Feasibility of Gd Contrast Agent in Spectral Computed Tomography

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Abstract

X-ray computed tomography (CT) is currently a vital diagnostic tool in hospitals the world over. To be able to image a patient’s interior quickly can facilitate a diagnosis so that proper treatment can be administered. In some cases a contrast agent is administered intravenously prior to the CT-scan, in order to enhance image quality. Most contrast agents are heavy-element based and have a sudden increase in attenuation at the k-edge due to photoelectric absorption of the photons.

New technology utilizing multi-bin spectral CT is under development. This technology opens up for the possibility to isolate the image contribution of this sudden increase in attenuation at the k-edge.

This report investigates the feasibility of using gadolinium-based contrast agents (GBCA) in multi-bin spectral CT. With a high k-edge, gadolinium is well suited for k-edge imaging. However, GBCA are currently only endorsed for magnetic resonance imaging (MRI), raising the question if currently used concentrations are sufficient for CT practice.

We model two cross-sections containing targets of various areas and determine the detectability of said targets for concentrations currently endorsed in MRI. Higher concentrations are considered when motivated.

We conclude that detection of lesions and haemorrhaging in soft tissue, as well as cerebral haemorrhaging, is possible with the concentrations currently exercised in MRI. Additionally, we conclude that to detect residual blood flow in the case of ischemia caused by thrombosis, higher concentrations must be considered.

These results clearly indicate that currently endorsed concentrations of GBCA, in combination with k-edge imaging, could provide sufficient contrast in CT-practice.
1 Introduction

CT is a medical imaging procedure based on X-ray imaging where two-dimensional cross-sections, tomographic images, of a patient’s interior are taken along a single axis of rotation. The images can be analysed separately to detect abnormalities, or used to create a three-dimensional model to plan a surgical procedure, for example.

Tomographic images are obtained by analysing the attenuation of X-ray photons along a projection line. To enhance contrast in target areas a contrast agent can be injected into the bloodstream. Most contrast agents contain heavy elements with a sudden increase in attenuation at the k-edge, the binding energy of the K shell electrons, which makes them easily detectable. This sudden increase in attenuation is used in the k-edge imaging technique, which is further explained in section 2.2. Current CT practice is to use an iodinated contrast agent. However, in some cases the k-edge of iodine (33.2 keV) provides insufficient contrast, which leads us to explore the use of contrast agents with potentially higher contrast abilities.

Gadolinium, with a k-edge of 50.2 keV, can prove useful in cases where the low-energetic photons are attenuated to the point where the distinguishability between the target and the background is compromised. However, GBCA are currently only endorsed for MRI procedures [1], not for CT procedures. Today little is known about what concentrations of GBCA are needed to obtain acceptable image quality. New technology is currently in development utilizing multi-bin spectral CT and k-edge imaging[2, 3].

The aim of this project is to investigate what image quality can be expected when the GBCA concentrations currently endorsed for MRI are used together with this new technology. Furthermore we will investigate if additional administration of contrast media, resulting in concentrations higher than those in current clinical practice, will provide sufficient image quality for acute cases.

The report is structured as follows. The Background describes the role of CT today, some of the challenges faced, and the opportunities presented by recent research and development. We explain the figure of merit used for image quality, signal-difference-to-noise-ratio (SDNR), and the theory behind energy weighting and k-edge imaging. In Model and Methods the models used are explained, along with approximations and delimitations. In Results and Discussion the obtained results are presented and discussed. In the last section the conclusions are presented and the report is summarized.

1.1 Scope

A simulation study is performed where simplified and idealised conditions are assumed. The imaging protocol used is k-edge imaging, well suited for contrast elements with a high k-edge, such as gadolinium. The SDNR is calculated in the reconstructed domain.

Two imaging cases are modelled. One where the target area is located within the skull, and one where the target is located within the torso. Different concentrations of GBCA are assumed and a cut-off area for sufficient SDNR is obtained. These two general cases
are reasonable approximations of most clinical imaging cases, and chosen to give indications of what image quality can be expected in reality.

1.2 Objective

The objective of this project is to determine whether GBCA are a viable option for spectral-computed tomography. Acceptable concentrations of GBCA are investigated by obtaining present MRI-protocols from a meta-analysis of peer-reviewed papers within the medical field. Simulations are run to determine if acceptable SDNR can be obtained from said concentrations, depending on the imaging case.

2 Background

2.1 Clinical

Since the introduction of CT-scans in the early 1970s the usage of CT has grown dramatically. In 2005 approximately 60 million CT-scans were performed in the US alone, compared with 3 million in 1980 [4]. Part of this increase is due to increased usage of CT in emergency departments (ED). In 1996 about three percent of ED patients were given a CT scan; by 2007, the figure had grown nearly fivefold, to one in seven ED patients [5]. Imaging cases in ED are often associated with a time factor and the quality of the tomographic images can be a decisive factor in whether a successful diagnosis can be made.

To increase the contrast of the image a contrast agent can be employed. For example this is done in the case of a stroke. After a stroke it is of vital importance to determine whether the blockage is partial or total in order to determine whether surgery should be performed.

In CT practice the difference in attenuation of the photons is used to produce the image. Since the majority of the high-energetic photons are not absorbed, no clear difference between the target and the background can be obtained from these. Instead it is the difference in absorption of low-energetic photons between the target and the background that produces an image. In occluded imaging cases, such as a stroke, the low-energetic photons can be attenuated by the skull to such a degree that image quality is critically impaired. A possible solution is using a different contrast agent, with potentially higher contrast abilities.

We investigate GBCA, in combination with the use of multi-bin spectral CT and k-edge imaging, as a viable option. The k-edge of gadolinium, at 50.2 keV, will result in a larger quantity of photons under the k-edge, which could result in contrast improvements. The sufficiency of currently used concentrations of GBCA is yet to be determined for CT practice.

Most contrast agents are associated with a certain toxicity [6], GBCA included, which adds a risk factor that needs to considered before administration. Critical, urgent cases
can motivate higher doses of contrast agent. This raises the question of what concentrations of GBCA are sufficient for such cases, where the trade-off is made between gadolinium exposure, and the potential consequences of a failure to diagnose.

### 2.2 Theoretical

The quality of an image, i.e. the ability to distinguish a target’s features from the background, can be described as the ability to identify and quantify a perturbation of the background noise. If this perturbation, the signal, is above the variations of the noise, the signal is visible. To quantitatively assess target visibility the signal-difference-to-noise-ratio (SDNR) is formulated. A threshold value of SDNR $\approx 5$ has been determined sufficient to identify a target against a flat background [7]. It has been shown that a larger target area requires a lower SDNR per pixel to be detectable. To compensate for this we implement the Rose-model [8].

The SDNR for photons, bound by Poisson statistics, is

$$SDNR = \frac{\text{mean signal}}{\sigma_{N_b}} = \frac{\langle \Delta N_s \rangle}{\sqrt{\langle N_b \rangle}},$$

(1)

With the Rose-model implemented:

$$SDNR_{Rose} = \frac{\langle \Delta N_s \rangle}{\sqrt{\langle N_b \rangle}} \sqrt{A_t},$$

(2)

where $A_t$ is the target area, $\langle \Delta N_s \rangle$ is the mean excess of photons compared to background in a signal area and $\langle N_b \rangle$ is the mean number of photons in a background area of equal size. Depending on the CT-technology used, different approaches are available to maximize the SDNR.

The imaging protocols considered in this project are based on X-ray detectors with multi-bin spectral capabilities. These detectors make it possible to determine the energy of individual X-ray quanta [2, 3]. This information can be used to enhance the detectability of features in certain imaging tasks in two basic ways: energy weighting and material decomposition.

#### 2.2.1 Energy Weighing

The first protocol is the energy weighting protocol. The possibility to determine each photon’s energy makes it possible to sort them into different energy bins. Photons with energy $E_i$ are sorted into energy bin $B_i$ if $T_{i-1} < E_i < T_i$, where $T_i$ are energy-threshold values. It is possible to use the information from each of the energy bins to generate an image, however these images can also be combined to form an image with maximum SDNR. To find this optimal image the optimal weight factor [9]:

$$w(E) = \frac{\langle I_t \rangle - \langle I_b \rangle}{\langle I_t \rangle + \langle I_b \rangle},$$

(3)

is used, where $\langle I_t \rangle$ is the expectation value of photons passing through a target and $\langle I_b \rangle$ the expectation value of background photons. This can also be expressed in terms of the
linear attenuation coefficient as:

\[ w(E) = \frac{e^{-\mu_b(E)d} - e^{-\mu_t(E)d}}{e^{-\mu_b(E)d} + e^{-\mu_t(E)d}}, \quad (4) \]

where \( d \) is the thickness of the target structure, \( \mu_t(E) \) is the linear attenuation coefficient of the target structure and \( \mu_d(E) \) is the linear attenuation coefficient of the background. The total projection image, in terms of expected amounts of photons per pixel, is then given by:

\[ I(x') = \sum_{i=1}^{N} I(x'; B_i)w_i, \quad (5) \]

where \( I(x'; B_i) \) is the expected number of photons in energy bin \( B_i \) and \( w_i \) is the average value of the weight factor over the bin:

\[ w_i = \frac{\int_{T_{i-1}}^{T_i} \Phi(E)w(E)dE}{\int_{T_{i-1}}^{T_i} \Phi(E)dE}, \quad (6) \]

### 2.2.2 K-edge Imaging

The second protocol that uses the knowledge of each photon’s energy is the method of decomposing the projection images prior to CT-reconstruction. To do this, first the linear attenuation coefficient is decomposed, as shown by [10, 11, 12], into three or more bases, with known energy dependency:

\[ \mu(x, y; E) = a_1(x, y)f_1(E) + a_2(x, y)f_2(E) + a_3(x, y)f_3(E). \quad (7) \]

Secondly, the expected number of photons detected in each bin can be expressed as:

\[ I_i(x') = I_0(x') \int_{T_{i-1}}^{T_i} \Phi(E)D(E)e^{-\int_{I}^{E} \mu(x, y; E)dl}dE, \quad (8) \]

where \( I_0(x') \) is the total number of photons impinging on the area of the object projected onto the pixel at \( x' \) during the projection image acquisition time, \( \Phi(E) \) is the X-ray spectrum on the target such that the fraction of X-rays with energy in the interval \( (E, E + dE) \) is given by \( \Phi(E)dE \) and \( D(E) \) is the detection efficiency.

With (7) in (8) the expected photon count in each bin is:

\[ I_i(x') = I_0(x') \int_{T_{i-1}}^{T_i} \Phi(E)D(E)e^{-\int_{I}^{E} \mu(x, y; E)dl}dE = I_0(x') \int_{T_{i-1}}^{T_i} \Phi(E)D(E)e^{-\sum_{j=1}^{3} f_j(E)A_j(x')}dE, \quad (9) \]

where

\[ A_j(x') = \int_{I} a_j(x, y)dl \quad j = 1, 2, 3. \quad (10) \]

In the case of more bins than components in the linear attenuation coefficient, this yields an overdetermined system.
Once the contribution of each component, \(a_j\), is determined, the SDNR due to each different component is:

\[
SDNR_j = \frac{a_j}{\sigma_{a_j}},
\]  

(11)

where \(\sigma_{a_j}\) is the standard deviation and \(a_j\) is the correct value obtained by solving (7). This is actually a "signal-to-noise-ratio" (SNR), but the equality stands for regions where the background signal is zero. The standard deviation in the reconstructed domain is given as \([13]\):

\[
\sigma_{a_j}^2 = \frac{\sigma_{A_j}^2 k^2}{ma^2},
\]  

(12)

where \(m\) is the number of projection angles, \(a\) is the pixel-parameter and \(\sigma_{A_j}\) is the standard deviation of \(A_j\) and \(k\) is the noise coefficient.

Several methods have been proposed for the solution of the system of integral equations. No new solution methods are introduced in this paper but instead we apply noise and solve the integral system with a maximum likelihood (ML) method. Since the ML method is an asymptotically consistent estimator, the estimated expectation value of \(A_j\) converges towards the real value for a large number of photons. This is achieved during a CT-scan and the correct standard deviation is obtained.

3 Model and Method

3.1 Simulation Parameters

A 100 kVp spectrum with 2 mm aluminium filtration is assumed along with a system with a detection efficiency \(D(E) = 1\). The conditions are idealised so that unintentional scattering is neglected. Pre-patient flux of photons is set to \(10^8\) s\(^{-1}\) mm\(^{-2}\) and the detector’s pixel area is 0.25 mm\(^2\). All imaging is made from a single source-detector rotation, with 3142 projection angles per rotation. The detector system is assumed to have six bins, with energy thresholds determined so that the counts are equally distributed over the bins, with one threshold on the k-edge.

Two different cross-sections are modelled, both symmetrical around the rotational axis. One is modelled to be soft tissue with a diameter of 20 cm to resemble the torso. The other one is modelled to be 15 cm soft tissue surrounded by 7 mm bone to resemble the skull.

All tissue composition is taken from the ICRU-44 report \([14]\) and the linear attenuation coefficients are taken from the XCOM database \([15]\). The target areas are modelled as soft tissue with a concentration of Gd, in a background of soft tissue. Concentrations of Gd range from standard 0.1 mmol/kg bodyweight \([16, 17]\), to 0.5 mmol/kg body-weight, which has been suggested safe for healthy adults \([18]\). Larger concentrations are considered when motivated by the imaging case. A standard patient weight of 80 kg is assumed, with a total blood volume of 5 litres. Assuming all the GBCA is deposited in the blood stream, a blood concentration is calculated and assumed to be the target...
volume’s concentration.

3.2 K-edge Imaging using Material Decomposition

For imaging tasks where material decomposition is employed the attenuation coefficient is split into three terms:

\[
\mu(x, y; E) = a_{t1}(x, y)f_{t1}(E) + a_{t2}(x, y)f_{t2}(E) + a_{Gd}(x, y)f_{Gd}(E)
\] (13)

Our interest lies in the \(a_{Gd}\) term since this illustrates the k-edge contribution to the image. The SDNR is calculated through (11).

First the numerator \(a_{Gd}(x, y)\) is calculated. This is done by modelling \(\mu(x, y; E)\) in the manner described in section 3.1 and solving (13) for \(a_{t1}(x, y), a_{t2}(x, y)\) and \(a_{Gd}(x, y)\) in a least-squares sense.

Secondly we calculate the denominator \(\sigma_a\). This can not be calculated directly but instead it is obtained by determining \(\sigma_{A_{Gd}}\), in the projection domain, and then using (12). \(\sigma_{A_{Gd}}\) is estimated in the following way.

By using the already determined \(a_{t1}(x, y), a_{t2}(x, y)\) and \(a_{Gd}(x, y)\) the values of \(A_{t1}^0, A_{t2}^0\) and \(A_{Gd}^0\) are calculated, according to (10), and assumed to be the correct values. Using these values, an expected detected spectrum is calculated according to (9). A Poisson-noise generated in the programming language MATLAB® (The Mathworks Inc., Natick, Massachusetts) is then added to this spectrum resulting in a new spectrum \(S_{noisy}\). Then a new set \(A^*\) is fitted to \(S_{noisy}\) using the following ML method:

\[
A_{t1}^*, A_{t2}^*, A_{Gd}^* = \arg \min_{A_{t1}, A_{t2}, A_{Gd}} \mathcal{L}(A_{t1}, A_{t2}, A_{Gd}),
\] (14)

where we use the the log-likelihood function [19]:

\[
\mathcal{L} = \sum_{i=1}^{6} [\lambda_i - n_i \ln \lambda_i]
\] (15)

where \(\lambda_i\) is the expectation value of photons in the \(i\)th bin according to [9], depending on \(A_{t1}, A_{t2}\) and \(A_{Gd}\), and \(n_i\) is the number of photons detected in the \(i\)th bin for \(S_{noisy}\).

By repeating the algorithm for a 1000 iterations, thus obtaining different sets of \(A^*\), the standard deviation, \(\sigma_{A_{Gd}}\) in the projection domain is obtained. The SDNR in the reconstructed domain is then determined using (11) and (12).
4 Discussion and Result

4.1 Imaging Case: Soft Tissue

In Fig.1 the SDNR for the cross-sections composed of soft tissue is depicted. The cut-off areas for the concentrations currently used in MRI, 0.1-0.2 mmol/kg, are presented in the table in Fig.1. The clinical implications of these results being that if GBCA were to be endorsed for CT-examinations, concentrations currently in clinical use would provide sufficient contrast when examining a patient with indications of haemorrhaging, or the existence of a lesion, located in areas mainly composed of soft tissue. If the target area is smaller than required, the decision to administer additional GBCA, to a concentration of 0.5 mmol/kg, would reduce the minimum detectable area, see table in Fig.1, increasing the chance of successfully diagnosing a patient even with small diagnostic indicators.

A relevant question is whether it is reasonable to model the cross-sections as composed only of soft tissue. Abdomen (liver, kidneys, ovaries, colon etc), legs and neck, are well represented by this generalisation as the only neglected parameter is the bone tissue in the center. For imaging cases involving the thorax, neglecting the ribcage will lead to an overestimation of the image quality. However, the data can still be seen as a strong indicator of the feasibility, since the composition is otherwise similar. Another aspect of accuracy is how the diameter of the cross-section impacts the results. To use a 20 cm diameter of the cross-section represents the abdomen well, although smaller imaging cases, like the neck, will have a lower attenuation of photons than depicted. This results
in an underestimation of the image quality for such imaging cases.

Another approximation affecting the accuracy is the concentration of GBCA in the target volume. To assume blood concentration is an overestimation, with the exception of internal haemorrhaging.

4.2 Imaging Case: Skull

![Graph showing the SDNR vs area for different concentrations of GBCA](image)

<table>
<thead>
<tr>
<th>Conc. [mmol/kg]</th>
<th>0.20</th>
<th>0.50</th>
<th>0.75</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area [cm²]</td>
<td>0.34</td>
<td>0.14</td>
<td>0.09</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Figure 2: Cut-off area corresponding to concentration of GBCA

The SDNR obtained for the imaging case involving the brain are depicted in Fig.2. The cut-off values obtained are shown in the table in Fig.2. For concentrations currently deemed safe, 0.2-0.5 mmol/kg, the cut-off areas imply that any substantial haemorrhaging would be detectable. However, in the case of ischemia caused by thrombosis the target area is smaller still. Most cases of cerebral embolism occur in the arteria media cerebri, which has a diameter of ∼3 mm [20]. When assuming a target area of ∼0.09 cm², the allowed concentrations are insufficient. The cut-off areas obtained for 0.75-1 mmol/kg show that adequate contrast can be obtained with said concentrations. The clinical interest in such a case would be whether any residual blood flow occurs, raising the question of whether such a flow would be distinguishable. Allowing the GBCA-carrying blood to be diluted by the non-oxygenated blood beyond the thrombus would most likely result in too low a concentration of GBCA. The practice of fluoroscopy would however open up the possibility to track the bolus, which could result in local concentrations high enough to detect residual blood flow.
5 Summary and Conclusions

We have shown that, under certain idealisations, in MRI currently exercised concentrations of GBCA would provide sufficient contrast for soft tissue imaging. Furthermore we have shown that we can decrease the smallest detectable area by increasing concentrations beyond what is commonly used, up to 0.5 mmol/kg, while remaining within the bounds of what has been suggested safe.

We have also shown that, under similar idealisations, GBCA provides sufficient contrast to detect any substantial cerebral haemorrhage. To detect residual blood flow however, larger concentrations, 0.7-1 mmol/kg, were determined necessary. We speculate that such large concentrations might be achievable locally, in the blocked vessel, shortly after injection. With the technology of fluoroscopy, residual blood flows could be made detectable by tracking the bolus.

The results strongly indicate that GBCA, combined with the technique of k-edge imaging, could be used clinically with concentrations currently endorsed in MRI and provide sufficient image quality.

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References


