A few critical issues in biomedical imaging and therapy

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Abstract

This introductory chapter does not pretend to give a full overview of the biomedical imaging and therapeutic resources but some ideas about the problems to face and the breakthroughs that are on the way or will happen tomorrow. It will emphasize the importance to look outside its own field and understand how the new advances made elsewhere can help in solving specific problems or, and perhaps more, be the source of inspirations. It attempts to emphasize the efforts to make on therapy if we want to be coherent with the trend toward early diagnosis in caring patients.

1. Introduction

The availability of high resolution medical imaging, in space and time, and the subsequent access to morphological or functional features, the fast developments in image analysis (figure 1) and virtual augmented/mixed reality, and the emergence of microtechnology-based devices, have opened the road of challenging research. If the former provides the capability to collect precise and relevant data on the patient disorders, the others offer on one hand, new means for objective delineation and quantification of lesions as well as registration, instrument tracking and visualization for multimodal fusion and, on the other hand, the possibility to act in spatially constrained environments. These continuous improvements are far to be completed. However, the therapeutic resources at our disposal remain less developed and more efforts are required in the next future. Efficient targeted caring actions with less side-effect are more than expected because most of the present ones still rely on old principles with very few exceptions. This short paper reviews some of these paradigms and critical issues that need special attention.

2. The fast evolution of technology and its consequences

We must remember that major imaging sources, the first CT-scanner appeared in the 70s and MRI a few years later. The methods that were developed at this time were mainly devoted to segmentation and 3D visualization (such as slice interpolation to face the low spatial resolution, surface detection and shading to get the 3D shape, etc.). Detectors in CT, coils in MRI, transducers in ultrasound, etc. have been highly improved due to advances in physics and electronics. Chemistry through the contrast agents has been also contributing to these impressive developments. And this is true for X-ray based technology as for magnetic imaging, optics, etc. The conjunction of these resources with always faster computer systems opened the road for the implementation of image processing methods which were discarded for a while. This is the case for instance of statistical reconstruction algorithms. These real improvements and sometimes breakthroughs have however several important consequences that can be questioned.

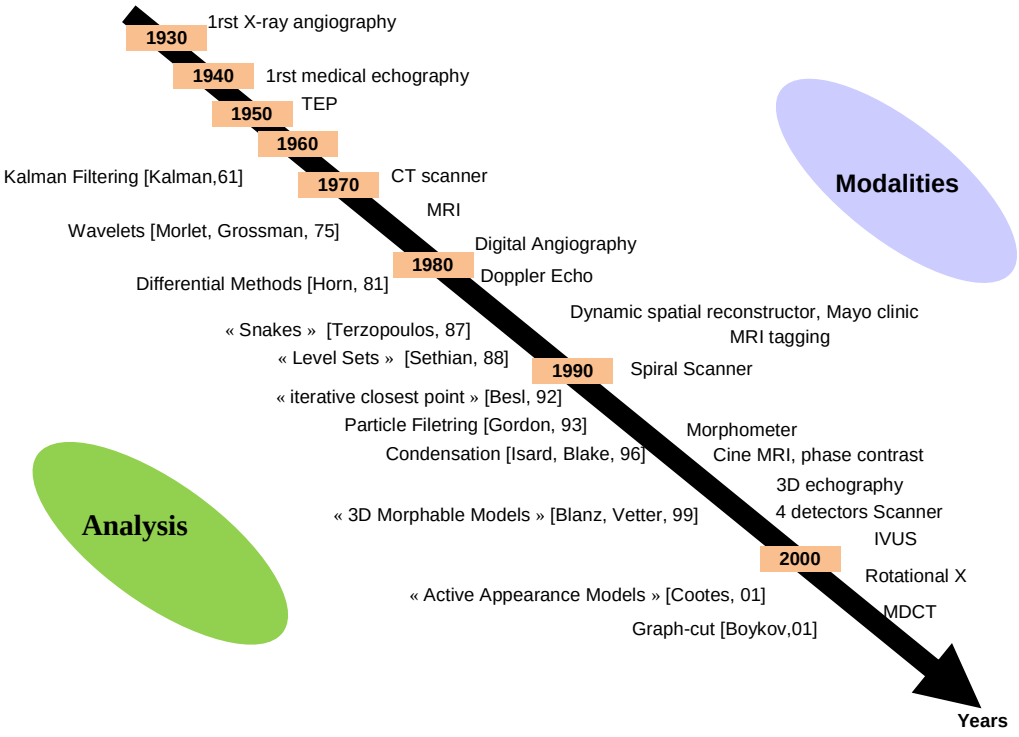


Figure 1. The advances in medical imaging modalities versus signal-image analysis methods over time *(Courtesy P Haigron, J.L Coatrieux, (Haigron, Luo et al. 2009))*

Do they fulfil the expectations they supposed to? We can understand for example that the competition between modalities like CT and MRI for the beating heart should force for new generations of systems and thus is surely a way to get better insights to the human body. Also, the search for higher field in MRI is a normal path to follow in order to characterize more precisely the nature and the extent of a lesion. Ultra-fast acoustic imaging may lead to reveal small and rapid movements of significance for diagnosis. But any technology-driven approach must also take into account the clinical and patient needs. They concern the effective demonstration of patient safety and patient benefits. They equally have to deal with cost savings: the multidetector CT is an excellent marketing reference where progressively the sources went from 4 to 64 and more detectors while a direct step to a high number of detectors was possible.

What are the consequences for research? They are major. First of all, any clinical study to be achieved fully depends on the sensors which are used. A researcher working on an imaging modality a few years old can not compete with the last version available in other sites. Therefore, there is a permanent fight for having the newest system at hands. The previous version has not been exploited yet that it is mandatory to access to the last one.

Are we free to develop potentially new solutions? Not really. An example of that is the access to raw data. These data, the immediate outputs of the sensors, are not available except if you are under contract with the providers. The images at our disposal are already reconstructed, filtered and sometimes interpolated, all things which are not under control. There is another critical issue to address.

What can be said about the information processing? Very little, in fact. This step relies completely on the input data. A segmentation algorithm, that fails or which not totally satisfies the expected outcomes, can work much better on an improved dataset. Rigorously, we shall revisit systematically the past methods in order to be objective in the assessment of performance. A huge task, of course, that nobody wants to do.

3. A mandatory target in biomedical engineering: the design of new therapeutic technologies

The major question for imaging people is: why to put such emphasis on early diagnosis if there is little means to care the disease? In other words, what after diagnosis? Our feeling is that the research efforts must be much more balanced. Imaging will remain of course mandatory to navigate and guide the therapeutic instruments as it has been shown in computer-assisted interventions and robotic systems. Beyond the advances made in, the demand of more efficient and safer therapies remains challenging. Most of the physics-based (or energy-based) therapeutic principles at our disposal have been established a long time ago. They all have a wide spectrum of clinical targets in terms of organs and pathologies, modes of application (external, interstitial, intraluminal, etc.) with advantages and side-effect drawbacks, indications and contraindications, some of them still facing controversies regarding their outcomes. They include radiofrequency (RF), high intensity focused ultrasound (HiFU), microwaves, cryotherapy and laser-based approaches (e.g. photodynamic therapy at large). Radiotherapy and its variants (hadrontherapy, brachytherapy, Gamma knife and Cyberknife) remain of course the reference technique in cancer treatment.

Radiofrequency ablation (RFA) is based on electric current-mediated heat applied through an electrode placed into the target. Resistive heating around the RFA electrode is produced by fast ion oscillations at frequency typically ranging over 450-500 kHz (Ni, Mulier et al. 2005; O'Rourke, Haemmerich et al. 2007). In order to avoid different sequential placements into large lesions, multitined electrodes or internal electrode cooling is sometimes used (figure 2). They may incorporate controlled sensors for measuring the temperature. Atrial fibrillation suppression is a major application of this thermoablative technique but applications for unresectable cancer increase significantly within the last years.

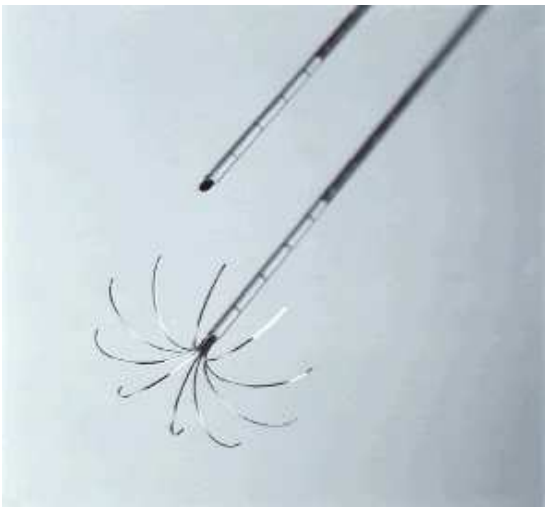


Figure 2. Radiofrequency needle electrode. The gauge needle is introduced into the tumor and then the retractable tines are deployed.

Microwave ablation (MWA) is obtained by creating rapid oscillations of water molecules, thus causing frictional heating leading to coagulation and necrosis. MWA probes are basically coaxial waveguides (Bertram, Yang et al. 2006). Several frequencies, 915 MHz and 2.45 GHz, are authorized and lead to treat volumes up to 4-5 cm in diameter. Improvements in antenna design (from triaxial to dielectric resonator antenna) have been recently brought with the objective to extend the treated area, to better conform the radiation pattern and to reduce the probe size.

High intensity ultrasound has raised a lot of interest for years (Bouchoux, Lafon et al. 2008) and is now widely disseminated. Focused transducers, *HiFU* (High Intensity Focused Ultrasound) and non (or weakly) focused transducers, *HiCU* (High Intensity Contact Ultrasound), operating at a few MHz, are marketed (figure 3). They incorporate ultrasound imaging sensors for guidance. The energy delivered over

a few seconds can induce high temperatures (typically >60°C) and generate irreversible tissue necrosis at the target region while not damaging surrounding tissues. Today assessed for prostate cancer treatment, they should find a wider spectrum of clinical applications, for instance brain metastases (figure 4) following the pioneering developments of M Fink and M Tanter.

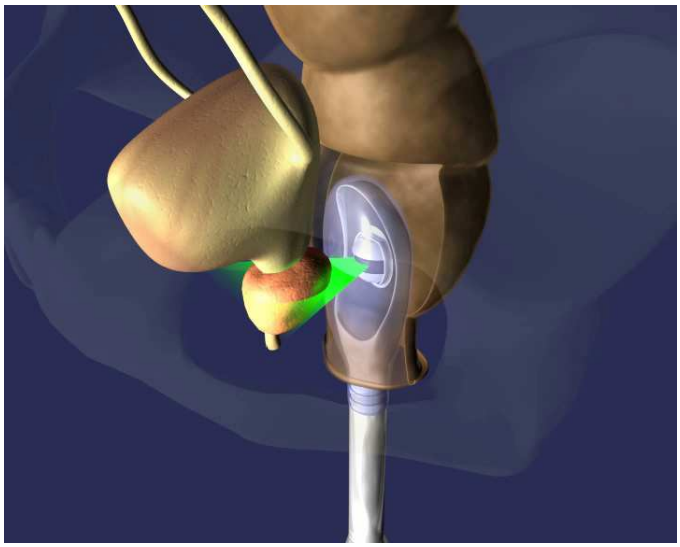


Figure 3. Computer graphics representation of the HiFU transducer for prostate cancer (*courtesy EDAP-TMS*)

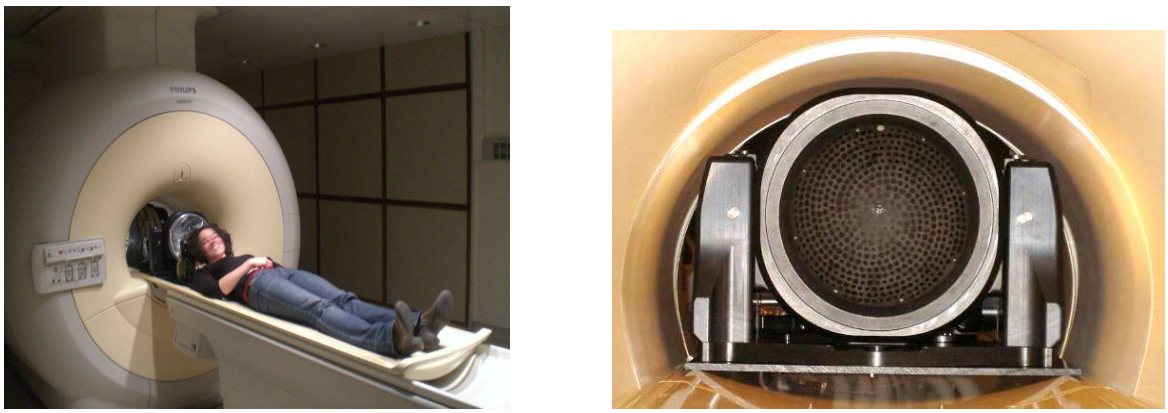


Figure 4. HIFU device for brain tumor therapy compatible with MRI. General view (left), device (right). Courtesy Mickael Tanter, Mathias Fink (Tanter, Thomas et al. 1998; Aubry, Tanter et al. 2003; Tanter, Pernot et al. 2007).

Laser ablation, e.g. laser-induced thermotherapy, is another approach with a large range of clinical applications (Schindl, Schindl et al. 2000). Light in the near infrared part of the spectrum – as from a NdYAG laser at 1064 nm or a semiconductor diode laser at 805 nm – can be effective up to 10 mm of tissue. Beams are transmitted via thin fibers, so that endoscopic procedures can be applied, and focused to small spots to destroy tissues. Interstitial laser photocoagulation can be performed over a few minutes via fibers through needles at low power (about 3 W, avoiding so tissue vaporization, to be compared with the 60-80 W used endoscopically).

Cryotherapy consists to locally induce very cold temperatures (-75°C) at a catheter tip below -75°C which results in irreversible cell destruction within a so-called “ice ball”. The adhesion of the tip to the tissue leads to a stable ablation (Seifert and Morris 1999; O'Rourke, Haemmerich et al. 2007). A recent breakthrough has been made by the introduction of argon gas rather than liquid nitrogen. Argon, taking advantage of the Joule-Thompson effect, provides a faster cooling of the cryoprobe (figure 5) which significantly speeds up the treatment and makes easier the sequential control of freeze-thaw cycles

(thawing is achieved by helium). Multiple cryoprobes, each with embedded thermocouple for temperature monitoring, allow for large tumor ablation as in liver.

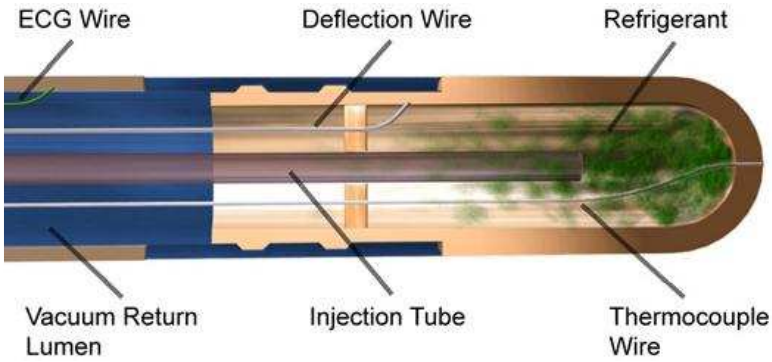


Figure 5. Cryotherapy device. The tip thermocouples offer a temperature feedback that allows controlling the flow of refrigerant delivery (*Medtronic & CryoCath*).

Conventional radiotherapy with photon beams (X-rays) is the main technique and the gold standard reference for cancer treatment. Incremental improvements have been made in the 70's and 80's with the access to imaging modalities leading to better plan and compute radiation dose by taking into account the different tissue attenuations. Advances have also been seen with *3D-conformal* and *intensity modulated radiation therapies* (IMRT) in order to limit the irradiation of healthy tissues, the main concern of all physical therapies as we have seen before. By conforming the dose to the target shape, a higher concentration can be achieved while minimizing the impact on the selected normal tissues. IMRT makes use of 6-10 beams, coplanar or non-coplanar, their intensity being varied across the irradiation field by means of computer controlled collimators ("multileaf collimators"). Conformal dose distribution can be improved through recent advanced techniques such as Volumetric Modulated Arc Therapy (VMAT) where the target is continuously irradiated while the source of the beam is rotated around the patient in single or multiple arcs. Sophisticated simulation planning programs (e.g. inverse problem) have been or have still to be developed to optimize the dose delivery. External beam therapy includes *Gamma knife* and more recently the fully robotized *Cyber knife* (figure 6 and 7) (Goetsch, Murphy et al. 1999; Andrews, Bednarz et al. 2006). *Hadrontherapy* is a new technique, also external, based on non-elementary particles (Levin, Kooy et al. 2005). However, an alternative is represented by *brachytherapy* (also known as *curietherapy*) where radioactive sources are placed inside or near the area to be treated.

Most of them are today combined with radiotherapy techniques leading to the concept of "*multimodal therapy*". The motivations can be to make use either of their different advantages and effects, or to face a failure of the first applied therapy (some evidence supports the consideration of cryotherapy and HiFU after external-beam radiotherapy, for instance). The multimodal therapy is similar to that known in medical imaging for a while. In such case, registration issues, so fundamental in medical robotics, are of concern. As with any other treatment for cancer, appropriate patient selection is critical and determines the outcome.

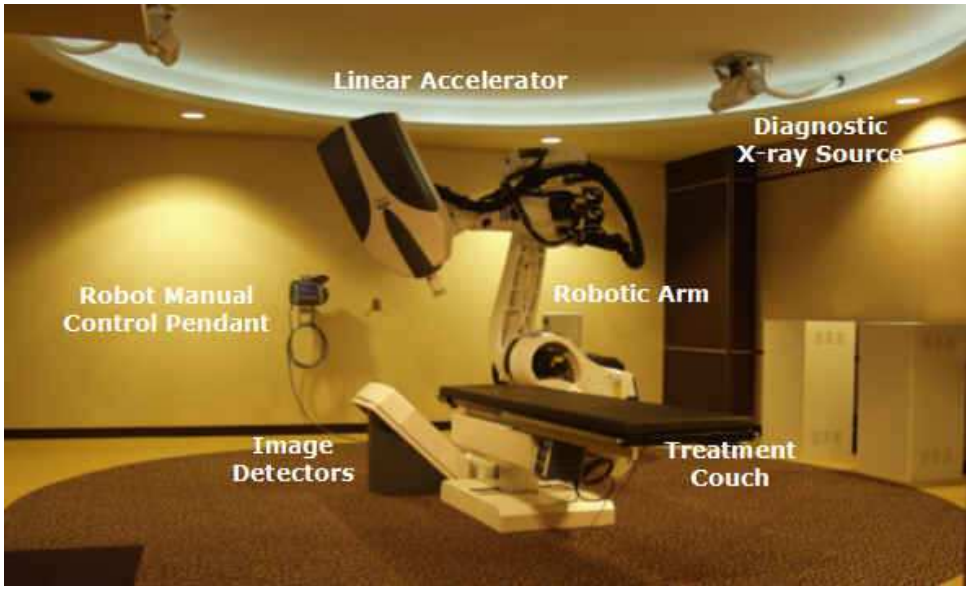


Figure 6. The Cyberknife in the treatment room set-up, based on a Kuka robot (*Accuray Company*).

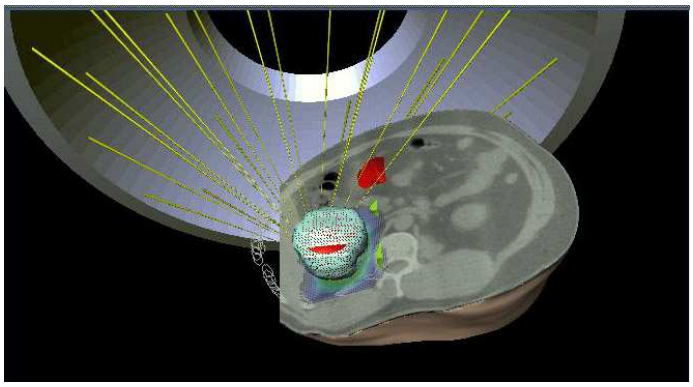


Figure 7. Illustration of treatment planning and simulation for Rotational Gamma System (*Courtesy LIST, SouthEast Univ., China*). Simulation for treatment of a abdominal lesion.

Medical robotics, Computer Assisted Surgery (CAS), Image-Guided Therapy (IGT) emerged more than 20 years ago and it must be recognized that many advances have been made (figure 7). Researchers in robotics, computer vision and graphics, electronics, mechanics, biomedical engineers, physicians and surgeons have been involved, thus demonstrating the enthusiasm for this field. Their commitments emphasize the transdisciplinary nature of the efforts to be made. However, the effective dissemination of CAS-IGT systems in medical disciplines remains limited. Two major trends have been in fact observed over the two last decades. The first one is related to computer-assisted surgery or image-guided therapy, which can be considered as “technology-driven” and the second one is due to innovations coming from clinicians that are identified under the names of “minimal access therapy” (MAT), “minimally invasive surgery” (MIS) or “minimally intervention therapy” (MIT). They have many aspects in common that have been already stated in the 80’s (Lavallée, Cinquin et al. 1997; Taylor and Stoianovici 2003; Peters 2006).

Figure 8. The pioneering robot, IGOR, designed by S Lavallée and P Cinquin, TIMC, in 1989, for brain biopsy (stereotactic frame on the left, robot arm on the right, with X-ray guidance of the needle, middle)

The range of image-guided therapies is very large. If the early applications dealt with biopsy, especially needle targeting for brain lesions in stereotactic conditions (figure 8), they quickly addressed the fields of orthopaedics (joint replacement) and more recently cancer treatment (i.e. prostate brachytherapy) and cardiology (such as mitral valve repair). A recent survey is provided by J Troccaz (Troccaz 2009) where three main periods are sketched: (i) accurate positioning tasks, carried out by a robot using numerical data with main applications in neurosurgery and orthopaedics for simple trajectories and rigid structures (1985-1995) ; (2) interactive schemes for more complex interventions (endoscopic surgery for instance) dealing with deformable tissues (1990-2005); (3) miniaturized robots (from 2000 and up) capable to perceive, communicate and act inside the human body.

4. Proof of performance for patient benefits assessment

The temptation to cut the body in parts is not new. If we look at the past decades, it is striking to see the focus given to the left ventricle of the heart like if the other parts could be neglected when diagnosing the cardiac disorders. The same comment applies to the physicians who rely more and more on technology while loosing the overall picture of the patient. Of course, such reduction can be observed in other sciences and especially in biology where the efforts have been concentrated on genomics. It takes time to understand that each entity interplay with others and that the whole behavior must be apprehended. The Virtual Physiological Human, following The Physiome initiative, is an attempt to inverse our views and complements this way the trend observed with Systems Biology. Modeling and simulation become key elements here. They have several major interests when established: less animal studies, personalized care, predictive value. Such approach is however confronted to new challenges: *how to get the observations required to validate the models? What can be stated on healthy persons for whom measurements are sparse?*

In fact, if we limit our objectives to patients, data can only be partially collected. We would like to have a full view of the organs under study, not only through the imaging modalities but also all electrophysiological, chemical,... signals that may bring relevant information to model, diagnose and care. But what can be done is ethically constrained and economically expensive. Only partial observations can be acquired and subsequently partial validation can be performed.

Let us take a concrete example: the on-going euHeart project (Ecabert and Smith 2008). Its aim is to integrate ICT tools and integrative multi-scale computational models of the heart in order to improve diagnosis, treatment planning and interventions for cardiovascular diseases (CVD). The optimization of the pose of implantable devices in heart failure is one of its objectives. The importance of multi-scale

modeling spanning sub-cellular level up to whole heart has been emphasized in many papers (Coatrieux and Bassingthwaighte 2006). It allows designing a coherent, biophysically-based framework for the integration of the huge amount of fragmented and inhomogeneous data and knowledge currently available. There is no doubt that new insights will be brought in the understanding of the fluid-electro-mechanical features of the heart via multi-scale and multi-physics cardiovascular models. They will be publicly available and re-use due to the standards used such as CellML and FieldML. In addition, euHeart will offer a library of innovative tools for the execution of the biophysical simulations, the personalization of the models and the automated analysis of multi-modal images. Therapeutic impacts are planned for heart failure through cardiac resynchronization therapy, cardiac rhythm disorder through radiofrequency ablation, heart failure through congenital cardiac surgery and left ventricular assist devices, coronary artery disease through revascularization using coronary stents, diagnosis and treatment of valvular and aortic diseases.

However, the demonstration that such approach will really be translated into clinical environments remains to be done and obliges, to build and validate the models, to access to the electrical processes by means of intra-ventricular mapping (figure 8). Such invasive technique will increase not only the duration of the patient examination but also the risk for the patient. These observations will be carried out at a macro-level and micro-mechanisms will be missed for which the only way to proceed should be based on an extrapolation of *a priori* cellular knowledge. Thus, multilevel modeling will require years of efforts

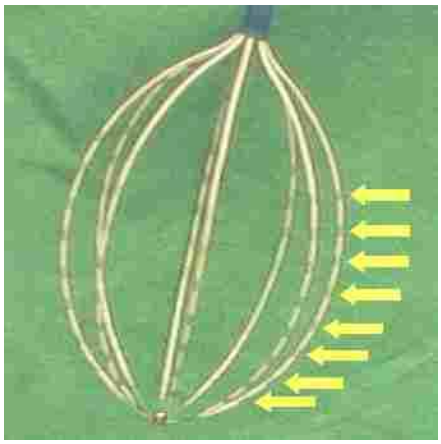
a.  b. 

Figure 8. 3D contact and non-contact endocardial mapping

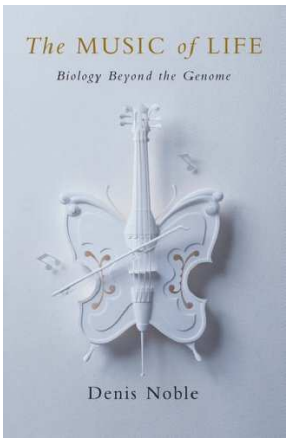
and new devices capable to explore on a multimodal way several structural scales are still to be designed. Scales has not only to be defined in space but also over time. This last aspect is poorly addressed up to now but needs to be because instantaneous observations will never be enough to render the long-term installation of pathological processes or the slow phenomena that may exist between physiological entities.

In all cases, more clinical, multi-centre and comparative trials are needed. Providing the proof of added-value with respect to the current state-of-the-art and patient benefits assessment are necessary (care efficiency**,** less invasive intervention**,** reduction of complication risk and of intervention length, less trauma to the patient, lower recovery time with improvements in action accuracy, decreased irradiation for the medical personnel, etc.). This is perhaps the major question to be answered. It will be even more acute with the new physical therapies which are in progress (Haigron, Dillenseger et al. 2010). Drug delivery activated by heat, ultrasound or light belongs to these new attempts. Several factors in fact limit the molecular target therapies among which the high fluid pressure, the balance to make between delivery, determined by perfusion, and accumulation, resulting from permeability. The molecular size of the agent has of course also a major role. The first way to improve this process consists to modify the drug in order to facilitate the accumulation at the target site. It may be performed for instance by adding a carrier vehicle encapsulating the molecule (liposomes, nanoparticles or polymers). An alternative is to modify the

physiological conditions of the tumor in order to decrease its resistance to accumulation and increase the perfusion. Dual monitoring low hyperthermia and drug deposit for this purpose is a sound and challenging way to do that. If some imaging agent (e.g. probe) is added, tracking the delivery becomes effective. In short, five components represented by a chemotherapeutic drug, a drug delivery vehicle, an imaging agent suited for MRI, PET, ultrasound, optical imaging, etc. together with an appropriate activation mean, define the next breakthrough to be accomplished. Radiofrequency, microwave, ultrasound and light are of interest to boost and control intracellular drug delivery. The major impact on cancer treatment that can be expected explains the many studies presently conducted on thermosensitive liposomes for example.

5. Conclusion

To summarize, imaging is only one part of the story. Although it has a central role in diagnosis and therapy, its fast evolution brings to us specific concerns regarding the performance of any image analysis method. Sensors remain the key players. Modeling and simulation will take a major place in the future as far as they demonstrate their capability to reach clinical needs. We have also to put more efforts on new therapeutic techniques, the current ones being still far to fulfill the patient needs. The next breakthroughs are based on the close association between imaging agents, drugs and some stimulation technique. New probe and transducer design, device miniaturization through MEMS technology will converge with the parallel evolution of medical robots, imaging modalities and drug delivery advances. Almost all, if not all, physical therapeutic systems described here are basically image-guided and can be merged into the medical robot frame. Dual sensing and actuating (or activating) devices are in progress, and even if there is a long way from the initial concepts to clinical applications (with inherent quality control and traceability), the trend toward more efficient, less invasive care will support the efforts made in the field. The advances that have been briefly reviewed here show that what we consider true today may be false tomorrow. So, everything in science is relative and this is exciting. The reader should read to Noble's book, a previous lecturer of the IEEE EMBS Summer School, which gives sense to this adventure.



6. References

Andrews, D. W., G. Bednarz, et al. (2006). "A review of 3 current radiosurgery systems." Surg Neurol **66**(6): 559-64.

Aubry, J. F., M. Tanter, et al. (2003). "Experimental demonstration of noninvasive transskull adaptive focusing based on prior computed tomography scans." J Acoust Soc Am **113**(1): 84-93.

Bertram, J. M., D. Yang, et al. (2006). "A review of coaxial-based interstitial antennas for hepatic microwave ablation." Crit Rev Biomed Eng **34**(3): 187-213.

Bouchoux, G., C. Lafon, et al. (2008). "Dual-mode ultrasound transducer for image-guided interstitial thermal therapy." Ultrasound Med Biol **34**(4): 607-16.

Coatrieux, J.-L. and J. Bassingthwaighte (2006). "Special Issue on The Physiome and Beyond." Proc IEEE **94**(4): 671-677.

Ecabert, O. and N. Smith (2008). "Matters of the heart." The Parliament Research Review **7**.

Goetsch, S. J., B. D. Murphy, et al. (1999). "Physics of rotating gamma systems for stereotactic radiosurgery." Int J Radiat Oncol Biol Phys **43**(3): 689-96.

Haigron, P., J.-L. Dillenseger, et al. (2010). "Image-guided therapy: evolution and breakthrough." IEEE Eng Med Biol Mag **29**(1): 100-4.

Haigron, P., L. Luo, et al. (2009). "Issues in image-guided therapy." IEEE Eng Med Biol Mag **28**(4): 96-8.

Lavallée, S., P. Cinquin, et al. (1997). Computer Integrated Surgery and Therapy: State of the Art. Contemporary Perspectives in Three-Dimensional Biomedical Imaging. C. Roux and J. L. Coatrieux. Amsterdam, IOS Press**:** 239-310.

Levin, W. P., H. Kooy, et al. (2005). "Proton beam therapy." Br J Cancer **93**(8): 849-54.

Ni, Y., S. Mulier, et al. (2005). "A review of the general aspects of radiofrequency ablation." Abdom Imaging **30**(4): 381-400.

O'Rourke, A. P., D. Haemmerich, et al. (2007). "Current status of liver tumor ablation devices." Expert Rev Med Devices **4**(4): 523-37.

Peters, T. M. (2006). "Image-guidance for surgical procedures." Phys Med Biol **51**(4): 505-540.

Schindl, A., M. Schindl, et al. (2000). "Low-intensity laser therapy: a review." J Investig Med **48**(5): 312-26.

Seifert, J. K. and D. L. Morris (1999). "World survey on the complications of hepatic and prostate cryotherapy." World J Surg **23**(2): 109-13; discussion 113-4.

Tanter, M., M. Pernot, et al. (2007). "Compensating for bone interfaces and respiratory motion in high-intensity focused ultrasound." Int J Hyperthermia **23**(2): 141-51.

Tanter, M., J. L. Thomas, et al. (1998). "Focusing and steering through absorbing and aberrating layers: application to ultrasonic propagation through the skull." J Acoust Soc Am **103**(5 Pt 1): 2403-10.

Taylor, R. H. and D. Stoianovici (2003). "Medical robotics in computer-integrated surgery." IEEE Trans Robot Automat **19**(5): 765-781.

Troccaz, J. (2009). Computer- and robot-assisted Medical Intervention. Handbook of Automation. S. Nof. Berlin, Springer 1451-1466.