed to this agent since the prenatal life and during the ages of major growth.
Therefore, the scientific community claimed the necessity to carry out EMF exposure assessment procedures tuned on this type of subjects, in order to provide support to the health risk assessment process. This includes also the necessity to investigate new methods for the quantification of the variability of the exposure in real environments. In the light of above, this dissertation aims to provide the exposure assessment of fetuses and infants exposed at low frequency fields (50 Hz) and at novel emerging communication devices such as tablets and femtocells. In details the various Sections address:

1) the exposure assessment of extremely low frequency magnetic fields (ELF-MF) in fetus as a function of the gestational age (GA), the fetal posture and the MF orientation;
2) the exposure assessment of radio-frequency (RF) EMF in infants due to tablet and cellular base station (femtocell) devices, operating in different modes and placed in different positions with respect to the exposed subject;
3) the use of advanced stochastic approaches to assess the variability of EMF exposure in real environments by means of the polynomial chaos theory.

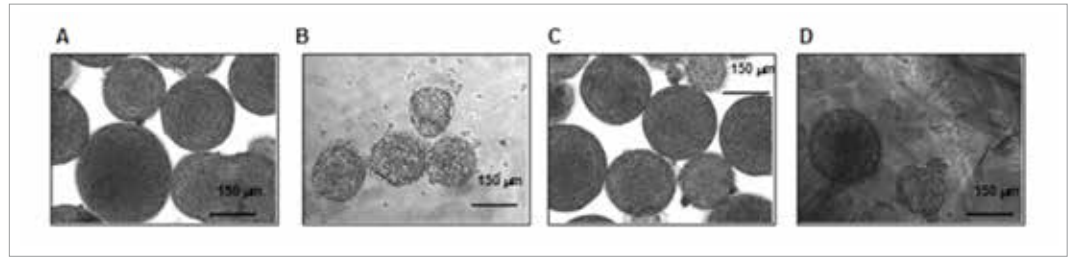
# ENHANCING ISLET TRANSPLANTATION AND FUNCTIONALITY BY THE USE OF COMPLEX POLYMER STRUCTURES

**Simona Marzorati** - Supervisor: Prof. S. Farè

Clinical islet transplantation has demonstrated superior blood glucose control in comparison with other therapeutic options for type 1 diabetic patients; however, this procedure presents still some limitations. Numerous events challenge islets, such as the failure of revascularization and immune attack of the graft. Various strategies have being investigated to overcome all these limitations, including immunoisolation using semipermeable biocompatible polymeric capsules for islet encapsulation. Immunoisolation is an appealing approach that is able to overcome two problems that limit the widespread of islets transplantation as therapeutic options: prevents immune destruction of islets and facilitates the use of xenogenic cell-based therapeutic options. Bioengineering approach (more specifically biomaterials) have the potential to improve the outcome of islet engraftment; even if in literature this approach is well explored, limited success due to processing and biomaterial limitations have still to overcome. The diffusional barrier suddenly, limits the free supply of oxygen and nutrients, resulting in hypoxia and lack of revascularization of islets. A major pitfall associated with the microencapsulation system may consist of poor standardization in selecting chemically suitable and endotoxin-free polymers to engineer the microcapsule's shell. Other significant differences occur in regard to the microencapsulation methodology and to the injection of the loaded microcapsules in vivo that can cause high shear stress to the islets. Thus, the development of novel strategies that improve islets encapsulation approach, could be highly beneficial. The central hypothesis of this PhD dissertation was the possible application of a new scaffold, optimized for pancreatic islets that would improve □-cell and islet viability and function *in vitro* and eventually *in vivo*.

An interdisciplinary approach was pursued, which included the synthesis of the proposed gelatin hydrogel, the analysis of *in vitro* interaction between matrix and human/murine pancreatic islets, and their characterization in physiological conditions in a preclinical *in vivo* transplant model.

Encouraging from recent successful literature data in the use of hydrogels in pancreatic field, we explored the idea to use a new gelatin crosslinked hydrogel recently patented at Biomaterials Laboratory, Politecnico di Milano. In perspective of regenerative medicine applications, the hydrogel should serve as a physical support, i.e. withstanding the complex stress conditions in the body, conveying the physiological loads to the surrounding tissue, and preserving the architecture integrity during or after stress condition *in vivo*. The results obtained during the mechanical compressive characterization of the proposed hydrogel allowed to detect a good viscoelastic behavior, even when the hydrogel exhibited a porous structure, ideal for pancreatic islet encapsulation. Morphological analysis by optical microscopy of pancreatic islets loaded in the hydrogel matrix showed that the proposed gelatin hydrogel not alters the complex pancreatic islet structure, maintaining intact the cell capsule (Fig 1); any sign of islets disaggregation was observed, even when the culture was lasted for a medium term (7 days).




**1. Representative images (bright field optical images,20X) of murine pancreatic islet 48 and 144 hrs post seeding into crosslinked gelatin hydrogel. A: murine pancreatic islets cultured free floating for 48hrs. B: murine pancreatic islets seeded onto dehydrated gelatin hydrogel for 48 hrs. C: murine pancreatic islets cultured free floating for 144hrs. D: murine pancreatic islets seeded onto dehydrated gelatin hydrogel for 144hrs.**

Either during a short (48 hrs) or medium (144 hrs) culture period, both human and murine islet cells are viable (MTT test) once seeded on hydrogels. Similary, the functionality of islets, measured trough glucose stimulation test, seems to be preserved: islets are able to answer to physiological stimulus and preserve their basal insulin secretion level. We were able also to demonstrated that the 3D culture is able to partially downregulate the proinflammatory state of islets, providing an insight into their characteristics *in vivo*. Since their isolation, until implantation, pancreatic islets suffer stress leading to the activation of inflammatory reaction. Our results in vitro demonstrate that recreate a 3D *niche* is essential for the maintenance of controlled inflammatory reaction that leads to an increase of survival and function of cells. With the intention to translate the proposed culture system in clinical practice, the effect of gas plasma and ethylene oxide sterilization technique, on the structure, morphological and mechanical characteristics of the proposed gelatin hydrogel were evaluated. We demonstrated that the two explored sterilization technique dosen't change the chemical-physical characteristics of the gelatin hydrogel and don't influence negatively the interaction gelatin hydrogel-islets. The characterization of biomaterials as implantable devices, cannot be complete without considering its biocompatibility, in order to test its performance in conditions similar to the human biological environment. We choose the peritoneum space as candidate site for gelatin hydrogel transplantation, due to the fact that this site has been already investigated for transplantation of free islets due to numerous advantages. We demonstrated that the cross-linked gelatin hydrogel is biocompatible maintaining its structure without a massive degradation. After several experiments to define the ideal islet mass, we moreover observed that in diabetic mice (alloxan induced), transplantation of 800 syngeneic islets seeded on the scaffold and transplant in the peritoneal space are able to revert hyperglycaemia (100% of mice). Our results showed how islets seeded into the hydrogel sustained normoglycemia and all the mice that initially reversed hyperglycemia, maintained their normoglycemic state up to 70 days.

With this thesis work, we demonstrated that the crosslinked gelatin hydrogel is a good support for pancreatic islets *in vitro* and once they are transplanted *in vivo*; beside that, we are convinced that future work (an implementation of the structure is already under investigation) is necessary for further optimization of these technology platforms for clinical application in the islet transplant model especially.

# A MULTISCALE MODEL OF CARDIAC BIOMECHANICS TO SIMULATE SURGICAL PROCEDURES IN PATIENTS AFFECTED BY HYPOPLASTIC HEART SYNDROME

**Alessio Meoli** - **Supervisor:** Prof. Giancarlo Pennati

This PhD thesis has been developed at the Laboratory of Biological Structure Mechanics (LaBS) of Politecnico di Milano within the PhD program in Bioengineering. This work was developed in the context of a large international project funded by the Fondation Leducq (Paris), entitled 'Multi-scale modelling of single ventricle hearts for clinical decision support'.

## Introduction and objective

Single-ventricle (SV) defect is a complex congenital heart disease commonly treated following a three-stage surgical procedure. In the last decades great improvements in the surgical procedures have been achieved with significant increase in the outcomes for the treatment of SV defects. However, univentricular circulation still represents a critical and peculiar condition.
In the last 10 years greater attention have been placed on developing CFD models to study patient-specific cases with main objective of planning surgical treatments. The concept of multiscale models that couple 3D model of vascular region of interest with 0D models that represent the whole circulation in a closed-loop fashion, allows for a better description of the univentricular circulation. The importance of the closed-loop approach is related to the changes occurring in the circulatory layout across the surgical procedure in SV patients. When investigating the efficiency of fluid dynamics in univentricular circulation, the functional ventricular chamber is commonly described by means of simplified lumped parameter (LP) models. Only in the very last years, a FSI study placed attention also on the ventricular mechanics. However, this study was focused only on the diastolic phase and disregarded the influence of the circulation highlighting the lack of multiscale models accounting for both the mechanics of the SV and the fluid dynamics description of the circulatory system. Since the ventricular mechanics plays a fundamental role in determining the behaviour of the whole cardiocirculatory system, the principal aim of this work is to adopt a simulation framework that allows to account in a multiscale and closed-loop fashion for a patient-specific 3D finite element model of the SV to patient-specific LP models of the pre- and post-operative circulations.

## Methods

The multiscale patient-specific model of SV heart is composed of four main components:

- A patient-specific LP model of the circulatory network to apply proper hemodynamics boundary conditions to the 3D model. The basic LP layout is comprised of four RLCRCR blocks (upper body, lower body, right and left pulmonary branches). The proper connection of the four blocks allows the description of SV circulations for different stages. A time-varying elastances represented the single atrium and non-linear diodes described the atrio-ventricular and aortic valves.
- An anatomic model of the SV that account for the anatomy and the fibre architecture. Hexahedral cubic-Hermite finite element mesh is constructed based on clinical images. Endocardial and epicardial contours at end-diastole (ED) were manually segmented and an initial template mesh was fitted to the reconstructed geometry to match the patient anatomy. Fibre architecture is assumed as in physiological ventricles since information for SV hearts are lacking.
- A passive model to describe the resting material properties of the myocardium. The transversely-isotropic form of the constitutive model proposed by Holzapfel and Ogden was adopted. The myocardial passive material parameters were estimated together with the identification of the unloaded geometry by means of an iterative method able to estimate the unloaded geometry from the ED ventricular geometry and pressure.
- An active material model to describe the contractile properties of the myocardium. The active parameters were determined to match the measured peak SV pressures and end-systolic volumes.

A key issue in the development of the multiscale model is the estimation of the patient-specific parameters of the different parts of the model. Thus, a sequential approach was carried out: (i) LP parameters were estimated by using a fully LP model; (ii) ventricular material parameters and unloaded geometry were identified by means of the stand-alone 3D model of the SV; and (iii) the 3D model of SV was coupled to the LP model of the circulation, thus closing the loop and creating a multiscale model. Once the patient-specific multiscale model is setup using pre-operative clinical data, virtual surgery is performed changing the LP model to simulate post-operative condition.

## Results and Discussion

Two patient suffering form hypoplastic left (HLH) and right (HRH) heart syndrome were investigated. The multiscale results of the stage 1 of the patients were compared with pre-operative clinical data. An overall good agreement was obtained for both patients in replicating the main clinical quantities (error < 5%). Moreover, a proper cardiac output (CO) indicates a satisfactory description of ventricular-arterial and venous atrial couplings.
The changes in the circulatory layout associated with the surgery, led to an increase in the afterload and to a decrease of the preload of the SV. Comparing stage 1 and stage 2 simulations, a decrease in the CO together with an increase of the ventricular peak pressure was observed. Mean aortic pressure increases as well as the systolic and diastolic ones. Conversely, the atrial pressure decreased. These significant changes of variables mean values in the post-operative state from the pre-operative were expected with ventricle volume unloading and the increasing in the afterload.
Concerning fibre stress in the preoperative state, at the systolic peak the HLH patient presented the higher value (46 kPa) while at end diastole HRH showed the higher value (5 kPa). In other works, similar values and patterns of stress in the fibre direction are reported, thus suggesting reliability of the obtained results. Regarding the fibre strain, HRH showed the higher values of strain reaching 25%. It is worth noting that both patients showed significant portions of the myocardial wall with fibre strains ranging from 20% to 25%. These values are known to be rather critical because they are very close to sarcomere decompensation. Postoperatively, stresses at the systolic peak remain similar due to the increase in the SV peak pressure, while at end diastole significantly decreases confirming the beneficial effect of the surgery. Under the hypothesis that the fibre orientation may change adapting to the higher work, for the patient HLH, both the fibre orientation of the healthy RV and LV were tested. Results showed that while the global hemodynamics were not affected by different fibre orientations, the wall kinematics and mechanics showed a clearly different behaviour. Thus, the model supported by additional clinical data could help to gain a more clear understanding of this peculiar condition.

## Conclusions

In this work two patient-specific cases were simulated demonstrating the goodness of the proposed methodology in simulating the behaviour of each patient considered. The pre-operative state of the patients was successfully simulated with errors in replicating the main hemodynamic quantities lower then 5%. The regional myocardial results reported were in agreement with other works and showed that SV hearts are subjected to heavier working conditions in respect to normal heart. The simulation of the post-operative state showed that: i) stroke volume significantly decreases; ii) the EDV decreases confirming the beneficial effect of the surgery; iii) aortic pressure increases in the mean value; iv) each patient presents specific response to the surgery confirming the need for patient-specific modelling.

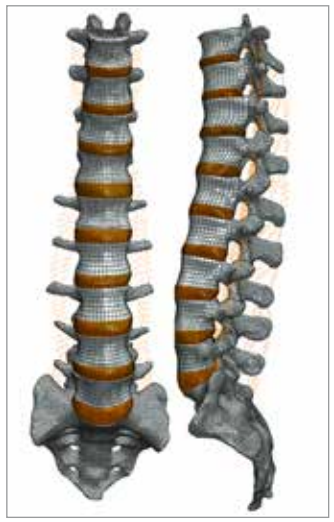
# STRATEGIES FOR THE BIOMECHANICAL EVALUATION OF SPINE SURGERY: COMPUTATIONAL MODELS AND EXPERIMENTAL TESTING

**Claudia Ottardi** - Advisor: Tomaso Villa

The spine is one of the most important structures of the human body, being fundamental to maintain the posture, to guarantee the motion and to protect the spinal cord and to sustain mechanical loads. However, it is also subjected to several pathologies that can involve the various components such as vertebrae, discs and ligaments. In order to understand the mechanisms that lead to a pathological condition and to suggest surgical strategies to clinicians, it is essential to study the spine biomechanics, in healthy conditions as well as after surgical treatments. Several methods can be used: clinical studies, in vitro testing on animal and human specimens or numerical models. Experimental tests and computational models are usually complementary, because the predictions of the latter should be validated with experimental data.
In the first part of my PhD thesis, a complete description of an experimental campaign conducted on human thoracic motions segments is presented (Figure 1). A stepwise reduction of the components of three different functional units (T2-T3, T6-T7, T10-T11) was performed, highlighting the role of each structure on the spine biomechanics. In all the cases, the Range of Motion

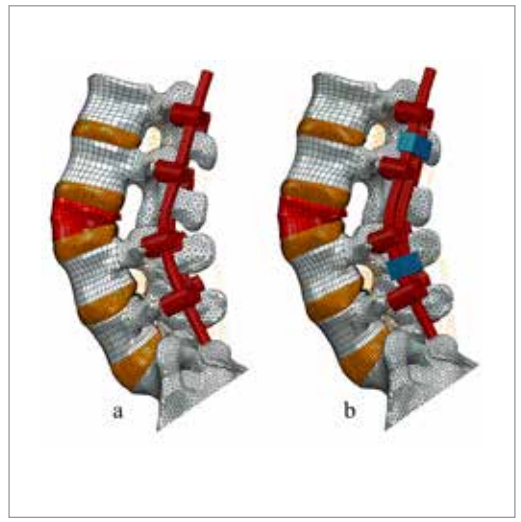
**1. human thoracic functional spinal unit embedded in PMMA prior testing**

increased after each resection while a decrease was noted going from the upper to the lower thoracic spine. The greatest effect was due to the removal of the posterior elements and to the nucleotomy.
The second part of the work consists in a precise description of the methods employed to create a complete finite element model of the thoraco-lumbar spine (T9-S1), shown in Figure 2.
The vertebrae were reconstructed from CT scans and then assembled to intervertebral discs and ligaments. The model underwent a validation to verify the correct material properties of the components and the kinematics of each motion segment. The validation was performed using experimental data and information found in the literature. This finite element



**2. finite element model of the thoraco-lumbar spine (T9-S1)**

model was then used to simulate different surgical techniques and possible configurations of devices. The first study was focused on the comparison of vertebroplasty and kyphoplasty on the thoracic spine (T9-T11), two techniques used in case of vertebral fractures and based on the injection of bone cement into the vertebral body. The analysis of various factors revealed that the stress reduction on the endplates following augmentation is more related to the height improvement, achieved after the surgical treatments with respect to the collapsed configuration, rather than the insertion of a stiffer material



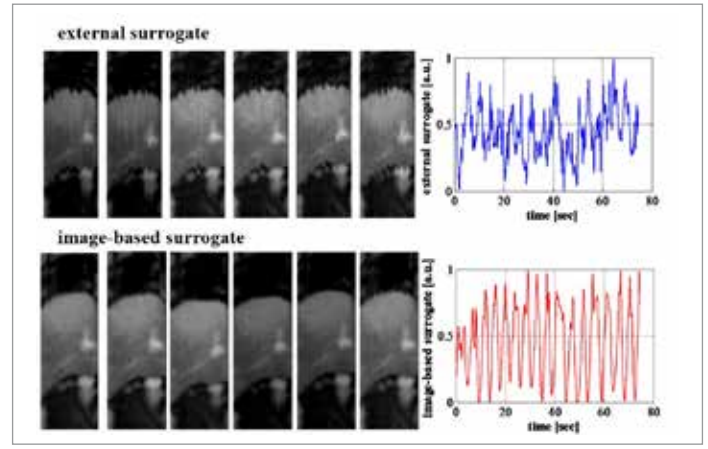

**3. osteotomy model treated with spinal fixator with a single (a) or a double rods configuration**

(cement).
A second application was the study of the Pedicle Subtraction Osteotomy on the lumbar spine (L1-L5): after a first analysis of the destabilization produced with the surgical technique, different configurations of devices (Figure 3) were tested in order to identify the best solution, that could minimize the risk of failure of the instrumentation. The results showed that performing the osteotomy on a lower level (e.g. L4-L5) seems to have a greater effect on the correction. Two materials of the spinal fixators were compared but no differences were found. A bigger rod diameter and the use of two parallel rods instead, seems to be favorable in order to enhance the hardware mechanical reliability. Also the use of an anterior support by means of cages was evaluated: the best solutions seems to be single rods and two cages or two rods and two cages.
The last example of application of the finite element model regarded the study of various surgical techniques used for the treatment of the lumbar spinal stenosis. In this case, the numerical model of two functional units (L3-L5) was refined, the effect of two degrees of stenosis was compared, as well as the outcome of the decompressions. However, no particular differences were found and further experimental studies are required.

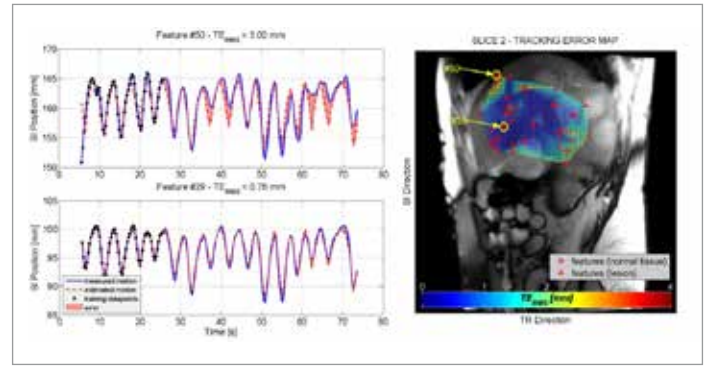
# MRI-GUIDANCE IN EXTERNAL BEAM RADIOTHERAPY: FROM PLANNING TO TREATMENT

**Chiara Paganelli** - Advisor: Prof. Marco Riboldi
Co-Advisor: Paul Summers

High precision conformal radiotherapy requires sophisticated imaging techniques to aid in target definition, especially when organ motion due to respiration is involved. Computed Tomography (CT) imaging in combination with time-resolved approaches (i.e. 4D CT) have become the standard basis of radiotherapy treatment planning. However over the last decades, the emerging properties and capabilities of Magnetic Resonance Imaging (MRI) such as being a radiation free imaging technology as well as providing good contrast with efficient temporal resolution, have elected this image modality for the improvement of image-guided radiotherapy treatment for organ motion management. In addition, the appealing properties of MRI motivated several recent technological developments towards the integration of MRI with radiation therapy treatment units, raising the prospect of fully MRI-guided treatments.
The PhD project aims therefore at the development of novel methodological contributions through the use of MRI in external beam radiotherapy, to tackle the issue of organ motion due to respiration focusing on both treatment planning and delivery.
Specifically for treatment planning, a feature extraction method based on scale invariant feature transform algorithm (SIFT) was implemented. This method able to identify and match characteristic features between images provided a tool for organ motion quantification. In addition, the excellent soft tissue contrast provided by MRI can allow a better identification of internal structures and the extension of the method with an adaptive local approach (i.e. adaptive-SIFT) can improve the quantification of motion of both contrasted and notcontrasted features.
In addition, a novel retrospective sorting method to create a time-resolved (4D) MRI dataset was proposed to improve treatment planning. Fast T2-weighted multi-slice acquisitions were performed to achieve the optimal trade-off between spatial and temporal resolution with good contrast, in order to describe internal anatomical structures during the respiratory cycle. The slices were then retrospectively sorted with the novel image-based approach, resulting less prone to artifacts than the usual method based on external surrogates (Figure 1), allowing a better quantification and compensation of organ motion in the liver site.
The development of advanced strategies for in-room MRI-guidance was also studied in order to account for organ motion during treatment delivery. The feature extraction method was therefore applied to fast 2D T2-weighted slices (cine-MRI) to quantify the performance of surrogate-based tracking methods and to provide a prospective comparison with respect to MRI-guided radiation therapy (Figure 2), which could support the definition of patientspecific optimal treatment strategies. The SIFT method applied on cine-MRI in combination with a point-based rigid registration was also used to quantify lung tumor rotation in addition to translation. This will allow a potential improvement in the definition of treatments margins, as well as the dynamic adaptation of a multi-leaf collimator during treatment.
A limitation of cine-MRI for in-room MRI-guidance is related to the lack of complete simultaneous 3D information. To overcome this issue, we therefore proposed (i) the creation of global motion models able to derive a "daily" 4D MRI and (ii) the implementation of a 3D reconstruction method by updating a pre-treatment volume on the basis of in-room orthogonal cine-MRI acquisitions, thus translating the 3D information obtained in the planning step into the treatment scenario.
Finally, we also presented a preliminary simulation of MRI sequences to derive a digital 4D MRI phantom for abdominal organs, with the aim of providing a tool for the evaluation of MRI-guided methods in external beam radiotherapy. An application of the digital phantom to a clinical scenario to evaluate the creation of a "virtual" 4D T1-weighted MRI was also reported, in order to overcome trade-off limits in acquiring a well-contrasted virtual T1- weighted 4D MRI and to provide a subsequent description of tumor motion and composition according to T1 and T2 weightings.




**1. Coronal six bins 4D MRI with corresponding surrogate signals for a representative patient. First raw: external surrogate; second raw: image-based surrogate.**

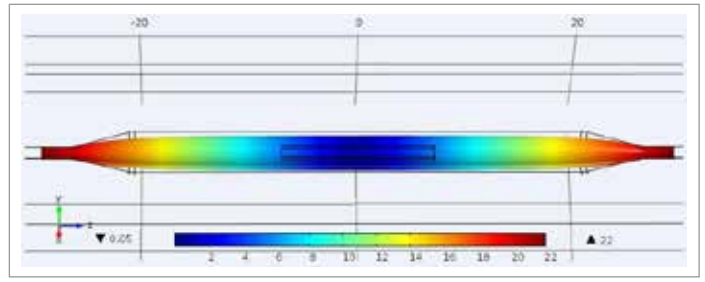


**2. Right panel: Tracking error map computed as root mean squared (RMS) error (transversal TR direction vs. superior-inferior SI direction). Left panels: measured (SIFT) and estimated (surrogate-based tracking) motion traces for features #50 and #29. Training data points were used to train the surrogate-based correlation model.**

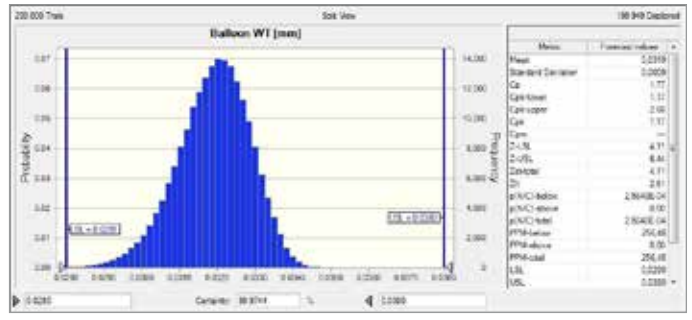
# PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA) BALLOON STRETCH BLOW MOLDING PROCESS: DEVELOPMENT OF A NUMERICAL MODEL AND OPTIMIZATION FOR LEAN DESIGN

**Francesco Piccagli** - Supervisor: Prof. Gabriele Dubini

An increasing number of patients are affected by severe disease of limb arteries that compromises their life. These pathologies are associated with a loss of quality of life (QoL), significant lifestyle-limiting symptoms, potential major limb loss, and death.
Chronic Critical Limb Ischemia (CLI) represents the major outcome of significant atherosclerotic diabetes-related disease of the lower-extremity vessels.
Percutaneous Transluminal Angioplasty (PTA) has become a widely used technique in the treatment of endovascular diseases.
The procedure is performed through a specific class of medical devices: PTA balloon catheters. These are manufactured using different types of technologies: the standard design consists of a shaft tube, with a balloon mounted and folded at the distal end. The balloon is placed through the vessel lesion and then expanded, to flatten the atherosclerotic plaque and restore the blood flow through the diseased vessel.
A PTA catheter has to fulfill requirements of diverse complexity. The main ones consist in the capability to track through vasculature and reach the target location, crossing the stenosis in order to position the balloon across the lesion. This way, a correct and precise treatment of the diseased portion of the artery can be achieved. Moreover, the device must guarantee a correct balloon expansion, since the outcome of the treatment depends on the correctness and on the efficacy of the inflation. In fact, by impressing a plastic strain to the stenosis, the plaque will adhere to the vessel wall restoring blood flow.
The role of the balloon component is essential for the success of the treatment: thus, the balloon is asked to satisfy challenging specifications.
Moreover, belonging to the medical devices class, PTA catheters must follow a highly demanding quality design flow, since regulatory and quality systems require a tight and monitored development and manufacturing workflow.
Accordingly, rules and recommendations are provided through International standards and Countries internal laws and Manufacturers are asked to demonstrate compliance to such regulations.
For these reasons, the development of a PTA catheter requires a complex and accurate path, and should be optimized and made as lean as possible.
These considerations were at the basis of the present project, started as collaboration between university (Politecnico di Milano) and a medical device company (Medtronic Plc.). The work aimed at developing a tool to be introduced and systematically used in the standard PTA balloon design and development workflow. The tool consists of a numerical (Finite Element, FE) model that starting from the initial extruded tube used for balloon production is capable to simulate balloon forming process, also known as Stretch Blow Molding (SBM). Ultimately, the model should predict the final balloon geometry, thickness and stress-strain distribution, depending on a set of boundary conditions reproducing the real process parameters.
A deep characterization of the balloon tubing at different temperatures and stretch speeds is at the basis of the model development. The material model is selected according to experimental data, leveraging on a literature review on SBM modeling.
Additionally, a set of tools proper of the Design For Six Sigma (DFSS) approach were introduced at different stages of the work: Design Of Experiments (DOE) and Response Surface Modeling (RSM) techniques were used in planning experiments during material characterization, as well as once the FE model is developed.
The deterministic analysis of the simulations enables the identification of a *transfer function* that relates a set of SBM design inputs to meaningful design outputs (i.e. balloon geometry and wall stresses).
Once the *transfer function* is determined, an optimization software (Oracle Crystal Ball) is used for predictive modeling: the software runs a series of simulations to determine a set values for input parameters that, when used as input for the *transfer function*, ensure fulfillment of certain requirements for the final balloon specifications (design outputs).
Thereafter, the use of Monte Carlo simulation enables the model user to account for inputs variability, that is introduced in the model based on experimental observations. Thus, an established number of Monte Carlo simulations are run considering the generated *transfer function* and input variability, and verify that requirements are still matched considering the natural and process-related distribution of the *best* set of nominal values for the selected inputs.
The final model is thus capable to optimize balloon design on a statistical basis.
Considering the *standard* balloon design and development workflow at Medtronic (Peripheral Vascular Department, Roncadelle, Italy), it is undeniable that such process is expensive in terms of time, resources, and cost: a considerable number of "design iterations" are necessary to develop the final balloon, involving engineering work, and a large amount of materials, testing, and re-iterations.
The combination of the FE model and of the DFSS capabilities developed in the present work represents a meaningful tool to improve the development process. Engineers could advance their standard approach with cost and time reduction, supported by a more reliable design path: indeed, the numerical model may contribute in reducing the number of design iterations, of materials used and of testing.
Overall, the use of the model could thus represent an outstanding source at different stages of the development process.
It is finally remarked that not only a specific model on balloon development is developed, but a general approach to the product development workflow. In our opinion, such approach should not only be limited to the balloon forming area, but should be extended at different device components and at different stages of the design process.



1. Color map of expanded balloon displacement as predicted by FE model.




2. Response distribution (Balloon Wall Thickness) according to the optimized model input parameters.

# INTEGRATING THE HOME AND THE PROFESSIONAL CARE ENVIRONMENTS THROUGH STANDARDS: A PROTOTYPE FOR TDCS HOME MONITORING

**Elena Rossi** - Advisors: Sara Marceglia, Giuseppe Pozzi

The first FDA regulatory guidance which defines the difference between mobile apps, mobile medical apps and medical devices, can be considered as a milestone for the regulatory requirements for mHealth apps. However, despite the widespread diffusion of mobile medical apps, their quality is still a matter of debate. Also, being mainly developed as independent, stand-alone systems, mobile medical apps are not part of the patient's health information flow. In fact, the literature includes some examples of connections between a mobile app and Electronic Health Record (EHR) systems, but all the examples maintain two independent datasets, and are not intended to implement an integrated monitoring system for chronic patients at home. According to the American Medical Association (AMA), an improvement of Electronic Health Record usability has to be urgently addressed, in order to reduce the dissatisfaction reported by clinicians during the use of modern technologies for the management of charts. Improving EHR usability and finding its proper place in the overall health information technology (health IT) ecosystem is an important goal to be achieved as soon as possible. The future health IT landscape includes not only EHRs as the centrepiece of the health IT ecosystem, but also mobile technologies which are viewed as one of the most spread tools allowing data collection. Moving from this context and from the vision of a future "health IT ecosystem", the integration between mHealth apps and EHR systems, where patient and caregiver are empowered and actively involved into care processes, is a predicted consequence.

The goal of the current study is to verify if the existing standards on electronic health data exchange can be applied when the clinical document is generated by a mobile app. The thesis aims at including data acquired in a domestic environment into the EHR, and at allowing the exchange of such data between clinicians, caregivers, patients according to a newly developed protocol for mobile applications. The study concerns the definition of an architecture and the set up of an information protocol for an innovative interface to exchange information between the home care process, the electronic medical record, and the professional environment, in accordance to international standards and recommendations. A standard review (Marceglia et al. 2015) reveals that HL7 draft standard PHMR (Personal Healthcare Monitoring Report) is a kind of clinical document that can be used for the definition of reports for the home monitoring system. In fact, PHMR carries personal healthcare monitoring information from PHM systems to different types of health records (EHR, PHR or EMR). Consequently, in the integrated care process here proposed, messages exchanged between mobile apps and EHR systems have to comply with PHMR even if some adjustments are needed to generate such reports by mobile apps in an anonymous format.

Chronic illnesses or neurodegenerative diseases are among the most common scenarios for home telehealth systems. The choice of the exemplary use case developed in this work is based on the type of pathology, the complexity of treatment and the active role of the caregivers. Transcranial Direct Current Stimulation (tDCS) meets these requirements because it is a non-invasive technique that can be used at home for the treatment of different diseases. However, for a safe home treatment, an active role from the caregiver is mandatory. An integrated home monitoring system for patients undergoing tDCS allows one to design a system customizable according to the caregiver's skills and to the evolution of the pathology or of the disease. The integrated home monitoring process for tDCS patients includes the following main phases. The process starts with a first visit in hospital: the doctor prescribes the parameters for the tDCS treatment, and a care pathway dedicated to the patient (according to the pathology and tDCS education of caregiver). Inside the EHR of the patient, the doctor can configure the app content according to the care pathway. During this visit, users authorized to access the app are identified and the system creates two accounts for the patient and caregiver respectively. When a patient or a caregiver at home accesses the mobile app using his/her personal account, the system recognizes the user and configures items of the main menu according to the care pathway dedicated to the patient. At the end of planned activities, the mobile app generates reports and sends them to the EHR system immediately: no data is saved on the smartphone. In this way, inside the EHR the doctor can view in real time all the data collected at home. From the analysis of data, he/she can evaluate the efficacy of tDCS treatment. In case of low efficacy, the doctor can call back the patient in the hospital and change the stimulation's parameters in order to optimize the tDCS treatment. The proposed integrated care system allows doctors to access not only the tDCS prescriptions, but also all the results of the patients' evaluations performed at home. This solution allows the doctor to continuously monitor the efficacy of daily home treatment, and eventually to adjust the stimulation parameters during the visits according to the patients' home evaluations.

A three-tier architecture characterizes the integrated home care system based on the clinical document exchange between the EHR system and the mobile app. The client tier includes three different user interfaces and the local registry used by doctors to manage the identified data. The middle tier implements the interface between the mobile app and the EHR system in order to use the same database. The data tier is entirely located in a cloud-hosted virtual machine and contains the unique database, the framework manager of the EHR system and the IIS (Internet Information Services) where the dedicated web service is installed. This architecture provides one with a good system scalability, flexibility and reliability.

XML documents used to code and to decode data comply with mHealth Personal Healthcare Monitoring Report (mPHMR), a new anonymous standard for clinical documents exchange between mobile apps and EHR systems. The new communication protocol between the mobile app and the EHR system is document-centred. The anonymous message exchange is the innovative aspect of the integrated monitoring system. For this reason, the main result of the thesis is the definition of the mPHMR. The HL7 draft standard PHMR was adjusted in order to allow the generation of such reports by mobile apps (mPHMR) as well as by monitoring devices. The Header of mPHMR differs from PHMR as:

- the author of the clinical document is the app's user (patient or caregiver) and not a doctor or a monitoring device;
- the document identifier depends on the EHR number for data storage;
- identifiers of author, patient, information recipient and custodian are defined during the app content configuration using the EHR system;
- name, surname, address and telephone number are masked.

The development of a proof-of-concept for such integration confirms that the adoption of the HL7 standard does not suffice to guarantee safety and privacy issues, both of them arising from the use of mobile apps. In conclusion, the main scientific output of the current study is to guide the decision to confirm or to adjust the current HL7 protocol, to include cases where patients and caregivers are actively involved into the integrated health care process, through a mobile application, taking into consideration not only the technical point of view but also the issues concerning access to health personal records.

# DEVELOPMENTS IN SEGMENTATION ALGORITHMS FOR PET MOLECULAR IMAGING

**Chiara Soffientini** - Tutor: prof.ssa Manuela Galli
Advisors: prof. Giuseppe Baselli, dr. Elisabetta De Bernardi, prof. Issam El Naqa

## Background.

In the interpretation of molecular images the improved segmentation and quantification of up-taking objects is an active research field. Given the limited SNRs, resolution, and variable object and background features, investigation has recently reverted to statistical approaches. 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) occupies a primary position in this research area: i) clinically, due to its major role in the detection and evaluation of oncological lesions; ii) technically and methodologically, due to the gap between its inherently quantitative potentials and the sever limits imposed by real acquisition and object features.

## Aims.

This thesis work addresses the segmentation of lesions in FDG-PET for improved contouring, robust against lesion vs. background features, and activity quantification capable to compensate partial volume effects (PVE) due to blurring.
The potentials and flexibility of Gaussian mixture model (GMM) clustering were explored and modified in order to exploit the knowledge of background features by constraining the further segmentation. Connection of objects was first forced by priors from neighbors in the voxelwise classification and, in a further development, by active contours (Level Sets, LS) iteratively modulated by GMM analysis. In order to test algorithms against known ground truth, both digital and physical phantoms were designed.

## Methods.

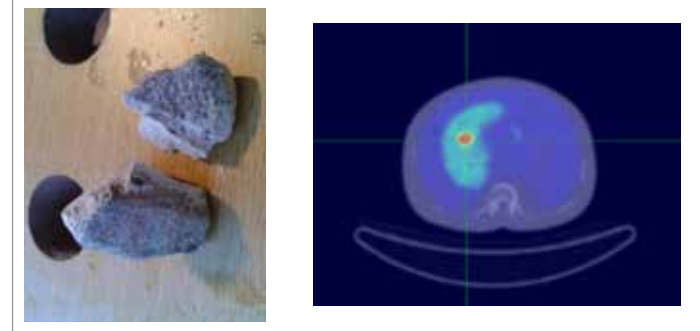
A novel modification of GMM clustering (constrained GMM - cGMM), was proposed: a background evaluation was exploited to constrain the following lesion-from- background separation. Preliminary studies optimized the number of clusters to four for the background modelling, while other 4 were added considering two classes for lesion volume, and the others representing transition and spill-out. A further modification was introduced by forcing connection of segmented objects by considering the status of neighbors as priors to the voxelwise Expectation-Maximization classification. This was named SoftGMM or HardGMM whether neighbor status was probabilistic or crispy, respectively. A further improvement was next achieved by the use of LS, automatically and iteratively tuned by a GMM analysis (LS-GMM). LS-GMM was compared to standard LS with parameters optimized with a groundtruth brute force comparison approach. Both were compared to SoftGMM. Algorithms were tested comparing the outcomes to the reference contours by means of the lesion volume % error (VE ), DICE index, and the classification error (CE). Data set for performances assessment included simulated data with realistic projection/ reconstruction processes, physically acquired phantom and clinical data. In particular, validation on clinical data was performed on 18 patients with two different reconstruction protocols, with lesions manually contoured by one/two expert operators.
For the above purposes, a novel physical phantom was developed based on natural clinoptilolite, chosen after the evaluation of several types of zeolites and characterized by its uptake characteristics. These porous stones permitted both to avoid cold wall effects and to introduce irregular shapes (see Fig.1). Moreover, two pieces of a broken stone, sunk in different activity solutions and reassembled, permitted to mimic inhomogeneous lesions.

## Results.

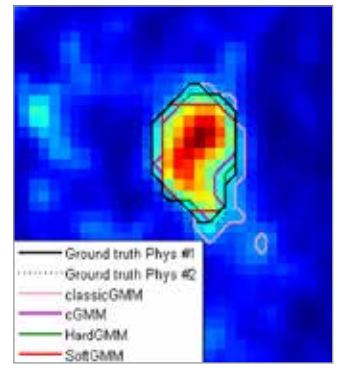
cGMM outperformed GMM and other tested algorithms performances, with VE < 10%, DICE > 0.85 and CE < 0.32. Neighborhood priors, in particular SoftGMM, displayed further improvements, which were significant in heterogeneous background, with VE < 7%, DICE > 0.81, and CE < 0.38 for simulated data (see Fig.2). LS-GMM well approximated the optimized LS; e.g., in the physical phantom, VE difference was 2% of absolute VE median, while DICE loss was limited to 0.03 and and CE difference was < 0.03. Thus LS-GMM displayed a good automatic solution for LS parameter setting. It could also outperformed SoftGMM: in patient data a 1% lower absolute median VE, 0.02 higher DICE and 0.07 lower CE were reported (see Fig.3).

## Conclusion.

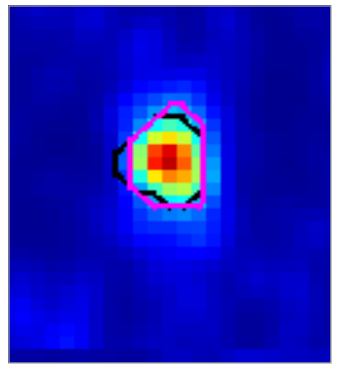
The fusion of proper constraints, priors, and active contouring with statistical voxelwise clustering methods as GMM maintains the versatility of such approaches and also introduce a-priori knowledge such as background feature, connection, and object vs. background differentiation, eventually providing higher classification robustness and accuracy. Better segmentations in FDG-PET significantly recovers the quantitative capabilities of this diagnostic tool, which are conversely obscured in direct image viewing. The data-driven solutions here adopted are foreseen to permit extensions to a great variety of clinical patterns for FDG-PET and also to permit translation to most molecular imaging.



**1. Experimental Phantom – The validation of segmentation algorithms requires a reference to a ground-truth, i.e. the objects from which the data-set was generated, either experimentally or digitally. In our experimental phantom, lesions are mimicked by porous zeolites (left panel) loaded with radioactive solution in mildly radioactive inhomogeneous background. Realism is improved as to shape, absence of walls between lesions and background, inhomogeneities (right panel.**




**2. Segmentation by Statistical Clustering – We improved the Gaussian Mixture Model (GMM) a classic Statistical Clustering by exploiting its versatility, though introducing elements specific to lesion segmentation in PET: blind classification – constraints relevant to a prior analysis of background were introduced (cGMM); voxel-wise segmentation – continuity was forced by considering neighbour voxels as priors (SoftGMM and HardGMM). The progressive amelioration in the segmentation of a lung lesion, compared to the groundtruth of two expert operators, is shown.**



**3. Fusion of Statistical Clustering and Active Contouring – Level Sets (LS) were tuned by GMM (GMMLS) thus obtaining further accuracy and robustness, as shown in the segmentation of lung lesion (magenta) vs. the manual groundtruth (black).**

# DEVELOPMENT AND OPTIMIZATION OF SIGNAL PROCESSING METHODS FOR THE CHARACTERIZATION OF EEG SIGNALS DURING MOTOR PROTOCOLS

**Giulia Tacchino** - Supervisor: Prof. Anna Maria Bianchi

Electroencephalography (EEG) allows noninvasive recording of the brain electrical activity, thus providing valuable information about the functional significance of brain rhythms. EEG recordings have a high temporal resolution and are simple to perform during the execution of either upper or lower limb movements. All these aspects make this technique suitable to explore movement-related changes of the sensorimotor rhythms (i.e. Rolandic mu and Central beta rhythms), which can be recorded over the sensorimotor cortex.
The investigation of movement-related changes in brain dynamics represents an important issue in both neurophysiology and neurorehabilitation. In fact, from a neurophysiological perspective, it would allow to deepen our knowledge about the mechanisms responsible for sensory input processing and motor output generation. Moreover, these findings could be used to define proper and effective rehabilitation therapies for the recovery of impaired motor functions.
In this work, we propose optimizations and improvements for some advanced signal processing methods with the aim of providing tools, specifically tailored on EEG signals characteristics, for a better understanding and interpretation of movement-related changes in brain dynamics. The optimized and improved methods are then applied to real EEG signals acquired on healthy subjects.
Firstly, we propose an optimized version of a Bivariate Time-Variant Autoregressive Model (TVAM) in which a time-variant forgetting factor and an empirical condition on the prediction error are implemented in the identification algorithm for the recursive update of model coefficients. These improvements are aimed to tackle the limitations of the standard TVAM, which are the need to find a compromise between the sensitivity and the robustness of the identification algorithm, and the effect of artifacts on the model coefficients estimate. We test the performance of both the optimized TVAM and the standard model on properly conceived artificial data. This validation procedure demonstrates that the optimized bivariate TVAM performs better than the standard model in tracking variations in the signals dynamics. The optimized bivariate TVAM is then applied to real EEG data acquired from healthy volunteers executing a visually guided cue-paced pointing movement with the right upper limb. In this framework, we use the normalized Directed Transfer Function (DTF) to describe directional interactions between three different brain areas (i.e. the premotor cortex, the motor cortex and the posterior parietal cortex) that are engaged in visually guided pointing/reaching movements. Our results show a predominant role of the contralateral motor cortex in the generation of the information flow toward the ipsilateral motor cortex, premotor cortex and posterior parietal cortex during movement planning and execution phases. In addition, the premotor cortex results to lead the posterior parietal cortex within a fronto-parietal network, which is involved in the sensorimotor transformation needed to plan a pointing movement towards multiple spatial targets.
Secondly, we exploit bispectral analysis (i.e. bispectrum, squared bicoherence and skewness function) for the detection of a particular case of nonlinear correlation (i.e. Quadratic Phase Coupling, QPC) between different brain rhythms. We propose a sensitivity analysis to evaluate if and how bispectral indices are influenced by the Signal-to-Noise Ratio (SNR) of the rhythms under investigation. We address this issue because movement planning and execution produce a power decrease of sensorimotor rhythms while the power of background EEG activity remains almost unchanged, resulting in a decreased SNR of sensorimotor rhythms. In this framework, we want to provide some guidelines to simplify the interpretation of results from bispectral analysis on real EEG data. We generate signals with different SNR levels (i.e. 5, -4, -10 and -16 dB) simulating both the absence and the existence of QPC. A significance threshold for statistically evaluating the presence of QPC from bispectral indices is obtained from surrogate data distributions. The results of the comparison of bispectral indices with the significance threshold show that they are reliable detectors of QPC for SNR levels higher than -10 dB. The bispectral analysis is then used to investigate QPC between Rolandic mu and Central beta rhythms during movement preparation and execution. For this purpose, we use real EEG data recorded from healthy subjects performing the same motor task described in the bivariate analysis. Our estimate of mu rhythm SNR shows values higher than -10 dB, meaning that the results from bispectral analysis are reliable, with respect to the guidelines drawn in this work, in the detection of either absence or presence of QPC. Our findings show a QPC between mu and beta oscillations in the resting state before movement initiation, suggesting a common neural generator for these rhythms. QPC disappears during movement planning and execution, suggesting that the two rhythms become independent and thus derive from separate neural generators, which work independently when the motor cortex is engaged in sensorimotor processing. Bispectral analysis is thus proven to provide reliable indices for the investigation of the relationship between mu and beta rhythms during all the phases of a motor task.
Then, we investigate the feasibility of brain sources identification using low-density EEG recordings. Independent Component Analysis (ICA) is used for source identification, as this method does not require a-priori knowledge of details about the signal sources (physical location or configuration of the source generators).
We propose a quantitative comparison of sources of mu activity identified from high-density (i.e. 61 electrodes) and low-density EEG recordings (i.e. 19 electrodes), both extracted from the same EEG dataset.
The results of this quantitative comparison do not show relevant statistically significant differences between sources identified from the low-density and the high-density montage, thus suggesting that sources of mu activity can be reliably found from EEG data recorded with a small number of electrodes.
Lastly, we describe a pilot study, carried out on 10 healthy volunteers, aimed at investigating and quantifying differences in the motor cortex activation induced by different motor conditions (i.e. active/passive, robotically assisted/non-assisted right hand movements). A commercial robotic glove for the neuromotor rehabilitation of the hand is used for assisting movements. Differences in brain activations between the exploited motor conditions are compared through the computation of ERD/ERS (Event-Related Desynchronization/Synchronization) patterns associated to both mu and beta rhythms. Our results show stronger and long lasting ERD patterns, suggesting a higher and more prolonged motor cortex activation, when the volitional intention and the glove support factors are combined. The volitional intention factor plays a key role at the beginning of the movement, when the motor scheme for the upcoming movement is generated. The use of the robotic glove reinforces the afferent proprioceptive feedback in the last part of the movement. These findings can be useful in neurorehabilitation, suggesting that active movements are likely to interact with the patient motor control loop pointing towards a better neurorehabilitation outcome.
In conclusion, the work presented in this dissertation provides quantitative tools, specifically tailored on EEG signals properties, for the characterization of brain dynamics during movement execution. The application of the optimized and improved methods on real EEG signals demonstrates that they are able to provide a better understanding and interpretation of movement-related changes in brain dynamics.

# PHYSIOPATHOLOGIC MECHANISM COORDINATION OF BREATHING AND SWALLOWING WITH OPTOELECTRONIC PLETHYSMOGRAPHY AND SURFACE ELECTROMYOGRAPHIC ANALYSIS IN ELDERLY COPD PATIENT

**Gianpaolo Tornatore** - Supervisor: Prof. Marcello Crivellini

## Introduction

Deglutition is generally defined as the swallowing mechanism allowing food to be safely and efficiently propelled from the mouth to the stomach. It's a complex and dynamic ability, mainly aimed to food intake, which evolves differently according to age and health condition.
The breathing and swallowing coordination is important in different kinds of pathologies. It has a fundamental role particularly in the chronic obstructive pulmonary disease (COPD), in which the possibility of prandial aspiration is a risk factor for exacerbation.
***Aim***: Evaluation of the synchronism between breathing and swallowing in patients with COPD during stable and exacerbation condition, in order to quantify how much the degree of the disease affects the swallowing ability.

## Methods

For this study 41 subjects were recruited. Patients making the three groups were selected homogenously for age, height, weight and BMI. Anthropometric data are illustrated in Table 1.
Acquisitions were all conducted in a sitting position. Only liquid boluses of 10 ml and 20 ml were administered.
The respiratory mechanics was acquired by an optoelectronic plethysmography system (OEP) and the breathing pattern before, during and after the swallowing act was evaluated.
The respiratory mechanics was evaluated through the volume computation of the three compartments of the rib cage before, during and after the swallowing.
The swallowing was analyzed by a surface electromyography (sEMG), synchronized to the OEP system. We acquired the sEMG activity of the following muscles: the anterior belly of the Digastric muscle (Digastr) and the Sterno-thyro-hyoid muscle (Sterno TH), bilaterally. The electrodes were placed on these muscles in the region above and under the Hyoid bone.
The swallowing was evaluated through the computation of the swallowing apnea duration, the synchronism between the two muscles belonging to the same side (vertical synchronism) and the synchronism between the two couples of homologous muscles belonging to the opposite sides (horizontal synchronism).

## Results

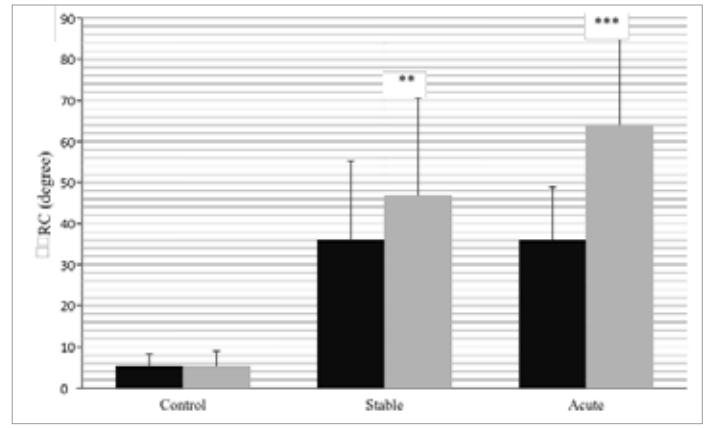
The study of the chest wall mechanics showed that patients in the acute phase had a greater volume alteration in the pulmonary and abdominal rib cage compartments, mainly after swallowing.
From the analysis of respiratory mechanics is evident as the act of swallowing create changes in the breathing pattern, in fact, after the act of swallowing increases the frequency of breathing increases and the current volume in all three groups, primarily in the group of patients in Stable phase and better patients in Acute phase with a statistical significance of $p$ <0.001.
Very importantly, the alterations of synchronous thoraco abdominal analyzed through the index PhAngle (Figure 1), this index shows how changes in the timing of the load compartments thoracic, already present in patients with COPD increases further after the act of swallowing.The analysis of sEMG showed differences in the duration of the act swallowing in three groups: patients in Acute phase increase the duration of the act swallowing, increasing the duration of the electromyographic burst to all muscles analyzed. It also increases the duration of swallowing apnea, increases the number of swallowing acts than the other two groups.
Also we can see a change in the load of both horizontal and vertical synchronism already expressed by the group being stable but strongly amplified in patients in the acute phase (Figure 2).

| N | GROUP | AGE (YEARS) | HEIGHT (M) | WEIGHT (KG) | BMI (KG/M^2) | GOLD STAGE |
|---|---|---|---|---|---|---|
| 15 | Control | 70.12+6.75 | 1.72+0.10 | 75.59+12.52 | 25.43+2.60 | 15 0 |
| 15 | COPD Stable | 69.89+8.25 | 1.70+0.03 | 72.94+12.24 | 25.24+4.14 | 10 IV / 5 III |
| 11 | COPD Acute | 70.80+12.29 | 1.69+0.03 | 74.90+5.96 | 26.36+2.29 | 7 IV / 4 III |

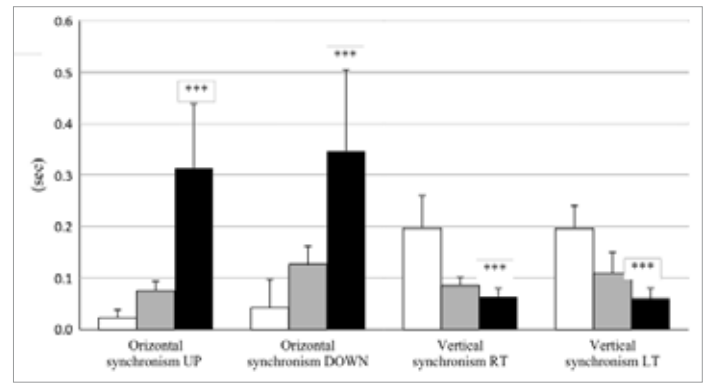
**TABLE 1. Anthropometric data.**

## Conclusions

Patients with COPD showed an important alteration in breathing and swallowing coordination, with the loss of synchronism in the Digastr and Sterno TH muscular activity during the swallowing act.
The abnormal timing of swallows within the respiratory cycle that we measured can help to explain the relationship between pulmonary disease and dysphagia.
The altered coordination increases the risk of aspiration in patients with stable COPD. All that could really contribute to the exacerbation.
The observed impaired breathing and swallowing patterns in the patients with COPD suggests a possible explanation for the presence of dysphagia in persons who do not have neurologic illness. Unrecognized prandial aspiration before or during COPD exacerbation may also contribute to the severity of the exacerbations.




**1. Thoraco-abdominal asynchronies. Phase angle $\Phi_{RC}$ between pulmonary rib cage and abdominal rib cage, before swallowing (black bars) and after swallowing (grey bars).**
****, ***: $p$<0.01, $p$<0.001 (before vs after swallowing).**

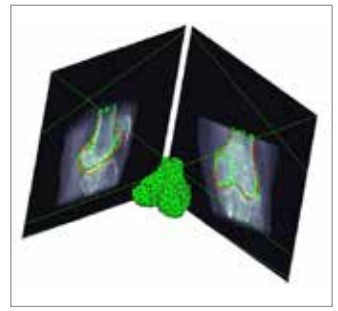



**2. Electromyographic index. Muscolar Synchronism control group (white bars), COPD Stable group (grey bars) and COPD Acute group (black bars).**
*****: $p$<0.001 (One Way Analysis of Variance Between Groups).**

# STATISTICAL SHAPE MODELS BASED 2D/3D REGISTRATION METHODS FOR KNEE ORTHOPAEDIC SURGERY

**Marta Valenti** - Supervisor: Elena De Momi, Guoyan Zheng

In orthopedic surgery, and in case of Total Knee Arthroplasty (TKA) for osteoarthritic subjects, planning of the intervention is of fundamental importance.
The insertion of the prosthetic components is extremely delicate because the deformations induced by the osteophytes must be resected and at the same time the mechanical axis of the leg must be corrected. The size of the implant and the plane of resection are estimated through a standing X-ray projection that covers the whole leg. This view gives a hint on the direction of the mechanical axis that must be restored, but cannot evaluate how the kinematics of the knee is influenced by the insertion.
The possibility to check the pre-operative kinematic of the knee under weight bearing conditions, in order to evaluate tension of the ligaments and the distance between the bones, would be of great importance for the success of the intervention, giving to the surgeon the possibility to check the bone's motion before entering in the surgery room.
This evaluation is currently intraoperatively performed by the surgeon, who performs passive movements of the joint to check the correct placement of the prosthetic components, although the conditions are not similar to the real stress applied during everyday life, as weight and muscles strengths are missing.
The use of fluoroscopic sequences is common in clinics to rapidly evaluate the knee kinematics. These fast and low dose X-ray images allow an accurate visualization of the bone movements without the invasiveness typical of other methodologies. Knee motion analysis is currently done manually superimposing the shape obtained from Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) on the fluoroscopic set acquired. The surgeon evaluates the projection of the shape on the image plane and through further approximations defines the best pose of the model onto the images. This procedure occupies the surgeon for a long time, and is affected by operator inaccuracies.
A completely automatic algorithm would solve the challenge, relieving the surgeon from the duty of detecting the correct pose and allowing a fast and accurate 2D/3D registration. Eventually, the shape could also be derived from a Statistical Shape Model, in order to reduce costs and radiation doses that would be higher with a subject-specific shape derived from CT or MRI.
The work herein presented shows two alternative methods to perform 2D/3D registration for femur kinematics estimation, starting from a set of fluoroscopic images and a SSM. Both algorithms allow the surgeon to have a more complete and functional evaluation of the knee performance under weight bearing conditions, that is essential for some type of operations, such as osteoarthritis and patellofemoral pain.
The thesis begins with the description of a new method for SSM creation, based on the Minimum Description Length algorithm. SSM are currently used in orthopedic surgery to allow accurate positioning of prosthetic components through bone morphing and to assess the correct post-operative follow up by virtually reconstructing the surgical site. Focusing on computer assisted TKA applications, a new approach for establishing landmark correspondence of 3D shapes is proposed, to build SSMs of anatomical structures of the knee joint. The method is based on landmark correspondence by MDL and introduces a new constraint on local geometric similarity. This local linear regularization ensures that the local shape geometry of corresponding landmarks on different shapes is similar. The method was tested building SSMs of three anatomical structures from MRI images of knees, namely femur, patella and tibia. Compared with the original method using only the MDL criterion, this new approach shows significant improvement both qualitatively and quantitatively. The landmarks are in fact better distributed on the shape surface, and can more accurately represent the underlying shapes.
The new SSM is the basis for the development of a 2D/3D registration algorithm for knee kinematics reconstruction. Starting from the acquisition of two calibrated fluoroscopic images, taken at different flexion-extension angles, the algorithm performs a feature based non-rigid registration. The projection of the model's silhouette and the contour extracted from the fluoroscopic image are matched using a one-to-many correspondence based on a nearest neighbor approach. To avoid local minima, the optimization is inserted in a Genetic Algorithm (GA), that solves the issues of the suboptimal results but slows down the time for the solution. The proposed approach was evaluated on 3 sets of digitally reconstructed radiographic images of osteoarthritic patients. Using the estimated shape, rather than that calculated from CT, significantly reduces the pose accuracy, but still has reasonably good results (angle errors around 2 degrees, translation around 1.5mm). The obtained results proved to be comparable with the literature, even if our trials were done using pathological femurs. Although



1.

accurate, the algorithm is very slow and it took a few hours for every femur pose to be properly reconstructed.
To overcome this limitation, a new algorithm based on Gaussian Mixture Models (GMM) is implemented. It is based on the definition of Gaussian mixture, so that each point of the 3D shape used for reconstruction is considered a mixture of Gaussian Probability Density Function.
Using a Maximum Likelihood Estimation (MLE) approach, the most probable position of the shape in the 3D space is obtained.
The algorithm was evaluated using Digitally Reconstructed Radiographies of both healthy and diseased subjects, with a CT extracted shape and a SSM as the 3D model. In vivo tests were done with fluoroscopically acquired images and subject specific CT shapes. The results obtained are in line with the literature, but the computational time is substantially reduced. This method proved to be accurate and fast, providing to the surgeon an efficient tool to check the pre-operatory kinematics of the knee in a virtual 3D environment.
Both the algorithms described show a millimeter accuracy, comparable with the results obtained in literature. The novelty of the GMM approach opens the way to a fast and accurate kinematic pose reconstruction for surgery planning, increasing the performance of the operations and reducing hospitalization costs. The registration is inserted in a clinical routine already performed: it does not imply additional examinations of the patient and provides a valid external help to the surgeon.