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[MRI quantification of rheumatoid arthritis: Current knowledge and future perspectives](#)

Pages 189-196

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Traditionally, radiography along with standardized scoring methods, such as Sharp, van der Heijde, or Larsen scores have been used to evaluate disease progression. While radiography is considered to be the pivotal method for diagnosing and monitoring structural change, it has been demonstrated powerless in capturing of the primary feature of rheumatoid disease, the synovitis (1). The latest research shows, that modern treatment strategy in rheumatoid arthritis (RA), oriented towards capturing early changes, requires engaging advanced imaging modalities such as MRI and US, as well as the development of highly sensitive to change scoring methods, which can quantify disease progression and patient treatment response.

In the early MR imaging, image contrast was focused on the basic NMR parameters of proton density, such as T1 and T2. Although these show a large variation between different tissues types, they are often non-specific. New MR techniques have the potential to make more specific characterisations of tissue. Imaging the uptake of Gd-based contrast agents is widely used to visualise bone damage and synovial enhancement. By imaging repeatedly and measuring the extent and time of the dynamic uptake and speed and clearance of the tracer, fundamental physiological parameters can be extracted. These parameters are related to blood flow, capillary permeability and the size of the extra-vascular extra-cellular space. These methods provide a framework that can be used to link the physics of MRI signal acquisition and the underlying pathophysiology that governs contrast agent kinetics (2,3,4).

Pharmacokinetic methods rely on a common set of assumptions regarding the properties of the principal compartments and their interactions, but adopt different representations for temporal variations of the contrast agent concentration in the blood plasma. Implementation of these methods in clinical settings is difficult, especially when high spatial resolution and multi-slice coverage are required (5). In clinical practice, it is impossible to assess the accuracy with which pharmacokinetic variables reflect the true underlying changes in concentration of the contrast agent. The accuracy of the estimates will depend on the pharmacokinetic model used and the signal to noise ratio in any individual case (6). This is a particular problem with applications where noise is the dominant, or only, cause of variation of contrast agent concentration (6). Comparative analysis of these methods can be found elsewhere (5,7).

A relative short time ago, the OMERACT MRI collaboration addressed issues reading MRI data analysis and proposed a scoring system, named Rheumatoid Arthritis MRI Scoring System (OMERACT-RAMRIS), (8,9). Synovitis, bone marrow oedema and erosions were defined and quantified using the EULAR-OMERACT-RAMRIS reference atlas, which contains

standardized reference images of the MCP joints and carpal joints and requirements of examination techniques along with detailed protocols. The main drawback of this scoring system is its relative insensitivity to change, due to the rigid boundaries imposed on scores and high dependence on the reader's experience.

In response to that, several computer-aided diagnostic solutions were proposed. Some of them made an attempt to measure the volume of synovium, bone erosion, synovial fluid, and cartilage directly, in cubic or square millimetres in contrast-enhanced or unenhanced images. Such measurements correlate well with the disease activity and have been used as biomarkers. The simplest way to estimate the volume is to outline the anatomy on the post-contrast images and measure the volume. Another approach is to consider the subtraction images and calculate a number of pixels, whose intensity level is above a certain threshold value. This approach of course requires definition of an optimal threshold level.

The reproducibility of synovial volume measurements has been analysed (10,11,12). Intra-observer, inter-observer and inter-scan errors were approximately 5% in the knee and wrist and reproducibility errors were 18%. The studies have shown that small changes in synovial volume are better detectable with volume measurements than OMERACT scoring. Some work has been done looking at erosion volume (12,13), synovial fluid (10,11), and cartilage volume (14). The reproducibility of these methods is good, however inter-observer agreement is poor with little evidence of benefit from training or thinner slices.

Principal component analysis (PCA) and k-means techniques have also been applied for data segmentation (15); however, these methods require initialization and knowledge of the underlying physical procedure, which are often user defined and data dependent.

It should be taken into account that the volume measurements and measurements resulted from PCA-based techniques can be influenced by the dose of the contrast enhancing agent and acquisition parameters. The acquisition protocol as well as patient motion during the examination can affect the edges or borders of tissue of interest. The procedure of outlining the volume is time-consuming and subjective. With the use of efficient software algorithms, the speed of volume measurements as well as accuracy can be significantly increased.

Alternatively, contrast enhancement can be quantified in terms of heuristic parameters such as maximum enhancement (*ME*), initial rate of enhancement (*IRE*), and time of onset of enhancement (T_{onset}). These heuristic parameters have been seen to correlate with pharmacokinetic measurements of inflammation and reflect underlying behaviour of the tissues in response to the contrast agent (16,17,18). In contrast to pharmacokinetic parameters, heuristic estimation is relatively straightforward and fast.

Most such analysis hitherto has examined individual signal intensity curves derived from user defined regions of interest (ROI) analysis (19) or on voxel-by-voxel basis. ROI-based analysis only captures changes within a small region and misplacement of the ROI might result in 20-30% variability in diagnosis (20).

Recently a new fully-automated voxel-by-voxel analysis approach was developed (21). This approach relies on measuring changes, such as *ME*, *IRE*, and *Tonset* on voxel-by-voxel basis and incorporates efficient pre-processing techniques such as registration for patient motion correction. All pixels with dynamic contrast-enhanced MRI studies are classified into 'interesting', e.g. responding to the contrast agent and 'non-interesting', e.g. not enhancing in response to the injection. All signal intensity vs. time curves, located at interesting pixels are then analysed to quantify the height and slope of the enhancement and extract the parameters of *ME*, *IRE* and *Tonset*. To visualize the extent of inflammation, these parameters are presented in the form of the parametric maps, which are 2-dimensional images depicting these parameters. Thus, a parametric map is a 2D representation of a chosen property of interest (e.g. *ME*, *IRE*) superimposed on the anatomy image.

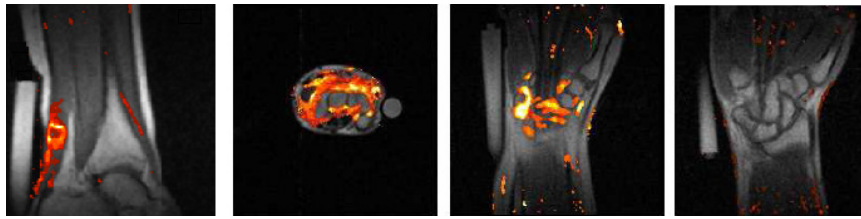


Figure 1: Parametric maps of maximum enhancement acquired from an active patient's tendon, wrist, and hand. At the far right: parametric map constructed for a dynamic slice acquired from a healthy control. Brighter colours (white-yellow) correspond to higher activity, dark red colours - to lower.

This type of display has a number of advantages including an appreciation of heterogeneity of enhancement and removal of the need for selective placement of user-defined ROIs. The risk of missing important diagnostic information and of creating ROIs that contain more than one tissue type is thus reduced.

Further, each of the parametric maps is quantified to provide accurate measurements of disease progression and repose to treatment. These measurements are corrected to patient motion due to incorporation of the motion reduction algorithms.

These functions have been incorporated into the software, Dynamika, which is available for research purposes from www.imageanalysis.org.uk and www.dynamike-ra.com

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