Advancing Technologies – A Permanent Challenge for Medical & Biological Engineering & Science (MBES)

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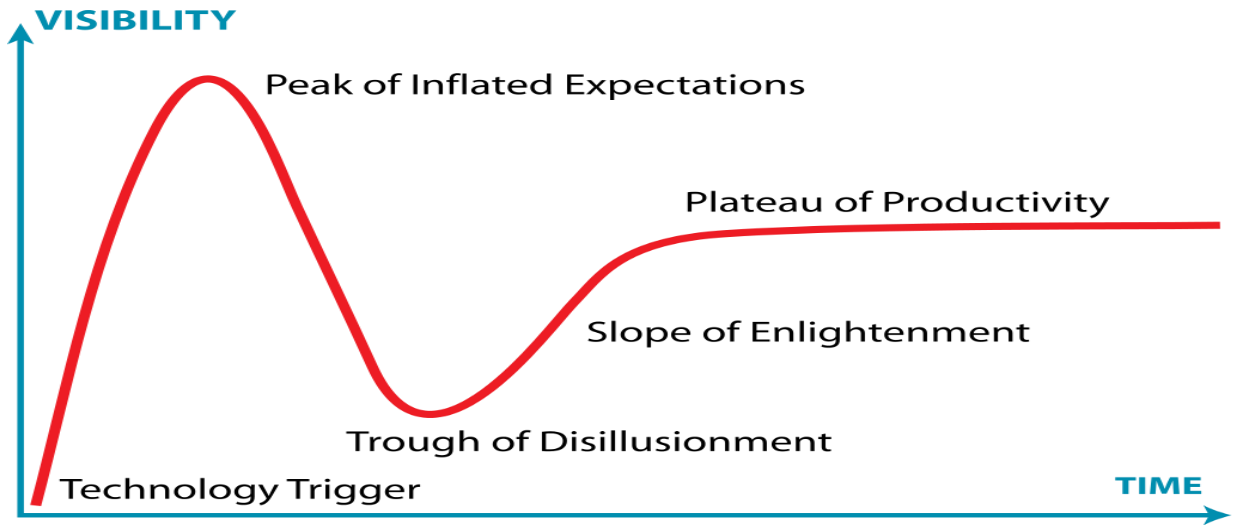
Content

Introductory Statements (I)

Advancing Technologies are technologies which – to our understanding – have not yet reached the final state of their possible development.

Usual graphics for the development of technologies: the Hype Circle with 5 key phases:

(1) Technology Trigger, (2) Peak of Inflated Expectations, (3) Trough of Disillusionment, (4) Slope of Enlightenment, (5) Plateau of Productivity



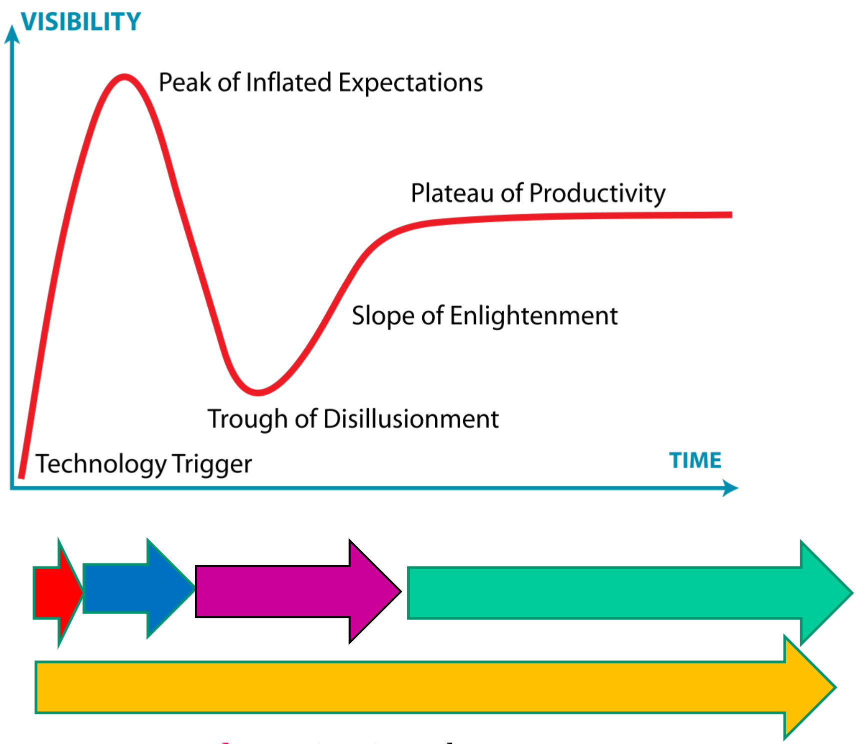
The hype cycle is a graphical representation of the life stages a technology goes through from conception to maturity and widespread adoption.

The hype cycle is a branded tool created by Gartner, a consulting company for technology research, development, management and business affairs.

Introductory Statements (I)

Advancing Technologies are usually described by the Hype Circle with 5 key phases. Here another description is used with 4 phases:

(1) Gemination phase, (2) Growth phase, (3) Flowering phase, (4) Harvesting period



yellow: key enabling technologies

red: gemination phase

blue: growth phase (or: dying phase, i.e. not reaching the following phases)

violet: flowering phase

green: harvesting period

Introductory Statements (II)

Life Sciences

Life Sciences are concerned with processes or structures in living beings from the cellular level to complex systems, and with processes and structures in which living beings are involved. Life Sciences comprise different disciplines, e.g.:

- **Basic sciences**: biology, medicine, pharmacy, biochemistry, biophysics, bioinformatics, molecular biology
- **Engineering sciences**: electrical engineering, mechanical engineering, material science, informatics, computer engineering, robotics, controlling
- **Applied sciences**: health care, biotechnology, mechatronics, ecology, environmental technology, agricultural technology, life assisting technology
- **Natural sciences**: mathematics, physics, chemistry
- **Related disciplines**: economy, social sciences, quality control, sustainability, ethics, management, law

Introductory Statements (III)

Life Science Engineering (LSE)

is bridging the gap between the life sciences and different engineering disciplines. LSE is primarily concerned with

- the application and utilisation of engineering knowledge and expertise for living beings and the quality assurance of life conditions
- the transfer of knowledge about living systems to engineering problems

Both approaches are gaining increasing relevance for industrial processes, e.g.

- pharmaceutical production
- biotechnological methods and processes

Life Science Technology (LST)

represents the technology that is employed for the tailored solution of different complex problems, e.g.:

- personalized medicine
- systems biology
- sustainable use of biological resources

Glossary: Definitions and how they are used here

Technology: The sum of techniques, skills, methods and processes used in the production of goods or services or in the accomplishment of objectives. It can be represented in usable knowledge or can be embedded in equipment and machines.

Engineering: The application of scientific principles to design, develop, construct and produce machines, technical products, means for transport, communication devices and networks, systems for information processing, buildings (e.g. houses, tunnels, roads and bridges), etc.

Invention: A unique or novel device, method, composition or process, or relevant parts of existing devices, methods, compositions or processes that render possible new applications or provide higher or safer applications.

Innovation: New ideas, products or methods which have not been used before. Innovations are based on the results of new technological developments and advanced scientific knowledge. Innovations respond to societal or economic needs and demands. They generate new products, services, production processes or business. They are successfully introduced into an existing market or create new markets.

<u>Product innovation</u>: The introduction of a new or a significantly improved good or service into the market.

<u>Process innovation</u>: The implementation of a new or significantly improved production process, distribution method or support activity for goods or service.

Knowledge: Familiarity, awareness, or understanding of someone or something, such as facts, information, descriptions, or skills that is acquired through experience or education by perceiving, discovering, or learning. It should at least be justified, true, and generally accepted.

Information: Structured, organized and processed data which have been transformed and classified into an intelligible form that can be used for decision making and further processing.

Key Enabling Technologies (KETs)

- They provide the basis for innovation in a wide range of products across all industrial sectors.
- They are characterized by rapid development of subsequent derivative technologies in diverse fields.
- They enable equipment and / or methodology that alone or in combination with associated technologies provides the means to generate giant leaps in performance and capability of the user, product or process.
- The EU has recognized KETs as one of Europe's major weakness in the difficulty converting knowledge into marketable KETs-based products and services. This innovation gap has been identified as the European „Valley of Death".
- The EU has recognized that, while each individual KET already offers huge potential for innovation, their cross-fertilisation is particularly important as combinations of KETs which offer even greater possibilities to foster innovation and create new markets.
- KETs with remarkable relevance for MBES are:
  - Electronics
  - Digitalization
  - Information Processing Systems and Devices
  - Materials Sciences
  - Microtechnology
  - Nanotechnology

Key Enabling Technologies (KETs)

Electronics

- is based on and has begun with the identification of the electron in 1897 by J.J. Thompson as first subatomic particle;
- is comprising physics, engineering, technology and applications, e.g. semiconductor devices;
- is using active devices for the control of processes like amplification, rectification, signal processing, data processing, pattern recognition;
- has different branches, e.g. digital electronics, analogue electronics, microelectronics, optoelectronics, power electronics;
- has led to the development of complex integrated circuitry, e.g. microprocessors, microcontrollers, memory chips, field-programmable gate arrays;
- has a special derivative:

  medical electronics in which electronic instruments and equipment are developed for medical applications as diagnosis, therapy, rehabilitation and research in nearly all medical fields including such special devices like
  - intelligent implants (cardiac pacemakers, drug delivery pumps, cochlear implants etc),
  - imaging equipment (X-ray, NMR, ultrasonics, optics, impedance, temperature etc.),
  - controlled devices (respirators, anaesthesia, artificial kidney, baby incubators etc.),
  - signal acquisition and monitoring systems for ecg, eeg, emg, eog, blood pressure, blood cells, blood gases, body temperature, gait analysis, audiometry etc.
  - special equipment for sterilization, calibration, data transmission etc.

Key Enabling Technologies (KETs)

Digitalization (I)

Digitization, i.e. the process of changing information from analog to digital form so that it can be processed by a computer. The analog information can be text, pictures, sound or others.

Mathematics, i.e. the basics how the data are handled and which operations shall be performed (e.g. software: mathematical tools and operational programs).

Technology and technical equipment. i.e. hardware (e.g. mechanical calculators, electronic computers, quantum computers).

Timetable and Milestones

• (8000 years ago?)	digits for exact counting
• 800 years ago	introduction of Arabic digits in Western Europe
• 1805	invention of the programmable loom by Marie-Joseph Jacquard using punched cards (binary code).
• 1823	Charles Babbage described the Difference Engine which could tabulate calculations for up to 20 decimal places using the principle of finite differences, i.e. a mathematical method of resolving polynomial expressions by addition.
• 1941	presentation of the first programmable electro-mechanical computer by Konrad Zuse.
• 1945	Alan Turing developed an electronic stored-program digital computer, and John von Neumann circulated his first report on the EDVAC.
• 1934 – 1945	Development of the semiconductor technology (e.g. the transistor), followed by the Integrated Circuit (IC) technology: microchip technology, monolithic technology since the 1960s.
• 1980	Begin of quantum computer development by Paul Benioff.

Digitalization (II)

Digital Transformation (Digital Revolution): the Basic Enablers

It describes the effects and impacts of digitalization on processes and structures in social systems, in health care systems, in economy, culture, education, politics. The most powerful enablers are:

Digital Technologies, e.g. Software Engineering, Systems Engineering, IT-Security, Data Analytics, Big Data Processing, Cloud Computing.

Digital Infrastructure, i.e. all components of a technical system that enables the exchange of data and the sharing of information.

Applications, i.e. the software for fields with a benefit from the fast (near real time) and secure exchange of data and information in the proper format for further processing including visualisation, pattern recognition and extraction, and the use of expert knowledge.

Digitalization (III)

Digital Transformation (Digital Revolution): the Promotors

Usability Potential: i.e. possible benefits from the availability of information and data with special regard to effectiveness, efficiency, functionality, costs, worker satisfaction, user friendliness, and error avoidance.

Business Models: i.e. the rationale of how an organisation creates, delivers, and captures values in different contexts, e.g. economic, social, cultural, strategic, competitive context.

Value Creating Networks: i.e. regional, national or global networks that render possible to generate a value that is larger than the sum of values generated by each single player without the network whereby value is not only financial value.

The **EU** emphasizes

- that **Digital Transformation** is characterized by a fusion of advanced technologies and the integration of physical and digital systems.
- that the industry should seize the opportunities which are offered by technologies such as the Internet of Things, big data processing, advanced manufacturing, robotics, 3D printing, blockchain technologies, and artificial intelligence.

Key Enabling Technologies (KETs)

Information Processing Devices (I)

Information is defined - here – as structured, organized and processed data which have been transformed and classified into an intelligible form that can be used for decision making and further processing.

Information may be expressed in analog form (synonym: continuous signal) or digital form (synonym: data).

Information processing is the purposeful change of information. It includes the acquisition, recording, storage, organization, retrieval, display, dissemination and interpretation of information.

Information processing in humans is primarily based on analog information, in advanced technical devices preferrably applied to digital information.

A computer carries out instructions, i.e. sequences of arithmic or logical operations, set in the program. Algorithms are used to perform calculations, data processing and automated reasoning tasks.

1941: Zuse presented the first programmable computer Z3 equipped with mechanical relays.

1955: Bell Laboratory presented with TRADIC the first electronic (transistorized) computer.

1964: Control Data Corporation presented with the CDC 6600 the first supercomputer (i.e. the world fastest at that time).

1971: With the release of the first commercially available microprocessor by Intel Corporation the era of the „fourth generation" of digital electronic computers has been started.

1981: IBM presented the first Personal Computer, stimulating the „MS-DOS"- and the „Windows"-era.

2000+: Multi-core Central Processing Units became available.

The clock frequency was 5.3 Hz for the Zuse Z3, some MHz in the 1980 decade, and reached 4 GHz in 2015.

Information Processing Devices (II)

Information is understood here as the knowledge obtained by investigation, study, or instruction.

Information processing means the change of information in such a way that its relevant content is prepared, enhanced or isolated for further use.

The information processing unit is that component of the device that performs this change.

A computer is an Information Processing Device that contains at least one processing unit.

Typical examples of processing units for data may be:
- central-processing units
- computer motherboards
- network cards
- graphic-processing units
- sound cards

An Information Processing Device must at least contain an input unit and an output unit.

Furthermore, most Information Processing Devices contain a storage unit and a controlling unit.

The purpose of most Information Processing Devices is to change (or transfer) the input information
- into a desired format
- into a format that enhances or isolates the interesting part of the input information

Materials Sciences

Progress in material research, advanced measurement equipment, production technology and new applications had always had strong impact on medical technology. Especially the entrance to the nanometer world has opened many new aspects.

- Scanning probe microscopes, e.g. the scanning tunneling microscope and the atomic force microscope, both providing a way to probe the local properties of a sample with nanometer resolution, especially force measurement, topographic imaging, and manipulation;
- Carbon fiber reinforced plastics: composite materials with challenging and adjustable properties with regard to stiffness, strength, weight, and manufacturing for special applications;
- Advanced manufacturing, e.g. rapid prototyping, additive manufacturing, advanced robotics;
- New materials for semiconductor devices, e.g. lasers, LEDs, and for sensors and batteries;
- Carbon nanotubes and fullerene cages with outstanding mechanical, electrical, optical and thermal features that may enable exciting new applications, e. g. microfabrication techniques, tissue engineering, for implants and integrated circuit technology;
- Metamaterials, i.e. materials with properties that can not be found in classical materials, e.g. for the construction of lenses with a resolution unlimited by fundamental physics, or materials for new production methods, e.g. by 3D-printing.

Key Enabling Technologies (KETs)

Microtechnology

It is concerned with the miniaturization of mechnical processes, systems and devices in order to accomplish tasks impossible to achieve on the macro level.

Microsystem technology involves micromechanics, microelectronics, microfluids, micro-optics.

Microtechnological systems and instruments are:
- micromanipulators
- micro transport and delivery devices
- microchips and microprocessors
- micromachines, e.g. consisting of sensors, processors, actuators
- MEMS: microelectro-mechanical systems, e.g. for controlled drug delivery
- microrobots
- micro monitoring devices
- microreactors, e.g. lab-on-a-chip devices
- microfluidics, e.g. for the analysis or separation of small volumes of fluid

All types of microtechnological systems and instruments have some – more or less – relevance for Medical and Biological Engineering and Science.

Key Enabling Technologies (KETs)

Nanotechnology

Manipulation of matter
- on an atomic, molecular, or supramolecular scale.
- with at least one dimension sized from 1 to 100 nanometers.

Promising and emerging nanotechnology derivatives:

Molecular nanotechnology: Precise manipulation of atoms and molecules for micro-fabrication.
Nanoelectronics: The use of nanotechnology in electronic components in which inter-atomic interactions and quantum properties are relevant.
Nanomechanics: The use of fundamental mechanical properties of physical systems at the nanoscale, e.g. elastic, thermal and kinetic material properties.
Nanobiotechnology:
(a) devices for the study of biological micro-systems
(b) production or manipulation of biomolecular systems
Nanophotonics, nano-optics: Study and utilisation of the interaction between light and nanoscaled objects.
Nanomedicine: Applications ranging from the use of nanomaterials for medical purposes to the development of nanoelectronic biosensors and biological micromachines.
"theranostic" nanoparticles are nanoparticles that have both therapeutic and diagnostic agents on a single platform. They have been developed for optical imaging, magnetic resonance imaging, ultrasound, computed tomography, and nuclear imaging comprising both single-photon computed tomography and positron emission tomography.

Harvesting period

Those technologies have already reached a certain level and for some time stable state of maturity:

- **Medical Electronics**
- **Medical Imaging**
- **Materials, Biomaterials**
- **Non-electric Microtechnologies**
- **Medical Informatics**

Medical Electronics (I)

A branch of electronics in which electronic instruments, devices, apparatus and equipment are developed, produced and used for such medical applications as research, prevention, diagnosis, therapy, treatment and rehabilitation including assist devices.

This branch of electronics may also include special equipment for calibration and maintenance.

Furthermore, equipment developed for active assisted living purposes (AAL) may be included.

In general, all devices which contain electronic components and are regulated by one of the three current EU directives are considered to represent medical electronics:

- Active Implantable Medical Devices (Council Directive 90/385/EEC)
- Medical Devices (Council Directive 93/42/EEC)
- in-vitro Diagnostic Medical Devices (Council Directive 98/79/EC)

Those new regulations have been adopted on April 5, 2017, and entered into force on May 25, 2017.

Medical Electronics (II)

Promising and still emerging subdisciplines with relevance for medical electronics are:

- **Microelectronics**
- **Microcircuitry**
- **Active implantable medical devices**
- **Microarray technology for medical purposes**

Harvesting period (I)

Medical Electronics (III)

Microelectronics

Microelectronic components usually are in the micrometer scale or even smaller.

Those components are typically made from semiconductor material.

Microelectronic circuits are assemblies of electronic components, fabricated as a single unit, i.e. integrated circuit (IC). Synonyms: Chip, solid-state circuit.

Active components (e.g. transistors, diodes) and passive components (e.g. resistors, capacitors) and their interconnections are built on a thin substrate of semiconductor material (i.e. semiconductor wafer).

Integrated circuits can be classified into analog, digital and mixed signal devices. Mixed signal devices consist of both analog and digital circuits on the same chip.

Advantages for use in medical devices and equipment are:
- small dimensions, enabling high packing density and thus small devices;
- small power requirement, i.e. usually no additional cooling is required;
- low voltage supply, usually DC voltage, rendering possible operation by batteries;
- high reliability and long operating time without maintenance;
- smart and high complexity, enabling the operation and application by users without special electronic education and training.

Medical Electronics (IV)

Integrated Circuitry

Typical examples for Integrated Circuitry are

- Analog devices
  - operational amplifiers
  - linear regulators, power supply chips
  - phase locked loops
  - oscillators
  - active filters
- Digital devices
  - microprocessors
  - digital signal processors (DSPs)
  - field-programmable gate arrays (FPGAs)
  - memories (RAM, ROM, flashs)
  - application-specific integrated circuits (ASICs)
  - micro-controllers (processor, memories, and input-output circuitry)
- Mixed devices are usually converters and controllers
  - analog-to-digital converters
  - digital-to-analog converters
  - delta-sigma modulators
  - digitally controlled analog amplifiers

Special devices, e.g. multiplexer that is a selector for either analog or digital signals.

Recent devices (e.g. graphic processor) can contain up to 3 billion transistors.
Question: Is already reached the end of Moore‘s Law: The number of transistors in a dense integrated circuit doubles about every two years?

Harvesting period (I)

Medical Electronics (V)

Active implantable medical devices (AIMDs)

EG Directive 90/385/EEC defines AIMDs as any medical device
- relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity; and
- which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

A short survey of AIMDs

- for electrostimulation purposes
  - cardiac pacemakers and defibrillators
  - spinal cord stimulators
  - brain stimulators
  - peripheral nerve stimulators, neural stimulators
  - cochlear prothesis
  - retinal prothesis, either subretinal with a photodiode array, or epiretinal with external video-camera and signal transmission to an implanted electrode array
  - muscle stimulators, e.g. bladder stimulation
- for drug delivery, insulin pumps, artificial pancreas
- for remote-controlled hydrocephalus treatment
- for monitoring of internal quantities, e.g. intracranial pressure, blood pressure, temperature, glucose, pH, pO_2, pCO_2, electrolytes, metabolites
- orthopaedic active implants, e.g. meniscus implants, acetabular components for use in hip joint reconstruction applications
- dental implants for monitoring, electrostimulation and oral drug delivery applications

Harvesting period (I)

Medical Electronics (VI)

Microarray technology for medical and biological purposes

A microsensor array (synonyms: biochip, biosensor array)

-is a two-dimensional array on a solid substrate, usually a glass slide, nylon membrane, or silicon thin-film cell; recently, 3D structures have been developed;
- whose surface is provided with thousands of minute pores or cavities in defined positions;
- renders possible large numbers of through-put tests;
- can assay large amounts of biological material, usually by binding or fixation on the carrier;
- is suitable for fingerprinting, for mapping and for gene sequencing applications;
- uses multiplexed and parallel processing and detection methods;
- can be combined with micro-fluidics, i.e. Lab-on-a-Chip, e.g. Patch-Clamp-Chip
- may be a multiplex lab-on-a-chip with up to thousands of sensor elements;
- can detect or monitor quantities like
    - antibodies, antigens
    - proteins and peptides
    - carbohydrates, lipids
    - nucleic acid biomarkers
    - DNA, RNA
    - living cells, including histological details
    - chemical compounds for drug screening and drug research
    - PCR products
    - multi-analyte measurement of different biological and chemical analytes

The detection principle can be based on:
- optical methods, e.g. laser-photometry, spectroscopic methods, fluorecence methods
- electronic methods, e.g. impedance, FETs
- electro-chemical methods, e.g. amperometry, chemFETs, ISFETs

Harvesting period (II)

Medical Imaging (I)

- is the technique and process of creating visual anatomic representations of organs and tissues from the interior of a body for clinical analysis and medical intervention, and the visual representation of the function, motion and other properties of different organs and tissues and related processes.

- employs different technologies, modalities and physical qualities, e.g.
- **X-ray: fundamentals, radiography including CT**
- **Magnetic resonance imaging (MRI)**
- **Nuclear Medicine, PET, SPECT**
- **Ultrasonography, Ultrasonic Doppler, Photoacoustic Imaging**
- **Optical and Photonic Medical Imaging**
- **Bioimpedance, Elastography, Thermography**

- is usually applied in non-invasive mode.

- is supported by digital processes, e.g. for
    - equipment control and calibration,
    - image processing and evaluation,
    - image interpretation and pattern recognition
    - storage purposes.

Medical Imaging (II)

X-rays, physical fundamentals

X-rays (or Roentgen-Radiation) are high-energy electromagnetic waves, usually with
- a wavelength ranging from 0.1 to 10 nm (corresponding to frequencies from $3x10^{16}$ Hz to $3x10^{19}$ Hz),
- energies in the range 100 eV to 200 keV.

X-ray photons can ionize atoms and disrupt molecular bonds (ionizing radiation).

Interaction of X-rays with matter are
- photoabsorption (low energy range),
- Compton scattering (high energy range),
- Raleigh scattering (elastic scattering).

Standard X-ray imaging techniques, e.g. radiography, computed tomography (CT), use the decrease of the X-ray intensity (i.e. attentuation) along the penetration pathway through the body or tissue.

Projectional radiography (also: conventional radiography) is used to produce two-dimensional images of the remanent beam intensity, i.e. contrast images representing the remanent beam intensity. The contrast depends on the density difference of the transversed matter.

Contrast can be enhanced by application of contrast agents, e.g. for improving the visibility of vessels, hollow organs (e.g. bladder, heart, bronchial tubes, digestive tract), cavities, etc..

Phase-contrast X-ray imaging or phase-sensitive imaging use changes in the phase of the X-ray beam that transverses an object. Used for structure analysis, until now not for medical imaging.

X-ray microscopy uses soft X-rays to produce magnified images of micro- and nanoscale objects, e.g. living cells and biological samples in their natural state, with growing relevance for biology.

Harvesting period (II)

Medical Imaging (III)

Radiography in Medicine

Radiography includes different methodological approaches:

- Projectional radiography, i.e. X-ray absorption, X-ray fluorescence, X-ray excited optical luminescence, is based on the X-ray interactions in matter;
- Computed tomography, i.e. an image procedure that uses computer-processed X-ray attentuation measurements taken from different angles (scan) to produce cross-sectional images of the scanned object. By digital geometry processing a 3D-volume of the inside of the object can be generated, presented by 2D-images.
- Dual energy X-ray absorptiometry is used primarily for osteoporosis tests by the measurement of bone density, i.e. amount of calcium, with two narrow X-ray beams, which are 90 degrees from each other.
- Fluoroscopy provides moving projection radiographs, that render possible to view movement of tissue or of contrast agents, e.g. in angiography, or to guide medical intervention, e.g. angioplasty, pacemaker insertion, or joint replacement. Especially useful is biplanar fluoroscopy, when two images are displayed in two planes.

X-ray medical imaging can be employed for

- Structural imaging, i.e. anatomical structures, their shape, pathological abnormalities and diseases, different deviations, e.g. calcinations;
- Functional imaging, i.e. physiological and biochemical processes, including blood flow, cardiac activity, metabolism, regional chemical composition.

X-ray fluorescence uses the emission of characteristic fluorescent X-rays or gamma rays from a material that has been excited by being bombarded with high-energy X-rays. Until now without relevance for medicine and biology.

Sometimes imaging modalities as MRI, PET, SPECT are also grouped in radiography.

Harvesting period (II)

Medical Imaging (IV)

Magnetic resonance imaging (MRI)

This medical imaging technique uses a magnetic field, magnetic field gradients, and computer-generated radio waves to generate detailed images of the organs and tissues in the body.

Certain atomic nuclei, e.g. hydrogen, absorb radio frequency energy when placed in an external magnetic field.

The resultant evolving spin polarization induces a radio frequency in a RF coil and thereby can be detected.

In organs and tissues, the magnetic field temporarily realigns water molecules, and the emitted radio waves can be processed to deduce position information which are used to create high-resolution cross-sectional images.

Image contrast is created by differences in the strength of the NMR signal recorded from different locations within the sample.

2D and 3D image reconstruction is another application of computed tomography.

By data processing the cross-sectional images or slides can be arranged to 3D-images.

The 3D-images can be viewed from different angles or be processed for different purposes, e.g. volume determination, pattern regonition.

Functional MRI (fMRI) is a special mode of MRI that renders possible to generate images of blood flow in the considered tissue or organ.

Contrast agents, e.g. gadolinium, after injection in a vein are used to enhance MRI scans.

Medical Imaging (V)

Magnetic resonance imaging (MRI)

Spin-lattice relaxation time T1: return from a higher, non-equilibrium state caused by longitudinal magnetisation to thermodynamic equilibrium.

Spin-spin relaxation time T2: decay of the transverse component of magnetisation caused by a 90° pulse to the longitudinal orientation, i.e. loss of phase coherence..

Spin echo: refocusing of spin magnetisation by a pulse resonant electromagnetic radiation.

Echo time TE: Time between the excitation pulse and the peak of the signal.

Real-time MRI: continuous imaging of moving objects (e.g. the heart) in real time.

Magnetic resonance spectroscopy: Monitoring the levels of different metabolites in body tissues, by analysing the spectrum of resonances related to different molecular arrangements.

Interventional MRI: Guided therapy with certain interventional measures, e.g. application of high-intensity focused ultrasound, by MRI.

Multinuclear imaging: Not only hydrogen, but any nucleus with a net nuclear spin can be imaged with MRI. Some of those nuclei are abundant in the body, others must be administered in sufficient quantities.

Molecular imaging by MRI: Imaging of biomarkers which are specific for certain diseases, e.g. peptides, antibodies, small proteins, small ligands. Recent advances focuse on imaging of gene actions.

Magnetic resonance microscopy (MRM): Very high resolution MRI down to 10 μm.

Magnetic resonance elastography (MRE): MRI combined with the generation of shear waves in tissue in order to image their propagation and to generate a stiffness map (elastogram.

Harvesting period (II)

Medical Imaging (VI)

Nuclear Medicine Imaging, SPECT, PET

Nuclear medicine imaging (sometimes called endoradiology) creates images of the inside of the body using the gamma rays of radioactive tracers which have been injected into the blood circulation or been applied by inhalation or swallowing.

External detectors, usually gamma cameras, capture and form images from the radiation emitted by the tracers, usually pharmaceuticals.

The images are digitally generated on a computer. 3D images can be produced.

In contrast to nearly all other imaging methods, the emphasis of nuclear medicine imaging is not on imaging anatomy, but on the function (hence: physiological imaging).

The three most common imaging modalities in nuclear medicine imaging are:

- Scintigraphy: Conventional approach with a gamma camera to generate planar imaging (projections).
- Single photon emission computed tomography (SPECT): 3D tomographic technique using gamma camera data acquired from many positions (multiple projections) by rotation around the body and with subsequent tomographic reconstruction (3D data set). Preferrably for myocardial perfusion monitoring, and for functional brain imaging.
- Positron emission tomography (PET): This technique uses as tracer a positron-emitting radioligand, most commonly fluorine-18. Positrons (or antielectrons) undergo instant annihilation when they collide with an electron, thereby producing two high-energy gamma rays which exit in exactly opposite directions, i.e. on a line that passes through the point of annihilation. The 3D data set can be reconstructed from multiple gamma rays acquired from many different positions around the body. PET is especially suitable for neuroimaging and applications in oncology and cardiology.

Image fusion by superimposing nuclear medicine imaging with other imaging modalities is used for combining anatomic with functional information: SPECT/CT, PET/CT, PET/MRI

Harvesting period (II)

Medical Imaging (VII)

Ultrasonography

U**ltrasonography** describes a technique that uses the emission of ultrasound waves (most commonly applied frequency range 100 kHz – 10 MHz) and the reflection (or echo) if those waves meet a border with a change in the acoustic impedance. The greater the change in acoustic impedance, the higher the amount of reflected energy with nearly complete reflection at hard tissues like bones. The depth of the reflecting border in the body is calculated from the time between transmitting and receiving a pulsed ultrasound wave (echo time).

Single-element probes emit an ultrasound beam in a fixed direction, i.e. a line. Such a probe must be physically moved or swept, to emit the beam through the area of interest. With the phased-array technique the beam can be swept (and focused) electronically without moving the probe. The phase array probe is made of multiple single elements, each of them can be pulsed individually at a computer-controlled timing. The form and the travelling direction of the beam are resulting from the superposition of all single emitted waves. The displayed area is a slice or 2D image.

Different modes of ultrasound technology in medical imaging:

A-mode (Amplitude mode): One-dimensional application in which the amplitude of the reflected sound (i.e. brightness) is displayed as a function of depth, i.e. the echo time. Pseudo 2D-images are recorded by moving the transmitter-receiver probe.

B-mode (Brightness mode): 2D-application is based on the automatic movement (linear or rotational) of the emitted ultrasound beam. Linear movement is usually generated by a linear array, rotational movement by a rotating probe. The image displays a cross section or slice of the body or organ.

C-mode: The C-mode is formed in a plane normal to a B-mode image by processing of data acquired by A-mode and obtained by a gate that determines the selected depth.

M-mode (Motion mode, synonym: TM-mode = Time-motion mode): Pulsed ultrasound waves are transmitted with high repetition frequency. The echoes are used to create either A-mode or B-mode images. In the A-mode imaging the movement of the reflecting boundaries is displayed over time, in the B-mode imaging the movement of the boundaries in the considered section is displayed in a kind of video.

Harvesting period (II)

Medical Imaging (VIII)

Ultrasonic Doppler and other special applications

Ultrasonic Doppler-mode: The Doppler effect is used for measuring and visualizing motions. The Doppler effect is the change in frequency of a wave seen by an observer who is moving relative to the wave source. In medicine with the observer in fixed position, the shift in frequency is caused by the motion of the reflecting boundary that may even be cells (e.g. erythrocytes) and renders possible the measurement of relative velocity of the moving boundary, e.g. the blood flow velocity.

- Color Doppler: Velocity information is presented as color-coded overlay on a B-mode image.
- Continuous wave (CW) Doppler: Doppler information is sampled along the beam line and displayed along a time-line.
- Pulsed wave (PW) Doppler: Doppler information is sampled from a small volume and displayed along a time-line.
- Duplex: Simultaneous imaging of 2D and PW Doppler information.

Ultrasound endoscopy: The ultrasound endoscope uses high-frequency sound waves emitted from a probe at the tip of an endoscope, i.e. a long flexible tube, inserted either into natural openings or by minimally invasive surgery. It can be combined with optical endoscopy or with a camera for imaging, but also with the biopsy of tissue or aspiration of fluid.

Ultrasound microscopy (synonym: Acoustic microscopy): It uses ultrasound waves with frequencies ranging from 5 MHz to beyond 400 MHz, thus reaching micrometer size resolution. In contrast to optical microscopy, biological samples need no special treatment, e.g. staining, before imaging. Commonly employed are scanning acoustic microscopes (SAM).

Photoacoustic Imaging uses the photoacoustic effect, i.e. the stimulation of sound waves following light absorption in a material sample. Light absorption causes thermoelastic expansion which generates ultrasound waves. It delivers images of optical absorption contrast in tissues.

Challenges: Quantitative blood flow measurement in microvessels,
imaging of microcirculatory architecture in living tissues

Harvesting period (II)

Medical Imaging (IX)

Optical and Photonic Medical Imaging

Medical imaging based on optical and photonic techniques uses light either for direct observation and presentation of biological objects or after processing the received information and/or image processing. The most commonly applied methods are:

Microscopy: Optical microscopy is the oldest imaging technology in medicine for objects which are too small to be seen by the naked eye. It uses light that passes through the object and optical components thereby producing a magnified image.

Endoscopy: Use of an endoscope to examine the interior of a hollow organ or cavity of the body after direct insertion into the body or organ. In rigid endoscopes the image is transmitted by a lense system to the viewer or receiving device, in flexible endoscopes the image is transmitted by a bundle of fiberoptics. The receiving device can be a camera or computer. Both types of endoscopes can have an additional channel for medical (surgical) instruments or manipulators.

Photometry: Quantitative measurement of the reflected or transmitted strength of electromagnetic radiation, usually in the range from ultraviolet to infrared and employing monochromatic light. One of the principal methods used in biochemical and analytical laboratory medical equipment. Sufficiently high repetition rates allow the imaging of dynamic changes during chemical reactions.

Harvesting period (II)

Medical Imaging (X)

Optical and Photonic Medical Imaging

Optical imaging: Noninvasively looking inside the patient’s body and obtaining images that can offer cellular resolution based on the detection of photons emitted in the visible and near-infrared (NIR) range from bioluminescent, fluorescent, or even Raman probes. It can be used to monitor theranostic nanoparticle uptake and drug release

Optical tomography: It is a form of computed tomography that creates a digital volumetric model of an object by reconstructing images made from light transmitted and scattered through an object.

Fluorescence tomography: Fluorescence that is stimulated by light in certain (mostly applied) substances renders possible imaging of the 3D-distribution of that substance within the body.

Optical coherence tomography (OCT): Use of low coherence light (interferometry principle) to capture 2D- and 3D-images from within optical scattering media with micrometer resolution.

Medical Imaging (X)

Bioimpedance

The passive electrical properties of biomaterials are characterized by 3 dispersions:
- α dispersion (10 Hz – 10 kHz) is assumed to depend on cell membrane and tissue features.
- β dispersion (1 kHz – 10 MHz) is associated with the polarization of the cellular membranes, i.e. is a structural relaxation process, the Maxwell-Wagner relaxation.
- γ dispersion (above 10 GHz) is associated with the polarization of molecular dipoles, e.g. water.

The most commonly used methodological approaches for medical imaging are:
Impedance plethysmography: a volumetric method for assessing a volume or imaging the changes of a volume.
Electric Impedance Spectroscopy (EIS): monitoring of the bioimpedance over a large or the whole frequency range in order to image changes in structure and function.
Electrical Impedance Tomography (EIT): imaging the 3D geometry of compartments with the same material-specific parameters (impedance, conductivity, or permittivity) within the body by electrodes attached to the surface preferrably in the 4-electrode mode.

Elastography

The passive mechanical properties (elasticity and stiffness) of soft tissue, e.g. liver, muscle, tumours, are captured after deformation by pushing, vibration, or acoustic radiation force. Observation of the response, e.g. shear waves, is possible by tactile sensors, ultrasound and magnetic resonance imaging.

Thermography

A thermographic camera is used to record the infrared radiation with wavelength ranging between 9 to 14 µm. Different thermosensitive technologies are employed in the cameras, e.g. focal plane arrays (FPA), using InSb, InGaAs, HgCdTe, or CCD or CMOS sensors, or microbolometers.

Harvesting period (III)

Materials, Biomaterials

Definitions:

<u>Material (as it is understood here)</u>:

- the elements, constituents, or substances of which something is composed or can be made;
- has qualities which give it individuality and by which it may be categorized;
- can be formed by mechanical, thermical, chemical or other external forces;
- can be classified into:
    * metallic materials and alloys
    * ceramic materials and glass
    * synthetic and semisynthetic materials
    * biological materials, organic matter, natural polymers
- no clear difference can be found between the definitions of material, matter and substance, although material seems to be most suitable for this presentation.

<u>Composite (as it is understood here)</u>:

- solid material which is composed of two or more substances having different physical characteristics and in which each substance retains its identity while contributing desirable properties to the whole;
- examples of special interest for medical application:
    * fibre-reinforced polymers
    * carbon composites
    * ceramic matrix composites
    * semi crystaline composites
    * high-strain composites

Harvesting period (III)

Materials, Biomaterials

Definitions:

<u>Biomaterial (as it is understood here</u>):

- may be natural (biological or organic material) or synthetic;
- is used as nonviable material in medical applications to support, enhance, or replace damaged tissue or to interact with biological systems;
- has direct contact with biological tissues and organs;

  material totally enclosed in a container and with no contact to biological tissues and organs is not categorized as biomaterial, e.g. the battery and the electronic components in a cardiac pacemaker;
- is characterized by its substantial properties, i.e. its chemical, physical, electrochemical and mechanical properties;
- must be sufficiently biocompatible with regard to the intended application and purpose, the site of contact and the surrounding medium (tissue, fluid)**;**
- its biodegradation must be adjustable to the intended application.

<u>Biocompatibility:</u>

- the quality of not having any toxic or injurious effects on biological systems;
- is defined in ISO 10993 as the „ability of a medical device or material to perform with an appropriate host response in a specific application“;
- quasi-synonyms are bio-tolerance, bio-inertness, and intended bio-activity;
- the most important endpoints to be addressed in a biological risk assessment are:
  * toxicity (acute, chronic, systemic, cells, reproduction system)
  * genotoxicity
  * carcinogenicity
  * hemocompatibility
  * degradation (effects of degradants, especially metallic ions and monomers)

Harvesting period (III)

Materials, Biomaterials

Metals and Alloys

Important properties are (dependent on the intended application and purpose)
- biocompatibility
- corrosion resistance
- mechanical resistance, tensile strength, high wear resistance, fatigue strength
- elasticity
- machinability and formability

Metals

- the best candidates are Ti, Nb, Zr, and Ta, especially cp-Ti (commercially pure titanium);
- Ni, Co or V are toxic or can cause allergic problems and should be avoided;
- are the material contained in many medical products such as dental implants, craniofacial plates and screws, parts of artificial hearts, pacemakers, clips, valves, balloon catheters, medical devices and equipments, bone fixation devices, medical radiation shielding products, prosthetic and orthodontic devices for biomedical applications.

Alloys

- metal alloys which are frequently used for medical requirements include titanium (Ti-6Al-4V), cobalt–chromium (Co–Cr), aluminium, zirconium–niobium, and tungsten (wolfram);
- 316L type stainless steel (316L SS) is the mostly used alloy in all implants ranging from cardiovascular applications to otorhinology.

Diamond-Like Carbon (DLC)

- a mixture of diamonds and graphite is used for biocompatible coatings.

Biometals

- are those metals which are normally present in biological tissues and are relevant for living organisms, e.g. metal ions, metalloproteins, metalloenzymes, enzymatic cofactors.

Harvesting period (III)

Materials, Biomaterials

Ceramics

Bioceramics:

- are ceramic products or components employed in medical applications, mainly for the repairment or replacement of musculo-skeletal hard connective tissues, for implants and protheses (especially for extremities);
- are most commonly based on aluminium oxide;
- can serve as porous media to support the ingrowth of new bone tissue, as materials that bioreact with bone, or as „scaffolds“ that are completely resorbed after establishing a template for tissue growth.

Dental ceramics:

- are used for applications that include resin-composite restorative materials, cementations agents, and fixed protheses, e.g crowns and inlays, made of porcelain-fused-to-metal cermets;
- belong to the group of advanced structural ceramics.

Advanced structural ceramics:

- demonstrate enhanced mechanical properties under demanding conditions, e.g. erosive, corrosive, or high-temperature environments, related with strong chemical bonding;
- are chemically inert, i.e. biocompatible, and are used for bone replacements;
- can be reinforced by microstructures with fibrous or interlocked grains;
- can be toughened by phase transformation to so-called „ceramic steel“;

Glass

- is used for:
    * contact lenses
    * laboratory glassware
    * container for pharmaceutical and diagnostical products, and for ampoules
    * optical instruments, e.g. microscope, endoscopes

Harvesting period (III)

Materials, Biomaterials

Synthetic materials

- are made from natural resources by changing the starting substance to create a material with different and desired characteristics;
- for medicine are primarily employed synthetic polymers;
- are materials for which the physical and chemical properties can be determined in a wide range by appropriate selection of the monomer units, addition of co-polymers, and the polymerization reaction;
- are used primarily for:
  * implants designed for orthopaedic, cardiovascular and dental applications;
  * semipermeable membranes for hemodialysis and drug delivery systems, e.g. including the degradation of microcarriers or nanospheres;
  * sutures, clot removal devices, ductus arteriosus devices;
- can develop self-reinforcement by integration of fibers of the same material into the matrix;
- can have highly advanced mechanical properties, e.g. shape memory effect with return to the original shape after deformation by a special stimulus which may be pH, temperature, magnetic field or light;
- may cause problems due to an interference with rest-monomers and other leachable products, e.g. degradation products, or additives like plasticizers with biochemical pathways.

Semisynthetic materials

- produced by chemical synthesis that uses chemical compounds isolated from natural sources (i.e. microbial cell cultures or plantmaterial) as the starting materials to produce other novel compounds with distinct chemical and medicinal properties;
- generally have a high molecular weight or a complex molecular structure;
- require for their production fewer chemical steps than regular synthesis that does not involve the aid of biological processes;
- can be drugs which are produced in a bioreactor that supports a biologically active environment.

Harvesting period (III)

Materials, Biomaterials

Biological materials

- may be proteins, cells, tissues, and organs

Naturally derived biomaterials:

- organic macromolecular matter of animals, plants, and microbes;
- polysaccharides, proteins, and polyesters derived from both plants and animals;
- native tissues like collagen and glycosaminoglycan, skin, kidney, liver, heart etc.;
- promising applications from scaffolds for tissue engineering to adhesives in drug delivery systems;
- may have shortcomings like impurity, unwanted immune reaction, limited mechanical properties;
- stem cells have great potential for regenerative medicine and treatment of various diseases;
- biomaterial and microfabrication technology can be employed for creating an artificial stem cell niche, i.e. the micro-environment for the desired differentiation into the specific cell types.

Biopolymers

- are produced by living organisms and are made of repetitive monomeric units that are covalently bonded to form larger structures;
- are frequently called „renewable polymers“, i.e. are biodegradable;
- often have a well-defined structure (usually described by a three-order structure):
  * primary structure: exact chemical composition and sequence in which the units are arranged;
  * secondary structure: pattern of hydrogen bonds, i.e. determining the general 3D-form of local segments of the biopolymers;
  * tertiary structure: the global structure of specific atomic positions in 3D-space.
- can be:
  * polysaccharides (e.g. cellulose, starch, chitin)
  * polynucleotides (e.g. RNA, DNA)
  * polypeptides and proteins (e.g. collagen)
  * polyesters, especially thermoplastic polyesters
  * phenylpropanoids (e.g. lignin)

Harvesting period (IV)

Non-electric Microtechnologies

Microfluidics

- is typically a set of up to millions of microchannels etched or molded into glass, silicon or polymer;
- is the technology used for applications as lab-on-a-chip, i.e. a miniaturized device that integrates onto a single chip one or several analyses done in a laboratory, e.g. DNA sequencing, PCR analysis, or biochemical detection;
- can be combined with integrated pumps, electrodes, valves, and electronic components;
- is used in the micro total analysis system that is suitable for all operations from sample collection to analysis;
- deals with the behavior, precise control and manipulation of fluids that are geometrically constraint to a small, typically sub-millimeter scale;
- is utilized in devices and techniques for culturing, maintaining, and experimenting with cells at the microscale;
- can mimic the cell micro-environment for the control of the regulation of cell structure, function, behavior, and growth;
- has the ability to produce stable gradients that in-vivo are important for chemotactic, durotactic and haptotactic effects on cells.

Digital Microfluidics is used to manipulate droplets, i.e. droplets are dispensed, moved, stored, mixed, reacted, or analyzed with a set of insulated electrodes.

In a **Digital Microfluidic Biochip,** cells in the microfluidic array can be employed for analytical analysis procedures such as mass spectrometry, colorimetry, electrochemical monitoring, and electroluminescense measurement.

Harvesting period (IV)

Non-electric Microtechnologies

Micromechanics

Surgical micro-devices:
- are useful for access to very small spaces;
- are serving different fundamental surgical functions requiring the manipulation and handling of small tissues and structures including grasping, cutting, and monitoring.

Endoscopic micro-instruments (for rigid as well as for flexible endoscopes):

* scalpels, forceps, scissors, dissectors, retractors, rasparatories, hooks, elevators
* biopsy devices
* microdrill, micromotor operating handle, remote-control manipulators, burrs
* irrigation and suction instruments, suckers

Micro-manipulator: An instrument for moving, dissecting, or otherwise manipulating minute specimens under the micoscope.

Special instruments for minimally invasive surgery and robot-assisted surgery

* trocars
* inflating devices
* rotating sinusoidal wires for thrombus removal
* electrocautery suction device
* guiding devices, fixation devices
* vessel-sealing instruments, suturing instruments
* surgical scopes
* vitrectomy-cutting instrument for cataract surgery

Harvesting period (V)

Medical Informatics (I)

- Biosignal acquisition
- Biosignal processing and information extraction
- Pattern recognition
- Biosignal interpretation and medical diagnosis

Harvesting period (V)

Medical Informatics (II)

Biosignal acquisition

Biosignals

- are any signals from living systems or identified samples that can be acquired, monitored, processed and analysed with regard to their origin, generation, meaning, and relevance;
- can be classified with regard to their generation as
    * intrinsic signals that are generated spontaneously within a living system or sample,
    * extrinsic signals that are stimulated by an external device with appropriate energy modality that is introduced into the living system or sample;
- can be assigned to one of the following physical modalities (with typical examples: intrinsic generation /// extrinsic stimulation):
    * electrical (ecg, eeg, emg, eog /// evoked potentials, bioimpedance, X-Ray imaging)
    * acoustical (phonocardiogram, lung sound /// ultrasound imaging, blood flow by Doppler effect)
    * thermical (body temperature /// gas flow monitoring, chemical reaction)
    * optical (skin cancer /// blood oxygenation, Laser Doppler flowmetry)
    * mechanical (blood pressure, apex beat /// shear waves in soft tissue)
    * magnetical (magnetoencephalography, magnetocardiography /// MRI)
    * chemical or molecular (-- /// glucose concentration, pH, SPECT, PET)
- can be static or vary with time;
- reflect the deterministic or stochastic characteristics of the signal source;
- represent the linear or nonlinear dependency of the signal source from other impacts;
- can be disturbed or blurred by
    * noise and interferences
    * mixture or superposition with other biosignals
    * non-identifiable interaction with other modalities
- can be analysed with the same methods as non-biological signals;
- can provide different temporal or spatial resolution with regard to the information of interest;
- can be carrier of 1D-, 2D-, 3D- or even 4D-information.

Harvesting period (V)

Medical Informatics (III)

Biosignal processing and information extraction

- Biosignals can be either analog or digital signals, representing space, time, or space-time records;
- Signal processing is the usual procedure to extract the useful (or relevant) information;
- Analog signals can be processed by analog methods including
  filtering, addition, subtraction, integration, differentiation, multiplication, peak detection, convolution, Fourier and Laplace transformation;
- Digital signal processing, i.e. processing of digital signals sampled in time and quantitized in amplitude, is more usual than analog signal processing;
- 2D- or even multi-D-signals can be transformed to 1D- (or time-dependent) signals by sequential scanning, preferrably with equal time intervals;
- Processing can be performed in
  - time domain (one-dimensional signals)
  - spatial domain (two- or multidimensional signals)
  - frequency domain
  - wavelet domain
- Information extraction in medicine aims for the information that is relevant for the assessment of a health problem, e.g. to end up with the optimal differential diagnosis;
- This relevant information can:
  - directly be visible in the record of the ecg, i.e. that the heart is beating;
  - be calculated from the record of the ecg, i.e. the mean heart rate during a given period;
  - be based on the occurence of pathological events, i.e. of cardiac extrasystoles or premature heart beats which can be identified by form analysis and / or by the exact time of their occurrence;
  - ask for the differentiation between atrial and ventricular extrasystoles that require a more detailed analysis of their signal morphology and time of occurrence;
  - be the deformation of cells, e.g. sickle cells, i.e. deformed red blood cells;
  - be represented in a summarized assessment of different signals, e.g. gait analysis;
  - be acquired by evaluation of fusion images, e.g. neurological functional disorders displayed in SPECT/CT images;
  - be displayed by combination imaging technologies, e.g. Doppler blood flow in US B-mode images

Harvesting period (V)

Medical Informatics (IV)

Pattern recognition

Pattern recognition is
- generally the process of classifying input data into objects or classes based on key features;
- frequently combined with pattern simplification by concentration on relevant features;
- based on methods like
  * supervised training
  * unsupervised training
  * machine learning and deep learning that both originate from artificial intelligence
  * texture analysis with processing algorithms that can be structural, spectral, or statistical
  * wavelet decomposition in order to extract desired features
- using algorithms that generally aim to provide reasonable answers for all possible inputs and to perform „most likely" matching of the inputs, taking into account their statistical variation and thereby being different from pattern matching algorithms that look for „perfect" matching.
- in medicine concerned with the computer-based discovery of regularities or irregulatories in data using algorithms with the intention to support information-dependent actions like
  * classifying the data ino different categories
  * making a diagnosis, i.e. the determination of the nature of a disease, injury, or congenital defect
  * improving preventive healthcare

Patterns with relevance for medical decision making can be
- regularities in time series as well as irregularities defined by algorithmically defined features;
- structures and features in images which are defined by geometric criteria as well as by non-geometric criteria;
- the identification of an interrelationship network between data of different modalities;
- useful for finding individuals with sufficient similarity as members of groups in big data collections.

Harvesting period (V)

Medical Informatics (V)

Biosignal interpretation and medical diagnosis

Biosignal interpretation:
- is the next step following biosignal processing and information extraction to reach a medical diagnosis;
- is based on, however not restricted to the usual methods of signal analysis in the time, frequency, time-frequency domain;
- needs expertise in the evaluation of the extracted information taking into account other (all) relevant and available data of the individual, e.g. age , sex, physical fitness, former or acute health problems, intolerances (food, drugs etc.), social, environmental and mental impacts;
- is a fundamental requirement for the development of advanced clinical decision support systems.

Medical diagnosis:
- aims for the identification of a disease by appropriate consideration of its symptoms and signs;
- is classifying the health state of an individual, e.g. in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10, with ICD-11 at Jan. 01, 2022), issued by the World Health Organization WHO;
- is the result of one or more diagnostic procedures;
- is based on an interview with the patient, on the medical history (including family members) and on the results of physical examinations and various laboratory tests;
- can be a multi-step process. e.g. with the following steps
  * tentative or preliminary diagnosis
  * differential diagnosis
  * exclusion diagnosis
  * concluding, closing or final diagnosis
- should at each step be interpretable as guideline for next diagnostic or for therapeutic measures.

Flowering phase

- Telemedicine
- e-health, m-health
- Virtual Reality
- Augmented Reality
- Sensor-based Communicative Wearables
- Smart Rehabilitation Technology, Rehabilitation Robotics
- Active Assisted Living (AAL)

Flowering phase

Telemedicine

is the utilization of all kinds of information and communication technologies (ICT) to transfer health care information, i.e. medical information with relevance for diagnosis, therapy, rehabilitation, health management, and education.

Two important branches are:

Telecare utilizes ICT to support the delivery of healthcare to patients in their place of domicile;

Telehealth utilizes ICT to support clinical, administrative and educational services;

Telehealthcare summarizes features of both Telecare and Telehealth. Hence, it is comparable with (or may be seen as synonym for) Telemedicine.

Typical transfer modes of health care information are:

- Teleconsultation between patient and doctor;
- Teleconferencing between several doctors (e.g. for interdisciplinary knowledge exchange);
- Data transfer, e.g. from a doctor office or hospital to an insurance institution or another medical care service, e.g. drug stores;
- Telemonitoring and Telesurveillance of patients (clients) by specialised services, especially home telemonitoring of patients with chronic diseases and high risks;
- Teleeducation and Teletraining in special fields (e.g. pathology, surgery).

Flowering phase

e-health

Oh, H.; Rizo, C.; Enkin, M.; Jadad, A. (2005): „What is e-health: A Systematic Review of Published Definitions“ found **51** different definitions (Journal of Medical Internet Research 7 (1)).

- Virtually everything in medicine that is related to digital information processing.
- Use of information and communication technologies (ICT) for health (WHO).
- A broad group of activities that use electronic means to deliver health-related information, resources and services (WHO-Europe).
- Others wordings, some with a slightly differing meaning:
  - internet medicine, i.e. exchange of medically relevant information using the internet;
  - health care systems based on electronic data recording for further processing;
  - health informatics, i.e. computerized information processing;
  - clinical data management, i.e. providing the necessary data availability for decision finding;
  - cybermedicine, i.e. the use of the internet to deliver medical services, such as medical consultations and drug prescription.

m-health

- Medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring systems, personal digital assistants (PDAs), and other wireless devices.

  M-health involves the use and capitalization on a mobile phone‘s core utility of voice and short messaging service (SMS) as well as more complex functionalities and applications including general packet radio service (GPRS), third and fourth generation mobile telecommunications (3G and 4G systems), global positioning systems (GPS), and Bluetooth technology (WHO report 2011).
- Mobile medicine, i.e. exchange of medically relevant information using mobile communication systems.
- Mobile health care, i.e. exchange of information to support health care including health care management.

Flowering phase

Virtual Reality (VR)

- is a computer created simulation of real-life situations, but also of situations that are completely different from real world;
- combines human senses such as hearing, sight and touch, with software and hardware to create a computer-generated 3D immersive virtual environment;
- uses immersive technology to emulate a physical world by hardware technologies, to stimulate the physiological senses and to create perceptually-real sensations:
    - visionary technology,
    - auditory technology,
    - haptic technology,
    - olfactory technology,
    - gustatory technology;
- enables individuals to explore this environment and to interact with it, e.g. to perform a series of actions or to manipulate objects within that environment.

Where it can be used in medicine and healthcare:

• treatment of chronic pain by blocking pain perceiving processes including phantom pain;

• delaying the progressing memory loss by challenging information processes in the brain;

• enhancing surgery training by employing realistic models based on 3D real-time imaging;

• treatment of incurable autism by developing life skills that may lead to independent living;

• regaining muscle control after stroke with motoric disorders and other impairments;

• stabilizing mental health by using the Virtual Reality Exposure Therapy (VRET), e.g. to support controlled reaction to simulated confusing scenarios in cases of post-traumatic stress disorders (PTSD) after exposure to traumatic events.

Global Industry Analysts projects that the worldwide market for virtual reality in healthcare will reach $3.8 billion by 2020

Flowering phase

Augmented Reality

- is the integration of 3D virtual objects with the user's 3D real world environment in real time;
- offers real-time interaction capability;
- uses the existing environment and overlays new information on top of it whereas Virtual Reality creates a totally artificial environment;
- provides the users with additional computer generated information that enhances their perception of reality;
- generates perceptual information, sometimes across multiple sensory modalities, including visual, auditory, haptic, somatosensory and olfactory modalities;
- is realized by overlaid sensory information that can be constructive (i.e. additive to the natural environment), or destructive (i.e. masking of the natural environment);
- can be used in medicine and healthcare for many applications, e.g.
    - overlaying images (X-ray, CT, MRI, PET, SPECT, ultrasonics, endoscopy) with supplementary information to provide guidance during diagnostic and therapeutic interventions, especially during minimal-invasive interventions and neurosurgical processes;
    - reminding patients to take medications or for other time-related activities;
    - training medical professionals.

Mixed Reality

- is a hybrid of real world and virtual world, encompassing both augmented reality and augmented virtuality via immersive technology;
- until now, no application in medicine or healthcare has been published;
- may be useful for the combination of smart glasses with surgical processes.

Flowering phase

Sensor-based Communicative Wearables

- provide such essential features as portability, usability, autonomy of and comfort for the patient;
- render possible remote patient monitoring in real time for early diagnosis and risk surveillance, with alerting functions, and for advisory support by healthcare professionals;
- can be combined to a body-area network (BAN), a refinement of the former body-sensor network (BSN);
- can cooperate with active, intelligent implants;
- can be integrated into smart environments, e.g. smart houses;
- can use services provided by the Internet of Things (IoT) with cloud capabilities including support of decision making, and analysis, storage and tracking of data;
- are promising for personalized therapy and healthcare management;
- may become essential for realizing the virtual hospital, especially for reducing healthcare expenses, and for remote service utilizing digitalisation;
- need more accuracy and consistency for acceptance by clinical professionals and health insurance providers;
- must meet high standards for security, privacy, and authorized access to data;
- are based on connectivity media like cellular systems, NFC, Bluetooth, Wi-Fi, and ANT+;
- facilitate algorithm development for automated health event prediction, prevention and intervention.

A recent report from Research & Market predicts global sales of wearable devices will exceed $60 billion by 2025. However no details are known about the market for medical wearables or for wearables for fitness and outdoor sport activities.

Flowering phase

Smart Rehabilitation Technology

- utilizes intention-driven exoskeleton equipment that is controlled by EMG signals in the respective muscles and supports voluntarily driven movements;
- utilizes EEG control with external muscle stimulation;
- is equipped with haptic feedback.

Rehabilitation Robotics

- uses devices tailored for assisting different sensorimotor functions and performance of patients, e.g. flexion, extension and rotation of arm, hand, finger, leg.
- are equipped with applications of techniques that adjust the level of exercise, i.e. active assisted exercise, active constrained exercise, active resistive exercise, passive exercise to the individual necessities and progress;
- robots are used mainly as therapy aids instead of primarily assistive devices.

Gamification

- uses techniques which are utilizing people's natural desires for e.g. learning, fitness, health or optimal response to the framing of a situation as game or play;
- commonly employs game design elements to improve user engagement;
- can be used as a virtual medical expert (with speech recognition, artificial intelligence, decision making) to train patients to ask the right questions and to make their goals and wishes clear for their consultation.

Flowering phase

Active Assisted Living (AAL)

Assistive or service robots

- are reprogrammable multifunctional devices with sensoric and actoric capabilities;
- can increase the quality of life and personal autonomy of elderly people when living in their private home;
- can monitor health care data and transmit them to an authorized medical center;
- can be integrated into intelligent domestic systems;
- should be equipped with intelligent functions, e.g. speech recognition, delivery of drugs in due time, communication with the user for decision making;
- will improve care for elderly people in nursing homes and hospitals;
- train users by presenting them with simple exercises individually designed to improve their physical, intellectual, cognitive or mental condition.

Risk surveillance

- should integrate harmonically in the domestic environment without restricting the independent daily living;
- should not damage the privacy of the user;
- must be capable to receive and evaluate information from wearables and fixed sensors;
- must bidirectionally be connected to an authorized center to transmit an alarm and to answer questions.

Growth phase

- Computational Medicine
- Computational Models
- Model-based Simulation
- Personalized Medicine
- Digital Health
- Robot-assisted Surgery
- Autonomous Healthcare Devices and Systems
- Tissue Engineering
- Biomolecular Engineering
- Agriculture and Animal Husbandry

Growth phase

Computational Medicine

- should not be confused with Medical Informatics;
- aims to improve the understanding of disease mechanisms, the prediction of disease progress, and the individual planning of complex treatments by mathematical modelling, simulation, and optimization;
- has strong interest to develop computational models of the anatomy, molecular biology, and physiology of diseases, and apply these models to understand the mechanisms of diseases and to improve patient care;
- seeks to develop multi-scale physiological and patho-physiological models that integrate information from the level of molecular networks to cells, tissues, organs and organ systems;
- can provide insight into and across many areas of biology, including genetics, genomics, and molecular networks, of cellular and tissue physiology, organ systems, and whole body pharmacological interrelations;
- uses advanced methods like
    * model validation, especially assessing to what (quantitative) level the output of the simulation sufficiently represents the real system behaviour;
    * agent-based modelling, taking into account emergence and complexity;
    * data modelling, e.g. exploring data-oriented structures,
    * machine learning, e.g. data mining and learning approaches;
    * Artificial Intelligence, e.g. transforming data into usable knowledge.

Computational Models

- are mathematical models for the study of complex biological systems using mathematics, physics, chemistry, biology, physiology, pathophysiology, anatomy and computer science;
- are hypothetical descriptions of real systems in terms of constitutive objects and the relationships among them (are sometimes called „formal models“);
- can range from black boxes over grey boxes to white boxes, depending on the information including data and process parameters that is available about the internal structure of the studied system down to the required level, e.g. whole-body, organs, cells, subcellular organisms, macro-biomolecules or atoms;
- contain numerous variables that characterize the system, its structure and its behaviour,
- are usually dynamic multi-scale models with a wide-ranging time-scale;
- can be classified as SISO, SIMO, MISO or MIMO models;
- can enclose sub-systems which are essential for the structure and behaviour of the main system, whereby sub-systems may be compartments or distributed quantities;
- are based on the following steps:
    * model selection, considering scaling and acceptable simplifications;
    * mathematical formulation, description of the considered interrelations and processes;
    * parameter introduction, eventually followed by parameter fitting;
    * implementation on the computer;
    * validation including sensitivity analysis.

Growth phase

Model-based Simulation

can be used for

* testing the hypothesis formulated in the model, primarily by falsification;
* observing the response of quantities which are not directly measurable to different external stimuli:
* changing systematically the relationships between selected quantities or subsystems;
* predicting the reaction of the real system to applied stimuli;
* optimizing procedures like drug application;
* prototyping new devices and assessing their usefullness;
* designing new experiments with the real system including the proper consideration of limits which should not be surpassed in the real system;
* removing redundant subsystems with regard to special questions and applications;
* selecting appropriate discretization in time or space with regard to special questions and applications;
* interpretating test data acquired from real systems;
* employment as powerful tool for education and training.

Growth phase

Personalized Medicine (or individualized medicine)

With data of November 2016 the EU has officially launched the

International Consortium for Personalized Medicine, ICPerMed

The EU defines personalized medicine as “a medical model using characterization of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention”.

The ICPerMed vision for 2030 - How can personalized approaches pave the way to Next-Generation Medicine?

Perspective 1: Informed, empowered, engaged, and responsible citizens

Perspective 2: Informed, empowered, engaged, and responsible health providers

Perspective 3: Healthcare systems that enable personally-tailored and optimized health promotion, prevention, diagnosis, and treatment for the benefit of citizens and patients

Perspective 4: Availability of health-related information and data for optimized treatment, care, prevention, and research

Perspective 5: Economic value by establishing the next generation of medicine

A first project report was on Big Data, Electronic Health Record and Health Governance

Growth phase

Personalized Medicine (or individualized medicine)

- takes into account all relevant aspects of the respective patient with regard to diagnosis, therapy and rehabilitation;
- considers appropriately all relevant facts and available differences in people's genes, socio-economic status, professional and private environments, and lifestyle behaviour;
- is the tailoring of medical treatment to the individual characteristics of each patient;
- aims for minimizing harmful side effects and ensures a more successful outcome;
- is a first step towards Theranostics, i.e. a new field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests;
- uses predictive tools to evaluate health risks, to design personalized health plans to help patients mitigate risks, and to prevent diseases for which the predisposition is known;
- is pushed by "-omics" (genomics, proteomics, metabolomics, and pharmagenomics) studies concerning the contribution of genes, proteins, and metabolic pathways to human physiology and pathophysiology, and how genes affect a person's response to drugs.
- is enabled by **Computational Healthcare** that exists at the interface of biomedical signal processing, computational modelling, machine learning, and health informatics – all exploiting electronic health record (EHR) data, physiological time-series data, genomics, etc.

Growth phase

Digital Health

- is the convergence of digital technologies with health, healthcare, living, and society;
- its aim is to promote public health by making medicine more personalized and precise;
- is based on technologies both from the hardware and from the software world;
- includes solutions, applications and services provided by telemedicine, web-based information and communication, email, mobile phones, wearable devices, remote monitoring systems, smart home installations, assistive equipment, and rehabilitation robotics;
- is defined by the FDA: „The broad scope of digital health includes categories such as mobile health, health information technology, wearable devices, telehealth and telemedicine, and personalized medicine. These technologies can empower consumers to make better-informed decisions about their own health and provide new options for facilitating prevention, early diagnosis of life-threatening diseases, and management of chronic conditions outside of traditional care settings.“
- is defined by Healthcare Information and Management Systems Society, Inc. (HIMSS): „Digital health connects and empowers people and populations to manage health and wellness, augmented by accessible and supportive provider teams working within flexible, integrated, interoperable and digitally-enabled care environments that strategically leverage digital tools, technologies and services to transform care delivery.“
- is defined in a more recent approach: „Digital Health is the convergence of the digital and genomic revolutions with health, healthcare, living, and society.“

Growth phase

Robot-assisted Surgery

- shall overcome the limitations of most minimally-invasive surgical procedures;
- shall enhance the capabilities of surgeons performing open surgery;
- can be realized in two different methodological approaches:
    * the direct-controlled method employing a telemanipulator which, through electronic, hydraulic, or mechanical linkages, allows hand-like actions under the control of the surgeon;
    * the computer-controlled method using robotic arms that carry out the movements and are equipped with end-effectors and manipulators to perform the surgery. This approach does not require the presence of the surgeon, i.e. it can be executed as remote surgery (or telesurgery);
- can be guided by imaging methods, e.g. direct imaging with an endoscope camera that provides a true stereoscopic picture transmitted to a surgeon‘s console;
- can be provided with instrumentation for haptic or force feed-back;
- can detect and filter out any tremor in the surgeon‘s hand movements;
- can be provided with down-scaling of movements for precise micro-surgery;
- allows the surgeon to perform the surgery in sitting position thereby avoiding physical tiredness;
- has still limits and is combined with different complications, e.g. necessity of re-operation, damage of certain tissues like nerves, and permanent injury;
- as long-distance surgery is limited by the time delays between the control end and the operating end.

Growth phase

Autonomous Healthcare Devices and Systems

- Autonomy means that those devices and systems are capable of performing a series of operations where the sequence is determined by the outcome of the previous operation or by reference to external circumstances that are monitored and measured in the device or system itself.
- Autonomous Healthcare Devices and Systems can include types of antropomorphic automatons that interact with humans.
- Wireless sensors and universal connectivity together with onboard processors enable the handling of continuous real-time data exchange and the activation of appropriate responses.
- Intelligent functions, decision-making software and IoT capabilities qualify these devices and systems for transforming the hospital into a smart hospital.
- Equipped with pervasive sensing technology such devices and systems will be integrated in Intensive Care Units (ICU) and in emergency departments.
- They provide a high potential for application in outside resuscitation and emergency medicine, especially if transportation by drones is possible.
- They can take over hospital-internal logistic services, e.g. transportation of patients within the hospital, distribution of food, drugs and medical products.
- Those devices and systems can enable older people to retain their independence for longer, especially if they are mobile and if speech communication (or other communication adjusted to the individual) is possible.

Growth phase

Tissue Engineering

- is the use of a combination of biomaterials (e.g. biomolecules, cells), engineering methods, materials knowledge, and physiological and biochemical expertise to breed or to assemble biological tissues and organs with desired features;
- can involve the use of a tissue scaffold that mimic the extracellular 3D matrix of the native tissue and become seeded by cells to generate viable tissue for a medical application;
- aims for changing the course of acute or chronic disease, e. g.
    * by regenerating tired and failing organ systems;
    * by replacing portions of or whole organs;
- shall deliver products that are functioning and effective in the required mechanical (active and passive), electrophysiological, metabolical, pharmacological, immunological, and secretory way as the native tissue or organ;
- can use autologous cells that are reimplanted after culturing;
- includes regenerative medicine, i.e. the possibility of growing functional human tissues and organs in the laboratory (mostly using stem cells which may be multipotent or pluripotent) and implanting them in the body;
- utilizes advanced methods like
    * tissue culturing in bioreactors that replicate the required specific environment;
    * 3D bioprinting by combining cells, growth factors, and biomaterials to fabricate biomedical tissues and organs with the aim to optimally imitate the characteristics and functions of biological tissues and organs;
    * autonomous self-assembly, primarily based on the utilization of embryonic cells and tissues with their unique feature for self-development.

Growth phase

Biomolecular Engineering

- purposeful production and manipulation of biomolecules by application of engineering principles, methods and knowledge;

- use of key biomolecules, e.g. carbohydrates, proteins, nucleic acids and lipids, but also other molecules, for the production of biomolecules with desired structure, functions, and properties that are effective as drugs, for diagnostics, for enhancing compatibility of artificial surfaces and for other purposes;

- is focused, but not limited to the production of antibodies, enzymes, hormones, therapeutic lipids, and vaccines;

- can be controlled by data banks that provide the details of the tertiary structure;

- most important applied methods are

  * genetic engineering (or gene modification), e.g. to produce recombinant DNA for human insulin, human growth hormone, factor VII;

  * site-directed mutagenesis to create certain nucleotide sequences on a gene;

  * bio-immobilisation and bio-conjugation by physical entrapment, adsorption or covalent modification;

  * polymerase chain reaction used to replicate a piece of a DNA molecule by several orders of magnitude;

  * enzyme-linked immunosorbent assay (ELISA) utilizes antibody-antigen recognition to test for the presence of certain substances.

- a very recent approach is the use of mRNA for the production of vaccines, e.g. mRNA based vaccines against the corona virus SARS Covid-19 and other therapeutics, especially for personalized medicine.

Growth phase

Agriculture (IT Farming)

- utilisation of navigation systems, i.e. Galileo, for optimized spreading of seed, fertilisers, and herbicides without overlapping and vacant spaces;
- use of intelligent equipment and apparatus for the exact delivery of dosed quantities of seed, fertilisers, and herbicides;
- automatic or GPS controlled width section switching;
- remote monitoring of the state of the soil, e.g. temperature, moisture, pH-value;
- remote monitoring of the state of development and maturity of plants, crops and fruits;
- remote activation of actions like irrigation.

Animal Husbandry

- monitoring of activity (e.g. movement, drinking, feed uptake);
- monitoring the state of health (e.g. body temperature, pH-value in the gastro-intestinal tract, body fat);
- providing optimal living and welfare conditions in cages, containers and closed buildings (e.g. air conditioning);
- advanced smart automatic milking equipment, technologies in animal breeding;
- support of veterinary health care by use of equipment, informatics and data bases.

Germination phase

- 3D-Printing, Bioprinting
    - non-biological materials
    - biological materials
- Quantum Computers
- Biohacking
- Genetic, biomolecular and cellular engineering
- Regenerative medicine and synthetic biology
- Blockchain Technology
- Start-up techniques

3D-Printing

3D-printing (or additive manufacturing): the production of three dimensional solid objects from a digital file.

A layering process is used to add one layer after the other until the desired 3D-object is completed.

It allows to create more complex forms, much cheaper and in much less time than any other production method.

The used materials can be of biological or non-biological origin.

It may be used

- for quicker and cheaper production of medical equipment with unique features;
- for developing tissue and organ models with real biological structures for implants;
- as a powerful tool for tissue engineering, e.g. blood vessels including vascular branches, bones including joints and articulations shapes, heart including valves, or synthetic skin, and special shaped body parts like the auricle.
- for the production of
  - individual dental implants, e.g. complete denture protheses;
  - individually tailored drug mixtures;
  - personalized plastic ortheses with a high degree of comfortability;
  - personalized models for the training of surgeons before the operation.

Bioprinting means the printing of 3D-objects by using biological materials, which may even be living cells. With that method it seems possible to print organs like the heart or the liver. The cells are cultured and embedded in polymeric gel.

Germination phase

Quantum Computers

A quantum computer encodes data into bits that can represent a one, a zero, or some combination. The combination is known as a quantum superposition, and bits with these quantum properties are known as qubits.

There are two main approaches to physically implementing a quantum computer currently. Both approaches use quantum bits or qubits.

Analog approaches are further divided into quantum simulation, quantum annealing, and adiabatic quantum computation.

Digital quantum computers use quantum logic gates to do computation.

Fields of promising application in healthcare with huge amount of data are:

- radiotherapy utilizing 3D-visualization;
- personalised healthcare taking into account genomics;
- drug research and drug interaction with regard to pharmacokinetics;
- artificial intelligence utilizing machine learning;
- disease screening employing big data processing and evaluation;
- genomic medicine based on CRISPR technologies and super-resolution microscopy techniques;
- computational modelling and its employment for clinical studies and personalized therapy.

Biohacking („pro-active engineering of the body“)

A systemic approach to better understand and more effectively control biological systems including the own body.

This shall be achieved by utilizing biological, chemical and physical effects, but also genetic engineering and technical equipment, especially wearables and implant devices.

Objectives:
- improved lifestyle control for personal health management;
- disease prevention by risk assessment;
- optimized personal therapy, especially for chronic diseases;
- enhanced brain function;
- compensation of impaired brain function, e.g. Alzheimer, Parkinson;
- special fields like neurohacking for neurofeedback.

Problems:
- ethical conflicts;
- unintended effects or even fatal consequences;
- misuse by external impacts;
- external undesired impacts on the systemic behaviour.

Genetic, Molecular and Cellular Engineering

Genetic Engineering: Applied techniques for changing the structure of the genes of a living organism or system in order to modify or adjust one or more of its characteristics. The aims can be:

- synthesizing special active substances (e.g. human insulin);
- correction of genetic diseases;
- enhanced resistance in plants against environmental impacts or pest.

Biomolecular Engineering: Purposeful manipulation of molecules of biological origin with regard to their structure, function or other properties. The aims can be:

- immobilization in order to enhance biocompatibility of artificial surfaces;
- development of new drugs.

Cellular Engineering: Cell culture technology. The aims can be:

- processing of growing living cells as biological substitutes for damaged organs;
- use of living cells for manufacturing a biochemical product.

Germination phase

Regenerative Medicine

Application of stem cell therapy, tissue engineering, medical devices and other techniques to repair damaged or diseased tissues and organs. The aims may be:

- treatment of chronic pain, joint injury (with or without surgery);
- minimal invasive spinal surgery for repairing / replacing damaged discs;
- regeneration of cells, tissues or organs to restore normal functions;
- stimulation / enhancement of body‘s own healing processes.

Synthetic Biology

a. Medical: Design and construction of new biological parts, devices and systems, and the re-design of existing natural biological systems for useful purposes. The aims may be:

* tumor-seeking microprobes for cancer treatment;

* development of friendly bacteria.

b. Industrial: Production of fuels, chemicals, biological inspired materials and structures. The aims may be:

* development of sustainable industrial processes.

c. Environmental: Employment for nature conservation, remediation of contaminated sites, sensing and monitoring of contaminants, and control of invasive species. The aims may be:

* pollution prevention, remediation of contaminated environments.

Germination phase

Blockchain Technology

- is defined as a distributed system which records and stores transactions in a digital ledger;

- is similar to a data base that stores information, however, the data is stored in a decentralized network of personal computers;

- is not controlled by a central system, a central authority or organisation.

Special features are:

- all data is shared publicly;

- the content of data is only accessible for participants with permission;

- each participant has a secret private key and a public key that acts as an openly visible identifier.

Promises for Health Care

- enabler of a new, secure and efficient model for Health Information Exchange;

- a (nationwide) blockchain network for electronic medical records may improve efficiencies and provide better support regarding health outcomes for patients;

- trustless collaboration between network participants may be possible while an immutable audit trail of all interactions is recorded.

Start-up Techniques (I)

Flow Cytometry: It is a technique for the detection and measurement of physical and chemical characteristics of cells and particles which are contained in a heterogeneous population that is suspended in a fluid. It can be combined with other techniques, e.g. with cell sorting, with fluorescent labeling, and with computerized signal evaluation. The aims may be:

- detection of specific antigens to diagnose different diseases;
- monitoring the intracellular content of substances or intracellular processes.

CRISPR Techniques: CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) is a specialized region of DNA with two distinct characteristics: the presence of nucleotide repeats and spacers. CRISPR gene editing technology is a genetic engineering technique in molecular biology by which the genomes of living organisms can be modified. It was developed by Emmanuelle Charpentier (France) and Jennifer Doudna, who have been distinguished by the Nobelprice 2020 in Chemistry.The aims may be:

- enabling regenerative medicine by using stem-cell derived therapies following stimulation of immune evasion;
- enhancement of personalized medicine by the correction of disease-causing mutations directly in humans;
- cancer therapy by turning off the oncogenes and turning on the tumour suppressor genes.

Start-up Techniques (II)

Super-resolution microscopy techniques:

a. Optical far-field super-resolution microscopy techniques comprise two approaches:

- the deterministic super-resolution,
- the stochastic super-resolution.

Impressive recent progress has been achieved by the super-resolved fluorescence microscopy which uses the Stimulated Emission Depletion (STED) method. This methodological approach belongs to the deterministic group.

STED can be combined with atomic force microscopy.

It brings optical microscopy into the nanodimension and was developed by E. Betzig, W.E. Moerner and S. Hell. This development was acknowledged by the Nobel Prize in Chemistry in 2014. Hell was born in 1962 in Arad (Romania) and emigrated with his parents in 1978 to Germany.

The aims may be:

- imaging complex intracellular organelles like mitochondria;
- visualization of membran fusion controlled by proteins;
- investigation of living cells and intracellular processes, e.g. mobility;
- measuring the length of DNA fragments.

Start-up Techniques (III)

Super-resolution microscopy techniques:

b. High-speed photo-acoustic microscopy

Photo-acoustic microscopy (PAM) is based on the photo-acoustic effect, i.e. the generation of ultrasonic waves induced by the transient thermal expansion of molecules following the absorption of optical light.

Optical-resolution PAM renders possible spatial resolution in the μm range.

With high-rate pulsed lasers temporal resolution up to 1 ms has been achieved.

This methodological approach can be applied for surface-near in-vivo imaging.

The aims may be:
- imaging of the microvascular structure, e.g. tumour angiogenesis
- microvascular flow imaging
- oxygen supply monitoring
- skin melanoma detection
- investigation of hemodynamic effects and drugs on the microcirculation

Biotechnology

- **White Biotechnology:** industrial biotechnology, i.e biotechnology applied to industrial production processes, e.g. designing an organism that can produce a useful chemical, or using enzymes as industrial catalysts to either produce valuable chemicals or destroy hazardous/polluting chemicals.
- **Green Biotechnolog:** the use of genetically altered plants or animals to produce more environmentally-friendly farming solutions as alternative to traditional agriculture, horticulture, and animal breeding processes. Bioremediation is a very promising approach for treating contaminated media.
- **Red Biotechnology:** the use of biotechnology in the medical and pharmaceutical industries, and health preservation. It involves the production of vaccines and antibiotics, regenerative therapies, creation of artificial organs and new diagnostics of diseases, but also the development of hormones, stem cells, antibodies, siRNA, and diagnostic tests**.**
- **Blue Biotechnology:** based on the exploitation of sea resources to create products and industrial applications, e.g. the production of bio-oils with photosynthetic micro-algae. Plant based food biotechnology explores chemical and biochemical approaches for extraction, separation, and processing of plants and algae to harness their content of proteins, lipids, and carbohydrates as well as minerals, vitamins and others.
- **Gold Biotechnology:** computational biology addressing biological problems by the use of computational techniques. Biological systems are described in terms of molecules, and informatics techniques are applied in order to understand the behaviour and function of those systems.
- **Yellow Biotechnology:** food production.
- **Gray Biotechnology:** application to environmental systems and problems.
- **Brown Biotechnology:** management of arid lands and deserts.
- **Dark Biotechnology:** bioterrorism, biological weapons and biowarfare which uses microorganisms, and toxins to cause diseases and death in humans, livestock and crops.
- **Violet biotechnology:** related to law, ethical and philosophical issues around biotechnology.

Ecology

- is the science of the study of ecosystems, i.e. communities of different biological organisms and systems, and their interaction with their physical environment;
- is concerned with relations that exist and become effective
  - within a biological organism
  - between different biological organisms
  - between biological organisms and their surrounding environment
- is affected by both damaging and beneficial impacts from technology, i.e. technology is
  * the cause of air and water pollution, of the depletion of natural resources, and of the destruction of habitats with disastrous impacts on the habitat population;
  * the most promising solution enabler for these damages.

and its future development can by promoted by:

* comprehensive data collection in both time and space, e.g. by remote sensoring, and efficient data processing, e.g. for the assessment of global and regional changes, especially with regard to biodiversity loss and habitat destruction;
* development of complex models for the simulation and validation of the interaction relationship networks existing in and between ecological subsystems;
* advanced technologies for industrial processes with less damaging impacts;
* advanced technologies for the effective removal of the already existing pollution of air and water;
* advanced technologies for agricultural production and utilization of the products with the focus on avoidance of damaging the natural resources and on minimizing the waste;
* development of a (global) network for the early detection of disastrous trends, primarily by the application of Artificial Intelligence, combined with an efficient warning system.

Others with indirect relation to advancing technologies

Ethics and MBES

There are not only different definitions for ethics, but also many different modes of ethics.

Here, ethics shall be understood as the presentation of moral values in rules and principles that ought to govern human decisions and behaviour.

The two most relevant modes of ethics for MBES are:

• bioethics: is concerned with problems and questions that arise in the relationships among life sciences, medicine, ecology, biotechnology, but also politics, law and philosophy in connection with research and other activities;

• ethics of responsibility: is concerned with all facets of decisions and actions, their outcomes and consequences, and is appealing to all individuals involved in those decisions and actions to be sufficiently informed and competent for that accountability.

Some modes of ethics may be controversial with these two modes of ethics, e.g. utility ethics, ethics of conviction, business ethics, and professional ethics, since they may lead to an ethical dilemma, i.e. a decision-making problem between two (or even more) controversial moral imperatives.

Other ethics, e.g. Kant‘s categorial imperative, are not applicable to MBES problems and questions.

A code of ethics is a guide of principles which might be helpful to acquire the competence for making the ethically best decision by considering appropriately the agreed moral values, however, it cannot guarantee ethical behaviour.

A code of ethics is different from a code of conduct that is frequently used by professional and business organisations.

A code of ethics for problems and questions related with MBES should closely be adapted to the codes of ethics adopted in medicine (clinical as well as scientific medicine), natural sciences, and engineering sciences, and it must respect the human rights, animal rights, and ecosystems.

The European Alliance for Medical and Biological Engineering and Science (EAMBES) has adopted the EAMBES Code of Ethics[1] in March 11, 2019 (eambes.org/Portals/0/Documents/2019_03_11_EAMBES_CodeOfEthics.pdf).

1) accepted as it had been submitted on February 16, 2018 to EAMBES by Prof. Dr. H. Hutten.

Others with indirect relation to advancing technologies

Economy and Medical Technologies

The presented data are valid only for the subfield Medical Technologies or Health Care Technologies.

In 2018, the global market for medical devices was about US$ 425,5 Bn (approx. € 378,2 Bn).

For 2024 the global market for medical devices was estimated to reach about US$ 579,4 Bn (approx. € 515,0 Bn) with a mean Compound Annual Growth Rate (CAGR) of 5,4%.

The 4 dominating types out of 10 types with more than 60% of the global market are

- In-Vitro-Diagnostics (IVD)
- Orthopedic Devices
- Cardiovascular Devices
- Diagnostic Imaging

Emerging trends with a direct impact on the dynamics of the medical device industry are primarily attributed with increasing use of AI-optimized medical devices, increasing acceptance of wearable medical devices, growing use of miniaturized medical devices, and growing adoption of 3D-printing in medical devices.

The worldwide research and development spending in medical technology in 2018 was estimated to about US$ 30,0 Bn (i.e 7,05% of the global market revenue) and in 2024 to about US$ 38,9 Bn (i.e. 6,7% of the global market revenue).

The European medical technology industry employs directly 675 000 people in 2019.

95% of 27 000 medical technology companies in Europe are Small and Medium-Sized Enterprises (SMEs).

In 2017, more than 13 000 patent applications were filed with the European Patent Office (EPO) in the field of medical technology, i.e. 7,9% of the total number of applications (40% of these applications were filed from European countries EU28, Norway and Switzerland).

In Europe, an average of approximately 10% of the Gross Domestic Product (GDP) is spent on healthcare, with around 7,2% of the total healthcare expenditure attributed to medical technology.

In 2017, Europe had a positive medical devices trade balance of € 19,7 Bn.

European Patent Office Report: Patent Index 2019

The key patenting trends in 2019 have been in the following 10 technical fields

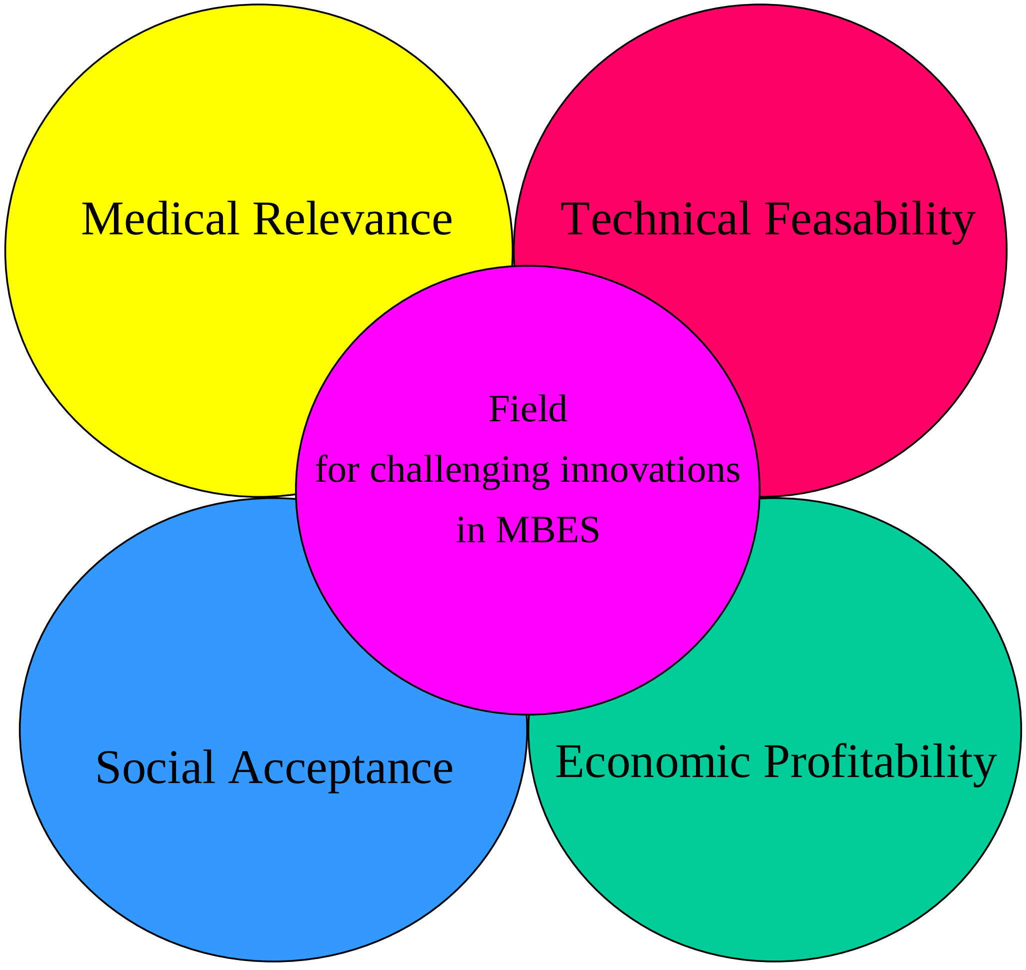
Field of patent application		Number of patents	Growth against 2018
1.	Digital communication	14 175	19.6 %
2.	Medical technology	13 833	0.9 %
3.	Computer technology	12 774	10.2 %
4.	Electrical machinery, apparatus, energy	11 255	5.5 %
5.	Transport	9 635	6.6 %
6.	Measurement	9 045	3.8 %
7.	Pharmaceuticals	7 697	4.4 %
8.	Biotechnology	6 801	1.7 %
9.	Other special machines	6 436	1.5 %
10.	Organic fine chemistry	6 167	- 0.5 %

Medical technology lost its leading position (since 2006) in 2019 for the first time to digital communication!

Digital communication as new fastest growing field was reflecting the rapid development of 5G technologies.

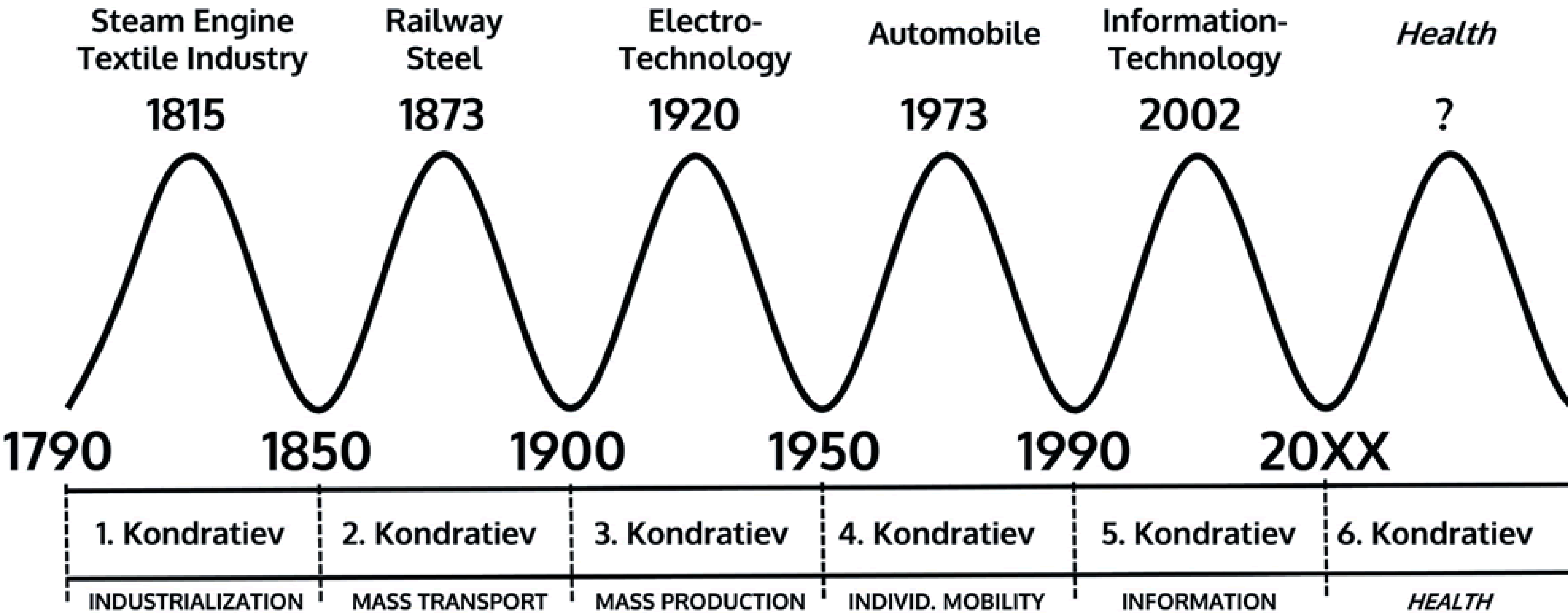
Computer technology was fuelled by the growing importance of Artificial Intelligence, i.e. machine learning, data retrieval, image data processing, and pattern recognition.

Challenging innovations in MBES are based on 4 pillars



The Kondratiev-Cycles

Up-and-down-cycles of the world economy



Will MBES be an enabler of the next Kondratiev Cycle 2020 – 20yy?

Others with indirect relation to advancing technologies

Impact of advancing MBES technologies on the change to a humanistic society

The development of the human society in the past can be subdivided into the following periods:

- the hunting society (Society 1.0),
- the agricultural society (Society 2.0),
- the industrial society (Society 3.0),
- the information society (Society 4.0).

Will the next society be the humanistic society, i.e. focused on humanism and serving humanity (Society 5.0)?

Beginning with the agricultural society, human advancement had always strongly been promoted by advances in technology.

Humanism emphasizes the value and agency of human beings, individually and collectively.

The humanistic society shall be a human-centered society

- whose members feel obliged on voluntary basis to the human rights as declared in the UN Universal Declaration;
- that balances scientific, technological and economic advancements with the resolution of social and ecological problems;
- in which each and every person can lead an active and enjoyable life.

One of the greatest challenges to technologies, especially to MBES technologies, is the expectation for their future contribution to a worldwide increase of quality of life which is more than only „health“.

WHO defines:

- Health: „A state of complete physical, mental, and social well-being not merely the absence of disease.“
- Quality of Life: „An individual‘s perception of their position in life in the context of the culture and value systems in which they live and in their relation to their goals, expectations, standards and concerns“.

Advancing technologies like the Internet of Things (IoT) and artificial intelligence (AI) have impacts not only on the producing industry, agriculture etc, but directly on the daily life of nearly the whole mankind.

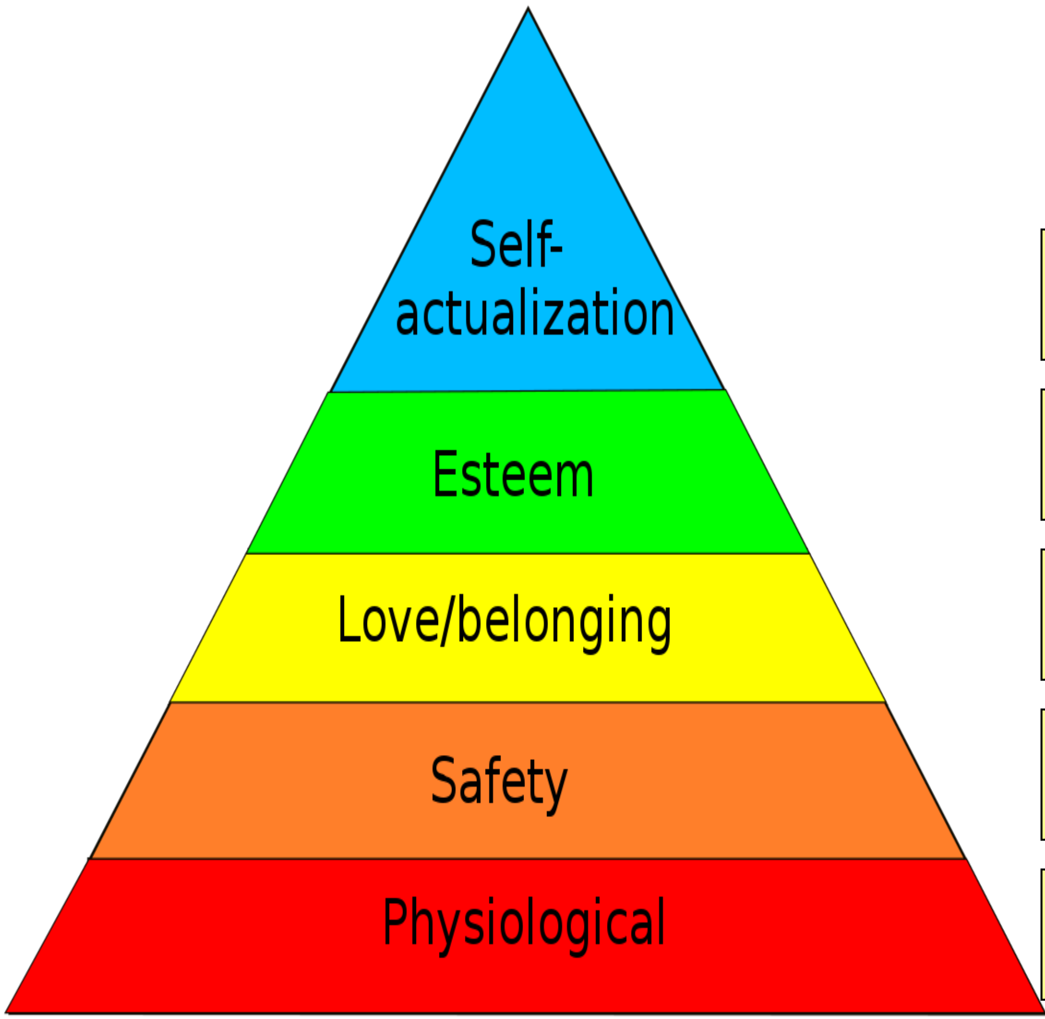
Can MBES contribute to reach the top of „Hierarchy of Needs“ (Maslow, Abraham: „A Theory of Human Motivation“ (1943)**)?**

Hierarchy of Needs

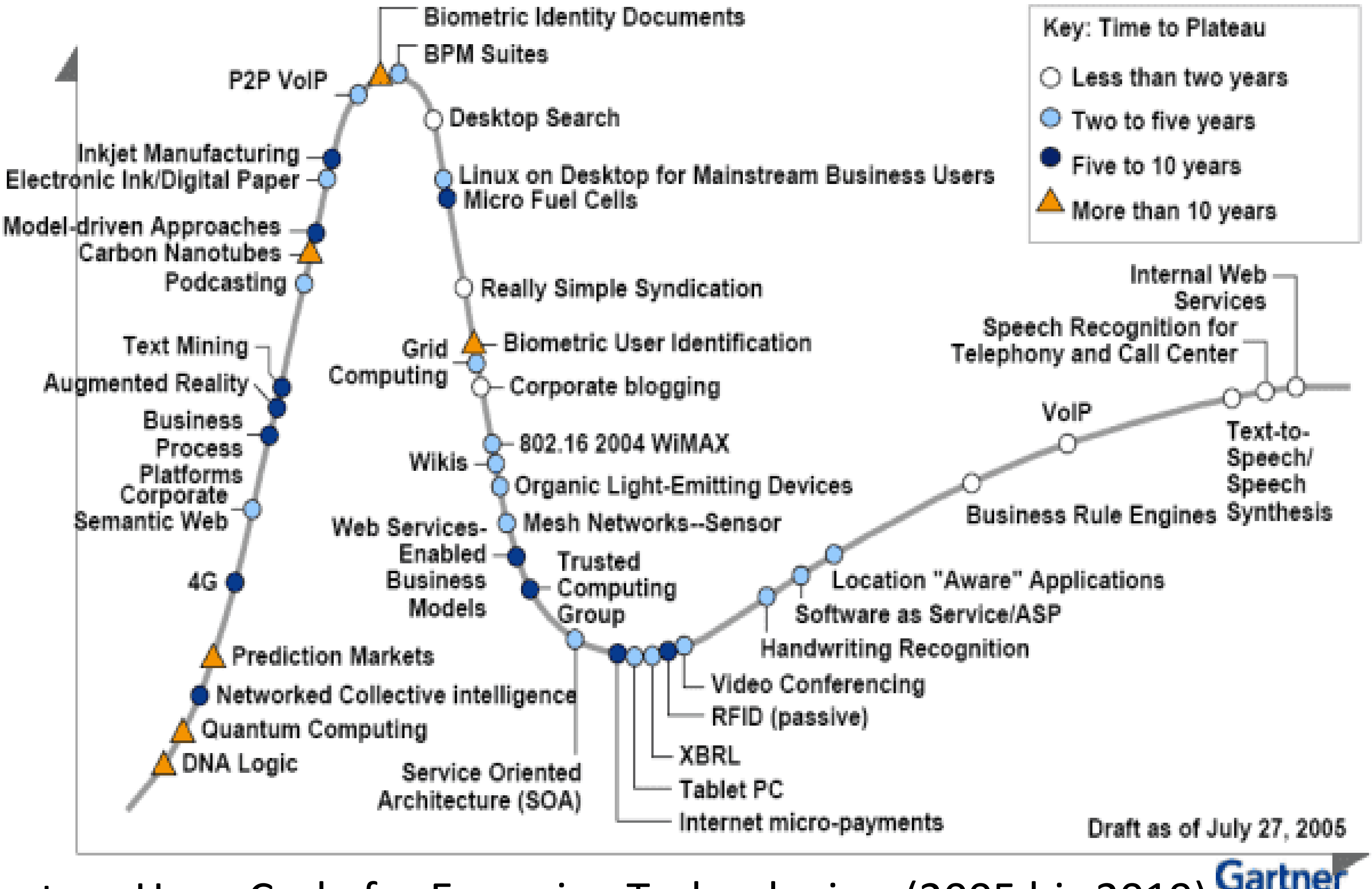
Maslow, Abraham: „A Theory of Human Motivitation“ (1943)

modified and adopted to demonstrate the contribution of MBES on the way and necessary steps to the top level, i.e. to the

Humanistic Society



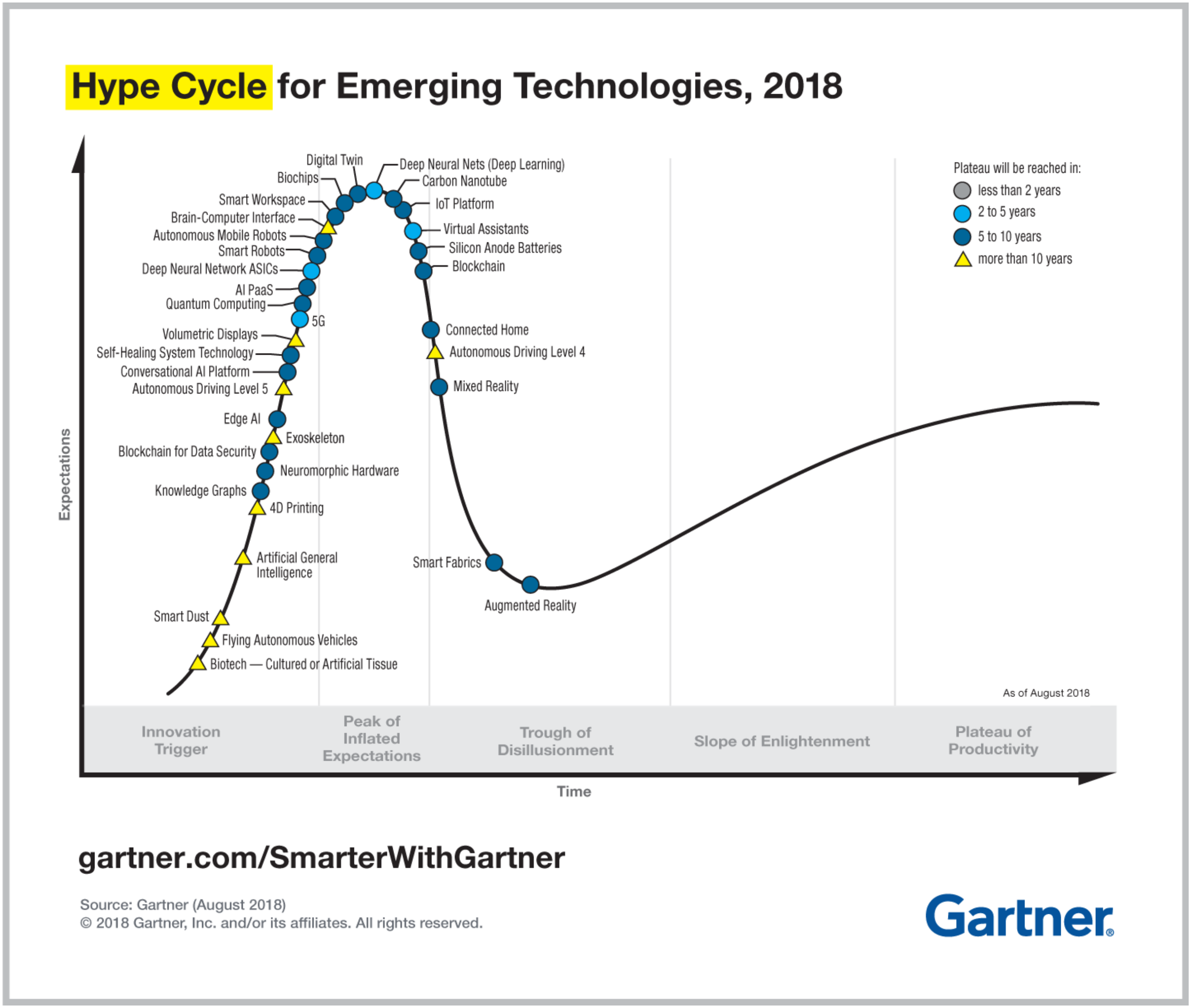
Personal development **Creativity**	**?** **Challenge for MBES**
Inclusion, Acceptance **Respectation**	wheelchairs, prothesis, hearing aids, visual aids, speech aids, implantable drug infusion pumps, etc.
Rehabilitation, Ass. Living **Social Needs**	devices for physical, mental and neurological training, wearable monitoring systems, roboters, etc.
Diagnosis, Care **Safety Needs**	equipment for monitoring, imaging (X-ray, NMR, Ultrasound etc.), for laboratory diagnosis, etc.
Survival, Life saving **Basic Needs**	cardiac pacemaker, defibrillator, respirator, dialysing machine, infusion pumps, rescue packs, etc.



Gartner Hype Cycle for Emerging Technologies (2005 bis 2019)

Please consider: (1) No important MBES technology is listed!

(2) Which of those technologies have been correctly predicted in 2005?



Please consider the current development state (2018) of the following technologies with MBES relevance:

(1) Biotech: Cultured or Artificial Tissue (more than 10 years), (2) Exoskeleton (more than 10 years), (3) Brain Computer Interface (5 to 10 years), (4) Biochips (5 to 10 years), (5) Augmented Reality (5 to 10 years)

Predictions

Predictions are difficult, especially about the future!

Danish Proverb, however mostly attributed to Niels Bohr, but also to Mark Twain and others

Whatever we may know in detail about the future of our civilisation – we can not know what we will know in future because then we would know it already now!

Sorry – author is unknown! The most probable candidate is Sir Karl Popper!

What should be done to be prepared for the future?

The worst way to drive into the future is trying to steer by using only the rear-view mirror

Alan Kay (1971): Born 1940, pioneering work on **object-oriented programming** and **windowing graphical user interface design**

The best way to predict the future is to invent it.

Alan Kay (1971)