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BIOMEDICAL TECHNOLOGY – 2011 AND BEYOND

Fundamental advances in knowledge and understanding across a range of specialized fields in medicine, biology, engineering and other natural sciences; the discovery of novel sensor concepts for non-invasive function diagnostics of diseases and abnormal developments at early stages; the development of cost-effective, automated measuring procedures that can be miniaturized to the cellular and molecular level; the implementation of new imaging techniques for optimized therapies and therapy-control – these are just some of the reasons for the rapid growth of biomedical technology as an independent field of study and research in the past decades.

Furthermore, in a contemporary health-policy context marked by health-insurances', patients' and society's demands for reduced health spending, the advances and high-quality, interdisciplinary knowledge available in biomedical technology today have a highly significant role to play in medico-technical process optimization and cost-benefit analyses.

There is increasing demand for highly competent staff with the interdisciplinary qualifications and open-mindedness needed to venture beyond the core areas – staff capable of realizing innovative, individual advances in a structured way, while also advancing the field as a whole. Thus the question as to the future prospects of biomedical technology and the young generation of students, researchers and professionals can be decisively answered: "exciting, promising and highly rewarding."

All in all, biomedical technology continues to be both an excellent profession and field of study and research at the intersection of animate and inanimate matter – though excellence always comes with responsibility.

1. Selective hindsight into the history of medical technology is beneficial for new excellence initiatives

Medicine, especially in the past five decades, has made highly significant progress and thereby achieved marked improvements in the diagnosis, treatment and prevention of different diseases. Biomedical technology, an autonomous and recognized field of study since the mid-twentieth century as well as a bridge between medicine and engineering sciences [1, 2], has contributed enormously to these advances. Thus, in Germany alone, the number of organ transplants (including live-donor transplants) since 2000 has increased by 25% since 2000 [3]. Nonetheless, some 12 000 patients in Germany are currently waiting for a donor organ. At present, medico-technical progress is a trend that continues unabated, and has led to the quality of life and life expectancy we enjoy today – unthinkable in former generations.

However, interdisciplinary thinkers and innovators in medical technology are nothing new. Over many centuries, a wide and diverse range of experimental, theoretical and technological discoveries have contributed to our present standard of living. Thus the ancient Egyptians already had an astonishing concept of the human vascular system. Homer, in his poetry, mentions blood vessel injuries; Hippocrates, the most-famed doctor of antiquity, was the first to describe the function of the aortic valves; Aristotle knew the aorta, the vena cava and its tributaries; while Claudius already recognized the existence of pulse waves in the second century B.C.

Nonetheless, many more centuries were needed for the functionalities of the human body to be discovered and understood. Thus in 1492, Leonardo da Vinci (1452–1519) drew the Vitruvian Man in one of his diaries, while around the same time Albrecht Dürer (1471–1528) undertook a first attempt to determine the proportions of the human body and render the movement of bodies in space by mathematical means – a far from trivial problem of descriptive spatial geometry. One can therefore justly identify Dürer as the founder of biometrics, although the term was used explicitly only in 1841 by Christoph Bernoulli (1782–1863).

The discovery and localization of the heart as motor of circulation and impulse-creating system was achieved around 1618 by William Harvey (1578–1657), who is therefore recognized as the founder of modern medicine. His calculation of the heart's pumping rate is the first significant application of mathematics in the physiology of circulation; but he too severely underestimated the heart's pumping capacity – he assumed that the left ventricle expelled approximately ½ an ounce (18 grams) of blood per minute. He multiplied this quantity by 1000 heart beats in half an hour and calculated a total of 500 ounces of blood. It appeared logical to him that such a quantity of blood could impossibly be produced somewhere in the body in such a short time and thus – through a simple quantitative examination – Harvey discovered the closed blood circulation system. Many more discoveries were to follow, which cannot all be listed here. Interested readers can find some of the most significant and highly instructive advances in the natural sci-

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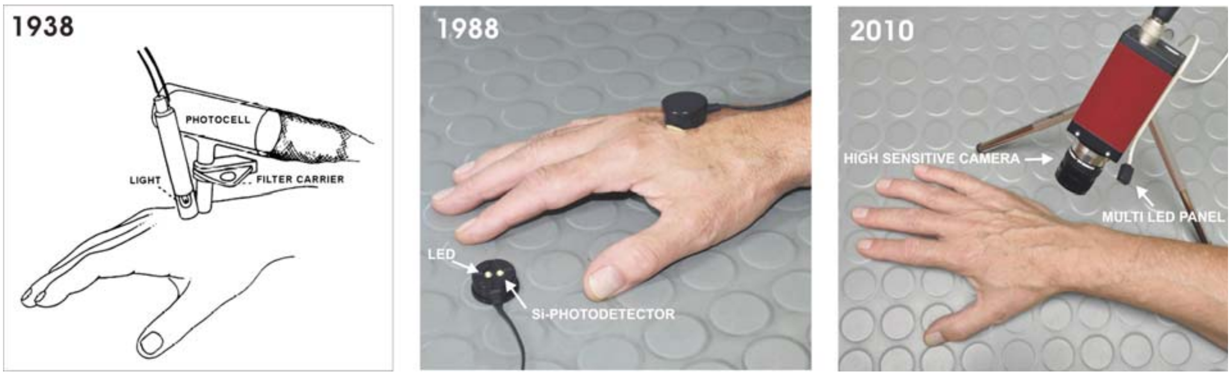

Fig. 1 Progress in photoplethysmography and its sensor concepts: First optoelectronic sensor by Hertzman [6] with incandescent lamp as polychromatic light source and selenium cell as photo detector (left); a PPG sensor on the market today (middle); new video camera-based PPGI sensor (right).

ences, which ultimately came to culminate in our present day medical system, summarized in the literature [4]

2. Exemplary technological and diagnostic progress: from the Hertzman Plethysmograph in 1938 to the contactless Photoplethysmographic Imager in 2011

As only one example of progress in biomedical diagnostic systems in recent years, this chapter presents recent advances and developments in classical photoplethysmography (PPG) and the role played by the novel camera-based, contactless photoplethysmography Imaging method (PPGI®) and the quantification of space-resolved dermal blood circulation changes in a resting state, as well as after defined pharmacological and mechanical skin irritations.

Optoelectronic sensor concepts have come to play an important role in functional blood circulation diagnosis because of their non-invasive and non-damming nature. They are generally accepted by patients not only during vascular screening-examinations since they cause neither pain, nor harmful radiation or ionizing phenomena. Analogously to classical PPG with skin attached discrete sensors, PPGI utilizes the fact that blood has a much higher absorption in the visible and near-infrared spectrum than the surrounding bloodless tissue. When illuminating the skin with a selective light source, a detector can assess the optical attenuation, which is modulated by the time-variable blood content.

Using a highly sensitive video camera as a detector array brings advantages over the current state-of-the-art technology: not only a non-invasive assessment of the dermal blood perfusion status can be performed in vivo – it is also contactless and spatially resolved. A wide spectrum of new applications of optoelectronic sensor systems in functional peripheral vascular diagnostics is hereby opened.

The experimental details and perfusion signal processing and visualization strategies by the PPGI system will be explained with some clinically relevant examples and perfusion protocols. The analysis of the PPGI video sequences can either be done interactively by selecting skin regions for which the skin perfusion is calculated, or automatic algorithms for functional mapping can be executed. Together with the necessary software tools, a sound basis for assessment, evaluation and visualization of space-resolved dermal perfusion changes is provided.

2.1. Hertzman's discovery in 1938

After the pioneering work by Matthes [5], Cartwright, Haxthausen and Molitor et al., Alrick B. Hertzman, Physiologist at St. Louis University School of Medicine, discovered a relationship between the intensity of backscattered polychromatic light and blood volume in the skin in 1938. His instruments consisted of three essential components still found in modern systems: a light source, a light detector (Fig. 1 left) and a registration unit. He called the device photoelectric plethysmograph and described his findings ([6], p. 336):

- "Volume pulse of the skin as an indicator of the state of the skin circulation at rest" and,
- "amplitude of volume pulse as a measure of the blood supply of the skin".

The basic principle behind the measurement of blood volume changes in the skin by means of PPG is the simple fact that hemoglobin in the blood absorbs infrared light many times more strongly than the remaining skin tissues (Fig. 2), [7–9]. For example, as blood pressure in the skin vessels decreases, the surface area of the vessels is reduced. This increases the average reflection in the measuring window under the sensor, so it will be recorded as an increase in PPG signal. Following this principle, the PPG signal reflects the blood volume changes in the cutaneous and partially also the subcutaneous vessel plexus and consists of a high constant part which is independent from the perfusion (light scattering in tissue), a smaller quasi static vein signal and a very small, periodical modulated arterial signal (Fig. 3). Therefore this non-invasive technique allows one to acquire functional data from the dermal venous and/or arterial circulation.

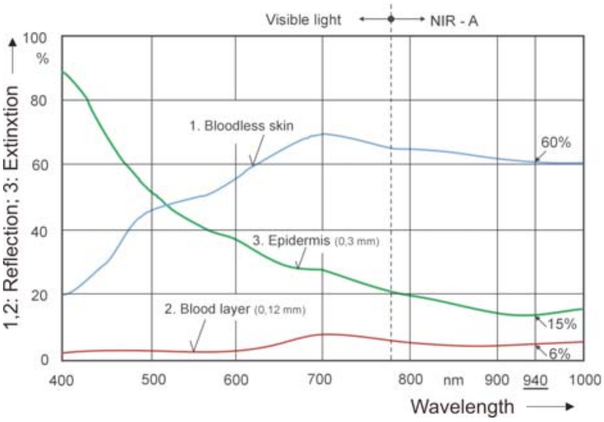

Fig. 2 Optical properties of human skin and blood in the visible and near-infrared area of the spectrum. Typical reflection spectra of anemic skin and of a 0.12 mm thick blood layer on glass are shown as well as an extinction spectrum of a 0.3 mm epidermal layer. The difference in reflectivity between the skin tissue and the blood is evident and results in a high optical contrast between skin and dermal vessel plexus. The optical attenuation of the epidermis is very high in the ultraviolet and blue regions and lowest at IR wavelengths of about 950 nm.

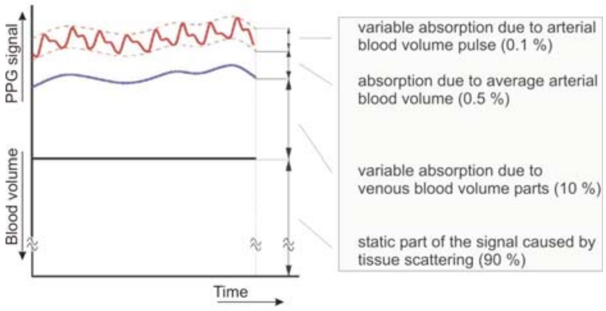

Fig. 3 Composition of the photoplethysmographic signal. The intensity of the backscattered light depends on the blood volume in arterial and venous vessels in the measuring zone. Reducing blood volume in the monitored area under the PPG sensor increases the PPG signal. A separation of venous and arterial parts of the detected signal is possible by electronic signal-filtering.

In contrast to the conventional PPG version with skin-attached discrete sensors (Fig. 1 in the middle), PPGI operates remotely, i.e. not in contact with the tissue. The measured large area of the skin is illuminated by quasi monochromatic LED light of selected wavelengths and is filmed by the camera from a distance of typically 50 cm. This detects small fluctuations in the tissue brightness, which is synchronous with the venous and / or arterial blood-volume dynamics. The fluctuations are caused by parts of the light which are reflected or transmitted towards the camera by passing the skin tissue.

2.2. The Photoplethysmographic Imager – functions and typical recordings

The PPG Imager was developed at the RWTH Aachen University [7–9] and is a computer-based system comprising both hardware and software parts (Figs. 4 and 5). The core of the PPGI

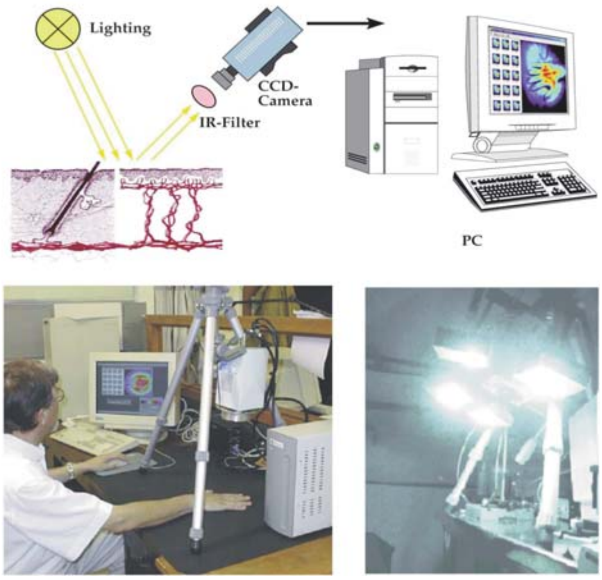

Fig. 4 Photoplethysmography Imaging setup. The skin is illuminated by a custom LED floodlight (different wavelengths can be selected), the backscattered light intensity dynamics are recorded by a high-sensitivity CCD camera.

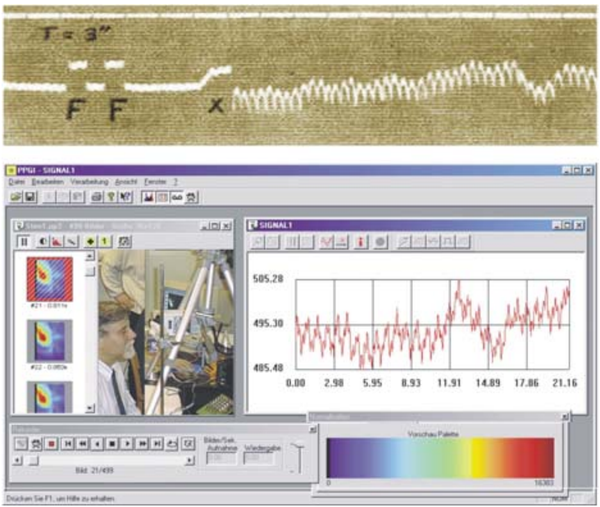

Fig. 5 Comparison of typical photoplethysmograms of the forehead taken in 1938 (above) and 2010 (below), illustrating progress in medical devices using modern computer aided detection and visualization strategies. To quantify plethysmograms in terms of arbitrary units, Hertzman [6] had to insert a filter in front of the detector manually (two F-marked signal steps in the registration below). Today calibration is fully automated [8].

is an imaging strategy capable of contactless recording, processing and displaying of image sequences of the selected skin area, so as to visualize the skin vessels and analyze dermal perfusion. The selected body area is illuminated by monochromatic light (multiple LED panels). In contrast to Hertzman's original device and all other plethysmographs on the market, we use green light to visualize the arterial skin perfusion, as this spectral range offers a good optical contrast between blood and skin tissue and the limited penetration of this light enables a targeted collection of perfusion dynamics in the microcirculation area of the skin [9]. The size of the observed skin/body region and the spatial resolution can be arbitrarily chosen, depending on the utilized camera lens and distance between camera and measuring object. To minimize motion artifacts, which can be created by the separation of the camera sensor from the skin, we prefer measurements in the recumbent patient; the selected skin region is fixed in a foam cup.

To detect the weak light modulation backscattered from the skin, which is caused by the arterial perfusion (dermal blood volume pulse), a high-sensitivity scientific camera has to be used. Our setup utilizes the UltraPix FE 250 camera from Life Science Resources because of its high dynamic range of 14 Bits and high readout speed of 5.5 MB/s. The sensor, a silicon frame-transfer black-white CCD chip with a pixel volume of 512×512, is sensitive in the visible and near infrared range of the spectrum. Typical PPGI recording lasts about 100 seconds, consisting of nearly 1.000 images of the same scenario and has a mean data volume of 700 MB.

In the 'interactive operator' system-mode, the observer can directly select one or more arbitrary regions of interest (ROI) in the test field after each video sequence. For these marked regions, the mean backscattered light intensity is calculated and displayed as a perfusion sensitive parameter over time. An example of (not spatially resolved) 1 ROI PPGI registration, which can be compared with the classical PPG-examination, is shown in Fig. 5.

A particular advantage of PPGI systems is the ability to freely select several skin areas in the same measurement scenario in order to analyze and visualize the spatial resolution in perfusion dynamics. A typical recording with three closely adjacent and corresponding PPGI signals can be seen in Fig. 6, done on a left hand with a small fresh wound in the skin of the middle finger. As can be seen, the perfusion patterns from healthy skin and the wound on the middle finger show significant differences. When looking only at the heart beat, it is slightly increased inside the wound; however, the slow rhythms of about 0.1 Hz are strongly reduced inside the wound. Not only is it possible to discriminate the wound and the healthy skin when comparing the different three regions, it is also apparent that the low perfusion pattern has strong local variation. Even the two ROIs on healthy skin at a distance of a few mm show evident differences in the 0.1 Hz band.

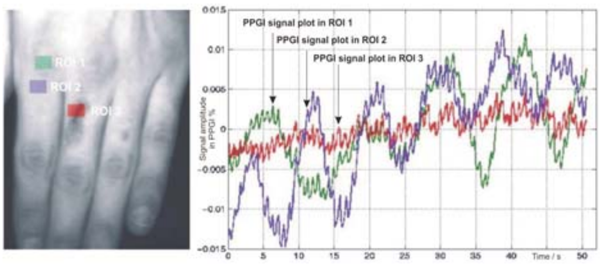

Fig. 6 PPGI recordings of a hand with a wound on the middle finger. Calculated photoplethysmograms (blood volume changes against time) in the three selected ROIs. The curves allow a direct comparison of blood perfusion in the healthy skin and the small fresh wound close by. The absence of lower frequency vasomotion rhythms in the wound-area is clearly visible.

2.2.1. Advanced signal processing provides new insights into the phenomenon of distributed dermal blood-circulation rhythmicity

When trying to analyze further the perfusion patterns with a classical Fourier transform (FT), not much new information is revealed. It is possible to recognize differences at low frequencies; however the resolution is quite limited. The frequency spectrum can't reveal much advanced information, the reason being that the FT is not well suited for analysis of transient signals.

However, using the Wavelet transform (WT), many new insights into the distributed perfusion patterns are obtained. An example of a WT of PPGI signals from Fig. 6 is shown in Fig. 7. Here, the evolution of different frequency components (vertical axis) can be directly recognized against time (horizontal axis). For the first time, the generated advanced PPGI signal visualization reveals that the slow rhythms in the skin perfusion are not stationary but fluctuate in amplitude and also slightly in frequency.

Apart from the strong temporal fluctuations in dermal perfusion, a new behavior of distributed spatial rhythm fluctuations was observed in our lab at IHF/RWTH Aachen University. This phenomenon, which can only be observed in animated video representations of the PPGI recordings, consists of "blood volume clouds" moving on the forehead in a coherent but complicated pattern [10, 11]. Fig. 8 tries to illustrate this with screenshots of a recording; for the animated video presentation please refer to the web page http://www.medit.hia.rwth-aachen.de/aw/cms/medit/Themen/forschung/~ttj/Photoplethysmographie_Imaging_PPGI_/?lang=en

2.2.2. Completely detached – assessment of human hemodynamics under micro-gravity

Astronauts complain about fluid shifts from their lower extremities to the head caused by weightlessness during flight in space. To study this phenomenon, RWTH Aachen University in cooperation with Charité University Berlin participated in two parabolic flight campaigns undertaken by the German Aerospace Centre (DLR) in September 2005 and June 2006 (the 7th and 8th DLR parabolic flight campaigns in Bordeaux and Cologne respectively). The characteristics of the rapid fluid shifts during hyper- and

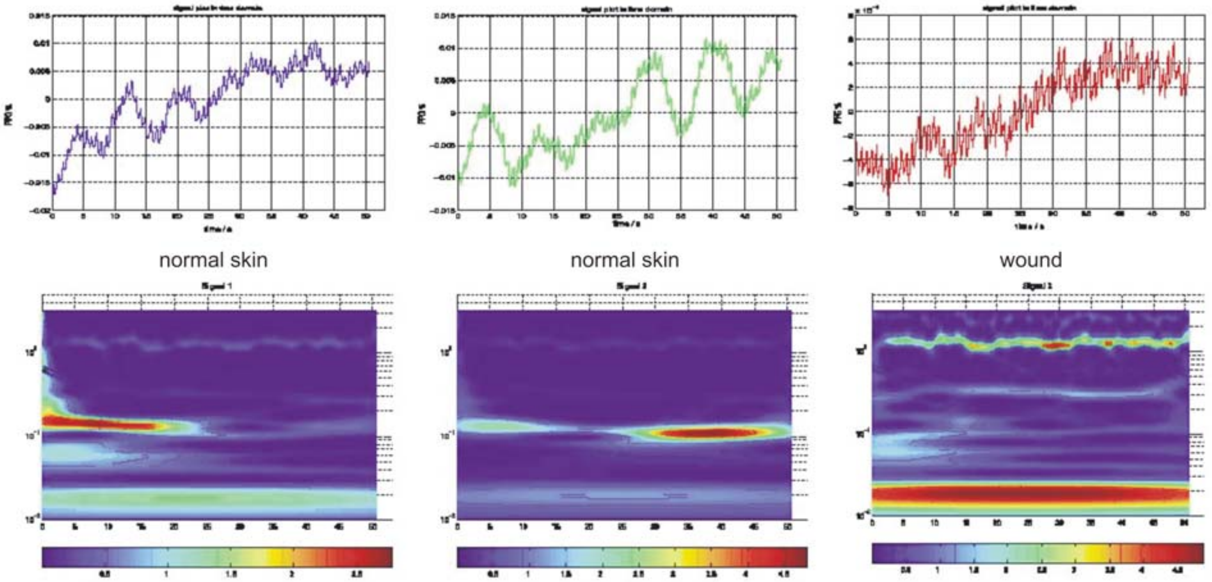

Fig. 7 Example of advanced analysis of transient signals: Wavelet transform of selected PPG signals from Fig. 6.

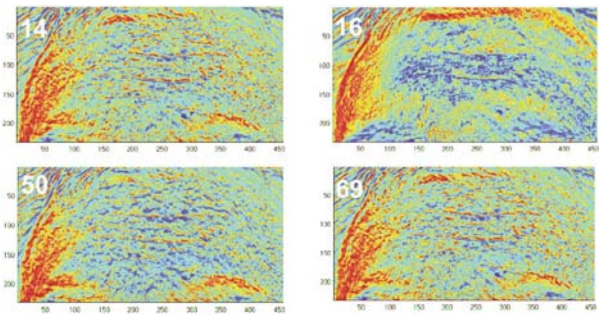

Fig. 8 Distributed "blood volume clouds" observed with PPGI on the forehead of a subject in sitting position and relaxed steady state, first observed in 2005. The post-processed and -colored pictures show perfusion coded images taken at 14, 16, 50 and 69 seconds of a PPGI video sequence.

micro gravity were measured in flight by a combination of PPG and PPGI optoelectronic sensor systems.

For the parabolic flight campaign, a specially prepared Airbus A300 is equipped with up to twelve separate experiments from different university research groups. The campaign consists of 4 to 5 flight days. In one flight, the aircraft accomplishes 31 parabola maneuvers. These flight maneuvers follow a special trajectory, resulting in up to 22 seconds of microgravity conditions inside of the aircraft (Fig. 9). The maneuver is divided into 3 phases. In phase one, the aircraft gradually pulls up its nose from a steady horizontal position and starts climbing at an angle of approximately 47 degrees. This "injection" phase takes about 20 seconds, during which the aircraft experiences an acceleration of around 1.8 times the gravity level at ground, i.e. 1.8 g. The engine thrust is then reduced to the

Fig. 9 Novespace Airbus A 300 Zero-G directly before initiation of the micro-gravity phase (left), flight phases of the parabolic maneuver (right).

minimum required to compensate for air drag, and the aircraft follows a free-fall ballistic trajectory – i.e. a parabola – lasting approximately 22 seconds, during which weightlessness is achieved. At the end of this period, the aircraft must pull out of the parabolic arc, a maneuver which gives rise to another 20-second period of 1.8 g inside the aircraft, after which it returns to normal-level flight altitude. Thus, the entire parabolic phase takes about 1 minute. These maneuvers are flown repeatedly, with a period of 3 minutes between the start of two consecutive parabolas, so that there is a 2 minute "rest" period at 1g. After parabolas 10 and 20 however, the resting interval is increased to 6 minutes.

Viewing the data from different subjects participating in the flights ascertained that fluid shifts occurred in all subjects. This proves that the small time span of about 20 seconds of a single parabola is already sufficient for a clear detection. Furthermore, and as predicted, a clear shift from the lower body parts to the head was verified.

Fig. 10 shows typical PPG measurements. These recordings were taken from one male and one female subject, using sensors with green and infrared light sources. They were placed on the subjects' foreheads. The detected light-intensity changes are displayed in curve 1 (green light) and 2 (infrared light). The lower black curve shows the development of g-forces during the parabola. As

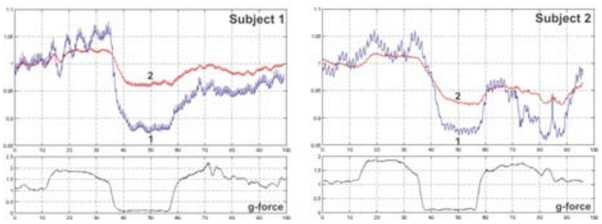

Fig. 10 Dynamics of blood volume shifts of two subjects during the parabolic flight maneuver. Measuring point on the forehead, using green (1) and infrared (2) light sources, normalized at start of measurement.

can clearly be seen, the detected backscattered light intensity is in rapid decline immediately after the implementation of zero-gravity. This corresponds to an increasing blood volume in the transilluminated skin beneath the sensor. Astonishingly, comparing the data of the different subjects reveals that all of them reacted very quickly to the altered gravitational force. The time span between a change of gravity and the minimum detected light intensity (or maximum if measured at the legs) was very short (only a few seconds) [12].

3. Modern technology and medicine in tandem: new diagnostic concepts and medical strategies pave the way into the future of Telemedicine, Homecare and Ambient-Assisted Living

Diagnostic measuring methods based on biomedical technology are in widespread use today, typically involving patients' visits to a doctor or a hospital, where measurements are then made. However, in certain circumstances patients are too far away from the required facilities – be it while traveling in remote regions, or even inside an orbiting spaceship. A range of telemedical sensor concepts, systems solutions and procedures – some already on the brink of clinical implementation – have been developed for such situations. These include:

- Intra-corporal telemetric diagnostic and monitoring systems for physical (e.g. bladder pressure) and chemical (e.g. intra-corporal laboratory) parameters,
- Mobile diagnostics using "labs-on-chips" (e.g. in aeronautical medicine),
- Autonomously active, telemetrically controlled implants (e.g. cardiac pacemakers, gastric pacers, nerve-stimulating devices, etc.),
- Implantable and extra-corporal modular micro-system platforms,
- Wearable smart medical devices and intelligent wearable devices,
- Extra-corporal telemetric diagnostic and monitoring systems for personal healthcare,
- Miniaturized sensor systems for 24/7 surveillance of high-risk cardiovascular patients.

Pioneering these developments in Germany is the "Micro-Medicine" initiative launched by the Germany Society for Biomedical Technology (DGBMT), part of the Association of Electrical Engineering (VDE) [13]. With help of substantial research funds, the initiative supports and accompanies the introduction of new micro-medical procedures and, co-jointly with renowned professionals from all parts of the healthcare system, has successfully established telemedicine/disease management, neuro-prosthetics and instrument/implant invasivity as key research areas.

The advantages of improved efficiency in medical care, including home care, due to these ongoing biomedical research and development projects are apparent. While patients and doctors mostly take a positive view of telemedical applications, the entire economic, technical and legal framework is still evolving. Propriety systems in hospitals and doctors' practices are one reason why companies and investors are still reluctant to market specialized solutions and products.

The following illustrations show two exemplary developments from our research group at RWTH Aachen, respectively concerned with micro-sensor systems for long-term applications and tele-self-monitoring.

A 24/7 monitoring system based on a micro-optic in-ear PPG sensor was developed for early diagnosis of irregularities in the human cardiovascular system [14] (Fig. 11). By means of a miniaturized electronic unit, the native plethysmogram can simultaneously be acquired for selected wavelengths and processed locally by a microcontroller. The resulting signal is then transferred wirelessly to a personal digital assistant (PDA) or PC, where heartbeat, heartbeat variability, oxygen saturation (SPO2), breathing and slower perfusion rhythms can be evaluated. The sensor geometry was optimized for the novel in-ear application scenario by means of Monte Carlo Simulations [11].

Tele-medical procedures have been used since approx. 30 years. For example, already in 1984, an on-board ECG was transmitted

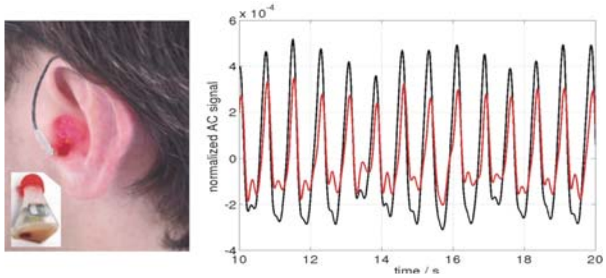

Fig. 11 Miniaturized optoelectronic sensor concept for in-ear pulse oximetry and typical photoplethysmograms obtained simultaneously for infrared and red illumination.

from a cargo ship around the entire globe. Telemedicine is useful for bridging large distances between doctors (with diagnostic systems) and patients, or between general and specialist doctors– notably during long-distance travel and expeditions, as well as in military or space missions [15]. Likewise, healthcare systems in countries with small and highly dispersed populations have long since taken an interest in such systems.

Nonetheless, a frequent disadvantage of telemedicine is the lack of bio-data sensor systems on site. Here, standard mobile telephones will soon offer a viable alternative (Fig. 12), since today's integrated video-camera technology is in principle already capable

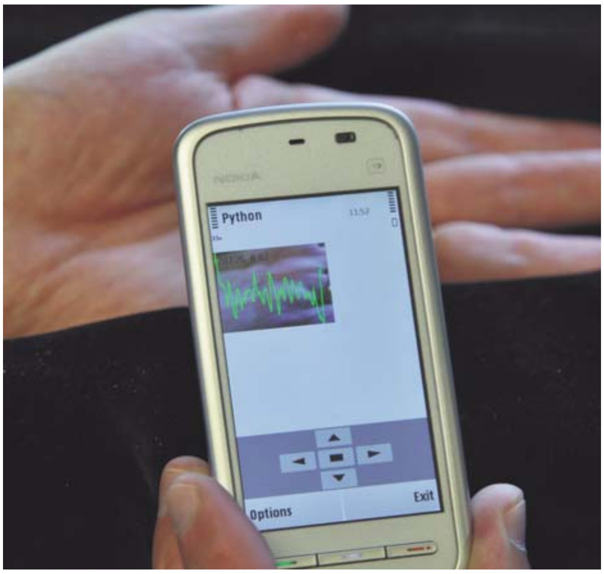

Fig. 12 Tele-monitoring of skin perfusion using a standard mobile phone. For online self-monitoring, data recorded by the camera is passed continuously to a tele-monitoring center. In case of (non-acute) retro-monitoring, data can be recorded first (and preprocessed at regular intervals), then forwarded on.

of recording and transmitting patients' vital parameters – such as local skin perfusion in the case of injured, inflamed or wounded skin – to 24h call-centers with qualified medical staff. If needed, a doctor can establish contact with patients to guide them through a 'cinematographic' recording of the relevant parameters, inform them about their condition, suggest appropriate measures, or dispatch on-site medical assistance, such as the well-known Flying Doctors in Australia.

4. Training and studying of biomedical technology

Present and future healthcare systems are becoming ever more technical. Making effective use of today's possibilities and knowhow requires more than just engineers or doctors. More than ever before, what is needed now are competent experts with interdisciplinary working knowledge of the intersections between medicine, man and technology, and possessing the ability to think and communicate pluralistically – in accordance with the varied distribution of competencies across different disciplines.

University degree courses in Biomedical Engineering focusing precisely on these qualifications are on offer in virtually all European countries. The degrees are organized in consecutive parts, depending on the particular specializations and degree structures offered by different universities (vocational bachelor degrees or research-oriented master's degrees, with subsequent doctoral programs). Most degrees are still situated in the faculties of electrical engineering, since the theoretical foundations of electrical engineering and information technology form an important basis for medical technology. More and more combined medical-technology degrees are offered jointly by different universities, such as in Stuttgart (engineering sciences) and Tübingen (medicine) as of winter term 2010/11. International compatibility is also set to increase amongst partner universities and courses offered by various national bodies.

Graduates, in particular those with master's degrees, can find suitable employment in many areas:

- Research institutes and universities
- Hospitals and healthcare systems
- Companies in various areas of medicine and medical products
- Pharmaceutical industry
- Biotechnology companies
- National and international bodies
- Self-employment

Their qualifications equip them with a broad knowledge base in engineering sciences, are in highly demanded and honored accordingly by industry, and enable them to quickly and competently specialize in different areas. Thus all students of biomedical disciplines can look confidently towards the future – and be part of it.

5. Concluding remarks and outlook

In summary, one can say that if medical treatment today has become subject to evaluation as never before, this is in no small part due to biomedical technology. It provides us with impressive data on both the efficacy and costs of a treatment.

Needless to say, the applications of biomedical technology briefly outlined here represent only a very limited and subjective selection. Around the world, intensive research is underway in many other important areas, such as the quantification of pain sensations, e.g. in caring for mother and fetus (incl. prenatal and perinatal pain sensations), as well as in early- and new-born children. For a long time, babies and small children have been considered less pain-sensitive in relation to adults, and the reactions of early- and new-born children to pain were classified accordingly as subcortical (and thus unconscious) reflexes [16]. While pain was thus rightly viewed as a subjective experience, it was almost exclusively relegated into the domain of conscious, speakable and cognitively apprehended adult experience. This assessment is increasingly considered to be mistaken [17, 18].

Likewise, research and development of adapted Ambient Assisted Living (AAL) systems solutions and in particular of assistance systems for elderly and handicapped people is on the increase. While these and other modern sub-areas of biomedical technology are today still in their infancy, they are certain to become highly significant in future, not least due to demographic trends.

On the other side, achieving this requires policy-makers' clear commitment to research and financial support of the healthcare system. Yet the politicians who look to Lancet, Nature or Science as a basis for decision-making and allocation of public funds are few – if any [19].

Nonetheless, the future of biomedical technology is assured. We can all count on this technology, as well as standing to benefit from it personally – bearing in mind that excellence comes with responsibility.

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