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INTERVENTIONAL THERAPY PROCEDURES ASSISTED BY MEDICAL IMAGING AND SIMULATION. THE EXPERIENCE OF U 703 INSERM (LILLE – FRANCE)

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Abstract. Since the early 1990s, minimally invasive techniques have been increasingly used in ever more and diversified fields of application. These techniques have some shared characteristics (predominant role of medical imaging, intensive use of new communication technologies, a multidisciplinary medical and scientific framework, etc.) but also shared specific problems (high-tech tools unfamiliar to the medical users, a major and long period of time for technological development, unavailability of training systems, difficulties in obtaining regulatory approval). For a long time, our Laboratory of Medical Physics (U 703 Inserm) has developed an innovative research activity in biomedical engineering in the field of assisted therapy, medical imaging and medical simulation. This paper presents the general context of interventional therapy procedures assisted by image and simulation and describes our scientific activities based on realistic objectives close to medical practice.

Key words: Computer Assisted Radiotherapy, Computer Assisted Radiographic Image Interpretation, Image Guided Surgery, Computer simulation, Training Program.

I/ THE RATIONALE IN IMAGING AND SIMULATION-ASSISTED THERAPY

Since the early 1990s, interventional therapy using large incisions is increasingly being replaced with more preservative techniques or so-called minimally invasive techniques. This evolution, which is positive for patient safety, is also cost effective because it reduces risks and hospitalization time. These techniques have numerous and extremely diversified fields of application (osteoarticular surgery, maxillofacial prosthesis, computer-assisted neurosurgery and radiosurgery, image-guided digestive and gynaecological coelioscopy, interventional vascular imaging, etc.) but have some common characteristics: the predominant role of medical imaging, intensive use of new communication technologies, and a multidisciplinary medical and scientific framework. Substantial improvements have been made in recent years. However, these techniques are still in progress and they can only be used in clinical daily practice after solving certain technological and medical difficulties. In addition, research in this field has encountered specific problems, as for example:

(i) The high-tech tools required to implement these techniques are unfamiliar to the medical users and medical developers usually involved.

(ii) Because it is essential to develop specifications for these tools, a constant dialogue should occur between physicians and researchers in new technologies. This dialogue is not always easy because of, on one hand, the frequent low time availability of physicians and, on the other hand, the lack of knowledge of the medical environment by non medical researchers.

(iii) To study the feasibility and the evaluation of these new methods, fundamental research has always to be followed by a major and long period of technological development. This could be difficult to achieve from an academic standpoint (e.g. by academic publications).

(iv) International ethical guidelines for biomedical research involving human subjects rightly demand long and complex human experimentations. On the other hand, other regulations (e.g. European) forbid the use of clinical equipment (notably medical imaging devices) in animal experimentation.

(v) Training for junior physicians to use new tools is not provided by medical schools and must be created and made available

(vi) Because new medical devices have to be approved by the regulatory authorities (e.g. FDA or EC approval) and need to be user-friendly for clinical use, a partnership needs to be established between research laboratories, clinical departments and manufacturers. This will also allow to overcome the well-known problems of information transfer costs of prototype manufacture and also industrial property rights.

Because of these difficulties, and although new technological tools, increasingly present in industry, are being made available to the general public, their introduction into the medical field is not so rapid. Thus, in spite of great progress, high-tech medical research is too often limited to some prestigious laboratories without evident medical spin-offs.

Since its creation in 1992, the Medical Physics Laboratory of the Faculty of Medicine of Lille (UPRES-EA 1049, Medical University of Lille 2, France) has been very active in biomedical engineering. Because of its advantageous situation within a teaching hospital, the Laboratory is in a position to bring into contact health care and engineering sciences. A permanent preoccupation to produce devices that can be used in everyday clinical practice has enabled it to create two start-up companies derived from our previous technological developments. The Laboratory was labelled as an INSERM Unit (U 703) on January 2005, not to undertake fundamental research but for practical objectives close to medical needs, as an ongoing application center of previously made methodological and technological developments.

II/ U703 PREVIOUS ACTIVITIES AND RESEARCH PROJECTS

The scientific knowledge necessary to solve the problems coming from the development of interventional therapy assisted by image and simulation includes image analysis and data processing, data classification and fusion, pattern recognition and training, electronics and robotics, haptic interface techniques, biomechanical tissue and organ characterization. All these topics requiring multi-disciplinary scientific and medical collaboration, our activities are based on four scientific themes concerning the use of medical imaging and simulation techniques. This allows us to assist medical operators, surgeons, clinical radiologists and radiation oncologists, in the training, the preparation, implementation and monitoring of their therapeutic procedures. These themes differ from their clinical fields of application but their coherence comes from the methodologies involved, the common fields of the respective skills, and from the geographical and institutional proximity of the main partners.

1) Conformal radiotherapy assisted by imaging and simulation

a) Previous activities

The aim of conformal radiotherapy is to accurately irradiate pathological tissues while sparing surrounding healthy tissues and organs. There remain major underlying medical and technological difficulties in the fields of patient immobilization, patient and organ set-up monitoring, the localization and definition of the irradiation doses and normal tissue volumes, and the automation and optimization of increasingly complex irradiation devices. The medical demand is strong and the industrial market is large, for this topic containing numerous technological difficulties. Our previous works involved the definition of irradiation doses and normal tissue volumes, dose planning optimization, image-assisted patient positioning and immobilization.

i) Volume definition. We have established a new method for defining and characterizing pathological and normal anatomical tissue volumes obtained from magnetic resonance imaging (MRI) or from computerized tomography (CT) [1]. The determination of a volume envelope observed in tomography is very difficult because of insufficient and noisy data. Moreover, the transition between tissues of different types is generally progressive and is often ill-defined. Usual methods are very operator-dependent and they are generally based on contour extraction in the different slices, which results in a loss of data. A new approach was developed, based on a fuzzy logic method taking into account the possible uncertainty of the object segmentation during the definition of 2-D contours by the medical expert. Because the method merges the volumes from contours obtained in various orientations and takes into account the local signal-to-noise ratio, the contrast-to-noise ratio as well as the sensitivity profile of the slices, it is possible to eliminate uncertainties of volume reconstruction usually made from a single orientation [2].

ii) Optimization of micro-multileaf collimators. For conformal treatment of small cerebral tumors, a possible technique is to use a micro-multileaf collimators (µMLC). We have developed a methodology of µMLC irradiation parameter optimization. The orientation of the irradiation fields, delimited by the beam's eye view technique, is determined by a genetic algorithm method. The weighting of the fields, and of the sub-fields in the case of intensity modulation, as well as the position of the leaves, are optimized by a simulated annealing method. The results obtained were compared with those of two radiosurgery techniques (Gammaknife and multi-beam radiotherapy) using the indices defined by the Radiation Therapy Oncology Group (RTOG)[3]. We have shown that using a µMLC with intensity modulation improves RTOG indices although the peripheral healthy tissues are less irradiated with the usual radiosurgery techniques. We also showed the difficulty of obtaining high dose homogeneity with radiosurgery techniques when the irradiation plan uses several isocentres. We have shown that when correctly used, µMLCs may constitute an interesting alternative to the usual techniques of radiosurgery [4].

iii) Location and immobilization for the cerebral irradiations. Because tomographic imaging allows increasingly accurate irradiation of cerebral vascular or tumoral malformations, it is also essential to monitor as much as possible the patient's motion and successive repositioning. We have developed a new non-invasive localization, immobilization and positioning device showing a satisfactory accuracy. A carbon fiber prototype was designed and was manufactured [5]. A study of the location accuracy was carried out on radiological phantoms (specific targets) with MRI and CT. This study showed a sub-millimetric accuracy. An evaluation of the positioning and re-positioning errors on healthy volunteers was carried out with MRI and showed that the deviations remained lower than 1 mm. The prototype showed than it was usable for image localization, patient immobilization and positioning. A comparative study of the positioning errors between our experimental system and the most widely used systems is in progress. An international patent of this new device has been obtained and it is now being marketed [6].

b) Future work

The general aim of our project is to make currently available technologies available for radiotherapy (from a point of view of imaging techniques as well as of the digital techniques of optimization, simulation and image processing) to increase the therapeutic indexes and to decrease the associated hazards. Our specific contribution relates to planning, simulation and optimization of the treatments by the use of the different imaging methods.

i) Use of MRI for therapy simulation. Conformal radiotherapy requires a preliminary planning of the treatment during which the relative positions of the patient compared to the irradiation device are defined, as well as the incidences, the shape and the weighting of the irradiation fields. The volume dose distribution is therefore simulated in the images. The method most used today is CT because of its relatively easy access, and because the electronic densities obtained from the studied tissues are very similar to their capacity for radiation absorption (Hounsfield units). However, MRI is often more suitable because of its excellent contrast for soft tissues and its ability to differentiate tissues. Its availability, which is still difficult, will certainly improve in the future. However, the absence of absorption coefficients is a major problem. A solution is the combined use of MRI and CT, therapeutic targets being defined on MRI images and planning on CT images. The problem is very difficult for abdominal structures subjected to anatomical displacements and physiological deformations. We are currently developing algorithms of matching of deformable structures between methods by using shared reference markers or by using local (or total) statistical data between images such as mutual information [7]. This matching could also be applied to other types of images such as those resulting from positron emission tomography (PET) whose interest has been proved in oncology. Another solution is virtual simulation using MRI alone to determine at the same time the sensitive and target volume contours and also the dose planning. To do this, tissue identification of the structures will be carried out in a sufficiently accurate and robust way to be able to assign to each image voxel the electronic density characteristic of the tissue in question. An anatomical modeling derived from the tools of computer-assisted design (CAD) and from computer graphics will call upon various concepts of texture, structure or simply of geometrical and descriptive analysis of the structures concerned. The integration of expert knowledge as well as from the available data (e.g. clinical data, physio-pathology, physiology, imaging physics, etc.) will enable us to enhance and improve the process of image analysis. The problem would be to determine what degree of confidence can be assigned to the information provided by a series of heterogeneous sources. Thus, we will use high-level methods such as probability theory and fuzzy logic.

ii) Control positioning by ultrasonic tomography. The previous methodology of volume definition will be used to control the patient's positioning and repositioning by using pre-operative ultrasound (US) imaging of the patient under the irradiating device. The problem of positioning moving organs for each irradiating session has been already mentioned. To solve this, a real-time or quasi real-time system of US localization will be developed by merging the US images and CT or MR images, the latter having been used for the definition of the targets to ensure the correct positioning of the patient [8, 9]. A stereo-localisation device will be used to locate the US probe relating to the position of the irradiating system [10]. Although most of the theoretical aspects necessary for realizing this project are well known by the team, significant technological developments have still to be made, both in data-processing and in mechanical and electronic set-up. These developments are borderline between research and industrial transfer.

2) Interventional MRI

The use of MRI to carry out interventional procedures for diagnostic or therapeutic purposes is a very promising prospect. The possibility of visualizing not only the diseased target but also the surrounding normal tissues and, with more difficulty, the surgical instruments in the surgical field, makes it possible to monitor per operatively the surgical pathway. Thanks to the excellent MRI contrast for soft tissues and to the high sensitivity of this MR signal to temperature changes, it can be considered to be a minimally invasive procedure (transcutaneous biopsies, drainage of liquid accumulations, laser or RF thermo-therapy, vascular angioplasties or dilations, etc.).

a) Previous activities

We undertook a research on the conditions to implement interventional MRI by using a 0.2T MR scanner (OPEN 0.2, Siemens, Erlangen, Germany) having an open resistive magnet and thus giving a large access to the patient under examination.

i) Tool localization and guidance in interventional MRI. The localization of the surgical tools was obtained by matching the surgical field observed by optical sensors in the MRI field of view. We had to correct the image distortion, which is very large at the boundaries of the field of view, and we had also to perfectly monitor the artifacts generated by the tools. A software was developed to visualize and to choose the relevant images for the surgical planning. Once the definition of the entrance point and the target is made, the orientation and the position of the MRI slice are calculated to monitor the biopsy or drainage pathway. To locate the entrance point of the surgical tool on the skin of the patient, we have developed a motorized LASER pointer with two degrees of freedom, controlled by an optical stereo-location system equipped with four CCD cameras. This optical system also monitors the surgical instrument and indicates to the expert the possible errors compared to the planning [11]. The particularly constraining electromagnetic MRI environment made it essential to use an optical fiber data communications system. The system developed showed its effectiveness and its reliability during in vitro experiments as well as during in vivo surgical procedures performed on animals. This procedure is described below.

ii) Bile duct drainage in interventional MRI. Interventional procedures under x-rays to drain the intra-hepatic bile duct remain difficult even for a well-trained operator (projection imaging, low visibility of the bile ducts, risk of hepatic artery puncture, ionizing radiation, iodine injection). We have defined and tested an MRI interventional procedure based on a T2-weighted TurboFlash sequence whose acquisition time is compatible with short-time breath-hold and which provides a high visibility of the biliary liquid without major artifacts coming from blood flows. Because only few MRI-dedicated tools are available, we have tested some materials (needles, guides, probes) in vitro and during usual interventional radiology procedures. In vivo experiments were performed on 6 female piglets after surgical creation of a bile duct stenosis. Our preliminary results show the feasibility of gall bladder and intra hepatic bile duct punctures with simple and double obliqueness by interventional MRI. The localization of the point entrance to the skin and the guidance of the instrument were carried out using the laser pointer previously described [12].

iii) Vascular interventional MRI. We have also tested the possibility of carrying out dilations of aortic stenoses under MRI control to substitute for the X-ray fluoroscopy. We have developed a passive tracking method based on magnetic susceptibility [13]. The angioplasty tools included a guide, a probe with a standard small balloon and an MRI-compatible endo-prosthesis. To improve the visualization of the guide, ferrite markers were inserted on its distal extremity. This material was tested using an in vitro flow model. In vivo experiments were performed on pigs previously operated by coelioscopy to create a stenosis on the descending aorta. The installation of the guide and the balloon could be carried out and visualized in an in- vitro model as well as in an in- vivo model. The balloon was inflated with DTPA-Gd to obtain a high contrast between the inflated balloon and blood flow. The controls carried out after dilation did not show any aortic rupture. The endo-prosthesis, visualized because of its susceptibility artifacts, could be installed after the dilation. We have proved the feasibility and the interest of this minimally-invasive surgical technique in MRI.

b) Future work

A Hitachi AIRIS II low-field open-magnet MR 0.2 T scanner dedicated to scientific and technological innovations has been installed recently in our laboratory. The exceptional possibility to freely dispose of an experimental MR scanner, without the usual clinical constraints, will enable us to test our developments on an in vitro model and animal model using minimally invasive therapy guided by MRI.

The subject of our project is laser therapy guided by MRI. Laser-induced thermo therapy (LITT) and photodynamic therapy (PDT) are two ways used for laser therapeutic treatment in oncology. LITT destroys deep tumors by thermal effects while minimizing the impact on adjacent healthy tissues. PDT acts on the neo-vascularization by producing intra-cellular free radicals. These two methods have demonstrated their efficiencies and potentially belong to the therapeutic arsenal. Laser diodes are in rapid development and offer a large area rendering laser-therapy conceivable to therapists. However, the restriction of the treated area to the tumor remains a difficult problem especially when, for large-size targets, it becomes necessary to use several optical fibers. In addition, medical imaging is indispensable for planning, for the placement of optical fibers, for per-operative monitoring of thermal changes and post-operative ablation. MRI is the only imaging method whose capacities of tissue differentiation provide all these functions. It also offers unique possibilities for real-time per-operative thermal effect cartography or post-operative necrotic evaluation. Finally, by its nature of light emission, laser therapy is perfectly compatible with MRI. The objective of our project is the production, installation and clinical validation of a prototype of interstitial laser therapy and photodynamic therapy guided by MRI. Its aim is to destroy deep tumors while sparing adjacent healthy structures. Our project of laser therapy guided by MRI is organized into four interactive and simultaneous sub-projects.

i) The multi-fiber laser therapy system. This sub-project concerns the therapeutic instrumentation, especially the definition of therapeutic laser sources for LITT and PDT. This phase will determine the specifications of lasers by comparing costs to the method of delivering laser energy to the tumor. We have first to model and simulate the interaction between the laser and tissues and the thermal or photochemical actions in function of the different parameters: wavelength, power, time parameters and the spatial distribution of the applicator. The parameters thus obtained will be evaluated on physical models, then on small animals (rats) by associating the effective technical measurement, such as interstitial infrared thermometry for LITT and the measurement of singlet oxygen for PDT. The second aspect concerns the automatic 3-D tissue segmentation to determine the position of the lasers. This work has to allow us to automate the therapeutic process by making the 3-D laser dose conform with the pathologic volumes. This project will be undertaken by transposing our experience in dose planning for conformal radiation therapy.

ii) Applicators for optical fibers. To satisfy optical fiber requirements in the area of LITT and PDT guided by MRI, we propose to produce ceramic applicators to make the optical fiber extremity rigid. The ceramic material has to be MRI compatible without artifacts, to be sufficiently rigid to allow the introduction of the optical fiber into the tumor to be treated, to resist thermal shocks caused by the laser heating and to be biocompatible in case of possible loss of broken pieces. Possible materials include aluminum, zirconium, hydroxyapatite and carbon.

iii) MRI guidance. We propose to produce and install a prototype of MRI guidance of optical fibers, based on our previous know-how in stereovision and skin pointers. Corrections of image distortions in the limit of field of view will be analyzed and precisely corrected [14]. It will then be necessary to determine sequences for temperature measurements (diffusion, chemical shift, T1 mapping, etc.) to satisfy the best possible compromise between acquisition time, precision of temperature measurement and image quality.

iv) In-vitro and in-vivo evaluation. The biological models chosen to evaluate and validate techniques of laser therapy concerns the hepatic metastases that are a frequent pathology especially derived from gastro-intestinal cancers. It is currently proven that surgical resection of hepatic metastases clearly improves the patient's survival. So as to decrease the operative morbidity, a radio frequency (RF) percutaneous technique is often used. This technique consists in puncturing the tumor under US or CT with a suitable RF probe, and then obtaining thermal necrosis. Nevertheless, it can be conducted only on a few patients, as the diameter of necrosis obtained by this way does not exceed 3 to 4 cm. The first criterion of validation of the method will be therefore the diameter of necrosis obtained in vivo, a diameter of more than 4 cm with a mono-fiber system being indispensable to prove that the method has a potential interest as compared to the RF technique. The second validation criterion will be the accuracy obtained by the system guidance, a precision better than 0.5 cm being essential. Particular attention will be equally focused on the safety and on the clinical compatibility of the whole procedure.

3) Vascular Imaging

Currently, X-ray digital angiography is still the gold standard in vascular imaging. This kind of study needs to use a contrast agent to make the vessels visible. Visualization is also improved with the digital subtraction techniques (Digitally Subtracted Angiography, DSA) that subtracts the bony structures. Recently, breakthroughs in MRI have made Magnetic Resonance Angiography (MRA) an elegant alternative procedure to DSA. Our previous works have enabled us to increase and the diversify our skill in signal and image processing for segmenting, re-building, quantifying or analyzing vascular structures observed with several imaging methods such as DSA, MRA or Computed Tomography Angiography (CTA).

a) Previous activities

Multi-disciplinary skills were used during our collaboration with numerous clinical and industrial partners but always retaining our connection with the specific problems of medical practice. The results described below prove the whole methodological set, required for digital image processing, as being almost controlled for multimodality brain imaging, either for diagnosis or for interventional imaging.

i) DSA analysis. We have developed a new and original method for automatically reconstruct the intracranial vascular tree as well as for 3-D localization of arterio-venous malformations (AVM) from a minimal number of views [15]. We have also worked on new algorithms for correcting the pincushion distortion due to the magnetic fields and to the curved aspect of the image intensifier [16].These works have been exploited in the development of a method using DSA for AVM treatment planning in multi-beam stereotactic radiotherapy and radiosurgery.

ii) Vessel reconstruction in MRA. A “one click” method for 3-D reconstruction of intracranial vessels has been developed. Its principle consists in choosing on a MIP (Maximum of Intensity Projection) image and through a growing region approach the part of the vascular tree to be reconstructed [17]. The search for the vascular tree selected on each native slice is achieved by reversing the MIP process. An analysis using data fusion based on the fuzzy set theory enables us to identify each voxel of a MRA slice belonging to the vascular tree.

iii) Matching of multimodality vascular imaging. The previous methods were applied for matching 2-D and 3-D multimodality imaging of the brain vascular system, DSA and MRA. The main goal was the follow-up, through MRA, of aneurysms embolized using interventional radiology. This follow-up is performed with the fusion of the diagnosis and the post-operative images [18]. These real time algorithms have been developed from our recent works on image registration using the ICP algorithm (Iterative Closest Point) or the thin-plate splines algorithm. In an interventional radiology context, our latest developments provide an accurate three-dimensional quantification of aneurysms and an optimal adjustment of the coils and embolization materials.

b) Future work

Our past work has given us a large and diversified base of knowledge in multimodality cerebral imaging. This will be integrated into the developments of projects aimed at diagnosis and minimally invasive interventions in the following fields: interventional neuroradiology and radiosurgery of arterio-venous malformations (AVM).

i) Vascular multimodality imaging for neuroradiology. Our abilities in registration and matching MRA and DSA will be turned to account for the treatments of some pathologies, either for diagnosis, intervention or follow-up. The originality of the MRA/DSA procedure that we have developed is based on the fact that no ARX projections are required. This is not the case with previous methodologies. Our new approach will simplify the procedure especially by relieving the medical practitioner from additional unacceptable constraints. An operation simulator placed in the interventional room would be developed using DSA/MRA matching. It will offer the possibility of a 3-D reconstruction of the vascular structure being treated and its pathology. In the case of an aneurysm diagnosed through MRA or DSA, the matching and the reconstruction will enable the volume to be treated to be estimated accurately, isolating the vascularized part (visible from DSA) from the necrotic part (visible from MRA). An easy and precise treatment planning will be available. During the intervention, the 3-D data from MRI will offer helpful information in the guiding of the catheter required to opacify the blood vessels and to place the coils. The MRA studies acquired during the years following the intervention will be matched with the first DSA images to make the follow-up easier and to allow the study of potential aneurysm permeabilization. Subsequently, these techniques will be also applied for non-vascular pathology imaging when a radiotherapy treatment of brain tumors will require registration between PET and MRI for example.

ii) Arterio-venous malformation radiosurgery. In AVM radiosurgery (e.g. Gammaknife radiosurgery), the therapeutic decision is achieved after the acquisition of a diagnostic DSA study without a stereotactic frame. Since MRI or CT, required for dosimetric planning, do not offer sufficient results in terms of resolution for AVM, a second DSA study is acquired including a stereotactic frame, with the well known constraints of time and cost of such an examination. A new methodology for AVM localization will use only the diagnostic DSA and will place the acquired data of the AVM in the space of the MRI or CT acquired with the frame. This breakthrough would have an important impact in terms of public health. Of course, this research theme is connected with the project dealing with conformal radiotherapy. In the future, the application of these registration techniques will be designed for neuronavigation, since accurate localization of the vascular system is an essential information for the optimal course of these neurosurgical interventions. Once again, these techniques could be extended to tumoral pathologies.

4) Surgical simulators

Surgical training simulators share some tools with the robotics area (sensors, visual and haptic interfaces, etc.). However their objectives are different: simulators are intended for the acquisition and assessment of skills in a specific medical procedure. The requirements about gesture realism are therefore stronger. In particular, to simulate the mechanical behavior of organs lying in the surgical field, mechanical models of these organs need to be created. This constitutes a particularly innovative domain of biomechanics, studying highly deformable "objects".

a) Previous activities

Our works in this domain have been in two directions: training and learning simulators and pre- and post-operative therapeutic decision-making tools.

i) Training simulators. We have developed several simulators dedicated to the acquisition of surgical skills and to skills assessment. Various prototypes were designed in domains such as ophthalmology (retinal photocoagulation by laser) [19], laparoscopy (gynecological and visceral), echoendoscopy and echoguided needle biopsy [20], with the active involvement of surgeons from the concerned disciplines. This activity lies in the field of virtual reality: we have designed new tools for preliminary and continuous medical education in various medical and surgical specialties, allowing the trainees to learn on virtual patients. The realism of the simulation - and specially the use of a force feedback- requires models for the identification of the "living objects" (the organs and organic components, walls, ligaments, etc.) that constitute the operation field. Then, the problem is about determining the behavior of these soft and deformable components during the surgical interventions: the real-time simulation of elastic distortions is currently a major scientific challenge. Tuning descriptive models requires establishing the values of their characteristic parameters from experiments. However, few quantitative data concerning the living human deformable body domain are available. One of the difficulties resides in the highly deformable character of these "soft objects" that leads to mechanical values (forces, torques) of very low amplitude (of the order of about ten mN). Our preliminary works have dealt with the investigation of the static behavior of isolated sow's ovaries, by analyzing stress / strain and relaxation curves measured by means of a strain gauge with vertical forcing and shrinking in the organ. Various sets of measurements were made to define a first model of the ovary (non-linear viscoelasticity) during simple monoaxial interactions with a rigid object. In order to more precisely simulate the in vivo characteristics, we have developed an instrument designed for laparoscopic per-operative measurements on animals. The use of such a device was critical, given notably the low values of the physical variables (forces, torques, positions) measured when related to the various interferences from "mechanical noise" components, such as rubbing between instruments that we had to neutralize. Then, the in vivo measurements of acts conducted on sows during training sessions were performed according to a study protocol defined by surgeons [21].

ii) Help in therapeutic decision-making. With regard to their activity in the reparative surgery of pelvi-genital prolapse, obstetricians try to explain with biomechanics the therapeutic problems they have to deal with (high rate of recurrences). The present aim is to build a mechanical model of the vaginal cavity for quantifying the different types of prolapse and for allowing pre- and post-operative assessments. The objective is to be able to propose a customized surgical management for every patient with different types of prolapse and to improve the surgical strategy (choice of prosthesis materials, of the locations of anchorages) from a simulation performed on customized models. The methodology adopted combines the in situ measurement (in vivo, by means of a probe) of the intracavitary pressures on healthy subjects, the determination of the elastic features of tissue samples and the 3-D reconstruction, from MRI for example, of the organic volume concerned. The geometric models built from medical imaging hold the 3-D mechanical models of the cavity, including the 3 "objects": bladder, rectum and vagina [22]. A set of constraints and parameters were introduced to take account of the anatomo-physiological reality (thickness and elasticity of the walls, spring links at the utero-sacral suspensory ligaments, etc.). Then, we validated the numerical stability of the system in specific conditions (gravitational model in standing or lying position, according to the measurement conditions on patients).

b / Future work

The objective of this project is to finalize previous work in two domains: training simulators and help in per-operative decision-making.

i) Training simulators. The improvement of the realism required by the production of surgical simulators poses a whole series of problems that constitute many technological hurdles to overcome. Among these, the restitution of the spatio-temporal behavior of the various components considered (both organic and instrumental) requires that they can be characterized from a mechanical point of view. The previous work and the planned one illustrate this preoccupation. The ability we acquired during studies carried out in gynecologic laparoscopy, will be used for a new application in ophthalmology. Phacoemulsification is a very expanding operative technique for cataracts which consists in the surgical ablation of the opacified lens. The currently used technique splits up the lens by ultrasound then sucks it out, before replacing it by an intra-ocular implant. The operative phases judged to be the most applicable from a pedagogical stand point will be retained, among them those involving either the mechanical behavior of organs (injection/aspiration of the viscoelastic gel, capsulotomy, hydrodissection and phacoemulsification itself), or solely the behavior of the prosthesis (placing the intraocular implant). Some convenience and ethical constraints will limit our survey to the study of different types of cataracts, conducted on isolated pig eyes. The mechanical rigidity will especially be studied to characterize the possible diversity of behaviors at the time of their mobilization by micromanipulators after the phase of hydrodissection. The objective is to outline a possible differentiation between the different layers of the lens. Otherwise, viscoelastic models of the mechanical behavior of different models of implants will be analyzed with the help of the test bench that we previously developed.

ii) Help in the operative decision-making. The study of the vaginal cavity we started two years ago, will continue by the survey of the robustness of our model, in particular towards the scattering on the measured values of tissue rigidity, towards the anatomical variants in the location of the anchorage points (buttresses of the pubic bone and the sacrum), the location of the surfaces of contact between the "objects" and the influence of the vesical and rectal contents. Application to this model of stresses imposed during intravaginal pressure measurements (efforts of thrust, cough, Vasalva's maneuver) will be compared with the values measured on patients. The parietal tissues (vaginal, vesical and rectal) are hyper-elastic and very deformable materials. A new survey of behavior will be performed on biological samples. The influence of the tool velocity (characterization of viscosities) will be examined. In addition, a physical model of the mechanical system is considered to assess the measurements made with the intravaginal probe (reproducibility, sensitivity) and to improve the control of the experimental conditions (influence of the vesical and rectal contents, taking into account the uterus, the anatomical contacts between the organic components, etc.). The work will also be extended as a matter of course to radiotherapy, when it will involve characterizing distortions of the organs placed under the treatment device during every session of irradiation.

III/ ORGANIZATION AND PARTNERSHIP

The U 703 members are University/Hospital Assistants, with an initial scientific education. The team is located at the Medical Institute of Technology (ITM) of the University Hospital of Lille (France). From an institutional point of view, the U 703 is defined within the Medical Physics Lab UPRES EA 1049 of the Faculty of Medicine of Lille. The unusual Hospital/University position of the team members with a scientific background allows them to establish an easy and constructive dialogue with multi-disciplinary partners and to have a favored access to the different facilities (medical imaging devices, surgical facilities, animal room, IT, etc.) necessary for the development and the evaluation of the research products. Thus, we will maintain the team strengths and dynamics previously shown in our activities in fundamental and applied research.

The main medical and scientific partners are either clinical departments of the University Hospital of Lille (Gynecology, Nuclear Medicine, Ophthalmology, Neurosurgery, Neuroradiology, Radiation Therapy), or Laboratories of the Technical University of Lille 1 (LIFL URA CNRS 369, Mechanics UMR CNRS 8107, Robotics UMR CNRS 8146). A start-up company (Aquilab SAS, www.aquilab.com), created from our activities in transfer technology is our preferred industrial partner.

In summary, the aim of the U 703 is to create new tools for interventional procedures assisted by imaging and simulation. The challenge could be summed up in three words : user-friendliness, safety, and cost, because these new tools have to be easy to use, have to guarantee a enhanced safety as compared to the current procedures and especially do not have to be consuming of medical staff time.

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REFERENCES

1. Vial S, Gibon D, Vasseur C, Rousseau C, 2001, A fuzzy logic method for volume delineation in tomographic imaging: IEEE Trans.Med.Imag, 20 (12), 1362-1372
2. Caudrelier JM, Vial S, Gibon D, Kulik C, Fournier C, Castelain B, Coche-Dequéant B, Rousseau J, 2003, MRI definition of target volumes using fuzzy logic method for three dimensional conformal radiation therapy: Int.J.Radiat.Oncol. Biol.Phys, 55 (1), 225-233.
3. Kulik C, Caudrelier JM, Vermandel M, Castelain B, Maouche S, Rousseau J, 2002, Conformal radiotherapy optimization with micro-multileaf collimators. Comparison with radiosurgery techniques: Int.J.Radiat.Oncol.Biol.Phys, 53, 1038-1050.
4. Kulik C., Castelain B., Maouche S., Rousseau J., Comparaison de plans de traitement optimisés pour différentes modalités de radiochirurgie et de radiothérapie conformationnelle. ITBM-RBM 2002, 23 : 254-262.
5. Caudrelier J.M., Gibon D., Bourel P., Rousseau J., Définition et évaluation d'un système non invasif de repérage en imagerie et d'immobilisation

pour les irradiations cérébrales. Meeting of the Soc. Française de Radio-oncologie 2001.
6. Bourel P.,Caudrelier J.M.,Gibon D.,Rousseau J. "Non invasive contention device for radiation therapy treatment", Patents 2004, FR2829686 and WO03024351.
7. Palos G., Betrouni N. Coulanges M. Vermandel M. Devlaminck V. Rousseau J. Multimodal Matching bu Maximisation of Mutual Information and Optical Flow Technique , IEEE EMBS , San Francisco, USA, 1679-1682, 2004.
8. Betrouni,N.; Vermandel,M.; Pasquier,D.; Maouche,S; Rousseau,J., Segmentation of abdominal ultrasound images of the prostate using a priori information and an adapted noise filter, Comput.Med.Imag.Graphics 2005, 29(1), 43-51
9. Betrouni N., Palos G. Vermandel M. Pasquier D. Maouche S. Rousseau J. Ultrasound to MR / CT registration system for use in conformal radiotherapy of prostatic carcinoma. Proceedings of CARS. PP 1241, Chicago, USA, 2004
10. Betrouni N., Palos G. Vermandel M. Maouche S. Rousseau J. A New System For Freehand Ultrasound Tracking Application in Multimodality Image Matching. Proceedings of the Second International Conference Biomedical Engineering, Innsbruck (Austria), 141-144, 2004.
11. Daanen V, Coste E, Sergent G, Godart F, Vasseur C, Rousseau J, "Accurate Localization of needle entry point in interventional MRI", J Mag Reson Imag 2000, vol. 12 : 645-649.
12. Sergent G., Daanen V., Nicol L., Occelli B., Godart F., Cahill M Rousseau J., Percutaneous MR-guided bile duct drainage : first in vitro and in vivo results. ESMRMB 99 - MAGMA 1999, 18 : 100
13. Godart F, Beregi JP, Nicol L, Occelli B, Vincentelli A, Daanen V, Rey C, Rousseau J, "Balloon angioplasty of stenosed aorta : in vivo evaluation using near-standard instruments and a passive tracking technique", J Mag Reson Imag 2000, 12 : 645-649.
14. Bourel P, Gibon D, Coste E, Daanen V, Rousseau J. Automatic quality assessment protocol for MRI equipment. Med. Phys. 1999 ; 26(12) : 2693-2700.
15. Coste E, Vasseur C, Rousseau J. 3-D reconstruction of the cerebral arterial network. Med. Phys. 1999 ; 26(9) : 1783-1793.
16. Verdonck B., Bourel Ph, Coste E., Gerritsen FA, Rousseau J., Variations in the geometrical distortion of X-ray image intensifiers. Proc. SPIE Conference on Physics of Medical Imaging, 1999, SPIE 3659 : 266-275.
17. Vermandel M., Kulik C., Gauvrit J.Y., Vasseur C., Rousseau J., Registration and matching of projection imaging and tomographic imaging. Application to X-rays angiography and MR angiography. CARS'2002 Proceedings, 2002, 419-424.
18. Vermandel M, Betrouni N, Palos G, Gauvrit JY, Vasseur C, Rousseau J, 2003, Registration, matching and data fusion in 2-D/3-D medical imaging: application to DSA and MRA. Lecture Note In Computer Science 2003, Springer, 778-785.
19. Dubois P., Rouland J.F., Meseure P., Karpf S., Chaillou C. Simulator for laser photocoagulation in ophthalmology. IEEE Trans. on Biomed. Eng. 1995, 42, 7, 688-693.
20. Dubois P, Thommen Q, Jambon AC, In vivo measurement of surgical gestures, IEEE Trans. on Biomed. Eng, 49, 1, 2002, 49-54.
21. P. Dubois, G. Delmar, G. Picod, “Measurements of mechanical interactions between a surgical instrument and an organ: methodological aspects”, Proc. of the IASTED Intern. Conf. “Applied Simulation and Modelling”, Heraklion, 25-28 june 2002, 174-179
22. Dubois P., Thommen Q., Jambon A.C., Mechanical Model of Warping Living Organs : Application to Sow’s Ovaries. Lect. Note In Proc. of the IASTED Intern. Conf. On Applied Simulation and Modeling 2001 : 183-187