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The Futures of Biomedical Imaging

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Abstract

This introductory chapter does not pretend to give a full overview of the biomedical field but some ideas about 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 also attempts to show the rationale behind the scientific program set for this summer school edition by pointing toward the lectures that will be given.

1 Introduction

Quoting Elias Zerhouni, during his keynote address of the 2007 IEEE International Symposium on Biomedical Imaging of April 12, in Washington DC, "Biomedical Imaging is the science of extracting spatially and temporally resolved biological information at all physical scales." It is a highly multidisciplinary field at the crossroads of many scientific disciplines including physics, chemistry, physiology, biology, engineering, computer science, etc. It is characterized by an important fragmentation from various viewpoints whether in terms of imaging modality, clinical interest, biological and medical targets, etc.

It is also a fast evolving field with driving forces coming again from various disciplines. The first advances in this field were pushed by fundamental discoveries in Physics which, added to the engineering contribution, has given raise to the development of technologies that have had and still have a major impact in clinics. In parallel, Chemistry has also profoundly contributed to the improvement of the performances of medical imaging systems in terms of sensitivity and specificity. Biology can be seen as another important area that interacts with Medical Imaging, and the genomics revolution poses new questions to biomedical image engineering. Many theoretical problems, among which inverse problems are the most frequent in the imaging community, have been solved thanks to Applied Mathematics. In addition, Information and Communication Technology is an active engineering area which is at the origin of numerous technical achievements in Biomedical Imaging.

Last but not least, clinical applications and biological needs are also part of the driving forces of this widely expanding area. After the analysis of the background of biomedical Imaging, this paper briefly surveys some recent evolutions and breakthroughs in medical imaging field and tries to highlight some prospective areas that future research may explore in the next decade.

2 Recent evolution

2.1 Breakthroughs coming from Physics and Chemistry

Many famous scientists from various disciplines have paved the way to contemporary biological and medical imaging technology since the discovery of X-Rays by Roentgen in 1895. For instance, Cormack and Hounsfield, and Lauterbur and Mansfield have been awarded the Nobel Prize in Medicine for their pioneering work on respectively X-ray Computed Tomography scanner and on Magnetic Resonance Imaging.

Here, we will not review the history of biomedical imaging. Instead, we will limit ourselves to mention three recent developments coming from the physics field that are just about to bring disruptive technologies to the biological labs and to the clinical imaging departments. In a second step, the outcome coming from chemistry will be discussed in more general terms. It must be emphasized however that, before getting images, a reconstruction process represents a key component in place. This issue will be surveyed by Frank Natterer in tomography. He will start from the Kaczmarz method for the linear case and then show how to handle nonlinear problems that are governed by partial differential equations, such as impedance tomography, diffuse tomography, and wave equation imaging. Mathews Jacob, the junior lecturer, will provide nice complements to these talks.

2.1.1 Diffusion MRI

Diffusion MRI has been introduced in the early 1990 [Le Bihan, 1991] [Basser, 1994]. This modality measures the random thermal displacement, i.e . Browian motion, of molecules in tissue, typically water molecules. Two aspects of Diffusion MRI render the modality very powerful. First, the microscopic lengthscale of water diffusion in tissue gives DT imaging microscopic spatial sensitivity. Second, in fibrous tissues, such as cerebral white matter or organized gray matter, the diffusion is anisotropic, that is, orientation dependent. The orientation dependence of the diffusion signal enables DT imaging to measure the fiber orientation within each voxel of the image.

More specifically, in the latter case of anisotropic, orientation-dependent diffusion, the diffusion is described through the diffusion tensor. The direction of greatest diffusion is given by the principal eigenvector of the diffusion tensor. As the direction of greatest diffusion, the principal eigenvector parallels the local fiber direction within each voxel. The principal eigenvector maps, which display the fiber orientation, can be visualized as vector-field or color coded maps. To visualize the fiber direction map in the context of a conventional structural image, the fiber map can be registered and superimposed on a structural image, such as a high-resolution T1-weighted MR image.

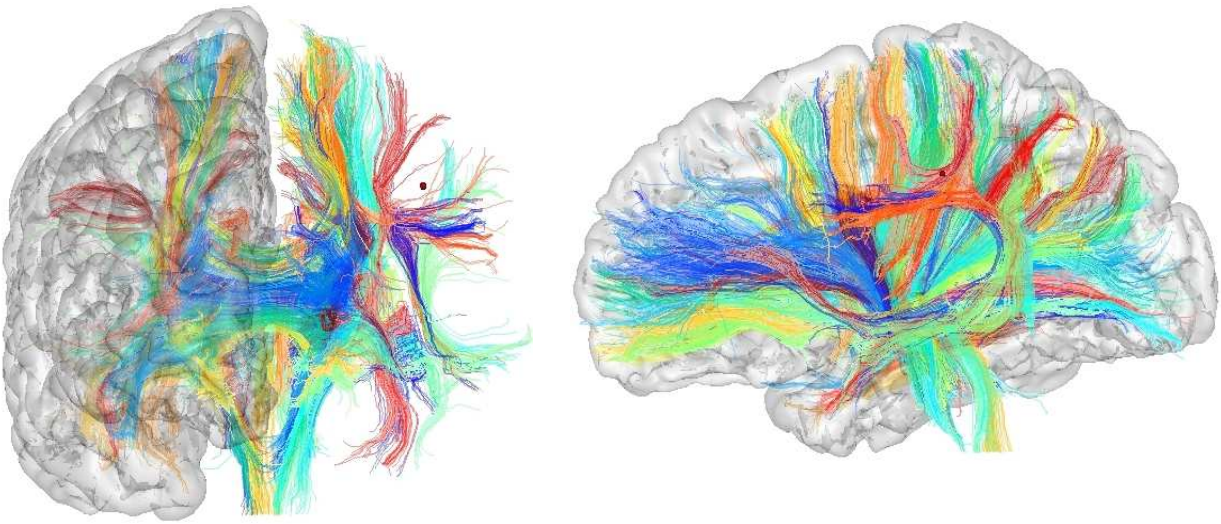

Figure 1. Water diffusion in tissues is anisotropic. As a consequence, using echo-planar MRI sequences along with 6 diffusion gradients, it is possible to obtain diffusion tensor images containing the directional information. Because of the anisotropy of water diffusion in brain white matter, it is possible to determine for each voxel of the image the direction in space of the fibers. The voxels can then be connected to produce color coded images of the possible white matter tracts. (Images courtesy of Y. Cointepas, M. Perrin and D. Le Bihan, SHFJ/CEA, France.)

Since its introduction, the technique has generated a tremendous amount of interest as it allows for studies to understand brain connectivity as its makes it possible to address both structural and functional aspects [Le Bihan, 2007]. In addition, temporal response of diffusion MRI is another powerful tool to study dynamic behavior and properties of the brain. For instance, temporal responses in the visual cortex can be measured by diffusion fMRI without showing delays as important as those

obtained using the standard BOLD protocol. Diffusion MRI can also be used in cancer as the produced images show areas that correspond to regions where the water diffusion coefficient is decreased. Such regions have been shown to correspond to areas where malignant cells are present.

Figure 2. Diffusion MRI in cancer. Colored areas correspond to regions where the water diffusion coefficient is decreased. Such regions have been shown to match areas where malignant cells are present (primary lesion or metastases). Image courtesy of Dr. Koyama (Radiology Department, Kyoto University, Graduate School of Medicine, Kyoto, Japan).

The trend toward high magnetic field, illustrated in France by the Neurospin project, does not mean that other areas are not developing fast. An example is brought by the research conducted on MRI real-time temperature mapping for the control of thermal therapies that will be presented by Chrit Moonen. High Intensity Focused Ultrasound techniques (HIFU), for instance, offer today an attractive alternative or complement to other classical therapies like radiotherapy or curietherapy, with applications going to prostate to liver cancer. However, to be fully optimized, they need a coupling (i.e to build a real-time closed-loop system) with a measure of temperature in order to guarantee the tissue death without damaging the surrounding tissues. If available, then the pre-operative planning can be adapted on-line.

2.1.2 From Microscopy to Nanoscopy

In optical imaging, it is well known that spatial resolution of an objective lens is related to the size of the focal spot, the smaller, the better! Ernst Abbe discovered that the focal spot size decreases with the microscope's aperture angle i.e. with the size of the spherical wavefront that is produced by the objective lens. But a regular objective lens, even of the largest aperture, produces just a segment of a spherical wavefront coming from a single direction. As a result the focal spot is longer (z) than wide (x,y) By contrast, a full spherical wavefront of a solid angle of 4π would lead to a spherical spot and hence to an improvement of spatial resolution in the z-direction.

The solution found by Stefan Hell [Hell, 2006] to overcome this physical intrinsic limitation is to use two opposing objective lens coherently to produce a focal spot sharper in the z direction by about 5 to 7 times. To get even closer to the ideal 4π spherical wavefront, linear filtering is used to perform a deconvolution which produces an even sharper spot. This is a typical example that shows how powerful combinations of physics and image processing are.

The idea developed by Hell and his team [Schrader, 1996], [Dyba, 2002], [Egner, 2002] is as follow. Since there are no lenses or mirrors that could provide such a wavefront across a significantly large field of view, the idea behind their 4π -microscope (Figure 3) is to mimic the 'close to ideal' situation by using two opposing objective lenses coherently, so that the two wavefronts add up and join forces. The sketch in Figure 3 gives an idea about the optical setup - although modern versions are more sophisticated.

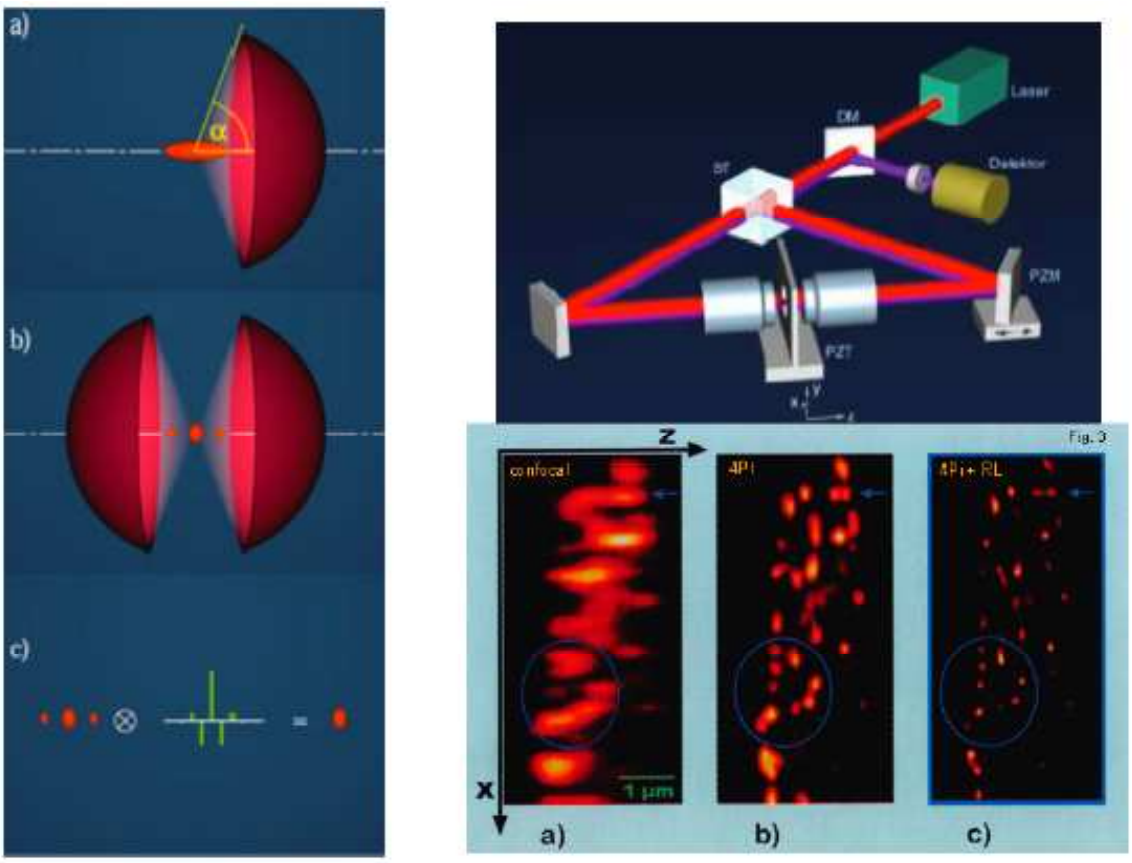

Figure 3. By combining 4π-microscopy with image restoration, an axial resolution of 30 nm is reliably achieved. Images courtesy of Hell.

If the two segments were full spherical halves, the focal spot would be a (nearly) spherical spot, too. But since a considerable solid angle is not provided by the lenses, interference typically spawns off 2 axial side-lobes which, if not taken into account, lead to artefacted images. This challenge is dealt with by an appropriate image filter. This filter does not require any information about the object, apart from the height and location of the lobes. Linear filtering is possible if the lobes are significantly less than 50% of the main sharp maximum. This can be reliably fulfilled if multiphoton excitation of the dye is applied. Linear mathematical filtering is fast and a single effective spot is readily achieved. The obtained images show the improvement in terms of resolution that reached now 33 nm compared to standard microscopic techniques. Microscopy is becoming Nanoscopy!

Last, 4π -microscopy has recently been implemented as a fast CCD-based, beam scanning, multifocal multiphoton microscope, so that image acquisition time was cut down to about 1 second/slice. In addition the method was refined for later immersion. As a result, and using more sophisticated non linear restoration tools, this microscopy technique delivered for the first time 3D-images of live cells in the 100 nm range.

Micro-nano technologies (especially NEMS devices, i.e Nano-Electro-Mechanical-Systems) and information processing applied to proteomic analysis with high sensitivity will be introduced by Pierre Grangeat. He will described the last achievements made in CEA-LETI on Mass Spectrometry and microfluidic techniques to detect a set of proteins and their isoforms.

2.1.3 Supersonic shear imaging and multi-wave imaging.

Acoustics is a domain of physics that has produced important technologies including the well known echographic and Doppler imaging modalities. More recently, a great deal of effort has been directed toward elastography, a technique that represents the electronic version of the palpation procedure performed by hand by physicians. This innovative imaging modality is based on a multi-wave approach. Among the various methods proposed, the coupling of an ultrafast echographic imaging

system with a low frequency vibration to allow for imaging Young modulus of biological tissues which is characteristic of their pathological nature (e.g. carcinomas can be as much as thirty times harder than their surrounding healthy tissues) is a promising avenue explored by M. Fink and his team [Bercoff, 2004].

It is indeed a quantitative palpation technique based on 2D and soon 3D imaging. The low frequency shear wave (the "push" wave) induces tissue displacements measures through ultrafast echographic imaging (the "imaging" wave) allowing to compare two by two images in the sequence by the way of correlation which give the estimation of local movements induced by the mechanical solicitation (Figure 4). Acquisition time is typically about 20 ms and imaging is performed at a time rate of 5.000 images per second.

In fact the low frequency shear wave, initially produced by a vibrator, can be produced by a series of focalized ultrasound waves at different depth, allowing for more flexibility avoiding shadow areas, which gives the echographist to target virtually any internal tissue. In addition, by creating several shear waves simultaneously at different locations has been shown to produce a shear source moving at supersonic speed. This shear source generates two planar waves propagating in a Mach cone inside the organs. Indeed this is analogous to the sound barrier for the elastic shear waves created by a supersonic plane.

The conical shear wave propagating in the tissues is deformed by the heterogeneity of the local shear properties, as we can see here on a phantom experiment where a circular inclusion harder that its surrounding has been created provoking a deformation of the conical wave during its propagation through the inclusion. The reconstruction of the map of the shear modulus is presented here superimposed to the echographic image long with the scale of this parameter allowing for quantitative analysis.

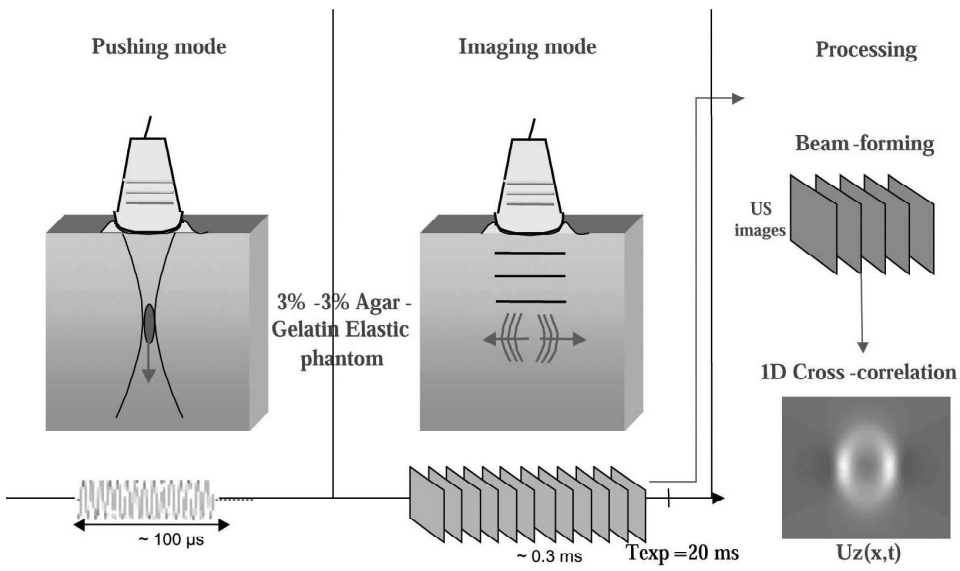

Figure 4. Instrumentation principle of super sonic imaging. It is based on a multi-wave principle composed of a "pushing" shear wave (left) an imaging wave, an ultrafast "imaging" wave of the shear wave displacement induced by the force at a typical frame rate of 5.000 images per second, and a post processing step involving time reversal techniques, beam forming and cross correlation

Initial clinical trials on patients with breast cancer show the complementarities of this technique with the gold standard mammography. It has also to be pointed out that this ultrasound technology compares very favorably with other approaches based on MRI elastography in terms of cost, which could lead to its rapid diffusion among radiologists whether in hospitals or not.

2.1.4 Breakthroughs coming from chemistry

Chemistry provides various imaging probes that allow for visualization of specific targets non-invasively in living subjects.

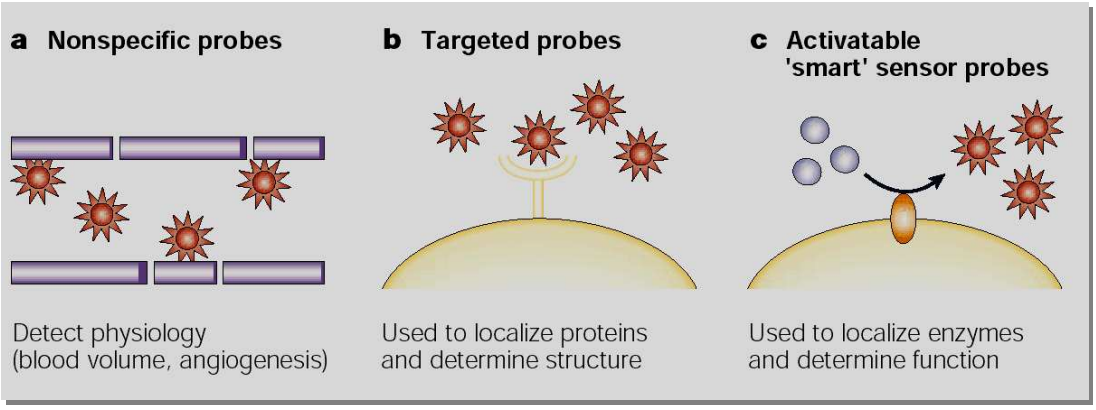

Figure 5. The three categories of imaging probes

In general, imaging probes can be categorized into three main groups: nonspecific, targeted, and activable probes [Hengerer, 2005]. Nonspecific probes, currently the most commonly used imaging probes in radiology, do not interact with a specific molecular target. They accentuate dissimilarities between tissues such as differences in permeability or perfusion. These probes are helpful to characterize physiological processes such as blood volume, flow, or perfusion, changes of which occur rather late in disease processes.

Targeted probes are used to localize bio-molecules and to reveal their distribution, gaining structural information. Such probes are detectable regardless of their interaction with the target. As a consequence background noise can be fairly high.

Activable or “smart” sensor probes do not give a signal in their native injected state (silent probe), but become detectable only after activation by the target. Therefore the signal-to-noise ratio is significantly enhanced.

2.2 Breakthroughs coming from Biology

The past decade has seen an immense growth of knowledge in the field of molecular biology and related areas. The completion of the human genome project gives us an opportunity to better understand the function of genes and proteins and their role in disease processes. The exact number of genes encoded by the human genome is still unknown. Latest analyses suggest that there might be only 24.500 or fewer protein-coding genes, much less than previous estimates of approximately 100.000 genes. Genetic tests have been among the first commercial translation of these discoveries. They can be used to diagnose diseases even before symptoms occur, provide prognostic information, and predict disease in progeny. However, they will not provide location or extent-of-involvement information. (Molecular) imaging will be necessary to add spatial localization to identified abnormalities. For example, identifying the presence of a lesion through a genetic test will immediately require pinpointing the lesion for intervention.

Some of the genetic markers will provide suitable imaging targets as well. As our understanding of genomics and molecular biology grows, the number of possible probes and potential applications also rises. There are hundreds of molecular imaging targets and probes currently under development. The predominant probe, as well as the most appropriate imaging modality for any clinical application, will be determined by efficiency, patient workflow compatibility, and reimbursement.

Besides generating novel targets for diagnostic imaging, discoveries in genomic and molecular biology present new questions. Some of these might be answered by molecular imaging. The analysis of protein interactions that are encoded within the genome is the focus of proteomics. Each of the

thousands of proteins in the human body is attributed with up to 50 different functions and is involved in numerous complex interactions. Molecular imaging is also a valuable tool to study and reveal these molecular networks and their dysfunction in pathogenesis, since it allows repeated examination of molecular processes within a living organism.

In addition, functional genomics, which studies gene expression patterns as a response of an individual to his or her overall environment, can be investigated by linking the expression of endogeneous genes to reporter genes such as green fluorescent protein (GFP) or its derivatives. Similar concepts can be applied for imaging the sequence and timing of an organism's development in embryogenesis. In recent years imaging has been used to follow development of organisms, from simple *Xenopus* embryos to more complex mice.

2.3 Breakthroughs coming from ICT

Computational modeling and information technology in biology and medicine is becoming to have a major role in the interdisciplinary attempt to elucidate functions of living systems and structure-to-function inter-relations. The recursion between description levels, at all space and time scales, for highly dynamical, interacting and complex systems, i.e. the integrative approach, is a very challenging topic where formal models, observational tools and experimental investigations have to be closely designed and confronted together.

Physics, chemistry, applied mathematics and engineering science are all needed to design relevant biological and physiological models. The targets range from molecules, genes, proteins, cells, substructures, organs and systems up to whole organisms. The understanding of their biological or patho-physiological behaviors is first challenged by the intrinsically complexity to deal with and to the fact that a number of mechanisms are still ill-understood. The elucidation of the inter-level processes relies on structural and functional information: the capabilities to extract, quantify and interpret the information directly impact the possibility to build quantitative models to describe the relationships, to verify and validate such models, and to maintain them as relevant approaches and as testable working hypotheses.

Modeling can be seen as a major tool in order to integrate knowledge, to drive experiments, to optimize measurements in biological and clinical research. A key objective behind modeling is also, by determining the deviations of model parameters in pathological states from their normal behaviors, is to conjecture the reverse process, in other words, to derive ways to go back from abnormal to normal states (figure 6). Coupling multimodal, multilevel and multi-scale models are among the most challenging problems to address.

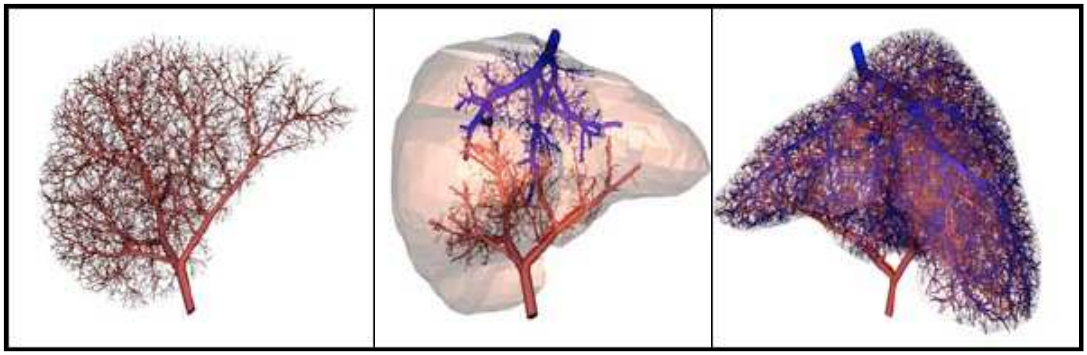

Figure 6. Model of the vascular trees of the liver [Kretowski, 2003]

The acquisition systems give accurate 3D information and the quantitative analysis of three-dimensional (3-D) shapes in terms of morphology and functionality is one of the most challenging problems in medical image analysis. Jacq and Roux [Jacq, 2003] propose a general methodology that aims at solving part of this problem. They introduce a nonparametric hierarchical partitioning approach that operates on any arbitrary 3-D shape described as a triangle mesh. They first extend the concept of basin districts to the case of curved spaces through a partitioning process on a valuation

representing the main curvatures over a polyhedral support. A hierarchical construction of basin districts is obtained from a watershed transform. The speed of the front propagation on the polyhedral surface is controlled by the local characteristics of the surface geometry. As a prerequisite, a set of co-processing tools has been developed that operates directly on a triangulated domain. This includes classical signal processing tasks (e.g., re-sampling, filtering) on a polyhedral support performing a trade-off between accuracy and efficiency. The ability to provide an intrinsic shape partition from any triangular mesh is useful in a wide range of applications from accurate geometric modeling, and hierarchical shape dissection to robust mesh compression.

Having obtained the geometric support of the information, the following step is to solve the problem of the robust registration of multiple observations of the same object. Such a problem typically arises whenever it becomes necessary to recover the trajectory of an evolving object observed through standard 3-D medical imaging techniques. The instances of the tracked object are assumed to be variously truncated, locally subject to morphological evolutions throughout the sequence, and imprinted with significant segmentation errors as well as significant noise perturbations. The algorithm, proposed by Jacq and al. [Jacq, 2008], operates through the robust and simultaneous registration of all surface instances of a given object through median consensus. This operation consists of two interwoven processes set up to work in close collaboration. The first one progressively generates a median and implicit shape computed with respect to current estimations of the registration transformations, while the other refines these transformations with respect to the current estimation of their median shape. When compared with standard robust techniques, tests reveal significant improvements, both in robustness and precision. The algorithm is based on widely-used techniques, and proves highly effective while offering great flexibility of utilization.

Both following examples show that mathematics and especially the probabilities theory are essential in the image segmentation.
The wavelets theory can be efficient to automatically detect microaneurysms in retina photographs. Microaneurysms are the most frequent and usually the first lesions to appear as a consequence of diabetic retinopathy. So, their detection is necessary for both screening and following up the pathology. Automating this task, currently performed manually, would bring more objectivity and reproducibility. Quellec et al. [Quellec, 08] propose to detect them by matching locally a lesion template in sub-bands of wavelet transformed images. To improve the method performance, they have searched for the best adapted wavelet within the lifting scheme framework. The optimization process is based on a genetic algorithm followed by a Powell's direction set descent. Results are evaluated on 120 manually segmented retinal images and the optimal wavelet is compared to different conventional mother wavelets.

Accurate volume estimation in PET is crucial for different oncology applications. Unfortunately, the contrast and noise give images very difficult to segment. In [Hatt 2008], the authors develop a new fuzzy locally adaptive bayesian (FLAB) segmentation for automatic lesion volume delineation. FLAB was compared with a threshold approach as well as the previously proposed fuzzy hidden Markov chains (FHMC) and the Fuzzy C-Means (FCM) algorithms. The performance of the algorithms was assessed on acquired datasets of the IEC phantom, covering a range of spherical lesion sizes (10-37mm), contrast ratios (4:1 and 8:1), noise levels (1, 2 and 5 min acquisitions) and voxel sizes (8mm3 and 64mm3). In addition, the performance of the FLAB model was assessed on realistic non-uniform and non-spherical volumes simulated from patient lesions. Results show that FLAB performs better than the other methodologies, particularly for smaller objects. The volume error was 5%-15% for the different sphere sizes (down to 13mm), contrast and image qualities considered, with a high reproducibility (variation <4%). By comparison, the thresholding results were greatly dependent on image contrast and noise, whereas FCM results were less dependent on noise but consistently failed to segment lesions <2cm. In addition, FLAB performed consistently better for lesions <2cm in comparison to the FHMC algorithm. Finally the FLAB model provided errors less than 10% for non-spherical lesions with inhomogeneous activity distributions. Future developments will concentrate on an extension of FLAB in order to allow the segmentation of separate activity distribution regions within the same functional volume as well as a robustness study with respect to different scanners and reconstruction algorithms.

2.4 ICT and Clinical-driven breakthroughs

The knowledge and practice of medicine is actually evolving by the contribution of new exploration and therapies techniques. Several factors can explain this evolution in the medical practice and among them: 1) The integration of several available image technologies allows new exploration and new understanding of simultaneously several aspects of the patient anatomy but also its metabolic functions. 2) The development and the miniaturization of new imaging technologies allow the replacement of older invasive procedures by new more endurable explorations or therapies. 3) The recent introduction of minimally invasive surgery techniques open new pathways. Three examples will be given in order to illustrate these new challenges.

Rapid advances in imaging technology are a challenge for research and health care professionals who must determine how best to enhance or to use these technologies to optimize patient care and outcomes. Hybrid imaging instrumentation which combines existing technologies such as PET and CT, each with its own separate history of engineering advances or clinical evolution, may be especially challenging. For instance, integrated CT/PET provides CT and PET images acquired nearly simultaneously and so produces superimposed, co-registered images with complementary anatomic and functional information [Townsend, 2003],[Hatt, 2008]. Many other integrated combinations are also of concern. Critical issues and concerns regarding image acquisition protocols, processing, supervision and interpretation would need to be addressed in the next future that may change our present viewpoint.

New imaging techniques must also avoid some invasive and painful exploration protocols. For example the advance in biomedical imaging enables non-invasive microscopy scans through the surface of intact organs or body systems. New optical biopsies without removal of tissue are so available (Cellvizio®, MKT Mauna Kea Technologies, http://www.maunakeatech.com/). Optical biopsy refers to the illumination of tissue by light of selected wavelengths and the subsequent spectroscopic analysis of light returning from the tissue to obtain a diagnosis of disease (Figure 7). New imaging techniques lead directly to the development of new image interpretation processing methodology for the diagnosis. On the other hand, over the past year endoscope-compatible photonic methods and instrumentation for in vivo pathological assessment have been explored. The planning and the guidance of these endoscopic optical biopsies are still open questions.

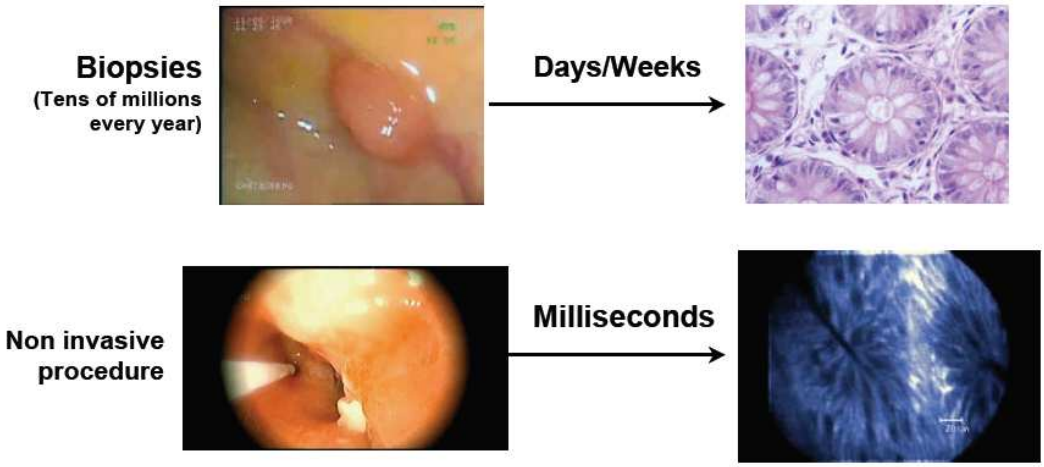

Figure 7. Invasive biopsies versus optical biopsies (credits MKT Manau Kea Technologies)

As an alternative to open surgery, minimally invasive techniques have been introduced for a while based on innovations either coming from surgeons or engineers. They make use of up-to-date technologies and aim at patient-specific therapy or personalized care. Almost all medical disciplines are today concerned: neurosurgery, the first area where computer-assisted techniques have been developed, orthopedics, etc... up to cardiac interventions. The state-of-the-art in this topic will be given by Philippe Cinquin together with the trends that can be expected in a near future with the miniaturization revolution. The image guided intra-operative pose of abdominal aortic endoprostheses is one example of such new interventional procedure (Therenva, http://www.therenva.com). Analytical

or virtual exploration of the patient preoperative volume [Haigron, 2004], [Göksu, 2004] allows delineating the patient specific anatomy within the context of the sizing of the last generation aortic stent-graft. The planning phase can be performed in a simulated virtual environment in order to design the optimal instrument to use, the best gesture to perform and the sequencing of the various phases of the operative plan [Dardenne, 2007]. In the intra-operative phase, the use of matching techniques allows the localization of the tools within the organs for a real-virtual cooperation. The virtual environment contributes also in the intra-operative phase by providing new available information for the guidance of the intervention. Such approach is also of relevance for clinical training (Figure 8).

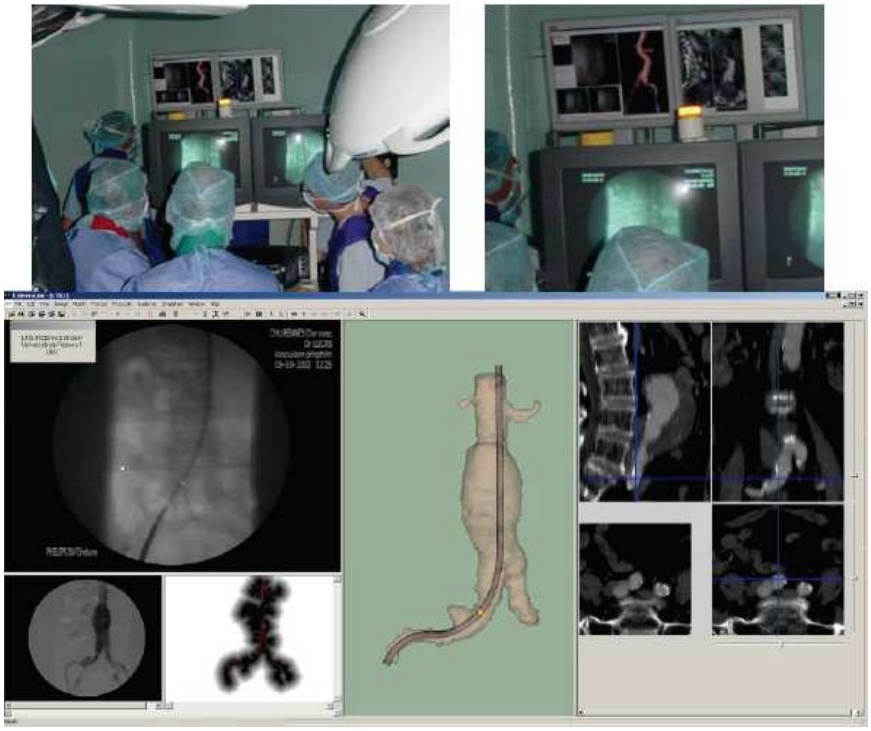

Figure 8. Image guided intra-operative pose of abdominal endoprostheses (credits Therenva)

Whatever the clinical targets, diagnosis or therapy, screening or follow-up, there are at least two issues that must be kept in mind. The first is that we have to design appropriate tools to be used in clinical setting, bringing sound solutions to users. Some of the multiple applications will be highlighted by Roel Truyen under the heading of "Computer Aided Detection". All his examples will point out how they are extremely demanding and how the user involvement is of major importance in our field. Milan Sonka will point out another major topic, cardiovascular image analysis whatever the imaging modality used (i.e intravascular ultrasound, biplane angiography) and will make the link with another recurring issue, segmentation. Solutions here are mandatory for quantitative, objective, accurate and reproducible feature extraction. Multiple methods have brought partial answers over the last 15 years like 3D/4D active shape and active appearance models, total variation, minimal path, etc. As far as we take into account the all situations we have to deal with in medical imaging (noise and artefacts, low contrast, inhomogeneous patterns, blurred boundaries, etc.), fully automatic algorithms fail and some interactive inputs have to be brought by the end-user. A very recent and innovative view has been brought by Yury Boykov with the graph-cut method. The last developments he has made will be reported and also the relationship between this method and the level-set framework.

3 Research trends

3.1 Molecular Imaging

A precise definition of molecular imaging is difficult to formulate. Rather the term reflects a shift in emphasis and a shift in attitude, moving from the diagnostic imaging approaches that are currently employed in the clinic, to targeting specific genes and proteins that are known to be linked directly or indirectly to human disease. Molecular imaging has been around for a while. Fluorescently and radioactively labeled contrast agents that bind to specific proteins, particularly cell-surface receptors,

have been employed for decades in cell culture, tissue slice and autoradiographic studies. These techniques have since migrated to the *in vivo* environment, and, with the advent of nuclear imaging modalities such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), into humans.

What has changed over the last several years, acting as a catalyst for the explosive growth and popularity of molecular imaging, is the extraordinary flow of information regarding the specific genes and proteins involved in disease mechanisms, the sequencing of the human genome and the advent of combinatorial chemistry and mass screening techniques that produce large numbers of candidate molecules that can interact with a particular biological target of interest. In addition, the imaging field has embraced this opportunity by discovering and developing a range of novel approaches for generating protein and gene specific contrast in an image, and through stunning improvements in the imaging technologies themselves, particularly at the level of *in vivo* small-animal imaging. A further catalyst has been the erosion of traditional boundaries that separated physicists, engineers, mathematicians, computer scientists, chemists, cell and molecular biologists and physicians and the establishment, at many leading institutions, of interdisciplinary programs where the imaging sciences and biology are seamlessly integrated.

A highly simplified schematic overview of how molecular and genomic imaging relates to modern biology and conventional diagnostic imaging is presented in Figure 9. The first goal of molecular imaging is to image specific proteins, genes or the biochemical and molecular pathways they are involved in, within intact living subjects. The ultimate goal is to know where specific proteins or genes are expressed in the body, the level at which they are expressed and how that distribution and level changes over time or following an intervention.

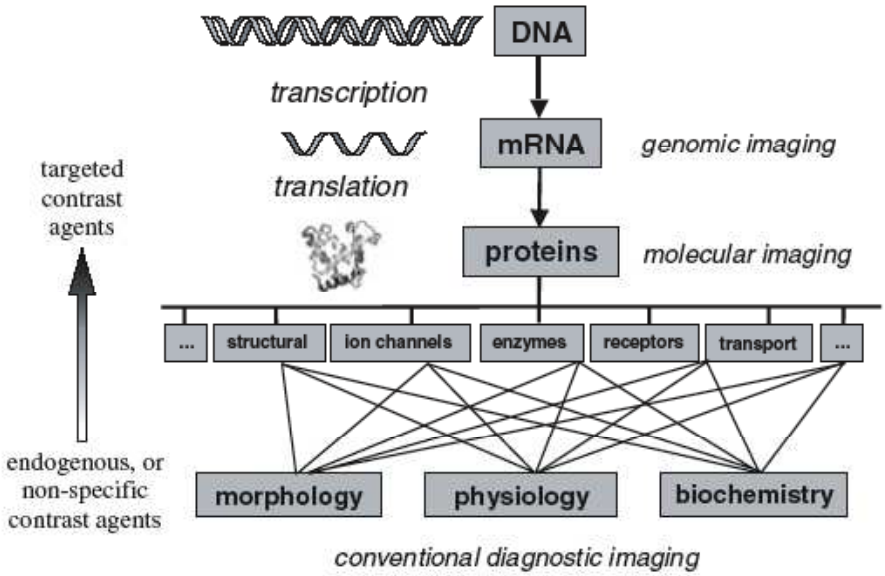

Figure 9. [Cherry, 2004] Schematic representation of molecular and genomic imaging. Conventional diagnostic imaging are modalities that generally visualizes non-specific changes related to morphology (CT, MRI, ultrasound), physiology (MRI, ultrasound, PET, SPECT) or biochemistry (PET, SPECT, MRS) that could be caused by alterations in many different proteins or genes. In molecular imaging, the goal is to image the location and expression levels of specific genes and proteins that are thought to be involved in a particular disease. Targeted contrast agents normally are required to isolate the signal from the gene or protein of interest.

The field of molecular imaging faces a number of critical challenges which it must meet in order to secure a leading role in addressing problems of health and disease in animal models and in humans. One of the major rate-limiting steps is the development of well designed and carefully validated contrast agents that are selective for major molecular pathways implicated in disease. Developing a high-quality contrast or diagnostic imaging agent is not dissimilar from developing a good drug, and therefore partnerships with the pharmaceutical and biotechnology industries, and some integration of drug development with the development of imaging contrast agents, are important.

Another challenge is the transition between the many genes, many proteins environment of high-throughput screening techniques and the one gene or protein capability of most current molecular imaging technologies [Cherry, 2004]. Methods that allow high degrees of multiplexing of protein and/or gene imaging signals *in vivo* would be extremely valuable. Finally, notwithstanding the tremendous promise of these techniques, the translation of molecular imaging methodology into the clinic, and its role in the diagnosis and staging of disease, and the monitoring of therapy, is yet to be defined and demonstrated.

At the imaging system level, many challenges and opportunities remain in molecular imaging. In all modalities there is a need to improve imaging performance, either by increases in spatial or temporal resolution, sensitivity, or commonly both. The ability to accurately quantify molecular imaging studies is of great importance when these tools are used to track disease and the effects of interventions. Attempts to integrate molecular imaging studies, either with software approaches, or by building integrated instrumentation, are still relatively crude and make multi-modality studies difficult and time consuming. There are also many practical challenges associated with the efficient handling, visualization and analysis of the large volumetric datasets produced by many molecular imaging technologies. The field is young enough that there has been little attempt to standardize and cross-validate methods, data acquisition, analysis and image formats between modalities, instruments and centres.

There also has been little characterization of the quantitative accuracy or reproducibility of molecular imaging methods, nor a careful statistical analysis of to what degree longitudinal molecular imaging studies provide an advantage over generally more accurate, but usually much more invasive, methods and techniques. In all these areas, and many more, there are opportunities for biomedical physicists to make significant and important contributions which will help build the solid foundation required for the future anticipated growth of molecular imaging.

3.2 Multilevel imaging

3.2.1 New frontier

The frontier for biomedical imaging is now to produce and deal with data immersed in a huge multidimensional space. The traditional 2D image that is still used daily is just one piece of a more complete set of images that are at hand or that will be available in the future thanks to the new generation of imaging systems. 3D is now routine, 4D is also a need in the observation of moving organs like the heart and the lungs. When using multispectral images, one more dimension is added. In addition, scale whether along time or across space is becoming also a challenge to imaging.

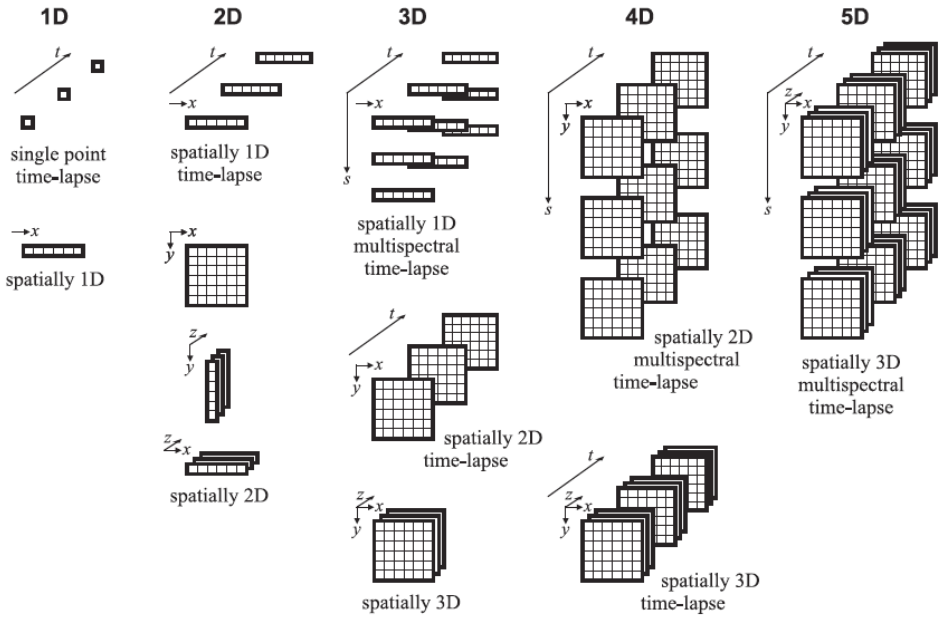

Figure 10. From early 1D observations to N-D [Olivo-Marin, 2008]

3.2.2 Multilevel approaches

"Integrative" is certainly one of the most popularized term today in almost all Life Sciences and particularly in Biology and Physiology [Coatrieux, 2004]. It is opposed to the "*reductionist"* approach whose goal consists to identify always finer molecular and cellular events studied in isolated systems (like it is performed in genomics, proteomics, biochemistry and cell biology). *"Integrative"* is seen as the studies targeted to the understanding of physiological functions in the context of organ or organ systems. Behind these views, there is the perception that molecular biology can not provide all the answers to understand the genetic, proteomic and cellular mechanisms involved in tissue organization, growth, differentiation, etc. However, fundamental questions are posed at the same time by this debate. One of the key points is how to derive findings or to extrapolate the observed behaviours to global, in-vivo, organs or systems at specific life stages. Let us take epilepsy as an illustrative case. The data that we may access ranges from the properties of membrane ion channels observed through patch clamp techniques, to neuronal *in-vivo* characteristics available by means of multiple micro arrays (MMA), populations of neurons using stereo-electro-encephalography (SEEG) or electro-corticography (EcoG), up to extended brain activities with high density EEG and magneto-encephalography (MEG). Beyond single channel data, the higher levels of data are all too rough or too information-sparse to reflect the continuum we are looking for, among which are synaptic delays, excitation and inhibition, afferent and efferent connections and distant loops, etc. These data types provide only insight into electrical mechanisms, a first step of the frame required to understand the intra-level coupling and the inter-level transitions. This understanding will perhaps open other pathways where not only genomic features but also cellular interactions (cellular microenvironment, tissue structure) are involved. *Much remains to discover at nano-, micro- and macro-levels in living systems and re-assembling them into global pictures in order to capture their key collective properties remains to be carried out.*

3.2.3 Multiscale over time

Multiscale is sometimes associated with multilevel. However, the former refers more to granularity in space or time when the latter is related to distinct entities or organizations (e.g. object-based), from membrane, neuron to brain structures for instance. Multiscale methods have been mainly exploited in signal and image processing, through wavelet transforms (decomposition on detail levels) and pyramidal approaches (allowing coarse-to-fine spatial analysis). The meaning we give here to multiscale over time is aimed at discriminating the long-term dependences from the immediate responses to local events. From this standpoint, we are interested is identifying responses to short impulse (sub-milliseconds) and long-range time horizon effects (i.e. seconds, minutes or much more). This restriction to time, for our purpose, does not mean that we ignore the immediately adjacent spatial interactions or very distant ones (from nanometers up to centimeters or more).

Many research questions can be formulated from that viewpoint, only some being described. Transient events or almost stationary episodes, scattered over very long periods, are of concern. When we are talking about these patterns for a patient or between patients, there is an implicit reference to a unique behavior, in other words, their reproducibility is assumed. Even if it has been effectively shown in many cases that there is high similarity, differences are always detectable. Do these differences have any significance? Another aspect related to long time horizon is our capability to analyze sequences of events. Can we think that there is some regularity (or temporal structure) in and between these sequences? Do transient and oscillatory patterns relate each other? What can be the role and influence of the background, i.e. non-pathological activities? All these issues require long term analysis and call for innovating methods in signal processing capable to detect, disambiguate and track subtle differences. They also question the paradigm of determinism like it is considered in molecular biology. In cell physiology, particularly in gene regulation, there are often only a few copies of particular molecules per cell, so that stochastic behavior can be expected in each cell, and the question turns to what can be expected of an ensemble of cells in a tissue. Fluctuations in regulatory networks, in the activity of neurons or in proteins and nucleic acids, which can in certain cases look like noise, have been recognized as major features. There are many problems to be solved before capturing these fluctuations and understanding how the biological entities control them in pathological disorders.

3.2.4 Imaging across spatial scales

There are many levels of scale in biology: molecular, micro, organ, organism, population, where imaging can make a contribution. Spatial scales are a special case of multiscale biological phenomena that encompass molecules, single cells, tissue (histology), gross anatomy of individuals, and extension to population atlases representing arbitrarily large groups of individuals.

The users of multiscale imaging systems are researchers such as biologists, biomedical engineers, industry, and ultimately clinicians—internists, surgeons, oncologists (radiation, surgical, medical), radiologists, and others. Motivation to pursue multiscale imaging is also provided by clinical needs, unaddressed with current methodology—allowing investigation in vivo that correspond with underlying mechanisms in vitro. One example of routine clinical situation where the multi-scale dimension is crucial is the case of An operating room microscope integrated with CT/MRI/PET scans in neurosurgery is a typical example. The surgeon works at the micro scale guided by information at that level, as well as at macro levels provided by clinical scans. There is often a need to translate from one imaging system (at one scale) to another (at another scale) so image registration across scale—in real time is required.

We are currently witnessing a convergence of two evolution processes which are the upscaling of small animal imaging initially developed for basic biology studies and the downscaling of the radiological imaging side initially meant for organ studies and clinical applications.

Developing imaging systems across spatial scales needs to address first difficult questions like: How can we best characterize imaging modalities and methods? How can be chosen the imaging modality of method that answers a specific biological or clinical question? Whatever the answers to the former questions are, multiscale imaging solutions are likely to rely on multiple modalities that overcome limitations of any single modality [Carson et al., 2003]. The product of a multiscale imaging system may be a combination of modalities, a protocol, an image, a parameter (predictor, for example), a decision, a therapy or intervention, but most generally a parametric map.

To meet the requirements of multiple scales, new instruments and methods are needed to collect more and better data, often by applying specific molecular agents and probes. The integration of imaging systems that accommodate multiple modalities, cooperative developments of instruments with the drugs or agents that can be optimized for specific tasks, with validation of these elements early in the development phase are needed.

How can we translate multiscale imaging developments into practice? The strategy would be to adapt technology from medical imaging (and other disciplines) to microscopy and vice versa, further emphasizing the need for multidisciplinary teams. One system–one scale is common today, where imaging instrument developers define a field-of-view as a design parameter. This imposes a limitation on the instrument's ultimate range of application in multiscale studies. For any intended application, multimodality systems need optimization—and this has not been done to date in a rigorous manner.

Nanoscale technologies, including multifunctional agents (and multimodality agents) are potentially synergistic with imaging instruments, including micromachines. New contrast agent/radiopharmaceutical/ optical probe development is essential for multiscale targeting and verification (related to mechanism of action). New image contrast mechanisms (imaging physics; biophysics; biomechanical properties) can provide tools that enable discoveries where quantitative imaging is especially valuable as metric.

In addition, 2D/3D/4D data acquisition, management and analysis are important *across spatial and time scales,* coupled to the requisite information infrastructure. Post-processing software tools for registration and segmentation, establishment of image databases, and image analysis tools are required. Sharing images and related data opens new opportunities for data processing tool development. Synergistic technologies like image registration (fusion), visualization, integration (with gene/protein expression data, pharmacodynamic, pharmacokinetic, and pharmacogenetic databases) across modalities & scales are needed. Extended software tools capable of relating individual images

with populations (e.g., atlases) and comparing populations with spatial statistics are potential areas for fruitful development of new technology.

The impact of multiscale imaging research will be seen in pharmaceuticals— as more and better agents, reduced time to market, reduced clinical trial sample size & time requirements—and potentially a new framework for evaluating agents taking them from the laboratory through preclinical and ultimately to clinical trials. New agents for research can aid imaging, as contrast agents or labeled radiotracers, as well as for individualization of therapy. There are important potential benefits to patients: better quality of life, lower cost for medical treatment; and more therapeutic options for a broader spectrum of diseases.

3.3 Bridging with Systems Biology, Physiome, Science of Complex Systems

Several initiatives have been launched over the last decade that point out the critical importance of relevant biological and physiological models, including projects like E-cell, Virtual Cell, and the Physiome Projects. The latter consist of socially related but scientifically independent projects on integrative systems physiology and biology undertaken by individual investigators in Western countries. Most have gathered support from national health research agencies and/or international support and are aimed at sharing tools, data and knowledge bases, experimental platforms, etc. Some of the most visible developments are biophysical and biochemical in nature, and related to subcellular scales where proteins, substrates and product solutes, and ions interact to provide quantitative descriptions of cell level functions. Almost none of these currently provide kinetic descriptions linking these cellular events to gene signaling and to regulation of transcription and translation, although the structuring of the protein-protein relationships is proceeding rapidly by diagramming associations. At the higher physiological levels, the developments have been less biophysical and more descriptive, therefore less precisely defined. The behaviors of populations of neurons and other cells, tissues, organs, and their central control loops are less quantitative, mainly because of their complexity, even though such models are essential in detecting the onset of diseases, for tracking the spread of disorder, and to understand the impact of therapeutic agents and their potential side effects. The Physiome projects (and the more focused efforts on the kidney, heart, lung and so on, represents current attempts in this direction) gather modeling work, information processing methods and tools, data banks, etc., and make then available to a large research community.

Peter Hunter, one leading reference in this field, will point out the current Physiome initiatives launched worldwide. He will describe the efforts made to facilitate model reuse among researchers in computational physiology through XML markup languages for encoding biological models, CellML (www.cellml.org) & FieldML (www.fieldml.org) and the open source software tools for creating, visualizing and executing these models currently available (www.cellml.org/tools) and under continuous development.

Rod Hose will describe the construction and implementation of a clinical workflow that includes a simulation chain. The procedure will be illustrated by description of the processing chain for morphological, structural and haemodynamic analysis of cerebral aneurysms that is under construction in the Framework 6 Integrated Project @neurIST. This project includes registration methods and simulation of fluid-solid interaction (ANSYS-CFX) to compute for instance the aorta valve dynamics and in-stent restenosis.

There are many possible topics to address within the Physiome: it is transdisciplinary and, as such, most of the engineering sciences are concerned from automatic control to computer science, from information processing to computer graphics, from system design to micro and nanotechnology. There is no doubt that more involvement of engineering disciplines is central to bring together different pieces of knowledge, methods and techniques. In addition to things like setting standard for archival versions of models, making them available worldwide, designing languages, there are open theoretical issues to be addressed and applied research to be conducted. The effort made some time ago to acquire full anatomical and morphological data through the “Visible Human” demonstrated the need for detailed information on the human being. The Visible Human project has a long way to go before it can provide sufficiently quantitative data to help in physiological analysis, but it did launch a series of

studies around the world to picture the whole body qualitatively in three dimensions. The intensive use of imaging techniques like segmentation, rendering, shape modeling is leading to detailed descriptions of organs, and needs to be extended to providing quantitative measures not only of dimensions but also of composition and material properties. It is recognized today that understanding the functions is the next goal and that this should be take into account the all scales, from genes to supra-organs.

3.3.1 Core elements beyond The Physiome

Understanding the interactions within networks in cells or at a global level (like the Autonomic Nervous System) is a critical step in biology and physiology. Such studies open the way to discover the common principles governing the collective behavior among cooperative entities, operating under strong environmental constraints. Modeling, by the capability it offers to generate hypotheses that could be experimentally tested, should provide new insights into large-scale systems and their evolution. *While models can never be proven valid, they gain power and acceptance by resisting multiple attempts to invalidate them against data, so establishing themselves as working models representing a composite view of accepted wisdom.* Some cautions must be however emphasized first. Models used in clinical setting should be particularly robust and therefore be adaptive, even changing configuration as conditions change. The science aspect of it is central: if integrating knowledge is what modeling is best used for, we still do not know well how to develop really comprehensive models. There is a continuing tension between building them bigger and better, versus being able to compute them in short time, using them in practical situations, and maybe not even knowing if the large ones are sound. Validation gets more difficult the bigger they are; emergent phenomena may occur and could tend to degrade the confidence we may have about their real correctness, even when that is exactly what should occur. To achieve this task, new paradigms have to be considered, some of which being examined here.

3.3.2 Looking for new multimodal observation techniques

This trend toward multimodal data acquisition is not new. It has been widely emphasized in macro-imaging for years, either by coupling in the same device different techniques (for instance, Computed Tomography and Positron Emission Tomography) or by registering data sets (3-D/3-D and 2-D/3-D) recorded at different times. It will take more importance with the emergence of *Nanomedicine*. This new area aims as "the comprehensive monitoring, repair and improvement of all human biological systems, working from the molecular level using engineered devices and *nanostructures* to achieve medical benefit". It identified *nanomaterials* and devices, *nanoimaging* [Minoshima, 2005] [Kovacevic, 2006] and analytical tools, novel therapeutic and drug delivery systems, as the major technological components to address. The objective is the *in vivo* measurement and characterization of biological processes at the cellular and molecular level, and to be more precise, beyond the standard anatomical and functional mapping, the *in vivo* detection and quantification of molecular disease markers or therapeutic agents via specific probes. It is expected that early disease manifestations will be detected by enzymes or signaling molecules. Succeeding in such challenges should take time of course and should address many faces among which patient-specific patterns and adverse drug reactions.

As an example of what can be expected is represented by optical imaging [Hell, 2006] [Coatrieux, 2007]. The advances brought by FRAP, FRET, FLIM lead up to high dimensional observations in cellular biology with access to the fluorophore environment (Ca concentration, membrane potential, protein-protein interactions, etc.). Their applications range from cellular signaling to physico-chemical parameters and metabolic studies. Their extension to multiphoton imaging, which has the advantage of non-linear near-IR in terms of spatio-temporal resolution and prolonged tracking, deserves today a special attention. Multi-Harmonic Light microscopy with active non-linear chromophore is another example of new tools for dynamic, non-invasive and in-vivo exploration of cells that can complement recent microtechnologies (multiple micro-arrays). The multimodal dimension is, here too, of concern with the capability to couple optical systems like FRET and FLIM with electrophysiological techniques or others. *In fact, beyond this example, it is believed that the design of devices capable to simultaneously capture chemical, electrical, mechanical, etc. characteristics, at a given entity level or even better at several levels, is one of the major challenge for the future.*

3.3.3 A Bridge between Systems Biology and Physiome

Systems Biology is focused on the studies of intra- and intercellular dynamics, using systems and signal-oriented approaches. One of the goals is to identify structural characteristics and variables in order to derive mathematically models and mainly simulate the sub-cellular and cellular dynamics [Hartwell, 1999]. The emphasis is put here on regulation, prediction and control [Sonntag, 2004], signals and information, mathematical modeling [Murray, 2004], predictive behavior, all terms referring to engineering and applied mathematical sciences or physics. The mammalian cell has been widely explored and parts of the main circuitry identified with growth, differentiation and apoptosis controls. The fascinating features of such cell modeling, and consequently the challenges to face, are related to the sensing capabilities, catalyze reactions, switches, actuators and to the number of distinct inputs/outputs that are present, some being known, others being only approximated or assumed. Many questions for *Systems Biology* arise about internal information processing, the transduction pathways, the types of reactions, the non-linear relations involved, the robustness, the effects of multiple loops, the mix of discrete and continuous components, etc. Here too, models provide insights on the plausible roles of network topologies (chains, lattices, fully-connected graphs), on the mutual synchronization of cells (uniform or non-uniform pulse-coupled oscillators), on traveling waves and non-linear dynamics, etc. All these issues are of concern for Physiome and motivate their convergence. Historically, Systems Biology is basically at this point a statistically-based bottom-up approach, from genotype to phenotype, whereas the Physiome approach takes a quantitative biophysical and deterministic approach to describing molecular, cellular, organ and overall system behavior in an attempt to establish a top-down path to meet up with the genomic and proteomic information and so provide a path that can be understood the whole way from Gene to Health.

3.3.4 Engineering Complex systems

The science of complex systems is exactly focused on these issues. It starts from the assumption that all disciplines (from physics to ecology, from economy to sociology) are concerned and, in some way, traversed by generic emerging behaviors. Von Neumann, McCullochs and Pitts, Thom, Prigogine and many others have brought elegant theoretical contributions during the last century. But much remains to be done. What class of models is the most appropriate? Are we able to mathematically state how they behave under specified conditions? Issues like the emergence of organization levels, the robustness of processes to perturbations or actions, the universal properties of interaction networks underlying the system under study are some of the features that are addressed. Systems with a large number of differentiated entities, structured in cascades or highly intricate, interacting through complex local and global mechanisms (non-linear, feedback loops, adaptation) and evolving over time in their architecture are concerned. A key generic point in complex systems is to aggregate successive levels by identifying appropriate variables that can be omitted, averaged or approximated, using relevant physical and mathematical arguments. Another key point deals with the reconstruction problem of revealing the spatio-temporal dynamics from the observed data. This “inverse problem” leads to even more challenging issues when it applies to multilevel system control and prediction of effects of therapeutic intervention. We may also be interested in finding, within the possible actions (for instance therapy if we refer to medicine) to perform, those that are the most relevant: such questions should take into account the distributed nature of the entities involved. It can be easily perceived from these considerations that there is a strong interest to merge the on-going theoretical advances coming from this field with the fundamental and very close questions posed in Systems Biology and Physiome. This is perhaps the only way we have to build sound modeling approaches where system properties (impact of approximation, robustness, validity domain, etc.) are to be established and interpreted.

3.3.5 The diagnostic and therapeutic challenges

An important issue is to avoid « modeling for modeling’s sake ». The practice in biological and other experimental sciences is to start with an hypothesis about a variable, an object or a system, and to design the right experimental protocol to test if the hypothesis is valid (meaning not invalidated by the particular experiment) or is disproved by the resulting observations. This is a non-trivial, closed loop approach requiring multiple iterations. It may involve new sensing techniques and innovative information processing methods. The requirements for clinical studies are in principle similar, except

for the huge difference that a patient is there requiring a decision with respect to treatment. Experiments and analyses in the biology laboratory can yield genetic, proteomic and cellular knowledge that may lead to new drug designs, new diagnostic tests, and improved therapy. For the patient in the clinical trial, the testing of the therapy again becomes stochastic or at least probabilistic. Given that patients respond differently from one another, maybe some of the stochasticity of the gene regulatory network remains in play. This is beyond the Physiome projects per se.

There is a wide gap between in vitro observations and in-vivo animal or human trials, between a cell and an organ in its whole functioning environment with limited access to the information that would be required. This incompleteness of data, combined with many other factors like the multiple interactions between functions, diseases, environmental conditions, drug actions, etc. makes highly difficult to establish a link between modeling and clinical requirements, i.e. patient-specific diagnosis and therapy. Nevertheless, and apart integration, indexing, retrieval of knowledge, there are several ways in doing that. As mentioned above, in some cases the reconstruction or inverse problem can be solved in order to fit the observations to the models of concern. Prior knowledge of structures and functions can be used to parameterize and initialize the models: such approach has been widely used for registration and matching purpose between multimodal patient data and atlas maps for instance. Inverse problems are central to electromagnetic source identification in electroencephalography and magneto-encephalography. And the capability to identify multiple closed-loop models from physiological signals allows predicting the effects of a given action (drug for instance) on the whole system as far as relations between some variables with the action are known.

All these topics are of course inter-related and represent the many attempts to understand the overall facets of living bodies. The “flags” they display express the search for new paths. The convergence of Physiome projects and of Systems Biology really aims at merging biology, medicine, physics, mathematics and engineering science. Biomedical engineering -with competences in computer science (database management), automatic control (modeling and control), information processing (recognition and fusion for signals and images), microtechnology (sensing devices)- must be fully part of this future, in order to provide answers to basic questions and better care for human beings.

The Physiome is knowledge driven. It represents a long-term effort, simultaneously requiring innovative data acquisition and comprehensive yet detailed modeling. It is critical to have close interaction between well-designed experimental protocols guaranteeing the reproducibility of biological/clinical data collection and the testing of the hypotheses for validity. The Physiome’s future depends on the mutual involvement of biological and engineering scientists. It also depends on the development of understanding at national and international levels of the value of integrating knowledge of human biology to a level permitting prediction. While it will be a very long time before a drug’s side effect will be predictable from Genome, Proteome and Physiome, that day will come. What is needed now is recognition of this potential, and sure strides toward its structuring and funding at a worldwide level. We hope that this special issue will motivate both new competences and institutional interest.

4 Conclusion

This chapter was aimed at providing an overview of major trends and prospects in medical imaging. Its objective was also to make links with the lectures that will be given during the 2008 school. Of course, the all topics that have been addressed are still a minor part of the whole picture. Biomedical imaging has a long story but its future is certainly expanding in so many directions that young researchers, not only will find many windows to work in, but will be actively part of. One fundamental point is perhaps to favor multidisciplinary collaborations and, for sure, to keep open eyes and open minds on the research world which is under development. All competences and profiles are needed without any hierarchy: from basic sciences to applied sciences, from physics to biology, from information processing to technology with a confident and active relation with physicians. A better care for anybody, anywhere and at any time is an objective that should motivate a life or better said, several lives.

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