Extracting 3D Angiography Data from Simulated Computed Tomography Angiography Scans Using Low Iodine Contrast Agent

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Abstract

The purpose of this research is to investigate the feasibility of using low contrast agent concentration with X-ray computed tomography in visualizing and diagnosing the human vascular system while minimizing the risk of toxicity to the patient. This research investigated the effect of several iodine contrast agent concentrations on the ability to extract and visualize human vessels using simulated computed tomography scans. Monte Carlo simulation was used to perform these computed tomography acquisitions. The simulated patient was based on actual computed tomography angiography data, where a technique was developed to simulate brain vessels with contrast agents ranging from 0 mg to 20 mg of iodine. The simulation used segmented patient data along with basic image processing techniques to model the various levels of iodine concentrations. Cone beam computed tomography projections of a patient injected with and without iodine were acquired in the simulations. Subtraction of the corresponding projections was performed to generate images caused by the contrast agent. Then, histogram analysis of these differences was used to assess the validity of extracting and visualizing the human vessels. The smallest amount of iodine, 0.5 mg, helped better visualize the brain vessels and 2 mg of iodine was high enough to show almost 90% of the vessels. Additionally, the vessels were clearly visible in all the subtracted images. This research showed very promising outcomes in using low concentrations of iodine. Thus, this study proposes for the pharmaceutical companies and others interested to clinically investigate and evaluate the efficacy of using low concentrations of iodine and the associated side effects.

Keywords

GEANT4 Simulation, Computed Tomography Angiography, Iodine Contrast Agent

1. Introduction

Computed tomography angiography (CTA) is the medical imaging modality that focuses mainly on evaluating the human vascular system. In computed tomography (CT), multiple tomographic high contrast images between bony structures and soft tissue are reconstructed. This is one of the main signatures and differentiators of CT over the other tomographic medical imaging modalities. However, visualization of blood vessels using conventional CT is difficult due to the similarity and overlap in the CT numbers (CTN) between vessels and their surrounding soft tissues.

On the other hand, in CTA the vessels' CTN compared to the surrounding tissue is enhanced and thus, the vessels are visible. This enhancement is due to the use of a contrast agent injected into patients before the acquisition of the CT scan. Consequently, this increases the vessels' X-ray attenuation coefficients leading to an increase in the vessels' CTN and thus enhances the contrast with the surrounding tissues [1]. Clinicians may then visualize vessels in 2-D tomographic views, which is a tedious task and not optimal for diagnosis. Vessels are 3-D tree-like structures that are much better represented using 3-D visualization techniques [2].

3-D visualization techniques, such as maximum intensity projection or volume rendering are known techniques that help in visualizing 3-D data [3] [4] [5]. However, the high CTN for bone (e.g., the skull in a head scan) creates a major external barrier in visualizing internal blood vessels. Excluding high CTN with basic image processing may cause the removal of some vessels filled with contrast agents. This is due to the overlapping CTN distributions for bone and contrast-filled vessels. Most of this is due to the partial volume averaging effect where each voxel contains more than one tissue which renders the voxel value to be higher or lower than expected [2].

Current diagnostic techniques in CTA employ semi-automatic editing techniques to eliminate bones [6]. The tracing is usually performed in exclusive or inclusive editing mode which both require a lot of operator time. In addition, the results are influenced by the intra- and inter-operator variability. Investigators have developed hybrid semi-automated editing programs in an effort to reduce the operator time [7]. In these techniques, an automated 2-D segmentation procedure is performed to produce a set of labeled images. The user then selects a small number of labeled images along with a connectivity algorithm to collect related segments for the inclusion of the edited sections. This method is computationally intensive and not suitable for clinical practice.

Additionally, automatic bone removal techniques have been developed to extract bone which allows 3D visualization of the vessels [2]. Although these techniques require only one set of CTA data, the required concentration level of the contrast agent is not addressed. Another approach proposed in the literature involves the use of warped matching for digital subtraction of data sets corresponding to pre- and post-contrast injection [8]. This method requires the avail-

ability of two data sets (pre- and post-) contrast patient injection, encounter the issue with misregistration of the two data sets, and the amount of contrast agent required is not addressed.

All of the aforementioned techniques involving CTA data do not address the minimum required concentration level of the contrast agent that should be administered to the patient. Some patients cannot handle the typical concentration level of contrast agent due to kidney dysfunction [9] [10]. Therefore, there is a need for a new technique that uses a low concentration of contrast agents. Exploring the acquisition of X-ray CT with the use of different concentrations of iodine while accomplishing the required clinical tasks is greatly needed, which is the main idea of this research.

Monte Carlo simulation helps in achieving this task without subjecting the patient to any radiation dose or discomfort [11]-[17]. The aim of this research is to investigate the feasibility of developing a model through simulating computed tomography angiography (CTA) data with different iodine concentrations. This research studies the feasibility of visualizing blood vessels using a low contrast agent. The proposed technique should render the vascular data in 3-D, unveiling any aneurysms or calcifications in a clear manner. This enhancement in vessel visualization is expected to increase the sensitivity of clinical diagnoses.

2. Materials and Methods

2.1. X-Ray CT Simulation

Monte Carlo simulation based on GEANT4 (GEometry ANd Tracking) via vGATE (Virtual Geant4 Application for Tomography Emission) mimics the acquision of X-ray computed tomography (CT) projections [11]-[17]. **Figure 1** shows the X-ray CT setup in our simulation, where the patient was rotated while keeping the source and the detectors fixed. The X-ray source emits a typical poly-energetic spectrum of a CT scanner at a maximum of 120 KeV energy photon.

The X-ray source was set as a planar source and the focal point size is assumed to be a point source that emits X-ray photons covering the simulated patient.
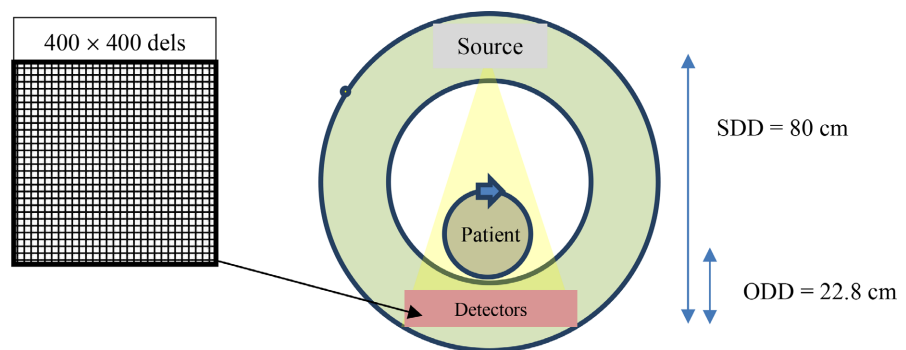

Figure 1. The simulation setup for the X-ray CT scanner. The source to detector distance (SDD) was equal to 80 cm and the object to detector distance (ODD) was equal to 22.8 cm. Note the array of detector elements (dels) consisted of 400 × 400 dels.

The setup simulates a cone-beam CT with a detector consisting of 400 × 400 2-dimensional detector elements (see **Figure 1**). However, unlike the typical X-ray CT acquisitions, the patient X-ray projections were generated by fixing the X-ray source and detectors while rotating the patient. The source to detector distance (SDD) was set to 80 cm and the center of the object (patient) to detector distance (ODD) was set to 22.8 cm. This provided a mean magnification factor of 1.4.

2.2. Patient Simulation

Figure 2 shows the flow chart of the main steps used to simulate patient data with different concentrations of iodine contrast agents. First, a computed tomography angiography (CTA) data set of a patient's head was used in the simulation. The original CTA consists of 512 × 512 × 180 isotropic voxel data. It was scaled down to 256 × 256 × 90 to speed up the simulation. The CTA data was acquired with 120 KeV maximum photon and ISOVUE-300 iodine contrast agent. The vessels were clearly visible in this data set (see **Figure 3**) [18]. This data was then segmented using the AM Alyassin *et al.* bone removal technique, which removes the bone from the CTA data allowing the vessels to be the dominant voxel values [2]. Then, a simple thresholding technique was used on the boneless data to generate a binary mask of the brain vessels. The segmented vessels were the ground truth in our research.

The vessels' binary mask identifies the location of the blood vessels within the CTA data. Therefore, replacing the vessel voxel data with other CT numbers is easily accomplished using a logical operator that masks the two data sets, the
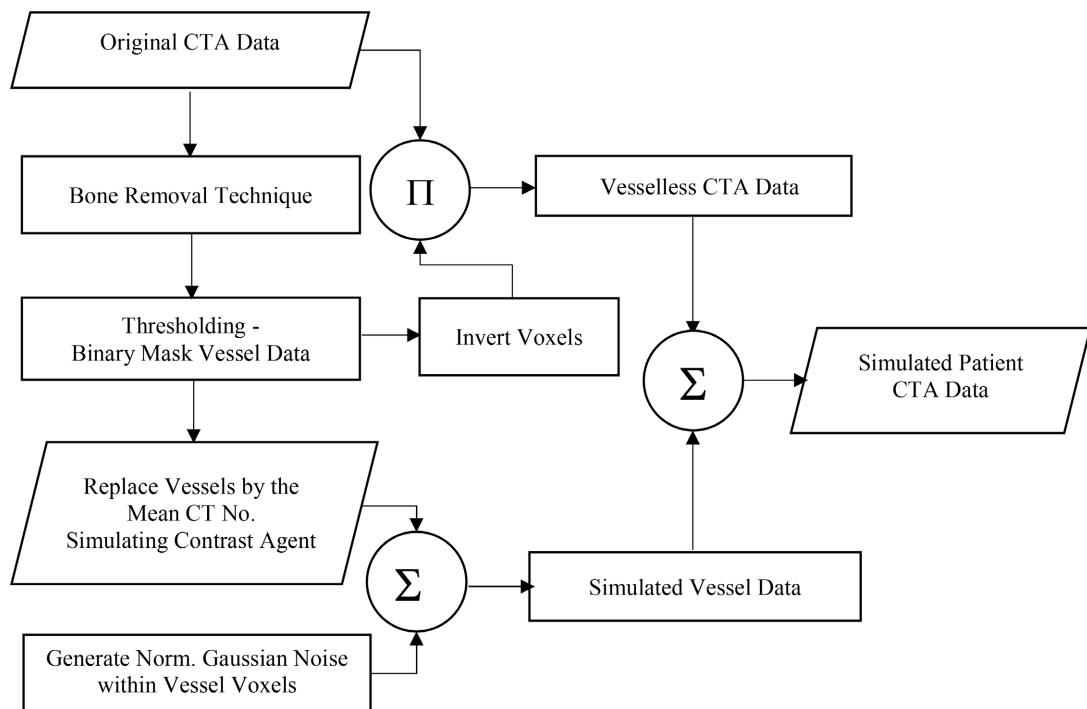

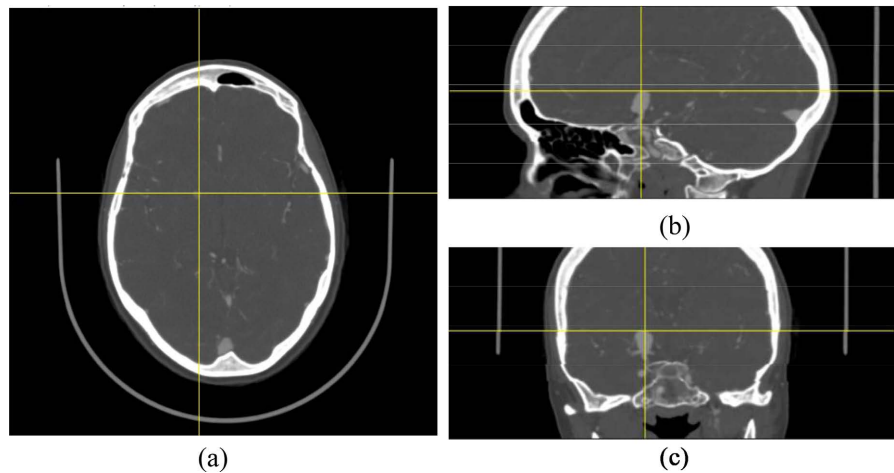**Figure 2.** The main steps in generating the simulated patient data.

Figure 3. Shows the three orientations of the original CTA data set. (a)-(c) are the axial, sagittal, and coronal orientations.

original CTA data and the vessel binary mask. Note that an inverter of the vessel binary mask was used before masking the original data to remove the vessels from the data set (see **Figure 2**). Also, the vessel voxels were replaced with the desired CT number simulating the concentration of iodine. Furthermore, normalized gaussian noise was added to the simulated vessel data to represent s more realistic CTA data set. Based on regions of interest analysis of the original CTA data, the standard deviation of the normalized gaussian noise was set to 15.

In the simulated blood vessels, the mean CTN for blood without a contrast agent was set to 50 [19]. For the standard deviation in the blood vessels, CTN was estimated to be 15 and that was based on a statistical region of interest analysis performed on the original CTA data. An increment of 25 CTN was used for every additional 1 mg of iodine per cc [19]. Based on the amount of iodine, the volume of iodine was calculated from the density. The complement to 1 cc of the calculated iodine volume was assumed to contain blood. Using these as fractional volumes in the weighted sum of densities between iodine and blood, the density for the simulated contrasted vessel was estimated (see **Table 1**).

Based on the technique explained in **Figure 2**, several CTA simulated patient data were generated for different levels of iodine concentration.

2.3. Preparation of CTA Acquisition

Using the GEANT4-GATE software, the materials and tissues within the CT scanner setup were estimated. Many of these materials were already defined by their elemental components and densities within the GEANT4-GATE software [11] [20]. **Table 2** shows the elemental compositions of the main simulated materials and their estimated densities. The simulated contrasted vessels were estimated by adjusting the volume fraction for the blood that was estimated in **Table 1** and then adding the remaining fraction as iodine. **Table 2** shows only a few samples of contrasted vessels and the rest of the prepared contrasted vessels were estimated in a similar manner.

Table 1. Generate contrasted vessels at different concentrations. Each contrasted vessel will have unique density and Hounsfield CT Number.

Blood Density = 1.06 g/cc		Iodine Density = 4.93 g/cc			
Simulated		Fractions in 1 cc		Weighted	
Blood Vessel	mg of Iodine	Blood	Iodine	Density g/cc	Mean CTN
0	0.0	1.0000	0.0000	1.0600	50
0.5	0.5	0.9999	0.0001	1.0604	63
1	1.0	0.9998	0.0002	1.0608	75
2	2.0	0.9996	0.0004	1.0616	100
3	3.0	0.9994	0.0006	1.0624	125
4	4.0	0.9992	0.0008	1.0631	150
5	5.0	0.9990	0.0010	1.0639	175
10	10.0	0.9980	0.0020	1.0678	300
15	15.0	0.9970	0.0030	1.0718	425
19	19.0	0.9961	0.0039	1.0749	525
20	20.0	0.9959	0.0041	1.0757	550

Table 2. Shows the elemental compositions of the main simulated materials and their estimated densities.

Tissue	Air	Skin	Brain	Blood	Vessel 1	Vessel 5	Vessel 10	Vessel 20	Skull
Density g/cc	1.29×10^{-3}	0.92	1.04	1.06	1.0608	1.0639	1.0678	1.0757	1.61
mg of iodine	-	-	-	0 mg I	1 mg I	5 mg I	10 mg I	20 mg I	-
Elements	Mass Fraction (Sum = 1.0)								
Oxygen	0.2318	0.229	0.712	0.745	0.74485	0.74424	0.74349	0.7420	0.435
Carbon	0.0001	0.640	0.145	0.110	0.10998	0.10989	0.10978	0.1095	0.212
Hydrogen	-	0.120	0.107	0.102	0.10198	0.10190	0.10180	0.1015	0.05
Nitrogen	0.7553	0.008	0.022	0.033	0.03299	0.03297	0.03293	0.0329	0.04
Sulfur	-	-	0.002	0.002	0.00200	0.00200	0.00200	0.0020	0.003
Sodium	-	-	0.002	0.001	0.00100	0.00100	0.00100	0.0010	0.001
Phosphor	-	0.002	0.004	0.001	0.00100	0.00100	0.00100	0.0010	0.081
Chlorine	-	-	0.003	0.003	0.00300	0.00300	0.00300	0.0030	-
Potassium	-	-	0.003	0.002	0.00200	0.00200	0.00200	0.0020	-
Iron	-	-	-	0.001	0.00100	0.00100	0.00100	0.0010	-
Argon	0.0128	-	-	-	-	-	-	-	-
Magnesium	-	-	-	-	-	-	-	-	0.002
Calcium	-	0.001	-	-	-	-	-	-	0.176
Iodine	-	-	-	0.000	0.0002	0.0010	0.0020	0.0041	-

GEANT4-vGate CT simulation requires defining the range of the corresponding CTN for all materials and tissues within the simulation setup. Table 3 shows the ranges of CTN assigned for the different materials and tissues used in the simulation. This was required by the simulation software because the simulated patient was based on actual CTA data.

2.4. Acquisition of CTA

Cone beam CTA acquisitions provided projection images around the patient. In our simulation, we used fixed Forced Detection CT that was based on statistical analysis and the Monte Carlo technique [21]. Since the projection images, which contain the attenuation coefficients, provide 3-dimentional views of the simulated patient. We focused our analysis on these projection images. Furthermore, the filter back reconstruction technique may use on these projection images to provide tomographic images.

The patient data with and without contrast agents were acquired by our simulation using 120 KeV. Projection images of attenuation coefficients were estimated using the simulation technique. The projection images contained voxels that represent the sum of the attenuation coefficients of several tissues that may be encountered along the projection rays such as air, skin, brain, blood, and bone.

Cone beam CT acquisition of the simulated patient with iodine concentrations of 0, 0.5, 1, 2, 3, 4, 5, 10, 15, 19, and 120 mg were performed. Subtraction of images was performed between without- and with- contrast for all the different iodine concentrations.

Histogram analysis was then performed on the subtracted images. The number of voxels was counted within the attenuation coefficient between 0.00001 and 1.0 cm^{-1}. A count ratio was also estimated between the voxel count in each the images

Table 3. Shows the estimated range in CT numbers (CTN) for each of the simulated materials.

Simulated Materials	CTN Minimum	CTN Maximum	Simulated Materials	CTN Minimum	CTN Maximum
Air	−1000	−900	BV-5	163	187
Skin	−901	0	BV-10	288	312
Brain	1	24	BV-15	413	437
Blood	25	56	BV-19	513	537
BV-0.5	57	68	BV-20	538	562
BV-1	69	87	Skull	563	3095
BV-2	88	112			
BV-3	113	137			
BV-4	138	162			
			BV stands for blood vessel		

over the maximum voxel count obtained within all the iodine concentration difference images. A plot of the count ratio versus each of mg of iodine concentration data sets was performed.

A further study of the patient with 5 mg of iodine was performed at eight different projections around the patient (every 22.5 degrees). Similar acquisitions were acquired without iodine contrast agent. The difference in the CTA projection images with contrast and without contrast was conducted for the following angle projections: 0, 22.5, 45, 67.5, 90, 112.5, 135, and 157.5 degrees all the angle projections.

3. Results and Discussion

3.1. Patient Simulation

Figure 4 shows axial images of the same slice within the simulated CTA data. Each simulated CTA has different iodine concentrations. Note that as the amount of iodine concentration increases, the CTN increases and the vessels are more visible from the surrounding brain tissues.

3.2. Acquisition of CTA

The cone beam CT projection images at different iodine concentrations are
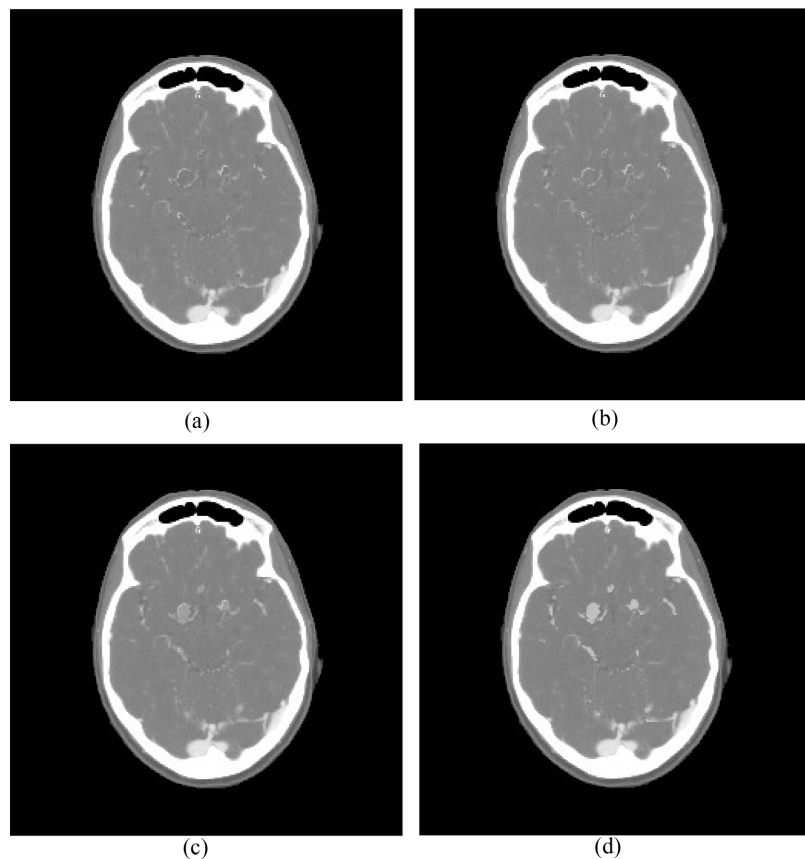

(a)　　　　　　　　　　　　　　(b)

(c)　　　　　　　　　　　　　　(d)

Figure 4. Show an axial simulated CTA data. (a) No contrast agent was added, (b) 1 mg of iodine was added, (c) 5 mg of iodine was added, (d) 10 mg of iodine was added.
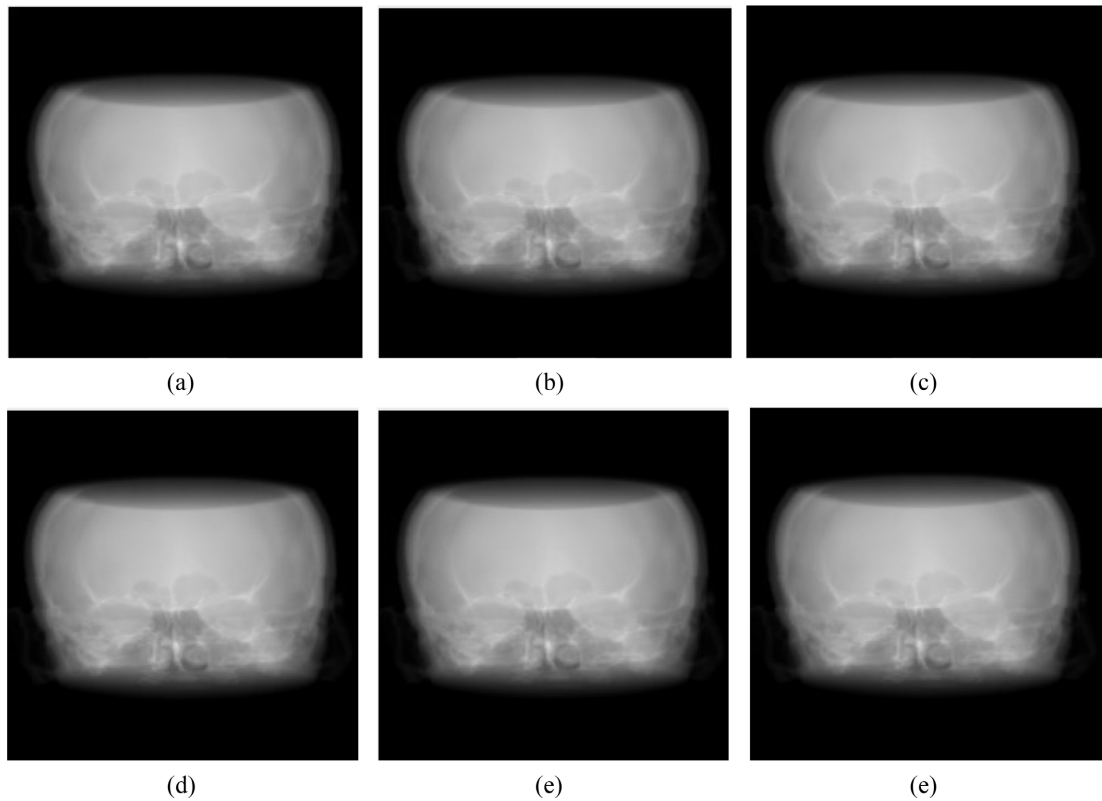
(a)   (b)   (c)

(d)   (e)   (e)

Figure 5. Shows the acquired images of the patient with different concentration in mg of iodine. (a) Projection image without iodine. (b)-(f) are the projection images with 1, 2, 3, 5, and 10 mg of iodine respectively. Note all these projection images were displayed at the same window and level.

shown in **Figure 5**. The projections were acquired at 0 angles (see **Figure 5**). Note that it is difficult to see the vessels in these projections even with the highest iodine concentration. The X-ray attenuation of the skull and the brain overshadows the X-ray attenuation of the vessels. Thus, two simulated CTA data are required: the with and the without iodine contrast. Then the difference image between them is performed for the different levels of iodine concentrations (see **Figure 6**).

Table 4 shows the results of the histogram analysis that was performed on the different images between the projections with- and without- contrast. The maximum and the mean of the histograms for the attenuation coefficient linearly increased with increased levels of iodine. The R^2 linear fits were 0.996 and 0.999 for the maximum and the mean linear attenuation difference coefficient respectively. The number of voxels was counted for the attenuation coefficient between 0.00001 and 1.0 cm^{-1}. Then, the ratio count which is the counted voxels in each of the difference iodinated/non-iodinated data over the maximum counted voxels in all the iodinated/non-iodinated simulated data sets, increased in a non-linear fashion (see **Figure 7**).

There were 8806 voxels in the original segmented vessel binary mask. It is expected that the vessel voxel counts in the projection images to be higher than the original vessel voxels due to the magnification factor and the volume averaging effect. **Figure 7** shows that 2 mg of iodine injected into the vessels of the patient
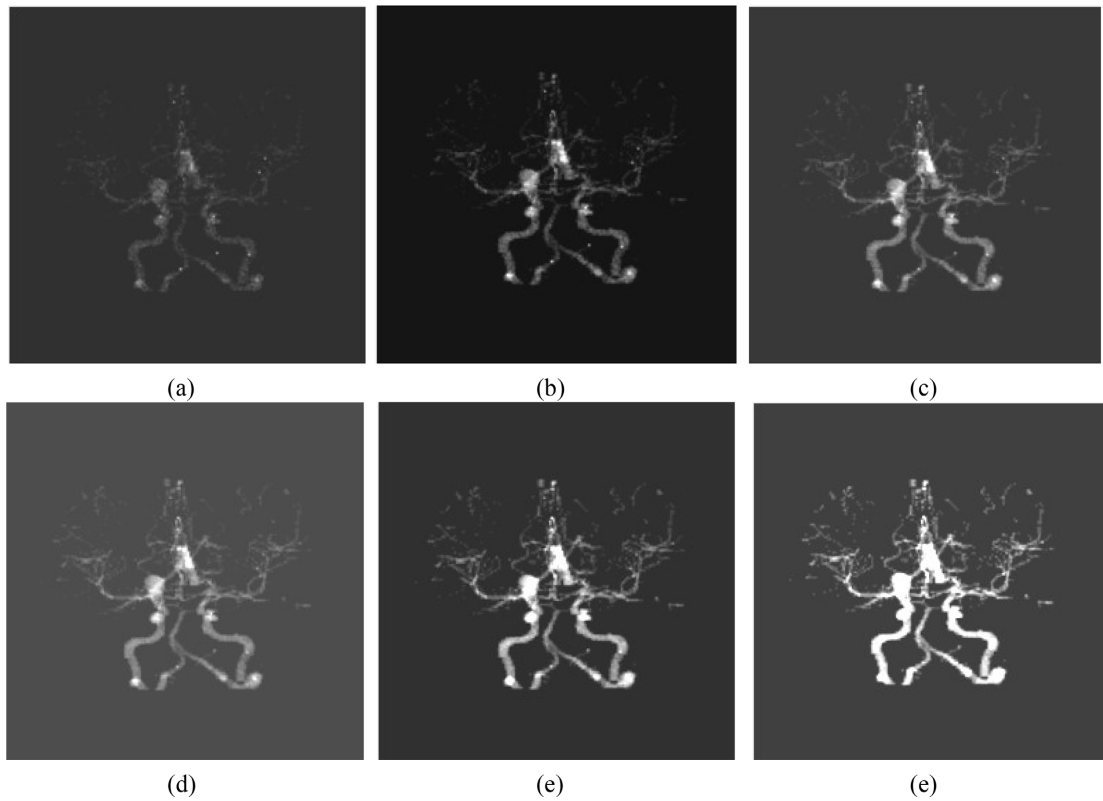
(a) (b) (c)

(d) (e) (e)

Figure 6. Shows the difference images of the patient with and without different concentration in mg of iodine. (a)-(f) show the difference image between 1, 2, 3, 4, 5, and 10 mg of iodine (a) Note all these difference images were displayed at the same window and level.

Table 4. Histogram analysis of the difference images in a patient with contrast and without iodine. The ratio count is ratio of the detected voxel count for each iodine concentration over maximum the voxel count (20 mg of iodine).

Iodine	Min	Max	Mean	Count	Ratio Count
0.5 mg I	0.00001	0.00274	0.000128	6185	0.661
1 mg I	0.00001	0.00303	0.000182	7578	0.810
2 mg I	0.00001	0.00349	0.000326	8568	0.916
3 mgI	0.00001	0.00435	0.000470	8864	0.948
4 mgI	0.00001	0.00568	0.000614	9005	0.963
5 mg I	0.00001	0.00668	0.000761	9084	0.971
10 mg I	0.00001	0.01350	0.001500	9243	0.988
15 mg I	0.00001	0.02020	0.002240	9307	0.995
19 mg I	0.00001	0.02630	0.002900	9341	0.999
20 mg I	0.00001	0.02910	0.003150	9351	1.000

demonstrated more than 90% of the injected vessels were visible in the different projection images. Even 1 mg of iodine shows a ratio count of 81% indicating a small amount of iodine will make a difference in the visibility of vessels. Recall

that all of the aforementioned results were for only the 0 angle projection CT projections. In addition, the simulation data does not consider the possible motion of the patient between the pre- and the post iodinated acquisitions and reply on the various registration techniques to correct for any possible error.

The CTA projection images around the patient with- and without- contrast are shown in **Figure 8**. **Figure 8** shows the images between the projection image without and with 5 mg iodine contrast agent at 8 different angle projections. The
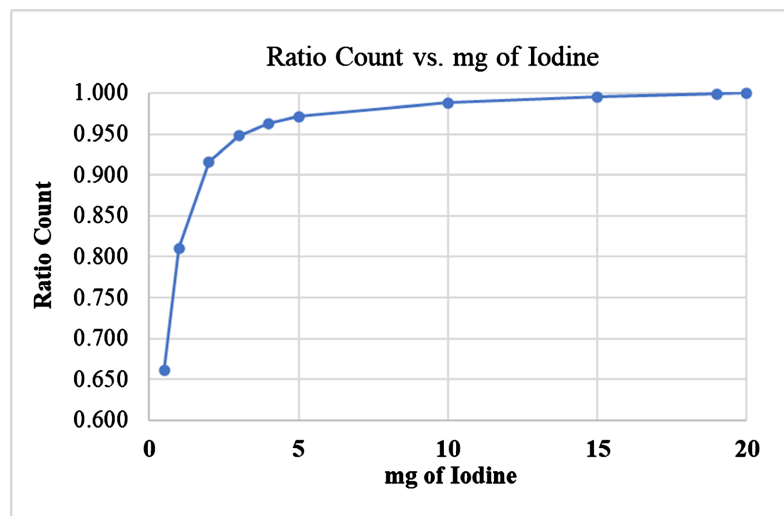

Figure 7. Shows the ratio count between the voxel count in the difference images between contrasted iodine and without iodine over the maximum voxel count (here is the 20 mg of iodine).
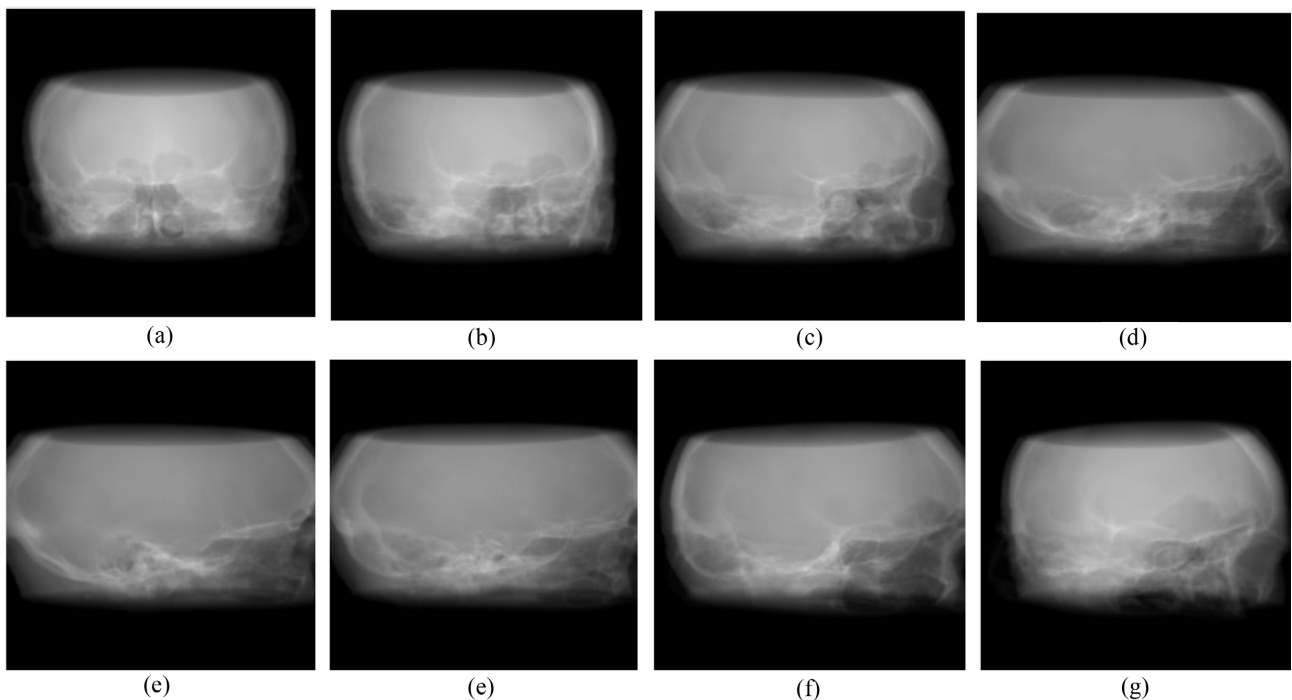

Figure 8. Shows the projection images of the patient with 5 mg iodine around the patient. (a)-(g) are projection images at 0, 22.5, 45, 67.5, 90, 112.5, 135, and 157.5 degrees respectively. Note all the projection images were displayed at the same window and level.

projection images were acquired of the patient at 0, 22.5, 45, 67.5, 90, 112.5, 135, and 157.5 degrees. Note the vessels were not visible in these data sets. It was impossible to see the contrasted vessels in these projections due to the higher X-ray attenuation values of the skull and the brain, but the different images clearly show the vessels even at smaller amount of iodine concentration (see Figure 9).

Table 5 shows the results of the histogram analysis of the subtracted images. Note that the projection images may contain more voxels than the original number of vessels voxels due to the magnification factor and the volume averaging effect. According to Table 5, for 5 mg of iodine contrast agent, the mean ratio count for the eight projection angles was 0.95 with 0.03 standard deviation. There were some variations in the ratio count and that was due to the variation of the volume averaging which was affected by the shape of the vessels within the skull. Nevertheless, the vessels were clearly visible for eight projections. It also assumed the vessels would be visible for any angle projection subtracted image.

The outcome of this study demonstrates that a small amount of iodine will make a significant difference in visualizing the vessels. Therefore, a further clinical study with low iodine concentrations is recommended to be investigated outlining the benefits and risks of CTA data acquisitions. It is our belief that this research might provide useful clinical outcomes for patients with kidney diseases. Finally, this study should help in providing a simulation technique to improve the sensitivity and specificity in diagnoses CT Angiography data.
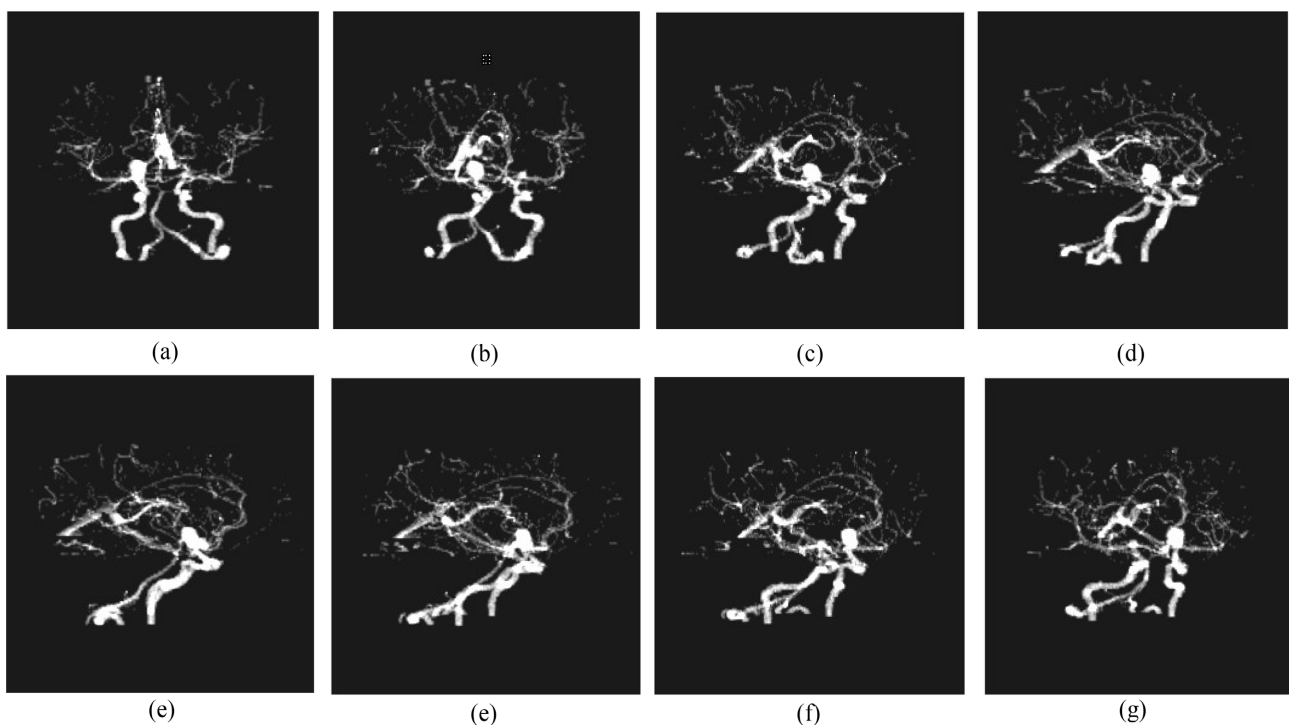

| (a) | (b) | (c) | (d) |
| (e) | (e) | (f) | (g) |

Figure 9. Shows the difference images of the patient with without 5 mg of iodine acquired around the patient every 22.5 degrees. (a)-(g) are the difference images at 0, 22.5, 45, 67.5, 90, 112.5, 135, and 157.5 degrees respectively. Note all the projection images were displayed at the same window and level.

Table 5. Histogram analysis of the difference images in a patient with and without 5 mg of iodine. The difference in the projections around patient varied from 0 to 157.5 degrees. The ratio count is ratio of the counted voxels for each projection over the maximum voxel count (9759 at 67.5-degree projection) found.

Projection Angle	mg of iodine	Min	Max	Mean	Standard Deviation	Voxel Count	Ratio Count
0	5 mg I	0.00001	0.006680	0.000761	0.000926	9084	0.931
22.5	5 mg I	0.00001	0.005280	0.000757	0.000834	9168	0.939
45	5 mg I	0.00001	0.005120	0.000772	0.000791	9023	0.925
67.5	5 mg I	0.00001	0.007540	0.000717	0.000815	9759	1.000
90	5 mg I	0.00001	0.010800	0.000741	0.000949	9441	0.967
112.5	5 mg I	0.00001	0.005730	0.000734	0.000855	9487	0.972
135	5 mg I	0.00001	0.006820	0.000767	0.000844	8986	0.921
157.5	5 mg I	0.00001	0.006260	0.000730	0.000824	9338	0.957
Mean			0.006779	0.000747		9286	0.952
Standard Deviation			0.001818	1.97E-05		269	0.028

4. Summary

Finding the minimum amount of iodine contrast agent required to validate a CTA study is of great importance to patients with kidney diseases. Thus, the rationale behind this research was to offer a valid alternative technique for simulating computed tomography angiography (CTA) data at various concentrations of iodine contrast agents.

This study provided an alternative technique to image patients with CTA at various concentrations of iodine contrast agent without subjecting the patient to radiation doses or contrast agent toxicity. The technique proposed used Monte Carlo simulation via GEANT4-VGate application. The simulation was based on actual CTA data that was subjected to segmentation and image processing techniques to generate several CTA data with various iodine concentrations. In addition, the technique generates CTA projections with and without a contrast agent and performs histogram analysis on the subtracted images.

Clearly, the higher amount of iodine injected into the vessels showed clearer 3-D brain vessels but even a small amount of iodine was able to help visualize to some degree the brain vessels. Therefore, the outcome of this study demonstrates that even a small amount of iodine will make a big difference in visualizing the vessels. A further clinical study is recommended to study the benefits and risks of CTA data acquisitions with a low amount of contrast agents. It is our belief that this research might provide useful clinical outcomes for patients with kidney diseases. Finally, this research should open the gate to performing CT and CTA simulations for various research topics.

Acknowledgements

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Smirniotopoulos, J.G., Murphy, F.M., Rushing, E.J., Rees, J.H. and Schroeder, J.W. (2007) Patterns of Contrast Enhancement in the Brain and Meninges. *RadioGraphics*, **27**, 525-551.

[2] Alyassin, A.M. (2009) Obstacle Exclusion from X-Ray CT Angiography Data for 3D Image Diagnosis. *Jordan Journal of Physics*, **2**, 59-72.

[3] Kuszyk, B.S., Heath, D.G., Bliss, D.F. and Fishman, E.K. (1996) Skeletal 3-D CT: Advantages of Volume Rendering overs Surface Rendering. *Skeletal Radiology*, **25**, 207-214.

[4] Lorensen, W. and Cline, H. (1998) Marching Cubes: A High Resolution 3D Surface Construction Algorithm. *ACM Computer Graphics*, **21**, 163-169.

[5] Alyassin, A.M., Lancaster, J.L., Downs, J.H. and Fox, P.T. (1994) Evaluation of New Algorithms for the Interactive Measurement of Surface Area and Volume. *Medical Physics*, **21**, 741-752.

[6] Shiffman, S., Rubin, G.D. and Napel, S. (1996) Semiautomated Editing of Computed Tomography Sections for Visualization of Vasculature. *Proceedings of the SPIE*, **2707**, 140-151.

[7] van der Heyden, B., Wohlfahrt, P., Eekers, D.B.P., Richter, C., Terhaag, K., Troost, E.G.C. and Verhaegen, F. (2019) Dual-Energy CT for Automatic Organs-at-Risk Segmentation in Brain-Tumor Patients Using a Multi-Atlas and Deep-Learning Approach. *Scientific Reports*, **9**, Article No. 4126. https://doi.org/10.1038/s41598-019-40584-9

[8] Bani-Hashemi, A., Krishnan, A. and Samaddar, S. (1996) Warped Matching for Digital Subtraction of CT-Angiography Studies. *Proceedings of the SPIE*, **2710**, 428-437.

[9] Boonn, W.W., Litt, H.I. and Charagundla, S.R. (2007) Optimizing Contrast Injection for Coronary CT Angiography and Functional Cardiac CT. *Applied Radiology*, **36**, 51-57.

[10] Kariyanna, P.T., Aurora, L., Jayarangaiah, A., Das, S., Gonzalez, J.C., Hegde, S. and McFarlane, I.M. (2020) Neurotoxicity Associated with Radiological Contrast Agents Used during Coronary Angiography: A Systematic Review. *American Journal of Medical Case Reports*, **8**, 60-66. https://doi.org/10.12691/ajmcr-8-2-6

[11] Sarrut, D., *et al.* (2021) Advanced Monte Carlo Simulations of Emission Tomography Imaging Systems with GATE. *Physics in Medicine & Biology*, **66**, 10TR03. https://doi.org/10.1088/1361-6560/abf276

[12] Sarrut, D., Bardiès, M., Boussion, N., *et al.* (2014) A Review of the Use and Potential of the GATE Monte Carlo Simulation Code for Radiation Therapy and Dosimetry Applications. *Medical Physics*, **41**, 64301. https://doi.org/10.1118/1.4871617

[13] Morris, R., Lakshmanan, M., Fong, G., Kapadia, A. and Greenberg, J. (2016) Coded

Aperture Coherent Scatter Spectral Imaging of the Breast: A Monte Carlo Evaluation of Absorbed Dose. *Medical Physics*, **43**, 3398-3399.

[14] Tirao, G., Quintana, C. and Valente, M. (2010) Mammography Image Quality Optimisation: A Monte Carlo Study. *International Journal of Low Radiation*, **7**, 276-297. https://doi.org/10.1504/IJLR.2010.034916

[15] Taha, E.M. and Alyassin, A.M. (2016) Feasibility of a Novel Gamma Radiography Mammo System. *Insights in Medical Physics*, **1**, 1-8.

[16] Taha, E.M., Alhawsawi, A., Siddig, M. and Balamesh, A.S. (2021) Exposure Determination in Gamma-Ray Radiography for Mammography Applications. *Arabian Journal for Science and Engineering*, **47**, 7583-7591.

[17] Abolaban, F.A. and Taha, E.M. (2020) Representation and Illustration of the Initial Parameters in GATE 8.1 Monte Carlo Simulation of an Elekta Versa-HD Linear Accelerator. *Journal of Radiation Research and Applied Sciences*, **13**, 642-647.

[18] ACR Committee on Drugs and Contrast Media (2021) ACR Manual on Contrast Media. American College of Radiology, Reston.

[19] Bae, K.T. (2010) Intravenous Contrast Medium Administration and Scan Timing at CT: Considerations and Approaches. *Radiology*, **256**, 3261.

[20] Abbani, N., *et al.* (2018) OpenGATE Collaboration vGate Software Package Version 8.1. https://opengate.readthedocs.io/en/latest/vgate.html

[21] Cajgfinger, T., Rit, S., Létang, J.M., Halty, A. and Sarrut, D. (2018) Fixed Forced Detection for Fast SPECT Monte-Carlo Simulation. *Physics in Medicine and Biology*, **63**, Article ID: 055011.