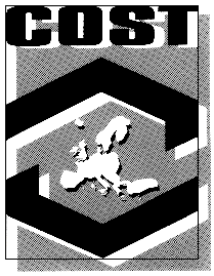


European Cooperation in the field of Scientific and Technical Research
- COST -

Secretariat

Brussels, 19 December 2002

COST 284/02

DRAFT MEMORANDUM OF UNDERSTANDING

Subject :	Draft Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action B21 "Physiological Modelling of MR Image Formation"

Attached is the text of the abovementioned Memorandum of Understanding.

DRAFT

Memorandum of Understanding

For the implementation of a European Concerted Research Action designated as

Memorandum of Understanding

COST B21

Physiological Modelling of MR Image Formation

The Signatories to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the Technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 400/01 "Rules and Procedures for Implementing COST Actions", the contents of which the Signatories are fully aware of.

2. The main objective of the Action is to establish how software technology based on the development of magnetic resonance imaging (MRI), simulation techniques and data processing algorithms can offer a flexible and economically feasible environment for the modelling of tissue physiology.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EURO 3.2 million in 2002 prices.

4. The Memorandum of Understanding will take effect on being signed by at least five Signatories.

5. The Memorandum of Understanding will remain in force for a period of four years, calculated from the date of first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter 6 of the document referred to in Point 1 above.

COST B21

Physiological Modelling of MR Image Formation

A. BACKGROUND

Since its introduction in the mid eighties, the growth in the use of magnetic resonance imaging (MRI) in medicine has been spectacular to the present position where it is widely used throughout the USA, Europe and Japan as a primary diagnostic imaging modality. Indeed, Young (1990) has hailed MRI as 'possibly the most powerful in-vivo diagnostic tool yet discovered' with 'the single most exciting thing about it being its scope'. There is considerable opportunity for further advances in utilisation and efficacy through making full use of *all* the quantitative image information available in MRI experiments and this Action seeks to take advantage of these possibilities, drawing together this data in order to *interpret tissue structure and physiology* in a totally original way as described on page 3.

Current biomedical research (like drug development, genomics or the investigation of the mechanism of many natural and pathological processes such as ageing, cancer or multiple sclerosis), and clinical diagnosis depend more and more strongly on the availability of in-vivo information about local morphology or physiological processes on the cellular level. During the last few years, the development of cellular imaging techniques has introduced the possibility of overcoming some of the underlying problems and establishing new innovative ways of gaining insight into the functioning of living organisms.

The Action will draw on the significant progress made during COST Action B11 ‘Quantitation of Magnetic Resonance Imaging Texture’, extending and developing the work into the fundamental issue of linking NMR and MRI measurements and other complementary image information with tissue structure and function. It also seeks to take full advantage of the effectiveness of the exceptionally strong working partnership developed during B11. At least 80% of the work proposed is entirely new and was not included in B11.

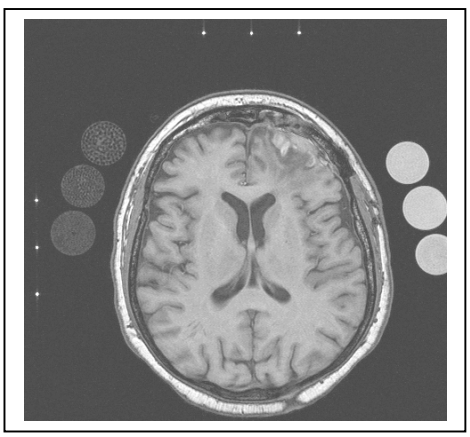
B. OBJECTIVES AND BENEFITS

The main objective of the Action is to establish how software technology based on the development of magnetic resonance imaging (MRI), simulation techniques and data processing algorithms can offer a flexible and economically feasible environment for the *modelling of tissue physiology*. This is an innovative idea which could have a dramatic and exciting outcome, opening up the detailed characterisation of disease processes by MR and other imaging methods. The health benefits to the European citizen could indeed be great and a planned outcome of the work would be a European software product, not existing in the USA or Japan and entirely *ground breaking* in its scope and application.

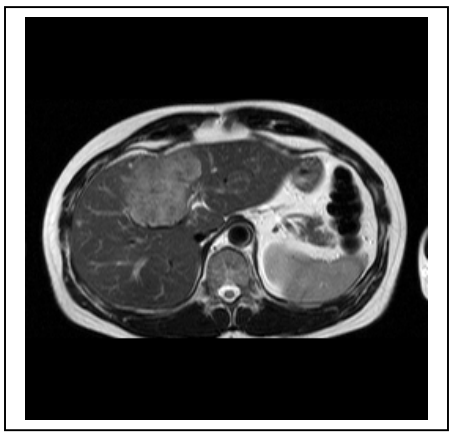
C. SCIENTIFIC PROGRAMME

- Image quantitation

The structure and contrast of MR images depends in a complex way on the underlying tissue structure and function. Different ways of collecting the MR signal (sequences) can draw out particular features and a multi-parameter analysis of the data should allow a full characterisation of tissue pathology and function. This, fundamentally, is the topic of this



Axial brain image



Axial liver scan

new proposal. It aims to understand how the use of multiple MR data acquisitions can map out the underlying physiology of the tissue imaged, exploring both the average signal intensities in defined regions of interest and the inter-pixel relationships or texture in the image.

There are many parameters that MR techniques allow us to measure and the table lists some of them.

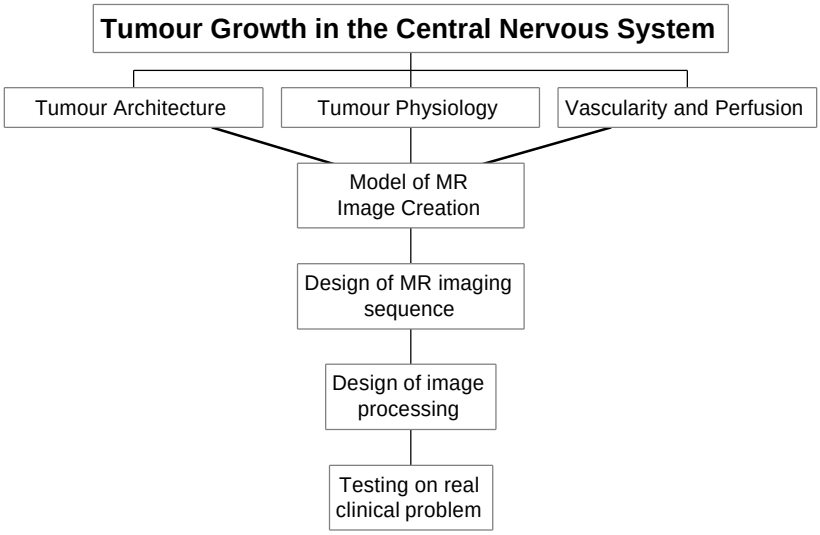
ρ	proton density (Hydrogen nuclei)
T1	spin-lattice relaxation time
T2	spin-spin relaxation time
ADC	apparent diffusion coefficient
CBF	cerebral blood flow
CBV	cerebral blood volume
MTC	magnetisation transfer

It is well known, that MR contrast formation is basically dependent on the local cellular environment of protons, which indicates that this extremely flexible imaging modality could be a basis for cellular imaging. A vast collection of pulse sequences is available measuring a broad range of morphological and physiological properties of living tissues – examples are diffusion or perfusion.

New approaches for tissue characterisation are available from building blocks for MR acquisition techniques and image analysis procedures. However, the collection of those building blocks into an ideal algorithm for the purpose intended is from a limited set of established pulse sequences with no clear design strategy.

The Action will investigate if it is possible *to turn this way of working upside down*. This means, that one would start with formulating the biological or medical goal to be reached in particular clinical problems, based on the current knowledge about related histology, physiology and pathology of the disease. From this knowledge the needs for MRI information would be specified. A possibly generic toolbox covering the areas of image formation (MR physics), biophysical simulation modules and image and signal processing algorithms would then be developed, which

would enable the fast and efficient implementation of a corresponding imaging protocol to achieve the goal. The diagram *illustrates* the proposed procedure in outline (with particular reference to a possible example test application – the central nervous system).



As shown in the diagram, the basic building blocks of the modeling process will include knowledge of the tissue properties and structure, information on physiology and blood flow (including perfusion and diffusion) data. Some of this additional data will come from 'other' imaging modalities, e.g. laser doppler, ultrasound, nuclear medicine. This information feeds into a model of MR image creation based on the phenomenological Bloch equations. This scheme will allow the prediction of the NMR response of the system for the particular physiological changes anticipated (i.e. that are the aim for detection).

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— *Texture analysis*

In addition to these pixel by pixel parameters or Regions of Interest (ROI) averages, it is possible to study the spatial relationship of pixels commonly called the *texture*. This links to tissue microstructure, as investigated under COST Action B11, and will continue to be a part component of this Action in the sense that tissue microstructure and pathology links to texture. What is new here is the extension into 3D texture (see next page).

Computer based methods of texture analysis were originally developed for use in military applications and a very wide range of techniques are in existence. Much basic mathematical work has been performed. These methods are able to increase the level of information extracted from the image - this information being inaccessible to human observation. The output is a series of *texture parameters* representing the texture of the region of interest chosen. Whether this information is useful in discrimination has to be determined for each application studied.

In certain medical imaging techniques, e.g. ultrasound, the *visual* texture is recognised as conveying diagnostic information. In other methods, e.g. X-ray CAT, or magnetic resonance imaging (MRI), its use is not widely established, except in a few key centres. Medical applications of computerised texture analysis date back to the early 1970s and the explosion in the use of digital techniques has led to the possibility of utilising texture analysis for most medical imaging modalities. Typical work has been carried out on chest X-rays (e.g. Desaga et al (1988), Powell et al (1988)), ultrasound (Lerski et al (1979), Raeth et al (1985), Kratzik et al (1988), X-ray CAT (Coleman et al (1982) and MRI (Lerski et al (1993), Schad et al (1993)).

To date the studies carried out, although having demonstrated a good measure of success, have not yet been accepted into routine clinical practice. The current successes demonstrate an ability to extract more diagnostic information from the images than can be done by a human observer. The fundamental content of the work programme is the use of appropriate texture methodologies for the MRI task with their subsequent multi-centre testing as a tool in investigating physiology.

Although the field of 2D texture analysis has been very extensively studied, there has been very little work done in the area of characterisation and estimation of 3D textures, with few notable exceptions. Waksman and Rosenfeld (1993, 1996) specifically dealt with the problem of characterising 3D textures consisting of opaque planar texels uniformly distributed in volume ("snowflakes"). Their main concern was the evaluation of visibility through such a medium for various texel orientation models. In general, extension of 2D methods to 3D has largely been confined to the development of 3D edge detectors (see Morgenthaler (1981)). However, the use of edge detector filters for the estimation of gradients for texture analysis in 3D is hindered by the fact that most edge detection methods assume that they are dealing with isolated edges and they cannot cope with the interference caused by the presence of multiple edges. Liou and Singh (1994) developed gradient estimation operators that are more appropriate for high resolution medical

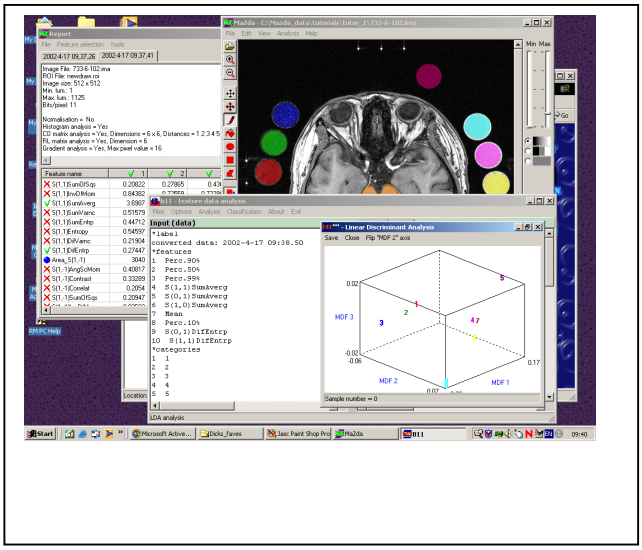
images. In a similar way, when the density of lines is very high, the optimal linear filters (Petrou (1993)) suffer from interference and fail.

Two approaches to the characterisation of 3D textures will be investigated. One based on gradient vectors and one on generalised co-occurrence matrices. They will be investigated with the help of simulated data for their behaviour in the presence of noise and for various values of the parameters they depend on. They will also be applied to MRI volume images characterised by the presence of micro-textures and their potential as diagnostic tools for quantifying and monitoring the progress of various pathologies as discussed. The gradient based method appears to be more appropriate for the characterisation of micro-textures. It also shows more consistent behaviour as a descriptor of pathologies than the generalised co-occurrence matrix approach.

- Image analysis software

A major and significant advance to the possibilities of collaborative image analysis work has been the introduction, within COST Action B11, of the software programme MaZda which runs on PCs of medium to high specification. This has been distributed as a platform on which to perform multi-centre trials of image quantitation and successfully installed at many European centres.

The figure (right panel) illustrates a typical screen with MR image displayed and regions of interest (ROI) defined. This software allows the display of MR images from a whole series of different commercial equipments. ROI can be defined, simple first order parameters measured or standard texture analysis performed and the resultant parameters written to ASCII log file for detailed discriminant and classification studies (as indicated in the figure).



Fundamental to this Action is the need to further refine and extend this platform. The MaZda software will be the *cornerstone* of image analysis necessary in validating the modelling procedures in test MR image acquisition.

Specific Applications

In order to better focus and shape this very generic research, a number of specific applications should be considered to drive the development. For example, a small but comprehensive team of corresponding experts (covering neurology, histology, neuroanatomy, neurophysiology, neuropathology, MR physics, image analysis and biophysical simulation) will investigate the clinical application area of brain tumours implementing problem-specific solutions along the ideas sketched above. Other complementary teams will similarly deal with liver disease and with food quality imaging (an ideal test system where conditions can be easily varied). The opportunities for networking and for adding to the basic research with nationally funded complemetary studies are self apparent.

MR image analysis and numerical methods

With the use of routine clinical MRI expanding from simple anatomical imaging to the investigation of physiological function, there is an increasing need to develop and evaluate more complex pulse sequences. Simulation of such sequences allows their characteristics to be determined in advance of their implementation on heavily-used scanners.

In the isochromat summation (time-domain) simulation method, the evolution of the magnetisation of each spin is followed explicitly throughout the sequence, using the Bloch equations. The "biological sample" is considered as a 2-dimensional array of "spin elements" in the *x, y* plane, with each element having attributes of equilibrium magnetisation, T_1 and T_2 values. RF pulses rotate the magnetisation of each spin element by a specified flip angle about a specified axis, whilst evolution in between RF pulses consists of T_2 decay, T_1 recovery, motion, and the effects of applied gradients. During "sampling", the contribution from all the elements is summed at each sample time step, to form a **k**-space data array. The **k**-space data is finally Fourier transformed to yield an image. The method closely follows the "real" physical processes involved in spin manipulation and signal acquisition, and is inherently suited to the simulation of arbitrary objects. The complete time course

of magnetisation evolution is (in principle) available for every spin element. Magnetic field inhomogeneities, susceptibility effects and non-uniformities of the transmitter and receiver coils are readily incorporated, as are flow and motion.

The drawback of the method is its computational complexity, which scales as the fourth power of the image matrix size. For “proof of concept” calculations of tissue contrast, very small image sizes are acceptable, and simulation may take only a few seconds. However, simulation of 128×128 matrix images typically takes several hours running compiled code on widely available Unix workstations. In certain circumstances (notably the absence of motion), the spin elements behave independently, and the computation is then ideally suited to parellelisation. This may be achieved by manually “farming out” blocks of the simulation, or by implementing the method in a true parallel programming environment running on a cluster of workstations. Anticipated advances in computing power and accessibility should soon enable realistic 3D simulations to be run.

This outline is the basis of the modelling work to be performed.

D. ORGANISATION

It is anticipated that the Action would be organised into three principal Working Groups:

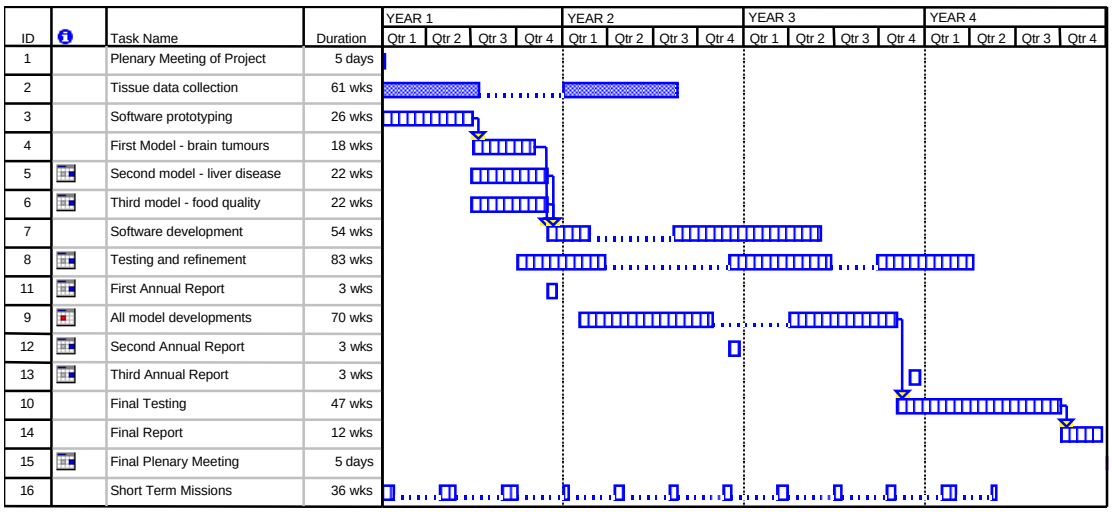
(1) Tissue parameters and physiological data
(2) Software and simulation
(3) Experimental verification and trials

Participants will be allocated to these Working Groups depending on their expertise and the existence of national funding to allow the work to progress. Short-Term Scientific Missions of scientists will aid in the co-ordination of work within the Working Groups. Information will be exchanged via the action Web site and joint seminars will ensure that everyone is well informed as to progress.

E. TIMETABLE

The Gantt chart given illustrates how the work will flow over the anticipated four years of the Action. Key to the progression of work are the Short-Term Scientific Missions.

Physiological Modelling of MR image formation – Gantt Chart



F. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: United Kingdom, Norway, Romania, France, Spain, Belgium, Czech Republic, Hungary, Denmark, Poland, Austria, Germany, Italy, Switzerland.

On the basis of national estimates provided by the representatives of these countries, the economic dimension of the activities to be carried out under the Action has been estimated, in 2002 prices, at roughly Euro 3.2 million.

This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

G. DISSEMINATION PLAN

All output from the Action will be widely published in scientific journals, in conference presentations and finally in a summarising book. An Action web-site will be established and carefully maintained with a part restricted to participants for working documents and a part for public access.