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IDENTIFICATION AND ASSESSMENT OF SUITABLE CONTRAST AGENTS

PRINCIPLES AND PRACTICAL ASPECTS OF CONTRAST AGENTS FOR NMR IMAGING

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Summary. – *Some principles for developing contrast agents for NMR imaging are first presented and discussed. They should involve local modifications of any of the NMR parameters responsible of the density of the image, either the spin density or relaxation times. Spin density modifications require rather different agents and techniques depending upon the nature of the nuclei under observation, protons or less abundant nuclei.*

Induced paramagnetic relaxation offers the easiest way for increasing the contrast between different water compartments. This may be obtained by using paramagnetic metal ions, dissociated or complexed by specific organic ligands, or stable organic free radicals, mainly nitroxides.

The development and the assessment of suitable contrast agents is a three-step process:

– the physical relaxation efficiency on water should first be analyzed in homogeneous then in heterogeneous phases, including living tissues and organisms, in order to estimate the concentration limitations and the importance of relaxation enhancement phenomena associated to the molecular dynamics and chemical exchange processes;

the pharmacokinetics of the agents should then be investigated in animals, and the compounds having specific affinities, metabolic or elimination pathways are selected for experimental imaging. These NMR images in animals can be also compared with those obtained with other techniques if suitable mixed contrast agents are developed;

acute and long term toxicity could be the most important limiting factor for clinical applications. It could depend on the nature of the paramagnetic center, 3d or rare earth ions or nitroxide free radicals, as well as on the structure of its chemical environment.

Riassunto. – *Vengono presentati e discussi alcuni principi per sviluppare agenti di contrasto per la tomografia NMR. Tali agenti dovrebbero comportare modificazioni locali di qualcuno dei parametri NMR responsabili della densità dell'immagine, cioè la densità di spin oppure i tempi di rilassamento. Modifiche nella densità di spin richiedono agenti diversi e tecniche che dipendono dalla natura dei nuclei osservati (protoni o nuclei meno abbondanti).*

Il rilassamento paramagnetico indotto offre il metodo più facile per aumentare il contrasto tra diversi compartimenti acquosi. Ciò può essere ottenuto usando ioni metallici paramagnetici, sia dissociati sia complessati con ligandi organici specifici, oppure radicali liberi organici stabili, soprattutto nitrossidi.

Lo sviluppo e la valutazione di agenti di contrasto opportuni seguono un processo a tre fasi:

– è necessario anzitutto analizzare la capacità dell' agente di alterare il rilassamento dell'acqua in fasi omogenee e in fasi eterogenee, compresi tessuti viventi e organismi, per valutare le limitazioni di concentrazione e il grado di importanza dei fenomeni di aumento del rilassamento associati alla dinamica molecolare e ai processi di scambio chimico;

– si passa quindi allo studio della farmacocinetica in animali e si selezionano i composti che presentano affinità specifica oppure particolari pathways *di metabolismo o di eliminazione. Le immagini NMR in animali possono essere anche confrontate con quelle ottenute con altre tecniche, nei casi in cui si riesca a sviluppare mezzi di contrasto misti;*

– la tossicità acuta e a lungo termine potrebbe essere il maggiore fattore limitante per le applicazioni cliniche. Essa potrebbe dipendere sia dalla natura del centro paramagnetico (ioni della serie 3d o terre rare, oppure radicali liberi quali i nitrossidi) sia dalla struttura dell'intorno chimico.

The spectroscopic character of NMR imaging is responsible for the selectivity of the method with respect to a given (isotopical) nucleus, generally the proton. Furthermore, the intensity of the signal is not simply a function of the volumic density of this nucleus, but also of its relaxation properties. In pratice, the proton density, mainly that of water and fat, varies little among the various organs and from normal to pathological tissues

and the contrast, as defined by differences in the signal intensities for neighbour pixels in the image, may increase dramatically when pulse techniques enhancing the effect of the longitudinal (T_1) and/or transversal (T_2) relaxation times are used selectively, e.g. by inversion-recovery or spin-echo techniques. The clear distinction of white and grey matter in the brain is the best demonstration of the new capability, resulting from a number of parameters, such as the microscopic dynamics of the molecules, chemical exchange or paramagnetic perturbations.

Though these specificities give a non invasive character to the method, the natural contrast may be still too low for a clear distinction of normal and pathological tissues or for the direct visualization of a given physiological compartment. The possibility of increasing artificially the differences in magnetic properties has been considered early, and corresponding "contrast agents" are under development in several laboratories, but still with limited success due to the need of specific vectors and, mainly, to short and long term toxicity problems [1-4]. The identification and the assessment of suitable contrast agents rest on physical principles, chemical syntheses, physiopathological and toxical analyses. Though an empirical approach may overcome some of the difficulties of predicting and interpreting the complex properties of such agents in living systems, an overview of the theoretical and practical problems may simplify the approach.

The principles for the delevopment and use of a NMR contrast agent are comparable only to a limited extent to those for a contrast medium used for classical radiological investigations or for radioactive compounds used in nuclear medicine. They may share some of the problems of physiological target specificity, of selective pathways for distribution and elimination, of toxicity, but their physical efficiency as contrast agent may have rather different origins. It may be proportional to the nuclear spin density artificially introduced or it could depend upon modifications of the magnetic properties of nuclei already present in the organism, mainly by relaxation perturbations.

The first class of compounds includes diamagnetic substances. The largest physical selectivity can be obtained by introducing and observing a second kind of nuclei which is naturally absent or of low (isotopic) abundance in the organism. The best candidate for this multinuclear NMR imaging technique should be fluorine-19 since its resonance frequency is not far (94/100) from that of the proton at a given magnetic field strength, favoring an easy technological development. Some highly fluorinated substances have already been used in living organism, including man, with apparently little toxicological damage. They include mostly fluorocarbons used as oxygen carriers. Other compounds based on natural or synthetic substances heavily substituted by fluorine atoms could be developed and tested.

At the moment, most NMR imaging machines are still mononuclear, observing selectively the protons. Proton-rich substances can be used as contrast agents if high local concentrations can be obtained. Now, the contrast arising from these diamagnetic substances should result mainly from differences in relaxation behaviour as compared to the natural environment. Oils and emulsions, for example, could exhibit *in vivo* relaxation times intermediate between those of mobile physiological fluids (long) and immobilized macromolecules or lipidic membranes (short). They could be injected in a given physiological compartment and followed along their natural metabolic or elimination pathways. The use of diffusible substances of low molecular weight, such as glucose, is more questionable, mostly for sensitivity.

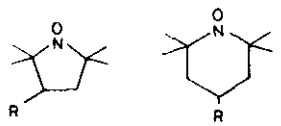
The second class of substances involves the selective perturbation of the relaxation times of nuclei already present in the organism. Since the relaxation of a given nucleus depends on the local magnetic field fluctuations created by motions of neighbour magnetic moments, the best method is to introduce an electron paramagnetic contribution to the nuclear relaxation. The magnetic moment of unpaired electrons is indeed three order of magnitude larger than that of any nucleus. Such paramagnetic species are already present under physiological conditions and contribute to the relaxation of water and lipid protons. They include molecular oxygen, which is paramagnetic in its ground state ($S = 1$) but forms a diamagnetic complex with hemoglobins and myoglobins. Free radicals associated with respiratory and metabolic processes are also present but at low concentrations. Metal ions of the 3d series are also present and can be paramagnetic in some oxidation-reduction states. They are usually complexed at specific sites of macromolecular structures and they are not expected to provide a very efficient contribution to the relaxation of water or lipid protons. However, in some pathological instances this contribution may increase up to a detectable level, e.g. after massive oxydation and degradation of oxygen carrier and storage hemoproteins.

Synthetic contrast agents for proton relaxation enhancement by paramagnetic interactions can be either organic free radicals or metal ions of the 3d or lanthanide series. Stable free radicals could be used directly though it should generally be advantageous to couple them to vector-molecules, either biochemical or synthetic, in order to enhance their efficiency or to control their physiological properties. Direct use of inorganic salts of metal ions which dissociate in water, forming aquo-ions, is conceivable experimentally but leads to serious toxicological difficulties for human purposes. Efficient relaxation of water should require large concentrations which are highly toxic for most of the ions of the 3d series. The lanthanide series offers more secureness. In both cases, metal accumulation may result from use of dissociable salts [5-7].

The metal ions should thus be incorporated within stable complexes. This should be highly profitable also for their physical efficiency. The mechanisms of proton relaxation enhancement are different for free radicals and metal ion complexes and must be considered separately before choosing a definite chemical approach [8-9].

I. Stable free radicals

The most stable organic free radicals are hindered nitroxides of tetramethyl substituted piperidinyl [II] or pyrrolidinyl [I] types,



Their amino derivatives are water soluble (R = NH_2) but they do not present a well defined solvation shell around the nitroxide group where most of the unpaired electron spin is located. The fluctuations of the magnetic field responsible for the relaxation of the proton of neighbour water molecules result mainly from dipolar interactions of the electron spin S and the nuclear spin I modulated by the random relative translational motion of the molecules in the water solvent. Such motions are characterized by a correlation time for translational diffusion τ_D of the order of 10^{-10} to 10^{-11} s. $\tau_D = \frac{d^2}{D}$, where d is the distance of closest approach of the solvent hydrogens and the free radical unpaired electron, assuming a point dipolar model. D is the relative diffusion coefficient,

$$D = 1/2\,(D_I + D_S) \qquad (1)$$

where both diffusion coefficients can be estimated from the Stokes law,

$$D = \frac{kT}{6\pi a \eta} \qquad (2)$$

where η is the solvent viscosity and $a_S + a_I = d$ are the radii of the partners.

The situation of pure interaction by translational diffusion has been treated for the relaxation enhancement of both T_1 and T_2 for the solvent protons. The paramagnetic contribution is given by the following expressions, assuming $\omega_I \tau_D \ll 1$,

$$\frac{1}{T_{1\,para}} = \frac{N_S \gamma_I^2 \gamma_S^2 \hbar \pi}{50\,D\,d}\left[\frac{28}{3} f(\omega_S \tau_D) + 4\right] \qquad (3a)$$

$$\frac{1}{T_{2\,para}} = \frac{N_S \gamma_I^2 \gamma_S^2 \hbar \pi}{50\,D\,d}\left[\frac{26}{3} f(\omega_S \tau_D) + \frac{14}{3}\right] \qquad (3b)$$

where $\frac{2}{15} f(\omega_S \tau_D) = u^{-5}\{u^2 - 2 + e^{-u}[(u^2 - 2)\sin u + (u^4 + 4u + 2)\cos u]\}$

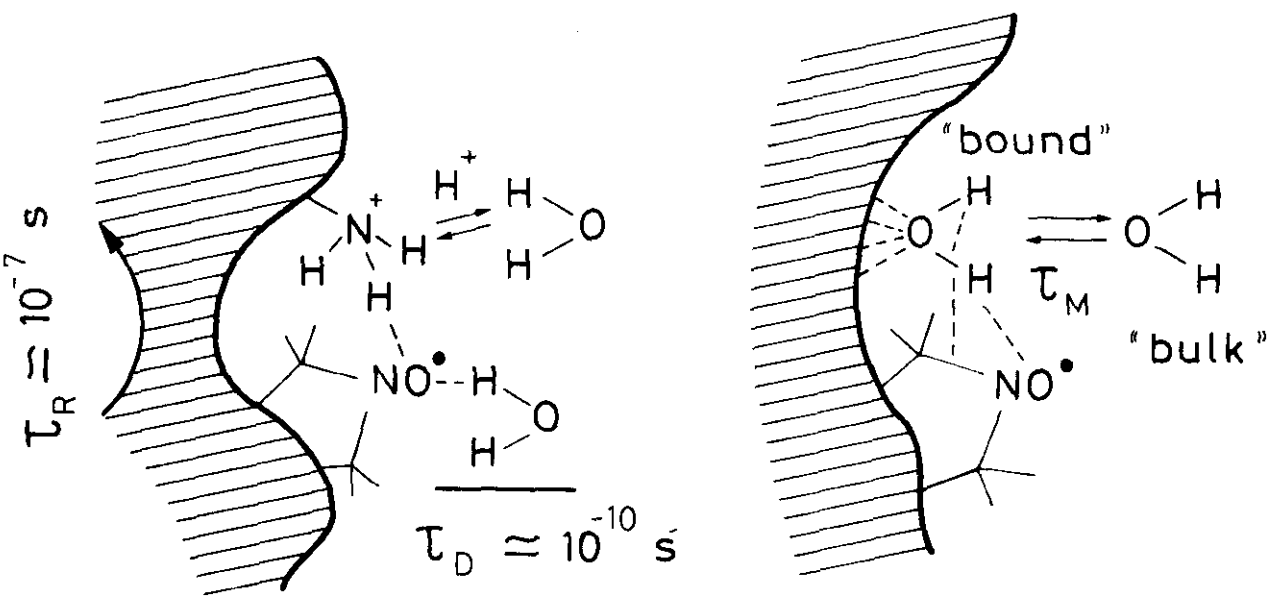
$$u = [\omega_S \tau_D]^{1/2}$$

The numerical analysis of such complex expressions gives us two important conclusions:

– there must be some relaxation enhancement upon immobilization of the nitroxide and the relaxation rates are proportional to τ_D and $1/d^3$;

– the ratio of $T_{1\,para}$ at high frequency ($f(\omega_S \tau_D) \cong 0$) to low frequency ($f(\omega_S \tau_D \cong 1$) is 10:3 and is a good test for the proposed relaxation mechanism.

Generally, this ratio is higher, due to the contribution of other mechanisms. When the nitroxide radical is bound to a macromolecule, either covalently or bi adsorption, there may be a contribution of proton or water exchange due to the presence of groups bearing exchangeable protons or of "bound" water molecules at the surgace of the macromolecule in the vicinity of the nitroxide (Scheme I):



The relevant correlation time for the intramolecular relaxation process for these bound protons is then the rotational time of the macromolecule. For a medium sized protein it is of the order of 10^{-6} to 10^{-8} s, as compared to 10^{-10} to 10^{-11} s for the correlation time for relative diffusion of the isolated free radical in water. This process may have a significant contribution, specially at low frequency. The immobilization of the nitroxide by grafting on a highly hydrophilic polymer matrix can thus result in high relaxation enhancement for the bulk water protons.

Other type of radicals may interact directly with exchangeable protons via a chemical exchange of the unpaired electron. This effect could be very efficient for the relaxation of water for radicals of the phenoxyl or semiquinone type. Even when hindered chemically such radicals are less stable than the nitroxide radicals, but this approach has not yet been explored systematically.

In practice, nitroxide radicals could be coupled to specific vectors. This should increase the water relaxation efficacy, as shown above, and this could physiologically select the affinity for some biological compartment, normal or pathological, or favor specific elimination pathways. Coupling to classical radiological contrast agents could provide mixed contrast agents useful for the comparative evaluation of X-rays and NMR images. Nitroxides as contrast agents for NMR imaging have already been tested with success in animals [2]. Their short-term toxicity appears low, and nitroxides have already been employed in man as radiosensitizers at high concentrations, but there is still some doubt for the long-term toxicity, specially about their cancerogenicity. This point requires an extensive investigation before use in healthy people [10].

II. Paramagnetic Metal Complexes

The solvent relaxation in the presence of metal ion complexes can be schematically summarized as a two-step mechanism, separating the relaxation of the "bound" water molecules, in the first coordination sphere of the complexes, and the contribution of chemical exchange of these "bound" molecules with bulk water (Scheme II).

a) Bound water

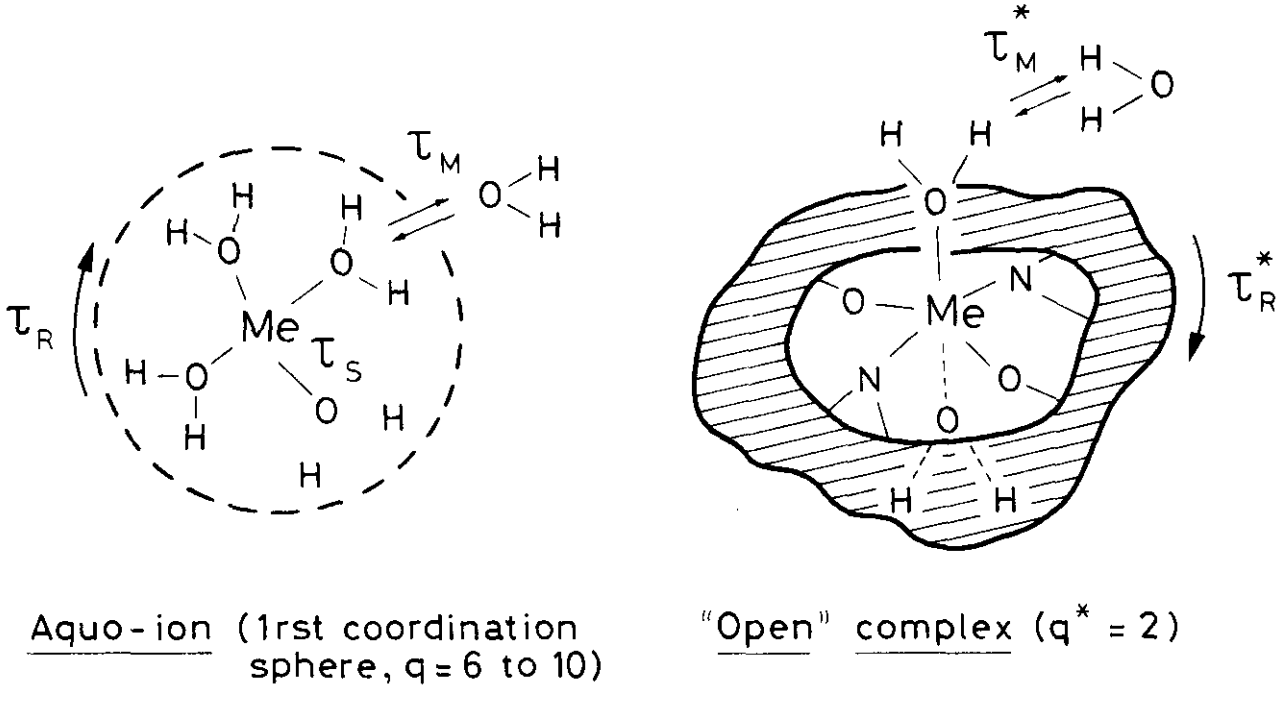
The paramagnetic contribution for intramolecular relaxation for a complex tumbling in solution is given by the Bloembergen-Solomon equations [9],

$$\frac{1}{T_{1M}} = \frac{2}{15} \cdot \frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^6} \left(\frac{3\tau_c}{1}\right) + \frac{2}{3} S(S+1) \left(\frac{A}{\hbar}\right)^2 \left(\frac{\tau_e}{1+\omega_s^2 \tau_e^2}\right) \quad (4a)$$

$$\frac{1}{T_{2M}} = \frac{1}{15} \frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^2} \left(4\tau_c + \frac{3\tau_c}{1+\omega_I^2 \tau_c^2} + \frac{13\tau_c}{1+\omega_s^2 \tau_c^2}\right) + \frac{1}{3} S(S+1) \left(\frac{A}{\hbar}\right)^2 \left(\frac{\tau_e}{1+\omega_s^2 \tau_e^2} + \tau_e\right) \quad (4b)$$

where the first term represents the dipolar contribution due to through-space interaction of the electron spin (assumed localized at the center of the metal ion) and nuclear spin moments ($g^2 \beta^2 S(S+1) = \mu_{eff}^2$). The second term represents the scalar or contact interaction due to direct delocalization of the electron spin on the nucleus and corresponds to the isotropic hyperfine interaction A.

Scheme II



The correlation times characteristic for these two types of interactions are different. They are respectively

$$\frac{1}{\tau_c} = \frac{1}{\tau_s} + \frac{1}{\tau_M} + \frac{1}{\tau_R} \qquad (5a)$$

$$\frac{1}{\tau_e} = \frac{1}{\tau_s} + \frac{1}{\tau_M} \qquad (5b)$$

where τ_R, τ_M and τ_S are the correlation times for rotation of the whole complex, the residence time of the water molecules within the first coordination sphere and the electronic spin relaxation time.

A large temperature dependence is expected for the values of these parameters. Depending upon the nature and oxidation state of the metal ion, the relaxation of the bound water protons can be dominated by the contribution of the rotational diffusion of the complex, $\tau_R \cong 10^{-10}$ to 10^{-11} s (Mn(II), Gd(III), Eu(II), Cu(II), V(II)), and the corresponding complexes exhibit large NMR line broadening and are referred as "relaxation probes" or $1/\tau_C$ can be dominated by the electronic relaxation, $\tau_S \cong 10^{-12} - 10^{-13}$ s (Co(II), Ni(II), Fe(II), Fe (III), most Ln(III)) and the corresponding complexes can be used as "shift probes" and are expected to be less efficient for the enhancement of water relaxation, as revealed by line broadening.

The most efficient contrast agents for NMR imaging should correspond to the first category, though this class contains metal ions of the 3d series which are highly toxic. Gd (III) appears therefore as a good candidate.

b) Bulk water relaxation in the presence of chemical exchange

Following the classical treatment of Luz and Meiboom and of Swift and Connick [9], the propagation of the intramolecular relaxation enhancement to the bulk water protons associated to water molecules exchange (or sometimes of dissociated protons) is given by the following expressions

$$\frac{1}{T_{1\,bulk}} \simeq P_M q \times \frac{1}{(T_{1M} + \tau_M)} \qquad (6a)$$

$$\frac{1}{T_{2\,bulk}} \simeq P_M q \times \frac{1}{\tau_M} \cdot \frac{\frac{1}{T_{2M}}\left(\frac{1}{T_{2M}} + \frac{1}{\tau_M}\right) + \Delta\omega_M^2}{\left(\frac{1}{T_{2M}} + \frac{1}{\tau_M}\right)^2 + \Delta\omega_M^2} \qquad (6b)$$

where P_M q in the fraction of water molecules within the coordination sphere, q being the coordination number. T_2 is thus dependent on both the exchange rate and on the paramagnetically induced chemical shift $\Delta\omega_M$ observed upon complexation. Other terms for diamagnetic contributions and outer-sphere effects are generally negligible.

c) Proton relaxation enhancement in large complexes

The above treatment indicates clearly that direct water coordination and exchange is required for an efficient relaxation of the bulk water protons. Very large proton relaxation enhancements could result from the fixation of the metal ion to a macromolecule, due to a large change in the correlation time τ_C for the dipolar interaction.

Considering T_1 in the framework of the Bloembergen-Solomon equations and neglecting outer-sphere effects, the contribution of the "free" metal ions of equation (6a) can be written

$$\frac{1}{T_{1\,bulk}} = \frac{M_t}{N_p} \; q \; \left(\frac{1}{T_{1M} + \tau_M}\right) \qquad (7)$$

where N_p is the water concentration (55M), M_t the total metal concentration and q the coordination number for the aquo-ion.

When the metal is bound to a large molecule, but still in exchange with the solvent,

$$\frac{T}{T^*_{1\,bulk}} = \frac{M_b}{N_p} \; q^* \left(\frac{1}{T^*_{1M} + \tau_M}\right)_{bound} + \frac{M_f}{N_p} q \left(\frac{1}{T^*_{1M} + \tau^*_M}\right)_{free}$$

where M_b and M_f are the concentrations of bound and free metal ions ($M_t = M_b + M_f$), and q^* is the coordination number for water molecules to the bound metal ($q^* < q$).

The resulting proton relaxation enhancement upon binding to the macromolecule, $\epsilon^* = T_{1\,bulk}/T^*_{1\,bulk}$ is then,

$$\epsilon^* = \frac{M_b}{M_t} \cdot \frac{q^*}{q} \left(\frac{T_{1M} + \tau_M}{T^*_{1M} + \tau^*_M}\right) + \frac{M_f}{M_t} \left(\frac{T_{1M} + \tau_M}{T^*_{1M} + \tau^*_M}\right) \qquad (9)$$

where the first term is the enhancement contribution of the metal-macromolecule complex and the second that of the aquo-complex for which it has been assumed that there were no changes in the microviscosity of its environment.

In stable organic complexes, the second term is eliminated and $M_b = M_t$. Clearly, the decrease in water coordination number (q^*/q) decreases the relaxation rate of the bulk water, but T_{1M}^* and τ_M^* in the complex can be quite different from the corresponding parameter for the free ion, resulting in a large overall relaxation enhancement, due most probably to a large change in τ_C upon binding.

Similar relations hold for T_1 and T_2, but the enhancement may be different for the two relaxation times. Let us consider two examples:

1) the case of Mn(II) ions bound to enzymatic proteins: τ_C in the free aquo-ion is determined by τ_R ($\tau_C \cong 10^{-11}$ s, q = 6); in the complex τ_C^* is determined by the electron spin relaxation time τ_S^* and the residence time τ_M^* and no longer by the rotational correlation time

τ_S^* . Then, if $\tau_c < 1/\omega_I$ the enhancement for T_2 will be less than that for T_1 because $1/T_{2M}$ is much larger than $1/T_{1M}$ since the scalar term dominates for T_2 and masks the dipolar effect (τ_c is not expected to change significantly upon complexation of the Mn(II) ions to the macromolecule). For complexes of lower molecular weight, τ_R^* may still be the dominant factor in the dipolar interaction, τ_c^*, and the situation may be rather complex, requiring an experimental analysis in a large range of temperature and frequency.

2) in the case of Gd(III) complexes, there is little scalar interaction since the unpaired electrons are deeply burried within the ion. In pure water ($q = 10$, $\tau_M \cong 10^{-8}$ s). $1/T_{1M} \cong 1/T_{2M}$ and the same enhancement is expected upon complex formation for T_1 and T_2, as long as $\tau_c^* < 1/\omega_I$.

The ideal complex for NMR contrast should therefore combine a strong immobilization of the metal ion on a large molecule (τ_R^*) with a free access for water coordination (q^*) and exchange (τ_M^*). Relaxation enhancements of several orders of magnitude may then be observed, even at low concentration, for both T_1 and T_2. Their estimation should take into account the frequency of observation used for NMR imaging (ω_I) and a maximum of relaxation for T_1, which is not expected for T_2, should occur for $\tau_C^* = 1/\omega_I$.

There are also many other reasons for using stable paramagnetic metal complexes, rather than dissociable inorganic salts, associated to their biological properties:

lower toxicity, though the 3d ions remain highly questionable for human use, even if protected in a stable structure;

selectivity for a target organ or tissue and for an elimination pathway;

– possibility of preparing radioactive analogs with isotopes for comparative assessment by NMR and gamma-camera imaging.

The brief survey of the principles of relaxation enhancement by paramagnetic perturbations therefore indicates that the assessment of the complexes used as contrast agents requires an extensive investigation *in vitro*, in a large range of frequency and temperature and on both T_1 and T_2, parallel to the *in vivo* toxicological and physiological studies, before testing in animal, then man, imaging.

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Discussion
Moderator: P. Servoz-Gavin

SERVOZ-GAVIN – I think we are left with a lot of questions about contrast agents. As Prof. Lhoste mentioned, we have a very small bibliography and I think there are many more groups working on contrast agents today than we have publications. It's clear that most people are working in collaboration with Companies and the bibliography is no more than 25 or 30 papers today, most of them being very general, so the literature in this field is rather limited. As we have been seeing since yesterday, NMR has its own intrinsic contrast technical means thanks to the various sequences of pulses we can use. We have been talking about off-resonance experiments very much here, but as you know, with off-resonance experiments we can induce relative variations of T_1 and T_2 contrast. So one of the questions is "is there really a need for chemical contrast agents?": I think this is a question which has not been really answered yet – maybe in some pathological cases, but I think the question is still open, because contrary to other imaging methods, NMR offers a unique technical tool to adjust contrast with rather simple techniques. Another problem which was not mentioned by Prof. Lhoste because he had too short a time is, of course, the role of paramagnetic oxygen which is very important and, as you know, a few experiments have been done. We would like to know more about this aspect.

LHOSTE – I'd like to make a short comment on this problem of oxygen, because it really bothers me. Oxygen is paramagnetic (S = 1 in its ground state) but once it is complexed to hemoglobin oxyhemoglobin or oxymyoglobin it gives diamagnetic complexes. So I think there is a lot of work to do to understand all these effects of oxygenation and to separate the contributions coming from haemoglobin and from oxygen itself dissolved in water.

SERVOZ-GAVIN – Thankyou. So we can now open up the discussion for any questions and comments on this very interesting field, which is complementary to everything we've heard up to now. Of course we have not spoken about contrast agents and their affects in NMR spectroscopy, which is another field. I don't think we can enter into that now. We shall therefore keep ourselves confined to imaging contrast agents.

MARAVIGLIA – To give an idea of how much contrast one can obtain in NMR imaging without the use of contrast media, it is sufficient to remember that the difference in T_1 between grey and white matter is around 20 %.

LUITEN – I'd like to comment on the need for contrast media. It is not the fact that in NMR imaging we have a lack of contrast. It's actually surprising how much contrast can be reached in NMR images. All radiologists would dream of having the contrast we have here. The question is "is it possible that we can do other kinds of examinations we cannot do with NMR, if, in a certain case, the contrast is lacking?" I'm not medically educated, but one of the important problems is the difference between tumours and surrounding oedema, wich is very difficult to see, and by using X-rays in conjunction with contrast media this can be seen. So there you see why it can't be seen in NMR. Another point is, if you want to look at, say, blood streams and perfusion of organs, maybe you could think of a kind of angiography by using fluorides: one way of contrasting it of course is changing the properties of the hydrogen, another way is using another nucleus which replaces the hydrogen. You might say that to add fluorine in this system is not to use a contrast medium. Okay, that's a matter of definition of course. You're talking again about injecting something which gives you a sort of contrast whereas maybe your proton contrast does not. So the point is to make some examinations possible which require a contrast not readily available in the present techniques. I just remember there are a few cases, where the contrast in NMR was less than in CT.

SERVOZ-GAVIN – I think we should also say that the use of contrast agents in NMR leads to a loss of information, of sensitivity first, but also we lose the intrinsic information of relaxation which we have been speaking about for two days. We all agree that we don't understand exactly what it is, but there is some intrinsic information that we lose. The paramagnetic relaxation just short-circuits the nuclear one. We should indeed use contrast agents in a more specific approach, for a very definite pathological problem but not as a universal contrast tool as they are used in other imaging techniques. It seems to me, from what we can read and think, that contrast agents in NMR offer more a complementary approach to many other approaches we already have, mainly technical, to adjust and vary the contrast of the image.

CHAMBRON – Most organs contain protons as water and fat, but in the lung we have air and in this case for NMR you need a contrast agent like fluorinated molecules. I've seen a lot of books on the use of fluorinated gases.

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STANDARDIZATION AND CALIBRATION METHODOLOGY FOR NMR EQUIPMENT

STANDARD PHANTOMS FOR NMR IMAGING EQUIPMENT

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Summary. – *The paper outlines the types of image that might be required in clinical imaging, principally signal amplitude and spin-lattice and spin-spin relaxation and investigates the experimental parameters on which they might depend. Sources of interference, cross-dependence and experimental artefacts are discussed. The types of tests that should be made are reviewed and specifications of ideal standards derived. In the final section some candidates are suggested as sample materials but this list serves as a guide only and is incomplete.*

Riassunto. – *In questa relazione vengono discusse le caratteristiche principali dell'immagine NMR, in relazione soprattutto all'ampiezza del segnale ed ai tempi di rilassamento spin-reticolo e spin-spin e alla loro dipendenza dai parametri sperimentali. Sono inoltre passati in rassegna i diversi* tests *da eseguire per il controllo della strumentazione e discusse le specifiche di* standards *ideali. Nell'ultima parte si propone l'uso di alcuni materiali per la progettazione di campioni standard; è qui proposto un elenco di tali materiali al solo scopo di offrire alcune linee-guida, senza perseguire intenti di completezza.*

Introduction

With the advent of NMR imaging techniques and the potential ready availability of equipment produced by different manufacturers, suggesting an increasing clinical use, the desirability of standardised phantoms being also available to permit a ready comparison of images and results obtained by different operators in different establishments using different equipment is readily apparent. In principle NMR imaging equipment can be used to produce maps giving a spatial resolution in up to three dimensions, of any of the parameters recorded in non imaging NMR experiments on any or several of the available magnetic nuclei. Alternatively, a region within the object under investigation can be *localised* and NMR measurements made upon that. Intermediate situations occur where a plane or line within the object is selected and a two or one dimensional image of that plane or line is produced. Alternatively the images obtained may represent projections onto that plane or line. In general, the image obtained reflects some mixture of selection and projection, the exact mixture depending upon the particular configuration. An extension to the time dimension reveals a comparable situation, the image obtained may ideally reflect a snap shot at a moment in time, or an average over a period of time. In practice it may well be that different parts of the image may correspond to different times. It is always possible that in order to investigate dynamic effects the equipment will be operated to produce an image with time as one dimension. Some of the NMR parameters recorded may be absolute, whereas others will only be relative. In general, all may be subject to experimental artefact. Parameters commonly recorded include the nuclear, usually proton, spin density and the two familiar relaxation times T_1 and T_2, but NMR spectroscopists also record many other quantities, and these are potentially available to the imager.

A problem arises immediately in that different possible idealised modes of operation can be identified. In one the measurement of a given quantity, e.g. signal amplitude, should be independent of the values of the others, e.g. relaxation times, whereas in a second we may wish to "window" and to record the signal amplitude for those components with relaxation times between specified values. Ideally the cut-offs should be sharp and the T_1 and T_2 windows should be readily and independently adjustable in position and width. This was one example and the roles of signal amplitude and relaxation time should be reversible. There is an analogy to the previous paragraph in that the signal amplitude and relaxation times could be considered as analogues of the spatial co-ordinates. The first mode of operation is then equivalent to a projection onto a plane, and the second or windowing mode to a selection. In practice a mixed mode of operation will occur, and the equipment, experiment and measurement will inevitably introduce their own windowing.

A measurement relating to one part of the sample should not exhibit an instrumental dependence upon the properties of any other region, although such a relationship may exist, because of the properties of the sample itself, in which case it should be recorded faithfully. Measurements on "pixels" that are NMR equivalent should give the same value irrespective of their position within the object under investigation. As might have been anticipated these ideals are not attained in practice.

Other complications are that the NMR measurements may not be simple. As an example, the NMR relaxation of biological tissue generally exhibits multi-exponential relaxation giving problems in representation and in the interpretation of windowing type observations. Furthermore, NMR measurements depend upon external factors such as temperature and the strength of the applied magnetic field. Well established theories exist which permit measurements made on simple systems, pure liquids and solutions of small molecular weight solutes, at one temperature and field to be transformed to other fields and temperatures. These theories are not applicable to the more complex systems that will be studied by imaging techniques.

The quality of the image and the accuracy of any measurement will depend upon the measurement time, the nature of the experiment, and the quality of the equipment. In this paper attention will be directed towards imaging of the proton spin density and the spin-lattice and spin-spin relaxation properties, and in the causes of non-ideality. Unfortunately the paper will be stronger on the causes than on the cures or even compensations or corrections of the non-ideality.

It soon becomes readily apparent that a single phantom will not be adequate for complete characterisation. Whilst many phantom geometries can be envisaged, a versatile arrangement could comprise a standard magnetically inert object, e.g. a block composed of teflon or some plastic whose protons have NMR relaxation rates outside the effective window range of the instruments. There might well be some merit in utilising a transparent block. The NMR active sample could comprise families of tubes of different diameters containing different materials which could be inserted in the block. The NMR properties of the materials within these tubes could be recorded separately using a conventional NMR spectrometer. The parallel provision of such a spectrometer operating at the same frequency and capable of accepting the sample tubes normally inserted in the inert block would appear to be desirable.

Spatial resolution

Tubes of different diameters would be filled with NMR equivalent material. By adoption of a matrix arrangement with a suitable mark-space ratio, and an examination of a series of images where the tube diameter is successively decreased, the spatial resolution within a plane could be determined. This method is effectively suitable for a planar projection image. For measurements on a selected plane the length of the NMR active material within the tubes could be limited and the position controlled. The position of the plane could be changed by a translation of the block perpendicular to the plane, or by an equivalent movement of the sample tubes. Rotation of the block would serve to change the plane under test. This test could be used for ^1H signal amplitude, or either of the two common relaxations. It will also serve to test the spatial linearity and fidelity of the image and to detect any dependence of the measured value of signal amplitude or relaxation rate upon position.

The spatial resolution may depend upon software or hardware considerations, prominent amongst the latter is the ratio of the applied field gradients to the NMR linear widths (the spin-spin relaxation rate $1/T_2$). Other factors of importance are the linearity of the field gradient in the specified direction and the magnitude of any orthogonal field gradients. The dependence of the recorded signal amplitude upon position within the object depends upon three factors. The first is that the r.f. field produced by a transmitter coil will not be homogenous within the sample volume. The result is that nominal 90°and/or 180°pulses do not have these values everywhere within the sample volume, and hence the nuclear excitation is not equivalent. The second related feature is that the voltage signal induced in a receiver coil by the precessing disturbed nuclei will be a function of their position with respect to the receiver coil. Whilst both of these factors are dependent upon the coil geometry and dimensions, a third factor is sample dependent. Skin depth considerations limit the penetration of the r.f. field into the sample and the detection of any precessing nuclei by an external coil. As the consequence of skin depth considerations an r.f. field is subject to attenuation and phase shifts. The skin depth is dependent upon the bulk electromagnetic properties of the sample and the applied radio frequency, being reduced at higher frequencies. The phantom object proposed earlier would not provide a test model suitable for investigating skin depth effects.

Bulk movement of proton containing material within the sample will have pronounced effects upon image quality and resolution, dependent upon the particular type of NMR experiment and the method of detection. Attempts to detect nuclei that have been excited at one position may fail if they move out of a detection sensitive region, and nuclei within this region which have not previously been excited will also fail to produce signals. The effect of flow can be simulated by passing liquid through the sample tubes, and it is possible to envisage measurements that will be discriminatory in favour of flowing components and allow their rate of flow to be determined.

In the equivalent determination of spatial resolution in the spin lattice and spin spin relaxation images the test object could comprise a matrix of alternating samples. These alternating samples would have the same proton density and spin spin (or spin lattice) re-

laxation but different spin–lattice (or spin–spin) relaxation rates. As before the dimensions of the holders of the two different samples would be reduced until resolution of the separate samples was no longer possible. The spatial resolution obtained will obviously depend upon the values of the relaxation times, especially the spin–spin, involved. No particular difficulty will be encountered in obtaining samples of different relaxation time but the same proton density. However, great difficulty will be experienced when attempts are made to change one relaxation time whilst proton density and the other relaxation time are maintained costant.

Dependence of signal amplitude upon proton density

A series of tubes containing measured stepped amounts of proton containing material of the same relaxation properties could be inserted into the block and the linearity of response determined. To maintain the same overall sample volume it will be necessary to disperse the proton containing material in a magnetically inert host medium. To avoid any possible dependence of signal amplitude upon the relaxation properties the relaxations should remain constant. As both intra– and inter– molecular interactions contribute to the NMR relaxations, this might be difficult to achieve if dispersal is made on a molecular scale, e.g. by utilising mixture of H_2O and D_2O. Hence the heterogeneity of the dispersion should be on a scale somewhat larger than molecular, but significantly less than the spatial resolution of the equipment. It will be necessary to establish that surface effects are not significant within the sample. A possible mechanism for achieving a suitable dispersion is to use a very large number of glass tubes of diameter significantly less than the spatial resolution. Whilst some would contain inert material others would contain protons. In addition there is the possibility of a cross–effect where the calibration might depend upon position within the sample. To test this a combination of the two tests will be necessary.

The equivalent relaxation measurements

To undertake measurements of the linearity of, and to calibrate, a relaxation experiment, samples should be prepared having identical proton spin densities and an identical relaxation whilst the other relaxation (the one under study) is changed in a controlled stepwise manner. Preparation of such samples will be very difficult and one suspects that at this point we do not have the skills to do this on other than an *ad hoc* random basis.

Independence of signal amplitude and relaxation

The signal amplitude inevitably has some dependence upon the relaxation properties of the sample, some of these dependences are inherent in the equipment and others in its operation. To select an example of an equipment dependence it is impossible to record an NMR signal at zero time immediately after a nuclear excitation. The reasons are two fold, firstly an r.f. pulse must have a finite duration and some evolution of the nuclear magnetization due to relaxation will occur during the r.f. pulse itself. Secondly, the application of such a pulse results in receiver saturation, and hence some signal decay has already occurred when observation commences. Various expedients are adopted to attempt to derive the original signal but their effectiveness and appropriateness are dependent upon the relaxation processes involved. An example of an operation dependence is that the resonant nuclear magnetic moments will not have recovered from one experiment before another is undertaken unless a waiting time of several spin– lattice relaxation times is allowed between successive experiments. The consequence of a failure to comply with this condition is that the signal amplitude is changed and usually reduced. In this manner the equipment and the operation effectively impose a relaxation window only between which are measurements possible. To test these effects a family of samples should be prepared having the same proton density but a wide range of relaxation properties. The production of standardised samples becomes critical if window type measurements are contemplated. In principle any combination of our three variables signal amplitude and the two relaxation rates is possible, but in the near future measurements will probably involve signal amplitude measurements and relaxation windows.

Independence of the two relaxation rates

As intimated earlier, whilst care would be needed it would appear feasible to select samples having the same relaxation time but different proton densities. In contrast the corrisponding task of preparing a family of samples, where one relaxation time is constant, whilst the other is changed over very wide limits, is very onerous.

Effect of temperature and frequency on the signal amplitude

Temperature is probably not too important a variable, as most clinical subjects will be examined at body temperature. In general, however, the signal amplitude has a direct dependence upon temperature *via* the Boltzmann factor and indirect ones through a possible temperature dependence of the electromagnetic properties of the coil system, and a temperature dependence of the NMR relaxations which might affect the effectiveness of the relaxation windows. A change in operating frequency has a comparable effect, changing the Boltzmann factor, the electromagnetic properties of the coil and the relaxation properties and hence the window effectiveness.

Factors influencing the relaxation properties

As this topic has been reviewed already in this meeting the discussion will be brief. For pure liquids and simple solutions of low molecular weight solutes, relaxation is reasonably well understood and is describable in terms of the theory originally developed by Bloembergen Purcell and Pound. Relaxation is induced by the oscillating magnetic field experienced by a nucleus as the result of the movement, rotation and translation, of molecules. The spin–lattice relaxation depends upon the components of motions at and at twice the resonance frequency, whereas the spin–spin relaxation has an additional dependence upon the low frequency components of motion. At high temperatures where the correlation frequency of those motions exceeds the resonance frequency, the two relaxation rates are equal, independent of operating frequency and inversely proportional to the correlation frequency. Hence, a knowledge of the relaxation rate at one temperature permits a deduction of the rate at another temperature if the activation energy of the molecular motion is known. Alternatively, a deduction can be made on the basis of the viscosity, or more correctly the microviscosity of the liquid or solution. Spin–lattice relaxation is at its most effective when the correlation frequency is comparable to the resonance frequency. At lower temperatures the dependence of the spin–lattice relaxation rate upon the correlation frequency is reversed and proportional to it, whereas the spin–spin relaxation maintains the inverse proportionality down to lower temperatures. In this region the spin–lattice relaxation rate is inversely proportional to the square of the resonance frequency, so again prediction of relaxation at a different temperature and measurement frequency is possible. Clearly by selection of an appropriate temperature or viscosity, it should be possible to obtain any ratio of T_1 to T_2. In practice limitations occur because more than one type of molecular motion can occur and the spin–spin relaxation attains a limiting value termed the solid line width. In general, by adjustment of temperature or viscosity it is only possible to obtain a T_1 value, a T_2 value or a T_1/T_2 ratio, but not all three simultaneously, unless we are very fortunate. The presence of anisotropic motion and/or a preferential molecular alignment results in additional contributions to the spin–spin relaxation.

Biological systems are generally more complex. At room temperature they may be to the high temperature side of any T_1 minimum but T_1 exceeds T_2, and is frequency dependent. At the T_1 minimum the T_1 to T_2 ratio vastly exceeds the 1.6 value obtained with the simpler system. The frequency and temperature dependences serve to exclude anisotropic motion or preferential alignment as a sole factor. The usual explanation is that the presence of surfaces or slowly moving macromolecules has an inhibitory effect on the motions of adjacent solvent molecules enhancing their intrinsic relaxation rates. However, above the bulk freezing point exchange between adjacent or bound and free or more distant molecules is rapid and population weighted averaged relaxation rates dominated by the bound component are observed. The observed averaged relaxation rates depend upon the relative proportions of the bound and free phases and the mobility of the bound phase. The exchange rate itself is not usually of significance. To explain the observed temperature and frequency dependences it is usually necessary to assume that the bound phase is complex and that a distribution of bound sites exists together with a distribution of bound phase correlation frequencies and intrinsic relaxation rates. Exchange between these sites is still rapid, however. To explain enhanced spin–spin relaxation rates it is convenient to invoke the occurrence of a preferential alignment relative to the surface and/or anisotropic motion. In general, the relationships are so complex that it is not possible to make realistic quantitative estimates of relaxation rates at a different temperature and/or frequency.

Non–exponential relaxation is explained by assuming the occurrence of different regions containing different proportions of bound and free water or bound water with different mobility. It is also necessary to assume that these regions are physically separated by a membrane or by a distance sufficiently great that exchange between the regions is slow. The mobility of the bound phase has two components, one relative to the substrate and the other due to the substrate itself. With small molecular weight substrates the latter dominates but above a certain size becomes insignificant. This can be used to explain the observation that in some aqueous protein gels the water proton relaxation is independent of the state of gelation.

Another contributing factor is a possible exchange with groups on the substrate itself, especially when this is effectively rigid, e.g. locked into a gel. The low substrate mobility gives OH, NH_3 groups, etc. a high intrinsic relaxation rate, and will allow them to dominate the solvent relaxation rate if exchange becomes significant.

Selection of suitable materials for standards

As most clinical NMR imagers will detect water protons, it would be convenient if the standards also contained water. The preparation of standards will not be trivial and hence the standards should be durable and their materials inert. This excludes most biological systems. The materials should be readily available and preferably inexpensive. In order to give short relaxation times it should be possible to select a reasonably rigid substrate and to vary the proportions of bound and free water by changing composition. We are effectively assuming that the equipment relaxation windows are set to exclude any substrate protons. If further reductions in the spin–spin relaxation rate are required it will be necessary to introduce exchange with the substrate protons themselves. The material could be selected to have a suitable number and, if necessary, the exchange rate can be varied by adjustment of the pH value.

In contrast, if it is necessary to produce standards

with reduced T_1 and T_2 values together with a relatively small T_1/T_2 ratio viscous solutions can be employed. If intermediate situations are required, gels containing solutions instead of pure solvent can be utilised. Muscle tissue injected with sugar solutions displays such properties.

All the systems listed below possess all or most of these features and can be considered as candidates. Most have already been subjected to some form of NMR investigation and all show promise:

1) gels of synthetic polymers, e.g. polyacrylamides;

2) systems incorporating cellulose derivatives;

3) porous glasses, e.g. Vycors where the pore size distribution can be changed;

4) zeolites where it is possible to change the cavity dimensions and the number and type of exchanging species;

5) clays.

Conclusions

The establishment of suitable standards will be difficult, but present indications are encouraging. Clearly their establishment is not of utmost priority, as useful clinical information can be derived in their absence. However, if the NMR imaging techniques are to become quantitative the development of standards will become necessary and it is in this context that development work might usefully be undertaken. At that stage interest will move inevitably towards the properties of the materials of the standards.

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SYNTHETIC POLYMERS: A POSSIBLE SOURCE OF PHANTOMS FOR NMR IMAGING

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Summary. — *The preparation of standard calibrated samples for NMR imaging requires inert materials, easily available, and not subject to magnetic hysteresis nor to degradation for long periods of time. Synthetic polymers, either in the solid state or in solution or in a gel form, are a possible source for them. In fact in many polymers it is possible to have T_1 and/or T_2 values in the same range as those of biological tissues. Most studies on synthetic polymers have been however performed at temperatures which are either very low or very high. Moreover very few studies have been performed at variable frequency. It will therefore be necessary to repeat most measurements.*

A great advantage of synthetic polymers is the fact that it is possible to prepare samples of different molecular weight or tacticity. These samples can have T_1 and T_2 covering an almost continuous range of values. Some polymers can form mixible blends in which, simply by varying the composition, it is possible to change the relaxation values. A special caution is due to the fact that in most synthetic polymers more than one relaxation component is present; for instance, in the solids, the cristalline and the amorphous fractions have quite different relaxations. Finally another advantage of synthetic polymers is the extremely high proton (or fluorine) concentration.

Riassunto. — *La preparazione di materiali per la calibrazione degli apparecchi che danno immagini NMR richiede materiali inerti, facilmente ottenibili, non soggetti ad isteresi magnetica né a degradazione per lunghi periodi di tempo. I polimeri sintetici, sia allo stato solido che in soluzione o sotto forma di geli, costituiscono una possibile fonte; infatti per molti polimeri è facile avere valori di T_1 e/o T_2 simili a quelli dei tessuti biologici. La maggior parte degli studi sui polimeri sintetici è stata tuttavia effettuata a temperature troppo alte o troppo basse; inoltre pochissimi polimeri sono stati studiati a frequenza variabile. Di conseguenza molte misure devono essere ripetute.*

Il maggior vantaggio dei polimeri sintetici è che questi possono essere preparati a differente peso molecolare e/o a differente tatticità. Questi campioni possono avere valori di T_1 e T_2 che ricoprono un intervallo di valori continuo. Inoltre alcuni polimeri possono formare leghe miscibili in cui, semplicemente variando la composizione, è possibile variare i valori dei rilassamenti.

Va prestata attenzione al fatto che nella maggior parte dei polimeri sintetici, nel rilassamento è presente più di una componente; per esempio, nei solidi, la frazione cristallina e quella amorfa hanno rilassamenti molto differenti.

Infine un ulteriore vantaggio dei polimeri sintetici è che questi presentano una concentrazione molto alta di protoni (o di atomi di fluoro).

Introduction

Synthetic polymers, both in the solid state as well as in solution or in a gel form, are a possible source of phantoms. In fact, in many polymers, it is possible to have T_1 and/or T_2 values in the same range as those of biological tissues. In the past years a large number of polymers have been studied by NMR techniques, mostly in order to characterize molecular motions.

The main source of literature can be found in two reviews, one devoted to relaxation studies in solution [1] and the other to relaxation studies in solid polymers [2].

I. NMR relaxation in solution

The dominant mechanisms of magnetic relaxation in polymers are local segmental motions, not involving large-scale motion of the chain. This conclusion was achieved through measurement of T_1 as a function of *molecular weight* (M.W.) and *concentration*. In fact above a fairly low critical molecular weight T_1 is independent of chain length. Below this critical molecular weight T_1 increases with decreasing M.W., thus indicating that overall motion influence the relaxation. Such a behaviour has been observed for most synthetic polymers (see Ta-

Table 1. – *Studies of T_1 of various polymers as a function of M.W. D.P. is the approximate degree of polymerization above which T_1 becomes independent of chain lenght*

Polymer	Solvent	Nucleus	D.P.	Frequency (MHz)	Reference
Ethylene oxide	D_2O	^1H	30	60	[3]
Dimethyl siloxane	C_2Cl_4	^1H	400	60	[4]
Styrene	$CDCl_3$	^1H	100	300	[5]
m-and-p-fluorostyrene	$CDCl_3$	^{19}F	120	56	[6]
Methyl-methacrylate	$CDCl_3$	^1H	300	60	[7]
2-6-dimethyl-1, 4-phenylene oxide	$CDCl_3$	^1H	85	60-30	[8]

ble 1). This means also that it is possible to use low molecular weight synthetic polymers in order to achieve longer T_1 in phantoms, when desired. A synthetic polymer whose relaxation parameter show extended molecular weight dependence is the poly (γ-benzil-L-glutamate) [9-10].

Regular polypeptides may adopt in solutions two conformations, helical or random coil, depending on the solvent and the temperature. The hydrogen bonds involved in the helix are responsible for the elimination of segmental motion; thus overall tumbling prevails and its consequence is an almost linear dependence of ^{13}C T_1 *relaxation on molecular weight*. For most synthetic polymers T_1 at room temperature (R.T.) is *independent of concentration* up to 15%molar, in spite of large changes in macroscopic viscosity. For very flexible macromolecules [4], such as poly-dimethyl siloxane, which is a viscous liquid at R.T., T_1 may be *independent of* concentration up to 50% solutions. As the polymer concentration increases, the relaxation times decrease, indicating that segmental motions are hindered by entanglement effects.

Relatively few studies of T_2 have been made, compared with those for T_1. For poly (ethyleneoxide) (PEO) in H_2O and polydimethylsiloxane in CCl_4, the ^1H T_2 is like T_1, independent of molecular weight up to a concentration of 100 mg/ml, but above this rather low limit, T_2 is a decreasing function of molecular weight. The rate of decrease increases with increasing concentration. It generally appears that T_2 is more sensitive than T_1 to both molecular weight and concentration. The difference in behaviour of T_1 and T_2 has been attributed to the presence of slower long-range motions affecting the J(0) spectral density in the expression for T_2. Again, chain entanglements must be avoked.

For some polymers ^1H relaxation times show a marked dependence on *solvent*; see for instance polystyrene in $CDCl_3$, CCl_4, C_6D_{12}, CD_3 -C_6D_5 and hexachlorobutadiene [5]. The reciprocal ^1H T_1 of PEO in a series of halogenated methanes and ethanes linearly increases with solvent viscosity. There are however examples indicating that the situation is rather complex; in fact PEO shows the same ^1H relaxations in water, C_2HCl_5 and α-chloro naphtalene.

Finally, specific solvent effects occur for block copolymers in solvents selective for one component [12]. The most studied synthetic homopolymer up to now is PEO, both in solution as well in the solid state and in the melt. At R.T. and 60 MHz its ^1H relaxation values are shown in Table 2.

Table 2. – *Spin-lattice and spin-spin relaxation times (s) of PEO in solution, at 25°C*

M	C	T_1	T_2
$4x10^3$	0.088	0.455	0.33*
$2x10^4$	0.088	0.420	0.27*
$3x10^5$	0.088	0.430	0.25*
$6x10^5$	0.088	0.445	0.21*
$4x10^6$	0.088	0.430	0.084
$4x10^6$	0.044	0.440	0.195*
$4x10^6$	0.132	0.425	0.072

C grams of polymer per pilliliter of solvent
M molecular weight
T_1 determined by saturation-recovery
T_2 (*) determined by line width measurement
T_2 determined by 90-180 pulse sequence

PEO has been also studied as a function of the frequency at different temperatures [13]; T_1 varies from 50 to 300 ms going from 10^4 Hz to 10^8 Hz. The same polymer, PEO, can form mixible polymeric blends, in which, simply by varying the composition, it is possible to change the relaxation values [14]. See Table 3 relative to ^{13}C relaxation values of the poly(ethylene oxide)/

Table 3. – *Linewidth, relaxation time (T_1) and NOEF for PEO in its blends with PMMA at different temperatures*

% PEO	linewidth	T_1 (S x 10^{-3})	NOEF	
100	1.7	840	1.8	
90	4.0	502	1.5	
80	4.8	488	1.5	T = 90°C
70	5.6	461	1.5	
60	18	345	1.5	
50	19	240	1.5	
100	3	283	1.5	
90	4.5	270	1.4	
80	6.5	246	1.3	T = 60°C
70	6.5	216	1.3	
60	20	198	1.2	
50	27	168	1.2	
100	200			T = 30°C
90	750			
80	50	(+ sharp signal due to C = O of PMMA)		
70	30	(+ sharp signal due to C = O of PMMA)		
60	780			
50	400	(+ observable solid PMMA)		

Line width data ± 5% or less
T_1 data ± 5% (obtained from linear regression of at least 11 experimental points)
NOEF ± 20% (nuclear Overhauser enhancement factor)

poly(methyl methacrylate) (PEO--PMMA) blend.

II. NMR of solid polymers

NMR studies in solid polymers have been developed significantly in recent years [2, 15-17]. This is mostly due to the introduction of the rotating frame experiment. In fact T_1 measurements extend to the ultra-slow region, the dynamic range of molecular motions sensitive to NMR. In solid polymers the translation of raw NMR data into molecular information is not unambiguous. *Complications principally arise from the non-*exponential character of the various magnetization decays, mostly at low temperatures. NMR relaxation data correlate extremely well with dielectric and dynamical mechanical measurements. The satisfactory agreement between the various measurements is typical of most polymers.

In most polymers two and sometimes three different components of the magnetization are usually observed. For instance nuclei in the amorphous region of a semi-crystalline polymer (above its glass transition temperature, T_g) have rather long T_2 values ($\sim 10^{-3}$ s), while the crystalline region may have $T_2 \cong 10^{-5}$ s. For the same polymer only one value of T_1 is usually observed (tipical values 100 ms -1s). These data refer to polypropilene [18], but are rather usual for many polymers above the T_g. By blending non compatible polymers, it is possible to have more than one T_1 component, and as many as four T_1 components [19]. For solid poly(ethylenoxide) (M.W. 30.000) a complete study of T_1 as a function of the frequency has been reported [13], between 10^4 Hz and 10^8 Hz; T_1 values vary between 100 and 300 ms.

Caution is always required in the use of solid synthetic polymers. For example Teflon exhibits specialized motions in the crystalline phase [20]; the two transitions occur at 293°K and 308°K.

In any case, in solid polymers, $T_2 \ll T_1$; tipical values are $T_2 \sim 10^{-3}$ s and $T_1 \sim$ 100ms-1s; when the glass transition occurs at temperatures higher than R.T. the relaxation values are those tipical of the crystalline phase, i.e. $T_2 \sim 10^{-5}$ s and $T_1 \sim$ 1s. It must be noted that the use of plasticizers can lower the glass transition, as observed in poly (dimethylsiloxane) plasticized by nitrogen or argon [21].

In any case before considering solid polymers as a possible source for phantoms, more accurate studies at R.T. and as a function of frequency are required, since most studies have been performed at temperatures extremely low or high, and measurements have almost always been performed at rather too high frequencies.

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Ann. Ist. Super. Sanità
Vol. 19, N. 1 (1983) pp. 173-174

Discussion on specification of relaxation properties required in substances for calibration
Moderator: J. S. Orr

ORR – In discussing and considering substances for calibration of studies of protons, the questions that we must consider for the purpose of this meeting are: what are the prospects for agreement on groupings of particular values of properties that we might desire and what are the prospects for agreement on standard substances with these properties. I would like to ask both M.me De Vré and Dr. Derbyshire whether, if we specify that we wish a substance with a particular spin–lattice relaxation which might be mono– or multi–exponential, with a particular spin–spin relaxation, and with a particular proton density, can they make us such a substance which would be stable and could be sent from one department to another, and from one country to another?

SEGRE – The answer is: yes and no. Yes for T_1, yes for T_2. Maybe the proton density must be changed because if we have the possibility of getting deuterated molecules, so that we can change the concentration without changing the proton density, the answer is yes. With normal molecules you can have only T_1 and T_2, not ρ. I don't think it's such a severe problem.

DERBYSHIRE – I would have thought that if we cannot solve this problem, we are going to meet severe difficulties further along the line. This looks to be a solvable problem, with care.

CHAMBRON – I have a question for Dr. Reisse. You described some ionic conditions of phantoms suitable for the main magnetic field B_0, but another point seems to be important i.e. B_1 the radio frequency field absorption. Indeed the B_1 amplitude, which governs the resonance conditions and the flip angle is affected by the energy absorption due to the ionic conductivity. This effect cannot be negligible in whole body imaging and an image distortion can arise from radiofrequency field inhomogeneity. Do you think it is important to control, for this reason, the conductivity of your samples?

REISSE – Yes, of course, you are certainly right. My feeling is that if you try to have good phantoms, it is better to have water solutions of micro–molecules than, for example, to use polymers in an organic solvent. Even if a solution of agar has probably not exactly the same dielectric properties as a tissue, I am ready to say that it is more similar than an organic solution of a polymer or a glass. So we have not tested this aspect, we have only tested what I have already described, but it is known that these gels have dielectric properties which are not very different from the dielectric properties of biological samples. A great advantage of synthetic polymers and the other systems that Dr. Segre has just discussed is obviously their stability. I have a question for Dr. Segre. What is the best system you suggest to use as phantom?

SEGRE – Polyethylene oxide in water.

REISSE – In water? You have also discussed other kinds of systems during your talk.

SEGRE – By the way, polyethylene oxide has exactly the same relaxation values in water and in α-chloronaphthalene, which is rather annoying. I mean, they are so different.

SAUZADE – I would like to show that the dimension of the sample is very important in the technique of imaging, not only due to the penetration depth of the radio frequency field, as Dr. Chambron said, but also due to the technique of reconstruction. It is very difficult to detect the low frequency spatial field, due to the Fourier transform as well as to the amplifier and to the procedures of sampling your signal, and so on. If you lose some components at the beginning of the decrease in signal, you lose all the low frequency components of the spatial distribution. So to have a small test sample is not the same thing as to make a large sample with a small part with the same T_1 or T_2 and the same concentration. The answer is very different, due to the low frequency of the spatial component of the Fourier transform.

ORR – Yes, perhaps that is really relevant to the design of the phantoms rather than specifications of substances.

SAUZADE – Yes, due to the resistivity, it is very important.

REISSE – I would like to say that it is not a problem to prepare agar solutions in bottles, it is even simpler to prepare large samples than small samples, I am quite sure that the reproductibility would be much better. During our study we have however used small samples in 5 mm tubes.

FOSTER – This is probably more related to the actual design of the phantom, but if you're using agar in the way that you described, by putting it in and then just heating up the entire thing in an enclosed vessel, wouldn't you get some sort of sedimentation of the agar during the heating process, which would give inhomogeneity if you wanted a very large sample, by the time you get the heating to the centre?

REISSE – No, I don't think so. Even in small samples we've never seen that. Of course the preparation of big samples would probably necessitate some precautions, to prepare gels without precipitation.

DERBYSHIRE – Could I make a comment on the problem of agar *versus* agarose. I think that some of Prof. Reisse's problems stem from the use of agar instead of the purified form, agarose. We've done some work on agarose and the related polysaccharides and provided we buy well–characterized sources, i.e. expensive ones, we do get better reproducibility than you were saying.

REISSE – I agree with you, and if we use agar it is effectively because agar itself is not an expensive substance. You can easily prepare macroscopic samples, let me

say, a kilogram of this kind of gel (it's like marmalade). Of course the use of agarose is certainly better with respect to the problem of reproducibility, but the price of agarose is a limiting factor.

ORR – Could we ask Dr. Segre about the costs or the possible costs of polymers that we might use.

SEGRE – Polyethyleneoxide is sold by many companies, in 1 kg bottles. I don't know the cost because it's a material like acetone or distilled water – I mean, the price will be of that order. Molecular weight spans from 200 to some million. I would suggest some caution in using the really high molecular weights because it is not very easy to dissolve them, it requires a month or so. You can increase the concentration in water, but it takes a long time for kinetic reasons. Dimethylsiloxane is not very cheap but I think you can find it in every hospital under the name of silicon rubber. A lot of other materials seem to me to be more interesting than these two, but I haven't done enough measurements, so I really don't know. But generally speaking, polymers are extremely cheap materials.

ORR – Would anyone like to comment on the choice of groupings of NMR properties that they would like in the substances? Would they want a range of substances with a fixed T_2 and different T_1 relaxations, for example?

STYLES – The only thing I'd like to say is that to try and design one phantom that we're going to carry about, put in a machine and expect to get measurements of some ten parameters is ludicrous. We cannot even do that for high resolution spectrometers where we still need a packet of samples. Perhaps what we should do is look at the various parameters and find out a way of measuring one parameter at a time – perhaps we can produce a phantom which will actually be useful for measuring more than one of those parameters, but to try and look at all aspects of performance in one phantom is not realistic. Talking about costs, I think people have got in mind that they are going to come up with some huge body–size phantom, and therefore we are discussing how we would produce that phantom and whether it would be cost–effective. Let's split the problem down into much smaller segments and decide how we can attack each of those separately, because we've got vastly different problems to solve.

ORR – That suggests to me that later on when we have looked at the test objects themselves and there has been discussion, not at this meeting but in the future, on the actual design and details of each kind of test object to measure each particular property, the groupings of properties that would be require for the substances will be clear.

STYLES – I think that if you want to measure, for example, simply the spatial resolution or the purity of geometry, you just take a bucket with a few partitions in it, and you can fill it up with water or whatever. We attack that problem in one way and attack the problems of resolution of T_1, or T_2, or a mixture of these parameters in a completely different way, perhaps on a much smaller scale.

SEGRE – I think that by using the fact that there is a high spin diffusion in polymers, you can just take a large piece of polymer and fill it with other polymers in the space having the proper T_1 and T_2 (for proton density that is not so easy), and simulate a phantom which has a spatial distribution and relaxation properties which are, maybe, of some interest.

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PRACTICAL CONSIDERATIONS IN THE ASSESSMENT OF NOISE–LIMITED MEDICAL IMAGES: WITH SPECIAL REFERENCE TO NUCLEAR MAGNETIC RESONANCE IMAGING

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Summary. – *Nuclear Magnetic Resonance Imaging (NMRI) has reached a stage of development at which the application of scientific methods of image evaluation can assist the further improvement of system performance, help to rationalize design and assist the prospective purchaser to select the device required. In addition the routine application of practical methods of image quality assessment after purchase will help to maintain optimum performance of the equipment throughout its operating life. A variety of methods has been developed to evaluate the range of medical imaging devices currently in use. Some of these methods may be relevant to the assessment of NMRI systems. In this presentation we hope to provide a general introduction to the subject of image quality evaluation with reference to its application to NMRI systems. Hopefully further discussion of the points raised will help to identify those aspects of the NMRI process which will necessitate the development of specialized assessment procedures. Medical images are limited not only by deficiencies in sharpness, grey-scale rendition, and geometrical form but also by the presence of extraneous noise processes. NMR images are no exception.*

Physical methods of evaluating medical images can be broadly divided into two categories; those which are objective and those which are subjective. The former rely on the measurement of certain objective characteristics of the image such as the modulation transfer function (MTF) and the Wiener spectrum. Subjective methods use the results of controlled psychophysical assessments by experienced observers to categorize the quality of images produced. Two particularly useful subjective image evaluation methods are the receive-operating characteristic *and the* threshold-contrast detail-detection *test.*

A fuller appreciation of the concept of image quality requires an understanding of the mechanisms of visual perception. Despite our present rudimentary level of understanding of the visual system, certain general principles of visual function have been identified. These will be briefly described.

The design of test objects suitable for NMR imaging system evaluation will be briefly discussed. Preliminary results obtained with two such test objects will be presented.

Riassunto. – *Le tecniche di immagine mediante Risonanza Magnetica Nucleare hanno raggiunto uno stadio di sviluppo, in cui l'applicazione di metodi scientifici di valutazione dell'immagine possono aiutare a migliorare ulteriormente le prestazioni strumentali del sistema ed a rendere più razionale la progettazione, nonché assistere il possibile acquirente nella scelta dell'apparato. Inoltre, l'applicazione di "routine" di metodi pratici per il controllo di qualità dell'immagine dopo l'acquisto aiuteranno l'utente a mantenere l'apparecchiatura in uno stato ottimale di funzionamento. Diversi metodi sono stati sviluppati per valutare le diverse apparecchiature di produzione di immagini, di uso corrente oggi. Alcuni di questi metodi possono essere interessanti ai fini di un controllo di qualità dei sistemi di* imaging *NMR. In questo lavoro si intende presentare un'introduzione generale alla valutazione della qualità dell'immagine, in relazione alle sue applicazioni all'*imaging *NMR. Ulteriori discussioni sui punti considerati permetteranno possibilmente di identificare gli aspetti del processo di produzione di immagine mediante NMR, che richiederanno lo sviluppo di procedimenti specializzati di valutazione.*

La qualità delle immagini utilizzate in medicina sono limitate non soltanto dalle carenze di nitidezza, di fedeltà nella scala dei toni di grigio e nella forma geometrica, ma anche dalla presenza di meccanismi di produzione di rumore. Le immagini NMR non fanno eccezione.

I metodi fisici per la valutazione di immagini mediche possono essere suddivisi in due categorie: metodi oggettivi e metodi soggettivi. I primi si basano sulla misura di certe caratteristiche oggettive dell'immagine, quali la funzione di trasferimento della modulazione e lo spettro di Wiener. I metodi soggettivi utilizzano i risultati di valutazioni psicofisiche controllate, espresse da osservatori esperti, per classificare la qualità delle immagini prodotte. Due metodi soggettivi di valutazione

dell'immagine particolarmente utili sono il receive-operating characteristic test *e il* treshold-contrast detail-detection test.

Un più pieno apprezzamento del concetto di qualità dell immagine richiede la comprensione dei meccanismi di percezione visiva. Nonostante che il livello attuale della nostra comprensione del sistema visivo sia piuttosto rudimentale, si possono tuttavia identificare alcuni principi generali della funzione visiva, che saranno brevemente descritti.

Verrà infine discussa la progettazione di campioni standard per la valutazione dei sistemi di imaging *NMR e verranno presentati i risultati preliminari ottenuti con due di questi campioni.*

Introduction

Nuclear magnetic resonance imaging (NMRI) has reached the stage of development at which the application of scientific methods of image evaluation will facilitate its further advancement. The need for such methods will become increasingly apparent as more imaging devices become commercially available and are installed in medical imaging departments. The use of image evaluation techniques can help the equipment manufacturer to rationalise their design effort. If all manufacturers were to adopt standardized assessment methods and make the data available this would prove to be of great assistance to the potential customer. In the absence of such a standard metholology each prospective customer may well adopt their own test procedure; this would prove inconvenient for all parties. Given the inherent flexibility of NMRI systems and the incomplete understanding of the mechanisms underlying the images produced, a unified approach to performance testing is at present untenable. It is probable that as the technology matures and the level of clinical experience increases the range of equipment designs and imaging techniques will decrease. Standardized testing may then become a realistic possibility.

In this presentation we will begin to consider what types of measurement technique could be included in an NMR image quality assessment procedure. Objective and subjective methods of evaluating imaging performance are dealt with in separate sections.

I. Objective methods of image quality evaluation

I.1. Background

Medical images are limited not only by deficiencies in sharpness, grey-scale (contrast) rendition, and geometrical form but also by the presence of extraneous noise processes. NMR images are no exception.

Objective descriptors (and methods of their measurement) have been developed which can characterise all the different aspects of imaging performance. Objective techniques can be applied to individual components of the imaging device or to the overall system. These measurement techniques are particularly attractive to system designers as they provide a controlled, accurate, reproducible and quantitative basis for testing imaging performance. Such methods are often less appropriate to the user of the equipment as the more complex objective techniques are difficult to implement under field conditions and require specialised test equipment.

I.2. Absolute calibration of signal sensitivity

The first factor which should be assessed is the absolute calibration of system sensitivity. A regular check of the reproducibility of system sensitivity is essential in clinical operation.

The absolute calibration of X-ray computerized tomography (CT) systems can be checked using test phantoms constructed from material which simulates the X-ray attenuation properties of soft-tissue material, bone, etc. A similar approach may prove successful in NMRI. It is as yet unclear what tissue-equivalent NMR properties the test phantom should simulate. Examination of this important problem along with a consideration of possible NMR phantom materials constitute two of the aims of this Workshop. In NMRI several test phantoms may be required to encompass the range and combination of NMR properties which can be used to generate clinical images.

I.3. Assessment of the grey-scale characteristics of the image

In measuring the grey-scale (contrast) performance similar problems to those outlined in section I.2. are faced. In particular it is as yet unclear of which properties the contrast should be measured. It may be necessary to assess the contrast transfer properties in terms of all the factors contributing to the NMR signal; *viz.* proton density, T_1 and T_2 relaxation times, fluid flow, etc. Alternatively contrast may be assessed in terms of the combination of NMR properties which are found to be clinically most useful. Having selected the contrast properties to be assessed it will then be necessary to select suitable phantom materials and produce accurate methods of producing calibrated increments in NMR signal intensity. The partial volume effect can be used to vary the intensity of NMR signal generated predominantly by proton density. Alternatively solutions of different concentrations of water and deuterium oxide can be used. Schneiders *et al.* [1] have described a method whereby relaxation times can also be varied by doping these solutions with differing concentrations of paramagnetic ions. Unfortunately such a method produces simultaneous changes in both T_1 and T_2 response. Schneiders *et al.* [1] also indicate that more sophisticated chemical combinations which have NMR properties similar to human tissue are under development. Such materials would obviously be very useful in the measurement of absolute sensitivity. Provided a suitable grey-scale test object can be manufactured

various useful imaging characteristics can be examined including contrast amplification (gamma), dynamic range and signal latitude.

As in all medical imaging devices the image display (and archiving) components can have a strong influence on the grey-scale properties. This is due to the high contrast amplification but low latitude of display monitor CRT's and medical recording film. For the purposes of quality control the provision of a linear grey-scale signal generated (say) by the computer can establish that the display component is set-up correctly.

I.4. Assessment of geometrical factors

In NMRI the spatial coordinate system is set up using three orthogonal magnetic field gradients. Inhomogeneities in these field gradients will generate geometrical distortion and possibly image field-dependent variations in image sharpness and signal sensitivity. These distortions may be localized or cover a large proportion of the image field. Non-uniformities in signal level may be produced by field-dependent variations in the sensitivity of the r.f. receiver coil and r.f. attenuation within the subject imaged. The use of carefully designed test objects should enable any distortion processes to be quantified. Given that they remain constant for a particular device it should be possible to compensate for them during the data processing. NMRI devices can define image planes at any orientation within the patient. It will be necessary to assess geometrical performance in the three principal coordinate planes.

I.5. Assessment of spatial imaging performance

The inherent unsharpness of an imaging system degrades image quality in two important respects. Firstly the aesthetic acceptability of a blurred image is low; this is particularly so when unsharpness is combined with a high level of noise in the image. Secondly an observer's ability to discriminate small or fine image details is markedly reduced by the unsharpness of the system.

Each NMRI system will have a characteristic unsharpness. This will largely be set by the magnitude of the field gradient and the temporal width of the data acquisition time. Unsharpness will also be influenced by other NMR properties (*viz.* the T_2 relaxation time) and by any image processing (smoothing or sharpening) algorithms which are applied prior to image display. Inhomogeneities in the magnetic field will also adversely affect image sharpness. Depending on the image reconstruction method patient movement during image acquisition can manifest itself as unsharpness.

The spatial imaging performance of an imaging device is generally described, in frequency space, using the spatial modulation transfer function (MTF). This is the Fourier transformation of the characteristic blur profile (or line spread function) of the device [2]. Two important analytical requirements for the use of the MTF are that the imaging process must be linear and isotropic. The application of the MTF in NMRI was discussed by Schneiders *et al.* [1]. The method developed to measure the MTF of X-ray CT devices is probably the most appropriate for NMRI [3]. In this method the imaging systems response to a discontinuous "edge" stimulus is measured. A suitable test object for use in NMRI would comprise a sharp interface between two materials one a weak NMR signal emitter (say perspex) and the other a strong NMR signal source such as doped water. Judy [3] has shown that the data sampling interval can be improved (reduced) by suitably orientating the interface with respect to the display matrix. Data averaging (parallel to the edge) is required to improve the signal-to-noise ratio of the measurement. The MTF is computed by differentiating the edge spread function (ESF) and Fourier transforming the resulting line spread function. Having measured the system MTF it is then possible to predict the degree to which the image of any other stimulus distribution will be spatially degraded. Several single number indices of unsharpness can be derived from the MTF. The most widely used single figure index is the "high contrast spatial resolution limit" which is a measure of the high spatial frequency limit of the MTF. This is often determined empirically using a suitable resolution test object. In this case the result is affected not only by the system unsharpness but also by the presence of noise in the image. The measurement of spatial resolution limit in NMRI has been discussed by Schneiders [1].

The width of the selected image plane affects both the sensitivity of the NMRI process and also the spatial resolution in the orthogonal direction. In filtered back-projection reconstructed images (e.g. X-ray CT) the partial volume effect of a thick slice section can generate image artefacts. The selected image plane of an NMRI device has an unsharp sensitivity profile. Schneiders [1] discussed this subject at some length and suggested that the NMR sensitivity profiles can be assessed using test methods developed for X-ray CT systems.

I.6. Assessment of noise processes

Radiological images must be generated with the minimum patient radiation exposure consistent with the required level of diagnostic information. Generating an image with a limited number of information carriers (e.g. X-ray quanta) means that the inherent variability in their detection manifests itself as random spatial noise in the image. Noise has a major impact on the ability of an observer to discern the low contrast details which are often of major diagnostic significance. Noise has an obvious effect in obscuring relevant image structures; work at Leeds [4] would indicate that static noise (mottle) is much more powerful in this respect than dynamic noise of the same measured noise power. In addition the presence of noise in an image degrades its aesthetic quality thereby undermining the degree of confidence that the diagnostician has in that image.

The very low intrinsic signal sensitivity of the NMRI process ensures that this too is noise-limited. The various

noise sources which contribute to the low sensitivity of NMRI have been described by McVay [5]. The principle noise sources arise from the random (thermal) movement of charge carriers in the r.f. detector coil and within the object to be imaged. In practice the latter noise source sets the ultimate limit to the sensitivity of the NMRI process. Unlike in radiological imaging the limiting noise source in NMRI is signal-independent. The noise is additively combined with the signal: therefore noise power is independent of grey-scale level within the image. In X-ray CT the standard deviation of the noise process is often used to quantify noise for the purposes of quality control. However the random noise in an image has two important characteristics. its power and its coarseness. The comprehensive method of describing noise is the Wiener spectrum which represents the result of analyzing the power density of the noise into component spatial frequency bands. The Wiener spectrum is the Fourier transformation, not of individual noise traces, but their statistical properties (i.e. their spatial auto-correlation function) [2]. Noise which has a coarse appearance has its power density concentrated at low spatial frequencies. Fine noise on the other hand has a power spectrum that encompasses a wide-band of spatial frequencies. Narrow-band noise has a pseudo-texturized appearance.

The Wiener spectrum of the noise generated by a conventional radiological imaging system is band-limited white noise. i.e. it has constant power density up to the frequency limit of the process. The Wiener spectrum of X-ray CT images on the other hand has a markedly different form due to the spectral modification produced by the filtered back-projection process which largely eliminates noise at low spatial frequencies. The perceptual influence of these two spectral forms are also distinct. Images containing band-limited white noise have a different aesthetic quality to those containing triangular (low frequency deficient) noise. One would also expect that images deficient in low frequency noise would provide a favourable large-detail low-contrast threshold detectability over those limited by white noise [6]. NMRI is unique among medical imaging modalities in that it is possible to generate noise with differing power spectra depending on the image reconstruction process used. NMR images can be produced for example by either filtered back-projection or by the Fourier transformation methods. The resulting images will be limited by triangular and band-limited white noise respectively. These two reconstruction methods may be appropriate for different imaging circumstances where the perceptual requirements are different. For the (relatively) coarse pixel arrays, often used in NMRI the pixel structure itself can contribute a powerful source of noise. Spatial interpolation or image smoothing can alleviate this effect.

Other sources of non-random (structured) noise can occur in computer reconstructed medical images such as X-ray CT, digital radiography, and of course NMRI. These can have a very powerful influence on image quality. Possible sources of image artefact are manifold in NMRI and different image reconstruction methods make them particularly susceptible to different forms of artefact. The problem of artefacts in NMRI has been discussed by Cho *et al.* [7]. The presence of artefact noise is immediately obvious to the experienced observer. The form or pattern of the artefact noise can be used to identify its source. Sensitivity to artefacts can best be judged using suitably designed test objects.

I.7. Assessment of overall imaging performance - signal to noise ratio

Estimates of signal-to-noise ratio [SNR] have been used to compare the image quality produced by a variety of NMR imaging methods [8].

$$SNR \sim \Sigma \cdot [\Delta x \cdot \Delta y \cdot \Delta z] \cdot T_i^{\frac{1}{2}} \qquad (1)$$

where,

Σ is a constant which embodies all factors relating to the magnetic field strength, the sensitivity of the r.f. receiver coil and sample parameters

$[\Delta x.\Delta y.\Delta z]$ is the image pixel volume.

$T_i^{\frac{1}{2}}$ is the effective image acquisition time.

This relation illustrates the extremely unfavourable trade-off between imaging time and spatial resolution in the NMRI process.

Two-dimensional Fourier transformation [2DFT] and filtered back-projection reconstruction (FBPR) represent efficient and practicable methods of producing medical NMR images. Echo-planar imaging represents an efficient method of imaging dynamic physiological and anatomical processes.

Signal-to-noise ratio and/or spatial resolution can be improved by increasing the overall imaging time (*viz.* the number of image samples averaged). In radiological imaging the price of improved image quality is often an increase in radiation exposure level (dose) resulting in an increase in the number of information carriers (X-ray quanta) contributing to the image. In NMRI the price of improved image quality is often an increase in imaging time. Excessive imaging time increases susceptibility to image degradation due to movement unsharpness and/or reconstruction artefacts.

McVay [5] has proposed a figure of merit, S, which takes the effect of imaging time on imaging efficiency into account.

$$S \sim \frac{SNR}{[N \cdot \Delta x \cdot \Delta y \cdot \Delta z] \cdot T_i^{\frac{1}{2}}} \qquad (2)$$

where,

S is the NMRI sensitivity.

N is the number of pixels contributing to the image and T_t is the overall imaging time ($T_t > T_i$).

The difference between T_t and T_i reflects the amount of redundant time in the image production process. T_t includes operational delays due to computation, relaxation processes, gradient switching times etc. [9].

In a recent analysis of the various factors contributing to resolution and signal-to-noise ratio in NMRI Libove and Singer [10] indicated that SNR varies with a

power law dependence on Larmor frequency (of index $\sim 7/4$). The improvement in SNR produced by increased magnetic field strength can be traded against an improved spatial resolution or a reduction in imaging time.

II. Subjective methods of image quality evaluation

II.1. Introduction to the mechanisms of visual perception

The range of objective characteristics of image quality previously described can give only an incomplete evaluation of the image quality as perceived by the human observer. As yet there is no universal formulation which can be used to synthesize the subjective impression of image quality from measurements of these objective characteristics. A comprehensive assessment of image quality must include the perceptual mechanisms of the observer. Despite the present rudimentary level of understanding of the visual system, certain general principles of visual function have been identified.

The human visual system functions as a very sophisticated image analyzing device. It does not function by mapping, point by point, the external image distribution onto an internal perceptual space. If the electrical activity of cells at various stages throughout the visual system is monitored electrophysically, one finds that elemental features of the images are coded by particular cells. At a retinal level the ganglion cells respond to circularly symmetrical regions of the retina; these regions are known as receptive fields. At progressively higher levels within the visual system the receptive field coding becomes increasingly sophisticated. Within the striate (visual) cortex, receptive fields exhibit diverse forms and selectivities. Certain cells are tuned to lines, bars (of various shape and size) and discontinuities (edges) within the visual field. These stimuli may have to be at specific orientations and positions within the visual field and indeed may have to move at a certain speed and direction before maximum cellular response is recorded. It appears that the human visual system functions by abstracting the most significant information from the images and rejecting redundant information.

Psychophysical evidence suggests that the human visual system can be described as a set of parallel medium band-width ($\sim \pm$ one octave) sensory channels tuned to different frequencies within the spatial frequency spectrum. These channels can alternatively be thought of as size-tuned detail detectors. It is conceivable that the receptive field organization measured neuro-electrically and the parallel spatial frequency channel model are alternative descriptions of identical processes.

The overall spatial frequency response of the human visual system, assuming that it is appropriate to apply such a concept, is a function of the adapting luminance and the contrast of the sinusoidal grating stimulus used. At photopic luminances and for very low (threshold) modulation levels the MTF of the visual system appears to have a band-pass characteristic. The attenuation at high spatial frequencies is thought to be due to the combined effects of dioptric unsharpness and possibly spatial integration mechanisms within the visual system. The suppression of the low spatial frequency response may be a manifestation of the excitatory – inhibitory response of the receptive fields. This results in an enhancement of the boundaries between structures within the image and a suppression of areas of homogeneous content.

Electrophysiological recording of neural activity reveals a background of stochastic activity which arises within the visual system itself. This "internal noise" can arise at a variety of sites. Possible sources of this noise include the variability in the number of photons absorbed within the retina and the unreliability in the transmission of electroneural signals synaptic gaps. It is believed [11] that internal noise sets the ultimate limit to the threshold perceptibility of details under noiseless viewing conditions. In medical imaging the limit to threshold detectability is usually set by external noise. However under sub-optimal image display conditions the observers own internal noise processes will contribute. It is believed that the same visual mechanisms function under both the external and internal noise-limited imaging conditions.

There are many diverse models of the function of the visual system at threshold levels of perceptibility; a full review of all these models is not appropriate here. Discussion is restricted to a single type of model which has proved useful in evaluating radiological images. This model [12] is based on the premise that the detection of a visual signal is ultimately limited by external noise, internal noise or a combination of these two. Both the incremental signal and the background noise are integrated by a psycho-physiological sampling aperture of an extent related to the dimensions of the stimulus signal. A signal is "detected" when the response to the signal recorded at a cortical decision site exceeds the standard deviation of the response to noise recorded at that site by a constant factor k_T. This factor is referred to as the threshold criterion. The value of k_T is determined by the false-positive detection rate which the observer is willing to accept. An improvement in threshold sensitivity is achieved by using lower values of k_T; however this improvement must be weighed against the increased probability of a false-positive response and hence, in the clinical context, an erroneous diagnosis.

An important consequence of this size-matched noise integration model is that it is the power of the noise in frequency bands overlapping the spectral content of the signal which limits perceptibility. Confirmatory evidence for this conclusion has been provided by Stromeyer and Julesz [15] in which they investigated the threshold masking effect of band-pass noise of variable bandwidth on the perceptibility of sinusoidal grating signals. Two practical results of this conclusion are worth mentioning briefly. Firstly detail detectability should not be materially improved by reducing (say by image processing) those bands of noise not represented in the signal spectrum. Secondly in the case where the

form of the noise power spectrum differs from the signal spectrum, there is a clear improvement in perceptibility for signals in frequency bands where the noise spectrum is deficient compared with the signal spectrum. A clear example is provided by X-ray CT in which the deficiency in low frequency noise produces an obvious advantage in terms of large-detail low contrast perceptibility.

Threshold detectability (and image quality) is affected not only by the presence of noise but also by the spatial filtering processes of the observer's visual system. Chesters [13] has explained how the localized blur and lateral inhibitory components of the spatial response profile of the visual system degrade small detail and large detail perceptibility respectively. Medical imaging systems exhibit their own inherent unsharpness which manifests itself as a preferential reduction in the visibility of small (or fine) details in the image.

Using the signal-matched noise integration [SNMI] model the process of visual threshold signal detection can be described by the following relationships:

$$S_T(d) \gtrsim K_T \cdot \sigma(d), \tag{3}$$

where the signal

$$S_T(d) = \int_{-\infty}^{\infty} S^*(v,w \mid d) \cdot D(v,w \mid S^*(d))\, dv dw, \tag{4}$$

$$\text{given} \quad S^*(v,w) = S(v,w) \cdot M_E(v,w) \cdot M_I(mv,mw), \tag{5}$$

and $S(v,w)$ is the Fourier spectrum of the input signal,
$M_E(v,w)$ is the MTF of the external imaging device,
$M_I(v,w)$ is the MTF of the visual system.
$S^*(v,w)$ is the Fourier spectrum of the modified signal received by the detector,
$D(v,w|S^*(d))$ is the Fourier spectrum of the signal-matched detector,
(v,w) are the spatial frequency coordinates
m is a scaling factor related to viewing distance.

The noise is given by

$$\sigma^2(d) = \int_{-\infty}^{\infty} [W_E(v,w) \cdot |M_I(v,w)|^2 + m^2 \cdot W_I(mv,mw)] \cdot |D(v,w|S^*(d))|^2 \, dv\, dw \tag{6}$$

where $W_E(v,w)$ and $W_I(v,w)$ are the Wiener spectra of the external and internal noise processes.

Clearly threshold detail perceptibility is limited by the same factors which are used to describe objective image quality. Quantitative psychophysical trials have been used to assess the imaging capabilities of radiological imaging equipment for several decades. The major advantage of this approach is that the function of the visual system is naturally included in the assessment. It is possible to maximize the sensitivity of the measurement to the characteristics of the imaging device [M_E (v,w) and W_E (v,w)] by allowing the observer a free range of viewing conditions and by optimizing the display conditions such that the contribution of internal deficiencies [M_I (v,w) and W_I (v,w)] are minimized.

II.2. Subjective methods of evaluating medical images

a) The Receiver Operating Characteristic (ROC)

The ROC method is based on statistical decision theory and signal detection theory [14]. Its application in radiological image assessment was described by Goodenough [15]. Recently Swets [16] has recommended the use of ROC analysis as a rigorous method of comparing the merits of different imaging modalities such as nuclear scintigraphy and X-ray CT. This method may prove particularly appropriate to the assessment of NMRI as the complex nature of the NMR signal and the difficulty of rigorously defining it should not prove a drawback. ROC analysis is primarily concerned with the response domain rather than the stimulus domain, therefore it is possible to obtain meaningful results without rigorously defining the stimulus.

There is a profusion of publications describing all aspects of the ROC method and therefore the subject will not be covered here; certain general points will be discussed however. The major advantage of the ROC method is that (in theory at least) it is insensitive to the natural variations in the subjective threshold criterion adopted by the observer. A comparison of ROC curves should therefore provide a rigorous method of assessing imaging performance independent of any psychophysical bias. A major disadvantage of the method is that a large number of observations (typically 200 or more) are required to generate a single ROC curve. In addition the method does not lend itself to application as a routine image quality evaluation procedure. Furthermore generalizing the conclusions drawn from an ROC curve obtained with a particular type of signal to predict the imaging performance with other shapes, contrasts and sizes of signal is not to be recommended. A comprehensive evaluation of system performance using the ROC method necessitates separate analyses for a range of different signal characteristics. This procedure would be extremely time-consuming and as far as the author is aware has never been attempted.

b) The threshold-contrast detail detectability test [TCDD]

TCDD has proved a useful method of assessing imaging performance in conventional (analogue and digital) radiological imaging [17], X-ray computed tomography [18], nuclear scintigraphy [19] and ultra-sonography [20]. The essential simplicity of this technique means that it can be applied both in the laboratory and under field conditions. A typical TCDD test object, which was designed for application in conventional radiology, is shown in Figure 1. This device comprises an array of disc-shaped details of varying (and calibrated) diameter and contrast. All such test objects, independent of the imaging modality, to which they are applied, embody these features. The test object is placed at the in-

put to the imaging system to be assessed and images are produced under specified experimental conditions. The resulting images are examined by two (or more) trained observers who determine the limit of visibility, or threshold contrast, for each of the detail diameters. The threshold contrast is usually determined by the limitations of the image production process and technical deficiencies within the imaging system itself. The TCDD method relies on the ability of the observer to maintain a constant threshold criterion level throughout the measurement programme. In our experience, threshold contrasts are reproducible within the limits of the expected statistical fluctuations and any small changes in criterion level can be monitored by including reference images in the measurement sequence. When equivocal experimental results are obtained it is advisable to apply a psychophysically more rigorous technique such as ROC analysis.

The variation of image quality (measured by threshold detectability), with signal-to-noise ratio is illustrated in Figures 2 to 4. These images were produced using a conventional radiological imaging system; the SNR was reduced by factors of three and ten respectively in order to produce Figures 3 and 4. The results of a TCDD assessment are normally presented in graphical form. The author favours a graph of "detection index" as a function of detail diameter. Detection index, H(d), is defined as the reciprocal of product of the threshold contrast detectability and detail diameter, *viz.*:

$$H(d) = [C_T(d) \cdot d]^{-1} \qquad (7)$$

Alternatively this result can be expressed as,

$$H(d) = \left[\frac{SNR(d)}{k_T} \cdot \frac{1}{d}\right] \qquad (8)$$

where SNR(d) is the detail SNR obtained by integrating the signal and the noise with an aperture of diameter d. The detection index (image quality) increases as the SNR of the imaging process increases. At very high SNR's however the internal noise of the visual system may limit the degree of improvement in detection index. If, as we believe, the human observer functions as a signal-matched noise-integration detector for a white-noise limited image the detail signal-to-noise ratio improves in direct proportion to the detail diameter. Correspondingly, under idealized circumstances, detection index assumes a constant value defined by the minimum SNR of the image and the threshold criterion level set by the observer(s). In practice the detection index exhibits a characteristic divergence from the ideal for both large and small diameter details. Large detail performance is perturbed by psychophysical processes (lateral inhibition). Small diameter performance is limited by the unsharpness of the imaging system (and conceivably by the unsharpness of the visual system).

The effect of system unsharpness on TCDD performance can be approximated by the relation;

$$H(d,u_s) = \frac{SNR(d)}{k_T} \cdot \frac{(d^2 + u_s^2)^{1/2}}{d^2} \qquad (9)$$

where

$$SNR(d) = SNR \cdot \frac{d}{u_s}$$

and u_s is an estimate of system unsharpness (which for the sake of this discussion is assumed to be circularly symmetrical). Therefore,

$$H(d,u_s) = \frac{SNR/u_s}{k_T} \cdot \frac{(d^2 + u_s^2)^{1/2}}{d} \qquad (10)$$

In NMRI the SNR is proportional to the element volume of the imaging process, *viz.*:

$$SNR \quad \alpha \quad u_s^3$$

Therefore, $$H(d,u_s \quad \alpha \quad u_s \cdot \frac{[d^2 + u_s^2]^{1/2}}{d} \qquad (11)$$

For large diameter details ($d \gg u_s$)

$$H(d,u_s) \quad \alpha \quad u_s \qquad (12)$$

For small diameter details ($d \ll u_s$)

$$H(d,u_s) \quad \alpha \quad \frac{u_s^2}{d} \qquad (13)$$

These relationships embody the trade-off between low contrast sensitivity and spatial resolution which is fundamental to NMRI. Detection index is also sensitive to the Wiener spectrum of the noise. For a triangular noise limited imaging process detection index improves in proportion to the square root of detail diameter for ($d \gg u_s$).

To summarize the TCDD method is sensitive to the type of deficiencies in image quality that are found in NMR images. Given the long image production times the essential economy of the TCDD technique make it, in the author's opinion, particularly appropriate to the evaluation of NMR images. The inevitable trade-off between magnetic field strength, spatial resolution, signal-to-noise ratio (low contrast sensitivity) and overall imaging time in NMRI have been discussed in earlier sections. The production of an NMR image inevitably necessitates a compromise in choosing the values of these (and various other) factors. The author believes that the measurement of the detection index represents a useful basis for assessing the optimum choice of imaging parameters and timing sequences. Weighting the detection index by the reciprocal of the square root of the overall imaging time would enable the efficiencies of different imaging procedures to be compared.

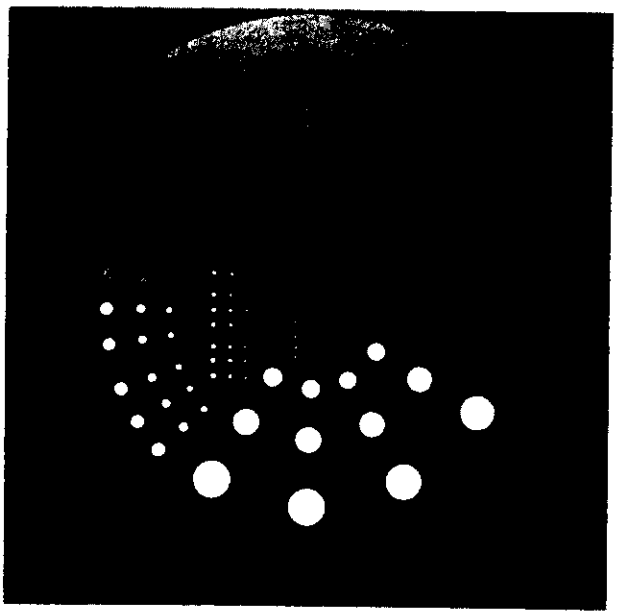

Fig. 1. – A typical TCDD test object designed for application in conventional radiology

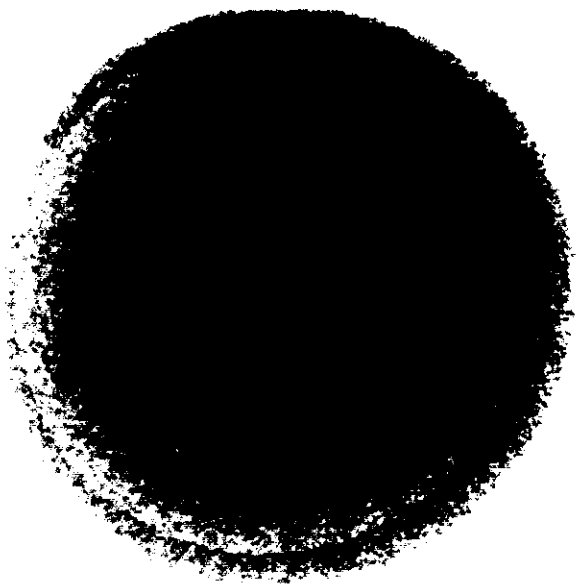

Fig. 3. – Radiological image of a TCDD test object: SNR degraded by a factor 3

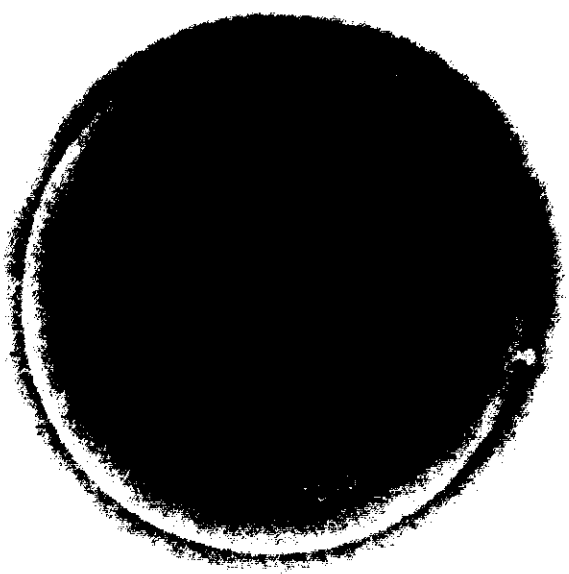

Fig. 2. – Radiological image of a TCDD test object

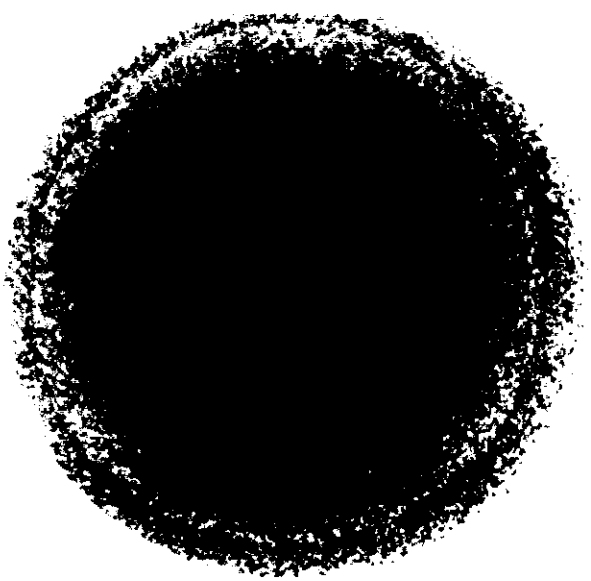

Fig. 4. – Radiological image of a TCDD test object: SNR degraded by a factor 10

III. Design of test objects for assessing the quality of NMR images

III.1. Background

In this presentation a clear distinction is drawn between a 'test object' and a 'test phantom'. The former is understood to be a device for evaluating the physical performance characteristics of NMR imaging equipment independent (as far as possible) from the specific details of the NMR process. On the other hand a 'test phantom' is understood to be a device designed to reproduce the NMR signal response of human tissue and may be designed to simulate human morphology and physiology (i.e. an anthropomorphic test phantom). If it proves feasible to decouple the calibration of NMR characteristics from the assessment of the image, the testing of NMRI systems will be very much simplified.

In designing test objects for assessing a new imaging modality it helps to have previously identified those aspects of imaging performance which need to be assessed. To date practical experience of NMRI is too limited to enable these critical factors to be identified. In the author's experience optimum results are obtained if a set of test objects is used which includes individual pieces designed specifically for each of the performance characteristics to be assessed. However to avoid an unwieldy procedure the number of test objects must be kept to a minimum consistent with the aims of the assessment. Care must be taken not to design single test objects containing too many features. Such devices often prove to be too complex to be practicable and are frequently insensitive to changes in the factors which they were designed to assess.

III.2. Preliminary results

In this final section some preliminary work on the design of test objects for assessing NMRI systems will be described. Initial results obtained on a 0.15 T (resistive) NMRI system will be used to illustrate the text. Two test objects have been produced. Both were constructed from perspex and incorporate a suitable NMR responsive material.

Test object No. 1 was designed to assess the cosmetic quality of the image including the degree of geometrical distortion, the homogeneity of the field and the presence of artefacts. It comprises a chequerboard pattern of materials which produce alternately a high and a low NMR signal response. The sides of each square measure 20 mm and the overall test object measures 24.5 cm at its widest parts. A radiographic image of the test object is shown in Figure 5. The test object was carefully centred and aligned transversely within the body coil of the NMRI chamber. An NMR image was produced using the 2DFT reconstruction method and the spin-echo imaging technique. The resulting data output is shown in Figure 6, which includes the real and imaginary parts as well as the modulus of the image. Certain qualitative conclusions can be drawn about the cosmetic quality of the image by inspecting Figure 7. By using the display cursors quantitative measurements can also be made. In fact this test object may provide a suitable configuration for objectively measuring SNR (and possibly field dependent aspects of image sharpness). This type of test object arrangement may also prove to be useful to the field engineer as it may facilitate adjustment of shimming magnets.

Test object No. 2 is a threshold-contrast detail detectability device. A concentric lay-out was selected to complement the rectilinear arrangement of test object No. 1. The details varied in diameter from 15 mm to 2 mm. Variations in signal intensity (contrast) was produced using the partial volume effect and a suitable selected slice thickness (20 mm). The arrangement of details can be seen in Figure 8, which is an X-ray computed tomogram of the test object. The test object was carefully positioned in the head coil within the NMRI chamber and an image produced using the method described previously. The resulting NMR image is shown in Figure 9. Superimposed on this image is a cursor read-out which can be used to check the calibration of the test object. Despite the fact that the cursor was only approximately aligned with the rows of details it is possible to see that the highest signal intensities have driven the system into saturation. In addition the effect of unsharpness can be seen from the progressive reduction in signal amplitude with reduced detail diameter.

As TCDD test objects are particularly useful for assessing signal-to-noise ratio we have attempted (at least qualitatively) to illustrate this in the context of NMRI. This was achieved using a technique proposed by Luiten [21], who suggested that images ought to be produced using subsequent spin-echoes. As the noise in the image remains constant whilst the signal intensity decays the signal-to-noise ratio is degraded in a systematic way. The resulting deterioration in detail detectability and image quality can be gauged from Figure 10.

Summary and conclusions

A variety of image quality assessment methods, based on both objective and subjective measurements, has been developed to evaluate the range of medical imaging devices currently in use. This presentation aims to provide a general introduction to some of these methods and to advocate the inclusion of image quality evaluation in any performance testing procedure for NMRI. Hopefully further discussions of the points raised will help to identify the techniques which are most relevant to NMRI and those features which will necessitate the development of specialized assessment procedures.

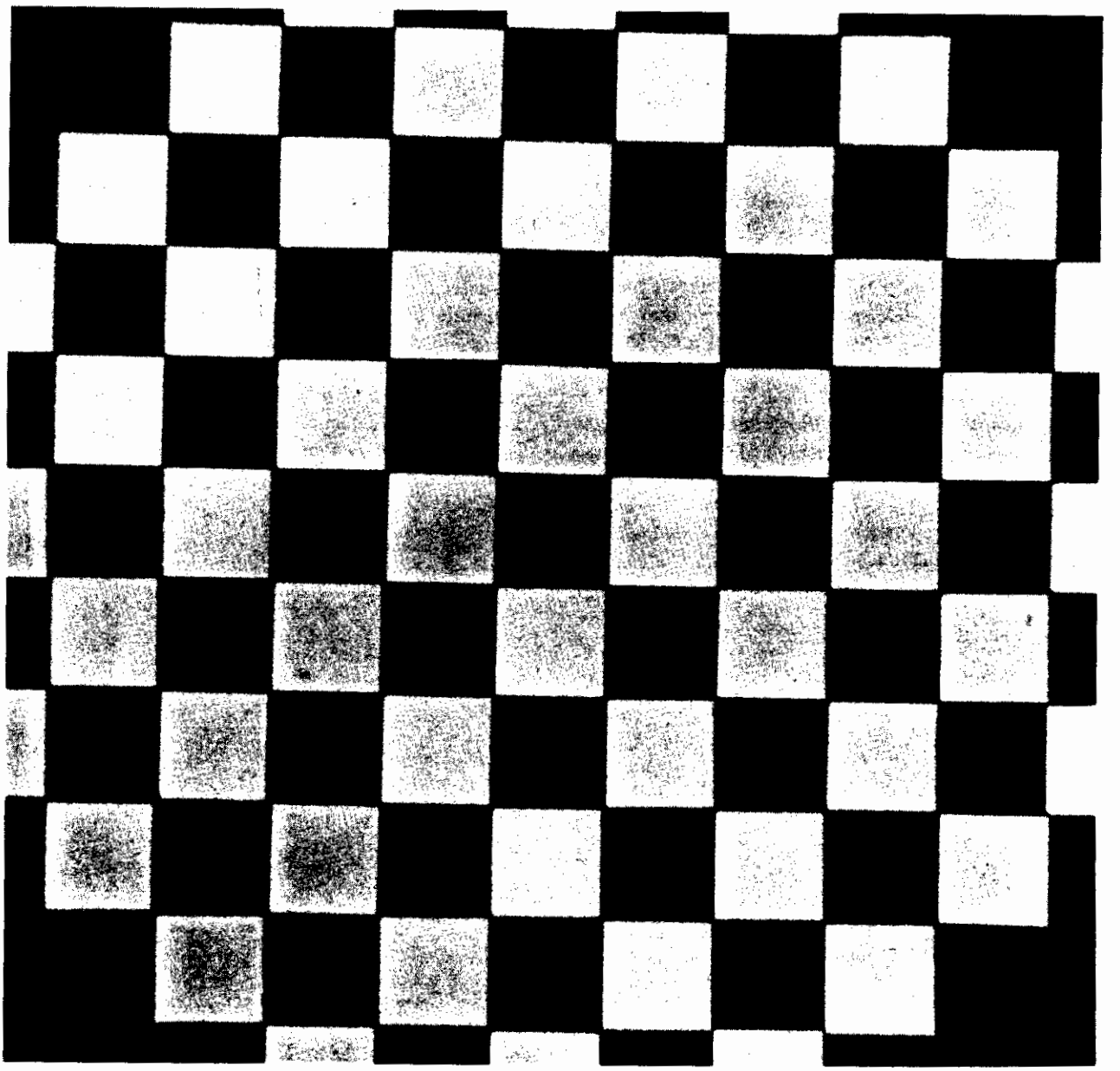

Fig. 5. – Radiographic image of test object No. 1

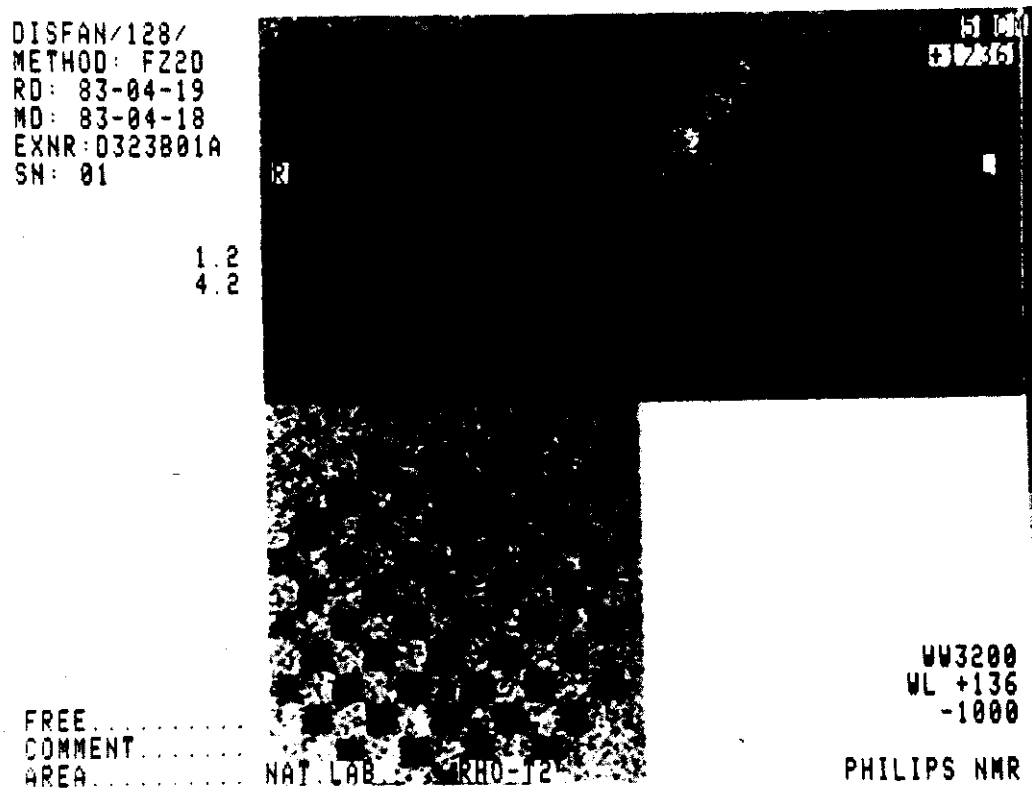

Fig. 6. – NMR data output of test object No. 1.

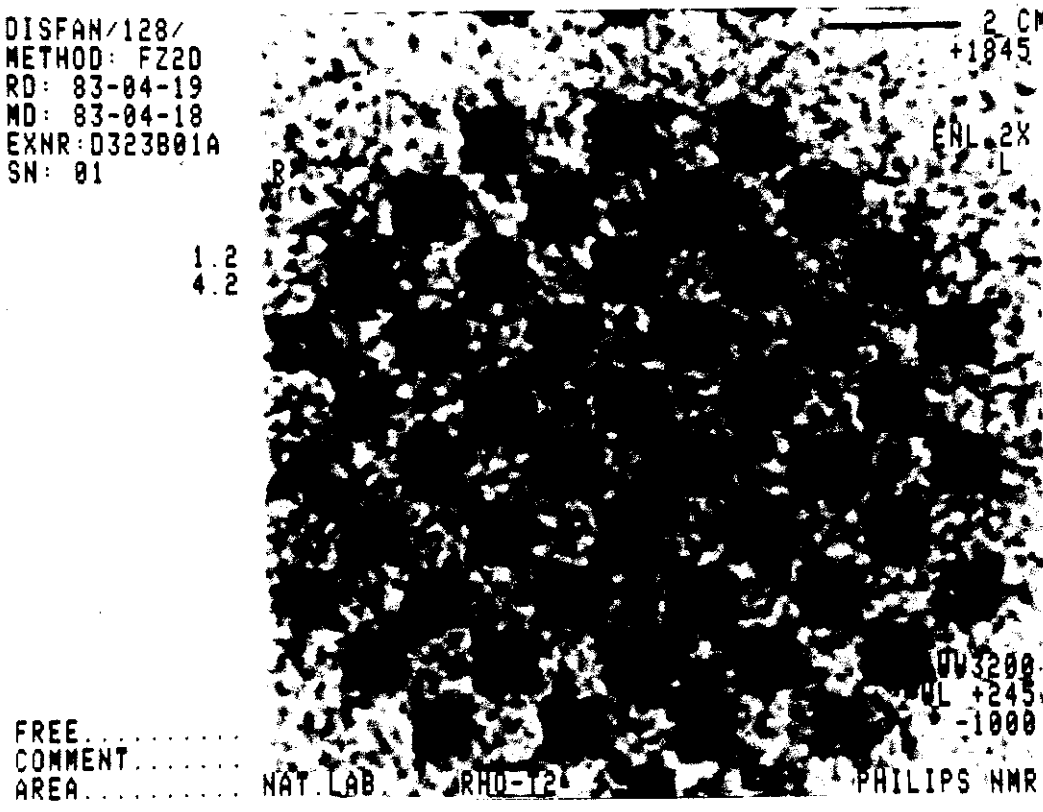

Fig. 7. – NMR image of test object No. 1.

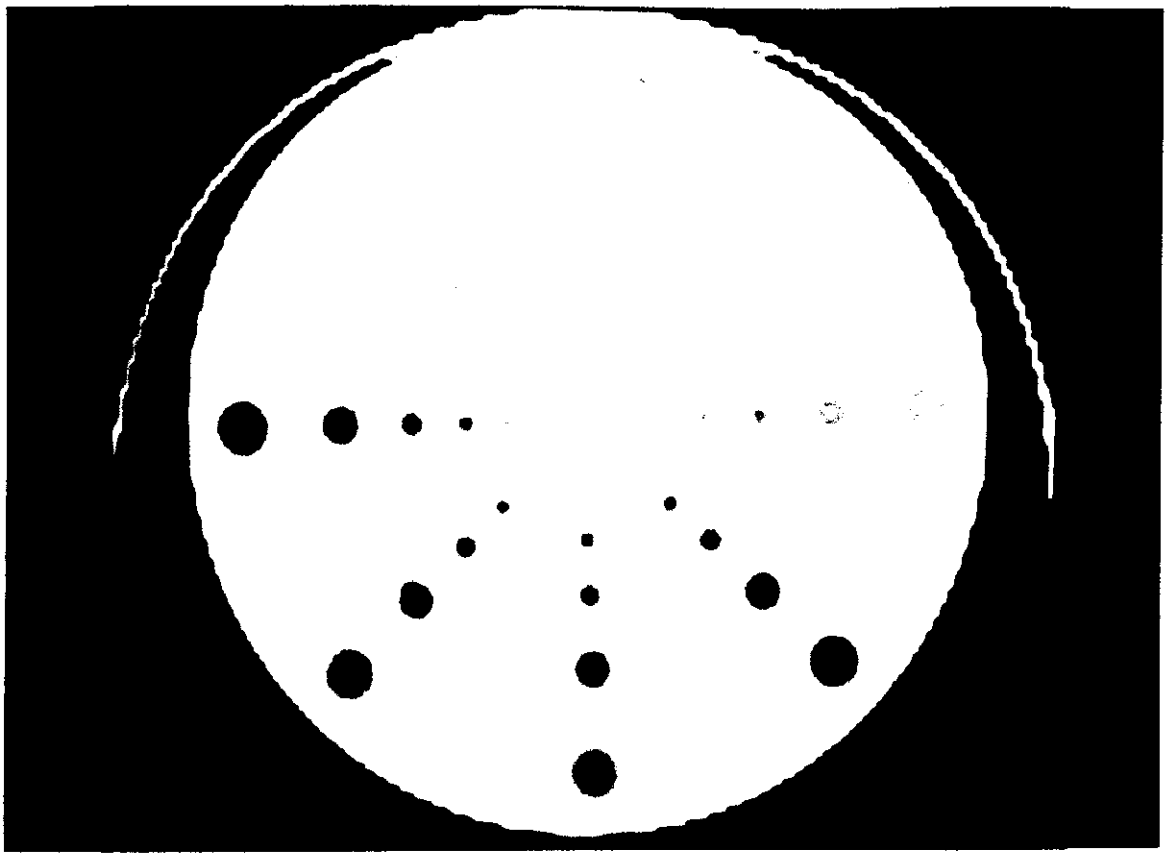

Fig. 8. – X-ray CT image of test object No. 2.

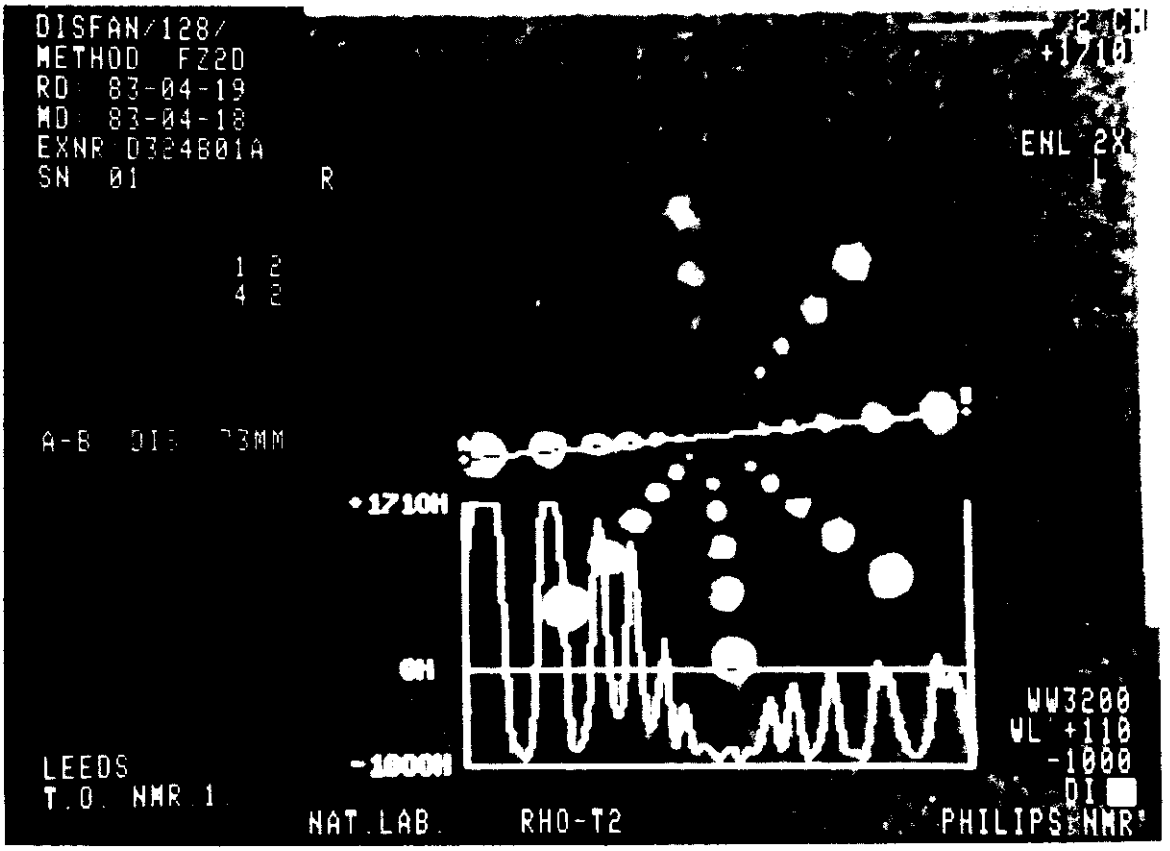

Fig. 9. – NMR image of test object No. 2.

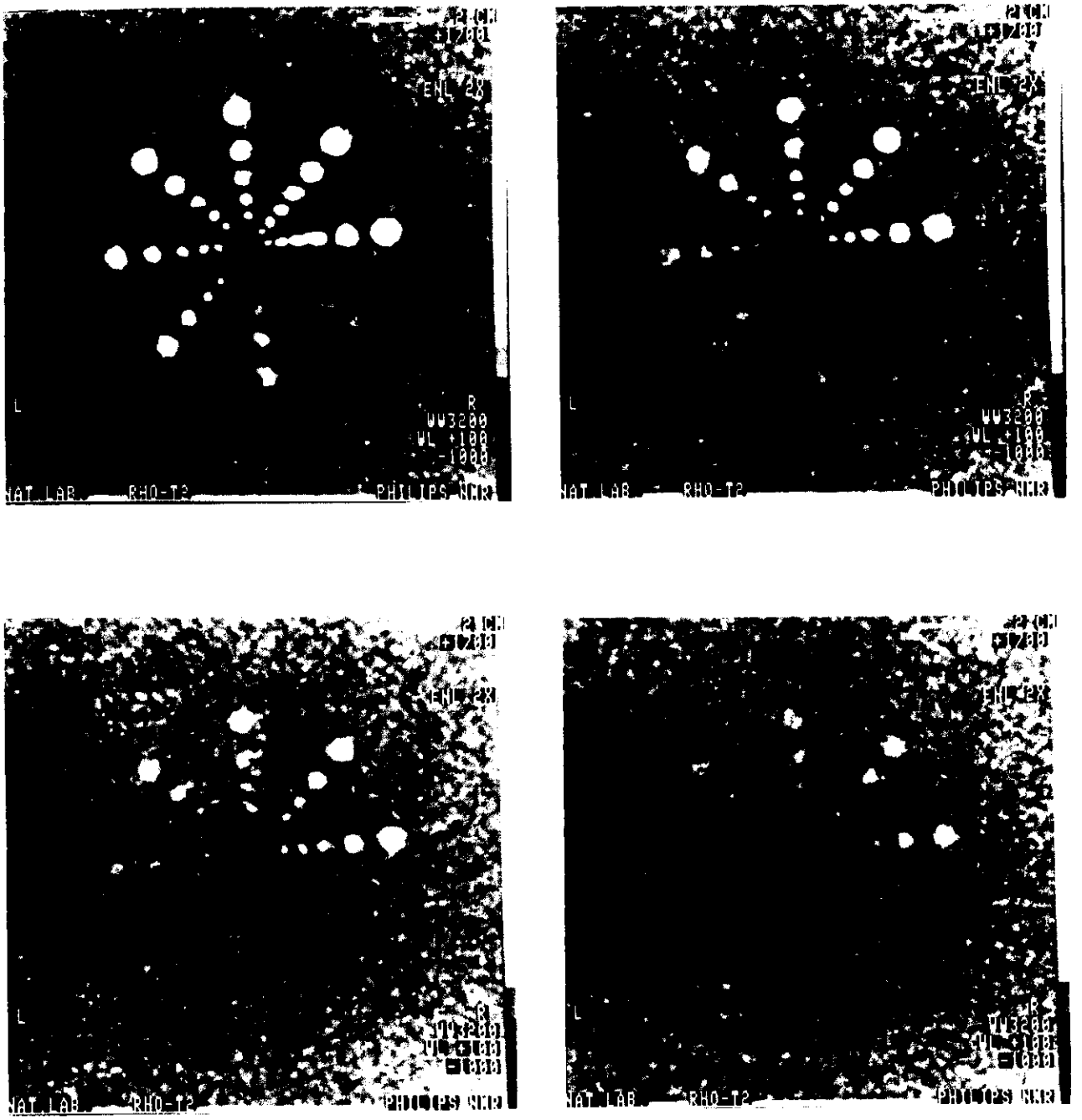

Fig. 10. – NMR image of test object No. 2 illustrating the effect of degrading SNR

List of abbreviations

CT	Computed tomography
ESF	Edge spread function
FBPR	Filtered back-projection reconstruction
MTF	Modulation transfer function
NEA	Noise equivalent aperture
NMR	Nuclear magnetic resonance
NMRI	Nuclear magnetic resonance imaging
ROC	Receiver operating characteristic
SMNI	Signal-matched noise integration
SNR	Signal-to-noise ratio
TCDD	Threshold-contrast detail detection
2DFT	Two dimensional Fourier transformation

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PRELIMINARY RESULTS FROM PHANTOMS FOR SPATIAL AND CONTRAST RESOLUTION, STANDARDISATION AND CALIBRATION, WITHIN NMR IMAGES

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Summary. — *A series of prototype phantoms or test objects for assessing image quality are described and preliminary results presented. Aspects mentioned include the uniformity, geometrical distortion, spatial resolution, and contrast of proton density, T_1 and T_2 images. For assessing machine performance in the production of complete images it is appropriate to assume mono-exponential relaxation.*

For calibration, standardisation and characterisation, on the other hand, non-exponential relaxation should be considered. Results from imaging equipment showing the linear relation between proton density and T_1 relaxation image values and laboratory values, and the changes in contrast with changes in T_1 sequence are presented. It is recommended that tests for image assessment and calibration for tissue characterisation should be linked but not amalgamated.

Riassunto. — *Viene qui descritta una serie di prototipi di fantocci o di campioni standard per i controlli di qualità dell'immagine NMR, insieme con alcuni risultati preliminari. Gli aspetti considerati includono uniformità, distorsione geometrica, risoluzione spaziale, contrasto nella densità protonica, immagini T_1 e T_2. Per controllare le prestazioni strumentali di un apparato per produzioni di immagini complete, è opportuno assumere che il rilassamento magnetico nucleare sia mono-esponenziale.*

D'altra parte, l'esistenza di rilassamenti non-esponenziali deve essere presa in considerazione nelle procedure di calibrazione, standardizzazione e caratterizzazione. Vengono presentati risultati ottenuti da apparati di "imaging" che dimostrano la relazione lineare tra la densità protonica e i valori del rilassamento T_1 nell'immagine e i valori di parametri sperimentali particolari, nonché le variazioni di contrasto associati a cambiamenti nelle sequenze di impulsi.

Si esprime la raccomandazione che le prove di controllo di funzionalità strumentale e i criteri di calibrazione nella caratterizzazione tissutale siano tra loro correlati ma non unificati.

Introduction

NMR images are extremely dependent on the details of the techniques used to form them. They represent maps of signal amplitudes determined by combination of the three basic properties, proton density, spin-lattice relaxation and spin-spin relaxation. Different pulse sequences can produce images whose principal dependence is on only one of these properties, but it is not possible to remove the influence of the other completely except by computation from the results of several different pulse sequences or, in some circumstances, by maintaining the other properties constant. Although proton density, ρ, is in general not very useful clinically it affects all the signal produced. Therefore, even though one may not wish to image ρ directly, it is important that the ability of equipment to image ρ be known, in order that the contribution of ρ to any other image may be well understood.

The analogy between NMR and X-ray CT imaging suggests that the obvious way to start is by using phantoms based on CT concepts. Examples of results obtained in the imaging mode are presented and discussed below, to form a basis of actual experimental trials on which proposals for improvements can be founded.

Results of experimental studies of rather primitive methods for standardisation, calibration and characterisation of single regions are then presented and discussed to illustrate the problems that will be faced by more complex approaches.

Phantoms for assessing image quality

For assessing machine performance in the production of complete images it is necessary to assume that only simple measures of relaxation are considered. That is, any substance will be assumed to have relaxation properties that can be specified by single values of T_1 and T_2.

The simplest phantom is a tank of water doped to produce representative values of T_1 and T_2, and perhaps

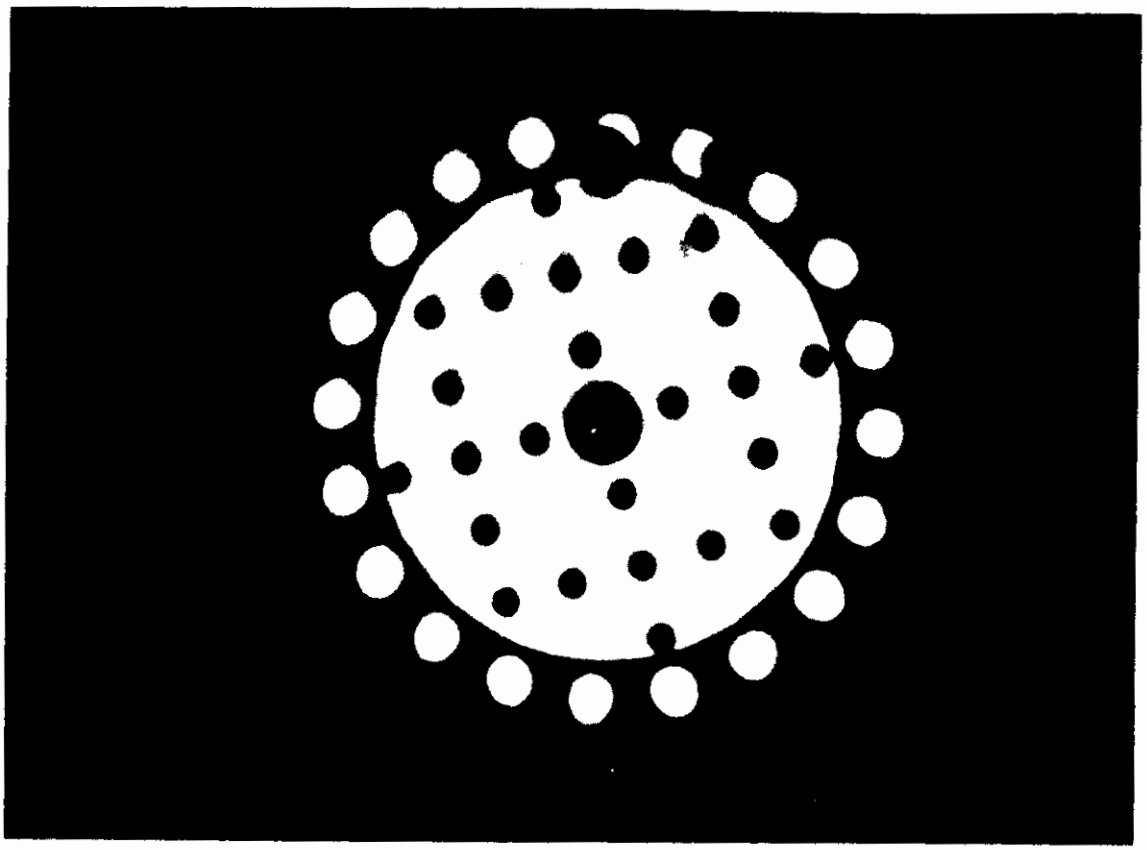

Fig. 1 – Image of a phantom for assessing geometry or distortion in the image field. The central tank and the small outer pots can be filled with solutions of any desired relaxation properties.

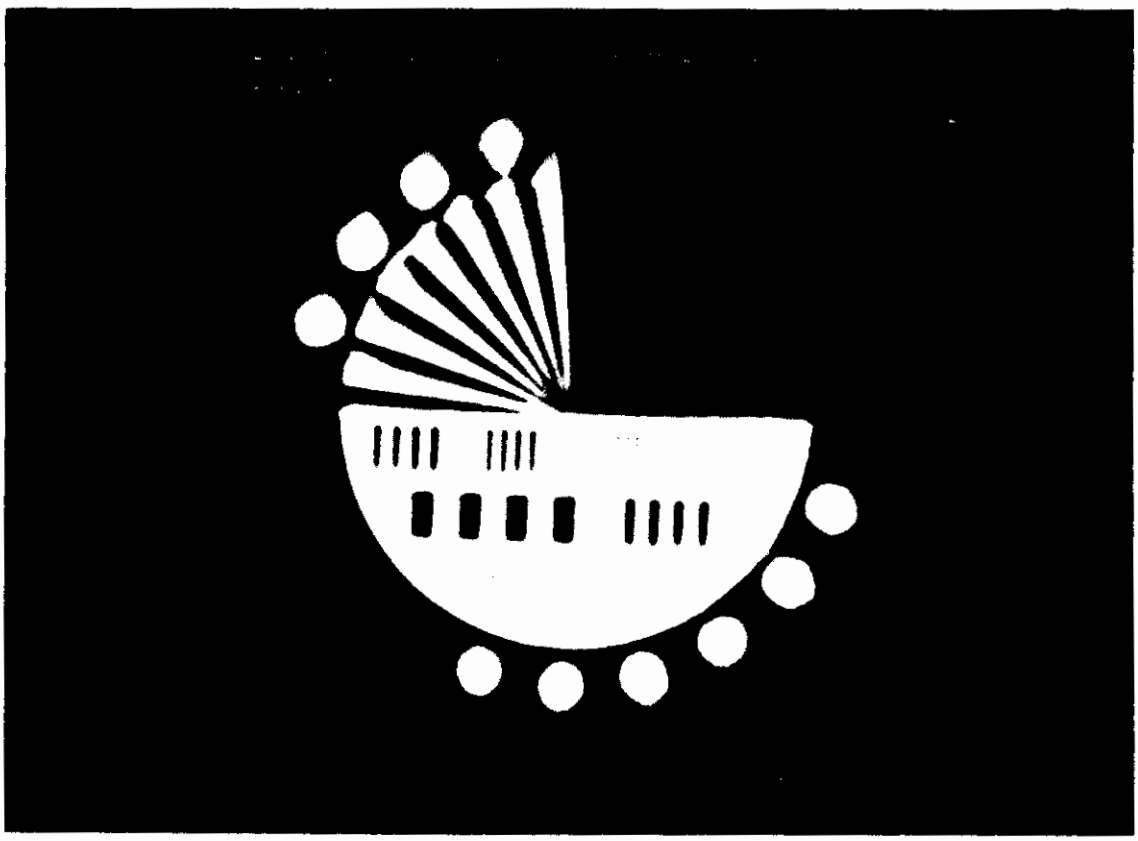

Fig. 2 – Image taken with an inversion recovery pulse sequence showing spin-lattice relaxation or T_1 properties. The phantom can be used for estimating spatial resolution and slice profile.

diluted to produce required values of ρ. With such a phantom the "flat field" uniformity can be measured by standard CT methods and the signal to noise can be evaluated at different parts of the images. Lack of uniformity, which may arise from main field inhomogeneity, gradient field non-linearity, or RF inhomogeneity, appears to detract little from clinical usefulness. An image of the next simplest phantom is illustrated in Fig. 1 by which the geometry or distortion in the image field can be assessed. The main central tank and the outer pots can be filled with solutions of any desired relaxation properties. The artefact near the top of the image is due to a very small metallic wire that was accidentally included. A more complex phantom is illustrated in Fig. 2 which is a T_1 image. This phantom can be used for estimating spatial resolution across the image from the bar pattern; spatial resolution at different orientations in the image from the inner ends of the radial spokes; and slice profile from the outer ring of small circular areas which are thin flat pots arranged in a double helix. For this particular image the water was Mn doped to give a T_1 of 200 ms. The purpose of having two helices is to check if the phantom is parallel to the slice.

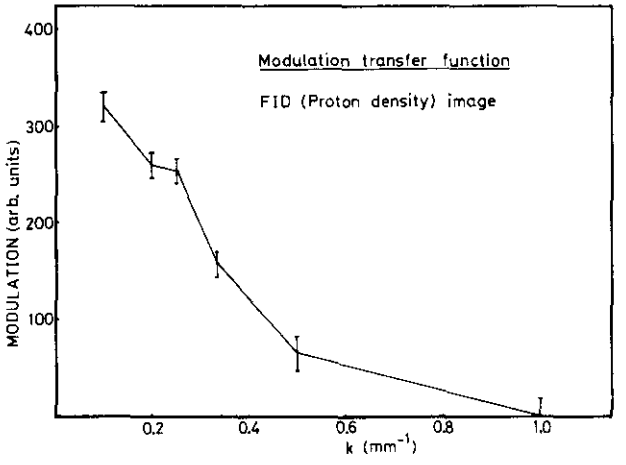

Fig. 3. – Modulation transfer function for proton density image taken with a saturation recovery pulse sequence.

Figs. 3 and 4 present modulation transfer function (MTF) data obtained for saturation recovery and for computed T_1 images from the bar patterns of the phantom in Fig. 2. The saturation recovery image exhibits appreciable modulation right up to the pixel size limit ($k = 1 mm^{-1}$) whereas the computed T_1 image does not, perhaps partly due to the reduction in signal to noise introduced by the computation, although other effects discussed later also contribute.

Fig. 5 illustrates an image from a phantom with which both contrast and spatial resolution could be determined. The image shown is a saturation recovery image. and the pots in the phantom can be filled with solution of any relaxation properties. In this image the pots are all the same, so only spatial resolution is demonstrated. If solutions of progressively differing relaxation

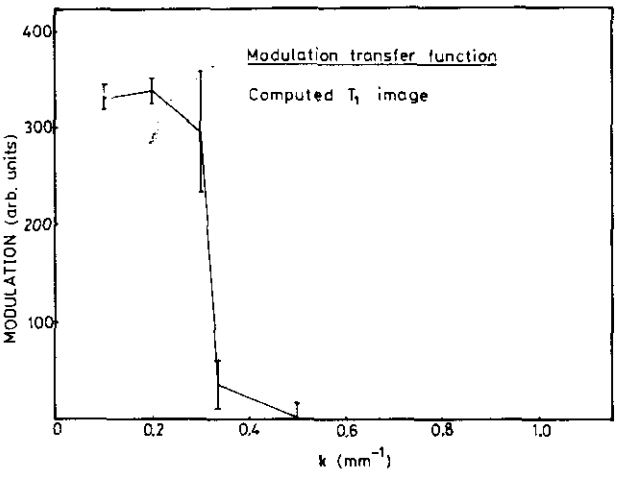

Fig. 4. – Modulation transfer function for a computed T_1 image.

properties were filled into each radial row of pots, contrast resolution at differing object size could theoretically be found. However, this approach is totally dependent on the establishment and maintenance of a high degree of field uniformity. Such uniformity is difficult to obtain and in any case is not vital for clinical imaging. It is therefore not entirely reasonable to enforce a condition of uniformity purely for the purpose of a test on contrast resolution when the condition is not essential for useful imaging. Some other method of determining contrast resolution should therefore be sought.

These phantoms and the results obtained and illustrated in the figures are regarded as very preliminary. Many lessons can be learned from the results. Further lessons relevant to phantom design can also be learned from the experiments relating to calibration, standardisation and characterisation described below.

Calibration, standardisation and characterisation

For these experiments a single region was studied in the form of a small polythene bottle placed always in the same place in the imaging field. Effects from lack of complete field uniformity were thereby eliminated.

a) Proton density

Solutions of variable proton density but fixed T_1 and T_2 may be prepared by diluting doped H_2O with its isotope D_2O, deuterium oxide. The doping is necessary to ensure a fixed T_1 in the clinical range and was performed with $MnCl_2.4H_2O$ (which gives paramagnetic ions in solution). Constancy of T_1 values was checked with a Bruker Minispec PC8 bench-top spectrometer. and was adjusted to 210 ms for all the solutions used.

Saturation recovery scans were performed for each mixture prepared. the mixture being contained in a polythene bottle in the same part of the magnetic field. Pixel values obtained in such a scan are given in the ideal case by the equation

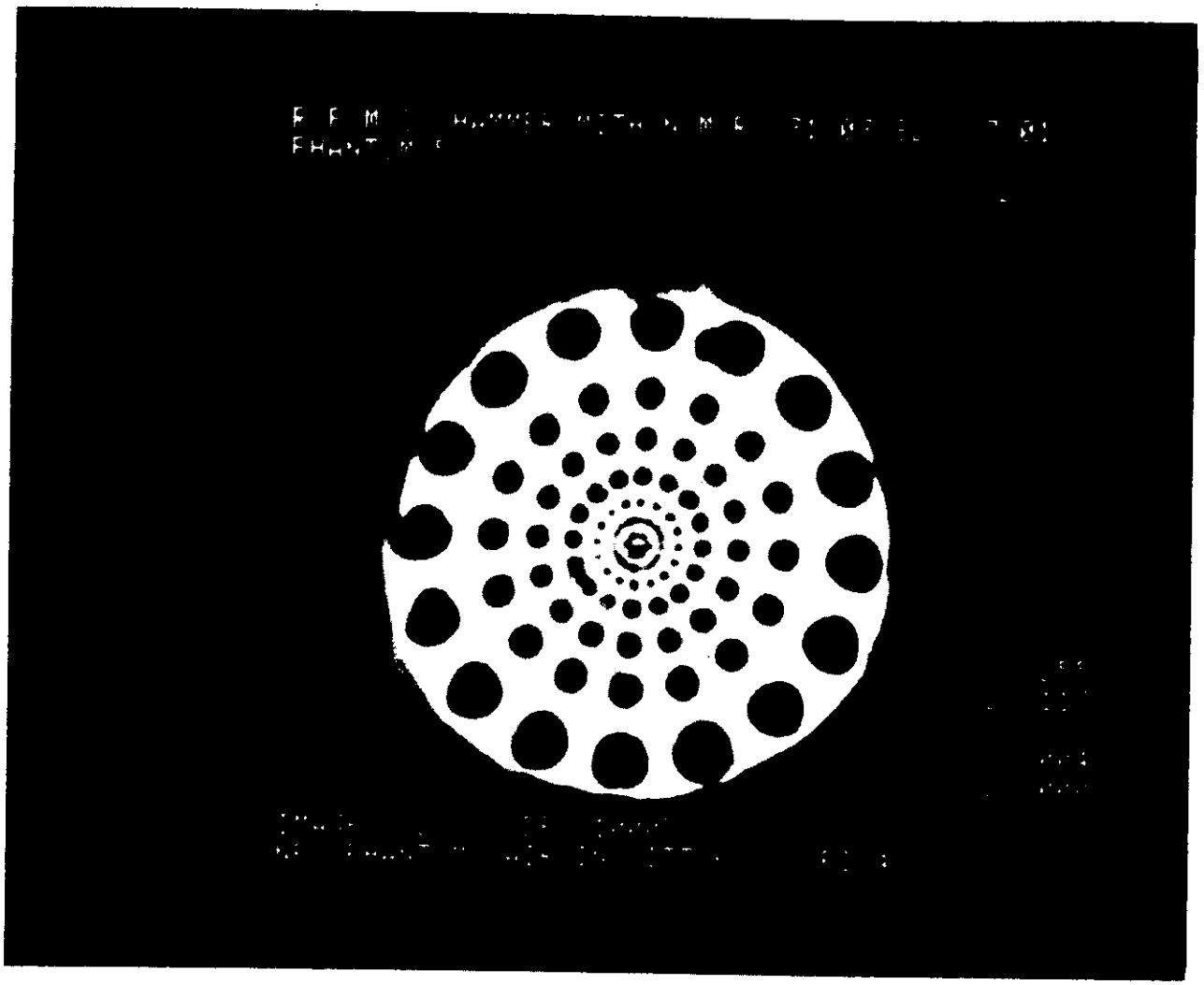

Fig. 5 – Image of phantom with both spatial and contrast resolution could be determined

$$N = k\rho(1-e^{-t_R/T_1})$$

where k is a constant, ρ is the proton density, t_R is the repetition time of the sequence and T_1 is the spin-lattice relaxation time. Hence for mixtures of constant T_1 the pixel value is directly proportional to the proton density ρ.

Average pixel values were extracted from the images using software and the image display facilities present on the computer of the prototype scanner. Values are corrected for changes in the input gain of the RF receiver which occur automatically during data collection.

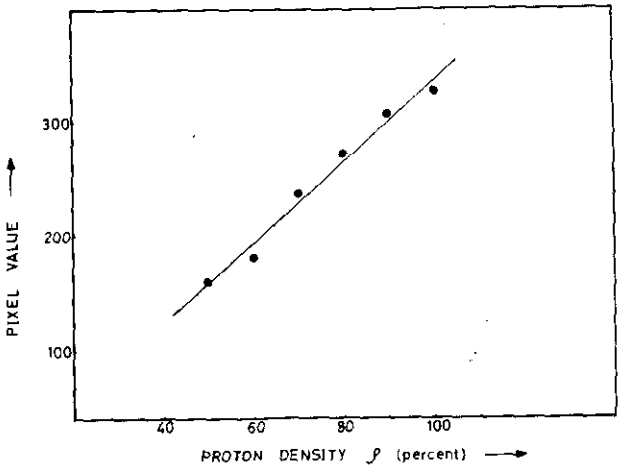

Fig. 6. – Test of calibration and linearity of proton density values in a fixed region of an image.

Fig. 6 shows a plot of average pixel values against proton density (calculated as 1 minus the fraction of D_2O). The result obtained shows that proton density as measured with the NMR scanner exhibits a linear dependence with actual proton density over the range of clinical interest. This confirms the simple theory used to derive the above equation.

b) Spin-lattice relaxation time T_1

Measurements to investigate the T_1 scale are necessarily more involved due to the fact that values may only be derived through computation based on the pixel values of a saturation recovery scan and an inversion recovery scan. This allows one to remove the influence of proton density and calculate the value of a function

$$S = \frac{1 - e^{-\tau/T_1} + e^{-(t_R+\tau)/T_1}}{1 - e^{-t_R/T_1}}$$

Here τ is the time between 180° and 90° pulses in the inversion recovery scan and t_R and T_1 the sequence repetition rates and spin-lattice relaxation time as before. Fig. 7 plots S for commonly used τ of 400 ms and t_R of 1400 ms. An interesting feature of this curve is that it passes through zero at T_1 around 700 ms because the inversion recovery pixel value goes to zero. Objects of T_1 = 700 ms will thus be invisible using an inversion recovery sequence of τ and t_R values as above. Negative values should be obtained for T_1 greater than 700 ms.

Measurements have been performed using a series of H_2O solutions of variable T_1 (adjusted through doping) measured on the Bruker Minispec. Again average pixel

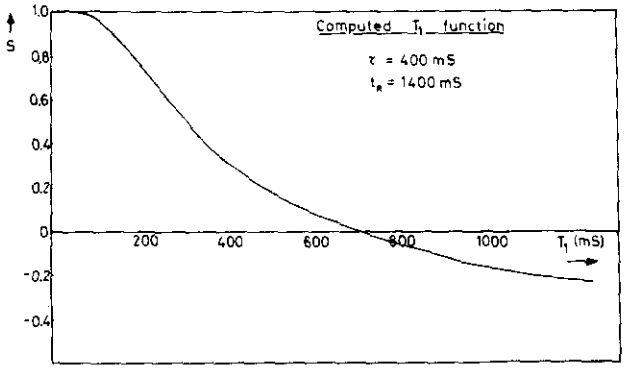

Fig. 7. – Calculated values of the signals obtainable under ideal conditions from a series of substances of different T_1 subjected to inversion recovery pulse sequences with τ = 400 ms and t_R = 1400 ms.

values were measured and the function S computed for each T_1. Fig. 8 shows the results. Experimental points tend to lie above the theoretical curve but follow its form quite well. The discrepancy may be understood in terms of the different NMR frequencies at which the Bruker spectrometer and the imaging machine operate, 8 MHz and 6.5 MHz respectively. If Bruker T_1 and imager T_1 are plotted directly (Fig. 9) then a good linear relationship is found, with T_1 (imager) < T_1 (Bruker) as would be expected from the frequency difference. Deviations are found at low T_1 where it is suspected that T_2 effects may be coming into play.

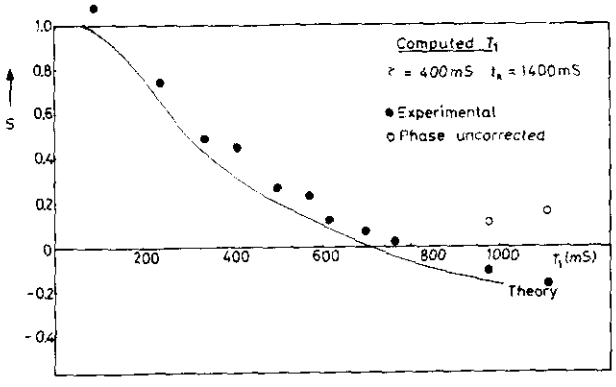

Fig. 8. – Experimental results (●) compared with calculated values of signals from substances of different T_1. The systematically higher experimental values are due to a frequency difference between the Bruker spectrometer (8 MHz) on which the T_1 values were measured and the imager (6.5 MHz) from which the signals were obtained.

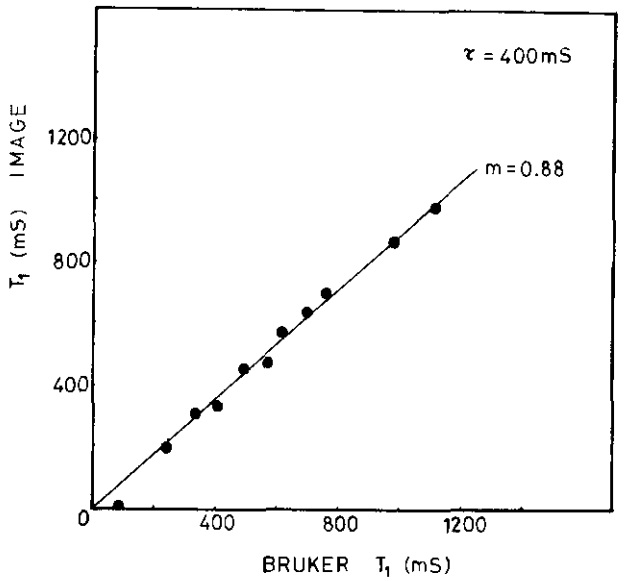

Fig. 9. – The same experimental results as shown in Fig. 8 but plotted as spectrometer T_1 values against image T_1 values.

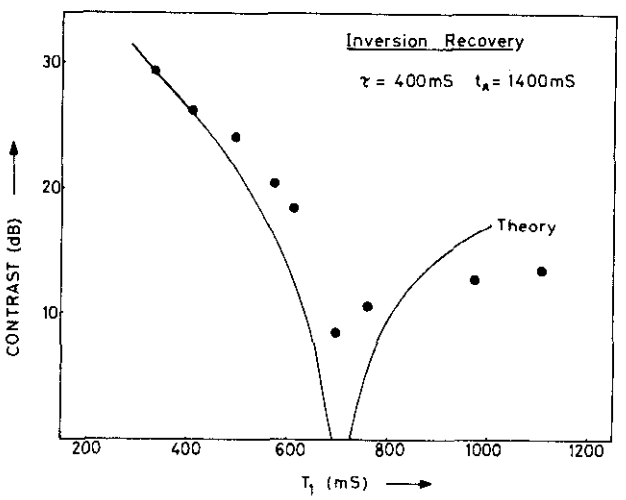

Fig. 10. – Experimental and theoretical values of contrast obtained with substances of different T_1 imaged using an inversion recovery pulse sequence. It can be seen that contrast tends towards a minimum when $T_1 = 700$ ms.

c) Contrast

As mentioned above the signal amplitude in an inversion recovery image is strongly dependent on T_1 and in fact passes through zero for a particular T_1 value determined by the sequence timings. This means that contrast behaves strangely and care must be taken to avoid losing diagnostic information through incorrect sequence selection.

Preliminary illustrative work has been performed where the variable T_1 solutions used above have been scanned and contrast defined as the ratio of signal amplitude in the bottle to that in the image field background. Fig. 10 shows the experimental data together with a theoretical curve calculated by fitting to the first experimental point. Agreement is reasonable and it can be seen that contrast falls from about 30 dB at short T_1 to less than 10 dB near 700 ms.

Conclusion

It can be seen that information relevant to clinical images can be obtained from these trials relating to calibration, standardisation and characterisation. Only simple measures of relaxation properties have been considered. It is suggested that every effort should be made to study the two kinds of requirement together in a coherent manner, so that three groups of tests can be envisaged. The first group would be those tests common to both imaging and characterisation. The second would be those specific only to imaging. The third would be those specific to characterisation and capable of handling a fuller study of relaxation properties than those dealt with here.

Acknowledgements

We are glad to acknowledge the support of the Department of Health and Social Security and the encouragement of Mr. J.L. Williams and Mr. G.R. Higson. We also acknowledge the collaboration of Dr. G.M. Bydder and colleagues of the Department of Diagnostic Radiology and Dr. I.R. Young and colleagues of Picker International Ltd.

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Discussion on specification of design of phantoms and protocols of use for performance assessment with respect to spatial and contrast discrimination
Moderator: J. S. Orr

ORR – Has anyone got any questions or comments? Prof. Sauzade, you were talking about the problem of differences in data frequency absorption, which is a very real problem that we haven't given sufficient consideration to.

FOSTER – I would just like to ask, all the phantoms that you showed are based on a radial type of design, and of course the method that you use is a reconstruction–projection method, which is a radial method of producing the image. Do you think that type of phantom would be equally suitable to a line–based method, or would it perhaps be a good idea to have at least a part of the image area with, say, a reversed fan system or lines radiating outwards to test the overall area?

ORR – There is indeed a need to consider the different ways of creating the image. That is something that we have not yet considered sufficiently.

LUITEN – I think we should also take into account that there are various ways of reconstruction in X–rays. There is always filtered back projection, and in the 2D Fourier transform imaging, the artifacts showing up from the same courses are quite different. We all know that, for instance, a lack of sharpness or inhomogeneity in the field produce, say, a lack of sharpness in projection–reconstruction – it can be corrected for in a sophisticated way, but if you do it in 2–dimensional Fourier imaging it works out a lack of sharpness in one direction only. It does not give any distortion in the prefacing direction. That means that the same unit, just by using another technique, shows up different artifacts. I think there is one advantage in NMR, i.e. there is actually no difference of a point being measured at the edge or in the centre, apart from the fact that there is, of course, the difference in sensitivity of the detection coil, but in CT there is a difference in reconstruction of particles at the edge and at the centre, and here the detector does not know where the signal is coming from, as a matter of fact it is coming from everywhere. That means I think that the sharpness or some of the image quality aspects like resolution in X–ray systems have to be checked in the various directions (and in that case sometime a star pattern has an advantage). I don't think this is of great importance for NMR because in NMR there is mainly distortion, and to check distortion I think a square or grid pattern is more illustrative than a star pattern. Besides that, you could apply the grid pattern as a calibration test and you could do some kind of performal mapping of compensating of the picture. So in NMR it is actually more the inherent qualities of imaging a point or lines, so I think in NMR the point span function would be the most illustrative, perhaps even more than the resolution between the lines, but that's only a provisional idea. We have made test objects (I haven't got them with me) built out of a box of water with an array of plexiglass plates which have a thickness of 1.2 and 3 mm space and 1.2 and 3 mm apart, so we had a number of line patterns. We could put them in different situations and we could have different compartments with the same phantom, even all containing water at a different relaxation time, just to see whether that makes any influence on the image. We didn't notice that. So I think that in NMR it is easily possible to separate out the sharpness properties as far as this makes the sharpness of the image obvious, and the resolution of course, apart from the measurement and the calibration of factors of analytical value. You might of course look at the relaxation time as a contrast medium and then you want to have a nice scale of contrasts, or you want to have the number because variations of that number by itself, like Hounsfield's numbers, will give you information on other diagnosis. I don't think it is very helpful to combine things in one phantom, so you should make imaging test–objects just to calibrate variations between contrast of the T_1 values in a numerical way. I think it is very important to separate these properties, although they may be done in the same machine.

FOSTER – Yes, I agree with you on that. Our normal test object is a simple grid, but it is very important to try to see how small a difference in T_1 you can distinguish when it is as close together as possible– very thin membranes between different pools of fairly similar T_1. I think that tells you a great deal about the resolution of your machine.

SAUZADE – A main source of noise is also due to the sample. You might need to design the test object in an appropriate way, in order to have a high conductivity, path inside.

LUITEN – I think you are bringing up an interesting point, but I don't know exactly what the situation is. Do we consider a measuring object or a tissue as being very inhomogeneous from the electrical point of view? I always try to see them as a homogeneous mass of material with certain electromagnetic and electrical properties. Because when the noise comes from the object, that is the noise you can do without, you cannot cool the object of course. I think a good deal of the noise is still coming from the system, and that's to do with the resistance of the detector coils and the resistance of the pre–amplifiers and so on.

SAUZADE – David Hoult calculated the noise of the coil, and he proved that when the size of the coil is very large, the main contribution is from the sample, not from the coil.

LUITEN – From my own experience I think that at least half of the noise comes out of the detector, even if you made the detector very thick (copper, and so on).

SAUZADE – The limit of the noise in the sample is this kind of size, surely.

STYLES – If you look at the noise coming from the spertrometer, it will always be equivalent to the noise generated by the pre–amplifier with a 50 Ohm source impedence. The effect of a conductive sample is to reduce the Q of the receiver coil, and this reduces the signal. Assuming that the coil is correctly tuned, the observable effect is constant noise, but reduced signal. It must be remembered, however, that the fundamental effect is that the sample introduces resistance (and hence noise) to the receiver coil.

LUITEN – That is correct. The sample introduces into the detecting coil an electromagnetic bending, and that reduces the Q factor of your coil. That means that the noise remains the same, but what you observe is that as the Q goes down, your signal goes down, because you are always working at 50 ohms of course and the noise is constant. But if you insert the head in the coil or you take it out, that makes the Q go down by, say, 30 % or 40 % That means that half the noise is still coming from your coil. The noise goes up with the square root of the resistance of the coil so the damping is doubled, the noise goes up as 2, so if I see 40 % change I can guess that still half of the noise is coming out of the system rather than out of the object.

ORR – Does that mean that to do a standard comparison between two imaging units, it would be necessary to have the conductivity of your test object match the system, and therefore a change in the test object might have to be made to do a fair comparison?

LUITEN – I think it is important to define very well the conductivity and the magnetic properties of your test object. I'm still not very convinced whether it should also be inhomogeneous in that way. I think that for the moment to the first approximation you could consider the human body inside as a homogeneous sample from the electromagnetic point of view with certain values of ϵ,μ, conductivity and so on.

STYLES – This is about sample conductivity in the human body. What I do know is that, certainly at the frequencies that we do our experiments at, the body just looks as if it's a big bag of 150 mM saline. I think that the only way that you can explain that is that, although there must be discontinuities (for example, the cell membranes) they must be thin enough to behave like a capacitor. Whether these arguments apply at 6 MHz I'm not quire sure, but I think that what we have to do is not only preserve the conductivity but the geometry of the sample, because we are talking about the area of induced current loops.

MARAVIGLIA – There is one detail which we have not touched and it is worth recalling. It's that just for these definitions of the sample and conductivity and Q, there is one element that we normally introduce – we don't know what the others do. It is a screen within the coil which should limit the direct loss.

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POSSIBILITY OF DESIGNING A STANDARD INSTRUMENT FOR SAFETY ASSURANCE BY MEASURING ELECTROMAGNETIC EFFECTS

DESIGN OF AN INSTRUMENT FOR SAFETY ASSURANCE IN NMR IMAGING PROCEDURES

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Summary. — *After a short review of the interaction of magnetic fields with biological tissues various methods for measuring the relevant effects such as absorbed power and induced potentials and currents are described. It is concluded that for safety assurance an instrument which measures the maximum absorbed power should be used. Measurements should be made in a phantom made of materials with resistivity and permittivity equal to tissues at the frequency used in NMR imaging. Since the frequency differs widely in the imaging techniques proposed, a compromise might be reached in constructing the phantom of materials with resistivity and permittivity corresponding to tissue at 10 MHz.*

Riassunto. — *Dopo una breve rassegna sulla interazione di campi magnetici con i tessuti biologici, vengono descritti vari metodi per misurare effetti importanti quali la potenza assorbita e i potenziali e le correnti indotti. Si conclude che ai fini della sicurezza si dovrebbe usare uno strumento in grado di misurare la massima potenza assorbita. Le misure dovrebbero essere eseguite su un fantoccio costruito con materiali aventi resistività e permissività uguali a quelle dei tessuti alla frequenza usata in NMR imaging. Poiché la frequenza varia molto nelle tecniche di immagine proposte, si potrebbe raggiungere un compromesso costruendo il fantoccio con materiali aventi resistività e permissività corrispondenti a quelle del tessuto a 10 MHz.*

Introduction

In recent years the public concern over possible risks associated with ionizing radiation has grown considerably. Although there has been no unequivocal demonstration of adverse effects of present diagnostic techniques such as CT, conventional X-rays and nuclear medicine, with the possible exemption of leukemia induction following X-ray exposure in utero, there is a need for introduction of a method such as NMR which combines the capability of providing new diagnostic information with a claimed absence of harmful effects. This claim of safety must be thoroughly investigated and proven before NMR is taken into clinical use especially since many different methods are used for obtaining two — or three — dimensional NMR images.

These considerations lead to a need for a standard instrument for measuring a kind of exposure to patients undergoing NMR imaging procedures. Before going into a detailed discussion on how such an instrument should be designed and what effects should be measured, a brief description of the interaction of magnetic fields with biological tissues is necessary.

Interaction of magnetic fields with tissues

The interaction of electromagnetic fields with biological tissue and living organisms has been covered in recent reviews [1, 2, 3] and only the main conclusions will be given here. Static magnetic fields may influence biological processes due to: 1) macromolecule orientation changes which may lead to changes in chemical kinetics and membrane permeability; 2) changes in enzyme kinetics by quenching possible superconductivity phenomena; 3) reduction of nerve conduction velocities and 4) superposition of low potentials on natural biopotentials. The threshold for effects in the first three cases are from 1 to 20 T or above. The electromagnetic field (EMF) in 4) due to magnetohydrodynamic effects e.g. in electrocardiography (ECG) measurements has not produced physiological effects and is typically of the order of a few millivolts. The strength of the static magnetic field is thus of little importance with respect to safety assurance provided the field strength is below 1 T.

In NMR a pulsed magnetic field of short duration is used to excite the nuclei under study. The frequency of this field is the Larmor frequency of the nuclei. The present proposed imaging techniques cover a frequency range of 1 to 60-80 MHz, the higher frequencies being proposed for ^{31}P and ^{23}Na studies.

We will now consider the NMR equipment as a "black box" which emits a magnetic pulse with a maximum

field strength B_o, duration τ and repetition rate T given as time between pulses

$$\vec{B} = B_o \cdot \exp(j\omega t)\,\vec{z} \qquad (1)$$

If an infinitely long cylinder of radius r_o of a conducting material co-axis is exposed to the field given by equation (1), the field inside the cylinder may be found using the wave equation

$$\nabla^2 B - \epsilon\mu \frac{\partial^2 B}{\partial t^2} - \frac{\mu}{\rho} \cdot \frac{\partial B}{\partial t} = 0 \qquad (2)$$

with ϵ = permittivity, μ = permeability and ρ = resistivity of the medium.

The solution can be written as

$$\vec{B} = Bo \frac{|\,Io\,(Kr)\,|}{|\,Io\,(Kr_o)\,|} \exp(j\omega t - \xi(r))\,\vec{z} \qquad (3)$$

The attenuation of the magnetic field amplitude is described by the ratio $|\,I_o\,(Kr)\,| / |\,I_o\,(Kr_o)\,|$ where I_o is a modified Bessel function of the first kind of order zero and $I_o\,(Kr_o)$ is an integration constant. The timevarying magnetic field will induce an electric field E as deduced from Faraday's law

$$E = -10^{-4} \frac{\partial B}{\partial t}$$

$$E = - \frac{j\omega B_o I_1\,(Kr) \exp(j\omega t)}{K\,I_o\,(Kr_o)}$$

(In a tissue with conductivity σ given as $\sigma = 1/\rho$ the current I is given by $I = E \cdot \sigma$. In these derivations we see that the pulsed magnetic field, electromotive force and induced current are related through simple equations containing σ and ϵ. If σ and ϵ are known E and I can be calculated from the measurement of B.

The frequency dependency of ρ and ϵ has been measured by Bottomley and Andrew [4] for rat lung, brain, liver, kidney, heart, muscle and liver hepatoma. Both ρ and ϵ change considerably from tissue to tissue and with frequency. An example is shown in Figs. 1 and 2. Lung and brain have high resistivities i.e. low conductivities. The absorbed power or SAR (specific absorption rate) is given by $P = {}^1/_2 \cdot \sigma\,|\,E\,|^2$ or if the pulse length is τ and T the pulse repetition period, P may be found as $P = \sigma \cdot \frac{\tau}{T} \cdot |\,E\,|^2$. An important point is that P is proportional to ω^2 as may be seen in the expression for E. The effects of the time-varying magnetic gradient fields used to obtain spatial information may be calculated from Faraday's law but they are normally much lower than effects of the pulsed field.

The present FDA (Food and Drug Administration, USA) guidelines for evaluating electromagnetic exposure risks for trials of clinical NMR systems are the following:

Static magnetic field : $B < 2T$

Pulsed magnetic field : $\frac{dB}{dt} < 2T/s$

Power absorption : SAR< 0.4 W/kg average over body and peak SAR< 2W/Kg for any g of tissue.

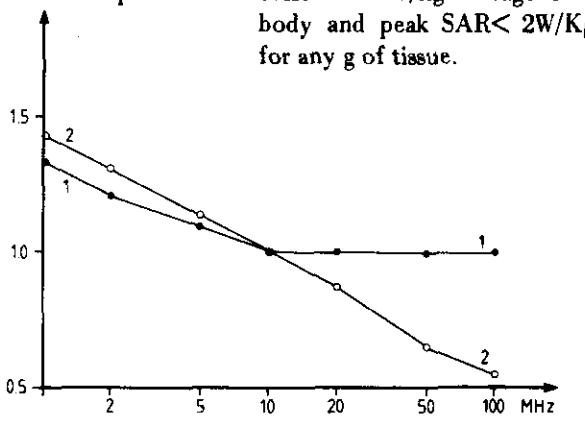

Fig. 1. – Relative resistivity of rat muscle (curve 1) and rat brain tissue (curve 2) as a function of frequency. Both curves are normalized to 1.0 at 10 MHz. Calculations are based on data of Bottomley and Andrew [4].

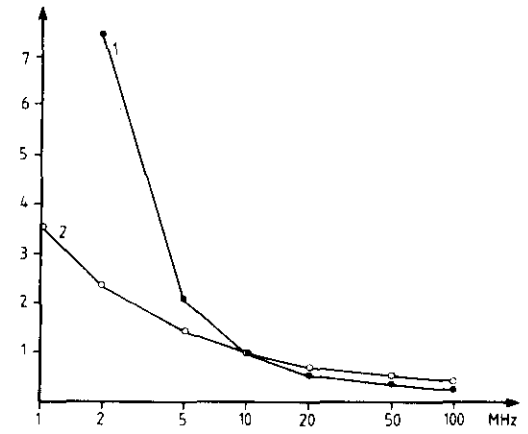

Fig. 2. – Relative permittivity of rat muscle (curve 1) and rat brain tissue (curve 2) as a function of frequency. Both curves are normalized to 1.0 at 10 MHz. Calculations are based on data of Bottomley and Andrew [4].

The equations for E, I, SAR and induced magnetic field show that measurements must be made in a phantom with ϵ and σ values identical to tissue. Guy [5] has devised phantom materials, composed of polyester resin, acetylene black and aluminium powder simulating fat and bone and a moist jellied plastic made from saline solution, powdered polyethylene and a jelling agent simulating muscle. By varying the content of polyethylene powder and the salinity the dielectric constant and conductivity can be controlled for muscle while for fat the content of aluminium powder and acetylene black controls the dielectric constant and conductivity respectively. From Figs. 1 and 2 it is seen that the conductivity varies with frequency and tissue. This also goes for the permittivity which varies by a factor of 10-20 over the frequency range 1-50 MHz, while the conductivity only changes by a factor of two over the same frequency range.

The fall in ϵ at higher frequencies decreases the skin depth to 10-20 cm i.e. at this depth the r.f. field

has decreased in magnitude by a factor of 1/e. The magnetic field B will thus decrease in strength corresponding to the attenuation term $| I_0 (Kr) | / | I_0 (Kr_0) |$. Maximum effect will be deposited at the surface of the phantom. The occurrence of hot spots should be improbable at frequencies below 100 MHz according to Kritikos and Schwan [6].

Practical design possibilities

The discussion of interaction of magnetic fields with tissues given above suggests three possible designs of a standard instrument for safety assurance. Common to all three is a standard composition of a phantom material. A composition corresponding to 10 MHz is proposed. Alternatively phantoms simulating a frequency range from 1-60 MHz should be constructed from the materials indicated.

Measurement of the pulsed magnetic field

This is the simplest method from a technical point of view. The field may be measured with a Hall probe. The output from the probe must be analysed to give both pulse shape, amplitude and duration. It is not known at present whether the pulse shape plays a role as in the electro-induced healing of bone fractures, where a large effect of asymmetric pulses is observed. From the measured B values the absorbed power, induced EMF and current may be calculated as already described.

Measurement of absorbed power

A simple method is the thermophotographic technique described by Guy [5]. Immediately following exposure of a phantom to a r.f. field the phantom is disassembled and thermographic photos taken. Alternatively holes may at made in the phantom. An empty glass tube closed in one end is placed in the hole. After exposure a thermocouple is inserted in the glass tube to measure possible temperature rises. Temperature rises may also be measured through small insulated calorimeters placed in the phantom.

These methods are suitable for detecting any possibility of local overheating, but they do not take into account the cooling effect of the blood flow. The present guidelines limits the r.f. power to a value corresponding to a SAR equal to the basal metabolic rate. It should be kept in mind that the SAR is proportional to the square of the frequency of the r.f. field. This may put restrictions on use of high frequencies for ^{31}P and ^{23}Na investigations. Bottomley and Edelstein [7] have calculated the power deposited in whole-body NMR imaging. They suggest measurement of surface absorbed power as a better guide to safe exposure levels than average power absorption.

Measurement of induced electromotive force

Bassen and coworkers [8] have described a miniature implantable field probe which may be used to measure the EMF. The probe have only been tested down to 450 MHz, but it should in principle be applicable also at usual NMR frequencies. The probe gives $| E |^2$ directly and may thus be used both as an E-field probe and as a SAR probe since SAR is proportional to $| E |^2$.

Measurement of induced current

This is probably the most difficult procedure experimentally and it is characteristic that no such measurement can be found in the literature. The current induced in the brain has been calculated by Budinger [1, 2] to be of the order of 1 μA/cm^2 for a field change of 1T/s. This is calculated for a loop of 20 cm radius. Davis *et al.* [9] have attempted to measure the current induced in metallic objects through an indirect method by measuring the heat produced by these currents. Apparently the currents were very small even though r.f. fields more than 42 times as great as in normal imaging conditions were used. The currents induced could be calculated from the measured EMF as described above.

Conclusions

In the absence of firm evidence of physiological effects of induced currents and EMF in NMR imaging it is suggested that safety assurance should be based on measurement of surface absorbed power and that an instrument should be constructed for this purpose together with a phantom having ρ and ϵ equal to tissue at 10 MHz. The most critical tissues will be brain and eyes and ρ and ϵ should correspond to these tissues. Corrections and conversions to effects on other tissues are fairly simple using the methods proposed by Bottomley and Edelstein [7]. This instrument will be useful to insure that local heating is kept at safe levels.

At the same time it is of prime importance, that the effects of NMR imaging conditions on tissues used for magnetic orientation both in birds [10] and in humans [11] are carefully evaluated.

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Ann. Ist. Super. Sanità
Vol. 19, N. 1 (1983) pp. 203-204

Discussion on safety assurance in NMR imaging procedures
Moderator: J. S. Orr

RADDA – Could I first of all, just for the record, put it right that Dr. Olsen made a statement that field strengths below 1 Tesla should be safe, and then he mentioned that at 10–20 Tesla one could expect effects. The 1 Tesla is entirely taken out of the hat, and if you look at the British and American standards they now talk about 2 Tesla or below, and even that I think is taken out of a hat. So I think it would be useful to say that certainly 2 Tesla is no different from 1 Tesla in this context.

CHAMBRON – Patient motion in the magnetic field can induce electric current. I suggest the patient should be introduced very slowly into the magnet. Another cause of risk is the break of the magnetic power supply, and in the case of superconductivity there are quenching effects. Some people claim that it is not dangerous. What is Dr. Olsen's opinion?

OLSEN – You are talking about the breakdown in the superconductivity system? I wouldn't think that would be unsafe, because it would take some time to break this magnetic field down. I don't think the dB/dt would be very high.

STYLES – It is not known exactly how a magnet quenches, but when you consider the currents induced in the surrounding metalwork, I think you wouldn't expect the field to die away in time scales of less than about a second, and that's no different from pushing somebody into the magnet on the same time scale. So I think you can do a very relevant practical experiment. Everybody worries about it because it is an exciting event, but I'm fairly happy that it is not likely to be dangerous.

FOSTER – Could I just make one more comment that we are discussing the effects of the magnetic field, and I think the general consensus is going towards the feeling that most of what we are doing in NMR imaging is working within very safe levels. But there is, however, another inherent danger working with magnetic fields that I don't think should be overlooked in any imaging laboratory, and that's the possibility of small flying objects attracted to the magnets. Things like scissors from a nurse's pocket could be actually lethal to the patient and this is probably far more important than the actual field effects on the patient. So we ought to control the people going into the laboratory, and we also have to look for things like this as well as the effect of the field on the patient's tissue. For example a patient with a metallic prosthesis which can actually be twisted by the magnetic field, and if this is a suture in the brain (and this is where commonly steel sutures are used), then again you can have extremely dangerous effects. So it's the effects of the magnetic fields on these other factors which in the long run are probably going to be more important than on the actual tissue itself.

ORR – Could Dr. Radda, who has perhaps had most experience of the highest fields in medicine tell us whether he has made arrangements to get non-magnetic scissors and other equipment? Is it possible to work with tools and small objects which would be quite safe?

RADDA – We have very stringent safety requirements which we have laid down already in our smaller clinical laboratory and certainly even more stringent ones in our large new building. These include, first of all, nobody entering the building without being questioned about pace-makers, all patients being asked a series of questions and screened on the basis of their notes for whether they have had operations or not and whether there is likely to be a metal implant, in which case they would be automatically excluded or X-rayed. Everybody entering the magnet room will enter through only one door, and there is only one entrance that goes inwards – you can escape from the lab by different entrances going through an extremely sensitive metal detector. This is after the people who have entered have been questioned and asked to get rid of all their metal objects, but even then we have a metal detector. We do not allow visitors into the laboratory at any time when there is anybody in the magnet, and they have to observe it from the outside, whether they are qualified or not. There are a number of other requirements like that, and we always have one or two clinicians present who question each individual at length before any examination.

ORR – This leads us to the possibility of an agreement on some such code that we might ask all departments with TMR or with NMR imaging machines to work to. It certainly would be very disappointing if one or two stupid accidents took place through flying objects or metal clips and got the subject into disrepute.

LUITEN – I've just got one other question, coming back to Dr. Olsen's talk. It seemed that various rates of change have been recommended as thresholds, namely 1 Tesla or 2 Tesla/s: Budinger claimed years ago 3 Tesla, and he has more recently released his condition somewhat. What I didn't exactly follow was this: was the 1 Tesla per second related to the 1 $\mu A/cm^2$ in induced current?

OLSEN – Yes, this is what Budinger has calculated for a radius of about 10 cm.

LUITEN – Is there any reason why, say, 1 $\mu A/cm^2$ per sq. cm. has any significance in relation to damaging effects or not? Might it not be the same with 10 $\mu A/cm^2$?

OLSEN – I think that, as Prof. Orr demonstrated in his lecture held in this Institute a few days ago, to produce an effect you have to go about 10–100 times higher in the induced current, so that 1 $\mu A/cm^2$ is really very low.

LUITEN – That means that the present requirements for safety are more based on individual feeling for being careful, rather than having an idea of when it becomes dangerous?

OLSEN – Yes. As Prof. Radda pointed out, the 1 Tesla

magnetic field is just pulled out of a hat.

DERBYSHIRE – I'd like to ask some information. Currently various electrical monitoring equipment is in use and one can envisage that signals or currents could be fed back into the body from the monitoring equipment. What are the acceptable standards with existing equipment?

OLSEN – I'm afraid I can't answer that.

ORR – We have been doing ECG gating and we have had no difficulties, no problems, no damage, no injury, no sensation even. So that doesn't look as if it is going to be a problem.

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CONCLUDING REMARKS

F. Podo

The main topics covered by the presentations and discussions held at the Workshop were the following: present trends in NMR technology in medicine; various technical approaches used in tissue characterization by NMR (imaging; *in vitro* and *in vivo* spectroscopy): problems of the expression of relaxation properties within the NMR image; biological significance of NMR parameters (relaxation times, chemical shift and signal intensity) in relaxation with histopathological, biochemical and physiological data *in vitro* and *in vivo*; technical aspects of the measurements of relaxation behaviour and its relationship with tissue properties; problems of standardization of the *in vitro* and *in vivo* measurements and of calibration of the equipment; possibility of designing a standard instrument for safety assurance of clinical NMR apparatuses.

The consideration of the effects of using different NMR approaches for assessing the relaxation behaviour of tissues and a critical review of *in vitro* and *in vivo* studies suggested the following conclusions. A large number of studies and analyses have actually shown that NMR relaxation properties can in many cases be used to discriminate between normal and diseased tissues. Work in pathology is still in progress, tumours often producing conspicuous results.

There is no doubt that clinical judgements on pathologies will be more reliable if: i) the extremes of the relaxation behaviour of normal tissues were also known; ii) the various intrinsic and extrinsic factors and the mechanisms contributing to the alterations of the NMR relaxation parameters could be better elucidated; iii) the results obtained in different laboratories could be made comparable, by establishing common criteria for the standardization of the procedures and test objects for equipment calibration.

The Participants agreed on the conclusion that the possibility of joining the efforts of individual laboratories in the framework of a collaborative working plan would represent a unique opportunity for solving a number of these problems and facilitating the development of NMR methods for the clinical objective of tissue identification and characterization. A proposal for the performance of a Concerted Action to be caried out under the auspices of the Commission of the European Economic Community (Committee on Medical and Public Health Research) should therefore be submitted to the EEC Biomedical Engineering Group, with the following objectives:

a) to define standardized methodologies in the field of tissue characterization by NMR. This should make a definite contribution towards establishing clinical evaluations of NMR imaging equipment, by making results obtained by various centres comparable and reproducible and therefore more informative;

b) to provide clinicians with up–to–date and more complete information on the relaxation properties of tissues and their relationship with metabolic, physiological and histopathological data;

c) to assist clinicians with the multidisciplinary expertise necessary in the application of these technologies and provide them with a sounder basis for performance assessment, for maintanace, for proper usage and for quality assurance;

d) to reach a better understanding of the most useful kind of information derived from these approaches, which will also help in defining the specifications of simpler less expensive equipment;

e) to focus and finalize the skill of multidisciplinary collaborative teams active in various European Centres;

f) to make available, on a broader multinational basis, the valuable and expensive research that can only be carried out in a limited number of Centres.

Five areas of research will represent the backbone of the working programme of the Concerted Action:

1) development of standardized methodologies for measuring NMR relaxation properties of tissues *in vitro* and *in vivo*;

2) development of test objects and materials for the calibration of equipments for measuring relaxation properties of tissues *in vivo* and *in vitro*;

3) coordination of the collection of NMR relaxation data, together with the relative histopathological and biochemical information;

4) systematic dissemination and exchange of information among laboratories and clinical centres;

5) assessment of the safety of NMR exposure during clinical use.

Linkages among the topics are illustrated in Fig. 1.

The specific content and goals of these research areas, as identified in the work, were the following.

1. Development of standardized methodologies for measuring NMR relaxation properties of tissues *in vitro* and *in vivo*.

Crucial objective of the whole proposal is the identification of abnormal tissues in living humans.

Measurements *in vitro* are important because they can provide information on the relationships between NMR relaxation properties and biochemical, histo– and physiopathological data. Modifications in the local relaxation properties may also, in some cases be referred to systemic effects.

Particular problems to be considered are related to the dependence of relaxation properties on extrinsic or intrin-

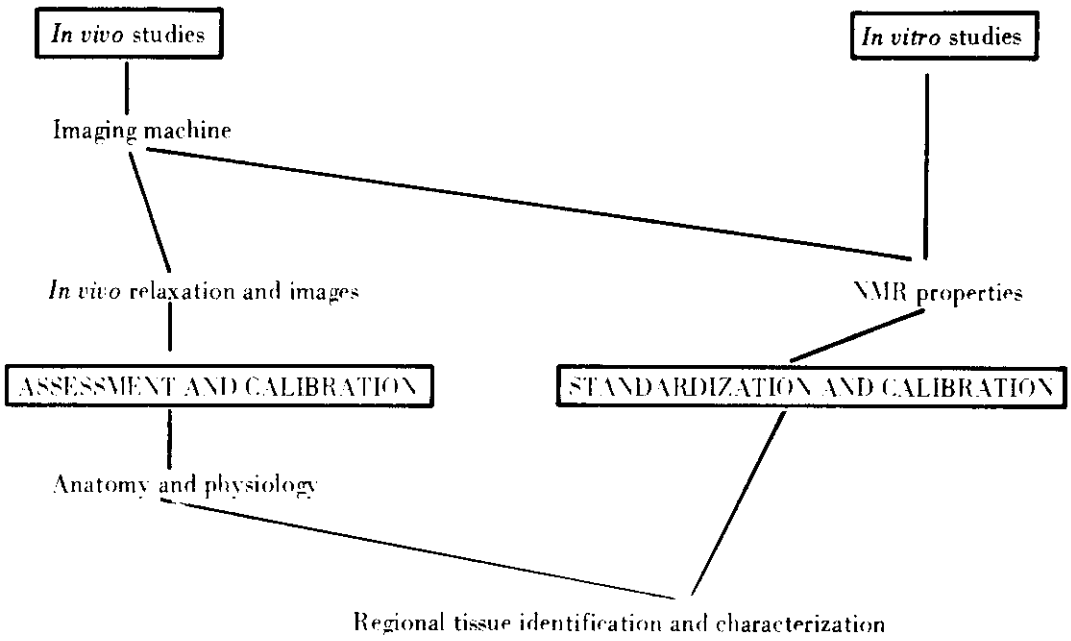

Fig. 1

sic factors (such as tissue handling and preparation, water content, paramagnetic content, temperature, pH, frequency, dependence, etc.) and on measuring approaches.

Specific goals to be reached are:

- development by a multi-centre agreement of protocols for tissue preparation, storage and handling;
- definition of parameters for a proper control of the environment during measurements;
- statement of all relevant experimental parameters which should be given in reporting quantitative measurements.

Further problems are encountered in the clinical measurements of relaxation properties of tissues *in vivo*.

These problems are mainly related to the complexity as well as to the large number of the imaging procedures in use. Because of our insufficient technological knowledge, the optimal approach which would permit the comparison and the evaluation of these different procedures has not been defined.

The main technical problems to be solved for quantitative measurements *in vivo* are related to instrumental parameters such as:

homogeneity and stability of the magnetic static field;

- deviation from a theoretical ideal of the time-dependent magnetic fields;
- effect of different pulse sequences;
- accuracy of the location of the anatomical region under study.

The solution of these problems will also take advantage of the progress achieved by complementary NMR methodologies relevant to tissue characterization, with particular attention to the development of spectroscopy approaches *in vivo*.

Specific outputs of these studies will be:

- presentation and diffusion of the results *in vitro* and *in vivo*;
- application of the protocols and standardized methodologies to a systematic study of an extensive range of normal and pathological tissues.

2. Development of test objects and materials for the calibration of equipment for measuring relaxation properties of tissues *in vitro* and *in vivo*.

Practical requirements for action in this area can be separated into three parts, each requiring specific research efforts at multidisciplinary level:

a) the tests to be carried out in the equipment and their protocols for the execution and analysis.

The instrumental parameters to be assessed and calibrated include: stability and reproducibility, uniformity, artifacts, signal-to-noise, localization and spatial discrimination. The techniques for localization or limitation of regional volumes for more intensive study in imaging machines may differ from the techniques used for the spatial location for the actual image. Such different techniques may be derived from those developed for localization for *in vivo* ^{31}P NMR spectroscopy. Methods and protocols for standardization and calibration of proton NMR parameters should be suitable for such special techniques:

b) the structure of the test objects for performance assessment and calibration.

Test objects should be suitable for use in head and body coils; be capable of covering multiple slices; be suitable for any pulse sequence and a wide range of practical clinical circumstances. Volume dependence should be studied.

c) the substances and their defined NMR parameters and properties to be used in the test objects. Test materials, that might well be based on developments in polymer science, should be identified and/or manufactured with appropriate properties, with particular attention to: electric properties, cost, stability in time and space, known frequency dependence; independent variation of proton density and relaxation properties (T_1 and T_2). For the standardization and calibration of proton NMR parameters for biological tissue characterization, the main additional features for test substances is a controllable deviation of relaxation properties from mono- exponentiality.

Collaborative research will be established in topics a–c, in view of a regular and systematic exchange of information, materials and standard samples between participating centres, on results and problems.

3. Coordination of the collection of NMR relaxation data, together with the relative histopathological and biochemical information.

Once the first area of research is progressed to a satisfactory level, the coordination of the collections of data for selected tissues and diseases will provide a thorough, rapid and systematic assessment of the feasibility and applicability of the NMR approach to the problem of tissue identification and characterization.

4. Systematic dissemination and exchange of information among laboratories and clinical centres.

A mechanism will be established by which data can be rapidly exchanged, active centres can be quickly identified by interested workers results from diverse multidisciplinary fields are not lost in specialized published literature. The attention of the participating Centres will be drawn on the interesting results by circulation of abstracts and newsletters, which will be collected and distributed with regular periodicity.

5. Assessment of the safety of NMR exposure during clinical use.

As increasing number of individuals are exposed to NMR in Europe, it would be valuable to have a means whereby information on clinical safety is exchanged, collected and compared.

Two extensive literature surveys have been carried out so far on behalf of the regulatory agencies in the U.K. and the U.S.A. Both of them are available and a summary of the U.K. survey will be published.

Some experimental work on thresholds of biological and medical effects as well as of potential hazards of human NMR studies is being carried out in several laboratories in the world.

The U. K. is also presently collecting information on all patients and volunteers to NMR exposure.

The conclusion of all these studies should be more widely known and the results from various centres made more comparable. For these reasons European centres interested in the field of safety of NMR exposure during clinical use should join their efforts, in order to collect all available information and provide a fast dissemination of the results, by utilizing the exchange mechanisms indicated above.

This work will also facilitate the task of developing appropriate test equipment to ensure that NMR instrumentation is performing within specification so far as safety is concerned.