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Differentiation of low-attenuation intracranial hemorrhage and calcification using dual-energy computed tomography in a phantom system

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Abstract

Objectives—Calcific and hemorrhagic intracranial lesions with attenuation levels of <100 Hounsfield Units (HU) cannot currently be reliably differentiated by single-energy computed tomography (SECT). The proper differentiation of these lesion types would have a multitude of clinical applications. A phantom model was used to test the ability of dual-energy CT (DECT) to differentiate such lesions.

Materials and Methods—Agar gel-bound ferric oxide and hydroxyapatite were used to model hemorrhage and calcification, respectively. Gel models were scanned using SECT and DECT and organized into SECT attenuation-matched pairs at 16 attenuation levels between 0 and 100 HU. DECT data were analyzed using 3D Gaussian mixture models (GMMs), as well as a simplified threshold plane metric derived from the 3D GMM, to assign voxels to hemorrhagic or calcific

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categories. Accuracy was calculated by comparing predicted voxel assignments with actual voxel identities.

Results—We measured 6,032 voxels from each gel model, for a total of 193,024 data points (16 matched model pairs). Both the 3D GMM and its more clinically implementable threshold plane derivative yielded similar results, with >90% accuracy at matched SECT attenuation levels 50 HU.

Conclusions—Hemorrhagic and calcific lesions with attenuation levels between 50 and 100 HU were differentiable using DECT in a clinically relevant phantom system with >90% accuracy. This method warrants further testing for potential clinical applications.

Keywords

Calcification; Hemorrhage; Spectral CT; Foci of Susceptibility

Introduction

The ability to characterize cerebral lesions in terms of material composition, especially at low Hounsfield values, has many important clinical applications, such as the distinction of hemorrhagic from calcific lesions. There is overlap in the Hounsfield densities of blood and calcium on conventional CT, particularly below 100 Hounsfield Units (HU). This difference is clinically important, for example in differentiating benign cerebral calcifications, which require no treatment¹, from cavernous angiomas which carry a risk of bleeding and are a contra-indication for anticoagulant therapy²⁻³. Oligodendrogliomas are commonly calcified, and need to be distinguished from glioblastomas, which commonly contain intratumoral hemorrhages. The treatment strategies for these tumors are completely different, and would be better informed if calcification and hemorrhage could be reliably separated.

Currently, conventional single-energy computed tomography (SECT) is considered the gold standard modality for the identification of calcification. In general, any lesion with SECT attenuation levels >100 Hounsfield units (HU) is classified as a calcification⁴. However, this gold standard fails for lesions with SECT attenuation levels <100 HU, where blood and calcifications overlap in attenuation.

In clinical practice, MR is often used as a characterizing modality to add to the information derived from CT. However, conventional MR is of little help in distinguishing hemorrhagic from calcific lesions. Both types of lesion manifest as signal voids on Gradient Echo images, with little characterizing information available without the use of specialized experimental phase contrast MR techniques⁵. There is a significant clinical need for an imaging technology to distinguish hemorrhage from calcification at low Hounsfield values, and Dual Energy CT is a strong candidate to fill this gap in our imaging armamentarium.

Dual-energy CT is based on the knowledge that the relationship between attenuation and x-ray energy is material dependent. By collecting attenuation information at two distinct energies, assumptions can be made about the shape of the energy-dependent attenuation curve for a given tissue, and thus about its material characteristics. This represents a

significant advance from SECT, where only a single attenuation value is derived, with no further information available on the material characteristics of the tissue⁶⁻⁸.

Dual Energy CT has already been used with success in distinguishing blood from iodinated contrast staining in patients after intra-arterial stroke therapies⁹⁻¹¹, in distinguishing iodine enhancement from calcification in artificial pulmonary nodules¹², and in distinguishing complimentary contrast media (iodine and tungsten, or iodine and bismuth subsalicylate)¹³. All are clinically significant problems where the attenuations of the two main differential diagnostic possibilities have significant overlap on conventional SECT. Dual-energy CT's success has also been shown in the characterization of renal calculi¹⁴⁻¹⁶, distinguishing non-enhancing and enhancing renal lesions¹⁷, distinguishing benign and malignant tumors in the liver¹⁸, thyroid¹⁹ and adrenal glands²⁰⁻²². It has also been shown useful in the detection and characterization of endoleaks, pulmonary embolism, liver metastases, urinary stones, myocardial ischemia and renal corticomedullary sodium gradients²³⁻³⁰.

In this study, we apply dual energy CT to the more subtle problem of distinguishing calcification and hemorrhage. We provide a phantom-based proof-of-concept that the differentiation of these two intracranial lesion types below 100 HU is both possible and clinically feasible using dual energy CT.

Materials and Methods

Calcification and Hemorrhage Phantom Models

Powdered ferric oxide (#529311; Sigma-Aldrich, St. Louis, MO) and hydroxyapatite (#289396; Sigma-Aldrich) were used to model hemorrhage and calcification, respectively. Ferric oxide and hydroxyapatite were added to separate sets of 1.8-mL cryo-vials (#375418; Thermo Scientific, Waltham, MA), and 500 μ L of 0.01% Tween-20 (#P9416; Sigma-Aldrich) solution was added to each vial as an emulsificant to promote a uniform mixture. The hydroxyapatite vials were agitated for 24 hours using a Max Q2000 shaker (#4314; Thermo Scientific). The iron oxide particles used to model hemorrhage were not adequately emulsified by Tween alone, and required the addition of small 7 mm $\times$ 2 mm magnetic stir bars (#14-513-63; Fisher Scientific, Waltham, MA) to provide mechanical agitation. Iron oxide vials were agitated for 24 hours using a PC-220 stirrer plate (Corning, Corning, NY).

The stirrer bars were removed from the iron oxide vials using a strong magnet, and both sets of vials were moved to a water bath, where they were heated to 75°C. Heated 1% agar gel solution (2 mL) (#0710; Amresco, Solon, OH) was added to both sets, and the vials were tightly capped. The warm vials were then manually agitated by vigorous shaking for approximately 10 minutes until the solution cooled into a gel with uniform compound distribution. These gel models were stored at 4°C prior to scanning.

An anthropomorphic head phantom (The Phantom Laboratory, Salem, NY) (Fig 1) consisting of a human skull cast in tissue-equivalent Alderson material with anatomical airways was obtained from the Radiological Physics Center (Houston, TX). A cylindrical insert was placed in the cranium, and a custom insert was fabricated that allowed for simultaneous imaging of six agar gels (Fig 2).

Imaging and Region-of-Interest Analysis

The calcification and hemorrhage gel model were scanned in the phantom on a Discovery CT750 HD CT scanner (GE Healthcare, Waukesha, WI) using two protocols: a) a single-energy in-house routine brain protocol and b) a dual-energy protocol designed to match the imaging parameters and dose of the single-energy protocol (Table 1). To improve the spatial resolution of the gel images, the display field of view was reduced to the minimum of 12 cm. Images were viewed with Gemstone Spectral Imaging (GSI) viewer software (version 2; GE Healthcare), and data were collected on eight consecutive images using a circular 39-mm² (7 mm diameter) region of interest covering approximately two-thirds of the vial diameter. The total number of voxels per region of interest was 754, for a total of 6,032 voxels in a volume of interest per vial. The 6,032-voxel volume of interest covered 952 mm³ and constituted 37% of the total gel volume of approximately 2.5 mL. For each voxel in the volume of interest, the following data were recorded: a) SECT attenuation (HU), b) calcium density from a water/calcium material decomposition based on the dual-energy CT data (see 'Dual-Energy Data Processing' below), c) water density from a water/calcium material decomposition based on the dual-energy CT data (see 'Dual-Energy Data Processing' below), and d) material composition of the gel model (iron oxide-based hemorrhage model or hydroxyapatite-based calcification model).

Fabrication of Attenuation-Matched Hemorrhage and Calcification Gel Models

Iron oxide and hydroxyapatite gels were created at concentrations between 1mg/mL and 100mg/mL and scanned in the phantom using the single-energy CT protocol (Table 1). Images were viewed as described above. Each gel model's mean SECT attenuation (HU) was calculated and plotted against the gel model's concentration. The SECT attenuation (HU) was fitted to a linear function of the known concentration of each material and the concentration required to achieve a given SECT attenuation (HU) was then calculated from the fit.

Pairs of agar gels were fabricated with similar SECT attenuation (HU) levels and differed only in their composition (iron oxide-based hemorrhage model or hydroxyapatite-based calcification model). These matched gel models were fabricated at SECT attenuation levels ranging from 0 to 100 HU, in roughly 10-HU intervals. Paired vials of similar attenuation (within 2 HU) were then scanned in the anthropomorphic head phantom and scanned using a) the single-energy in-house routine brain protocol, to verify the SECT attenuation (HU) level of each gel model, and b) the dual-energy protocol, to collect material density information.

Dual-Energy Data Processing

To extract the dual-energy signature of a material from the high- and low-kilovolt-peak data gathered in the dual-energy CT scan, GE Healthcare (Waukesha, WI) uses a process called material decomposition. This process is based on the concept that the energy-dependent attenuation of any material can be characterized as the linear combination of the energy-dependent attenuations of two basis materials³¹⁻³². One of the unique capabilities of this approach is allowing the user to independently choose the basis materials. Theoretically, any two materials could be chosen, but biologically relevant pairs such as water and iodine give

more meaningful results³³⁻³⁴. Materials with k-edges within the relevant x-ray energy range of 40-140keV should also be avoided as these discontinuities can give rise to erroneous material decomposition results. The materials chosen should also have sufficiently different atomic numbers and thus sufficiently different attenuation properties to produce meaningful material separation, thus generating clinically useful data³⁵⁻³⁶. We chose calcium and water as our working pair because of their biological relevance and dissimilar attenuation properties. Iron-water and iodine –water material basis pairs were also investigated, however, preliminary data indicated the calcium-water material density pair as yielding separation plots that were more meaningful and convenient for our application. (Data not shown)

Data from the dual-energy images were collected using the GE Gemstone Spectral Imaging viewer in material density mode with a water/calcium material density pair. These images express the density of water and the density of calcium in each voxel needed to produce the observed linear attenuation coefficient.

Matched Model Pair Data Analysis

For each SECT attenuation (HU)-matched gel model pair, single-energy and dual-energy voxel data (6,032 voxels/gel model) for both the hemorrhage model and the calcification model were loaded into MATLAB software (R2012a; MathWorks, Natick, MA). The single-energy and dual-energy voxel data were registered based on the image number and voxel location data included in the region of interest data file.

A Gaussian mixture model (GMM) was performed to group the voxels into two populations: calcification and hemorrhage. Using the measured SECT attenuation (HU), water density and calcium density values for each voxel as input, a probability of belonging to either the calcification or the hemorrhage population was calculated for each voxel (see Appendix), with a posterior probability of 0.5 as the criterion for population assignment (37-38). The analysis was performed using a 50% training set, 50% validation set approach to ensure that the data used to build the model (randomly assigned training set) was distinct from the data the model was used to evaluate (randomly assigned validation set) and was performed 1,000 times to ensure convergence in light of the non-stochastic nature of the GMM analysis.

The probabilistic assignments for the two populations (calcification and hemorrhage) were tested against the gold standard of actual gel composition, and an overall model accuracy was calculated as a function of the SECT attenuation (HU) of the matched gel model pair.

While Gaussian mixture model analysis can be quite powerful, its potential for application in a clinical setting is low due to the time and processing power needed to apply the technique. To provide a more clinically implementable test metric, a threshold plane was derived from the GMM data. For all matched model pairs included in the study, voxels receiving an assignment probability of $50 \pm 1\%$ (equal probabilities of being assigned to the hemorrhage or calcification cluster) were isolated, and a line of best fit was determined using regression analysis in three dimensions. Due to the correlated nature of the SECT attenuation (HU) and dual-energy material density data, gel model voxel data were found to be concentrated in a single plane in 3D space (Fig 3). Using principle component analysis,

the centroid and inertia axes of the plane were calculated and the equation for the plane of the data was determined. A second plane was then calculated which included the line fit of the equal-probability points and was orthogonal to the plane of the data, effectively bisected the voxel data into two groups. Based on the equation of this threshold plane, voxels were sorted into either a hemorrhage group or a calcification group according to their position relative to the threshold plane. For each matched model pair, the predicted material composition for each voxel was compared with actual composition, and the accuracy of the threshold plane's differentiation was calculated and plotted against the SECT attenuation (HU) of the matched model pair.

Statistical details describing the Gaussian mixture model formulation, fitting and analysis are included in the Appendix.

Results

Calcification and Hemorrhage Phantom Models

The results of the SECT attenuation (HU) calculation for all iron oxide and hydroxyapatite gels are shown in Figure 4, and indicate the concentration of the compounds in each of gel types needed to produce gel models of a specific SECT attenuation.

Fabrication of Attenuation-Matched Hemorrhage and Calcification Gel Models

The target concentration of iron oxide and of hydroxyapatite required to produce each desired SECT attenuation is presented in Table 2. The exact weight of each compound added to each gel vial is also presented and was calculated based on the concentration and the known volume of the gel vials used in the study.

Matched Model Pair Data Analysis

A total of 16 hemorrhage and calcification model pairs were matched. The average SECT attenuation (HU) of each pair, as well as the mean and standard deviation of the SECT attenuation (HU) for each gel model in the pair, is shown in Table 3.

As an example for the purposes of illustration, the voxel data for the 62-HU matched model pair along with the GMM predicted and actual gel model compositions are shown in Figure 5. For the GMM analysis (Fig 5), the accuracies for the calcification and hemorrhage models were 99.7% and 97.7%, respectively.

Matched calcification and hemorrhage gel model pairs were differentiated with >90% accuracy using GMM analysis starting at 50HU (Fig 6). A slight drop to just below the 90% threshold was seen at 60HU however, all subsequent matched model pairs exceeded 90% accuracy. All matched model pairs over 50HU, with the exception of the 60HU pair, possessed very narrow accuracy distributions, with standard deviations of <1%.

In order to derive the threshold plane, eight hundred thirty-six voxels with posterior probabilities of $50 \pm 1\%$ were isolated from the total 193,024 voxels on the basis of the 32 gel models included in this study. A coordinate system was established with the x-axis defined as the dual-energy CT water density, the y-axis defined as the dual-energy CT

calcium density, and the z-axis defined as the SECT attenuation (HU). The line fit to the equal probability points had the vector equation $\langle x, y, z \rangle = \langle 998.17, 11.88, 23.18 \rangle + t \langle 0.06, -0.41, -0.91 \rangle$ where t is any real number. The 3D threshold plane had the equation $-0.93x + 0.31y - 0.20z = -929.20$ and clearly bisected the hemorrhage and calcification model voxel data (Fig 7). Matched model pairs with SECT attenuation levels ≥ 50 HU were differentiated with $>90\%$ accuracy for both the GMM analysis as well as its more clinically implementable threshold plane metric (Fig 6).

Discussion

This study provides proof-of-concept in a phantom system that dual-energy CT can distinguish intracranial calcification from hemorrhage below the 100 HU limit imposed by currently available clinical modalities. Intracranial lesions over 100 HU are identifiable as calcification using SECT, however lesions under this attenuation are impossible to classify. Using conventional MR, both hemorrhage and calcification manifest as signal voids in Gradient Echo images. Without additional information, the cause of the signal voids, be it calcification or hemorrhage, cannot be determined.

The use of phase information in MR for the differentiation of diamagnetic materials, such as calcification, and paramagnetic materials, such as hemorrhage, has been under investigation for several years³⁹. Corrected gradient echo phase imaging⁴⁰, susceptibility-weighted imaging⁴¹, and quantitative susceptibility mapping⁴² have all been proposed to distinguish calcification from hemorrhage, however these methods have not yet found wide clinical acceptance. In each of these studies, SECT was used as the gold standard for presence of calcification, and thus the usefulness of these methods can be reported only for hemorrhage and calcification above 100 HU. Preliminary work suggests that calcification and hemorrhage in glioma may be differentiable under the 100HU limit using phase data derived from susceptibility-weighted imaging⁴³. However, the transition from research to clinical use of phase-dependent MR techniques has been difficult due to the sensitivity of the technique to magnetic field inhomogeneity, which is the rule, rather than the exception in clinical applications.

In this study, dual-energy CT in combination with Gaussian mixture model analysis was shown to be capable of differentiating intracranial calcification and hemorrhage models far below the level possible using currently available clinical modalities. Overall, the accuracy of the GMM differentiation of the hemorrhage and calcification model voxel data increased with the matched model pair's SECT attenuation (HU). Put simply, the denser the lesion model, the easier it was to differentiate hemorrhage from calcification. Strong differentiation with $>90\%$ accuracy can be seen starting at 50 HU. The dip in accuracy and associated increase in accuracy distribution at 60 HU in the GMM analysis (Fig 6) may be due to a higher heterogeneity in the SECT attenuation dimension from either the calcification or the hemorrhage gel model due to variability in gel model fabrication. Nevertheless, the overall trends in both the GMM and threshold plane accuracy results support the use of 50 HU as a threshold for highly accurate differentiation.

Gaussian mixture model analysis was chosen as the statistical analytic method for this study due to its ease of interpretation and to take advantage of the three dimensional and potentially overlapping nature of the data collected. The Gaussian assumption of the analysis was appropriate given the large amount of voxel data collected from each gel model. Traditional *t*-test analysis was contraindicated by both the vast amount of data and the differences in the manufacturing methods for the calcification and hemorrhage gel model. (Because of the large numbers of data points, slight differences in heterogeneity between the calcification and hemorrhage models resulted in statistically significant differences when in fact the model's voxel data overlapped to a considerable extent. This observation indicated that *t*-test analysis was inappropriate.) Additionally, the ability to perform training/validation data set analysis using GMM allowed for a more robust test of differentiation as well as lending itself to the development of a model-based threshold for classification of unknown lesions.

For practical implementation of the GMM statistical separation procedure, we derived a simple threshold plane to divide the voxels into calcification and hemorrhage population. The discrimination performance of this plane was similar to the original GMM analysis (Fig 6) and actually outperformed the GMM analysis at low densities, likely by linearly extrapolating from higher densities to lower where the GMM itself became noise-limited.

To establish the use of dual-energy CT to discriminate calcification and hemorrhage clinically, an initial phantom study is necessary to allow essential variables to be interrogated and analysis tools and methods to be designed, trained, and optimized in a controlled fashion. However, due to the inherent constraints requisite to use of a phantom system there will always be limitations in the modeling. First, both hemorrhages and calcifications were modeled as relatively large cylindrical lesions positioned centrally in the brain. Second, both lesion types were modeled using an agar background and scanned in a water-filled insert, which does not accurately represent brain tissue. Third, both lesion types were modeled as uniform distributions, with no attempt made to model heterogeneous distribution or influences of local environment on the lesion. Lastly, hemorrhage models were created without any form of calcium contamination. It is likely that cross contamination will occur clinically, where biology is always more complex than phantoms. For example, it has been shown that cavernomas calcify in anywhere from 11-40% of cases⁴⁴⁻⁴⁵, and in those cases we may expect to see both calcification and hemorrhage in the same lesion. Clearly there is potential for overlap and cross contamination between blood and calcium in clinical applications. Our current study lays a groundwork for a "clean" uncontaminated case, leaving more complex mixture phantom models and more importantly, clinical applications, to future work.

Future studies are planned to extend our approach to encompass other dual-energy CT vendors, as well as to further test the limits of our method by varying the size and location of the lesions, more accurately modeling the brain tissue background and environment, and varying the imaging parameters of the dual-energy protocols to potentially optimize differentiation. The resulting data will be used to develop appropriate scan protocols based on the size and location of intracranial lesions for use in a prospective human trial.

In conclusion, this work has shown that hemorrhagic and calcific lesions with SECT attenuation levels between 50 and 100 HU can be reliably differentiated in a phantom system using dual-energy CT and material decomposition. The equation for a simple threshold plane of differentiation derived from the more complex GMM analysis provides a simplified metric for future clinical application. The ability to differentiate between low-attenuation hemorrhagic and calcific lesions has multiple clinical applications, both addressing current clinical needs, and also likely, future unforeseen applications. This data provides justification for future clinical studies in patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Gaussian mixture models formulation

The basic data collected from our experiments had a three dimensional structure with the x-axis defined as the dual-energy CT water density, the y-axis defined as the dual-energy CT calcium density, and the z-axis defined as the SECT attenuation (HU). Our basic scientific question of characterizing this three-dimensional data cloud into distinct (sub-)populations corresponding to water and calcium can be construed as a clustering problem i.e. at each HU we wish to identify how well these distinct clusters are separated. Visually inspecting the data we found that at lower HU these clusters are not very well separated but the distinction increases with HU levels and we would like accurately quantify the uncertainty of this process. The most commonly used clustering algorithms are mixture models¹. Mixture models are a common statistical tool for clustering and allow properties of multiple subpopulations (distributions) to be statistically inferred from pooled-population data. Gaussian mixture models (GMM) are a special case of mixture models and was chosen for this study because of its ease of interpretation and to take advantage of the 3D and potentially overlapping nature of the data collected. The basic GMM can be expressed concisely as:

$$P(X) = \sum_{k=1}^K p_k N(\mu_k, \Sigma_k)$$

where $P(X)$ represents the joint distribution of the 3-D water/calcium/HU data, K is number of mixture components, p_k is the mixture weights/prior probability and $N(\mu_k, \Sigma_k)$ represents the Gaussian (normal) density with mean μ_k and variance-covariance matrix Σ_k corresponding to th cluster k respectively. All of these quantities are treated as unknown parameters and are estimated by the data as detailed below.

GMM fitting and analyses

We used MATLAB Statistics Toolbox™ software, and specifically the *gmdistribution* class to fit an unsupervised GMM analysis using a 50% training set, 50% validation set approach. GMM analysis uses an expectation maximization(EM) algorithm² to iteratively fit two potentially overlapping Gaussian distributions to the combined hemorrhage-calcification model pair data and consists of two steps: the Expectation (E) step which calculates the expected values for the membership weights of each data point as functions of the mixture weights p_k and the maximization (M) step which uses the membership weights obtained from the E step, and recomputes the distribution of the Gaussian distributions μ_k and Σ_k respectively. This procedure is repeated iteratively until convergence is achieved.

Posterior probability calculations

Once these distributions are optimally estimated using the EM algorithm, the analysis provides for each voxel the probability that the voxel belongs to the hemorrhage cluster and (vice-versa) the probability that the voxel belongs to the calcification cluster which is calculated using the Bayes theorem as:

$$P = \text{Prob}(Voxel|Cluster) = \text{Prob}(Cluster|Voxel) \text{Prob}(Voxel)$$

where the probabilities on the right-hand side are calculated using the (weighted) ratio of the Gaussian densities corresponding to each cluster estimated via the EM algorithm. An example plot of these posterior probabilities for one HU pair is shown in Figure A. Voxels were assigned to a cluster if their probability of belonging to a cluster (P) exceeded a median probability threshold of 50%. The voxel identities predicted by the GMM were then compared to the true voxel identities and the true hemorrhage and true calcification values were calculated. The accuracy with which the GMM differentiated the calcification gel model from the hemorrhage gel model was then calculated as the sum of the true hemorrhage and calcification values divided by the total number of voxels in the two gel model data sets. Because of the stochastic nature of iterative approaches such as GMM analysis, the method was repeated over 1,000 runs for each matched model pair to assess the stability of model configurations. Each run used a different starting point randomly selected as part of the *gmdistribution.fit* function. Any runs whose final log likelihood value differed from that of the median results by more than 3 standard deviations were presumed to be influenced by local minima⁴, and were removed from the results. The analysis was repeated with new initial values until there were 1,000 successful runs for each matched model pair. The accuracy was calculated for each successful run, and then the mean and standard deviation of the accuracy was calculated for the 1,000 runs of each attenuation matched model pair.

To determine whether the initial random separation of data into training and validation sets affected the accuracy results, the random selection, as well as the 1,000-GMM-run analysis, was repeated 10 times for each SECT attenuation-matched model pair. For each matched model pair, the 10 random splits were found to yield identical results (data not shown),

indicating the random separation of the data into training and validation data sets did not affect the final GMM accuracy results.

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Figure 1.
Anthropomorphic head phantom.

Figure 2.

(a) Custom water-filled insert for the anthropomorphic head phantom. The lateral view (top), the axial view (bottom left), and the relative position of the insert in the head phantom (bottom right) are shown. The orientation of the imaging volume is represented by the yellow shaded region. (b) A lateral scout image of the anthropomorphic head phantom with custom water-filled insert and gel models in place.

Figure 3.

3D plot of voxel data from all calcification and hemorrhage gel models used in this study, rotated to show the full distribution of the data (a) or the planar nature of these data in the 3D coordinate space (b). Hemorrhage gel model voxel data are shown in red; calcification gel model voxel data are shown in blue. A movie provided in the supplemental material illustrates the data distribution in more detail.

Figure 4. SECT attenuation (HU) for the concentration of iron oxide in the hemorrhage gel models and the hydroxyapatite in the calcification gel models. Linear regression equations and correlation coefficients are shown for each data set.

Figure 5.

GMM assignment results for the 62-HU matched gel model pair (1 of 16 pairs). Each point represents a voxel within the 6,032-voxel volume of interest in one of the two gel models.

Figure 6.

Accuracy of hemorrhage and calcification differentiation using the GMM and threshold plane analysis method for all attenuation-matched model pairs. For the GMM series, each point represents 1,000 iteratively filtered runs of the analysis. A third-order polynomial (Poly.) was fit to each series to facilitate visual interpretation of the data.

Figure 7.

3D plot of all voxel data ($n = 193,024$) from all 16 hemorrhage/calcification matched model pairs. Hemorrhage gel model voxel data are shown in red; calcification gel model voxel data are shown in blue. (a) Threshold plane viewed edge on as black line [equation: $-0.93x + 0.31y - 0.20z = -929.20$]. (b) Voxel data viewed from an angle showing hemorrhage and calcification data falling on the hemorrhage side of the threshold plane. Bright blue calcification data would be incorrectly identified as belonging to the hemorrhage population, with greyed-out blue data being correctly classified. (c) Voxel data viewed from an angle showing hemorrhage and calcification data falling on the calcification side of the threshold plane. Bright red hemorrhage data would be incorrectly identified as belonging to the calcification population, with greyed-out red data being correctly classified. A movie provided in the supplemental material illustrates the data distribution and plane placement in more detail.

Table 1

Imaging parameters for the single- and dual-energy CT protocols used in the study

Protocol	Scan	Rotation time [s]	Image thickness [mm]	Table speed [mm/rotation]	Pitch	Interval [mm]	SFOV* [mm]	kVp	mA	DFOV* [cm]	Reconstruction algorithm	CTDI _{vol} * [mGy]
Single-energy	Helical	0.8	3.75	10.62	0.531	3	Head	140	140	12	Soft	66
Dual-energy ⁸	GSI-26*	0.7	3.75	10.62	0.531	3	Head	80/140	375	12	Soft	67

* SFOV = scan field of view; kVp = kilovolts peak; DFOV = display field of view; CTDI_{vol} = volume CT dose index; GSI = Gemstone Spectral Imaging.

Table 2

Concentrations and weights of iron oxide and hydroxyapatite needed to create hemorrhage and calcification models of specific SECT attenuation (HU).

Target attenuation [HU]	Concentration [mg/mL] [*]		Weight [mg] [†]	
	Hydroxyapatite	Iron Oxide	Hydroxyapatite	Iron oxide
10	6.32	3.41	16.11	8.69
20	14.98	7.19	38.20	18.34
30	23.64	10.97	60.29	27.98
40	32.31	14.76	82.38	37.63
50	40.97	18.54	104.47	47.28
60	49.63	22.32	126.55	56.92
70	58.29	26.11	148.64	66.57
80	66.95	29.89	170.73	76.22
90	75.62	33.67	192.82	85.86
100	84.28	37.46	214.91	95.51

^{*} Derived from the linear-fit equation in Figure 4.

[†] Weights required to achieve the concentrations listed were calculated based on the volume of specific gel vial used in the study.

Table 3

Average SECT attenuation (HU) of each matched pair and mean SECT attenuations (HU) for the hemorrhage gel model and the calcification gel model in each pair

Average SECT attenuation of matched model pair [HU] *	Mean SE attenuation [HU] $\pm$ SD	
	Hemorrhage model (iron oxide)	Calcification model (hydroxyapatite)
12	11.4 $\pm$ 8.5	12.7 $\pm$ 3.4
14	13.9 $\pm$ 3.2	14.2 $\pm$ 3.4
17	17.1 $\pm$ 3.8	16.9 $\pm$ 3.3
20	20.8 $\pm$ 3.4	19.7 $\pm$ 3.2
30	30.4 $\pm$ 4.6	30.6 $\pm$ 3.5
32	31.3 $\pm$ 3.4	31.8 $\pm$ 3.3
39	39.2 $\pm$ 5.3	38.8 $\pm$ 3.5
50	49.4 $\pm$ 3.2	51.3 $\pm$ 3.9
60	59.7 $\pm$ 4.8	60.6 $\pm$ 3.6
62	62.3 $\pm$ 4.0	62.3 $\pm$ 4.4
71	70.7 $\pm$ 4.0	71.1 $\pm$ 5.0
75	75.7 $\pm$ 4.0	74.7 $\pm$ 9.5
82	82.4 $\pm$ 6.2	82.3 $\pm$ 4.4
88	88.7 $\pm$ 6.6	87.5 $\pm$ 4.2
89	88.7 $\pm$ 6.6	89.6 $\pm$ 7.6
90	90.1 $\pm$ 6.6	89.6 $\pm$ 7.6

* Hemorrhage and calcification gel models with attenuation levels within 2 HU of each other were organized into matched model pairs, and the average attenuation of each pair was the rounded average of the hemorrhage model attenuation and the calcification model attenuation.