Physikalisch-Technische Bundesanstalt
National Metrology Institute

Into the Future with Metrology

The Challenges of Medical Technology

The Challenges of Medical Technology

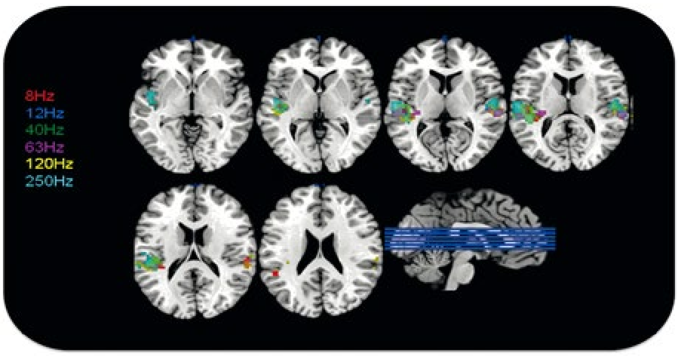
complex – individual – quantitative – interdisciplinary – cooperative

Medical measurements have a long tradition at PTB, but they have an even greater future as the development towards quantitative and individualized medicine represents a great challenge for metrology. The measurements have to be accurate and reliable, and they have to create confidence. This is where PTB has its core competence. PTB ensures the traceability of many important measurement procedures required, for example, by the EU's In Vitro Diagnostic Medical Devices Directive, but also by the German Medical Devices Act. With its measurement capabilities, PTB is the world leader in this field. According to the Measures and Verification Act, it is the only notified body in Germany to carry out type examinations of sound level meters. With its statutory mandate, PTB also plays an important role in dosimetry. Metrology is indispensable for one of the most important developments in medicine: the trend towards an increasing number of quantitative measurements. PTB is at the forefront of this research, for example, in the field of quantitative magnetic resonance imaging. Here, the aim is to make the measurements more and more reliable and comprehensible. In this extremely complex interdisciplinary field, intensive collaborations with suggestions and ideas coming from all participants are essential. Therefore, PTB wishes to further intensify its existing good contacts with physicians, hospitals and the medical technology industry. If you are interested, please do not hesitate to contact us!

Prevention

Hearing well into your old age

The field of acoustics is playing a pioneering role as we head towards medical treatment tailored to the individual patient. The aim of acoustics has, for a long time, been to establish quantifiable measurement data in a distinctly individual and age-dependent area. In a European project, PTB has, for example, co-developed an ear simulator which significantly improves hearing tests of newborns and enables the users to apply specific reference hearing thresholds for all age groups. Particularly in an aging society, protecting our sense of hearing plays an increasingly important role, especially because the loss of hearing can be accompanied by a loss of social contacts and increased loneliness. Another important task is the protection against noise. The European Environment Agency classifies noise as a growing environmental problem, and the measurement of noise must comply with legal requirements. PTB is the only notified body in Germany to carry out type examinations of sound level measuring instruments according to the Measures and Verification Act and the Measures and Verification Ordinance. According to the Medical Devices Act, PTB is in charge of the uniformity of metrology and the traceability of testing equipment – also in the field of ultrasound, where PTB maintains the national standards and carries out calibrations of, for example, hydrophones. All these tasks are concerned with the safety of patients and of the users of ultrasound (for example, physicians), and with the strengthening of the existing metrological infrastructure. At the other end of the hearing spectrum – in the range of infrasound, which can be generated by various environmental factors – this infrastructure has yet to be established, and the acoustics experts still see a lot of potential for research.



People can perceive infrasound if it is loud enough – this is one of the results of PTB's investigations in which acousticians worked together with specialists in functional magnetic resonance imaging. The mechanism behind the perception of infrasound will be the subject of future investigations.

Diagnostics and Therapy

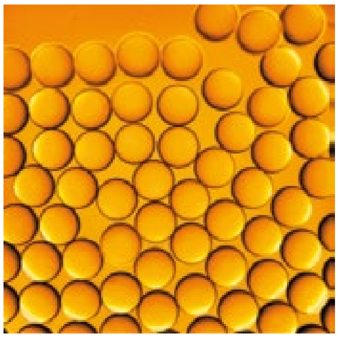
New sensors for biomagnetic signals

MEG and MCG (magnetoencephalography and magnetocardiography, respectively) measure the extremely small magnetic fields that are generated by the currents in the brain and heart. For this purpose, SQUIDs (superconducting quantum interference devices) have been used for decades, which require costly cooling with liquid helium. The new optically pumped magnetometers (OPMs), which have become commercially available in recent years, work at room temperature. It is even more important for OPMs that the Earth's magnetic field and artificial magnetic fields are minimized using shielded environments. These are available at PTB, which operates the world's best shielded room, the "BMSR2", in Berlin. It is used, among other things, to develop even more sensitive SQUIDs for the combined use of MEG and magnetic resonance imaging (MRI). This enables even sharper images than pure MRI and helps physicians to study Parkinson's, epilepsy and other neuro-psychiatric disorders with the aim of improved diagnosis and personalized therapy. PTB is currently setting up a laboratory for the rapidly expanding field of OPMs in order to further strengthen cooperation with physicians and hospitals. The demand for the measurement experts from PTB by the medical-clinical world is shown by the strong international use of the DFG core facility "Metrology of Ultra-Low Magnetic Fields". It operates the BSMR2 and other magnetically shielded rooms belonging to PTB.

MEG measuring device for the cross-evaluation of SQUIDs and OPMs

Laboratory values: valuable indicators for diseases

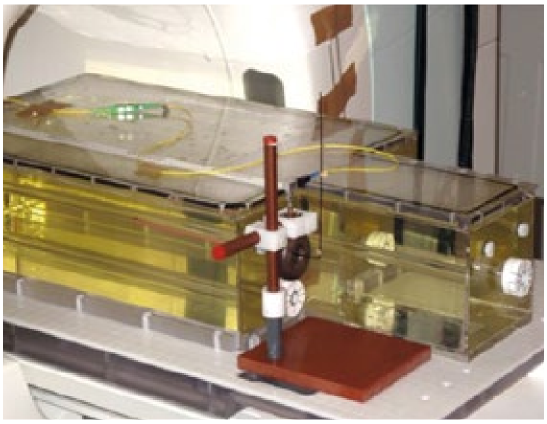
Since the beginning of the coronavirus pandemic at the latest, most people have learned how important test results of medical laboratories are in medicine. A large amount of all medical and diagnostic decisions are based on quantitatively analyzing the concentration of diagnostic markers in body fluids. According to the EU's In Vitro Diagnostic Medical Devices Directive, all control materials in laboratory medicine must be metrologically traceable. PTB therefore organizes international interlaboratory comparisons which ensure the reliability of those measurements. Due to its unique, internationally recognized measurement capabilities, PTB is known as one of the world leaders especially in quantifying proteins in blood serum and in flow cytometric cell counting. In flow cytometry, cells in body fluids such as blood, urine or cerebrospinal fluid are quantitatively analyzed with a high throughput. Hospitals use this on a large scale in hematology, infectiology and immunology as well as in biomedical research. The measurement of mineral salts, i.e. electrolytes, in blood is also of great importance. Some of them are important biomarkers for kidney stones, tumors, osteoporosis, stomach ulcers and other medical conditions. According to the guidelines of the German Medical Association (*Bundesärztekammer*), traceable measuring methods are required for the quality assurance of laboratory-medical measurements of the electrolytes of lithium, sodium, potassium, magnesium, calcium and chloride. These measurements are provided by PTB. The same applies to a series of organic biomarkers (e.g. the amount-of-substance concentrations of creatinine, which is a laboratory parameter for kidney function). The rapid progress in biomedicine and biochemistry has brought about many new approaches and improved methods for medical diagnosis and therapy, while the development of reliable measurement technology has not always kept pace. This will be an important future task for PTB, especially in the field of measurement methods for proteins, cells and nucleic acids (DNA, RNA). PTB is taking account of the international diversity of the market, legislation and research: Together with nine other European institutes, it has joined forces under the umbrella of EURAMET – the association for the national metrology institutes in Europe – to form a research network: the "European Metrology Network (EMN) for Traceability in Laboratory Medicine".



Reference measurement methods for the quantification of virus concentration based on Droplet Digital PCR open up new possibilities for the external quality assurance of medical laboratories.

MRI – safety first!

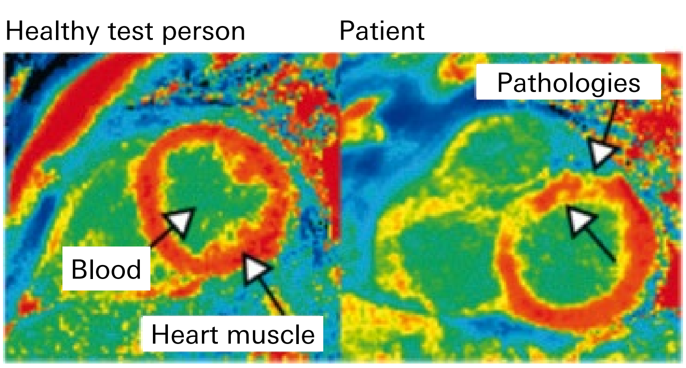
With well over 100 million examinations per year worldwide, magnetic resonance imaging (MRI) is the second most important medical imaging method (after X-rays). MRI provides sharp 3D images with a resolution down to the sub-millimeter range while being non-invasive and radiation-free. The trend is towards higher magnetic fields. These allow sharper images to be produced, but due to the higher RF frequency, tissue heating may be more severe. This might become a problem for the 8 to 10 percent of Europeans who have medical implants in their bodies, for example an artificial hip joint or a pacemaker. Therefore, especially in the case of the latest 7-tesla ultra-high field MRIs, which are currently in the clinical test phase, the electromagnetic fields applied to the patient must be measured reliably. PTB is developing measuring instruments for this, for example MR-compatible current sensors for monitoring the RF heating of wire-like implants, or special MR-safe devices for generating



Phantom with a wire in the „shoulder", together with a current sensor within the 3-tesla MR scanner of PTB well-defined electromagnetic fields for the in situ calibration of RF field probes. With these new methods, the electromagnetic fields can be determined in a traceable manner. In addition, special body phantoms as well as simulation methods are being developed for comprehensive safety assessments of MRIs. In this way, PTB spans the whole range of metrology for the safety of MRI.

When the MRI scanner does the analyses on its own

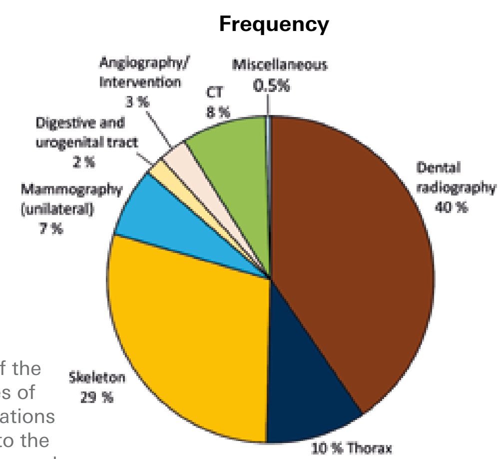
Most MR images provide qualitative information. They require the well-trained eye of a radiologist who can recognize differences in contrast and infer pathologically altered tissue characteristics. In the case of quantitative imaging, the device determines biophysical parameters (e.g. the speed of blood flow) itself, and these parameters can be used directly to objectively determine diseases. This has improved the comparability of test results and has allowed data to be consolidated for multi-center studies. Quantitative MRI is a worldwide trend in radiology; in the past few years, major international societies have launched initiatives to support this development. Quantitative MRI also plays a role in the NAKO Health Study – Germany's largest cohort study – in which 200,000 people between the ages of 20 and 69 are interviewed on their living conditions and medical history and undergo medical examinations. In close cooperation with hospitals and MRI equipment manufacturers – at the interface between industry and clinical applications – PTB is working on making quantitative MRI imaging procedures even more accurate and reliable. Examples of this are the development of faster scans for 4D Flow MRI with which the quantitative blood flow velocity during the cardiac cycle can be determined, or the determination of the tissue-specific relaxation time T1 to diagnose heart muscle diseases. The problem of organ movement due to respiration has also been solved. A patient's respiratory movements are recorded very accurately, and motion artifacts in the MR images are corrected. This helps, for example, to precisely and quantitatively assess liver tumors, while a patient can breathe freely during the examination. In the future, quantitative MRI will become increasingly important for MR-guided radiation therapy, which is still quite a new and rapidly growing field.

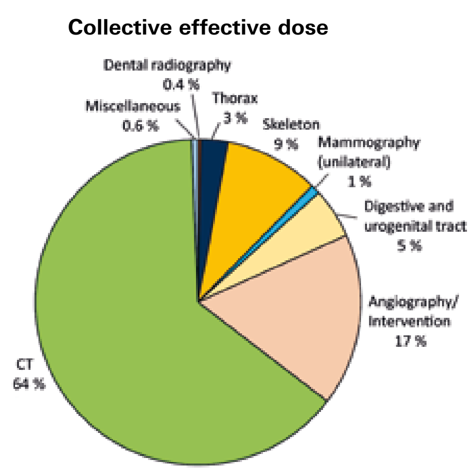


In MRI, the tissue-specific relaxation time T1 serves as a quantitative marker. T1 describes the temporal behavior of nuclear spins after excitation with an alternating magnetic field. Figure: T1 maps of the heart of a healthy test person and a patient.

It's the dose that counts

Around 140 million X-ray examinations are carried out in Germany every year; thus, X-rays account for about 40 % of the total effective dose per year received by the population exposed to ionizing radiation from natural and man-induced radiation. Hence, dosimetry is important for quality assurance in X-ray diagnostics, and it is also important to fulfill the requirement to achieve sufficient imaging quality with a minimum radiation dose. PTB plays a very important role for technical quality assurance in X-ray diagnostics where it realizes the basic dosimetric quantity – the air kerma. PTB operates numerous reference radiation sources for calibrations and tests in conventional X-ray diagnostics, computed tomography and, especially, mammography. An important customer for PTB is the International Atomic Energy Agency (IAEA) with its worldwide network of secondary standard laboratories. More than 80 countries are involved in this network. By statutory mandate, PTB tests diagnostic dosimeters which are used for acceptance and constancy tests of medical X-ray diagnostic equipment for examinations on humans and are subject to the German Measures and Verification Act. For this purpose, PTB carries out type examinations in accordance with the Measures and Verification Ordinance, so that dose measurements are reliable in practice and patients are protected in the best possible way. PTB participates – in a leading function – in the elaboration of relevant international and national standards, for example, standards which define reference radiations or specify requirements for dosimeters. PTB's research focuses on dose-intensive procedures such as computed



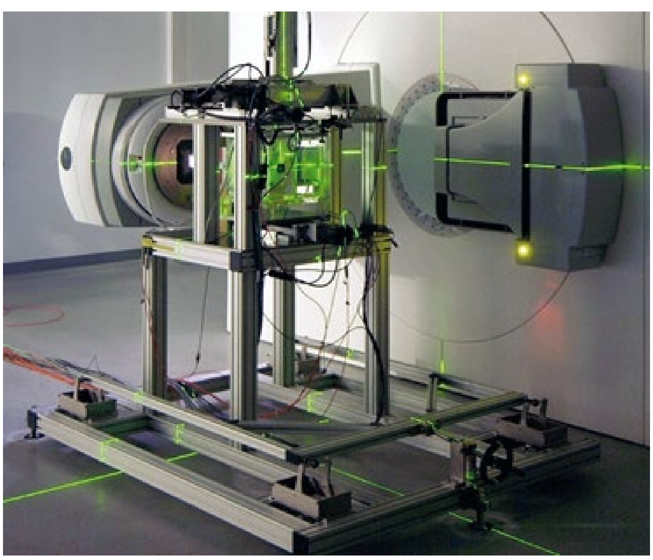


Percentage of the different types of X-ray examinations contributing to the total frequency and to the collective effective dose in Germany for 2014 (Source: BMU/BfS: Environmental radioactivity and radiation exposure in 2016).

tomography, which is used in 8 % of all X-ray diagnostic examinations, but accounts for 64 % of the collective effective dose (see figures). For example, PTB is developing a modern and fast method of personalized CT dosimetry. Its aim is to adapt the imaging parameters to the individual patient by precisely knowing the patient- and scanner-specific CT dose in order to reduce that dose.

Apply the right absorbed dose against the tumor

Every year, half a million Germans are diagnosed with cancer – with an upward trend due to an ageing society. More than half of all cancer patients receive radiation therapy, either on its own or in combination with chemotherapy or surgery. Radiotherapy uses high-energy ionizing radiation to damage the genetic material of cancer cells, thus causing them to die. This can also affect healthy cells. In order to avoid such undesired side effects as far as possible and to maximize the healing success of radiation therapy, the energy deposited in the cells by the radiation must be close to an “optimum” value, and the spatial distribution of the radiation energy in the patient must match the shape of the tumor as closely as possible. Both can be achieved with the aid of modern methods of radiotherapy, such as intensity-modulated radiotherapy, radiotherapy with protons/ions or MR image-guided radiation therapy (MRgRT); the precise measurement of the energy deposited by the radiation plays a fundamental role here. This energy is characterized by the measurand of “absorbed dose” (unit Gray, Gy). With PTB’s primary standards, this unit can be realized with the world-wide lowest measurement uncertainty and disseminated via the calibration of secondary standards. Ultimately, all dosimeters used for this purpose in German radiation therapy hospitals are traceable to PTB’s primary standards via an uninterrupted calibration chain. In addition, modern methods of radiation therapy require the use of special procedures for dose measurement. In the case of MRgRT, for example, it is necessary to take the influence into account which the strong magnetic field that is required for imaging has on the dosimeter. In close cooperation with national and international partners such as other metrology institutes, research institutes and university hospitals, PTB is developing dose measurement procedures to be applied in modern radiation therapy and is making them available to the users (i.e. the medical physicists in the hospitals) in the form of national and international measurement regulations (standards and codes of practice).



Measurement setup for the calibration of dosimeters in units of absorbed dose to water at one of PTB’s clinical linear accelerators.

Digitalization in the Health Care System

Model-based observer and machine learning for high-quality images

PTB scientists in Braunschweig and Berlin are both comparing and developing modern methods for measuring the image quality of X-ray images, for example in computed tomography or mammography. These methods must provide a measure of the uncertainty of the determined image quality while being, at the same time, objective and economical. For this reason, so-called phantoms are used to represent the patient and model-based mathematical observers (model observers) are used as a substitute for radiologists. Image quality analysis with model-based observers is a rapidly growing field of research. For example, PTB uses machine learning (Deep Learning) in order to determine – in a particularly efficient way – the so-called contrast-detail curves which are required for acceptance and constancy tests on mammography scanners. The large image database required for the training of the neural network was generated with a mammography simulation program developed at PTB. Both procedures – the procedures that are based on machine learning and the “classical” model-based

A procedure for quality assurance in mammography screening, which is based on machine learning, has been developed at PTB. Thereby, the contrast-detail curve – as a measure of the image quality – is determined for the first time on the basis of only one single image. The new method is robust and more precise than the methods used so far. (Credit: picture alliance / dpa) observers – are being developed with the aim of being able to use them for quality assurance and standardization in the foreseeable future. From the figures of merit for image quality and dose, a target value will ultimately be developed for the optimization of radiological diagnostics – with the aim of achieving the best possible image quality with a low dose.

Matters close to the heart: artificial intelligence

Cardiovascular diseases are among the most frequent causes of death worldwide. Consequently, examinations using electrocardiograms (ECGs) are a crucial aspect of healthcare. With the introduction of telemedicine, e.g. for monitoring long-term ECGs, the importance of such examinations will continue to grow. Automatic ECG interpretation algorithms based on Deep Learning can significantly reduce the workload of medical personnel. However, most algorithms have only been trained on non-public data sets. These data sets are usually not large enough to be reliable for this purpose. Furthermore, the evaluation methodology has not been standardized, so that results cannot be sufficiently compared. PTB has solved this problem by developing a large, publicly accessible database. It contains 21,837 so-called 12-lead ECGs of 18,885 patients and is the largest public clinical data set of its kind: about 40 times larger than the PTB Diagnostic Database used so far. The database provides machine-readable diagnostic findings and over 70 different annotations on the ECGs from up to two cardiologists. Furthermore, the data set contains many co-morbidities in addition to data of healthy patients. Healthy patients' data are often underrepresented in clinical data sets. Different signal qualities are also included. The database is therefore ideally suited for training and evaluating machine-learning algorithms on a real-world data set.

Coordinator of the Steering Group for Medicine

Dr. David Auerbach
Working Group 3.12 | Optical Analysis
Phone: +49 531 592-3102
E-mail: david.auerbach@ptb.de

Steering Group Members / Contact Persons

Dr. Jörn Stenger (Chairperson)
Member of the Presidential Board
Phone: +49 531 592-3000
E-mail: joern.stenger@ptb.de

Dr. Christian Koch
Head of Department 1.6 | Sound
Phone: +49 531 592-1600
E-mail: christian.koch@ptb.de

Dr. Bernd Güttler
Head of Division 3 | Chemical Physics and Explosion Protection
Phone: +49 531 592-3010
E-mail: bernd.guettler@ptb.de

Dr. Annette Röttger
Head of Division 6 | Ionizing Radiation
Phone: +49 531 592-6010
E-mail: annette.roettger@ptb.de

Prof. Dr. Tobias Schäffter
Head of Division 8 | Medical Physics and Metrological Information Technology
Phone: +49 30 3481-7343
E-mail: tobias.schaeffter@ptb.de

The texts of this Info Sheet and further information can be found in the internet: www.ptb.de > Research & Development > Into the Future with Metrology > The Challenges of Medical Technology

Physikalisch-Technische Bundesanstalt
Bundesallee 100
38116 Braunschweig, Germany

Press and Information Office

Phone: +49 (0)531 592-3006
E-mail: presse@ptb.de
www.ptb.de

As of: 11/2020

Federal Ministry for Economic Affairs and Energy

The Physikalisch-Technische Bundesanstalt, Germany's national metrology institute, is a scientific and technical higher federal authority falling within the competence of the Federal Ministry for Economic Affairs and Energy.

Cover photo: ©Rido.Adobestock