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MR imaged polymer gel radiation dosimetry: Disclosed yet unpatented.

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Abstract

The advent of complex radiotherapy techniques has created new challenges for radiation dosimetry. Intensity modulated, stereotactic, conformal radiotherapy, radiosurgery and brachytherapy present a field where both spatial and quantitative accuracy become crucial to the success of the treatment. Methods for true 3-D dosimetry are mostly based on various forms of chemical dosimetry such as Fricke dosimetry and the radiation-induced polymerization in solutions of monomers. The 3-D spatial information in these methods is preserved by embedding the radiosensitive chemicals in gel matrices which provide the necessary spatial stability of the dosimeter. The chemical changes in each of these dosimeters are measured by the NMR relaxation characteristics of it (longitudinal or transverse MR relaxation rate R1, R2) which are proportional to its absorbed dose. Advances in the chemical composition of the gels alleviated many irradiation, calibration and measurement uncertainties. Furthermore advances in MRI technology lead to a more robust and reliable measurement method for 3-D polymer gel dosimetry. It is the scope of this work to present a roadmap, of the progress made thus far in MR imaged polymer gel and offer a discussion for the reasons that such a large part of this progress had been disclosed yet unpatented.

Keywords: 3-D radiation dosimetry, Chemical radiation dosimetry, Fricke gel dosimetry, Polymer gel dosimetry, MRI gel dosimetry, NMR pulse sequence, MRI pulse sequence, MRI relaxometry, T2 MRI relaxometry, T1 MRI relaxometry

Introduction

The advent of complex radiotherapy techniques has created new challenges for dosimetry. Intensity modulated, stereotactic, conformal radiotherapy, radiosurgery and brachytherapy present a field where both spatial and quantitative accuracy become crucial to the success of the treatment. These complex radiotherapy schemes require accuracy in the “grey areas” of conventional dosimetric techniques. For example, mapping the dose in high gradient areas, (at the edge of a beam or near a field shaping block) or true three dimensional dose maps as opposed to low resolution multi point TLD or ionization chamber measurements always presents challenges for conventional dosimetry [1]. The sophistication level required in these contemporary radiation therapy techniques is implicitly declared by several patents pertaining solely to methods of calibrating radiation dose curves [2,3] and appropriate phantoms [4].

On the other hand methods for true 3-D dosimetry have been introduced and explored for quite some time. Most such methods are based on various forms of chemical dosimetry such as Fricke dosimetry which is based on the radiation induced oxidization of ferrous ions (Fe^{2+}) to ferric iron (Fe^{3+}) upon irradiation [6], the color changing of Folin's phenol [7] and the radiation-induced polymerization in solutions of monomers [8]. It is worth noting that one of the first patents in the area was filed as early as 1957 and awarded in 1960 [5]. The 3-D spatial information in all these methods is preserved by embedding the radiosensitive chemicals in

various gel matrices which provide the necessary spatial stability of the dosimeter. The optical density and the NMR relaxation characteristics (longitudinal or transverse MR relaxation rate R1, R2) of these specific chemicals are proportional to its absorbed dose [1].

As it becomes apparent the means for 3-D dosimetry were available a bit earlier than the need for their utilization. When, though, that need arose the interest in these methods became significant. This interest was reinforced when advances in NMR technology made MRI equipment widely available to the healthcare community.

Although methods other than NMR have been developed to assess irradiated gels, for example through optical computed tomography [9,10,11,12], MRI gel dosimetry became the current standard for true 3-D dosimetry. This is due to the fact that two of the three aforementioned methods, namely Fricke dosimetry and radiation induced polymerization can be quantitatively assessed through the measurement of respectively the longitudinal and transverse NMR relaxation times (T1 and T2) [1,13]. That combined with the widespread introduction of MRI systems in healthcare institutions led to the establishment of MRI read gel dosimetry as the de-facto standard of 3-D clinical dosimetry.

Additionally, significant ferric ion diffusion in Fricke gels seriously compromises their temporal and spatial stability [13]. Although significant work has been conducted in order to measure and compensate through various ways for that diffusion, [14-19] the introduction of radiosensitive polymerizing monomer gels [20] has considerably widened the scope of 3-D gel dosimetry.

In the past years some excellent reviews have been published. Day [24] presented a comprehensive introductory review on the subject while McJury and colleagues [1] in 2000 presented the current, at the time, state of the art on the subject. At the same time Chu [13] presented a comprehensive overview of current developments on the often overlooked subject of Fricke gel dosimetry. The last review on the subject, published in 2002 by MacDougal and colleagues [25], put forth the issue of accuracy and precision, certifiable by standard dosimetric methods (i.e. ionization chambers and TLDs).

The present work aims to present the both the pitfalls in the practical implementation of such a 3-D dosimetric system and the solutions that led to several patents in the field of biomedical engineering. The manufacture of the gels and the various chemical issues that can be introduced from the process, calibration errors and irradiation issues, measurement errors arising either from the MRI system or even from the mathematical models used to derive the relaxation parameters of the samples all comprise a chain of procedures each of which can introduce errors and uncertainties to the final dosimetric result. As it will become apparent, it is interesting that, although a large volume of applied scientific information is disclosed in the scientific literature there is a conspicuous absence of relevant patents. It is the scope of this work to present a roadmap, as documented in the current literature, of the solutions to the obstacles that await anyone interested in introducing, with an acceptable level of reliability, this sophisticated dosimetric technique in clinical practice. Furthermore some insights will be presented as to the reasons pertaining to the disclosure of such a large volume of applied scientific information without the filing of relevant patents.

The basics of radiation polymerized gels.

The principle of operation in a polymerizing dosimetric gel is radiation induced polymerization. Free radicals produced from the radiolysis of water react with the monomers of a gel (initiation stage) creating increasingly large macroradicals (polymerization stage) until two such macroradicals form a stable polymer macromolecule (termination stage). For a more thorough analysis of radiation induced polymerization the reader is referred to [26]. So, in principle, a polymerizing dosimetric gel consists of a hydrated gelling agent and a, usually crosslinked, monomer contained in either an airtight container devoid of any oxygen or, as more modern solutions suggest, containing a fair amount of antioxidants. The gelling agent is used to provide mechanical stability, to keep the formed polymers in their point of formation, thus preserving the spatial dosimetric information, and to provide the means to polymerization in the form of the water molecules embedded in the gel. On the other hand the monomer is the main actor in the process of polymerization. The anoxic conditions [20] or the introduction of antioxidant agents (for example copper initiated ascorbic acid or THPC) [27, 28] in the gels address the first significant issue that arises in the chemistry of polymer gel dosimetry which is oxygen contamination. The free radicals produced from the radiolysis of water are readily scavenged from any amount of oxygen existing in the gel thus inhibiting the polymerization process [20].

In the polymerized regions different populations of water vary their state of binding and exchange protons with the polymer structure. The NMR relaxation characteristics of these trapped protons are dependent on both the concentration of the polymers (which is directly proportional to the absorbed dose) and to the specific polymer

structure (which is dependent upon the specific chemical composition of the monomers) [1]. These dependencies lead to an increase in the transverse MR relaxation rate R2 of the gel proportional to its absorbed dose. It has been experimentally ascertained that R2 can be described by a model of fast exchange of magnetization between three pools of protons. These are a) the gel pool that remains unaffected from the gel's irradiation, it only defines the relaxivity background of the gel, b) a mobile pool consisting of water and monomer protons and c) the polymer pool. It is the transfer of protons from the mobile pool to the polymer pool due to radiation induced polymerization that leads to an increase in the total relaxivity of the irradiated gel [29].gel.

The evolution of the polymer gel dosimeters

All these factors as they were explored from the inception of polymer gel dosimetry have led to an evolution of the dosimetric gels. Although not an exhaustive reference Table 1 provides a detailed roadmap of the evolution of these gels' compositions. The initial composition of the polymerized radiosensitive gels useful in clinical radiation dosimety [20] was also the first to be patented [21] as such. There were of course some initial proof of concept patents in 1960 [5] and 1971 [22] but the field of application was not explicitly described in the patents. Furthermore a patent pertaining to the manufacture of a radiation sensitive material filed in 1989 [23] could not be construed as a predecessor in the medical dosimetry field since it was sensitive, as per its claims to doses: "…as low as 300 greys" while the largest total dose a radiotherapy patient is going to be exposed to in all radiotherapy protocols is in the order of tens of grays fractionated down to only several greys per session.

The first improvement to the initial composition of polymer gels [20] was to substitute agarose with gelatin as a gelling agent [34]. This resulted in an order of magnitude decrease of the relaxivity of the unirradiated gel improving in that way the gel's dosimetric dynamic range. Furthermore gelatin forms more transparent gels allowing for easier macroscopic visualization of the polymerization process. Additionally its slower transition from solution to gel helps to create more uniform gels, significantly reducing spatial non uniformities in the gel matrix which would create artifacts during the readout process [34]. It is interesting to note that while the patent for the initial invention of the polymerizing gel was filed by Maryanski, Gore and Schulz in 1992 the final patent awarded to them in 1994 includes this advancement in the polymerizing gel's composition by mentioning in the claims both agarose and gelatin as gelling agents [21]. Departing from this basic composition, the substitution of acrylamide in these gels with acrylic acid significantly increased its sensitivity [35], while an experimental study [36] of the effects of monomer and crosslinker concentration led to the conclusion that increased concentrations of them increases sensitivity. While these concentrations create problems in the manufacturing of the gels (namely solubility problems and gel homogeneity problems) adherence to good chemical practices can lead to the creation of gels both sensitive and homogenous [36]. Furthermore the introduction of liquid state monomers like N-vinylpyrrolidone in gel dosimetry [37] further alleviated these chemical issues but with a decrease in low dose region response. More improvements increased the sensitivity of these gels [38] and even addressed the problem of toxicity that exists, as most of the monomers used in these gels are highly toxic [39]. It is interesting to note that, while these advances led to significant improvements in the performance of polymerizing radiosensitive gels, there were no patents filed for them.

More surprising is the fact that probably the most significant breakthrough in the field of radiosensitive polymerizing gels is not patented. That one major breakthrough that made polymer gel dosimetry more accessible was the introduction of normoxic gels, that is, gels that can be manufactured in standard atmospheric conditions. That was achieved by introducing into the gel some form of antioxidant. The first antioxidant that was employed was ascorbic acid initiated by Copper (introduced in the form of $CuSO_4.5H_2O$). The lack of even trace oxygen amounts in the gel after their manufacture led to increased gel sensitivity to non radiation induced polymerization (such as spontaneous chemical or photopolymerization). For that reason hydroquinone, a free radical scavenger, was introduced in small concentrations to prevent this phenomenon from becoming prohibitively pronounced [27]. Subsequent modifications to both the concentration of the ingredients and even the type of antioxidant agents used [28,40,41] have led to the manufacture of sensitive gels, even in the relatively low dose area between 0.3 and 5 Gy [40]. As mentioned before, conspicuous in their absence are any filed patents for these significant breakthroughs that led to the development of more easily accessible three dimensional polymerizing gel dosimeters.

Solutions to errors and uncertainties pertaining to the manufacture and the chemistry of dosimetric gels.

Chemical composition

From the discussion made up to this point it becomes apparent that all chemical components of a gel play an important role in defining the NMR characteristics and subsequently its specific response to radiation. It has been proven [30] that the compactness of the gelatin matrix affects the transverse NMR relaxivity of the gel and subsequently its dose response. Furthermore the type of the monomer that is used in each gel has a significant effect on the relaxation characteristics of the water protons that are embedded in it. In fact it has been determined that while, at approximately physiological pH, there is a proportionality between magnetization transfer (MT) rate and OH surface density of the monomers a far more significant sensitivity of the MT to the presence of carboxyl groups exists [31]. Even crosslinker density has an effect on the NMR relaxation characteristics of a dosimetric gel. Experimental results have shown that increased crosslinker density can lead to increased rigidity of the polymer matrix which would result in increased transverse relaxivity of the gel [32]. In fact it has been established that the concentration of the gelling agent defines the minimum relaxivity of the gel [29,33]. This minimum relaxivity is the equivalent of the background noise level for other detectors. Any radiation dose that would cause a relaxivity change lower than that level would go undetected because the relaxivity of the gelling agent itself would overshadow it. Hence that minimum relaxivity defines the absolute lowest limit of detectable dose of the particular dosimetric gel before any other factors are taken into account. On the other hand the comonomer concentration defines the range of relaxivity values, the slope of the response curve, that such a gel can reliably distinguish [29,33]. An increase in comonomer concentration in fact increases the dynamic range of the gel while reducing the capability of the gel to detect slightly differing doses. From this discussion it becomes apparent that an assessment of the dosimetric problem that needs to be explored is necessary before the correct gel composition may be determined.

Oxygen diffusion

If there is one issue that can be considered a “showstopper”, if left unchecked, in polymer gel dosimetry, that is oxygen contamination of the gels. As was mentioned previously, oxygen aggressively scavenges free radicals therefore quenching the initiation stage of the radiation induced polymerization process. This definitive impact of oxygen contamination is the reason that a large volume of research in polymer gel dosimetry is dedicated to identifying, quantifying and alleviating that source of error.

The straightforward solution for preventing oxygen from infiltrating gel dosimeters was anoxic conditions during manufacture. For that reason several methods have been employed. The first method was bubbling inert gases (usually nitrogen even though other gases have been used too [37]) through the gels [20] and sealing them airtightly. The incorporation of gel dosimetry into clinical research put some of that area’s knowhow to good use, using prefilled nitrogen glass vials, thus far used for the containment of radiopharmaceuticals, as gel containers [42]., For manufacture of large volumes of gels into appropriate phantom shapes came the need for the use of a glove box with an inert gas atmosphere [43].

Oxygen contamination issues do not end in the manufacturing process of the gels. The material of the gel container plays a significant role in the diffusion of oxygen into the gels. It is established that plastic is not impermeable to oxygen [44]. So for gels stored in plastic containers oxygen will dissolve through the walls and will slowly diffuse into the gel rendering it inert as a polymerizing dosimeter. It has been suggested by more than one authors that for the anoxic gels care must be taken for them to be stored exclusively in glass containers which are impermeable to oxygen or, if that is not possible or desirable (possibly due to adherence to strict dosimetric considerations regarding inhomogeneities in phantoms), the gels must be irradiated as soon as possible after manufacture to avoid air forming a desensitizing front that would render the outermost part of the gel useless [34,36].

Unlikely as it may, at first, seem it has been postulated that oxygen contamination could have a beneficial effect in polymer gel dosimeters. It was theorized that once the gels have been irradiated and polymerized, oxygen could be used to terminate further polymerization, therefore stabilizing the dosimeter and providing a time independent three dimensional dose distribution [45]. Nevertheless it has been determined that oxygen diffusion does not affect uniformly the volume of a gel. In fact oxygen diffusion affects most severely the edges of the gel where usually there are strong dose gradients (due for example to the irradiaton field’s penumbra) which are crucial to be accurately mapped [46]. In that same study both theoretical and

experimental evidence point to the fact that exposure to oxygen would affect the gels only up to a certain depth and that artificial gradients in the dose distribution would be created by that effect.

Further research [43] has proved that, even in an oxygen-contaminated area of a gel, there is a dose threshold above which a gel responds to exposure. From this study it has been determined that up to a maximum oxygen concentration there is a linear correlation between that concentration and the dose threshold. That means that up to that maximum concentration oxygen acts as an ideal inhibitor; inhibiting the polymerization reaction by scavenging free radicals. When the dose is high enough that all oxygen is consumed by the inhibition reactions then the response of the dosimetric gel is not affected any more by oxygen in any way. For example there is not any change in the slope of the dose response curve. Beyond that maximum oxygen concentration (as is also the case for chemical induced emulsion polymerization [47,48]) oxygen acts also as a polymerization retarder, not only affecting the dose threshold above which the gel becomes responsive to irradiation, but affecting also the kinetics of the polymerization reactions modifying the slope of the dose response curve [43].

Photopolymerization

All the monomers used in the manufacture of radiosensitive polymerizing gels are susceptible to photopolymerization. So care is taken after manufacture of the gels that they are stored away from excessive exposure to light [20,34]. Furthermore in all normoxic gels a small amount of Hydroquinone is added in order to quench such spontaneous polymerization effect [27].

pH considerations

There have been strong experimental evidence that polymerizing gels' transverse relaxation rates depend strongly on the gels' pH. In fact poor reproducibility of the dose response of the first polymerizing radiosensitive gels has been observed at acidic pH [20, 32]. A number of explanations have been offered for this experimental find. A complex multi-equilibria proton exchange model that is not based on a simple acid based catalyzed chemical exchange process, surface group pK dependence or even a dependence of the morphology of the surface group from the pH are all possible explanations[31]. Nevertheless the fact of the matter remains that the gels with the best reproducibility in dose response are those that have near neutral pH [20]

Temporal instabilities

Radiation induced polymerization is a chemical process that does not end at the time of exposure termination. Even the unirradiated gels present a considerable change in relaxivity rates (R1 and R2) with the passage of time which was attributed to spontaneous polymerization of the gel due to the existence of free radical impurities in its components. Experimental results have shown that gel sensitivity to radiation increases rapidly in a time span of 1 to 4 days and then it considerably slows down, a fact which is attributed to polymerization chemical kinetics [45]. It has been suggested that the prolonged polymerization process that leads to a gradual and prolonged increase in R2 rates is related to the increase in viscosity of the gel as polymerization proceeds, which leads to slower chemical reaction kinetics [49].

Further studies [50] revealed that these relatively fast temporal instabilities that are followed by prolonged slow temporal evolutions are in fact two parallel chemical processes. One is the post irradiation polymerization which has a time frame of several hours, while the other is the gelation process that has a time frame of many days. In fact it has been shown that the two processes affect different components of the gels' dose response. Prolonged polymerization, a process which saturates approximately at 12 hours after irradiation [51], affect the slope of the dose relaxivity curve of the gel, while the continued gelation process, which spans approximately 30 days, affects the intercept, that is the baseline relaxivity of the unirradiated gel [50]. Furthermore it is interesting to note that normoxic gels present the opposite behaviour than that described so far for anoxic gels. These gels, probably due to differences in their polymer structure, show reduced sensitivity as time passes [30].

Taking into account the previous remarks concerning temporal stability of dosimetric polymer gels it has been suggested that while immediate imaging of the gel after irradiation is not preferred, a time interval no more than 4 days should be allowed to pass between manufacture and imaging of the gels while a time span of 12 hours ensures that the polymerization process induced by irradiation has reached an adequate point [45,50].

Chemically induced Edge enhancement

Spatial stability is one of the main positive characteristics of polymerizing dosimetric gels. In fact it is the main advantage that these gels have over Fricke gels which present serious diffusion problems, distorting in this way the spatial dosimetric information [20]. There is however a serious spatial instability that manifests itself several hours after irradiation. At high doses, free radicals saturate the irradiated area of the gel and create long lived macroradicals that react with monomers that are slowly diffusing from unirradiated areas of the gel near the edge of the radiation field. That creates an area of increased polymer concentration near the edge of the radiation field thus overestimating the dose there [30]. Since this phenomenon is dependent on the slow diffusion of monomers through the gel, a practical suggestion arising from the previous study is the timely measurement of both normoxic and anoxic gels before that effect becomes too pronounced.

Solutions to uncertainties pertaining to the calibration and irradiation of dosimetric gels.

Calibration

Polymerizing gels are not absolute dosimeters. The physical property that is measured by use of MRI on these gels is the transverse relaxivity of them and it must be translated to absorbed dose. This calibration process is accomplished, from the inception of the method, by exposing a part of the gel to known amounts of radiation and measuring its transverse relaxivity, this way creating a calibration curve. The most straightforward method, and that which has most extensively been used, for deriving such a calibration curve, is by homogeneous irradiation of a series of gel containers to known doses [20,34,52]. However this method requires a significant amount of gel to be spent on obtaining the calibration curve. As the relaxivity - dose curve of the gels depends on the specific “history” of each batch of gels, like small chemical differentiations between different batches, mixing time, thermal history of the gel and pre- and post-irradiation times [50,53], there is a need for producing a different calibration curve for each batch of gels that is manufactured. For that reason more efficient calibration methods have been suggested. The first is making the gel into a larger area container that can, afterwards, be irradiated to different doses at different locations [36]. Another method even more effective, as far as gel economy and accuracy is considered, consists of transversely irradiating a gel test tube into a water tank and obtaining a depth-relaxivity curve which then is compared to a depth-dose curve acquired by an ionization chamber to obtain the dose-relaxivity curve [53].

It has been assumed that the mathematical model describing that calibration curve is a simple linear one. For a large part of the dose ranges that are used in radiotherapy applications this has experimentally been proven to be correct [35,36,53]. However exploring a wider dose range field leads to the conclusion that the calibration curve shows reduced slope at very low and very high doses and can be better approximated with a bi-exponential model. The reduced dose response in these doses has been attributed, for the low dose part, to chemical inhibitors like oxygen competing with the polymerization process, and for the high dose part, to consumption of the monomers in the gel after a large part of it has been polymerized [50].

Tissue Equivalence, type of radiation, energy and dose rate dependence of the dose response

The mass and electron density of polymerizing gels makes them radiologicaly tissue equivalent for the range of energies usually encountered in external beam radiation therapy [35,27,41]. There is a number of reports in the literature that supports the consensus that the dose response of polymerizing dosimetric gels is independent of dose rate, energy and type of radiation for the types of radiation usually encountered in a radiotherapeutic clinical setup [35,52,54,55]. More recent studies though reported differences in the dose response of both normoxic and anoxic gels with different, clinically relevant, dose rates and energies [41,56,57], Furthermore tissue equivalence of the gels is violated at low energies (<60 keV) due to the predominance of the photoelectric phenomenon against Compton scattering that dominates standard external beam radiotherapy. Nevertheless the dose underestimation that occurs at these energies does not exceed 5% while the relevant corrections at these energies for standard TLD dosimetry sometimes exceed 40% [58]. On the other hand a study of a certain normoxic gel reported a more pronounced under-response at high LET

radiation, specifically where the linear energy transfer (LET) exceeds a certain threshold (4.9 keV/μm^2) [59]. To put this figure into perspective, for a 20 MeV electron beam LET does not exceed 0.5 keV/μm^2 while for the Co-60 γ-rays LET reaches only up to 2 keV/μm^2 [60]. In the previous study [59] it is postulated that the dose rate response of a gel at a much increased dose rate has approximately the same effect as a high LET radiation due to close proximity of the interaction sites increasing free radical yield and thus increasing the number of recombination reactions between free radicals as opposed to polymerization initiation reactions. Additionally there are collaborating indications, in a recent feasibility study of normoxic gels as internal dosimeters in targeted radionuclide therapy, that dose rate may be responsible for differing dose response of gels utilized at different irradiation setups [61]. Even in relatively small radiation doses such as those encountered in interventional radiology, an effect of dose rate in gel response has been observed. In fact it is postulated that the same chemical kinetics that lead to a decrease in gel sensitivity at dose rates encountered in radiotherapy have the opposite effect, (increase in gel sensitivity), in extremely low dose rates such as those encountered in radiologic irradiation setups [62]. However corrections for dose rate differences between, for example, calibration gels and the dosimetric gels would require prior knowledge of the absolute dose distribution and the dose rate distribution if that was varied over the irradiated volume (for example in intensity modulated radiation therapy) which is, for most applications of gel dosimetry, unfeasible[57]. So it is recommended that either the dose rate is kept constant, or if that is not possible, use of polyacrylamide based gels (PAG) is made, since these have significantly lower dose rate dependence [41].

Solutions to errors and uncertainties related to MR imaging of dosimetric gels

Image noise effects

Between the longitudinal (R1) and the transverse (R2) MR relaxation rate the latter is the parameter of choice in the mapping of dose distributions in polymerizing gels due to its higher signal to noise ratio (SNR) that leads to increased sensitivity vs the longitudinal relaxation rate R1 [20,63].

Nevertheless R2 maps are not perfect. The pixel by pixel calculation of R2 involves one of two methods. Either two base images with different T2 weighting are used to create a look-up table of signal ratios vs transverse relaxation time T2 (T2=1/R2) or an appropriate least squares fit is applied pixel by pixel on a set of base images of increasingly heavy T2 weighting. The random noise of these images propagates to the calculated maps through the calibration curve finally affecting the dose distribution imaged on the gel. That effect is dependent upon the pulse sequence's echo spacing, the method of relaxivity computation and the acquisition fraction (the ratio between each image's number of acquisitions and the total number of acquisitions).All these factors can be optimized for maximizing the end image's SNR It has been theoretically and experimentally supported that the effect of base image noise has a far more pronounced effect when utilizing the two point method than the multipoint calculations if the same number of acquisitions per base image is maintained [64].

Eddy currents effects

Eddy currents result in a time-dependent spatial variation of the magnetic field of the magnet [65]. This leads to loss of image resolution, geometric misregistration, signal loss, phase distortions and tilting of the image plane [65,66]. The effects mentioned above create spatial shifts in the base images which become more pronounced in areas of widely differing relaxivity rates thus creating edge artifacts [67]. Bearing in mind the importance of accurate edge registration in gel dosimetry the importance of compensating for eddy currents is obvious.

Eddy currents can be compensated at the hardware level by using a compensation network or active shielded gradients [68-70] while at the pulse sequence level they can be minimized by reshaping the imaging gradients [71,72]. If such capabilities are not readily available (as is the case with many clinical MRI scanners) the application of a gradient train before the excitation pulse in the multiple echo sequence brings the variation of the static magnetic field ΔB_0 to steady state. Therefore all spin echoes and stimulated echoes experience the same frequency offset eliminating the image to image spatial misregistrations that lead to the edge effects mentioned before [67]

Effects of B1 inhomogeneity

Apart from eddy currents B1 inhomogeneity is another reason for imperfect slice profiles which lead to artefactual voxel relaxivity measurements with subsequent dose distribution inaccuracies in the case of polymer gel dosimetry. Non ideal RF coil geometry and electronics, the digitization of the RF pulse and penetration of the scanned object [73 - 79], all factor in as reasons for B1 inhomogeneities. Suggestions for correcting them include scanning the sample piecewise to exploit the RF coil's area of high homogeneity, using the a combination of body coil as emitter and surface coil as receiver and mapping of the effective flip angles of the sample so that they can then be used to correct R2 maps [79].

Effects of Temperature drift during scanning

During MR scanning deposition of EM energy to the object scanned leads to a rise of its temperature [79]. Since T2 is a temperature dependent parameter [20,80], the temperature drift is translated to a T2 drift. So each base image will be differently weighted not only due to differing echo time but also due to varying R2(R2=1/T2) rate. This effect, through the calibration process, will introduce dose estimation errors in the case of imaging polymerized radiosensitive gels. It is interesting to note that it has been determined [81] that the gels with the highest dose sensitivity are those that are more adversely affected by temperature increase. As a first precaution it has been suggested that care must be taken to use pulse sequences that do not deposit excessive amounts of RF energy to the sample. Furthermore a simple solution that has been suggested was the application of a centric k-space filling instead of a linear one. That way the rising temperature as the sampling of the k-space proceeds, will affect only slightly and only areas of steep dose gradients [82].

Diffusion effects.

The thermal motion of water molecules that are affected by strong gradient fields causes attenuation of the MR signal [83,84]. The statistical nature of this diffusion means that its effect is variable between the different echoes that are employed to acquire the set of base images constructing the relaxivity map of a sample. This way the calculated relaxivity of a gel sample is increased by that diffusion phenomenon with obvious detrimental effects to the accuracy of its dosimetric behavior.

It has been experimentally determined that diffusion effects on relaxivity rates are strongly manifest only in very high resolution MR imaging where strong imaging gradients are used to provide the high resolution. Since there are cases, like dosimetry very close to brachytherapy sources that this high resolution is desired care must be taken to correct R2 maps for diffusion especially if the calibration samples are imaged in different resolution than the phantoms [85].

Pulse sequence considerations.

The pulse sequence that was first used to produce the base images for construction of dose maps from polymerized dosimetric gels was the golden standard for transverse relaxivity measurements CPMG [84,86] sequence [20]. It was not, however, the only one that was used for this reason in all the years that have seen the utilization of MR imaged polymer dosimetry as a 3-D dosimetric method. Classic spin echo [87], fast spin echo [88], turbo gradient spin echo [89], and echo planar imaging [90] have been utilized to image polymerizing dosimetric gels [91,92].

From these studies it has been determined that fast pulse sequences can produce accurate results in polymer dosimetry. Specifically an optimized fast multiple spin echo sequence is determined to be on par with the true and tested CPMG sequence.

For a quantified comparison and optimization of the performance of different pulse sequences within the scope of polymer gel dosimetry apart from the signal to noise ratio (SNR) the concept of dose resolution has been introduced in polymer gel dosimetry. This quantity, that is not applicable only to MRI polymer gel dosimetry but to every dosimetric method, is defined as "the minimal separation between two absorbed doses such that they may be distinguished with a given level of confidence" [93]. Through the use of this parameter each of the three aspects that define MRI gel dosimetry (MR parameters, estimated dose range and gel's composition) can be optimized if the other two are clearly defined [33].

Solutions to errors and uncertainties related to the calculation method of relaxivity maps

Relaxivity maps can be derived from two differently weighted Spin echo base images utilizing a simple look up table that translates the signal ratio to relaxivity rate [94]. Nevertheless the most common way for deriving transverse relaxivity maps, since the introduction of the multi-echo CPMG sequence and its variants have been to collect a series of base images and then do a pixel by pixel fitting of the signal values to a usually mono exponential mathematical model. T2 (and subsequently its inverse R2) can be derived either by applying a standard linear regression least squares fit to the semilogarithmic plot of the signal vs echo times or by applying a generalized maximum likelihood estimation of the mathematical model's parameters. Although the two methods seem identical the noise inherent to the signal differentiates them. Specifically it has been proven that a maximum likelihood estimation, in the form of a non-linear least squares fit of the data on a monoexponential mathematical model, is preferred to a linear regression parameter estimation based on the semilogarithmic plot of the signal vs echo times [64].

Even the algorithm that is utilized to solve the minimization problem in the least squares estimation of the relaxivity rates contributes to the dosimetric result that will be derived from them. Evolved from the older steepest descent and Gauss-Newton methods of function minimization the most widely used algorithm for least squares parameter estimation is the the Levenberg-Marquardt algorithm [95,96]. Although a robust method, in some cases this algorithm converges to a global minimum very slowly or not at all. Since usually the problem of parameter evaluation in relaxivity measurements is a constrained one (for example all the parameters in the physically relevant mathematical model are positive and their highest values are constrained by physical considerations) constrained minimization methods such as a trust-region algorithms have the potential to yield faster and equally accurate convergence [97,98]. Furthermore stochastic optimization methods such as the simulated annealing method for multi variable functions [99] have the potential to provide even more flexibility in producing relaxivity maps from base images that have more than one imaging parameter as variable (for example images with different T2 and T1 weighting).

Discussion

What has become apparent in its glaring absence in the article above, is the almost non-existent patent coverage of all the disclosed applied scientific information in that field. There are few patents pertaining to the field of gel dosimetry [5,22,23] and specifically only one pertaining to medical three-dimensional dosimetry read by means of an MRI scan [21]. That in itself is a fact worth exploring. It is common knowledge that for a patent to be legally awarded in its core it must have 4 distinct characteristics: **Novelty, Utility, Non-obviousness** and **disclosure**.

From the details reported in this review there can be no argument of non-**disclosure** since methods and materials reported here are routinely reproduced in medical facilities and research institutions with consistent and repeatable good results.

Another argument that cannot be raised for that fact is one of non **utility**. MR imaged polymer gel dosimetry combines three very desirable dosimetric characteristics. It is a 3 dimensional dosimetric technique, it combines detector and phantom and the material that constitutes the detector is, for the most part of clinically useful dosimetry, tissue equivalent material.

Oxygen diffusion, Free radical saturation at high doses and MR artefacts if left unchecked can cause serious distortions in the calculated dose maps especially in those important areas in the vicinity of the steep dose gradients. Additionally care must be taken so that both the chemical composition of the gels and the pulse sequence parameters used for imaging those gels are optimized for the expected dose range of each specific application for the best possible dosimetric result. Furthermore from the study of the behaviour of these gels in the "fringes" of dosimetric applications there are evidence that special corrections must be made since the characteristics of tissue equivalence is not maintained in all energy ranges [56]. Additional corrections have been devised since independence of the dose response from the energy and dose rate in these gels is also not maintained in the extremes of these parameters [59,61]. So an argument of insufficient **novelty** cannot stand since designs and methods of similar or even less novel scope have been patented (cf. [2,3,4]).

Similarly invalid are any arguments of **obviousness** of the applied scientific knowledge made.

As it appears the main reason for researchers not pursuing patents on this field of research is one of **scope of application**. This dosimetric method has yet to find routine use in everyday clinical environment. There are of

course advances in polymer gel dosimetry, with most notable the introduction of normoxic gels, which make this method far more accessible than what it was in the past. Nevertheless, while MR equipment capable of coping with the needs of polymer gel dosimetry is available in most clinical environments that host a radiotherapy department, the chemical equipment and expertise required for the manufacture of these gels are not yet to be taken for granted. So the limited as of yet scope of application discourages the filing of further patents regarding that subject.

Current and Future Developments

As further streamlining this dosimetric method from gel manufacture to dose map derivation is achieved and as the exotic radiotherapy techniques of the past are rapidly becoming the mainstream of the present, the scope of this research widens and three dimensional polymer gel dosimtry emerges as a reliable tool for supporting these sophisticated techniques. As recently as 2006 after a gap of almost 12 years another patent pertaining to “three-dimensional dosimeter for penetrating radiation and method of use” [100] was filed signifying an increase of interest in patenting the large volume of research exploring the capabilities of 3-D and especially polymer gel dosimetry.

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