

Progress in waves

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A portrait of Prof. dr. ir. Maarten Paulides, a middle-aged man with short, dark, wavy hair and light blue eyes. He is wearing a dark navy blue suit jacket over a white dress shirt and a dark tie with thin, light-colored diagonal stripes. He has a slight smile and is looking directly at the camera. The background is a blurred outdoor scene with green foliage.

Prof.dr.ir. Maarten Paulides
June 3, 2022

INAUGURAL LECTURE

Progress in waves

TU/e

**EINDHOVEN
UNIVERSITY OF
TECHNOLOGY**

DEPARTMENT OF ELECTRICAL ENGINEERING

PROF.DR.IR. MAARTEN PAULIDES

Progress in waves

Presented on June 3, 2022
at Eindhoven University of Technology

Prologue

Dear Rector Magnificus, College van Bestuur of Eindhoven University of Technology, colleagues, family and friends, esteemed audience.

Today, right now, I find myself back at the exact same place as when I visited TU/e for the very first time. The open days of 1997. And I can still recall walking down the infamous 'Limbopad' in my first days as a student and being overwhelmed by feeling daunted and excited at the same time. A young man taking his first steps in the big world. Not for a moment did I even imagine that one day I would stand here to be inaugurated as a full professor.

Needless to say, I am very proud to be standing in front of you today. Moreover, I am honored that so many of you are supporting me with your presence.

In the next hour, I would like to share with you my fascination with waves by guiding you along the waves of progress. Waves of progress induced by giants in the history of biomedical electromagnetics, as well as my own progress in waves. And ultimately, I would like to give you a peak at the waves of progress to come. In this hour, I hope to spark your excitement for waves, demonstrate their increasing role in healthcare and discuss the leading role of Eindhoven in medical technology.

Throughout this speech, I would also like to argue why I think that we should start relying more on modeling than on experimentation in medical device design.

The need for waves of progress

Improvements in hygiene, diet, disease prevention and healthcare have steadily increased our life expectancy, i.e., from 31 in 1850 to 72 in 2017. In the Netherlands, life expectancy increased from 40 to 82 in this period. Our aging society now poses the question of how to balance improvements within the available health budget. The tremendous improvements in healthcare also mean that financial requirements are rising steeply. In addition, the number of chronic and age-related diseases is increasing and ever older and more fragile patients are being treated, who cannot endure aggressive treatments and increasingly require substantial aftercare. In this landscape, how can our society provide broad access to the appropriate cure and care?

I firmly believe that electromagnetic-based technologies will form a cornerstone in our answer to the need of society for the highest quality sustainable healthcare. Medical technologies (MedTech) will play an important role in the balancing act by providing cost-effective monitoring, diagnosis and therapy approaches

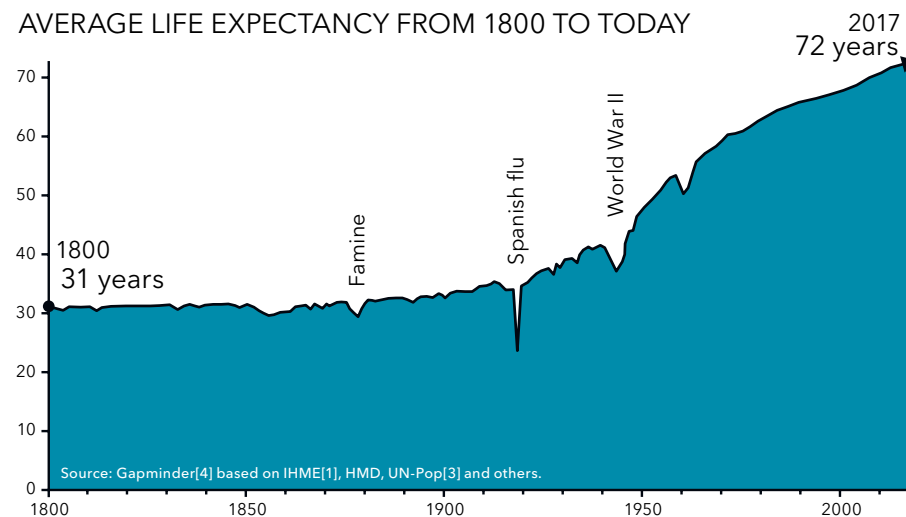


Figure 1. Average life expectancy worldwide, including the reasons for strong declines.

Source: <https://www.gapminder.org/>

for personalized care and cure. The distinct features and non-invasive nature of electromagnetic waves at different frequencies places them at the core of many medical applications. Devices like brain stimulators, magnetic resonance (MR) scanners and thermal tissue ablation devices rely on different types of electromagnetic waves. In addition, electromagnetics provides distant and in-body data transfer to enable point-of-care diagnostics and interventions closer to home.

Furthermore, I believe that the most effective way for developing and implementing these technologies is through tight collaboration between academia, clinical centers and industry. Waves of exchange in this 'Golden Triangle' are required to ensure a connection between engineering research advances and the needs of society and to crystalize the most cost-effective approaches.

Biomedical electromagnetics

Biomedical electromagnetism combines three elements: biology, medical applications and electromagnetics. The operating frequency determines the wavelength of the EM wave and the wave penetration into the tissue. Generally, only so-called non-ionizing wavelengths are included, i.e., waves that do not affect the deoxyribonucleic acid (DNA) of living cells. The range in frequency is generally defined from zero hertz (static fields) to waves comprising visible light. The field aims for the application of such electromagnetic waves to the monitoring, diagnosis or treatment of various conditions.

Historical progress in waves

FIRST WAVE - BIOELECTRICS AND BIO-ELECTROMAGNETICS

Few people realize how old the use of therapeutic bioelectrics is. The ancient Romans used electric stingrays. The fish were held against the scalp to ease headaches, depression, epilepsy and, surprisingly, hemorrhoids. Of course, the scientists of those days were still far from grasping the principles of brain stimulation.

Our real understanding of bioelectricity started in the late eighteenth century when the Italian physician and physicist Luigi Galvani discovered that the limbs of a dead frog started shaking when touched by different metals. Galvani thought that electricity was generated by fluids in the nerves of muscles. Italian physicist Alessandro Volta, however, hypothesized that the two different metals caused the current. Note that he developed the battery based on this notion. Other scientists built upon the ideas of Galvani. Around 1848, Emil Dubois-Reymond discovered that short-lived electrical events called action potentials occur in several types of cells. These action potentials are used to facilitate inter-cellular communication and activate intracellular processes; hence they can be found in brain, muscle and endocrine cells.

The work of Hermann Ludwig Ferdinand von Helmholtz (August 31, 1821 – September 8, 1894) moved the field from bioelectricity to bio-electromagnetics, i.e., electromagnetic 'waves'. A physician by training and a self-taught physicist, Helmholtz made many other notable discoveries, including on the conservation of energy and the perception of vision and sound. He researched how signals propagate through muscles and found that the brain orchestrates this activity. He was among the first to link thermal effects to electromagnetic waves, which is used in hyperthermia therapy today. Not surprisingly, Helmholtz's student Hertz proved the existence of electromagnetic radiation and another student, Wien, won a Nobel Prize for his work on heat-related electromagnetic radiation.

The works of Galvani, Volta and Helmholtz were instrumental in developing the field of bioelectromagnetics. In many ways, they also serve as models for our efforts in the Golden Research Triangle at TU/e since they combined a profound medical view with an applied research approach. Aided by the works of Dubois-Reymond and Helmholtz, the realization that the brain employs electricity to function emerged in the second half of the 1800s. Hence, this is when the search for effective brain stimulation really began. Various stimulators and implants were developed with the goal of locally influencing information processing in the brain. However, the first modern brain stimulation treatments were not very safe and, even in the 1950s, the mortality rates of some invasive procedures were about 10%. It can be said that the application of electromagnetism in e.g., brain stimulation preceded the fundamental understanding of the field-related effects. This is due to the fact that EM-related mathematics and physics grew in parallel to bio-electromagnetics.

SECOND WAVE - ELECTROMAGNETIC THEORY AND MODELING

Around the 1870s, electromagnetism was scattered over several principles. Scientists such as Gauss, Ørsted and Ampère had described the behavior of either electric or magnetic fields in specific situations. Michael Faraday postulated that electric and magnetic fields could extend through free space. Faraday also proposed a link between varying electric and magnetic fields.

Enter James Clerk Maxwell. Maxwell realized that an electric field generates a magnetic field and vice versa. The Scottish mathematician and physicist mathematically linked the laws describing electric and magnetic fields in 20 equations. Using vector notation, his laws were condensed by Oliver Heaviside from 20 to four equations (excluding conservation of charge), usually referred to as Maxwell's equations. Maxwell's notion that electromagnetic waves propagate at the speed of light sparked the idea that light is a wave. His work was later validated by Hendrik Lorentz, who could describe the scattering of light using Maxwell's equations, and by Heinrich Hertz, who experimentally showed that electromagnetic waves have behavior similar as light waves. Einstein built heavily on Maxwell's ideas on wave propagation for his theory of relativity. Note that the expected impact of the discoveries was small at the time. Heinrich Hertz even stated: "Electromagnetic theory is completely useless. The only interesting thing is that Maestro Maxwell is right". We now know differently...

THIRD WAVE - ELECTROMAGNETIC TISSUE PROPERTIES

At the atomic scale, the calculation of the electromagnetic fields inside tissue requires not only Maxwell's equations but also the so-called constitutive equations of tissues. These are theoretically determined by calculating how (the electron cloud of) a molecule responds to the local fields through the Lorentz force and other forces. Including all of the forces leads to changes in the molecules, which are used to calculate polarization (P) and magnetization (M) as a function of the local fields. The polarization and magnetization of nearby molecules affect those local fields. It is important to note that real materials are not continuous media; the local fields in real materials vary wildly at the atomic scale. Hence, the fields need to be averaged over a suitable volume to form a continuum approximation using quantum mechanics.

Zooming out from atomic to tissue scale, an inhomogeneous material is usually approximated by a homogeneous effective medium. Furthermore, the modeling of the electromagnetic properties of tissues relies upon measurement. In this domain, noteworthy is the 1996 experimental work of Sami and Camelia Gabriel, who summarized the literature and added a comprehensive set of measurements for many tissues. Their data-derived models still form the basis for most bioelectromagnetic modeling.

FOURTH WAVE - MODEL-BASED DEVICE DESIGN

Since Maxwell's equations cannot be solved analytically for many real-world scenarios, computational electromagnetics techniques are used. These computational numerical techniques provide approximate solutions to real-world scenarios, like electromagnetic field generation by antennas and the propagation of waves through tissues. Building upon progress in computational power and new imaging, computational electromagnetics enabled full-body simulations for electromagnetic safety to become possible in the 90s. The most popular method in bio-electromagnetics research is the finite difference time domain (FDTD) technique. In FDTD, space is discretized in terms of cubes ('voxels') and Maxwell's equations are solved in a cyclic manner: the electric field is solved at a given instant in time, then the magnetic field is solved at the next instant in time and the process is repeated over and over again. The basic FDTD algorithm traces back to a seminal 1966 paper by Kane Yee in IEEE Transactions on Antennas and

Propagation. Allen Taflove wrote a seminal book, originated the descriptor 'finite-difference time-domain' and made major contributions on computational design approaches to electromagnetic fields ranging from radiofrequency to light waves ('photonics').

Currently, FDTD is the primary means of modeling many scientific and engineering problems addressing electromagnetic wave interactions with tissue. Since about 2000, FDTD techniques have been making their contribution to medical device design. Following advances in computational power and imaging, patient-specific approaches have also become popular. However, the validation of the electromagnetic waves in tissue and the overcoming of uncertainties is still an ongoing topic of research. Following the discovery Helmholtz, a prominent method for validation is the heating effect of the electromagnetic waves. An important driver here is the extraction of tissue properties and their use in computational modeling in electromagnetic hyperthermia therapy. Ergo, an example of progress in the triangle: academia delivered FDTD, industry provided computational power and the clinics apply the combined results for hyperthermia cancer therapy.

HYPERTHERMIA CANCER THERAPY - VALIDATION OF ELECTROMAGNETIC MODELS

One of the oldest medical books known to man, the Smith papyrus, references a primitive form of heat-based ablation as a treatment for breast cancer. Romans and Greek philosophers also recommended thermal treatment in the form of hot baths for all kinds of diseases. German surgeon Carl D. W. Busch observed that high fever cured cancer in some patients, which spurred young American surgeon William B. Coley to study the injection of different types of bacterial pyrogens into tumors.

We now know that vasculature in tumors is chaotic, so tumors contain many regions with low blood perfusion which are therefore hypoxic (low oxygen pressure: pO_2), causing a low pH due to the resultant anaerobic metabolism. Such hypoxic regions are the regions where tumors typically recur after radiotherapy and chemotherapies. Temperatures around 43°C are specifically cytotoxic for cells in these hypoxic environments, in which radiotherapy (RT) and chemotherapy are less effective. Hyperthermia (HT) also has a number of other strongly temperature-dependent effects (Figure 2). When combined, the effects are a strong stimulus for radio, chemo and immunotherapy, but each combination has its own optimum temperature. Clinically, the beneficial impact of HT combined with ionizing

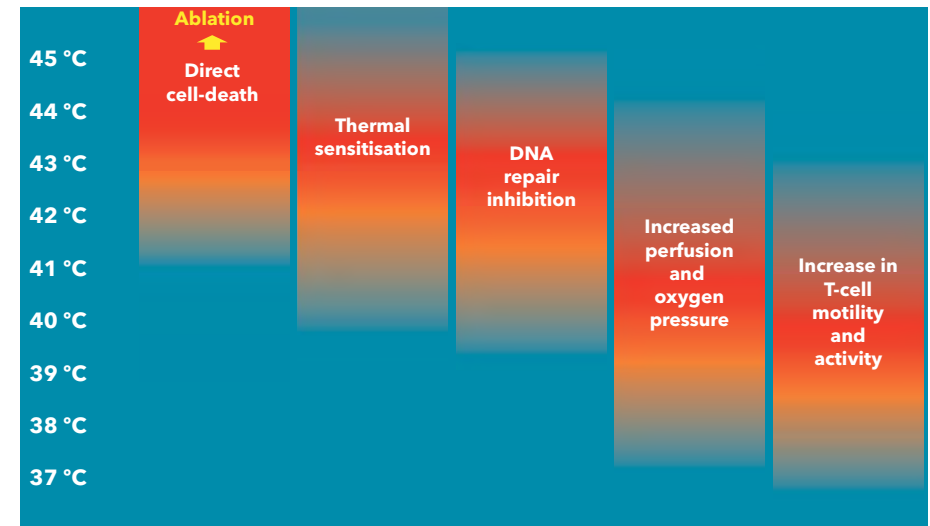


Figure 2. Temperature-dependent effects of hyperthermia.

radiation and a number of chemotherapeutics was demonstrated by phase III trials. Importantly, HT generally causes no increase in treatment side effects.

Current HT treatments are built on applying focused radiofrequency electromagnetic waves. Such approaches inevitably also heat tissues adjacent to the tumor. In addition, clinical data shows that heating at higher temperatures should improve treatment result. Unfortunately, the application of higher temperatures is prevented by the complex and imprecise treatment and monitoring technology. There is therefore a need for improved electromagnetic approaches in this field. Such advances would also enable the validation of the electromagnetic modeling in patients during treatment. Enter another wave of research on temperature-controlled hyperthermia, aimed at determining electromagnetic (and thermal) tissue properties.

My waves of progress

As researchers, we are very dependent on those that we meet on our journey. We are standing on the shoulders of those before us and leaning on the ones beside us. I would like to pay tribute to those giants by mentioning many of them while explaining what I learned during my own personal journey. This carries the risk that I forget some giants, for which I apologize. Of course, the true giants and the continuous inspiration were the patients, as well as the PhD students, postdocs, clinical staff and students.

GETTING READY FOR MY WAVES

My career as an engineer and a researcher started at my father's factory. Based on this, I tried to explain how a DC motor works in front of 11-year-olds at primary school. Although my father had helped by giving coils from the factory, I think that explaining all of the details was quite ambitious, especially since I am not sure if I myself really grasped the basics. It did spark excitement to know how movement can start by connecting just two wires. Later, at a motor drive company in Wales after secondary school, my interest in electrical engineering was further deepened. The director, Howard Kinsey, was vital in sparking my interest in engineering research. Hence, there was little question about which studies I would pursue. Coming from HAVO, I did need a short but pleasant stay at Fontys Hogeschool to start my studies here in Eindhoven. I remember that my learning had already been strongly accelerated by the connection of theory with application. For example, I found that Electrical Engineering is a nice way to learn advanced Math and Physics, since all theory could directly be connected to intuitive examples.

My research career started with an internship when I asked Professor Anton Tijhuis, who was heading the EM group, if he had an assignment related to doing "something useful" with EM. At the time, EM was seen as one of the most difficult subjects in Electrical Engineering and maybe still is. I wanted to get an experimental feeling for the topic that supports the theory. Despite that, Anton was unhappy with the formulation of my request, since "everything we do is useful." He helped me to get an internship position at l'École supérieure d'électricité (Supélec) near Paris. Here, I learned the details on experimentation from Dr. Jean-Michel

Geffrin in the world-leading lab of Professor Jean-Charles Bolomey in the field of microwave imaging. This work got me interested in the challenges of antenna near-field measurements and their medical application.

MY WAVE 1 - MODEL-BASED HEAD AND NECK HYPERTHERMIA DEVICE DESIGN

After this period, I started my graduation project and was supervised by Peter Zwamborn, who connected me to Gerard van Rhoon of the Daniel den Hoed Clinic in Rotterdam, now Erasmus University Medical Center. From the options Gerard presented, I found the development of an entirely new hyperthermia applicator for the head and neck region most interesting. From my later supervisor Peter Levendag, I learned that this was an excellent choice since the results of current treatments in this region were, and still are, dismal. Survival rates are as low as 40-60% at five years and conventional therapy causes tremendous treatment-limiting side effects. We therefore started analyzing the potential of focused microwaves in this region. I learned that a choice must be made between a higher frequency that permits a smaller heating focus or a lower frequency which penetrates deeper into the tissue. Focusing and deep penetration can be combined when using a so-called phased array approach, which was originally shown for communication purposes in 1905 by Nobel laureate Karl Ferdinand Braun. When placed in a ring around the body, phased arrays can be used to generate a rugby ball-shaped focus at depth, for which size depends on wavelength and which can be electronically steered by adjusting the phase-delays of the signals sent to each source.

We exploited this phased array concept and were the first in the world to design a hyperthermia applicator based on detailed electromagnetic simulations and using patient-specific models. Worldwide, we were one of the initiators of the wave in model-based electromagnetic device design. A major part was re-coding an FDTD solver developed at the Netherlands Organisation for Applied Scientific Research (TNO) to study how various applicator designs would perform. An important element of research was also an antenna design that can be accurately modeled to enable model-based design but also predictive treatment modeling. We collaborated with the Biomedical Imaging Group Rotterdam (BIGR) of Erasmus MC for an automated and accurate procedure for patient model generation as input for pre-treatment planning simulations. In addition, we developed the HyperCollar3D for a more predictable and comfortable patient setup. All of these elements were a crucial foundation for the last step, the implementation of a computer-guided

treatment procedure that informs the operators and helps to adjust the treatment to the patient's needs.

Focused microwave hyperthermia by the HyperCollar (clinical prototype 1) and HyperCollar3D (clinical prototype 2) have since been applied to over 80 patients suffering from head and neck cancer. Our data indicates that second-time radiotherapy combined with hyperthermia with the HyperCollar3D leads to clinical outcomes that match those of re-irradiation with chemotherapy. Importantly, focused microwave hyperthermia avoids the substantial long-term side effects of chemotherapy. The very encouraging clinical results strongly support the feasibility and benefit of our approach. Driven by the many requests from other clinics, the need for their input in multi-institutional clinical trials and the desire for broad application, we started the company Sensius (www.sensiusthermotherapy.com).

MAGNETIC RESONANCE TEMPERATURE IMAGING

The first-time application of model-guided device design in hyperthermia enabled predictive electromagnetic modeling. However, due to uncertainties in the thermoregulation of tissue, real-time invasive 'thermometer probes' are still needed to monitor the treatment. These probes are uncomfortable, can often not be placed and inform the operator only at a few locations. Ergo, the quest for 3D non-invasive assessment of temperature began.

Several techniques for non-invasive temperature measurements during HT are under investigation, but the only clinically applied method is based on nuclear magnetic resonance. Magnetic resonance is based on the spin (rotation) that the nuclei of molecules exhibit. These are excited into a high energy state when exposed to a matched radiofrequency (RF) pulse at the frequency of their rotation, i.e., the Larmor frequency (Figure 3).

The most common method of temperature measurement using MRI, i.e., MR thermometry (MRT), is measuring the shift in the resonance frequency of the hydrogen nucleus. When temperature increases, the water molecules move faster and are therefore spaced further apart. This higher spacing reduces the molecule bonding of hydrogens, which increases their self-shielding with their electron

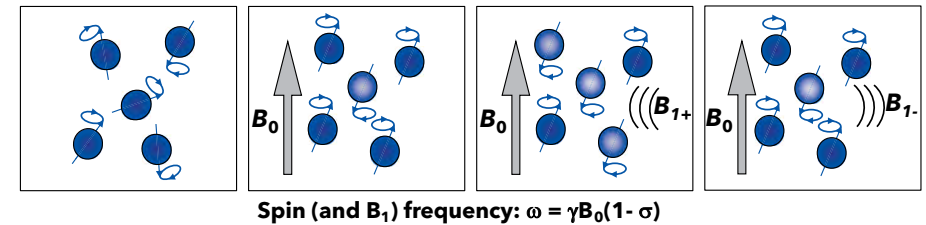


Figure 3. Steps to exploit the nuclear magnetic resonance (NMR) effect in magnetic resonance imaging (MRI). Note that ω denotes frequency in radians, γ is the gyromagnetic ratio and σ is the self-shielding caused by the electron cloud around the nucleus. From left to right: application of a strong magnetic field (B_0) aligns the spinning of the nucleus; pulsing a frequency-matched RF wave (B_{1+}) excites some more of the nuclei into the high energy state; when B_{1+} ends, the spins relax to their low energy state while generating RF magnetic fields (B_{1-}). These RF fields are measured by coils and the signals provide information on the number of nuclei that relaxed.

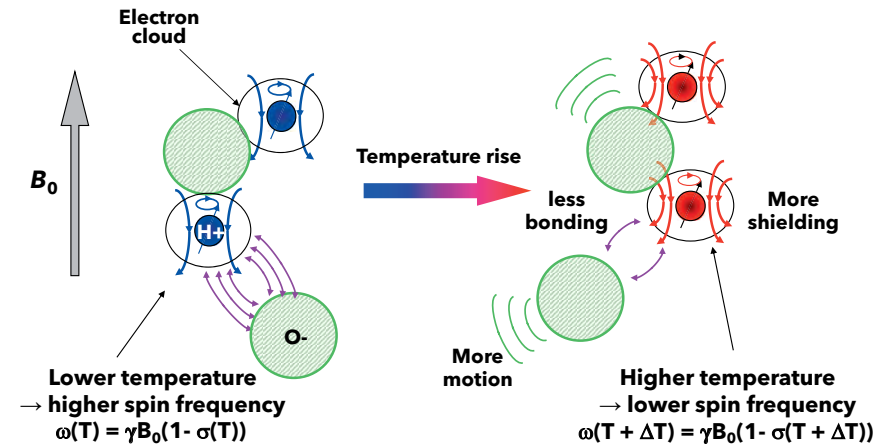


Figure 4: Temperature impact on the proton resonance frequency.

clouds and lowers their spin frequency. This frequency shift can be measured and is termed the proton resonance frequency shift (PRFS) method. Although this method is very powerful, since the shift with temperature is linear and equal in water-rich tissues, temperatures in fat and bone cannot be measured.

MY WAVE 2 - MODEL-BASED MRT IMPROVEMENT

Since the PRFS method is a differential method, magnetic field perturbations caused by perfusion and motion significantly affect PRFS-based temperature maps. Through a systematic review of the literature, we found that PRFS accuracy is generally better than 1°C in relatively static tissues, like brains and extremities, or when motion is reduced, like in sedated animals. However, measurement accuracy is unsatisfactory in or near moving tissue, like in the pelvic region. We recently discovered that inaccuracies in that region are caused by moving air bubbles in the intestines. These can be predicted by measuring the air motion before treatment. Hereto, we started to create model-based correction strategies in a collaboration led by Maurice Heemels. In a large consortium consisting of clinics, industry and engineering researchers, we developed a concept that aims to exploit the knowledge from simulations for the smart filtering of measurement data. We showed that our so-called 'POD-Kalman' approach improves the match between temperature prediction and the temperature acquired by intraluminal temperature probes by almost 50% (Figure 5).



Figure 5. BSD/3D/MR device at Erasmus MC for real-time MR guided hyperthermia in the pelvic region.

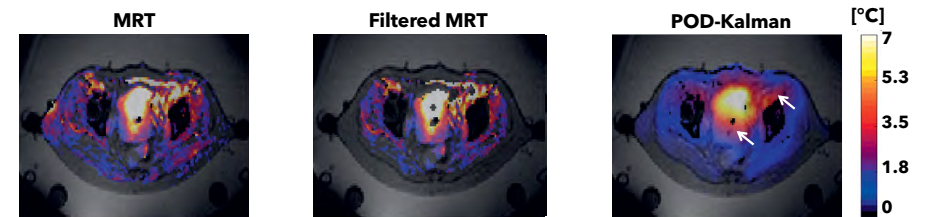


Figure 6. Temperature distributions after one hour of treatment: MR thermometry, filtered MR thermometry and POD-Kalman filtered temperature. With respect to the results after traditional filtering, the POD-Kalman filter reduced the mean absolute error from 1.3°C to 0.7°C and the standard deviation was reduced from 1.2°C to 0.6°C against intraluminal thermometry data. Note that the white arrow indicates the regions of the POD-Kalman filtered temperature where the temperature is underestimated compared to the filtered MR thermometry. This is expected to stem from a local error in the underlying simulations and can probably be solved by improving the simulations.

the simulations. Hereto, a data and physics-based approach is being developed for reducing the simulations from several hours to minutes. This step should enable re-simulation of the fields based on anatomy imaging during treatment and hence a better simulation-based interpolation of the measured temperatures.

MY WAVE 3 - THE MRCOLLAR

The focused microwave heating of the HyperCollar3D would also benefit highly from precise temperature control. To start developing such a system, we first investigated distortions by fast changes like breathing. In collaboration with Desmond Yeo and his team, we found that fast MR thermometry is needed to be able to correct for motion influences while sufficient signal is needed for accuracy. Since MR signal receive (B1-) is on the order of micro-Watts (uW) and the signals quickly decay, the signals should be measured nearby the region of interest (ROI). Hence, B1- is usually measured directly on the skin surface by receive (Rx) coil arrays. In HT, this was deemed impossible since the applicator obstructs this space. We therefore collaborated with Rob Mestrom and Bart Smolders on developing a novel printed antenna. This antenna was integrated into antenna modules and novel receive coils were designed and integrated, which strongly increases the SNR in a cylindrical phantom (Figure 7).

Building upon this device, we are working with the group of Juan Hernandez Tamames on MRI sequences tailored to this anatomical site and the coils inside the MRCollar. Together, we are gearing up to validate imaging performance in

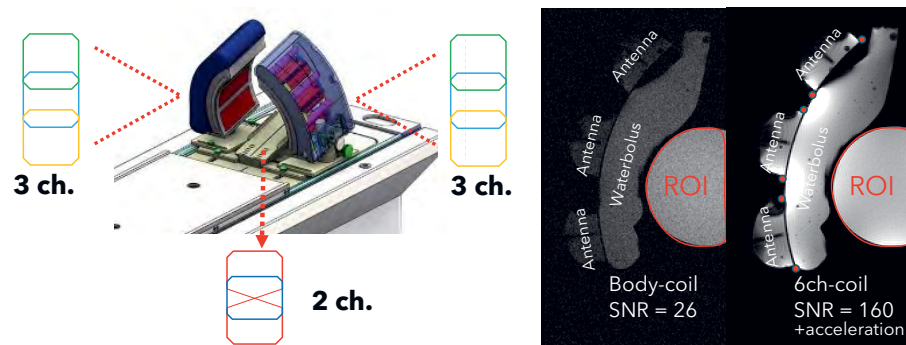


Figure 7. MR collar - HT system for the H&N region with six integrated Rx-coils (6ch-coil) that allow PRFS-based thermometry (1H-MRI) during heating. SNR in the region of interest (ROI) has been improved from 23 (body-coil) to 120 (6ch-coil plus 2 channel coil at the back).

volunteers and patients in preparation for the first world-wide application of MRT-guided microwave hyperthermia using the MRcollar. The MRcollar is expected not only to allow the close monitoring and control of temperature during treatment but also to enable the in-patient validation of electromagnetic and thermal modeling as input for the multi-physics model-based design of novel devices.

Future waves

Based on our research, a paradigm shift is also taking place: computational modeling is transforming the path to market for medical devices. Regulatory commissions throughout the world have started to recognize the great strength of computational modeling and digital evidence in medical device development and assessment. In the US, the food and drug authority (FDA) has recently released a guidance on “Computational Modeling Studies in Medical Device Submissions”, acknowledging the importance of computational modeling and simulation studies in the evaluation of the safety and effectiveness of medical devices. Meanwhile, the reinforcement of the new European Medical Device Regulation (EU MDR 2017/745) requires an increased number of studies even at the prototype level in order to meet new European standards.

These new provisions will reinforce the quality of the European medical device market but also increase the cost of medical device developments due to the higher requirements of pilot studies. MDR-compliant design means an exponential increase in preparation time and costs for early clinical trials. Reducing the number of (pilot) clinical trials by replacing them with virtual design processes based on accurate patient modeling is crucial not only for cost-effective development processes but also to prevent the need for safety studies involving animals. This strategy heavily relies on validated multi-layer bio-physics models based on rigorous clinically validated tissue models and standardized measurement approaches.

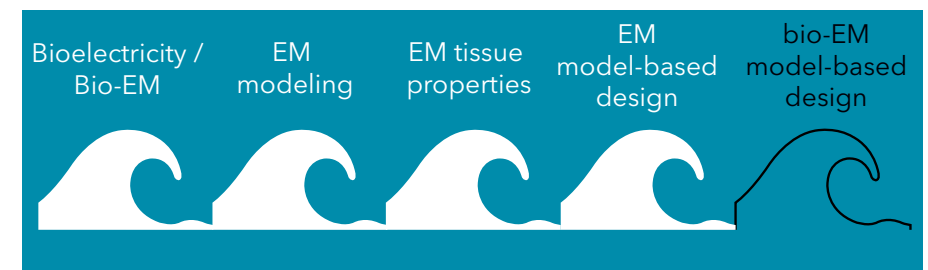


Figure 8. Historical waves of progress in electromagnetic medical device design, as well as the future wave on bio-EM-model-based design.

BIOELECTROMAGNETIC TISSUE MODELING

Computational bioelectromagnetic model-based design requires high-quality patient modeling. Worldwide, measurement standards are being defined for tissue properties assessment standardization. Triggered by the Society for Thermal Medicine, the American Society for Mechanical Engineering (ASME) has started defining committees for the creation of a lexicon, the standardization of terminology, and the definition of measurement standards. Due to their importance in the therapy, we are not only standardizing terminology and measurement standards for physics but also for bio-physics tissue modeling.

Bio-physics models are typically approximated. Direct measurement of tissue properties is difficult to carry out in tissue and rarely provides sufficient spatial sampling. An alternative to arrive at accurate bio-physics modeling is to infer the bio-physics tissue models from measurements. In this approach, the output (e.g., temperature) is monitored and the appropriate input (e.g., thermoregulation and thermal tissue properties) is determined by matching the bio-physics model predictions to real-time measurements during treatment. Since bio-physics tissue properties vary between patients, this procedure is needed for each patient. However, when aggregating the data obtained during many treatments, values for patient groups can also be estimated. This approach requires the following components:

1. Standardized measurement techniques for:
 - a. the quantitative monitoring of the relevant dose during treatment and, where possible, bio-physics tissue properties directly.
 - b. the imaging of patients in the treatment position to create patient-specific 3D models.
2. Big data collection through the large-scale application of 1a. and 1b.
3. Post-processing and model-based software to infer reliable and accurate bio-physics tissue properties.
4. Merging of the data from multiple clinics into (open-source) bio-physics tissue properties databases.

In this topic, collaboration in the Golden Triangle is vital to enabling broad access to high-quality data that enables the development and cross-validation of the tissue property reconstructions. For hyperthermia, I am in collaboration with groups at Erasmus MC, Ludwig Maximilian University in Munich and the University

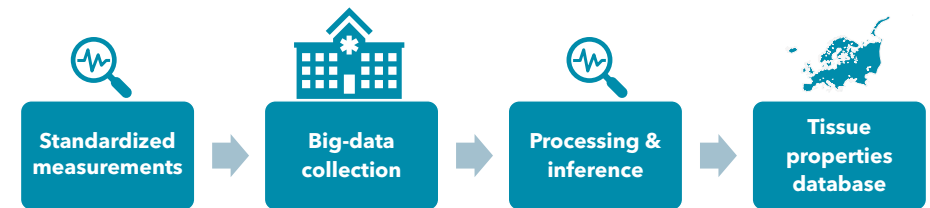


Figure 9. The development of tissue models for bio-physics model-guided device design.

of Cologne on data generation. Here, we are developing new MR imaging and tissue property inference methods to extract electromagnetic tissue properties and thermo-regulation tissue models. Besides applications in hyperthermia and MRI safety, such MR-based tissue modeling inference approaches are being investigated for our research at low frequencies (neuromodulation) and high frequencies (5G and 6G safety). In general, the beauty of MR approaches for tissue property inference is that this modality visualizes a combination of anatomical, physiological, thermal and metabolic tissue parameters while being non-harmful and therefore repeatable.

Spreading the waves

SUSTAINABLE HEALTHCARE ACCESS THROUGH TECHNOLOGY

Although global life expectancy is rising, there are still strong differences between countries in access to healthcare. An example is cancer therapy: although more countries have access to radiotherapy and imaging devices, the distance to these specialized centers is often very large. The travel time implies that patients need to stay around. The complete cycle from planning to final radiotherapy treatment can currently take up to 7-8 weeks. There would therefore be a great benefit to approaches that significantly reduce treatment time. A possibility is to combine diagnosis with therapy. Another option is to reduce the number of radio and chemotherapy sessions by personalizing them, i.e., adapting their dose to the individual patient, or by adding sensitizing agents like hyperthermia.

Besides enabling global access around the world, technology also has strong potential to make European healthcare sustainable. The budget for oncology in Europe is rising steadily (1995: 55 billion euros, 2018: 1 trillion euros). Looking more closely, expenses are rising due to the increasing use of expensive cancer drugs. Despite technological improvements, costs associated to MedTech have not increased over the last decade. This clearly shows that MedTech is a solution rather than a problem. Even if devices may be expensive to purchase, health technology assessment studies continue to show that the total cost of ownership per patient treated is generally low: the same device is used for many patients.

Besides model-based design approaches, there are a number of other accelerators of such value-based medical technology. Prominent in this respect are new clinical trial approaches that accommodate the comparison of design iterations, as well as education and the broad application of health technology assessment. The translation of technology into clinical applications is also being streamlined based on the better understanding of major clinical and commercial roadblocks. Of major importance for creating impact are therefore the extensive and early-stage collaborations within the Center of Care & Cure Technology Eindhoven (C3Te). From the TU/e perspective, such strong collaborations exist with academia

and start-ups but also with e.g., the major clinical and industrial partners in the region (Máxima Medical Centre, Catharina Hospital, Kempenhaeghe and Philips, i.e., e/MTIC). Such Golden Triangle research collaboration between industry, clinics and academia creates fertile soil for generating, developing and clinically validating new ideas. Outside of the Eindhoven ecosystem, an increasing number of collaborations are initiated for the validation and investigation of health effects within the networks of (academic) hospitals and industrial partners.

BIO-PHYSICS MODEL-BASED DEVICE DESIGNERS

Clinical problems feature a complex interplay of biophysical phenomena which clearly requires a *multi*-disciplinary approach. Most current medical device designers are schooled in one discipline, such as electrical engineering or mechanical engineering. The *multi*-disciplinarity of medical device design teams therefore tends to stem from efforts to combine the skill sets of a multitude of individuals. Such teams, however, are only realistic for large enterprises, while small and medium companies that often take the lead in MedTech innovations do not have this bandwidth. This situation can be vastly improved if companies include actual *inter*-disciplinary individuals who understand the multifaceted nature of the clinical problem at hand. Such bio-physics designers can span several disciplines and are well-suited to rapidly sharing, communicating and developing ideas. Foundational for the development of medical devices is the need not only for research and design skills but also knowledge of the entire clinical and commercialization pathway, i.e., clinical, regulatory, marketing and business expertise. This urgently demands *inter*-disciplinary designers that have in-depth knowledge on how to improve and apply computational and tissue models, as well

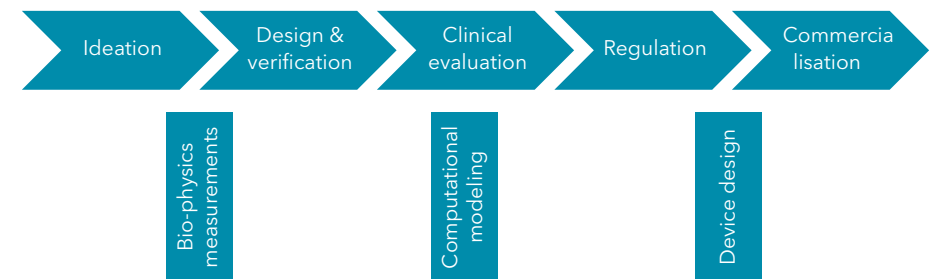


Figure 10. Interdisciplinary, M-shaped, MedTech designers understand the complete commercial and clinical pathways while specializing in the three required disciplines.

as a good overview of the entire development and commercialization process to streamline the development and validation processes of new medical products.

Training such interdisciplinary designers requires collaboration in the Golden MedTech Research Triangle. In Eindhoven, there are multiple developments connecting engineers to clinicians and industrial representatives. These connections are aimed at doing the research that has the highest chance of a direct impact in healthcare. Simultaneously, it provides a unique environment for training interdisciplinary designers. We are currently applying for European funding in which we will train M-shaped researchers that combine a good overview of the development, clinical and commercialization pathways with knowledge of the three research domains to create new solutions. This project also aims to introduce this way of working into the regular curriculum so a next generation of medical device designers will be trained that will create the sustainable healthcare solutions of the future.

Epilogue

During summer 2020, my brother-in-law and I cycled up the Albula Pass. This is a stunning climb on a scenic winding road. Each part of the climb has very different views, i.e., starting with very small rocky alleys, along many crossings of the famous Rhätische Bahn between green forests and ending with wide views and moonlike landscapes. Each upcoming scenery after every bend is unknown yet surprising. My research career matches this climb. Every bend brought new insights, new views and new directions. At each moment, I had someone to serve as an example or who guided me by a very new and exciting point of view. Some people have been acknowledged before, others I would like to mention here.

I cannot start with anyone other than Gerard van Rhoon, my mentor and much more. Together, we experienced the good and the bad, the sweet and the sour. I admire how you always turned each scenario to the benefit. You taught me what research in the medical field is about and the importance of the doctor's perspective. I thank you for always being supportive and always providing freedom. Looking back at the last two decades, I think I have been very lucky with such a knowledgeable, collaborative and supportive mentor. Here, I would also like to thank Cobi van der Zee, Sergio Curto, Michiel Kroesen, Martine Franckena, Remi Nout, and the staff of both the Hyperthermia group and the whole Department of Radiotherapy of Erasmus MC for teaching me the importance of patient's and doctor's needs when developing MedTech.

Secondly, my gratitude goes to Bart Smolders. Although I still had many plans at Erasmus MC, you convinced me to come to Eindhoven for a position that I couldn't refuse. The change has helped me to grow and I thank you for providing me with this opportunity. I admire the way you manage both the group and the department, while being approachable and maintaining a relaxed atmosphere. You are always supportive and provide the freedom needed to excel. In this context, I also want to mention the electrical engineering management platform as a whole and Jolie van Wevelingen, who enables us research staff to excel in what we do best.

In the medical technology field, I would like to specifically thank my 'partner in crime' Massimo Mischi and Jan Bergmans for showing me how to do research in the MedTech triangle. My gratitude extends to all principle investigators of

the C3Te from applied physics and electrical engineering, specifically those in the steering and vision boards. It is great to work with such passionate and knowledgeable people and in such a collaborative atmosphere. This inspires and truly is an asset. The connections to our C3Te collaborators in and outside of TU/e, like in e/MTIC, the NeuroPlatform, BENEFUS, TTNL, NeuroTechNL and many more, is something I value highly as well. In this respect, Carmen van Vilsteren, your elegant leadership in health at TU/e (still) provides direction and coherence, which is a major achievement.

In research, I thank all members of the (extended) Electromagnetics for Care & Cure (EM4C&C) research lab at TU/e, Gent and Rotterdam. Specifically, I would like to mention Rob Mestrom, whose expert knowledge and collaborative attitude are vital for the lab. Thanks be to Debra Rivera for the continuous inspiration and help with this oration. I am indebted to the larger Electromagnetics group for sharing their passion on electromagnetics in many different applications. Here, I thank Martijn van Beurden for his critical and supportive attitude and Mark Bantum for showing how passion and excellence can also be fun.

Many more people contributed to my international scientific career. Here, I would like to mention Mark Dewirst for driving and inspiring the careers of myself and many other (young) researchers in hyperthermia. Both Paul Stauffer and Desmond Yeo, who hosted me and provided the opportunity to expand my research in a new direction and gave an international perspective. The members of Z43 in Zurich, specifically Esra Neufeld, who supported with their continuous inspiration on multi-physics modeling.

The true understanding of research in the triangle came when we started Sensius. Paul van den Biggelaar, as captain you manage to keep all efforts focused in the right direction and the engine for success was Peter van Paassen. Both of you taught me how industry should play an important role already from the start of the MedTech research and development chain. I am honored to be part of this perfect example of public-private partnership in research, and look forward to a bright future. Herewith, I also thank all clinics, companies, patient organizations and funding agencies that I was blessed to work with for their pivotal roles in the research.

As indicated before, the work has been relying critically on all PhD students, postdocs, fellows and students who I was honored to supervise, and who did the important part of the research. Specifically, I'd like to mention Jurriaan Bakker,

Tomas Drizd'al, Gennaro Bellizzi and Kemal Sümser, who helped me understand that supervision means that both sides are being taught.

The C3Te team, Noortje Bax and Daniëlle van der Hagen, I am truly blessed with two such great supporters and friends. We became a good team very quickly and it is nice to experience how we complement each other. My parents, additional parents, extended family and friends, I thank all of you for your support, large and small. Your continuous support has meant, and means, a lot to me. Specifically, I thank my father and brother for their support and sharing of their passion for electromagnetics.

And finally, I thank our God to be blessed with the opportunity to work in such an exciting research field with a direct impact on the lives of so many patients. This inspires and drives to continuously seek better approaches, new science and more collaboration. On this road, I feel truly blessed being surrounded with Ruben, the leader, Elise, the creative, and Noëlle, the connector. Lastly, Petra, you continue to be my soulmate who keeps me "with my head in the clouds, and my feet on the ground."

'Ik heb gezegd.'

Curriculum vitae

Prof.dr.ir. Maarten Paulides was appointed full-time Professor of Biomedical Electromagnetics at the Department of Electrical Engineering at Eindhoven University of Technology on July 1, 2021.

M.M. (Maarten) Paulides (1979) holds an MSc degree in Electrical Engineering (2002) from Eindhoven University of Technology (TU/e). He obtained his PhD (cum laude) in Health and Medical Physics (2007) from Erasmus University Rotterdam working at the Daniel den Hoed, later Erasmus MC Cancer Institute, where he also continued his research on precision hyperthermia. In 2018, he returned to TU/e as director of the Center for Care & Cure Technology Eindhoven (C3Te), while maintaining an honorary associate professorship in Rotterdam. At TU/e, he founded and chairs the Care & Cure research lab of the electromagnetics group (EM4C&C) focused on applications ranging from neuro-stimulation and neuro-prostheses to magnetic resonance imaging (MRI) for guided therapy. All research is geared towards clinical impact. Maarten Paulides serves in the board of COST action CA17115 ("MyWave"), the Dutch Cancer Society (KWF) and thermal therapy task groups of ASME. He also served in the Dutch Health Council and the international committee for non-ionizing radiation protection (ICNRIP). In addition, he co-founded the hyperthermia therapy company Sensius.

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The logo for TU/e, featuring the letters 'TU' in a bold, sans-serif font, followed by a forward slash and a lowercase 'e'.

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