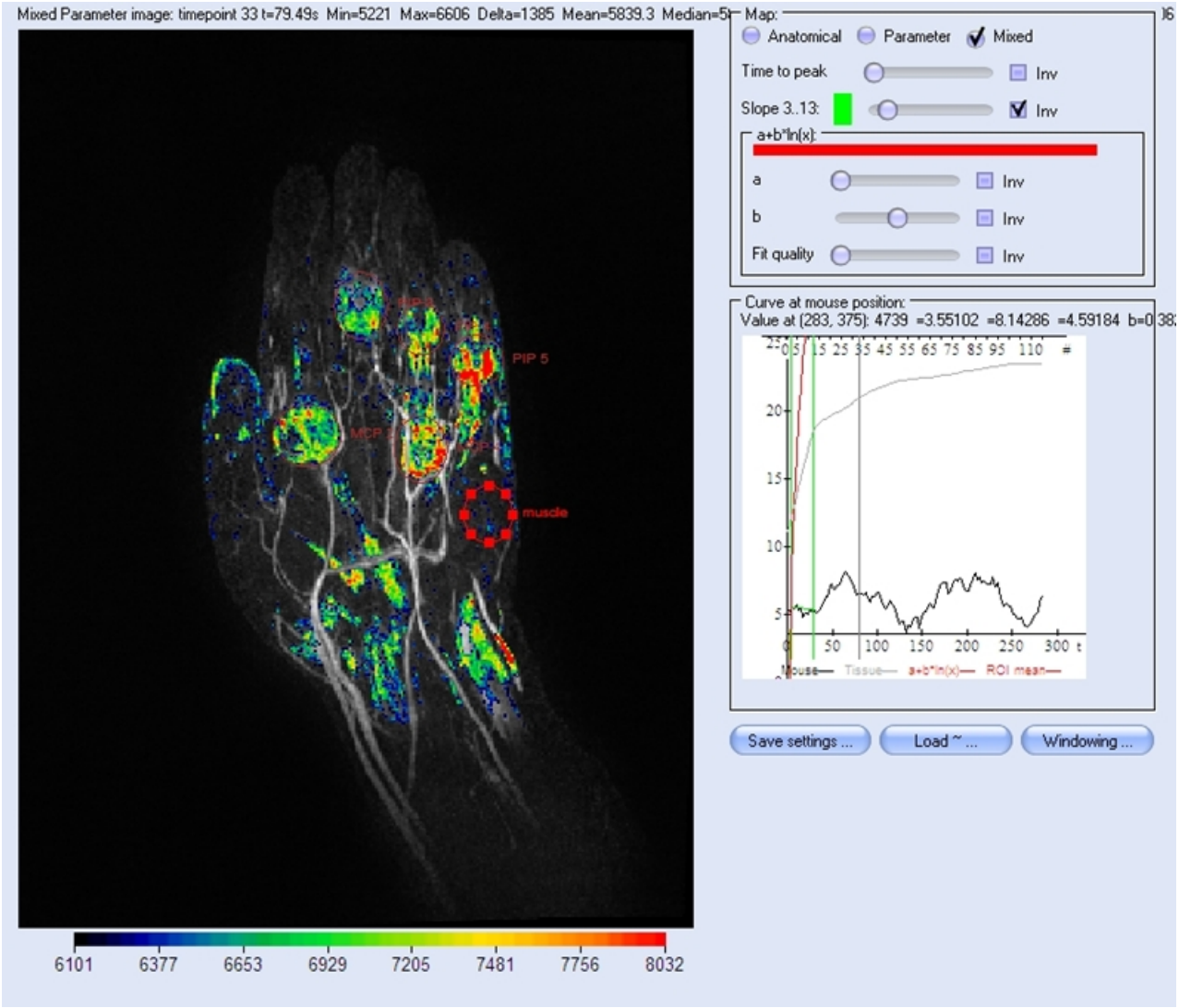
syneed imaging: precise visualisation of functional tissue properties

Functional medical imaging modalities are of great significance in modern medical diagnostics. By delivering information on changes in metabolism and blood flow, they make an important contribution to diagnosing diseases, in particular those of the central nervous system (CNS) such as acute stroke, brain tumours and neurodegenerative diseases such as multiple sclerosis (MS) and Alzheimer's. Existing ways of diagnosing diseases are now being expanded with the arrival of the innovative "parameter imaging method". syneed imaging, a division of the Konstanz-based contract research organisation syneed medidata GmbH focused on medical imaging, uses proprietary, highly sensitive software for the analysis of dynamic image data. This software complements standard methods such as computed tomography and magnetic resonance imaging and increases the significance of image data in clinical trials and therapy decisions.

This company is in the described form no longer active in the market.

The introduction of methods for producing computerised images of healthy and diseased tissue such as magnetic resonance imaging (MRI) and computed tomography (CT) was a quantum leap in radiological diagnostics. Up until now, the clinical application of these methods has been limited to the morphology, i.e. structural information, of the tissue under investigation. However, many diseases require therapy decisions to be made at a point in time when physiological alterations have not yet or only partially manifested themselves in the morphology of the tissue. Functions such as blood flow or nutrient consumption are affected a long time before tissue dies or the size of metastases changes. Therefore, it is not only the area in the brain tissue where a scar will later develop, but particularly the size of the brain areas characterised by a relative decrease in red blood cells (anaemia) that is key in the decision to initiate early stroke therapy, and therefore also in the functional prognosis of a patient. "Diseased tissue has a greater chance of recovering with early treatment," said Isabel Klör, head of drug safety and medical director of the imaging department at syneed medidata GmbH.

More effective contrast agents and high-field imaging systems along with new analytical algorithms now enable the collection and analysis of data relating to tissue function. Special techniques such as perfusion MRI can be used for evaluating blood flow in capillaries and venules; devices combining positron emission tomography (PET) and CT modalities allow doctors to link metabolic defects with a patient's anatomy. Other functional imaging techniques record signalling behaviour over time, thereby allowing information to be deduced on the composition and permeability of the tissue under investigation. syneed medidata GmbH uses an innovative software package that has been specifically developed for such applications. The Konstanz-based company specialises in medical imaging and provides innovative services and software tools for the development of new therapeutics, medical devices and diagnostic products. This specific competence complements the company's service portfolio, making it the only medium-sized contract research organisation in Germany that is able to provide complete solutions from the planning and execution stage to the evaluation of all types of clinical trials, including data management, image data processing and drug safety.



Representation of inflammatory alterations in finger and hand joints. In addition to selecting curve analysis formulas, PIViewer® allows the flexible and user-friendly adaptation of the measurement areas to the data by way of integrated sliders.
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Perfusion MRI is the most common modality for functional parameter imaging and involves the use of modern MR contrast agents. "Perfusion MRI is for example used to examine patients with suspected vascular disorders or oxygen deficiency in the tissue resulting from the blockage or narrowing of blood vessels. Perfusion MRI is commonly used for imaging the brain (e.g. of stroke patients) and the heart (e.g. of patients with myocardial infarction or coronary heart disease), but is also suitable for detecting changes in the lung tissue (pulmonary embolism) and for assessing blood flow in tumours," Dr. Achim Zinggrebe, CEO of syneed medidata GmbH explained.

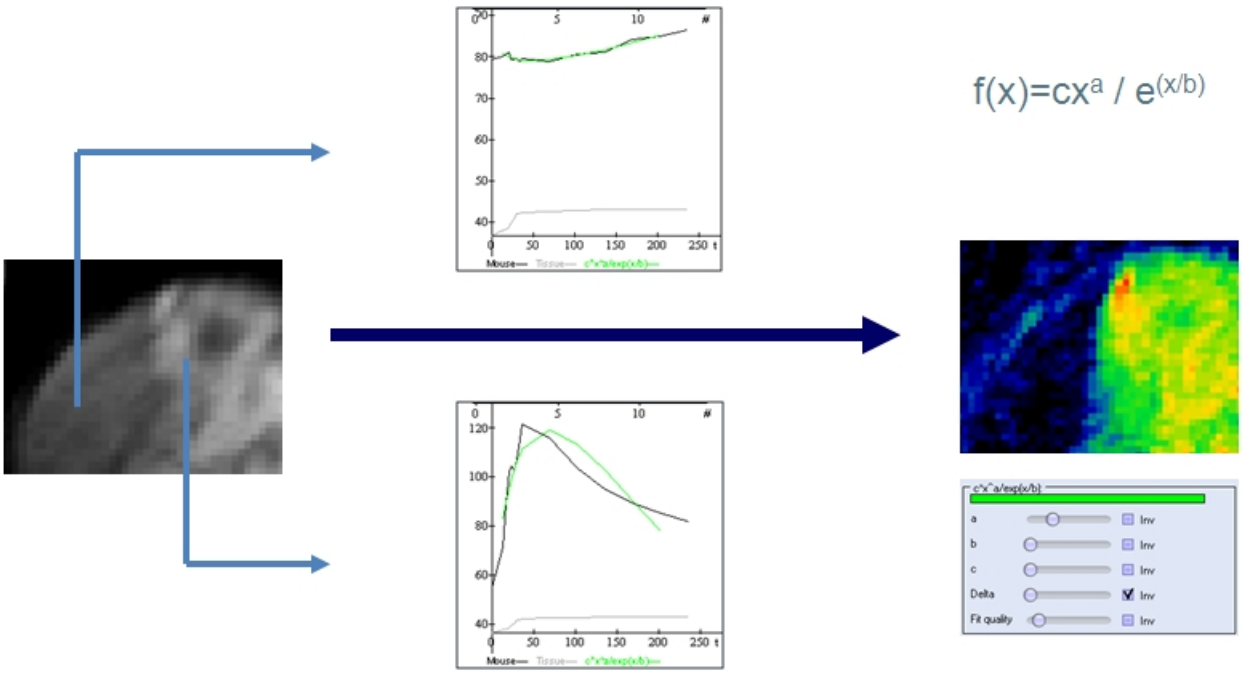
The dynamics of contrast agents is visible in fixed-images

The Parameter Imaging Viewer (PIViewer®) is a proprietary software tool developed by syneed imaging for the parametric analysis of dynamic image data. The analysis tool captures changes in signal intensities following the application of contrast agents, thereby providing information about tissue types and changes. "In contrast to the concentration of contrast agent in the tissue, the concentration of contrast agent in the blood rises rather steeply, but also declines rather quickly," said Dr. Thomas Plath, Director Medical Imaging Services at syneed imaging. Tissues differ in their ability and speed of accumulation and elimination of contrast agents. "PIViewer® represents individual aspects – i. e. parameters – of any image spot of the signalling curve in a particular colour. Much the same as photos taken of buildings with thermal cameras, the parameter imaging method provides visible and measurable information about the specific properties (heat leakage or sites of inflammatory activity) of the tissue being analysed," Plath said.

"Knowledge of the temporal course of contrast agent concentration at a specific location in the body is crucial for calculating such images. This is why CT or MR images are taken from the body section under investigation at intervals of a few seconds over a period of several minutes," Klör explained. "This requires systems that are able to cope with such comprehensive tasks, and systems of this kind have only been available for a few years," Klör added, explaining that effective analysis methods are equally as important. Without them, the results would be barely more informative than a film with changing brightness levels. Software solutions that are able to analyse intensity curves in MR or CT images have been on the market for quite a while. However, the

analysis methods used are based on the implementation of rigid kinetic blood flow models. syneed imaging's individualised software not only uses these methods for diagnostic purposes; the software also enables users to analyse the contrast agent concentration time course with own mathematical models (see figure).

"The 'gamma variate function' is a frequently used mathematical function to describe contrast agent dilution. However, there are cases where this function does not describe the actual physiological data well enough. In such cases, the model does not reflect precisely enough the data that need to be adapted and is therefore unsuitable for the parametric analysis of the whole range of possible clinical constellations," said Plath.



Parametric representation of liver tissue using PIViewer®. Intensity-time curves can be produced from any image point and turned into a parameter image in off-colours (right). Here, the coding aspects of the course of the curve are represented with a freely defined fit function. The parameter image shows the differences between healthy liver tissue (top signalling curve) and metastases (bottom signalling curve) in take up of the contrast agent.
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Quantification of haemodynamic parameters

Parametric imaging brings doctors somewhat closer to their medical ideal of being able to measure functional aspects non-invasively and in real time. Haemodynamics (i.e. blood flow) is one of the physiological functions that can be quantified with the parametric imaging method. "The analysis of images using the PIViewer® software works as follows: First, the concentration of contrast agent in the blood is derived from the signal intensity of the MR images. Then the software calculates the blood flow parameters - blood flow, relative blood volume and median flow-through-time through the tissue, for example - from the concentration of contrast agent in the tissue and in an efferent artery," Klör said.

Application in personalised medicine and anti-angiogenesis

The parameter imaging method is particularly suitable for the development of new therapeutics, medical devices and diagnostic methods. "Clinical data, including the imaging data, that achieve what they set out to achieve, highlight the potential of new therapies and point the way towards further targeted development," Zinggrebe said. "The crux with newer drug substances used for treating cancer is that they have an excellent effect in some patient subgroups, but hardly any in others. This is mainly due to the drugs' specific mechanism of action. Functional imaging provides information on whether a specific treatment scheme is effective or not at a relatively early stage. "This helps save valuable time, especially in cases where one drug proves ineffective and needs to be replaced by a different one," Klör added. For example, a relatively new class of substances, known as angiogenesis inhibitors, does not directly kill the tumour cells. These drugs prevent the growth of new blood vessels, which tumours need in order to grow larger. Klör explains that functional imaging has the potential to detect the success or failure of cancer therapies involving angiogenesis inhibitors much earlier in the treatment process than slice images, which simply provide information about changes in tumour size. In fact, many hospitals, especially larger ones, are already using the innovative parameter imaging method for the differential diagnosis of CNS diseases, in the fields of oncology and

rheumatology. “However, the application of such methods is not yet routine,” Zinggrebe added.

The next milestones in imaging diagnostics

One of the great challenges in MRI perfusion imaging is the inconsistency in the acquisition of data and the complexity of existing post-processing methods. There is therefore great need for standardisation. syneed imaging has initiated a study aimed at standardising perfusion imaging using CNS diseases as the example. This study pools the results from other studies in which MRI data of patients with acute stroke, brain tumours and Alzheimer’s were collected.

According to Isabel Klör, there is an increasing trend towards more effective MRI devices. “More and more study centres have access to high-field (7 Tesla) MRI devices; a growing number of clinical trials involve PET investigations, including the use of PET-MRI which is not yet very common,” Klör said. Magnetic particle imaging (MPI), another novel imaging modality used to perform measurements of local contrast agent concentrations, provides an unparalleled level of anatomical detail. Higher spatio-temporal resolution is a prerequisite for developing functional methods with an increasing level of differentiation. Moreover, the diagnostic meaningfulness of the new methods needs to be compared and validated before the methods can be applied. “However, cost pressures within the health system limit the broad application of cutting-edge imaging methods,” added Zinggrebe.

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