

Human intelligence in biomedical diagnostics

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A portrait of Prof. dr. ir. Massimo Mischi, a man with dark hair and glasses, smiling. He is wearing a dark blue button-down shirt. The background is a blurred indoor setting.

Prof.dr.ir. Massimo Mischi
November 9, 2018

INAUGURAL LECTURE

Human intelligence in biomedical diagnostics

TU/e

EINDHOVEN
UNIVERSITY OF
TECHNOLOGY

DEPARTMENT OF ELECTRICAL ENGINEERING

INAUGURAL LECTURE PROF.DR.IR. MASSIMO MISCHI

Human intelligence in biomedical diagnostics

Presented on November 9, 2018
at Eindhoven University of Technology

Introduction

Today we are facing an epochal challenge because of the exploding demand and cost for the healthcare system caused by our greying society (30% over 65 by 2060 in Europe) and related increase in chronic and age-related diseases. This cannot be paralleled by an adequate increase in the financial and professional volume available for care giving. In this situation, how can our society still guarantee high-quality care and assistance?

I firmly believe that the answer lies in technological innovation. Technology has the potential to transform the healthcare continuum by reverting the order of the conventional pathways for care giving. In particular, it is widely recognized that both considerable cost reduction and significant gain in quality of care and quality of life can be achieved by:

- Achieving prevention and early diagnosis to limit disease to levels that can be either treated at home, or by minimally-invasive intervention, reducing costly hospitalization.
- Making surgery minimally invasive, to minimize the duration of hospital stays and the associated costs. Minimally-invasive intervention is also expected to reduce side effects and morbidity, effectively improving the quality of life.
- Equipping homes with affordable assistive and care technologies so that most care can be provided at home.

It is self-evident that biomedical diagnostics plays a fundamental role in the realization of these objectives. Timely diagnosis is essential for effective prevention of disease progression and patient deterioration, and for limiting the disease to levels that can be treated either at home or by minimally-invasive intervention in the hospital. Timely and precise diagnosis may indeed enable replacing radical treatment by image-guided, focal treatment that is minimally invasive and can even be performed in outpatients.

Biomedical diagnostics

Already the etymology of the term, diagnosis, suggests a strong link with the human drive to learn, which is central in our academic world. From ancient Greek, “dia” meaning “apart” and “gignoskein” meaning “to learn”. As a whole diagnosis means to discern and distinguish between different conditions, for instance between benign and malignant tissue. It is therefore clear how diagnosis is the result of a learning process, referred to as diagnostics, which aims at understanding our physiology and pathophysiology in order to detect and evaluate the onset and development of diseases.

Physiology and pathophysiology, although already complex and not fully understood, represent only the first step of the measurement chain providing medical doctors with the inputs required to make their diagnosis, such as biomedical signals and images. Correct interpretation of these inputs requires understanding of the full measurement chain, from the (patho)physiological sources, to the physics underlying the sensing process, up to the electronics conditioning the measured signals and/or forming the displayed images (Figure 1).

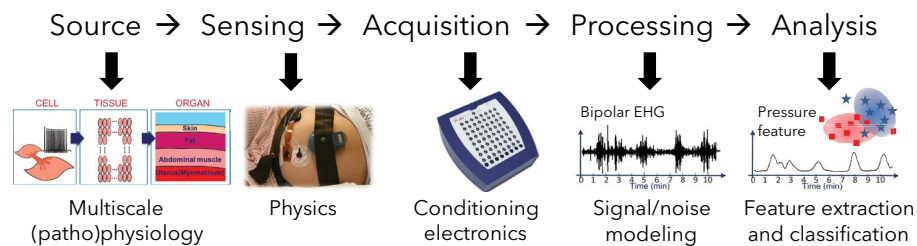


Figure 1. Representative example of measurement chain for the analysis of the electrical activity of the uterus, referred to as electrohysterogram (EHG), during pregnancy.

Based on our understanding of the full measurement chain, parametric mathematical models can be created that describe the measured (patho) physiological processes also accounting for the adopted measurement process. Modelling and parameter estimation therefore become key aspects in the process leading to medical diagnosis. In particular, the identification of the models providing an accurate representation of the underlying (patho) physiological processes leads to the generation of quantitative representations

of the physiological parameters of interest. Quantitative rather than qualitative representations facilitate the clinical interpretation and diagnosis, enabling objective evaluations that are more accurate and reproducible.

Besides providing quantitative information, model-based analysis of biomedical signals also allows adjusting the model parameters to account for specific patient conditions. This is a fundamental step towards enabling patient-specific medicine, starting with a diagnosis that is personalized and tailored to specific conditions. These parameters relate not only to a specific patient, but also to the acquisition procedure. Advanced models should in fact also account for specific noise sources and interferences. In particular, accurate noise characterization can support the process of model identification and lead to identification strategies that embed all the available prior knowledge on the desired signals, interferences, and noise sources.

Besides improving the interpretation of the measured signals and leading to actual quantification of the (patho)physiological parameters of interest, understanding and modelling the full measurement chain also permits improving the adopted measurement instrumentation and protocol. Improved diagnosis can then result from a multidisciplinary effort aiming at optimizing all aspects in the measurement chain. Without such an integrated effort and global view on all the key aspects influencing the measurement of biomedical signals, the signal quality may be hampered by sub-optimal acquisition and the final interpretation affected by uncertainties and inaccurate assumptions.

Indeed, uncertainty is a key aspect that requires careful consideration. Because of the trend towards multimodal, ambulatory acquisitions, the acquired signals may be severely affected by multiple, time-varying noise sources and artifacts, limiting the performance and applicability of deterministic signal analysis, and often resulting in misinterpretation and unreliable quantification. In order to cope with this problem, probabilistic frameworks can be developed where a-priori knowledge of the physiological sources and measurement chain is integrated with a probabilistic characterization of the parameter space, also including measurement uncertainty. Such a probabilistic framework is expected to improve robustness and accuracy of the parameter estimation by exploitation of the available domain knowledge on the models regulating the underlying physiological processes, together with the probabilistic distributions of the analyzed parameters, accounting for the unavoidable uncertainties accumulated along the measurement chain.

Within such a probabilistic framework, machine learning techniques have gained a prominent role for classification and diagnosis based on a number of features extracted from the acquired biomedical signals. In line with the model-based approach, the use of machine learning techniques can provide valuable support with the selection of the key features for interpreting and modeling the underlying physical and (patho)physiological processes. In general, model reduction techniques are valuable tools to search for an optimal compromise between noise-robust model identifiability and accurate description of the underlying processes.

Somewhat different from the long-lasting efforts of many scientists to develop models describing the human (patho)physiology, today increasing attention is directed towards the use of artificial intelligence, enabled by ever increasing computing power and the availability of large datasets for training convolutional neural networks. This is “deep learning”, often used as a “black box” tool for making diagnostic choices based on complex models that are learned by the network but unknown to the humans. Although the results are often astonishing, they are not immediately generalizable and may be affected by unknown dependencies on the training dataset. Moreover, diagnostic failures cannot be readily explained.

Instead of seeking a “shortcut” to find easy solutions overcoming the complexity of biomedical diagnostics, artificial intelligence can be considered as an extraordinary opportunity to achieve better understanding of the (patho)physiological processes regulating our function and diseases. This can be achieved through latent-space and deep-layer visualization. So called “transparent” deep-learning approaches can be designed with the potential to propagate back and gain additional knowledge about the underlying physics and physiology. This way, the learning process can be used to enrich our knowledge, yielding reliable diagnostic solutions that are based on domain knowledge and improved understanding of the physics and physiology behind our biomedical measurements. In return, improved modeling can provide us with the ability to generate synthetic data that are good representations of the reality, enabling the use of deep learning also in domains where only limited data is available. This win-win situation may indeed result from reestablishing the value and role of human intelligence in biomedical diagnostics.

Relevant solutions for biomedical diagnostics that can make an impact on our society should be driven by clinical need, based on domain knowledge, and suitable for implementation and clinical translation. This is facilitated by the establishment of a multidisciplinary research team combining academic, clinical, and industrial expertise. In particular, close collaboration and regular interaction

with clinicians represents a unique opportunity to generate ideas and develop diagnostic solutions that tackle relevant problems, providing valuable support for improving clinical workflow and healthcare sustainability.

Application domains

Aiming at a large societal impact, we pay major attention to those dysfunctions, diseases, and critical conditions that are widespread, and where timely and accurate diagnosis is crucial. Primary examples of this type are cardiovascular dysfunctions, cancer, and pregnancy, requiring different diagnostic solutions that are suitable for either high-end medical imaging (e.g., tissue and microvascular characterization) or unobtrusive, ambulatory monitoring (e.g., monitoring of pregnancy and atrial fibrillation).

Noninvasive diagnostic imaging has a major impact on the healthcare continuum, enabling screening and minimally-invasive intervention through timely diagnosis. Being widely accessible, cost-effective, and perfectly suited to perioperative use, ultrasound imaging is an important research area addressed throughout the full measurement chain, by innovative interpretations of the measured signals as well as by innovative use of the acquisition technology. In this application area, quantification is an essential yet lacking option that we are constantly reinforcing through innovative research findings. Ultimately, accurate and reliable imaging is expected to become suitable for image-guided minimally-invasive intervention.

Multimodal unobtrusive measurements combining e.g. electrocardiography, photoplethysmography, and accelerometry, provide the inputs required for reliable model-based system identification through accurate estimation of physiological parameters with high diagnostic value. Here the research efforts are directed at providing technological solutions to offload the diagnostic burden in the hospital while enabling early and accurate prediction of patient deterioration at home. Acquisition redundancy can be exploited to boost the estimation robustness. Emerging acquisition technologies, based e.g. on large arrays of contactless sensors, are providing important opportunities for long-term monitoring.

Medical imaging

CARDIOLOGY

Approximately one in four people die of heart disease. Nowadays, treatment of widespread cardiovascular disorders such as heart failure and atrial fibrillation can benefit from improved imaging strategies and, in particular, quantitative image analysis. In fact, medical image analysis can provide important and valuable additional insight for diagnosis, treatment, and follow up cardiovascular dysfunctions.

During my PhD work, in collaboration with the Catharina Hospital Eindhoven (Erik Korsten), I already worked on the characterization of the central circulation by dynamic contrast-enhanced ultrasound (DCE-US) imaging following a peripheral, intravenous injection of a small bolus of ultrasound-contrast-agents (UCAs). UCAs consist of a dispersion of microbubbles with sizes comparable to that of red blood cells. They can therefore flow through the tiniest microvessels, but their size does not allow for extravascular leakage. As a result, they are purely intravascular agents. When invested by ultrasonic waves, UCAs oscillate in a nonlinear fashion, enabling effective contrast-specific ultrasound imaging.

Model-based analysis of the evolution of the UCA concentration in the different cardiac chambers permits the estimation of the bolus transit times between these compartments. In particular, joint probabilistic (random walk) and deterministic (convective-diffusion) interpretation of the dilution process leads to accurate estimation of relevant physiological parameters characterizing the central circulation, such as the cardiac output, pulmonary blood volume, and ejection fraction of both ventricles.

Specifically, the pulmonary blood volume may play a predictive role for assessment of congestive heart failure and patient selection in the context of cardiac resynchronization therapy (implantation of a pacemaker). This is a relevant problem as many patients (between 30% and 40%) selected by current criteria do not respond to this expensive therapy. We have explored the predictive value of the pulmonary blood volume, measured both by DCE-US and DCE-MRI (magnetic resonance imaging), together with novel measures of mechanical dyssynchrony

of the left ventricle assessed by cine MRI, in a collaborative effort with Philips, Medtronic, Pie Medical Imaging, and the Catharina Hospital Eindhoven (Erik Korsten and Arthur Bouwman). Advanced spatiotemporal analysis of the UCA concentration in the left ventricle, combined with electrocardiographic gating and Navier-Stokes regularization, yields the visualization in 3D of intravascular flow (Figure 2) and pressure patterns, possibly providing additional prognostic features for patient selection.

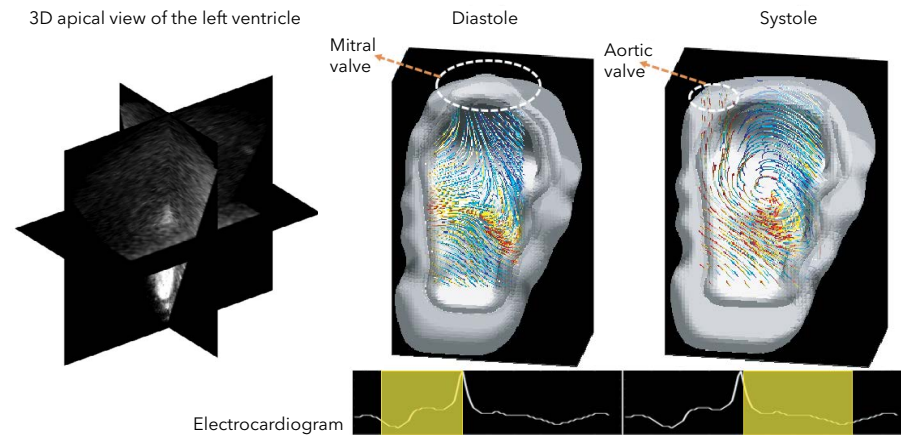


Figure 2. On the left, 3D dynamic contrast-enhanced ultrasound imaging of the left ventricle following a contrast agent bolus injection. On the right, dominating flow patterns during systole and diastole, with corresponding (bottom) synchronized electrocardiogram.

More recently, our research has been directed towards tissue characterization by multi-parametric ultrasound imaging with the aim of monitoring cardiac ablation procedures in patients suffering from atrial fibrillation and improving effectiveness and safety of the procedure. The combination of multiple complementary parameters is believed to provide the required information to assess the extent and depth of the ablation lesions as well as the presence of fibrotic tissue.

ONCOLOGY

Almost half of us will face the diagnosis of cancer, and one in four will die from it. Timely treatment saves lives, but is limited by the complexity, cost, and/or invasiveness of available diagnostics. A striking example is prostate cancer, the type of cancer with the highest incidence (19%) and second highest mortality

rate (9%) in western men. Similar to breast cancer in women, one in seven men are diagnosed with prostate cancer in their lifetime; however, different from breast cancer, no reliable diagnostic imaging is available. To date, prostate-cancer diagnosis is based on systematic biopsies, where patient discomfort, costs, and risks of hemorrhages and infections are serious drawbacks. Moreover, low sensitivity leads to repeated biopsy sessions, while poor patient selection results in one in four biopsy procedures which are unnecessary, in retrospect. In fact, one in three men present some sign of prostate cancer in their 50s already, but only a small fraction of these tumors are aggressive and require clinical intervention.

Although less invasive focal therapies are becoming available, their effective use is hampered by a lack of imaging solutions for precise and reliable prostate-cancer localization. As a result, radical treatment (surgical removal of the entire prostate) is the most common treatment, with serious associated risks for the patient to become impotent and incontinent. Therefore, not only late diagnosis and mortality, but also overtreatment with related high costs and impaired quality of life are large-scale problems associated with state-of-the-art diagnostic solutions.

This situation highlights the strong and urgent need for reliable prostate-cancer imaging, leading to noninvasive cancer localization and characterization. Because of the complexity of cancer onset and development, several imaging markers have been identified over the years that can contribute to the diagnosis of prostate cancer. In order to combine all the available information and achieve sufficient accuracy, multiparametric MRI has been gaining increasing attention in the past years. However, widespread introduction of multiparametric MRI is hampered by the limited availability of equipment, high costs, and complex workflows. Moreover, the clinical value of multiparametric MRI is not established yet.

Motivated by the high diagnostic challenges and clinical relevance of the problem, our research in oncological imaging has mostly focused on prostate cancer, in close collaboration with Hessel Wijkstra of the Academic Medical Center (AMC), University of Amsterdam, further extended to the Jeroen Bosch Hospital in 's-Hertogenbosch. Our primary ambition is to achieve accurate diagnosis of prostate cancer using ultrasound technology. Being affordable and widely available, ultrasound equipment is ideal to tackle the wide-spread problem of prostate cancer with an eye on healthcare sustainability.

In the past 10 years, we have made an extensive research effort to introduce novel imaging solutions based on DCE-US. This research was supported with my VIDi

Grant and ERC Starting Grant, as well as a KWF (Dutch Cancer Foundation) grant in collaboration with the AMC. DCE-US is a diagnostic tool that is suitable for analysis of the vascularization, by imaging the pharmacokinetics of UCAs.

As already established in the 70s-80s by the pioneering research of the medical scientist Judah Folkman, in order to grow beyond the size of few millimeters, cancer needs angiogenesis, which results in the formation of a dense, irregular network of tortuous and leaky microvessels intended to supply oxygen and nutrients to the tumor. The peculiar structure and architecture of angiogenic microvasculature provide a concrete opportunity for cancer imaging as well as for assessment of its aggressiveness, which translates in the risk of developing distal metastases. Extensive research has in fact established the link between cancer aggressiveness and angiogenesis.

Our approach, referred to as contrast ultrasound dispersion imaging (CUDI), is based on the assessment of the UCA dispersion kinetics as a marker for cancer angiogenesis. Translating the research of John G. Taylor on apparent diffusion (dispersion) through porous media, dispersion in the microvascular bed is dominated by the UCA transit times through the multipath trajectories imposed by the microvascular architecture. Therefore, UCA dispersion has great potential to reflect angiogenic changes in the microvascular architecture.

Following an intravenous injection of a UCA bolus, the prostate is scanned for about one minute. Dilution curves are then measured at each pixel and processed with spatiotemporal models to derive parametric maps of dispersion, which are then used for cancer localization. Several implementations of this method have been realized over the years, yielding ever improved diagnostic accuracy. These are based on model fitting in time domain or on the estimation of the similarity between neighboring dilution curves. Several similarity measures have been adopted ranging from spectral coherence, to temporal correlation, up to nonlinear measures such as mutual information. The obtained dispersion maps show good agreement with the histological results following radical prostatectomy (Figure 3).

By all these methods, independent estimation of dispersion was not possible due to the ambiguity between convection and dispersion. Further developments have led to the separate estimation of convection and dispersion by identification of the local (linear) dilution systems between pixels. The method also permits generating maps of the Péclet number, a physics parameter characterizing a dilution system. Currently, a large trial (150 patients) is being completed comparing

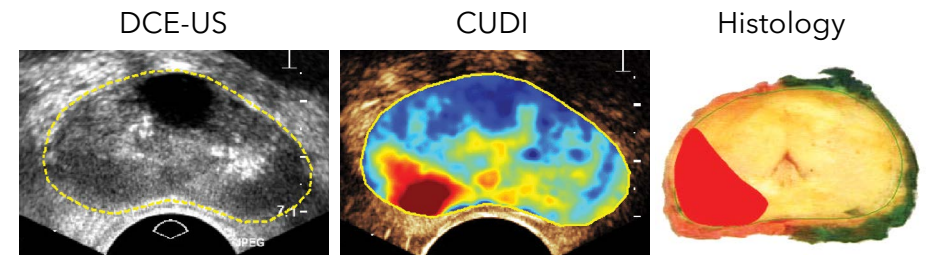


Figure 3. From left to right, dynamic contrast-enhanced ultrasound (DCE-US) imaging of the prostate with estimated dispersion map (CUDI) and corresponding histology. Cancer is depicted in red.

12-core systematic biopsies with image-targeted biopsies based on CUDI and multiparametric MRI. The results show CUDI alone to achieve the same cancer detection rate as multiparametric MRI, with the advantage of being cost-effective, widely available and ideal for perioperative use.

More recently, through our collaboration with Pintong Huang of the 2nd affiliated hospital of Zhejiang University in Hangzhou (China), accurate extension of CUDI to 3D DCE-US has also been proven in 43 patients, enabling the analysis of the full prostate gland by the injection of a single UCA bolus. Because of the 4D nature of the convective dispersion process, the availability of a 4D dataset also allows for improved modeling and estimation. We have produced velocity and dispersion maps generated by direct solution of the convective-dispersion equation, using accurate boundary conditions that can be measured by 4D imaging only. In addition, based on the reconstructed velocity fields, tractographic techniques, similar to those used in brain MRI, have been implemented to visualize the main streamlines characterizing blood flow (Figure 4).

While tractography leads the reconstruction of the main stream lines representing the (micro)vascular flow, currently the concepts introduced by Robert Eric Betzig (Nobel 2014) to achieve photo-activated localization microscopy are being translated to DCE-US, opening up new extraordinary possibilities. Ultrafast imaging at thousands of Hertz of low-concentration perfusion enables breaking the diffraction limit by deconvolution of the microbubble point spread functions, provided that they do not overlap. Super-resolved images can then be obtained that make the invisible visible, and the architecture of small capillaries that could not be resolved by standard ultrasound imaging can now be analyzed.

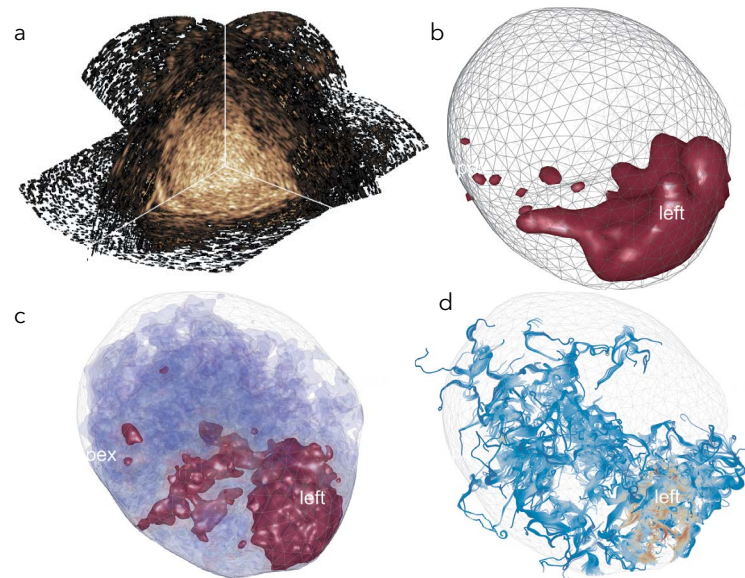


Figure 4. (a) 3D dynamic contrast-enhanced ultrasound imaging of the prostate with corresponding registered histology (b) and estimated dispersion (c) and tractographic (d) maps.

Clinical translation of these methods is however hampered by the need for long acquisition times that allow for sufficient coverage of the microvasculature at the required low UCA concentrations. Motion artifacts then become a serious limiting factor. By developing dedicated signal processing in collaboration with Yonina Eldar of the Israel Institute of Technology (Technion, Haifa), we can now resolve dense microbubbles with overlapping point spread functions using sparse recovery techniques. This allows the relaxing of requirements for ultrafast long acquisitions, and the method has proven applicable to standard clinical datasets. By injection of substantial domain knowledge, deep-learning techniques are also being explored for super localization at higher UCA concentration. Preliminary results in a rat spinal-cord show improvement over previous sparse-recovery approaches (Figure 5).

After moving from the millimeter to the micrometer scale, the use of novel targeted UCAs (BR55, Bracco Suisse) enables probing cancer even at the molecular scale. Targeted UCAs are microbubbles where the shells are decorated with ligands that have strong affinity with angiogenic expressions. Pioneering work by Hessel Wijkstra (AMC) and Juergen Willmann (Stanford University) has shown the first-in-

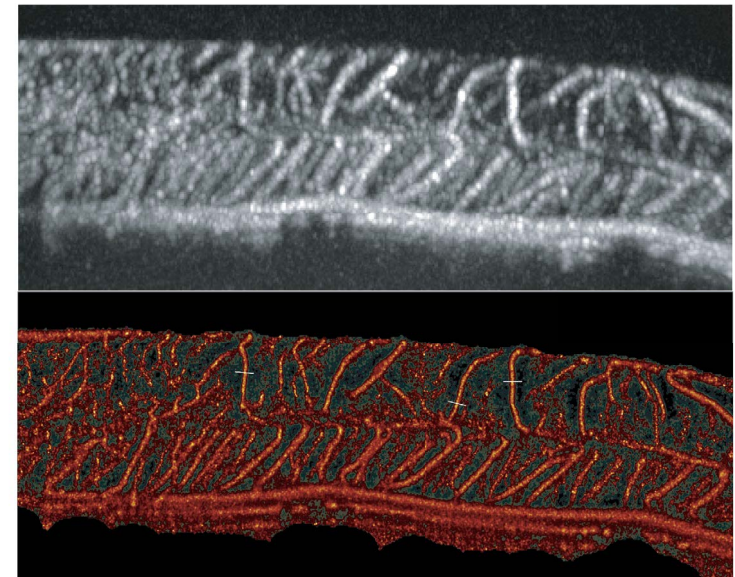


Figure 5. Above, contrast-enhanced ultrasound image of a rat spinal cord (courtesy of Matthew Bruce, University of Washington). Below, corresponding super-resolved image by deep learning.

human test of these agents with promising results for the diagnosis of prostate, ovarian, and breast cancer. However, application of this method requires waiting several minutes in order to determine qualitatively the area presenting bound microbubbles.

Quantification of the binding kinetics of these agents can lead to faster and more accurate diagnosis. We have integrated a convective-dispersion model describing the kinetics of circulating microbubbles with a single-compartment model describing the microbubble binding kinetics. Identification of this analytical model enables the assessment of both vascular and molecular features, determined by the dispersion and binding kinetics of the agent, showing promise for future applications aimed at cancer diagnosis. Preliminary results have already proven the feasibility of the method in prostate-cancer rat models in collaboration with Bracco. In general, the proposed methods for angiogenesis imaging are not specific to prostate cancer only, and future extension to other types of cancer can also be envisaged. In fact, our preliminary work in collaboration with Stanford University has already shown the potential of the proposed quantification to monitor the response to antiangiogenic therapy in colon-cancer mouse models.

Besides the development of multiscale methods from organ to molecular level, the estimation of multiple ultrasound parameters that are complementary cancer markers provides an additional dimension to be explored for better assessment of the complex processes underlying cancer growth. While setting the theoretical basis for the estimation of new ultrasound parameters describing the viscoelastic and nonlinear behavior of tissue, we have already started evaluating the accuracy of prostate-cancer imaging by combination of different DCE-US parameters, reflecting dispersion and perfusion. Registration tools have been developed to match the histological results with the obtained parametric maps for accurate training and validation of the designed classifiers. Using machine learning based on Gaussian mixture models, the diagnostic accuracy has been improved by approximately 10%. We are currently investigating the extension of the method by inclusion of shear-wave elastography in collaboration with Georg Salomon of the Martini Klinik (University Medical Center Hamburg-Eppendorf) for the estimation of tissue stiffness, which increases in the presence of prostate cancer (Figure 6). In fact, ultrasound technology provides immense possibilities for the estimation of complementary tissue parameters that are relevant for cancer diagnosis. Ultimately, once accurate cancer localization and characterization is achieved, we expect the proposed quantitative methods to fully replace biopsies and possibly provide image guidance for minimally-invasive focal therapy.

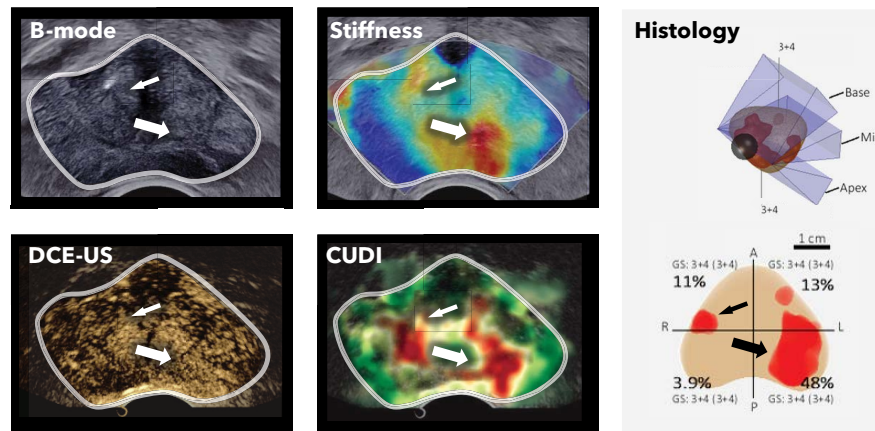


Figure 6. Multiparametric ultrasound imaging of the prostate showing B-mode and dynamic contrast-enhanced ultrasound (DCE-US) acquisition, together with the estimated parametric maps of stiffness and dispersion (CUDI), respectively. On the right, validation procedure based on 3D fusion with the histology results. Cancer is depicted in red.

Despite our considerable efforts towards prostate-cancer diagnosis by ultrasound technology, our focus has not been limited to the prostate nor to ultrasound. Model-based analysis for quantification of biosignals has value for different application areas, provided that domain knowledge is available throughout our clinical collaborations. We have therefore made our first steps in the direction of breast-cancer diagnosis by DCE-US, introducing a new specific marker for UCA imaging that is based on the cumulative phase delay of ultrasound waves propagating through UCAs. A tomographic use of this phenomenon by back-projection seems particularly suitable for breast imaging.

In spite of the limitations dictated by cost and availability, MRI offers fascinating possibilities. Different from UCAs, MRI contrast agents show extravascular leakage, providing the opportunity to detect the increase in microvascular permeability associated with cancer angiogenesis. To this end, several pharmacokinetic models have been introduced describing extravascular contrast leakage, often based on a single compartment model as introduced by Paul Tofts. All these models require a separate, cumbersome measurement of the arterial input function. Based on the convective-dispersion model developed for DCE-US, we have introduced a new model for DCE-MRI, combining intravascular convective-dispersion with extravascular leakage. Model fitting to dilution curves measured at each voxel results in the estimation of two parametric maps representing intravascular dispersion and extravascular leakage (Figure 7). Multicenter validation of dispersion MRI in 80 patients has shown improved results compared to standard Tofts analysis. Based on these results, quantitative dispersion MRI could be considered in the future for inclusion in the standard set of MRI parameters adopted in the clinical prostate imaging reporting and data system (PI-RADS).

In the future, after going all the way from the organ to the molecular level, additional insight can be obtained by further deepening into genetic cancer profiling. Extensive research in this area is evidencing a great potential not only for accurate diagnosis, but especially for accurate prognosis, with emphasis on the response to cancer therapy. Our ambition is therefore to enable the transition from invasive to noninvasive (image-based) cancer profiling by identifying the relations mapping relevant genetic profiles onto specific combinations of imaging markers. This challenging ambition requires the joint development of accurate quantification methods with a probabilistic framework enabling the identification of the mapping functions through e.g. machine learning.

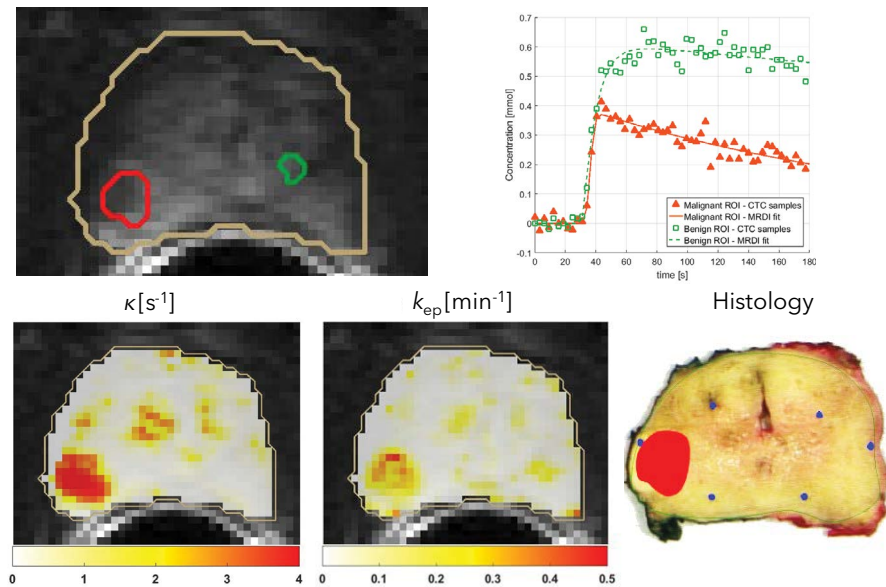


Figure 7. Dispersion MRI acquisition (top) with resulting dispersion (κ) and leakage (k_{ep}) maps, and corresponding histological results. Two examples of dilution curves with dispersion model fitting are also shown from single voxels representing malignant (red) and benign (green) tissue, respectively.

CONCEPTION AND FERTILIZATION

Alongside our extensive research on a major male disease, novel exciting research looks at women and the “miracle of life”. In developed countries, infertility represents a serious psychological and economic burden for up to 20% of couples. It is estimated that in-vitro fertilization (IVF) represents the only reproduction option for over 2.5 million couples in Europe. This number is progressively increasing due to the trend in postponing childbirth.

Despite major efforts to improve IVF, over 70% of the procedures fails. The number of failures progressively increases with women’s age to over 90% at the age of 40. Most IVF failures remain unexplained. As a result, infertile couples often undergo a series of IVF treatments. The emotional, societal, and economic implications of a series of repeated IVF failures are devastating. There is strong evidence of a major involvement of uterine contractions in IVF failure, especially during and after embryo transfer, when the embryo may be expelled. Pharmacological treatments are available that inhibit contractions, and their proper use can possibly favor

conception. Unfortunately, the role of uterine contractions in IVF failure is not yet understood, and the value of pharmacological treatments acting on contractions within IVF treatment remains to be established. The main reason lies in the lack of methods enabling noninvasive and quantitative characterization of uterine activity outside pregnancy.

Motivated by this strong clinical need, we are working in collaboration with Ferring, Samsung, the University Hospital Ghent, and the Catharina Hospital Eindhoven (Dick Schoot) on the development of dedicated ultrasound methods for uterine motion analysis. We are currently able to visualize the uterine contraction waves and determine their amplitude, frequency, and direction relative to the uterine anatomy (Figure 8). To this end, strain quantification is implemented by ultrasound speckle tracking, making use of blind separation techniques to extract the spatiotemporal components describing the uterine motion. Based on this technology, we are now able to distinguish between the different phases of the menstrual cycle and we are currently testing the value of uterine motion analysis as a potential predictor of IVF success in 20 women, followed during their IVF cycle at the University Hospital Ghent. In order to optimize our prediction model, different features, also describing the electrical activity of the uterus (electrohysterography) and the embryo quality are being processed by machine learning techniques.

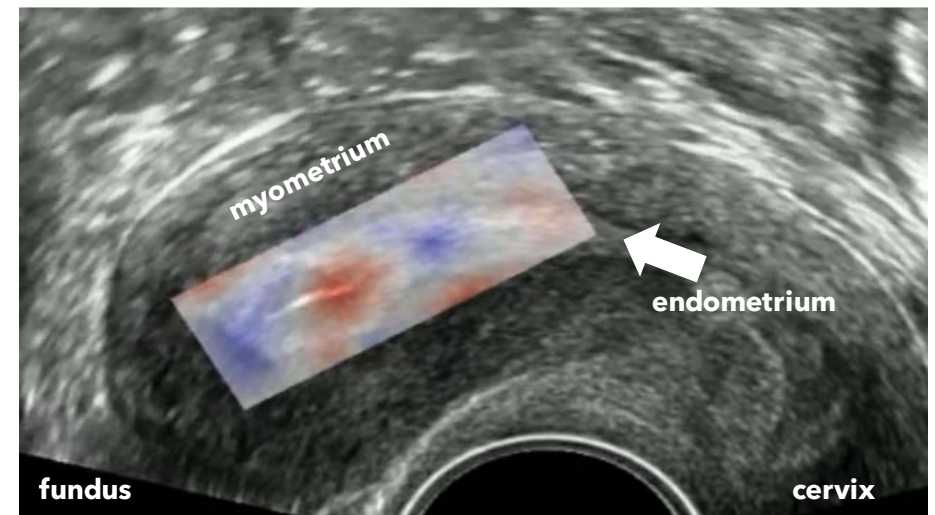


Figure 8. Strain map of the uterus based on ultrasound speckle tracking. A wavelike peristaltic movement can be recognized with contraction in red and relaxation in blue.

Besides tackling the fertilization problem, these methods can also be extended in the future for diagnosis of the uterine condition in relation to menstrual pain and several dysfunctions ranging from myomas, to adenomyosis, up to malignant lesions (sarcomas). The addition of DCE-US, based on the solid background established throughout our prostate research, is expected to add important complementary information on the microvasculature in order to achieve a full characterization of the uterine condition and to discern between benign and malignant lesions in the future.

Home monitoring

PREGNANCY MONITORING

High-risk pregnancies are associated with important morbidity and mortality rates for the newborn. Nowadays, over one in five pregnancies are complicated and considered high-risk. This number will further increase as a result of the progressive trend for women to postpone childbirth. Key risks, associated with a major fraction of mortality, include imminent preterm birth, intra-uterine growth restriction and fetal asphyxia. Preterm birth, i.e., birth before the 37th week of gestation, is still a major cause of infant mortality and morbidity. In Europe, as in other developed countries, the incidence of preterm birth is reported to be between 5% and 12%, producing 75% of perinatal mortality and over 50% of long-term morbidity, as infants born preterm are at increased risk for mortality as well as long-term health and developmental impairments. The current situation also represents a threat to healthcare sustainability. The annual societal economic burden associated with preterm birth in the USA is over \$30 billion. Most of this cost relates to the need for monitoring high-risk pregnancies, requiring a clinical dedicated setting and often hospitalization.

In order to address these clinical and societal problems, we have conducted extensive research, for over 14 years, on pregnancy monitoring in collaboration with Guid Oei of the Máxima Medical Center in Veldhoven. Our ultimate goal is to enable reliable ambulatory monitoring at home and prevent unnecessary and costly hospitalization. Accurate assessment of the health condition of mother and fetus enables timely intervention in case of complications such as a high risk of preterm delivery and fetal distress. Critical parameters for pregnancy monitoring are the fetal-heart and uterine activity. These are currently monitored in the hospital by tococardiography, a combination of ultrasound Doppler and strain gauges to detect the activity of the fetal heart and the uterus, respectively. Unfortunately, tococardiography is limited by low accuracy and the need for operator assistance to reposition the sensors over time.

Over the years, we have developed advanced methods for monitoring the fetal and uterine electrophysiological activity based on electrodes placed on the abdomen of a pregnant woman. Our focus is on the analysis of the fetal

electrocardiogram and the electrohysterogram, which are indicators of the fetal-heart and uterine activity respectively, and whose mutual relation is especially informative for diagnostic purposes. These can be measured noninvasively by electrodes placed on the abdomen (Figure 9). The measurement is however complicated by the low signal-to-noise ratio of the fetal cardiac activity (< -20 dB) and the low frequency content (< 1 Hz) of the electrohysterogram. Optimization of the full measurement chain is mandatory to deal with major interferences such as the maternal electrocardiogram, respiratory motion, and powerline.

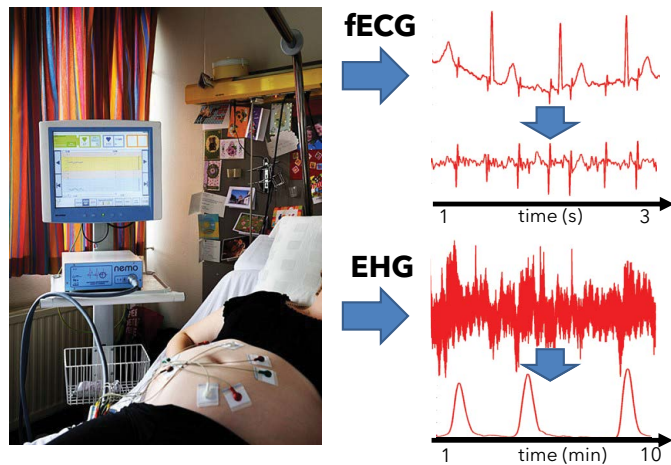


Figure 9. Electrophysiological pregnancy monitoring by measurement and analysis of the fetal electrocardiogram (fECG) and the electrohysterogram (EHG), reflecting the activity of the fetal heart and the uterus, respectively. After model-based de-noising, the fetal heart rate (above) and the intrauterine pressure (below) are estimated.

Based on the work of Rik Vullings, accurate monitoring of the fetal heart rate and evaluation of its variability is feasible nowadays. Moreover, based on a probabilistic framework embedding *a-priori* knowledge on fetal electrocardiogram and volume conductor, the full vectorcardiogram can be reconstructed and the standard electrocardiographic leads estimated. Doppler ultrasound has also been considered and dedicated signal processing implemented that uses larger grids of piezoelectric elements to estimate the fetal-heart location. This solution can possibly overcome the limitations of tococardiography by enabling operator-free monitoring of the fetal cardiovascular condition. Based on the work of Chiara Rabotti and our collaboration with Catherine Marque of the University of Technology of Compiègne, we are now in the position of measuring the

electrohysterogram at multiple scales and extracting spatiotemporal features that are predictive of preterm birth and time to delivery. Noteworthy, we can also measure the electrohysterogram in non-pregnant uteri, adding relevant features for assessment of the uterine activity and its condition. Because of its relevance, this research has always seen strong interaction with industrial partners such as TMS International (Enschede) and Philips. Moreover, valorization of the research outputs has been pursued throughout the foundation of the spin-off company, Nemo Healthcare.

According to our philosophy, signal analysis is developed in strong synergy with the acquisition system. This is pursued through close collaboration with other groups in our department and, in particular, the Integrated Circuits group (Eugenio Cantatore and Pieter Harpe). In this context, with the aim to achieve ambulatory monitoring at home, dedicated front-ends and signal analysis are being jointly designed to minimize the power consumption of the acquisition system and, more recently, to enable comfortable contactless sensing by the use of capacitive electrodes.

CARDIORESPIRATORY MONITORING

The ability to monitor the cardiorespiratory system has important implications for several wide-spread diseases. Alongside standard electrophysiological measurements, such as the electrocardiogram, we are now considering photoplethysmography, which is ideal for long-term monitoring because of the unobtrusive nature of modern implementations. We have been especially focusing on the design of signal analysis that is robust to motion artifacts. To this end, model-based adaptive filtering has proven valuable, enabling the detection of spontaneous cardiac activity even in complex scenarios such as cardiopulmonary resuscitation.

The use of a smart watch with embedded wrist photoplethysmography is also being investigated for the detection of cardiac arrhythmias. The prevalence of cardiac arrhythmias is strongly increasing because of the ageing population and improved survival of patients with cardiovascular disease. Atrial fibrillation (AF) is the most common arrhythmia, affecting 5.5% of the population of 60 years and older. AF is associated with increased mortality and increased risks of stroke and has been labeled a “silent epidemic” because often patients do not experience symptoms. When AF is detected in time, the risks of stroke

can be managed by treatment with e.g. anti-coagulants. There is therefore a strong need for early detection of AF. Our goal is to make a major advance in the photoplethysmographic detection of AF, by developing novel signal processing methods, so as to equip a watch with the capability to robustly detect AF during sleep and daily living conditions. To this end, in collaboration with Philips and the Catharina Hospital Eindhoven (Lukas Dekker), we are developing signal-analysis methods based on models describing the characteristics of photoplethysmographic signals and the (patho)physiology of AF.

Next to the cardiac activity, measurement of the respiratory activity is also necessary to monitor the progress of several dysfunctions. For instance, obstructive sleep apnea affects over 9% of the adult population in western countries, with many undiagnosed cases. Assessment of respiratory effort is essential in the detection of breathing-related arousals. However, the gold standard technology for measuring alveolar pressure (esophageal manometry) is invasive and hence unpractical for long-term monitoring overnight, specifically in children. We are now investigating, in collaboration with the Kempenhaeghe center for sleep disorders (Sebastiaan Overeem and Hans van Dijk), the feasibility of using surface diaphragm electromyography to measure respiratory effort. This would provide a nonobtrusive and comfortable alternative to esophageal manometry, facilitating monitoring and disease management.

In the continuous effort towards the development of new technology supporting sustainable and high-quality healthcare, relevant advances in sensing technology must be constantly monitored and considered. For instance, recent developments in ultrasound technology is now making ultrasound monitoring feasible. Capacitive micromachined ultrasonic transducers (CMUT) can be realized as thin, unobtrusive patches that can be easily positioned on the skin and used to transmit and receive ultrasound. By intelligent driving schemes, able to dynamically adjust to moving targets and changing geometries, operator-free ultrasound monitoring can in principle be implemented. This new opportunity is first being investigated in the context of hemodynamic monitoring. Poor fluid management, hemodynamic instability, and cardiac dysfunction are recognized as the leading causes of perioperative complications and poor outcomes. As such, there is an increasing clinical awareness that adequate hemodynamic monitoring can enable earlier and more appropriate therapy, improving clinical outcome and reducing costs. Existing monitoring solutions have important drawbacks in terms of clinical use and reliability, limiting their implementation into routine clinical practice. Therefore, dedicated, adaptive signal processing methods are currently being developed, in

collaboration with Philips and the Catharina Hospital Eindhoven (Arthur Bouwman), to enable the use of CMUT technology for unobtrusive and reliable hemodynamic monitoring of perioperative and critical care patients.

NEUROMUSCULAR MONITORING

Characterization and understanding of the neuromuscular system represents the basis for the design of effective training programs addressing different objectives, from boosting the performance in athletes, to improving balance and coordination to prevent life-threatening falls (70% of accidental deaths) in the elderly population. The neuromuscular system is generally intended as the combination of nervous system and muscles, working together to enable movement. More specifically, the nervous system is divided into the central nervous system and the peripheral nervous system, the latter being referred to as neuromuscular system and composed of peripheral nerves and muscles. The peripheral nerves connect the spinal cord to the muscles in a feedback fashion, enabling involuntary control of the muscle tension through neuromuscular reflex.

We have been focusing on the assessment of neuromuscular reflex mechanisms in order to improve the efficiency of muscle training and rehabilitation programs, in collaboration with the department of Sports Medicine at the Máxima Medical Center (Goof Schep), and other international institutes. A novel device has been realized over the course of 10 years that imposes vibrating loads to selected muscles in order to enhance and study their neuromuscular adaptation. Valorization of these efforts has also led to the foundation of HiPerMotion, a high-tech company producing systems for muscle training able to generate high-frequency (up to 80 Hz), force-modulated loads that are applied to the muscles through a pulley system (Figure 10).

Characterization of the neuromuscular system is carried out through extensive use of electromyography, i.e., the analysis of the muscle electrical activity. Advanced algorithms have been designed for the extraction of electromyographic features that carry relevant physiological information on the neuromuscular activity elicited by vibrating loads at different frequency and amplitude. For these studies, the removal of motion artifacts is crucial, and requires deep understanding of their formation throughout the acquisition system in order to solve the confusion between motion artifacts and muscle synchronization with the applied loads. Complex electromyographic measurements during transcutaneous electrical

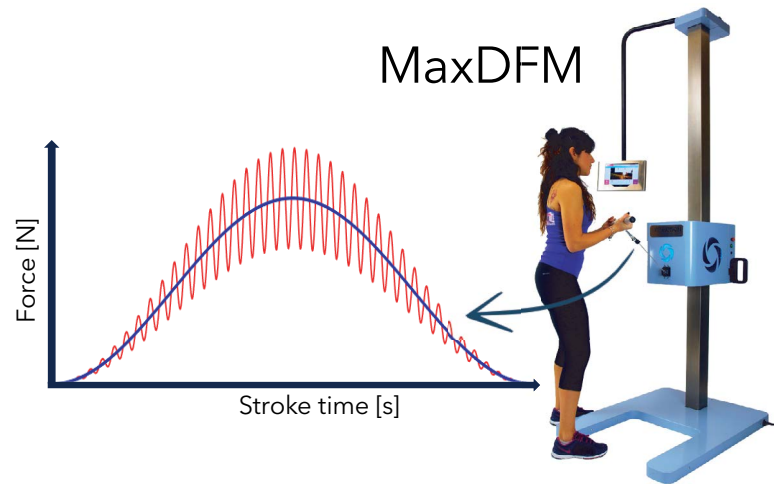


Figure 10. Maximized dynamic force modulation (MaxDFM) system for neuromuscular conditioning applying a dynamic load to the muscles consisting of a slow-varying force modulated at higher frequency.

neural stimulation have also been employed to characterize the effect of vibration on nerve excitability, in collaboration with Kempenhaeghe (Hans van Dijk). Moreover, measurements of balance during or after vibration exercise are being explored to elucidate on the effects on balance control of the induced variations in nerve excitability.

These activities are an additional representative example of a continuous effort in the development of models that provide a better interpretation of complex physiological processes, with the aim of addressing real clinical needs, such as the prescription of improved programs and exercises for muscle conditioning and rehabilitation.

Impact

All this research and the obtained international recognition could not have been achieved working alone. Over the years, I have established the Biomedical Diagnostics (BM/d) Research Lab in order to integrate the complementary knowledge required in such a multidisciplinary domain. Working as a team, we have been able to keep expanding our knowledge and efficiently leverage our complementary background. I firmly believe that a structured team, working in a coordinated manner, can accomplish much higher results and recognition than scattered individual researchers working on their own.

I would like to mention important scientific contributions from BM/d board members in the areas of fetal vectorcardiography (Rik Vullings), electrohysterography (Chiara Rabotti), molecular ultrasound imaging (Simona Turco), ultrasound quantification (Ruud van Sloun), and electromyography (Lin Xu), integrating physics-driven modeling with data-driven probabilistic interpretation. These achievements have also profited from the assembly of a laboratory equipped with state of the art biomedical sensing technology, and further enriched throughout transversal collaborations within our department, where expertise in photonics, integrated circuits, and electromagnetic fields can be combined with dedicated signal analysis to form new measurement chains leading to improved patient diagnostics and monitoring. Contactless capacitive sensors or optical fibers embedded in a bed are just some examples of the envisioned development of new technologies enabling unobtrusive home monitoring.

Without external input, however, we would never have achieved comparable results. Our research cannot stay barricaded within the academic walls. Together with clinical and industrial partners, we first need to learn about their needs and interest, and then work together towards the validation and implementation of the developed solutions. This has been pursued throughout strategic cross-appointments of distinguished experts from clinic and industry, such as Hessel Wijkstra (AMC University of Amsterdam), Guid Oei (Máxima Medical Center), Erik Korsten (Catharina Hospital Eindhoven), and Ronald Aarts (Philips), strengthening our bond with the outside world. Together we can generate ideas that have real potential to make an impact to our society.

In fact, I believe that technological innovation making a societal impact builds on a fundamental triangle combining academia, clinic, and industry. In this way, we develop solutions that address both clinical needs and industrial interest. This is required for the clinical translation of our results, supported by industrial implementations that facilitate their clinical validation and uptake. To this end, building on a unique ecosystem made of flourishing companies and research-oriented, regional hospitals, the Eindhoven area is shaping towards a more structured and efficient approach to research and innovation. The most representative example is the e/MTIC (Eindhoven MedTech Innovation Center), a synergic research program involving TU/e, Philips, and hospitals in the Eindhoven region. Not only does the e/MTIC bring together all the expertise required for research development and valorization, but it also has the ambition to accelerate research by optimizing the lengthy and redundant review processes for ethical approval of clinical research and validation of new technology, which are currently hampering Dutch and European biomedical research. This is essential to be innovative and ahead of international competitors.

Clinical translation and uptake indeed requires implementations that are suitable for clinical validation and use, and can be easily integrated in a clinical workflow. Larger companies often lack the flexibility required to support this process. More and more, small spin-off companies are formed that have the freedom and drive to push the implementation and promotion of new technology. This process creates unique opportunities for innovative technological solutions to make a real impact on society and healthcare.

I have had the possibility to lay the basis for two spin-off companies in the area of neuromuscular rehabilitation (HiPerMotion) and prostate-cancer diagnosis by ultrasound (CUDI). This experience provides a unique opportunity to enrich our view on research with different perspectives, accounting also for societal need, market size, and go-to-market strategies. In this context, promotional activities become essential, as well as good understanding of the main stakeholders playing a role in the intended clinical applications. To make a real impact, our research should already account, in the early phase, for the full socio-economic context, moving towards technological solutions that are suitable to raise industrial and clinical attention. Generation and protection of intellectual property is a key aspect in this process. Here, a timely and appropriate strategy should be defined that accounts for the full valorization process. I believe that, especially young researchers, should receive proper formation to effectively pursue the valorization of their ideas.

Mission

Indeed, we should keep our attention and focus on our young researchers and students. This refers back to the title of this inaugural lecture. The term “human” has multiple connotations. In particular, the drive behind most of our research efforts and achievements is human, based on our natural inclination towards curiosity. And I am especially curious and eager to know how the human body functions and how we can help people by detecting and curing their dysfunctions. Therefore, I believe that human rather than artificial intelligence should be dominating in order to achieve human rather than machine learning. Machine and deep learning provide extraordinary means to interpret the large amount of data that we now have available, providing an additional contribution to our knowledge and understanding. In fact, I firmly believe that effective and reliable healthcare improvements can only be achieved through understanding human (patho) physiology and the full measurement chain employed to acquire biomedical signals and data.

Restoring human rather than machine learning to the spotlight is especially valuable for our students. They represent the future of our society, and our mission is to teach them to effectively use their unique human inclination towards curiosity by asking questions rather than jumping to quick solutions. Curiosity and creativity is the basis of innovation and are prominent when we are young, while they often decline as we age. That is why our students and young researchers have immense potential to be innovators and to face the modern challenges in healthcare. Our mission is to provide them with knowledge and a scientific approach. Their task is to stay open, curious and creative, like a child. After all, I believe that inventive ideas occur in that very moment when, with all our knowledge, we are children again.

Acknowledgment

To conclude, I would like to express my gratitude for the support and guidance of several colleagues that have been fundamental in my career.

First of all, my deepest gratitude goes to Jan Bergmans, director of the Signal Processing Systems group at TU/e, who has represented a continuous reference in my career; an example to imitate in order to elevate my critical and conceptual thinking. He has always supported me, in good and bad times. And he has given me freedom, teaching me to strive for excellence, while doing the research I enjoyed the most. Looking back at the past 18 years in his group, I can really appreciate how lucky I have been with such a knowledgeable, demanding, and yet supportive mentor.

My career has definitely changed gear through my collaboration with Hessel Wijkstra. Rather than a collaboration, I would call it friendship, based always on transparency and loyalty. Together we have been very successful with our research on prostate cancer diagnostics. From Hessel I have learned how passion for research can be endless and how "engineer thinking" can be successfully translated into a clinical environment. And I have learned to think beyond technology, being always aware of the clinical needs.

My passion for research originates back to 1999. Rino Del Prete, my graduation supervisor in Rome, passed his passion onto me, as well as his scientific and meticulous approach. This is the greatest gift I could ever have received, changing and inspiring my entire life. The friendship that we have built over the years has always represented a fundamental reference for making all the important choices in my life.

Research can and should also be fun. I have learned this from Erik Korsten during my PhD work, when he showed me the magic world of the "bubbles" for the first time. Back then, Ton Kalker guided my first steps in research, forming the basis to grow as a researcher. I have great memories of that time and the open relationship we established, giving me great energy to face the daily challenges of PhD study.

Many more colleagues have in fact contributed to my scientific career. Here I would like to mention Steve Feinstein, who has constantly promoted my research in the International Contrast-Ultrasound Society, Piero Tortoli, a true Viola friend who has strongly aided my recognition in the ultrasound community, and Djan Khoe, an invaluable reference for all my personal grant applications.

My PhD work and everything that followed results from the sacrifice of my parents Anna and Mauro. They always supported my stay abroad with infinite love, despite their sad feelings and loneliness. But most importantly, they raised me with sound principles based on modesty, perseverance, and respect, establishing a solid foundation for a career made of learning and teaching.

And finally, I'd like to thank God for giving me the chance to pursue this fascinating career, and for enriching my life with two marvelous creatures, my children Mara and Michael. Their smiles give me all the energy I need in life. And my life is mostly identified in a special person, patient partner and careful mother, my greatest love, Federica.

Curriculum Vitae

Prof.dr.ir. Massimo Mischi was appointed full-time professor of Model-based quantitative analysis of biomedical signals at the Department of Electrical Engineering at Eindhoven University of Technology (TU/e) on March 1, 2018.

Massimo Mischi (1973) received an MSc in Electronic Engineering at La Sapienza University in Rome (1999). At TU/e he received a PEng degree (2002) and a PhD degree (2004), and became assistant professor (2007) and then associate professor (2011) in the Electrical Engineering Department. He was awarded a VIDI grant (2009) and an ERC Starting Grant (2011) for his research on angiogenesis imaging. At TU/e he heads the Biomedical Diagnostics (BM/d) Lab. This lab focuses on model-based quantitative analysis of biosignals, ranging from electrophysiology to diagnostic imaging. His research is widely recognized, via e.g. two Martin Black awards (2008 and 2018) and the EUROSON keynote lecture (2017). Massimo Mischi is chairman of the IEEE-EMBS Benelux Chapter, board member of the Urological Imaging Section of the European Association of Urology, and secretary of the Dutch Society of Medical Ultrasound. He is also associate editor of the Elsevier journal Innovation and Research in Biomedical Engineering (IRBM) and of the IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. He has contributed to over 300 scientific publications, 11 patents and patent applications, and 2 spin-off companies (HiPerMotion and CUDI).

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