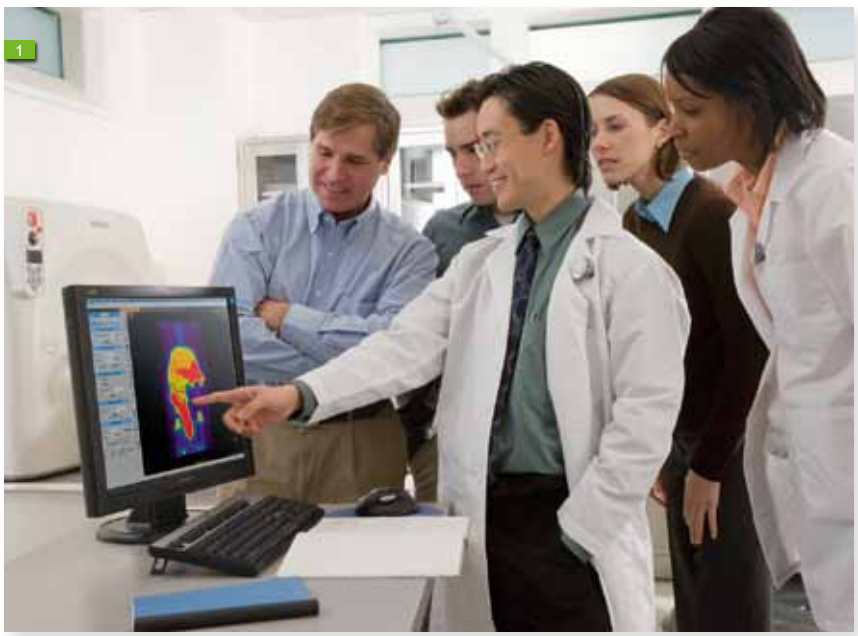
IMALYTICS: the Philips translational and research workstation

T. Paulus
A. Fischer
P. van Loon
B. Schweizer
E. Gegenmantel
R. Bippus

Philips Research Europe, Aachen, Germany.



▲ Figure 1. The IMALYTICS workstation.

IMALYTICS, Philips' translational research workstation, plays a central role in bringing new concepts into clinical practice.

Thanks to progress in genomics, proteomics and biomedicine it is becoming clear that diseases, as well as their potential cures, are associated with specific processes at the cellular and molecular level. The new paradigm of molecular medicine aims to detect the biomarkers for disease before patients experience symptoms, allowing much earlier diagnosis and personalized therapy. These are widely regarded as two of the best ways of meeting the demand for effective healthcare and longer-lasting human wellbeing, while also controlling costs. The effective translation of new concepts for molecular imaging and targeted therapy into clinical practice requires close cooperation between leading industrial, academic and clinical partners. Bringing together such partnerships is one of the underlying principles behind Philips' policy of open innovation.

IMALYTICS, Philips' translational research workstation, plays a central role in bringing new concepts into clinical practice. In collaborative open-innovation projects, it is being used in pre-clinical and clinical research for advanced analysis, quantification and visualization of molecular imaging data. Examples of such collaborations include research projects with the Fraunhofer Institute for Molecular Biology and Applied Ecology in Schmallenburg, Germany (Prof. Dr. S. Barth), the Institute for Experimental Molecular Imaging at the RWTH Aachen/University Medical Center Aachen, Germany (Prof. Dr. F. Kiessling) within the HighTechNRW Innovation Policy and Research Funding program [1], and participation in the Dutch CTMM (Center for Translational Molecular Medicine) [2] program. In all of these projects, researchers from different universities with their respective medical equipment employ the IMALYTICS workstation.

The IMALYTICS workstation is derived from the Philips' Clinical Workstations and is therefore very easy to implement in the research workflow. Because it is based on a commercially available product it also has the help and support of the local Philips Healthcare Customer Services.

The workstation features advanced tools for extracting quantitative information from images for systematic interpretation of research data. These include tools for registration and fusion of images (e.g. a time series of images or images from different imaging modalities), segmentation, pharmacokinetic modeling of a time series of images (i.e. analyzing the time-dependent behavior of contrast agents based on mathematical models) and presentation of the original data and the results.

IMALYTICS is developed and marketed by a dedicated business venture within Philips Research Aachen. It is supported by Philips Healthcare Customer Services, with various local service packages including a Premium Research Service that links to ongoing activities within Philips Research, and provides access to prototypes. The workstation is under continuous development, resulting in regular updates and upgrades. Based on the technological core components of the system, higher integrated packages addressing specific topics are under development.

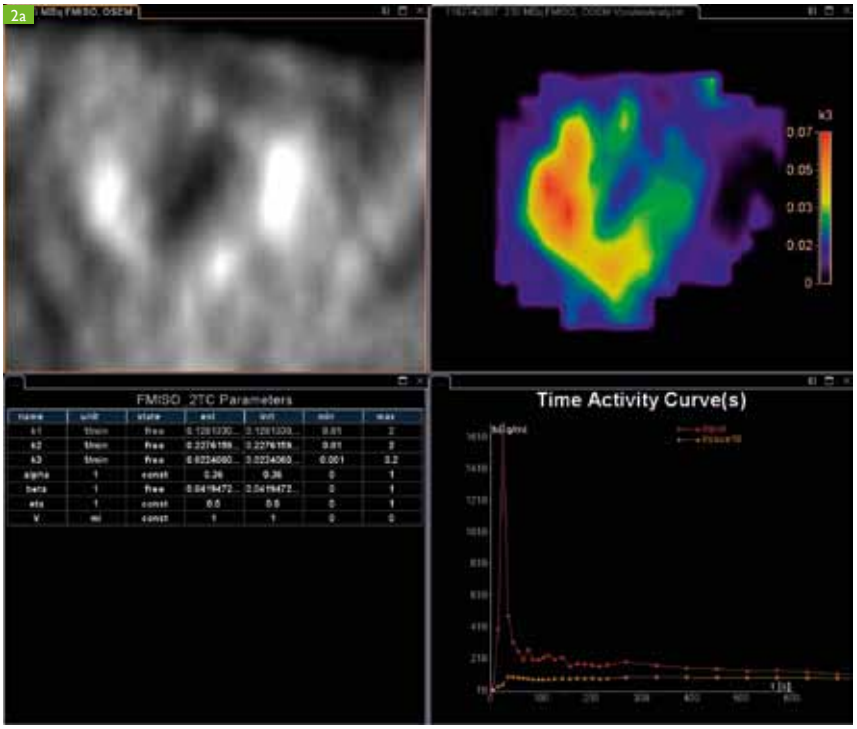
Examples of packages currently under development are:
• Dosimetry (STRATOS)
• Tumor follow-up (BIOSTAR)
• Dementia evaluation (CAD4D)

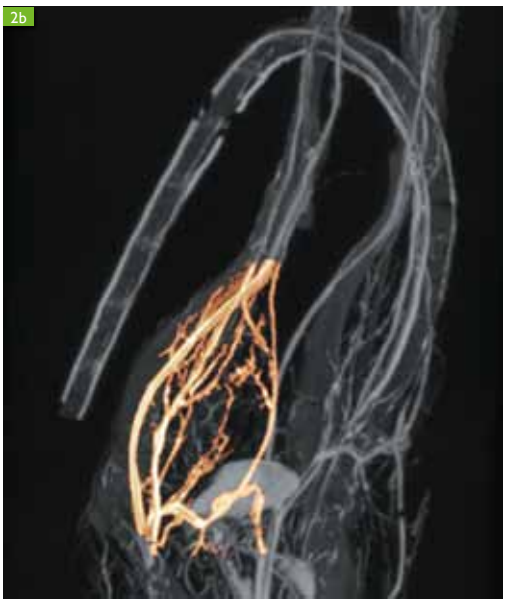
Dosimetry (STRATOS)
STRATOS is an advanced dosimetry solution for targeted radionuclide therapies (TRT). TRT is based on the injection of targeting molecules (e.g. antibodies or peptides), labeled with a therapeutic radionuclide, into the patient. The targeting molecules selectively attach to cancer cells; the radioactive decay of the radionuclide will then kill these cells. TRT has already been approved for treatment of Non-Hodgkins Lymphoma and lung cancer. Many novel drugs against other cancer types, such as prostate or colon cancer, are in clinical development.

While the absorbed dose in the tumor and normal tissue is an important predictor for therapeutic success and occurrence of side effects in TRT, current techniques either do not measure the dose distribution, or have a large relative error of up to 200%. This implies that it is not possible to prescribe a maximum injected drug dose for a specific TRT patient. With this "one-size fits-all" dosing approach, the dose for all patients has to be kept within the safety margin of even the most unfavorable drug distribution. This leads to under-treatment of a large proportion of the TRT patient population. K.E. Britton [3] suggests an under-treatment by a factor of 2 to 3 (!) for individual patients.

It is possible to monitor the biodistribution of TRT drug molecules within the patient's body in a planning study by means of SPECT (single photon emission computed tomography) or PET (positron emission tomography) imaging. The diagnostic version of the tracer is injected in a small amount into the patient prior to the scan. From the PET or SPECT data, the internal dose distribution can be calculated using the methods of voxelized, image-based dosimetry. This approach has the potential to deliver the full 3-dimensional dose distribution to the clinician, while at the same time the errors in dose calculation can be reduced to a level of about 20%. However, there is currently no commercially available voxelized TRT software.

STRATOS combines established algorithms for internal dose calculation with newest tools from the field of external-beam radiotherapy (EBRT) planning. It offers an interactive TRT dosimetry workflow and also to convey a broad range of the established Philips workflow technologies





▲
Figure 2. Registration (2a) and Pharmacokinetics study of dynamic PET data (2a) and segmentation of vessels in a contrast enhanced CT dataset (2b).
◀

(e.g. segmentation, registration, fusion display) to the customer base in nuclear medicine. Dose distributions within the patient can be visualized in three dimensions or be analyzed in the form of region dose tables and dose volume histograms.

Nuclear medicine experts have reacted favorably to this first integrated package. This software, offering fully interactive dose planning for TRT, allows more detailed understanding of the underlying therapeutic mechanisms and patient-specific optimization of treatment outcome. STRATOS also offers flexible analysis options for the development of new drugs in pre-clinical applications. This approach is unique to Philips and will allow novel therapy strategies to be

▶ **Nuclear medicine experts have reacted favorably to this first integrated package.**

▲ Figure 3. STRATOS visualizes the dose distribution of drug molecules for targeted radionuclide therapy.

applied in research. Furthermore STRATOS will allow accurately quantification of I^{131} in three dimensions and the DaTSCAN (Ioflupane I^{123} Injection) currently used in the diagnosis for Parkinson's disease.

Longitudinal follow-up of tumors (BIOSTAR)

Cancer is the second leading cause of death in the US, exceeded only by heart diseases [4]. The costs associated with cancer in 2007 have been estimated by the National Institutes of Health (NIH) to amount to $ 219 billion, of which 60% represents lost productivity due to morbidity and premature death - often due to side effects of cancer treatment or ineffective cancer care. In addition, "variability in the delivery of care leads to systemic errors causing up to 98,000 deaths and costing $ 50 billion a year" [5].

▶ Computer-aided decision support systems have a positive impact on reducing variability in delivery of care.

Computer-aided decision support systems have a positive impact on reducing variability in delivery of care [6]. Early response assessment of cancer therapy is essential in order to adapt the treatment to the patient's specific needs. However, the systems for personalized cancer treatment and management currently available to clinicians are limited in both availability and functionality. The BIOSTAR package supports response assessment using image data from morphological (CT) and molecular imaging (PET). The Standard Uptake Value (SUV) and other functional and physiological parameters of a tumor are tracked over a sequence of PET/CT scans in a sequence of three worksteps.

First, all follow-up studies are aligned using multi-resolution rigid registration. Then, a volumetric segmentation of the lesions is performed using region-growing on the PET data. Finally, the lesions are tracked via rigid registration and local block matching algorithms.

Dementia evaluation (CAD4D)

As a result of improved living standards and medical care, people now live longer than ever before. The average life expectancy for men and women in Western Europe, for example, is already almost 80 years. However, many elderly people are not free from disease. A high proportion of them suffer chronic disease, and one of the most debilitating of these in terms of quality-of-life is dementia.

Dementia currently affects well over 25 million people worldwide, and with the demographic shift towards older populations it is set to reach epidemic proportions unless effective treatments can be found. The cost of today's treatment is already putting massive burdens on healthcare authorities, and the societal impact on patients and their caregivers is immense.

Dementia is the end result of a number of progressive degenerative diseases of the brain. These diseases are associated with changes in brain chemistry that are thought to begin ten or more years before patients begin to suffer symptoms of cognitive impairment. The most common neurodegenerative diseases are Alzheimer's Disease, Lewy-Body Dementia and Frontotemporal Dementia. These three diseases account for around 60%, 15% and 10% of all dementia cases, respectively, and at present they are incurable [7]. Current treatments, such as cholinesterase inhibitors, provide symptomatic relief in the mild to moderate stages of the disease but do not arrest its progression.

Alternative therapeutic options, currently under development, attempt to interrupt the disease process at an earlier stage [8]. There is therefore a growing need for the early detection of neurodegenerative disease and reliable diagnosis of its underlying type. The highly effective blood-brain barrier in the human body makes it currently impossible to detect biomarkers for neurodegenerative disease in blood samples. In vitro analysis of cerebrospinal fluid (obtained via a lumbar puncture) and in vivo FDG-PET imaging (PET using the tracer fluorodeoxyglucose) are therefore used as diagnostic tools. By providing a quantitative indication of the amount of glucose being used to fuel brain activity in different parts of the brain, FDG-PET scans can reveal abnormal brain conditions. However, the resultant FDG-PET images are not easy to interpret. Particularly in the early stages of neurodegenerative disease, it requires the expertise of a highly skilled

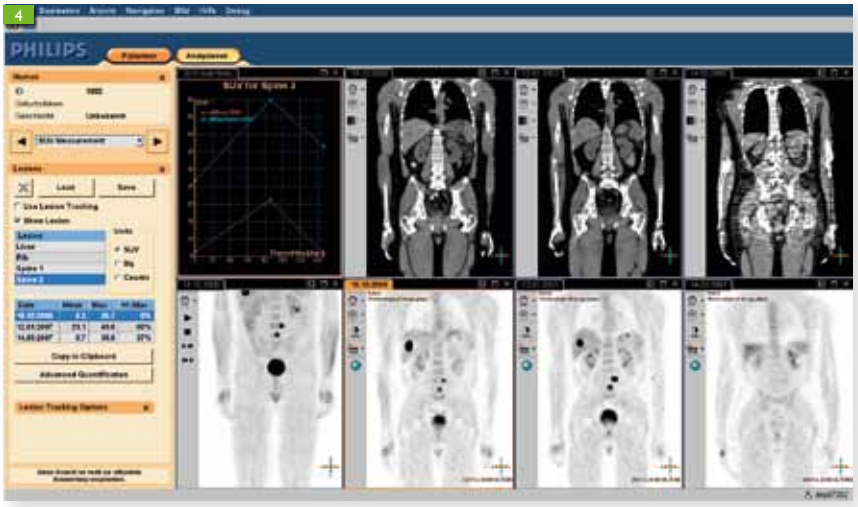
specialist to make an accurate diagnosis. The limited number of such specialists means that an easier, faster and more convenient method is needed to assist clinicians in diagnosing neurodegenerative disease.

The CAD4D package combines advanced image processing and computer learning techniques with a database of reference brain scans, so that deviations from the norm in the FDG-PET images are signaled automatically. Such a system could assist clinicians in the differential diagnosis of neurodegenerative diseases. The system has been retrospectively tested using historical brain-scan images of patients with known disease outcomes [9].

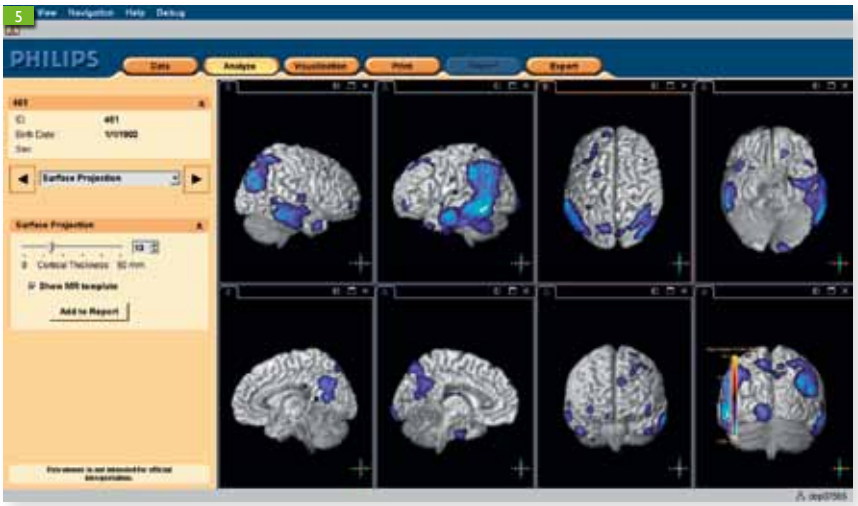
The potential of this computer-aided system to assist clinicians in detecting dementia-related diseases well before patients begin to suffer symptoms could make it a strong therapy monitoring tool, as well as a powerful tool in the development of new drugs to control or cure neurodegenerative diseases of the brain. Many of the new drugs under development are specifically targeted for use in the very early stages of diseases such as Alzheimer's, which means that their efficacy cannot be evaluated by symptom-based studies.

Conclusion

By employing the IMALYTICS Workspace and its Research Packages researchers are able to use novel diagnostic and therapeutic approaches not currently integrated in clinical workstations, without having to work in an exotic computing and software environment. IMALYTICS uses standard, commercially available hardware and standard DICOM tools, backed by Philips Healthcare first line support and scientific back-up from the Philips Research Organization ■



▲ Figure 4. Tracking physiological and functional parameters over a series of PET/CT scans.



▲ Figure 5. Computer-aided evaluation of degenerative brain disease.

References

[1] HighTechNRW Innovation Policy and Research Funding of the State of North Rhine-Westphalia in Germany (*http://www.innovation.nrw.de/forschung_technologiefoerderung/wettbewerbe/Hightech_NRW/index.php*)

[2] CTMM Center for Translational Molecular Medicine (*http://www.ctmm.ml*)

[3] Britton KE. *Radioimmunotherapy of Non-Hodgkin's Lymphoma* (Letter). J Nucl Med. 2004; 45: 924–925.

[4] American Cancer Society: Cancer Facts & Figures 2008, Atlanta, American Cancer Society, 2008.

[5] Weir CJ. *Cluster-Randomized, Controlled Trial of Computer-Based Decision Support for Selecting Long-Term Anti-Thrombotic Therapy after Acute Ischemic Stroke.* J Med 2003; 96: 143-153.

[6] Morris AH. *Developing and Implementing Computerized Protocols for Standardization of Clinical Decisions.* Annals of Internal Medicine. 2000; 132(5): 373-383.

[7] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. *Global Prevalence of Dementia: A Delphi Consensus Study.* Lancet. 2005; 366(9503): 2112-2117.

[8] Villemagne VL, O'Keefe GJ. *Molecular Imaging in Dementia: Journey to the End of the Night.* Medicamundi 2009; 53(2): 41-47.

[9] Sadowski MJ, Schaffer JD, Silfen E. *Towards Improving the Diagnosis of Alzheimer's Disease.* Medicamundi 2010; 54(1): 50-61.