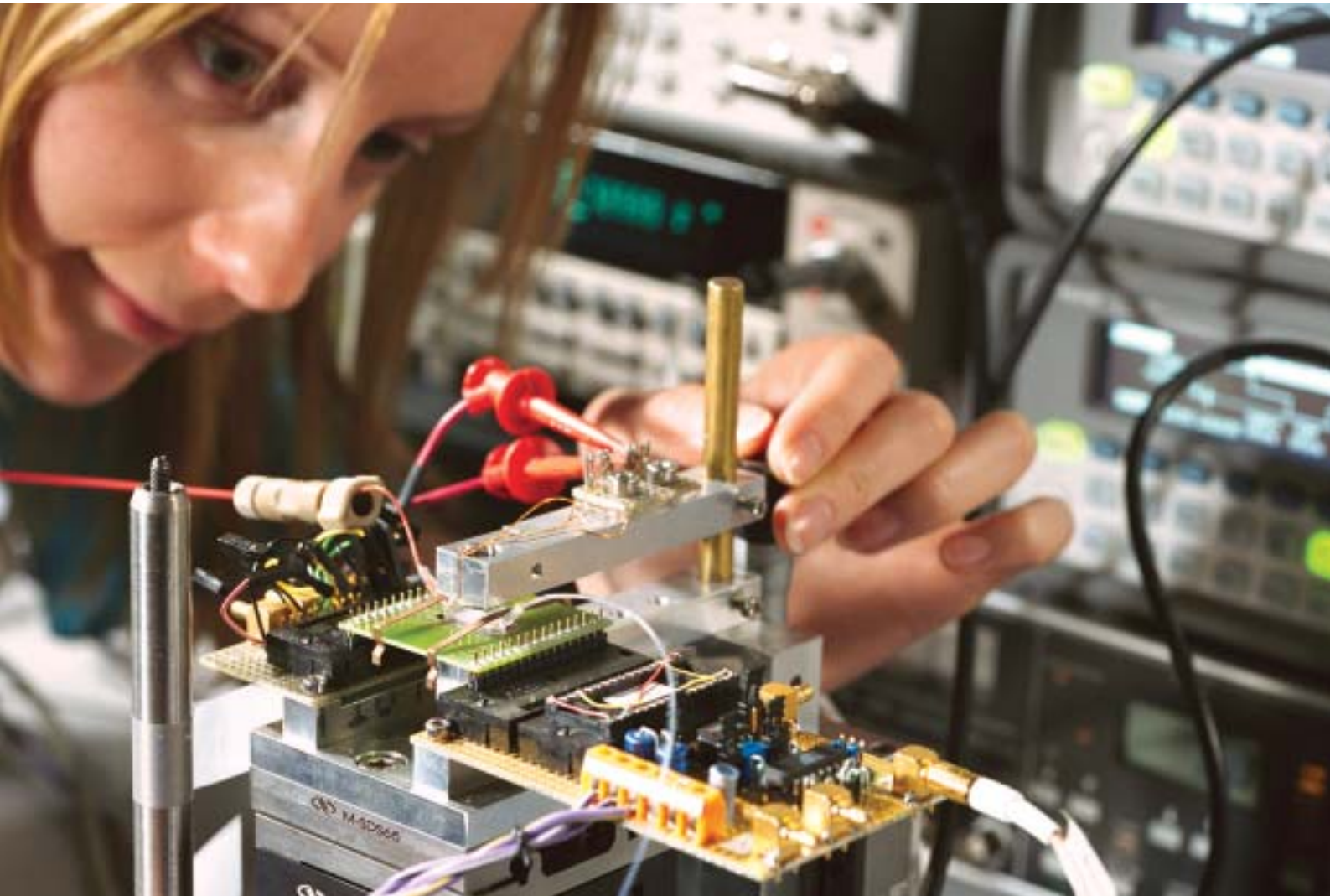


password

Philips Research technology magazine - issue **21** - October 2004



Healthcare

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Password is a quarterly magazine published by Philips Research.

Philips Research, part of Royal Philips Electronics, has five main laboratories in three continents where 2100 researchers investigate promising options for innovation.

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New biosensors for molecular diagnostics

Philips Research is investigating a new biosensor technology based on magneto-resistive sensors that promises to radically improve the speed, sensitivity and reliability of biomolecular diagnostics for applications such as protein and pathogen monitoring, near-patient testing in medical centers (blood, urine, saliva tests etc.), and ultimately home testing by individuals - 10

Better care through new technology



Ask our researchers what drives them most and I can guarantee that two reasons will top the list: working on the frontiers of science and seeing that work lead to innovations that improve people's lives. There are few areas where this combination is more pertinent than in healthcare research. Our scientists have contributed to the improvement of medical imaging for decades, and they still have plenty of challenges ahead.

This is exciting enough, but today we are on the verge of developments that will change the world of healthcare for good, and much of this future is being shaped in hospitals and research institutes, including our own laboratory. Molecular healthcare is one of these developments. Fueled by the rapid progress being made in the understanding of disease processes at the cell level, combined with imaging techniques to detect, localize and follow these processes in the body, scientists are busy finding out how this can be used to detect diseases at a much earlier stage and develop more efficient and less invasive therapies.

A comparably thrilling development is taking place in personal healthcare. Using progress in fields like wireless communication, miniaturization and sensor technology, we are investigating personalized healthcare devices that will help patients suffering from chronic illnesses to monitor their condition as an unobtrusive part of their daily routine. Other applications will allow people to make health, fitness and well-being an integral part of their lifestyle.

Both are truly disruptive developments where change is happening almost on a daily basis. In a field where established players and newcomers meet and traditionally separate disciplines merge. This is a challenging environment, requiring the ability to quickly master new matter, explore unknown territory and decide on the best ways to go forward. That is exactly the environment in which our researchers flourish best.

We are very much committed to actively participating in the new waves in healthcare. We are expanding number and scope of our projects and are planning the build-up of biological capabilities as part of our multidisciplinary laboratory. You'll find more about our Healthcare research program in this issue of Password. I hope it reflects some of the enthusiasm and drive I observe when seeing our people at work in the lab.

Rick Harwig, CEO Philips Research

Personal healthcare

Bridging lifestyle, healthcare and technology



Healthcare today is still generally reactive, focused on disease treatment, and centered around hospitals and other places for medical care. When there is no direct need to consult a doctor, most people are not linked to diagnostic and therapeutic systems. However, people are increasingly aware of their health as a very important value, and the willingness to take a proactive role in personal healthcare is growing. Moreover, the increasing demand for healthcare forces medical centers to look for options with higher efficiency and lower costs, and to focus more on prevention. Passive recipients of healthcare are being transformed into active participants. However, apart from recourse to professional medical diagnostic systems, there is still no accepted way to objectively assess your personal health status.



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People should not have to wait to see a physician or visit a hospital before getting an update on their current health status. Supported by appropriate technology tools, providing reliable information on their condition, people can be empowered to take timely action themselves. By being connected to a medical care center, immediate help is available in case of real emergency. This is what personal healthcare is about: turning uncertainty regarding your current health status into timely knowledge, moving from an indecisive state into action and treatment, becoming proactive instead of reactive.

There are other important drivers for realizing this personal-healthcare vision: with an ageing population, the demand on healthcare providers is increasing, so efficiency and cost reduction become crucial aspects. More needs to be done in less time and with fewer people, so that patients can be discharged from hospital sooner. With advanced technology, remote monitoring is a promising option for cost-effective health management: the patient can stay at home, but is constantly 'connected' to the hospital. Moreover, a shift is taking place towards personalization and preventative healthcare:

the enormous progress in the mapping of the human genome allows individuals to learn at an early stage what diseases they are at risk from, and to take timely steps to prevent them occurring, with the assistance of personal-healthcare technologies. Finally, the digitalization of healthcare increasingly provides the networked infrastructure that is needed to support individual-centric care.

Personal-healthcare applications and technologies

The personal-healthcare domain encompasses a large variety of application scenarios and associated technologies: from relatively simple, stand-alone devices, improving your well-being by giving personal feedback based on direct physiological measurements, to complex post-discharge health-monitoring systems, guarding your

measurements and communication of the results to the patient or, in an emergency, to the physician are the key elements in all these scenarios.

The starting point is to gain knowledge of a person's actual health status by continuous monitoring of vital signs. Different types of sensors are needed that measure specific physiological signals: for example, weight management, which is on the preventative side, uses relatively 'soft' parameters, while critical diabetes management requires continuous, accurate glucose level monitoring. Sensors need to be close to the body, but unobtrusive, for example as part of clothing: in some cases, it may even be feasible to embed devices into the body itself using implants.

Secondly, dedicated signal processing

“Intelligent, personalized healthcare technology will improve the quality of people's lives and the effectiveness of medical care.”

Eric Thelen, Philips Research Aachen.

health continuously via a direct link to an institute for medical care. Monitoring of physiological signals, interpretation of

algorithms are required to analyze the sensor input in the right, highly personalized context, leading to a diagnosis. A history of

recorded personal medical data is used to signal abnormalities and provide early-stage warnings.

Furthermore, well-designed user interfaces are vital to communicate a diagnosis unambiguously to the user, leaving no room for misinterpretation. The basis for this interactive design is the real-life, intricate interaction between physicians and their patients, closing the loop towards action, for example therapy or a motivation to adapt behavior.

Different types of network technology are needed to ensure optimal connectivity, for example personal-area or even body-area networks. In most cases, personal-healthcare devices will be connected to a professional medical care center to enable continuous monitoring services and provide immediate help in case of emergency. A strong, highly reliable network will be required to connect all points of personalized care and to ensure that vital data, images and other medical information are properly stored and easily accessible, any time, any place.

Personal healthcare and Philips

Philips has strong capabilities in the areas of healthcare, lifestyle and technology. Through a highly user-centric approach we aim to develop products and services that really enrich people's lives. Philips Medical Systems already has a strong position worldwide in professional medical systems. Recently, a new business unit called Consumer Health and Wellness has been established as part of Philips Domestic Appliances and Personal Care, which will focus on healthcare outside the medical profession. This gives Philips a

unique position to enter the personal-healthcare domain, focusing on products and services that improve or preserve the health of individual people both inside and outside institutional points-of-care (hospitals, physicians' offices). More and more technology will be available in the preventative stage, increasingly empowering people to take care of their personal health and well-being: personal healthcare will enable proactive monitoring, more accurate, personalized diagnoses, and, most importantly, a healthier population that lives longer.

Joined forces: MyHeart

MyHeart is a European project, led by Philips with a budget of EUR 33 million and 33 project partners from 11 countries, aimed at creating options for smart electronic systems and associated services that empower users to take control over their health status. It is an effort of industrial research institutes, academics and hospitals, covering the whole value chain from textile research, via fashion and electronic design, towards medical and home-based applications.

The project focuses on cardiovascular diseases (CVD), the leading cause of death in the western world. It is commonly accepted, that a healthy and preventive lifestyle as well as early diagnosis can systematically combat the origin of CVD and save millions of life-years. MyHeart explores technologies to support people to adopt a more healthy and active lifestyle in order to reduce risk for developing CVD, and limit the recurrence rate of earlier acute events.

One of the first results of MyHeart is a prototype of a wearable, wireless monitoring system that measures and diagnoses body signals of the wearer to detect abnormal health conditions. The measuring device can e.g. be integrated in wearable garments, such as women's bras.



Scenario building in the MyHeart project



HOMe Stroke Test (HOST)

With HOST, Philips Research is investigating a personal-healthcare system for the home environment, aimed at patients with an increased risk of having a stroke. The idea is to assist users in detecting the symptoms of a stroke and make an early decision to call the ambulance to reduce the extremely critical time-to-treatment. An example of such a symptom is sudden numbness or weakness of the face, arm or leg. The HOST project investigates methods for the early detection of a number of these stroke



symptoms. The interaction between the system and the user is vitally important for the success of the detection methods. In order to ensure the necessary domain-specific competence, this project is done in close cooperation with the stroke-unit of the University of Düsseldorf, providing real-life expertise on stroke detection.

Philips Research has developed a wearable, wireless monitoring system that can warn patients with underlying health problems. The system uses dry-electrode technology that can be built into common items of clothing like bras, shorts or waist belts.

Research projects

Fitness Coach

So, let's be honest: how many times have you started a fitness programme, only to quit because of a lack of motivation, or a training schedule that was too complicated? What if you could start exercising in your own home with a personal coach, stimulating you to persevere, giving you all the information you need on your performance, and telling you what to do next for an optimal result? This is the domain of Fitness Coach, a sports application that monitors specific physiological signals via smart sensors, calculates the training intensity through dedicated algorithms, and helps to regulate the pace of training, based on your own personal data. The interaction between coach and user is based on personalized feedback, improving performance and motivation. Philips Research is working on the required technologies to make this happen: an early demonstrator has been developed and built, and is currently being tested with potential users in HomeLab.



Reference Architecture for Care Everywhere (RACE)

With the RACE project, Philips Research is contributing to the platform-architectural developments that are required to support the wide range of personal-healthcare applications and services envisaged. As a first step, in the domain of professional healthcare, Philips Medical Systems is being supported in their development of a broadband-enabled remote patient management platform, called Motiva: a secure, personalized healthcare communication platform that connects chronic disease patients through their home televisions to their healthcare providers, support groups and family. When integrated with innovations from related Philips personal-healthcare activities (for example, MyHeart) this will allow disease management, emergency response, post-discharge surveillance, safety and security monitoring for patients outside clinical institutions, for example in their own homes. Future developments will include the extension of the reference architecture to incorporate personal wellness as well: the domain of self-care, prevention, and wellness where Philips Consumer Electronics and Philips Domestic Appliances may enter the market.

HeartStart

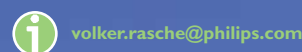
Sudden cardiac arrest (SCA) often strikes without warning, and the majority of cases occurs in people who have no previous symptoms of heart disease. When SCA strikes, the electrical system of the heart short-circuits, causing the heart to quiver rather than pump in a normal rhythm. Nearly 80 percent of sudden cardiac arrests happen at home. For the best chance of survival, a defibrillator should be used within 5 minutes. Defibrillation, an electric shock to the heart, is an effective method for restoring a normal cardiac rhythm of a

patient suffering SCA. Philips' HeartStart Home Defibrillator is the first of a new generation of defibrillators specifically designed for use in the home by virtually anyone. Clear aural instructions are given by a natural voice on how to use the device, and via a dedicated algorithm the device determines if the patient's heart needs a shock. Philips is the worldwide market leader in portable defibrillators with over 175,000 automated external defibrillators deployed.

Meet Volker Rasche



Volker Rasche has worked for Philips Research since he left university in 1990 and talks enthusiastically about a job that has posed him some of his greatest challenges but also given him some of his greatest moments of satisfaction. Nothing, he says, is more rewarding than helping someone. And it's the thought of helping someone to cheat death by avoiding or surviving a heart attack that makes his work in cardiac imaging worthwhile.



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1 How did you get into medical imaging?

I graduated with a degree in physics from Bielefeld University in Germany in 1990 and then joined the Philips Research laboratory in Hamburg, working half-time with their medical-imaging group and half-time back at university to complete my PhD. Naturally enough my thesis was on a medical-imaging topic – real-time Magnetic Resonance Imaging (MRI) for magnetic resonance fluoroscopy. One application for this technology is real-time viewing of a catheter as it is inserted into your internal organs. I later carried out research into Computed Tomography (CT) and volume imaging for X-ray fluoroscopy systems.

2 What was your particular focus area?

The focus was on cardiology applications and for the past five years I have concentrated on strategic issues about how the different imaging modalities, such as X-ray, CT and MRI, may be used in future cardiac care. Of particular interest was the tailored use of multiple modalities to provide physicians with the information they need to

answer specific clinical questions. This not only meant working closely with different groups in the Philips Medical Systems division, but also working directly with clinicians to answer questions such as: How are the different modalities currently being used? What are the limitations? What would the clinicians really like to see? What do they see for the future?

The outcome was our Cardio 2010 study, which assessed what cardiology might look like in the year 2010. We predicted a shift from the situation today where heart disease is normally identified after the patient reports symptoms or after an acute heart attack, to a scenario of much earlier detection and treatment. Then we looked at the consequences in relation to patient screening, diagnosis, treatment and long-term monitoring, and the way it will affect the demographics of cardiac patients. For example, improvement in the survival rate of patients suffering from coronary artery disease will increase the number of patients who later suffer from congestive heart failure or heart rhythm disorders, which will therefore increase the need for patient management in these groups. For me personally, the most satisfying part of this project was that it was really taken

on-board by Philips Medical Systems and is now helping to direct their future research into imaging and patient monitoring. What I find most challenging is the combination of physics, mathematics and medical know-how you need to do this type of research. You need knowledge of the interactions between X-rays and tissue and between X-rays and detector systems. But you must also understand the mathematics needed to reconstruct three-dimensional images. For cardiac fluoroscopy applications you then have to do it in real-time and compensate for the fact that the heart is beating while the images are being captured. And you need to know exactly how clinicians will want to use these tools.

3 What are you working on at the moment?

We have now solved many of the technical problems associated with cardiac imaging, so the next task is to put the technology into a clinical environment and see how well it performs. That is why I have just moved myself and my family from Europe to the USA, where I will be able to work closely with some of the world's leading clinical sites for cardiology.

In particular I will be focusing on the use of electro-physiology techniques in the treatment of heart arrhythmias, such as atrial fibrillation. These disorders will become far more common as a higher proportion of the population shifts into the over-60 age group. Most arrhythmias are caused by short-circuits in nervous pathways within the heart muscle, which upset the normal rhythmical contractions of these muscles.

Both the diagnosis and treatment of this condition typically require the insertion of a catheter into the heart of a patient, firstly to measure electro-cardiogram (ECG) signals directly from the heart muscle, and secondly to burn-out detected short-circuits by applying a brief pulse to the right spot via a separate catheter. Both procedures require the highly accurate three-dimensional positioning of the catheter within a beating heart, which is where the cross-modal integration of our imaging modalities comes in.

We currently collaborate with the Massachusetts General Hospital and the Cleveland Clinic Foundation on this work, but part of my

responsibilities in North America will also be to extend the number of Philips collaborations in electro-physiology research.

4 What will the major breakthroughs in medical imaging be over the next ten years?

I think one of the biggest breakthroughs will be the ability to add physiological information derived from imaging to the currently used structural information. This is what the emerging science of molecular imaging is enabling, by giving you access to processes at a metabolic level and visualizing them at the same time.

In cardiac care this will be an invaluable tool in the diagnosis and monitoring of conditions such as congestive heart failure. The end-stage of this disease is characterized by apoptosis, which is the process of natural cell death programmed into your genetic make-up. In congestive heart failure, this process seems to start in the muscles of the heart earlier than it should, probably because of their excessive workload. If molecular imaging could allow us to see sites where this was occurring, it may be possible to treat the disease by injecting stem cells into these sites in order to stimulate the growth of new heart muscle or to directly stop the process of apoptosis by gene/metabolic modifications.

“I think one of the biggest breakthroughs will be the ability to add physiological information derived from imaging to the currently used structural information.”

In the long term, treatment of cardiovascular disease should become largely non-invasive. The onset of the disease will be diagnosed at a pre-symptomatic stage by molecular monitoring or by analysis of your genetic predisposition. Systemic administration of specifically targeted drugs will then prevent the development or progression of symptoms and hence eliminate the need for further intervention. However, this ideal world is some way off, because the underlying genetic and metabolic disorders are not yet understood sufficiently well.

Vital signs

New, exciting developments in molecular healthcare



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A powerful medical tool

Molecular medicine describes a generalized molecular approach to screening and assessment, diagnosis, disease tracking and treatment. It encompasses a whole range of techniques that make use of molecules tagged with a contrast agent and which bind to target molecules in the body. The target molecules are keyed in some way to a specific cellular activity or disease process and the contrast medium carried by the molecular agents allows biochemical processes, including the presence and extent of disease, to be visualized and even quantified using conventional imaging techniques. If bound to a drug, molecular agents can provide targeted therapy.

Major developments in molecular medicine in recent years have provided a much deeper understanding of the underlying molecular mechanisms controlling disease. In particular, advances in molecular target identification have led to the development of new contrast agents and targeted drugs. Moreover on the imaging front, resolution is constantly improving in virtually all imaging modalities with some systems already achieving microscopic-resolution capabilities and sensitivities that would have been unattainable only a few years ago.

Bringing disease into focus

As an established manufacturer of medical imaging systems with many years' experience in clinical science, Philips is ideally placed to become one of the principal players in the emerging science of molecular medicine. The company recently formed a dedicated Molecular Imaging business unit. Its major strategic aims include supporting R&D in molecular medicine through the development of new ultra-sensitive imaging systems with exceptional sensitivity capable of observing phenomena at the molecular level, supporting academic groups working on new biomarkers, and forming alliances with contrast-agent and pharmaceutical companies.

In realizing its goals, Philips Medical Systems (PMS) is also supported by Philips Research, which has a whole range of R&D programs covering all imaging modalities. What's more, PMS and Philips Research are active in developing combined systems for molecular imaging, including X-ray/MRI systems, PET/CT systems, SPECT/CT systems and ultrasound/CT systems. Allowing for fast switching between modalities, these systems combine excellent anatomical detail for accurate drug administering using for

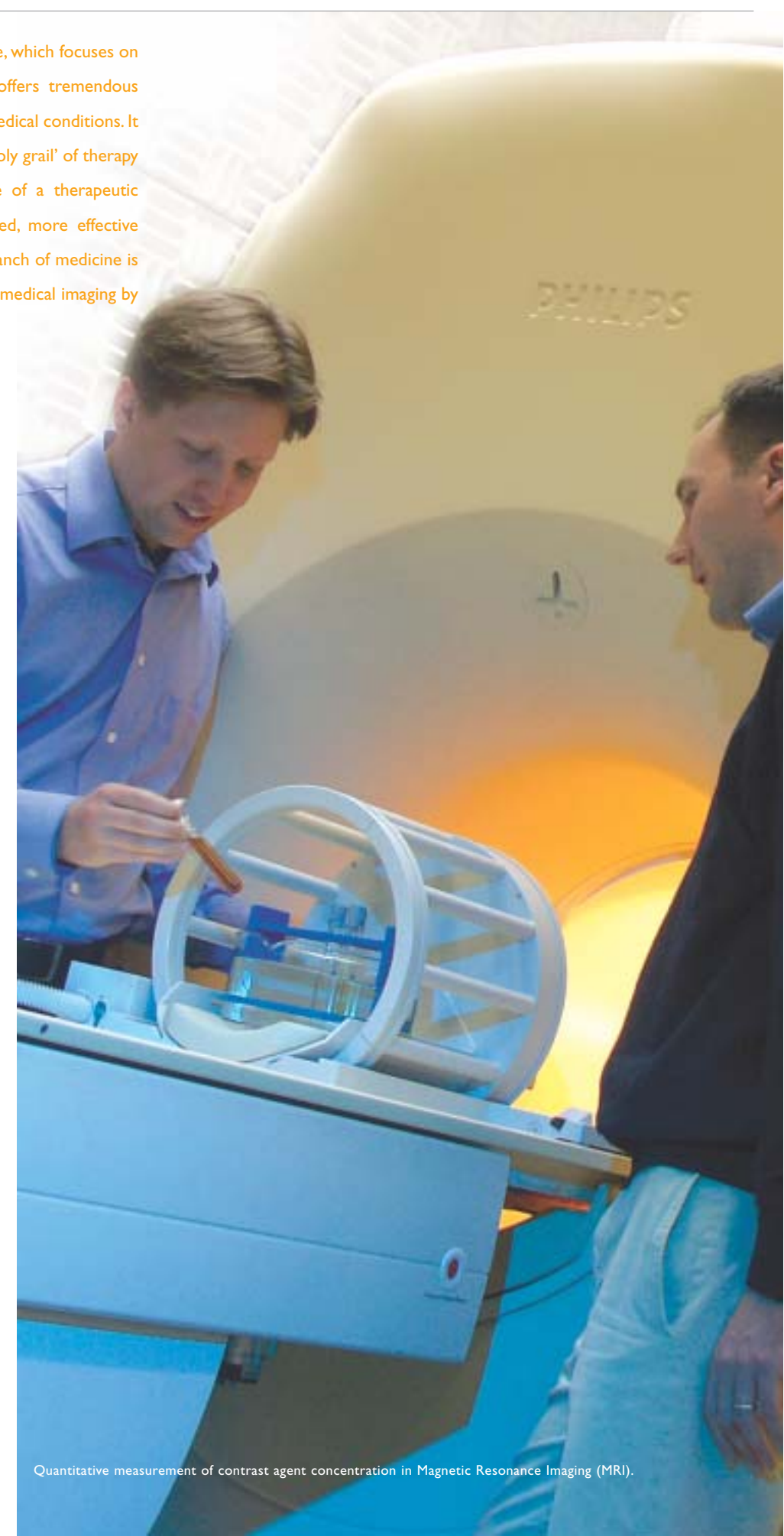
The exciting new science of molecular medicine, which focuses on the molecular processes underlying disease, offers tremendous potential for early detection and diagnosis of medical conditions. It also provides what many clinicians see as the 'holy grail' of therapy assessment – a quantitative, explicit measure of a therapeutic drug's effectiveness, allowing for more targeted, more effective therapy. Although still in its infancy, this new branch of medicine is developing rapidly thanks to major advances in medical imaging by companies such as Philips.

example X-ray's high spatial resolution, with high sensitivity using for example nuclear imaging to observe the drug's effect.

Therapy evaluation

Much of Philips Research's current R&D work on molecular imaging focuses on quantification, specifically on quantifying contrast-agent concentration. This is important for disease staging and therapy monitoring since it gives an objective measure of a treatment's efficacy. It also facilitates faster, more cost-effective drug development as quantitative results, statistical evidence and repeatability form the only bases on which new drugs receive approval by the national drug authorities (such as the US Food and Drug Association).

A valuable tool for objectively assessing drug transfer between blood and tissue is pharmacokinetic (PK) modeling in which mathematical schemes are developed that represent complex processes within the body. Accurate PK modeling is important for precise determination of drug take-up rate. Recent work by Philips Research Aachen has been directed towards the use of PK modeling techniques to quantify contrast-



Quantitative measurement of contrast agent concentration in Magnetic Resonance Imaging (MRI).

agent and drug diffusion rates between blood vessels and tissue. Results of this work include a new parameter-mapping program currently in the qualification phase that generates 2D maps of exchange rates and computes the variation of these parameters in the time domain to provide a clear and objective measure of a molecular agent's delivery and take-up rates.

Quantitative MRI

Classical Magnetic Resonance (MR) imaging deals with the interaction of a radio-frequency field with protons (water molecules) precessing in a large magnetic field. The MR-images obtained depend on the density of the protons and the tissue-

dependent relaxation times. These MR-images can be enhanced with gadolinium- or iron-oxide-based contrast agents that locally influence the T1 and or the T2/T2* relaxation times. Usually (T1, T2 and T2*) weighted images are obtained that allow only qualitative assessment of the pathology. Philips Research, however, has developed

“And by providing objective, measurable evidence of the effectiveness of new treatments, it will create a route to faster, more cost-effective drug development and therapy.”

Tobias Schäffter, Philips Research Hamburg.

new (T1, T2 and T2*) mapping techniques for Philips' MRI systems that provide a quantitative indication of pathology based on a pixel-by-pixel measurement of the

relaxation times during post-processing. The numerical output of the mapping technique allows MRI to provide information down to the bio-molecular level by, for example, comparing the behavior of a tumor (uptake rate) before and after targeted therapy to provide objective evidence of the effectiveness (or otherwise) of the therapy.

Other developments include a new software evaluation tool that corrects for errors introduced into (T2*) relaxation times by susceptibility effects at tissue-air boundaries.

By eliminating these errors, more reliable comparisons of T2* values between different locations within the body and even between different subjects become possible, allowing contrast agent concentration within tissue to be accurately measured. Standard (or classical) methods, usually based on exponential fitting algorithms, introduce large errors into the quantification of contrast agents and show lower sensitivity. Philips' technique provides an accurate measure of low contrast agent concentrations. This is important in stem-cell research, for example, since it allows the detection and tracking of small amounts of stem cells that are labeled with an iron-oxide contrast agent.

Advances in nuclear imaging

New developments by Philips Research have also led to major advances in the performance of SPECT (Single Photon Emission Computed Tomography) cameras including improvements in spatial resolution

and sensitivity. With a unique Sky Light feature, Philips' new SPECT camera incorporates two detectors that can arbitrarily move around a patient and make close approaches to increase spatial resolution. What's more, the camera features a new multi-acquisition window allowing for multi-tracer studies using several nuclear tracers with different energies, e.g. technetium which is taken up fast into tissue and indium which is taken up more slowly. This allows simultaneous acquisitions to be performed focusing on different clinical phenomena, for example, blood flow (perfusion) and controlled cell death (apoptosis) following a cardiac event.

Ultrasonic molecular imaging and therapeutics

Ultrasound has been traditionally known for its real-time imaging capability of anatomical features as well as functional changes in blood flow. For this, ultrasonic contrast agents consisting of micro-bubbles have become the industry standard for increasing the signal from the blood pool. A leader in the development of imaging techniques for

“By dramatically improving the power of diagnosis and therapy, molecular imaging is becoming one of the most important tools of modern medicine.”

Tobias Schäffter, Philips Research Hamburg.

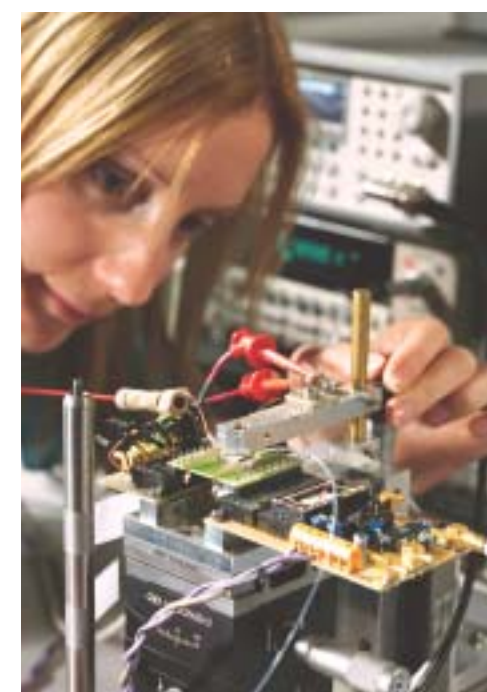
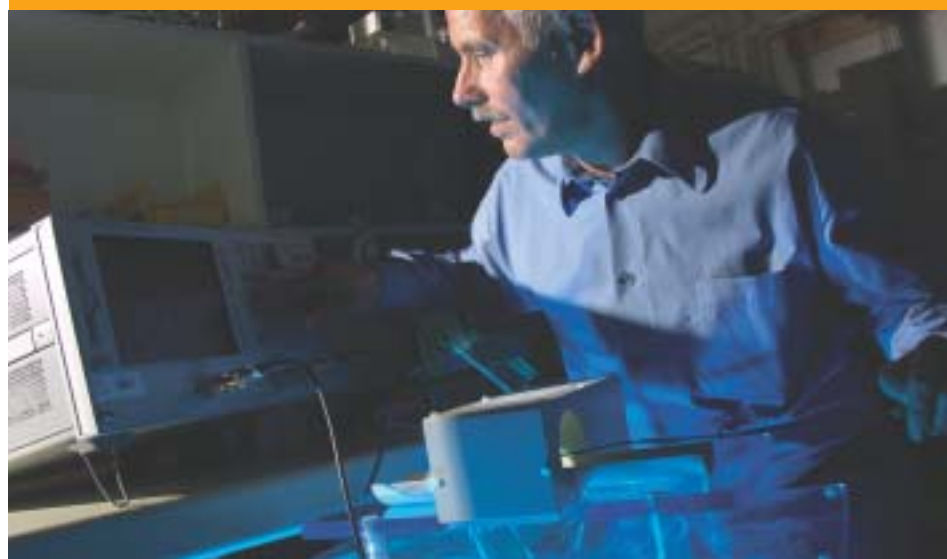
contrast agents, Philips is currently extending its expertise from blood-pool contrast agent imaging to molecular imaging and has formed several collaborations with leading academic institutions for the advancement of targeted ultrasonic contrast agent development. We have made significant advances in the imaging of newly formed blood vessels around tumors by targeting to the specific angiogenesis marker integrin with ultrasonic contrast agents, along with several important characterizations of the necessary conditions for successful binding of contrast agent to specific molecules. Philips is also actively engaged in what's known as 'ultrasonic-mediated molecular therapeutics' – the use of appropriate biochemical delivery mechanisms to control the delivery of a therapeutic intervention to allow user-controlled release of pharmaceuticals and immediate assessment of the effect of a chosen intervention.

Creating a new world of healthcare

Molecular medicine has been described as a medical breakthrough as fundamental and as significant as Harvey's discovery of blood circulation and the discoveries of antibiotics and the structure of DNA. Its development will revolutionize clinical practice. Molecular-based screening will provide information about a patient's predisposition to particular diseases that will allow clinicians to employ preventive care designed to help a patient combat risk factors. And in cases where disease is discovered, molecular-based techniques will allow specific imaging, identification of pathology and treatments. The advances currently being made by Philips Research are making a vital contribution towards turning these visions into reality to create a new world of healthcare in which many of today's most debilitating diseases will be consigned to history.

Animal imaging supports R&D

One of the major focuses of Philips' new Molecular Imaging business unit is the development of equipment to support the R&D chain from development of targeted contrast agents and drugs in the laboratory, through pre-clinical animal trials towards early clinical human trials. Philips now offers researchers in this field specially-developed animal-imaging equipment including Optical Imaging, PET, CT, MRI with dedicated animal coils, and animal probes for ultrasound. Many of these systems are based on the same back-ends as the company's established clinical-imaging systems. They therefore offer the important advantage of allowing protocols developed during pre-clinical animal-testing phases to be transferred directly to the clinical testing phases, saving time and costs in drug and contrast agent development. This is in marked contrast to current specialized animal-testing equipment in which transfer from pre-clinical to clinical trails requires the time-consuming development of completely new protocols for testing on humans.



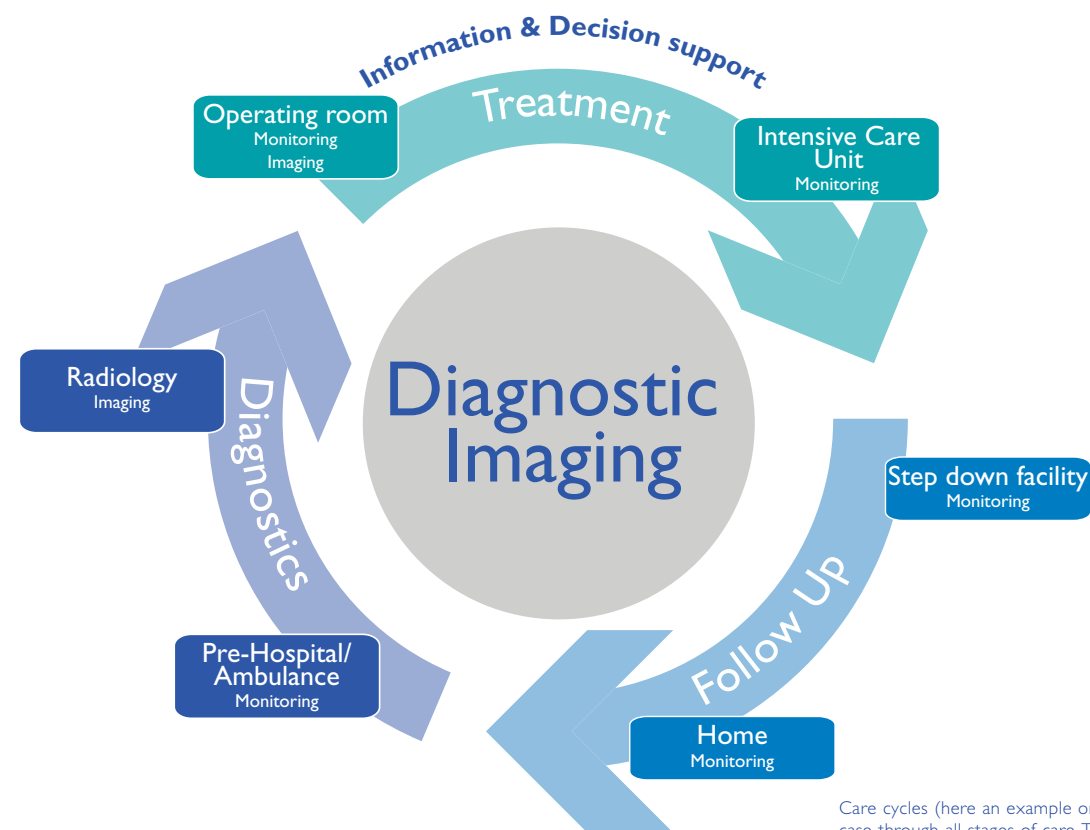
Development of a dedicated small-animal RF-coil for MRI

New biosensors for molecular diagnostics

Philips Research is investigating a new biosensor technology based on magneto-resistive sensors that promises to radically improve the speed, sensitivity and reliability of biomolecular diagnostics for applications such as protein and pathogen monitoring, near-patient testing in medical centers (blood, urine, saliva tests etc.), and ultimately home testing by individuals. Philips' biosensor measures the magnetic field created by magnetic nano-particles that bind to target molecules in a biological assay. Compared with optical sensing methods, the use of magnetic nano-particles not only eliminates the additional steps required to bind optical labels to the target molecules, it also results in biosensors that are up to a hundred times more sensitive than existing devices.

Philips' next step in the development of such systems is to demonstrate dose-response curves for relevant biological molecules and the company expects the technology could be ready for industrialization in about four to six years.

Shaping the care cycle with new technology



Care cycles (here an example on diagnostic imaging) are used to map a clinical case through all stages of care. This is a useful tool in developing system solutions that optimally match clinical needs.

Clinical practice is the starting point for everything that Philips Medical Systems (PMS) does. It collaborates closely with doctors and hospital staff to make sure that applications are designed to meet their needs as well as those of their patients. It takes an integrated approach, looking at how imaging applications can be optimized and combined to offer a systems solution to support, say, a cardiologist in his various tasks such as diagnoses, intervention, intensive-care monitoring and managing patient data in an efficient way.

A valuable tool in this process is the 'care cycle' – an integrated description of a clinical case through its various stages, from diagnosis to treatment and post-therapy follow-up. Care cycles can be made for diseases, but also for application clusters like patient monitoring or diagnostic imaging. The care cycle approach is particularly relevant to chronic illnesses, where patients are routinely checked for possible recurrence. As the quality of care rises, so does the number of people with chronic conditions. These now account for over 50 per cent of healthcare costs.

Paul Smit: "The care cycle is an excellent tool for developing an integrated clinical approach. It shows the complete picture and helps us optimize the total system around a clinical need. It also provides good guidance in deciding the best application and development direction of new technologies."

Oncology is a good example. Progress in imaging resolution allows doctors to locate tumors ever more precisely. Using the latest image processing techniques they subsequently simulate radiation therapy and calculate the optimal combination of radiation dose and beam direction to attack the tumor with minimal damage to surrounding healthy tissue and organs. During radiation, real-time imaging now allows the motion of organs in the body to be followed with automatic correction of the radiation beam to keep it focused on the right spot. Our system approach ensures the smooth flow of patient data through diagnosis and treatment. Doctors can perform the consecutive steps in a natural and efficient way rather than in a

The impact of new technologies and the need to control the escalating cost of medical care are expected to bring about considerable changes in the healthcare landscape in the next decades. As one of the world's leading makers of medical imaging equipment, Philips Medical Systems is determined to be among the shapers of this new world. Paul Smit, Senior Vice President Strategy and Business Development, talks to Password about the business's commitment to helping medical care advance in the right direction by offering the best integrated solution for each clinical situation.

station-by-station approach.

The acute-care cycle is another example. Here, new developments in healthcare IT and patient-monitoring technologies can be jointly applied at all stages of the care cycle to increase patients' safety and improve the quality and speed of diagnosis and treatment.

While advances in existing imaging modalities can be regarded as evolutionary progress, the developments in the new areas of molecular imaging and molecular diagnosis about to cause a true revolution in both clinical practice and in the world of the imaging industry (see also the article on page 10). Does the care cycle approach work here as well?

Paul Smit: "In such a new field it is particularly important to maintain the overview and keep the clinical perspective in mind. Molecular healthcare is a very exciting development that will allow us to make a big step forward in detecting diseases at a much earlier stage. At the same time it is very complicated, since it requires the integration of progress made in very different fields such as molecular biology, pharmacy, biomedical devices, bio informatics and medical imaging. With a diverse mix of players, including academics, start-up companies and established industries like ourselves."

"Even if we are not specialists in all these fields, it is essential for us to have a good knowledge of the entire system. This will help us to exploit the latest developments in adjacent fields and use them to develop molecular imaging modalities targeting meaningful clinical applications. It will also help us find the right partners to jointly develop integrated solutions, for example specific molecular agents that bind to proteins indicative of a certain disease, combined with dedicated imaging modalities to localize these binding events in the body."

There is a similar story to be told in personal healthcare, another development that is about to cause a major paradigm shift in medical practice, as it will move part of the healthcare system out of the hospital domain and into the consumer sphere (see also the article on page 4). Here the challenge is more to combine largely existing technologies into monitoring and service applications that will improve the quality of life for those receiving care for chronic conditions and lower the cost of the chronic-care system at the same time. It is less technology driven than molecular healthcare, but

it has the same system complexity where players from a lot of different backgrounds meet.

"In building up the required system knowledge, Philips Research plays an important role, because they have the capability to look over the borders of individual disciplines and efficiently set up and run projects to explore entirely new fields," Paul Smit concludes. "They are very well positioned to help us identify mid and long-term trends and respond to these in the right way. For us at Medical Systems, Philips Research is a highly valuable business partner in determining our future direction."



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Facts about healthcare

- With a worldwide expenditure of US\$ 3,300 billion in 2002, corresponding to 8% of the world's gross domestic product, healthcare is the world's largest service sector. 70% of this amount is spent in 5 countries: USA, Japan, Germany, France and Italy.
- 62% of healthcare costs are primary care costs (physicians salaries and cost of hospitalization), 13% are for drug prescriptions, 9% are for nursing and home healthcare. Medical equipment and devices account for 7%.
- Cardio and vascular diseases and cancer are responsible for approximately 60% of the deaths in the US. Yet, US average life expectancy has risen from 68 years in 1950 to 78 in 2000. In the last 25 years, the number of people under 65 years of age dying from heart disease has come down by more than 50%.
- Around 70% of the survival improvement in heart attack mortality is a result of changes in technology. Every US\$ invested in technology to diagnose and treat heart disease brings \$ 6 return in economic value.

Sources: Medistat, WHO, NIH, CDC, National Vital Statistics NCHS, Cutler & McClellan, 2001

Medical IT enhances clinical decisions

Longer life expectancy and an aging population have put greater demands on medical services. Heightened public awareness of healthcare issues has increased patient expectations. Doctors and nurses are under increasing pressure but cannot be expected to hold everything in their heads. They do, however, need up-to-the-minute patient information and expert knowledge at their fingertips to help them make the right clinical decisions. Thanks to recent advances in Medical Information Technology being made by Philips Research, that information is becoming increasingly accessible.



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Providing a helping hand

Over the past twenty years, medical science has given doctors the ability to see what is going on inside our bodies in ever-greater detail. Straightforward X-rays have been augmented with 3-dimensional CT (Computed Tomography), MRI (Magnetic Resonance Imaging) and ultrasound scans. And a whole new raft of optical, nuclear, and molecular imaging techniques is about to be added to their arsenal.

Doctors are now presented with an enormous amount of clinical data, which makes collating and evaluating this data a potential bottleneck in the diagnostic process. CT scans alone, for example, are some of the most difficult and time consuming to interpret.

One of the medical IT programs at Philips Research aims to give doctors a helping hand. Taking the detection and diagnosis of lung nodules (potential pre-cursors to full-

blown lung cancer) as a focus area, scientists at Philips are developing software that can recognize lung nodules directly from CT images.

Imagine having to review the 1000 image slices acquired during a typical chest scan in order to detect a millimeter sized lung nodule which is barely visible amid the maze of vessels that also appear as tiny circles in each slice. Only the 3-dimensional connectivity of the vessels tells them apart from nodules, with the risk of radiologists missing a nodule. Computers, however, excel at such tasks, and the Computer Aided Detection (CAD) algorithms being developed at Philips Research have already pinpointed nodules that even an expert radiologist might have missed.

From detection to diagnosis

A parallel program at Philips Research is investigating Computer Aided Diagnosis (CADx) techniques that will help to assess

the potential malignancy of these lung nodules.

At present, distinguishing between malignant and non-malignant nodules is more of an art than a science. Some doctors are simply better at it than others. In attempting to computerize the process, deciding on the appropriate set of image features to use is therefore far from straightforward.

In addition to conventional approaches, such as pure reasoning or the use of neural networks, scientists at Philips Research are applying the relatively new technology of 'genetic algorithms'. These algorithms exploit principles similar to that of 'natural selection' in genetics.

Philips Research's genetic algorithms start off by generating a very large number of random combinations of lung nodule features. The effectiveness of each combination in highlighting a malignant nodule is then tested

against a known set of lung nodule images for which the malignant or benign nodule status has been confirmed by biopsy.

As a result of this testing, each combination of lung nodule features is allocated a 'survival' rating. Combinations that are better at predicting malignant nodules are given higher survival ratings than those that do less well. The initial set of combinations is then used to 'seed' a new generation of

feature combinations, with higher survival-rating combinations allowed to have a greater influence on the seeding process.

Repeating the process over and over again results in the emergence of highly accurate

"One day it will be possible to utilize healthcare systems knowing that every doctor and nurse is armed with your complete patient history plus all the latest clinical information they need to deliver the most effective treatment."

Helen Routh, Philips Research USA.

solutions just like survival of the fittest has driven the evolution of every living thing on earth. In the same way that you don't know why one doctor can spot malignant lung nodules and another cannot, you don't have to know why a genetic algorithm solution



works, only that it does. What is important, however, is that you train the genetic algorithm with as much known good data as possible.

If successful, similar CADx techniques could be applied to other imaging modalities such as Magnetic Resonance Imaging (MRI), and to other types of tumor such as colon and breast cancers.

Improved intensive care

Accurate decision-making is nowhere more important or time-critical than in intensive-care units. It can literally make the difference between life and sudden death. As a result, intensive-care patients are typically connected to automatic monitoring equipment that continuously monitors parameters such as heart function, blood pressure, blood oxygen, pulse rate and

respiration. When any of these parameters moves outside pre-set limits, an alarm sounds to bring it to the attention of the nursing staff.

The problem is that in over 90% of cases there is actually no major cause for concern.

Either the patient has dislodged a sensor, or

“The problem is that in over 90% of cases there is actually no major cause for concern. Either the patient has dislodged a sensor, or something clinical has been done to cause the parameter shifts. Many drugs, for example, have a side effect of changing blood pressure, pulse or respiration rates.

Helen Routh, Philips Research USA.

something clinical has been done to cause the parameter shifts. Many drugs, for example, have a side effect of changing blood pressure, pulse or respiration rates.

In collaboration with the patient monitoring business group in Philips Medical Systems,

scientists at Philips Research are investigating ways of minimizing these false alarms by making intelligent decisions based on combinations of parameters. These systems could also dynamically adjust the threshold levels of monitoring equipment to automatically compensate for known side

effects of drugs or other therapies. Philips has already published important results on this topic in collaboration with MIT (Massachusetts Institute of Technology). A complete reversal of typical alarm statistics has been shown – from more than 90% to less than 10% being false.



From the exceptional to the routine

It is highly unlikely that you will end up in intensive care, but if you do it will be nice to know that there are intelligent monitoring systems watching over you. What is far more likely, however, is that your hospital visits will be routine. Not for you of course, but for the doctors and nurses who treat you.

Routine treatments account for the bulk of clinical time and effort, and the largest part of total hospital costs. In the quest for uniform and traceable treatment strategies throughout their healthcare systems, many governments are in the process of issuing written guidelines for these treatments.

To avoid the need for clinical staff to memorize or constantly refer to written guidelines, Philips Research is targeting the problem with departmental IT solutions. Collectively, these programs can best be described as Clinical Decision Support Systems (CDSS) that help doctors and nurses to deliver the highest quality of patient care, taking into account the latest clinical knowledge and your specific medical history.

The computerized CDSS solutions being investigated by Philips Research combine pre-programmed models of these guidelines with patient-specific information to provide hospital staff with instant recommendations on possible courses of action. These recommendations are not designed to replace the expert opinions of individual clinicians, but rather to make sure that they have all the necessary information at their fingertips in order to make a decision. They will not only increase the quality of decision making. They will also speed up the process, freeing up time for clinicians to concentrate on more complex cases. Philips Research works on these systems in collaboration with Columbia University (New York, USA), a world leader in medical-informatics research.

All the work done by Philips Research into medical IT is done within the context of departmental systems, largely linked to medical imaging and patient monitoring. By creating information in standardized formats, the data generated by these departmental systems is designed to feed seamlessly into wider IT systems within healthcare organizations.

Clinical guidelines and patient information integrated and prioritized to support the next needed care decision.

Binding software implementations to business objectives

Clinical Decision Support Systems are software intensive applications in which software architectures create the crucial bridge between business objectives and technical implementations. On the business side, the chosen architecture must take into account proposed business models, customer requirements and product features. On the implementation side it must accommodate the proposed enabling technologies and system development methods.

Everyone knows that business models, in particular, are extremely difficult to predict, which is why the software architecture group in Philips Research concentrates on what it calls 'required variation points'. These are points in the software architecture where change is likely to occur, either because of changing business models and customer requirements on the business side of the equation, or changes such as the shift from hardware to software solutions on the implementation side.

The ability of an architecture to accommodate change is then tested against possible future scenarios. And to ensure maximum relevance for these scenarios, they are developed by Philips Research scientists that are embedded three days a week within Philips Medical Systems.

One architectural component that is likely to have a significant impact on clinical decision support systems is grid computing (often referred to as 'next-generation Internet'). By making the sharing of distributed computer resources much more seamless and transparent than it is today, grid computing will not only provide better access to patient data. It will also provide access to the knowledge databases needed to interpret that data. Grid computing is even capable of bringing together widely distributed individuals into cohesive groups in order to pool their expertise. As such, it is an ideal way of accessing all the different types of clinical information needed to ensure the highest quality of patient care.

Technology news

EUSAI 2004

Following a successful first event last year, the 2nd European Symposium on Ambient Intelligence, will be held at the Eindhoven University of Technology, from November 8-10, 2004. It aims to provide a venue for an emerging multi-disciplinary community of researchers working on Ambient Intelligence. A wide range of themes relevant to Ambient Intelligence systems will be discussed at the symposium, including ubiquitous computing, context awareness, intelligence and natural user-system interaction.



For more information and registration (closing October 25), see www.eusai.net.

Published book

Wim Jonker and **Milan Petkovic** of Philips Research edited a book entitled 'Secure Data Management'. The book contains the refereed proceedings of the VLDB 2004 International Workshop on Secure Data Management in a Connected World, SDM 2004, held in Toronto, Canada in August 2004. The papers are organized in topical sections on encrypted data access, privacy preserving data management, access control, and database security.



<http://www.springeronline.com/sgw/cda/frontpage/0,11855,4-40109-22-34174664-0,00.html>

Best-paper awards

At the Asia Display/IMID'04 conference in Daegu, Korea, **Roy van Dijk** of Philips Research received the best-paper award. In the paper, entitled 'A flat thin display with RF electron generation', van Dijk and co-authors Gilles Vissenberg and Siebe de Zwart presented a new display principle that could potentially result in a flat display with viewing characteristics comparable in excellence to cathode ray tubes (CRTs). Like a CRT, the display attracts electrons to a phosphor screen, however, a new type of electron source is used that creates electrons directly behind each pixel instead of in a single electron gun, so no deflection is needed and a flat display is obtained.



Clemens Wust, Liesbeth Steffens, Reinder Bril and **Wim Verhaegh** of Philips Research were the winners of the best-paper award at the 16th Euromicro Conference on Real-Time Systems. Their article was entitled 'Quality of Service control strategies for high-quality video processing'.

Open Innovation in China

A delegation led by Rick Harwig, CEO of Philips Research and Amandus Lundqvist, President of the Eindhoven University of Technology visited four top universities in China to investigate opportunities for cooperation between the respective research institutes. The delegation visited Tsinghua University in Beijing, Zhejiang University in Hangzhou and Fudan and Jiaotong in Shanghai, all listed in the top 10 of the China College and University Rankings 2004. Several types of cooperation were discussed, e.g. staff-exchange programmes, joint education initiatives, joint R&D projects as well as the build-up and exploration of competencies through industrial-academic cooperation.

Building up a cooperative relationship between Philips Research, the Eindhoven University of Technology and these top-class Chinese universities provides unique opportunities for all parties to further



strengthen their Chinese-European collaboration in a joint industrial and academic setting. For both parties, it is a further extension of their existing and growing ties with China: Philips currently runs 13 research and technology centres in China, including the Philips Research East Asia laboratory in Shanghai, which already has a network of collaborations with Chinese universities in place. The Eindhoven University of Technology also has a number of joint projects and programmes running with Chinese universities.

IP Academy at Tsinghua University

Philips and Beijing-based Tsinghua University signed a strategic agreement for Philips to support and sponsor Intellectual Property Rights (IPR) education at the university. The agreement includes cooperation to cultivate local IPR talents and enhance the IPR knowledge of Tsinghua students. Philips will sponsor European IPR experts to give courses on legal and IPR matters and establish an IPR Scholarship program at Tsinghua. Philips will also sponsor IPR-related research at Tsinghua and invite professors from Tsinghua to visit universities in the Netherlands and other European countries. Two of Philips' IPR experts have already started

giving lectures at Tsinghua. "To contribute to innovation and become a respected partner in the global economy, a creative technology base must be accompanied by a professional IPR enforcement system. We know how hard the Chinese government is working to improve the country's IPR system and promote IPR throughout Chinese industry and institutions. With the establishment of this Philips IP Academy at the top-class University of Tsinghua we are trying to contribute to achieving these commendable goals," said Ad Huijser, Chief Technology Officer of Philips, who signed the agreement on behalf of Philips.

ElectroMagnetic and Cooling Competence Center opened

On September 3, the ElectroMagnetic and Cooling Competence Center at the High Tech Campus Eindhoven opened the doors of its new facilities. The competence center offers unique integrated capabilities to analyze and optimize the electromagnetic and thermal compatibility of electronic products and designs. It can handle samples ranging from on-chip components to complete systems, measure at frequencies up to 40 GHz, both in shielded test rooms as well as in the field using a dedicated test van. As a further step towards Open Innovation, Philips is encouraging other companies and institutions to use the facilities and expertise offered by the ElectroMagnetic and Cooling Competence Center.



Philips introduces first 1-16x DVD+R disc

Philips has announced that its new 'All-Speed' DVD+R blank medium is the first to be approved for 1x up to 16x recording speeds. This allows consumers to use the same disc in a flexible way, from real-time 1x video recording speed up to the maximum achievable 16x speed. A 16x DVD drive writes the full 4.7 GB DVD+R disc in about 5 minutes. The developments are a direct result of Philips Research's innovations in optical-storage technologies, which include the development of a new write strategy for high-speed recording.

When it comes to medical research, it is axiomatic that the welfare of the patient is the bottom line. In the past, however, the journey from bench to bedside was long and, often, bumpy, with weak lines of communication linking researcher, clinician and patient. Now, unprecedented levels of cooperation among Philips Research, Philips Medical Systems and clinical and academic institutions are speeding up the pace of innovation – and helping save patients' lives.

Fit for use

That truth would seem to be self-evident. Which leads one to ask: is clinical cooperation a new idea at all? Hasn't there always been a balance between the push of technological advancement and the pull of clinical needs?

There has, to some degree. But as advances in healthcare lead into more clinically driven directions, even closer cooperation is needed. The production model no longer resembles an assembly line, with researchers handing down discoveries to clinicians, who apply them to their patients.

“Working collaboratively, the results will propagate into accepted clinical practice more quickly.”

Gert Bruning, Philips Research USA

“Without clinical cooperation, the product may well turn out to be a very interesting technology solution which doesn't solve the exact clinical problem,” says Helen Routh, head of the Healthcare Systems and Information Technology group at Briarcliff Manor.

The growth of new knowledge has been so fast, especially in such areas as the molecular processes behind diseases, that no single institution can hope to harness it all. The better solution is to match strength to strength: to cooperate.

Combined strengths

Philips, for example, is strong in medical imaging, an area whose capital costs and level of sophistication place it out of the reach of most small companies and universities. Medical teaching centers have the clinical infrastructure for the entire translation chain (from phantom studies to small to large animal to patient studies) as well as top clinicians and students hungry to be on the cutting edge.

Clinical speeds up innovation



“Academic institutions want to publish,” says Peter Luyten, general manager for molecular imaging at Philips Medical Systems in Bothell, WA, USA. “They want their research to be applicable to the widest possible public – not an altogether altruistic desire, since funding for research in the USA in particular often goes more to practical research than to the purely theoretical kind.”

Philips' collaboration with the University of Virginia is just one of several productive relationships the company has with the academic world. Philips and the university are working together on contrast-enhanced ultrasound for molecular imaging, useful for the non-invasive imaging of tumor angiogenesis. The process makes use of targeted microbubble contrast agents to image the angiogenesis. Philips provides the imaging technology, while the university develops the contrast agents and the image processing.

cooperation

Philips has teamed up with research hospitals as well. In Boston, Mass., USA, Philips and Beth Israel Deaconess Medical Center are developing a fully annotated database of cases from Beth Israel's intensive-care unit. The database, which catalogs the histories of some 2,000 patients, incorporates the notes nurses write about the patients. This information, added to other patient data normally captured by computers, will allow doctors to make even quicker and more accurate diagnoses.

Exchanging experiences

Philips' close relationships with teaching institutions often involve sending a researcher to a university for a few years. This is the case with Henning Braess, a research scientist at Philips Research Aachen, Germany and a visiting scientist at the University of Maryland in Baltimore. An expert in diagnostic cardiology, Braess is teaming up with his University of Maryland colleagues to refine cardiac positron emission tomography/computed tomography. Cardiac PET/CT is an imaging method that allows for a more streamlined, more accurate, and less invasive diagnosis.

With today's technology, a cardiologist can detect blockages in the coronary arteries, insufficient blood circulation, scar tissue and decreased cardiac function. In order to collect that information, however, the cardiologist needs to take two or more steps, one of which involves running a catheter from the patient's leg to the heart. Needless to say, this procedure involves some discomfort on the part of the patient, and it's expensive.

Cardiac PET/CT fuses those procedures into one, non-invasive process. Instead of introducing a metal wire into the patient's body, the doctor injects a contrast medium into the patient's arm. Then, using Philips' state-of-the-art Gemini PET/CT scanning system, University doctors create a 3-D image of the patient's heart, allowing them to discover the disorders mentioned above.

“The purpose,” says Braess, “is that people are sent to the cath lab

only if there will be interventional treatment – only if the physician is really going to insert a stent. We try to avoid unnecessary interventional diagnostics.”

“The idea of collaboration is that if you work side by side, the technology can be matched better to the clinical application.”

Gert Bruning, Philips Research USA

Non-invasive therapy

But what about non-interventional treatment? Here, too, Philips and its partners are pioneering new techniques.

Philips is working with CellPoint, a U.S. biotech startup, to develop a system that combines a molecular-imaging agent developed by CellPoint and Philips' SKYLIGHT gantry-free gamma camera. Diagnostic applications are the first goal. CellPoint's imaging agent, Tc-99m-EC-deoxyglucose, targets tumors for imaging by nuclear-medicine cameras such as those produced by Philips. The possibility exists, researchers say, to move into treatments, in which tumors are not only imaged, but actually treated by substances similar to those used for imaging.

Like the research organizations with which it partners, Philips understands that a revolution is occurring in the realm of medical knowledge, one that it has a responsibility to profit from and contribute to, in accordance with its strengths and limitations. If ever there were a situation in which there were only winners, this is it. As Bruning puts it: “In the end, the patient wins, getting better and earlier treatment. The medical center and clinicians win because they rise in their rankings. We win, because we sell more equipment. Early detection of disease should bring the costs of healthcare down, since we can detect a potentially major problem while it is still minor. Philips simply has to be a part of this new world. And to be a part of it, we need to work with others.”

What's new?

Innovative technology from Philips Research enables exciting new Philips products and services to be introduced.

RapidView

The world's fastest system for 3D cone beam CT reconstruction

The challenge

- The number of detector rows used in modern CT (Computed Tomography) scanners is increasing rapidly to provide a larger scanning area and shorter patient scanning times. As a consequence, image reconstruction becomes more complex, because the cone angle of such large systems can no longer be neglected.
- In conventional systems using general-purpose processors, this results in unacceptably long computation times, and hence often the use of simpler but less accurate reconstruction methods.

The solution

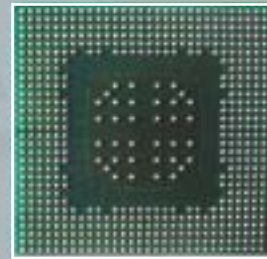
- An ultra-fast, dedicated processor developed by Philips Research to compute a patient's 3D volume data out of the thousands of 2D X-ray slices taken during a CT scan.
- This processor runs image reconstruction algorithms more than 100 times faster than state-of-the-art general-purpose solutions.

The benefit

- The processor allows the use of the most complex 3D reconstruction algorithms for the best possible image quality.
- Providing high spatial and temporal resolution and excellent images for cardiac and other highly demanding CT applications.

The product

- The processor is implemented as a high-density application-specific integrated circuit (ASIC), containing 14 million logical units.
- Several ASICs and signal processors are combined on an accelerator board that fits into standard PCs or other host computers with a PCI bus.
- The CT reconstruction accelerator is fully industrialized and available in the CT products of Philips Medical Systems.



www.medical.philips.com/main/products/ct/

