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(54) **Title:** CONTRAST DOSE REDUCTION FOR MEDICAL IMAGING USING DEEP LEARNING

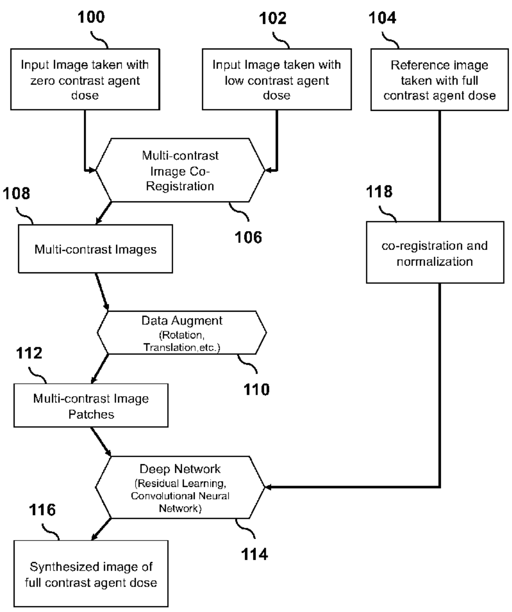

Fig. 1

(57) **Abstract:** A method for diagnostic imaging with reduced contrast agent dose uses a deep learning network (DLN) [114] that has been trained using zero-contrast [100] and low-contrast [102] images as input to the DLN and full-contrast images [104] as reference ground truth images. Prior to training, the images are pre-processed [106, 110, 118] to co-register and normalize them. The trained DLN [114] is then used to predict a synthesized full-dose contrast agent image [116] from acquired zero-dose and low-dose images.

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CONTRAST DOSE REDUCTION FOR MEDICAL IMAGING USING DEEP LEARNING

FIELD OF THE INVENTION

This invention relates generally to medical diagnostic imaging. More specifically, it relates to imaging techniques that use contrast agents.

BACKGROUND OF THE INVENTION

Many types of medical imaging use contrast agents to enhance the visualization of normal and abnormal structures. Examples include conventional angiography, fluoroscopy, computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI). It is often desirable to reduce the contrast agent dose in order to increase the safety of these agents. However, reduced dose reduces desired imaging enhancements, so this has not been possible.

For example, MRI is a powerful imaging technique providing unique information to distinguish different soft tissues and pathologies. Magnetic contrast agents with unique relaxation parameters are often administered to further boost the visibility of pathology and delineation of lesions. Gadolinium based contrast agents (GBCAs) are widely used in MRI exams because of their paramagnetic properties, for applications such as angiography, neuroimaging and liver imaging. However, although GBCAs are designed to avoid toxic release and have been widely applied in contrast enhanced MRI (CE-MRI) examinations to assist the diagnosis, there are several side effects resulting from GBCA administration. Therefore, there are many reasons why it would be advantageous to reduce the dosage of GBCA while preserving the enhanced contrast in MRI imaging. Similar problems are associated with administering contrast agents in other imaging modalities as well. Thus, it would be of benefit to be able to reduce the dose of contrast agents generally in diagnostic imaging techniques, without sacrificing the image enhancement benefits that the contrast agents provide.

BRIEF SUMMARY OF THE INVENTION

The present invention provides techniques to enhance image quality of diagnostic imaging modalities using a lower dose of contrast than is currently possible. This enables new opportunities for improving the value of medical imaging. In addition to MRI, the techniques are generally applicable to a variety of diagnostic imaging techniques including angiography, fluoroscopy, computed tomography (CT), and ultrasound.

Surprisingly, the techniques of the present invention are able to predict a synthesized full-dose contrast agent image from a low-dose contrast agent image and a pre-dose image. The low dose may be any fraction of the full dose, but is preferably 1/10 or less of the full dose. Significantly, naively amplifying the contrast enhancement of a 1/10 low-dose CE-MRI by a factor of ten results in poor image quality with widespread noise and ambiguous structures. Even though the low-contrast image cannot be used for diagnosis directly, or by simply amplifying its uptake, the techniques of the present invention remarkably are able to recover the full contrast signal and generate predicted full-contrast images with high diagnostic quality. Specifically, in experimental tests, the method yielded significant improvements over the 10% low-dose images, with over 5 dB PSNR gains, 11% SSIM increased, and improvements in ratings on image quality and contrast enhancement.

Embodiments of the invention use a deep learning network, such as a Convolutional Neural Network for image-to-image regression, with a pre-contrast image and low-contrast image as input, and with a predicted full-contrast image as output. A residual learning approach is preferably used in prediction.

The method includes preprocessing to co-register and normalize between different images so they are directly comparable. This step is important since there are arbitrary different acquisition and scaling factor for each scan. Preferably, the average signal is used for normalization. The preprocessed images are then used to train the deep learning network to predict the full-contrast image from the pre-contrast and low-contrast images. The trained network is then used to synthesize full-contrast images from clinical scans of pre-contrast and low-contrast images. The techniques are generally applicable for any diagnostic imaging modality that uses a contrast agent. For example, imaging applications would include fluoroscopy, MRI, CT, and ultrasound.

In one aspect, the invention provides a method for training a diagnostic imaging device to perform medical diagnostic imaging with reduced contrast agent dose. The method includes a) performing diagnostic imaging of a set of subjects to produce a set of images comprising, for each subject of the set of subjects, i) a full-contrast image acquired with a full contrast agent dose administered to the subject, ii) a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than the full contrast agent dose, and iii) a zero-contrast image acquired with no contrast agent dose administered to the subject; b) pre-processing the set of images to co-register and normalize the set of images to adjust for acquisition and scaling differences between different scans; and c) training a deep learning network (DLN) with the pre-processed set of images by applying zero-contrast images from the set of images and low-contrast images from the set of images as input to the DLN and using a cost function to compare the output of the DLN with full-contrast images from the set of images to train parameters of the DLN using backpropagation. The cost function may be, for example, an MAE loss function, or a mixture loss function with non-local structural similarities.

In another aspect, the invention provides a method for medical diagnostic imaging with reduced contrast agent dose. The method includes a) performing diagnostic imaging of a subject to produce a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than a full contrast agent dose, and a zero-contrast image acquired with no contrast agent dose administered to the subject; b) pre-processing the low-contrast image and zero-contrast image to co-register and normalize the images to adjust for acquisition and scaling differences; and c) applying the low-contrast image and the zero-contrast image as input to a deep learning network (DLN) to generate as output of the DLN a synthesized full-dose contrast agent image of the subject; where the DLN has been trained by applying zero-contrast images and low-contrast images as input and full-contrast images as reference ground-truth images.

The low contrast agent dose is preferably less than 10% of a full contrast agent dose. The diagnostic imaging may be angiography, fluoroscopy, computed tomography (CT), ultrasound, or magnetic resonance imaging. For example, performing diagnostic imaging may include performing magnetic resonance imaging where the full contrast agent dose is at most 0.1 mmol/kg Gadolinium MRI contrast. In one embodiment, the DLN is an encoder-decoder convolutional neural network (CNN) including bypass concatenate connections and residual connections.

In another aspect, the invention provides a method for medical diagnostic imaging including a) performing diagnostic imaging of a subject to produce a first image acquired with a first image acquisition sequence and a second image acquired with a second image acquisition sequence distinct from the first image acquisition sequence, where zero contrast agent dose is administered during the diagnostic imaging; b) pre-processing the first image and the second image to co-register and normalize the images to adjust for acquisition and scaling differences; c) applying the first image and the second image as input to a deep learning network (DLN) to generate as output of the DLN a synthesized full-dose contrast agent image of the subject; wherein the DLN has been trained by applying zero-contrast images with different imaging sequences as input and full-contrast images acquired with a full contrast agent dose as reference ground-truth images.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. 1 is a flow chart showing a processing pipeline according to an embodiment of the invention.

FIG. 2 illustrates a workflow of a protocol and procedure for acquisition of images used for training according to an embodiment of the invention.

FIG. 3 is a schematic overview of an image processing flow according to an embodiment of the invention.

FIG. 4 is an illustration of a signal model to synthesize full-dose contrast-enhanced MRI image according to an embodiment of the invention.

FIG. 5 shows a detailed deep learning (DL) model architecture according to an embodiment of the invention.

FIG. 6 is a set of images of a patient with intracranial metastatic disease, showing the predicted image synthesized from pre-contrast image and low-dose image, compared with a full-dose image according to an embodiment of the invention.

FIG. 7 is a set of images of a patient with a brain neoplasm, showing a synthesized full-dose image predicted from a pre-contrast image and low-dose image, compared with a full-dose image according to an embodiment of the invention.

FIG. 8 is a set of images of a patient with a programmable shunt and intracranial hypotension, showing noise suppression capability and consistent contrast enhancement capability according to an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention provide a deep learning based diagnostic imaging technique to significantly reduce contrast agent dose levels while maintaining diagnostic quality for clinical images.

Detailed illustrations of the protocol and procedure of an embodiment of the invention are shown in **FIG. 1** and **FIG. 2**. Although the embodiments described below focus on MRI imaging for purposes of illustration, the principles and techniques of the invention described herein are not limited to MRI but are generally applicable to various imaging modalities that make use of contrast agents.

FIG. 1 is a flow chart showing a processing pipeline for an embodiment of the invention. A deep learning network is trained using multi-contrast images **100**, **102**, **104** acquired from scans of a multitude of subjects with a wide range of clinical indications. The images are pre-processed to perform image co-registration **106**, to produce multi-contrast images **108**, and data augmentation **110** to produce normalized multi-contrast image patches **112**. Rigid or non-rigid co-registration may be used to adjust multiple image slices or volumes to match the pixels and voxels to each other. Since there can be arbitrary scaling differences between different volumes, normalization is used to match the intensity of each image/volume. Brain and anatomy masks are used optionally to extract the important regions of interests in each image/volume. Reference images **104** are also processed to perform co-registration and normalization **118**.

These pre-processed images are then used to train a deep learning network **114**, which is preferably implemented using residual learning in a convolutional neural network. The input to the deep learning network is a zero-contrast dose image **100** and low-contrast dose image **102**, while the output of the network is a synthesized prediction of a full-contrast dose image **116**. During training, a reference full contrast image **104** is compared with the synthesized image **116** using a loss function to train the network using error backpropagation.

FIG. 2 illustrates the workflow of the protocol and procedure for acquisition of images used for training. After a pre-contrast (zero-dose) image **200** is acquired, a low dose (e.g., 10%) of contrast is administered and a low-dose image **202** is acquired. An additional dose (e.g., 90%) of contrast is then administered to total a full 100% dose, and a full-dose image **204** is then acquired.

In an MRI embodiment, images are acquired with 3T MRI scanners (GE Healthcare, Waukesha, WI, USA) using standard neuro clinical protocol with high-resolution 3D T1-weighted inversion-recovery prepped fast-spoiled-gradient-echo (IR-FSPGR) imaging at 3T. Specifically, high-resolution T1-weighted IR-FSPGR pre-contrast images, post-contrast images with 10% low-dose and 100% full-dose of gadobenate dimeglumine (0.01 and 0.1 mmol/kg, respectively) full-dose images are acquired.

For other imaging modalities, similar setups are used to include at least one set of images without enhancement that is acquired without injecting contrasts. And optionally at least one set of images with low-level enhancement that is acquired with injecting low dosage of contrasts. For CT, the contrast is usually an iodine-based contrast agent. The CT contrast agent is usually administered based on preference of physicians, regulatory standard and patient weight. The administration of a low dose means injecting less than standard protocols. For CT there can be multiple set of images with different contrast visualization (possibly the same dosage but different visual appearance) by using multiple energy radiation. For CT, the ground-truth is a set of images acquired with 100% full-dose of CT contrast. For ultrasound, the contrast agent can be, for example, microbubbles. Similarly, the scans may contain at least one image with certain dosage of contrast and optionally images with variable dosage or images with dosage shown differently as acquired with different probe frequency.

FIG. 3 is a schematic overview of the image processing flow. The steps of the detailed workflow are applied to the multi-contrast images acquired for each subject. In acquisition stage **300**, scans are performed as described above to acquire a zero-contrast image **306**, low-contrast image **308**, and full-contrast image **310**. These multi-contrast images then pass through a pre-processing stage **302**. The resulting images then are used in a deep learning training stage **304** for training a deep learning network to synthesize a full-dose image **312**. Pre-processing steps include image co-registration and signal normalization. Normalization is used to remove bias in the images obtained at different dosage levels, which is performed using a mask **314** of non-enhancing tissues. Specifically, to remove the systematic differences between different signal intensity levels in non-enhancing regions (such as scalp fat), co-registration and signal normalization based on average voxel value within a mask is performed. Alternatively, the normalization can be based on max/min intensity of the images or certain percentiles. Also, the normalization can be based on matching the distribution of intensity to certain predefined or standard distribution. Mask can be applied to calculate the average, max, min, percentile or the distribution to get better normalization performance to match different set of images. This step is performed because the transmit and receive gains used for 3 sequences of the 3 different scans are not guaranteed to be the same. For CT and ultrasound the scaling and normalization is also applicable as there are possible intensity re-scaling steps in both acquisition and image storage process.

After co-registration and normalization, the remaining signal differences between different contrast level images is in theory only related to contrast uptakes and non-structural image noise, as shown in **FIG. 4**, which is an illustration of the signal model to synthesize full-dose contrast-enhanced MRI image **412**. Compared with the reference high-quality contrast uptake **406** between pre-contrast **400** and full-dose **404** CE-MRI, the low-dose contrast uptake **408** between pre-contrast **400** and low-dose **402** is noisy but does include contrast information. By using a deep learning method, we learn the denoising to generate high-quality predicted contrast uptake **410** and then combine this with the pre-contrast scan **400** to synthesize a full-dose CE-MRI image **412**.

After pre-processing, a deep learning network is trained using the true 100% full-dose CE-MRI images as the reference ground-truth. The non-contrast (zero-dose) MRI and the 10% low-dose CE-MRI are provided to the network as inputs, and the output of the network is an approximation of the full-dose CE-MRI. During training, this network implicitly learns the guided denoising of the noisy contrast uptake extracted from the difference signal between low-dose and non-contrast (zero-dose) images, which can be scaled to generate the contrast enhancement of a full-dose image.

The detailed deep learning (DL) model architecture in one embodiment of the invention is shown in **FIG. 5**. This model is an encoder-decoder convolutional neural network with 3 encoder steps **500**, **502**, **504** and 3 decoder steps **506**, **508**, **510**. In each step, there are 3 convolutional layers connected by 3x3 Conv-BN-ReLU. Encoding steps are connected in sequence by 2x2 max-pooling, and decoder steps are connected in sequence by 2x2 up-sampling. Bypass concatenate connections **512**, **514**, **516** combine symmetric layers to avoid resolution loss. The residual connections **518**, **520**, **522**, **524**, **526**, **528**, **530** enable the model to synthesize a full-dose image by predicting the enhancement signal **540** from a difference between pre-dose image **542** and low-dose image **544**. The cost function **532** compares the predicted full-dose image **534** and the reference ground-truth full-dose image **536**, which enables the optimization of the network parameters via error backpropagation **538**.
The above-described network architecture is just one illustrative example. Other architectures are possible. For example, the network can have different number of layers, image size in each layers and variable connections between layers. The function in each layer can be different linear or nonlinear functions. The output layer can have a different so-called activation function that maps to certain range of output intensity. There can be multiple number of networks concatenated, so called recurrent network, that further improves the capability that one single network can achieve.

In one test, the network was trained on around 300 2D slices of the co-registered 3D volumes in each patient, excluding the slices at the base of the brain which had low SNR and no valuable information for anatomy or contrast. Standard image rigid transformations are used to further augment the dataset in training to ensure the robustness of the model.

In training, stochastic gradient descent (SGD) was used for each subset of training datasets and backpropagation is used to optimize the network parameters with respect to a cost function comparing predicted and true full-dose MR images. In one embodiment, the mean-absolute-error (MAE) cost function, also known as the L1 loss, is used in training. Training takes 200 epochs with SGD and ADAM method for optimization and 10% of the training dataset with random permutations was used for validation to optimize hyper-parameters and pick out the best model among all iterations. SGD and ADAM are also examples of operators to solve the optimization problem in training the network. There are many other options including, for example, RMSprop and Adagrad. Basically, the optimizers enable faster and smoother convergence.

The loss functions can include, for example, a function map from the ground-truth image and predicted image pair to a set loss values. This includes pixel-wise or voxel-wise loss that is based on pixel/voxel differences which usually use L1 (mean-absolute-error) or L2 (mean-squared-error) loss. Also, the loss can be based on regions with certain size that considering similarity of the structures, e.g., SSIM structural similarities. Or the loss can be computed based on other previously or concurrently trained networks that so-called perceptual loss or adversarial loss respectively. Also the loss can be any arbitrary weighted combination of many loss functions.

In a clinical setting, the trained deep learning network is used to synthesize a full-dose image from zero-dose and low-dose images. The co-registered and normalized non-contrast (zero-dose) and low-dose images are loaded from DICOM files and input to the trained network. With efficient forward-passing, which takes around 0.1 sec per 512-by-512 image, the synthesized full-dose image is generated. The process is then conducted for each 2D slice to generate entire 3D volume and stored in a new DICOM folder for further evaluation. For both training and testing the neural network, we used the Keras framework with Tensorflow backend, CUDA8 and CUDNN5.1, on a Linux server with 2 NVIDIA GTX 1080-TI GPUs. This is but one illustrative example. There are many alternative software and hardware implementations of deep networks that may be used.

In tests of the technique, the synthesized full-dose CE-MRI images contain consistent contrast uptake and similar enhancement. Detailed comparisons for several representative cases are discussed below, demonstrating that the method can generate synthesized full-dose contrast-enhanced MRI with consistent enhancement but using lower dose (e.g., 1/10 full dose).

As shown in **FIG. 6**, in a patient with intracranial metastatic disease, the predicted image **606** synthesized from pre-contrast image **600** and low-dose image **602** has similar highlighting of contrast enhancement in the lesions as full-dose image **604**. The lesions show improved visibility in the synthesized full-contrast image **606** while they cannot be reliably appreciated in low-dose CE-MRI image **602**. Moreover, the synthesized CE-MRI image **606** shows a similar outline of a metastatic lesion in the right posterior cerebellum compared with the one in true full-contrast CE-MRI image **604**.

For another case in a patient with a brain neoplasm, shown in **FIG.** 7, the synthesized full-dose CE-MRI image **706** predicted from the pre-contrast image **700** and low-dose image **702** shows similar contrast uptake as in the real full-dose CE-MRI image **704**. Plus, the image quality of the synthesized full-dose image **706** is better compared with the acquired full-dose CE-MRI **704** which has more severe motion artifacts and aliasing. Surprisingly, this demonstrates that the synthesized results have additional advantages over the original full-dose CE-MRI for better denoising and artifact removal, e.g., suppression of motion artifacts and aliasing.

In a case of a patient with a programmable shunt and intracranial hypotension, shown in **FIG. 8**, results also demonstrate better noise suppression capability and consistent contrast enhancement capability. The engorgement of the dural sinuses and pachymeningeal enhancement are clearly seen on both the synthesized image **806**, predicted from pre-contrast image **800** and low-dose image **802**, and true full-dose image **804**, while there is less noise in non-enhancing regions on the synthesized image. Thus, the method generates diagnostic quality contrast from the low-dose acquisition, also demonstrating improved noise suppression and contrast enhancement.

Tests of the method by the inventors have demonstrated that the synthesized CE-MRI images are improved significantly (both $p < 0.001$) compared with the low-dose image on all quantitative metrics with 11.0% improvements in SSIM and over 5.0 dB gains in PSNR. Compared with the true acquired full-dose CE-MRI, the proposed method is not significantly different (both $p > 0.05$) for overall image quality and the clarity of the enhanced contrast. Comparably, the 10% low-contrast images are significantly ($p < 0.001$) worse in the clarity of the enhanced contrast, with a decrease of over 3 on a 5-point scale.

As **FIG. 7** and **FIG. 8** show, and as verified by neuroradiologists' ratings, the synthesized full-dose images show significant ($p < 0.05$) improvements over the acquired full-dose CE-MRI in suppressing artifacts in the non-enhancing regions, which was an additional advantage of the DL method.

Compared with real full-dose CE-MRI, no significant differences ($p>0.05$) in contrast enhancements information could be identified by neuro-radiologists blinded to image origin. The synthesized full-dose images also appear to better suppress image artifacts ($p<0.05$). This is because the high-intensity signal of the real full-dose enhanced contrast inevitably augments motion/aliasing artifacts which are better suppressed when estimating contrast from the low-intensity contrast enhancements. The impact of being able to reduce contrast dose by 90% while retaining diagnostic information could have a large impact on patient well-being and imaging costs.

The illustrative embodiment described above uses a 2D CNN. Further performance gains are achievable with 3D CNN models considering the correlated spatial information in adjacent thin slices. Thus, the implementation of the invention illustrated with a 2D CNN is only an illustration, and 3D implementations are envisioned within the scope of the invention. More generally, 2D (process single slice of image), 2.5D (multiple slices of image), 3D (entire volume) and patch based (crop from volume) algorithms are envisioned.

In addition, the inventors envision that with more datasets, more complicated but powerful models such as generative models can be trained to further improve the contrast synthesis. Finally, although the MAE loss is used as cost function to train the DL model in the above illustrative embodiment, other loss functions are envisioned, such as mixture loss functions with non-local structural similarities or using Generative Adversarial Network (GAN) as a data driven cost function.

In the illustrative embodiment described above, a fixed level of gadolinium contrast is used with 90% reduction from the original clinical usage level.

More generally, the term full-dose is used herein to refer to a standard dosage enabling certain defined visual quality. Usually the contrasts are treated as drug and they have FDA regulated full-dose that should be used. The full-dose means a standard dosage that is recommended or required by the FDA or clinicians to achieve good diagnostic quality.

However, it is envisioned that additional reduction of the low dose is feasible by using alternative network structures and loss function, using larger training datasets with various pathologies as well as other complimentary information such as multi-contrast MRI, multiple imaging modalities, and patients' clinical history information. It is also envisioned that the technique can make use of a patch based method wherein the input image size can be different than 128x128x1. It can be any $x{\times}y{\times}z$ size that uses a patch of size $x{\times}y$ and considering depth/thickness of z.

It is also envisioned that low dose levels higher than 10% may be used. In general, it is beneficial to minimize the dose subject to the constraint that the synthesized image retains diagnostic quality. The resulting minimal low dose may vary depending on contrast agent and imaging modality. It is also possible to base the training on more than two images having different dose levels, and it is not necessary to include a zero-dose image. In general, if the training dataset has a sufficient number of paired scans with two distinct dose levels, the network can be trained to automatically generalized to improve the lower dose d_{low} to the higher dose d_{high}, where the higher dose level is a full dose or less, and the lower dose level is less than the high dose, i.e., $0 \leq d_{\text{low}} < d_{\text{high}} \leq 1$.

The inventors also envision synthesis of high dose images from zero dose images, without the need for any contrast dose images. The zero dose images in this case include multiple MR images acquired using different sequences (e.g., T1w, T2w, FLAIR, DWI) that show different appearance/intensity of different tissues. The trained network can then predict a synthesized full-contrast T1w to be used for diagnosis. Thus, according to this method, the deep learning network is trained with a first image acquired with a first image acquisition sequence and a second image acquired with a second image acquisition sequence distinct from the first image acquisition sequence, where zero contrast agent dose is administered during the diagnostic imaging when these images are acquired. In addition, images with other sequences may also be used. For example, in one embodiment, there are five images with five different sequences acquired. The training uses a reference ground truth T1w image acquired with full contrast agent dose. The images are pre-processed to co-register and normalize them to adjust for acquisition and scaling differences. The normalization may include normalizing the intensity within each contrast via histogram matching on median. Pre-processing may also include bias field correction to correct the bias field distortion via N4ITK algorithm. Pre-processing may also include using a trained classifier (VGG16) to filter out more abnormal slices. The deep learning network is preferably a 2.5D deep convolutional adversarial network. Using the trained network, a first image and second image acquired with different sequences are then used as input to the deep learning network (DLN) which then generates as output a synthesized full-dose contrast agent image of the subject.

CLAIMS

1. A method for training a diagnostic imaging device to perform medical diagnostic imaging with reduced contrast agent dose, the method comprising:

a) performing diagnostic imaging of a set of subjects to produce a set of images comprising, for each subject of the set of subjects, i) a full-contrast image acquired with a full contrast agent dose administered to the subject, ii) a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than the full contrast agent dose, and iii) a zero-contrast image acquired with no contrast agent dose administered to the subject;

b) pre-processing the set of images to co-register and normalize the set of images to adjust for acquisition and scaling differences between different scans;

c) training a deep learning network (DLN) with the pre-processed set of images by applying zero-contrast images from the set of images and low-contrast images from the set of images as input to the DLN and using a cost function to compare the output of the DLN with full-contrast images from the set of images to train parameters of the DLN using backpropagation.

2. The method of claim 1 wherein the cost function is an MAE loss function, or a mixture loss function with non-local structural similarities.

3. A method for medical diagnostic imaging with reduced contrast agent dose, the method comprising:

a) performing diagnostic imaging of a subject to produce a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than a full contrast agent dose, and a zero-contrast image acquired with no contrast agent dose administered to the subject;

b) pre-processing the low-contrast image and zero-contrast image to co-register and normalize the images to adjust for acquisition and scaling differences;

c) applying the low-contrast image and the zero-contrast image as input to a deep learning network (DLN) to generate as output of the DLN a synthesized full-dose contrast agent image of the subject;

wherein the DLN has been trained by applying zero-contrast images and low-contrast images as input and full-contrast images as reference ground-truth images.

4. The method of claim 3 wherein
the low contrast agent dose is less than 10% of a full contrast agent dose.

5. The method of claim 3 wherein
performing diagnostic imaging comprises performing angiography, fluoroscopy, computed tomography (CT), ultrasound, or magnetic resonance imaging.

6. The method of claim 3 wherein
performing diagnostic imaging comprises performing magnetic resonance imaging, and the full contrast agent dose is at most 0.1 mmol/kg Gadolinium MRI contrast.

7. The method of claim 3 wherein
the DLN is an encoder-decoder convolutional neural network (CNN) including bypass concatenate connections and residual connections.

8. A method for medical diagnostic imaging, the method comprising:
a) performing diagnostic imaging of a subject to produce a first image acquired with a first image acquisition sequence and a second image acquired with a second image acquisition sequence distinct from the first image acquisition sequence, where zero contrast agent dose is administered during the diagnostic imaging;
b) pre-processing the first image and the second image to co-register and normalize the images to adjust for acquisition and scaling differences;
c) applying the first image and the second image as input to a deep learning network (DLN) to generate as output of the DLN a synthesized full-dose contrast agent image of the subject;
wherein the DLN has been trained by applying zero-contrast images with different imaging sequences as input and full-contrast images acquired with a full contrast agent dose as reference ground-truth images.

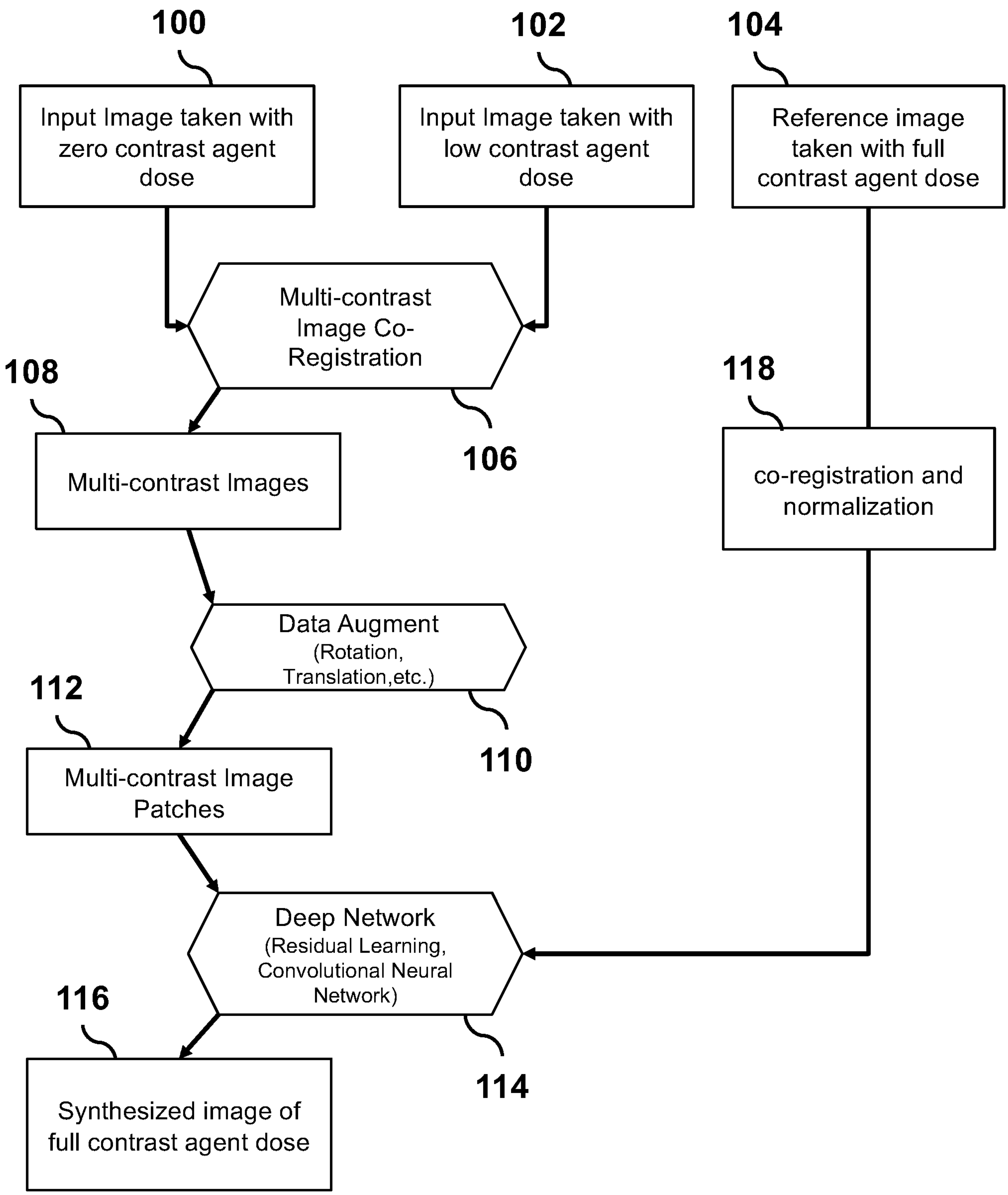

100
Input Image taken with zero contrast agent dose
102
Input Image taken with low contrast agent dose
104
Reference image taken with full contrast agent dose
Multi-contrast Image Co-Registration
106
108
Multi-contrast Images
118
co-registration and normalization
Data Augment (Rotation, Translation,etc.)
110
112
Multi-contrast Image Patches
Deep Network (Residual Learning, Convolutional Neural Network)
114
116
Synthesized image of full contrast agent dose

Fig. 1

Fig. 2

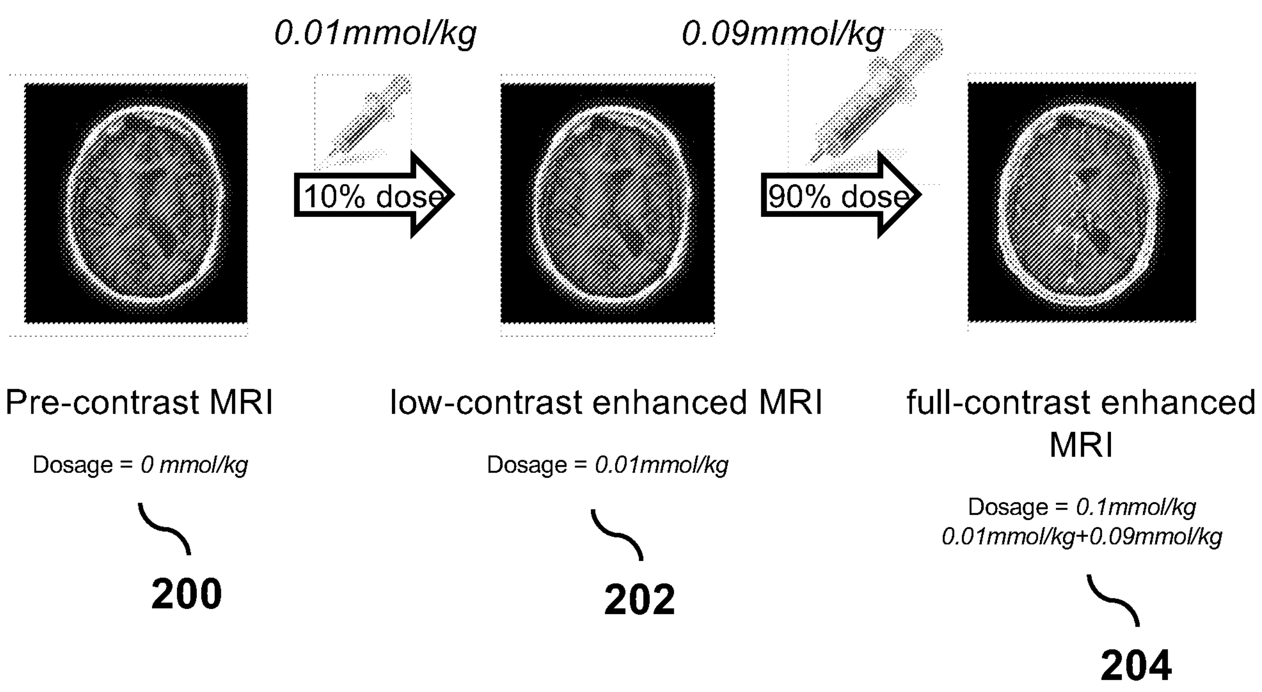

0.01mmol/kg
10% dose
0.09mmol/kg
90% dose
Pre-contrast MRI
Dosage = 0 mmol/kg
200
low-contrast enhanced MRI
Dosage = 0.01mmol/kg
202
full-contrast enhanced MRI
Dosage = 0.1mmol/kg
0.01mmol/kg+0.09mmol/kg
204

Fig. 3

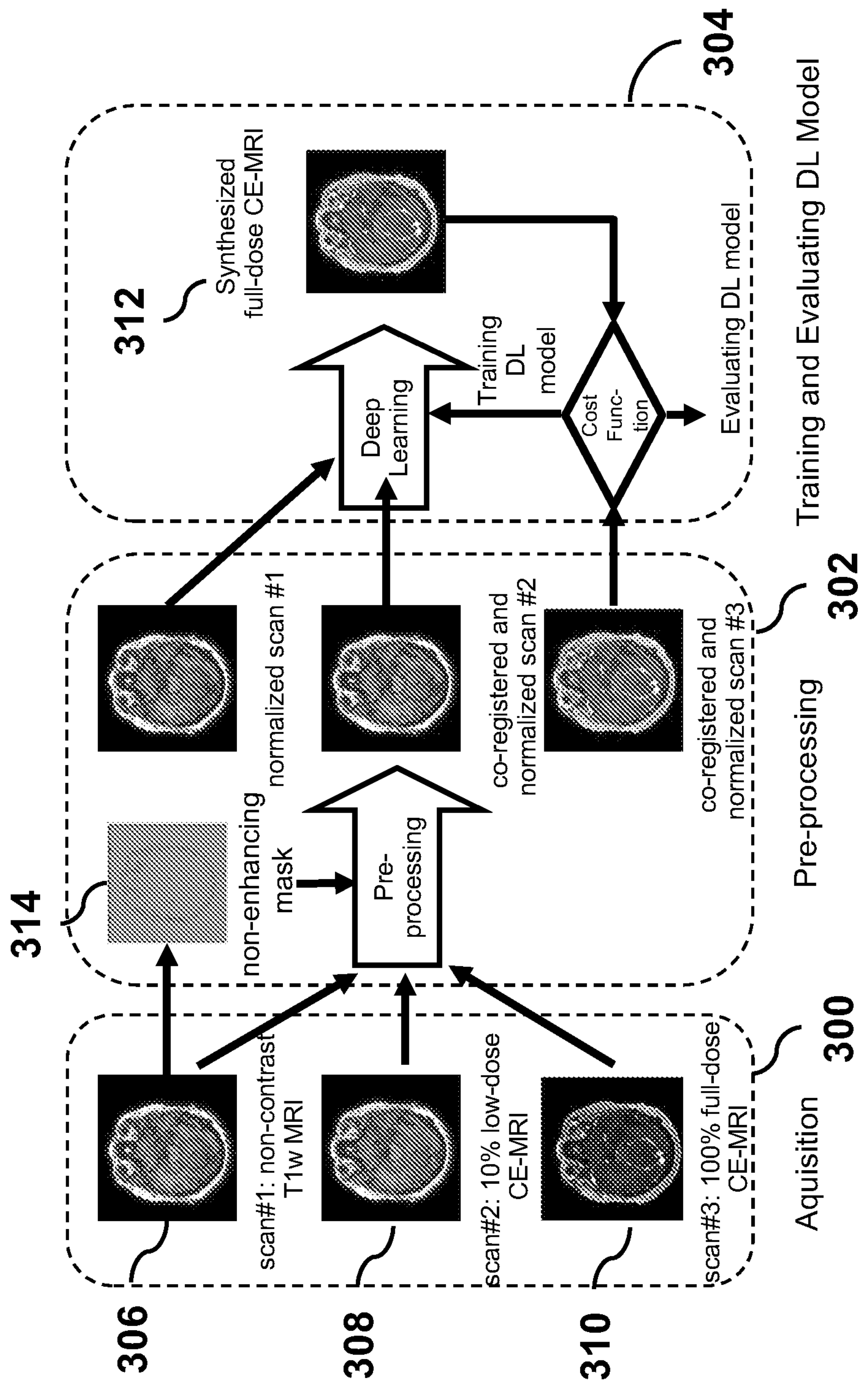
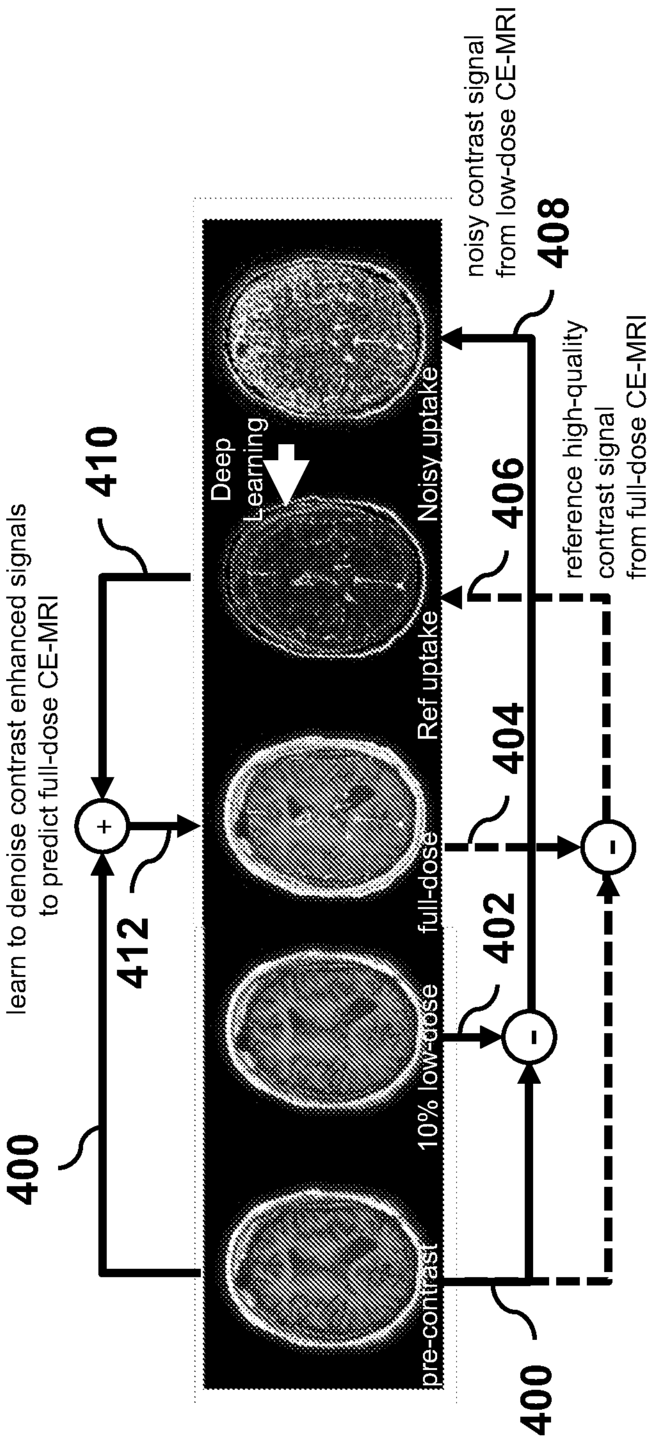

306
308
310
scan#1: non-contrast T1w MRI
scan#2: 10% low-dose CE-MRI
scan#3: 100% full-dose CE-MRI
Aquisition
300
314
non-enhancing mask
Pre-processing
normalized scan #1
co-registered and normalized scan #2
co-registered and normalized scan #3
Pre-processing
302
312
Synthesized full-dose CE-MRI
Deep Learning
Training DL model
Cost Func-tion
Evaluating DL model
Training and Evaluating DL Model
304

Fig. 4


learn to denoise contrast enhanced signals
to predict full-dose CE-MRI
400
410
412
Deep
Learning
pre-contrast
10% low-dose
full-dose
Ref uptake
Noisy uptake
400
402
404
406
408
noisy contrast signal
from low-dose CE-MRI
reference high-quality
contrast signal
from full-dose CE-MRI
+
-
-

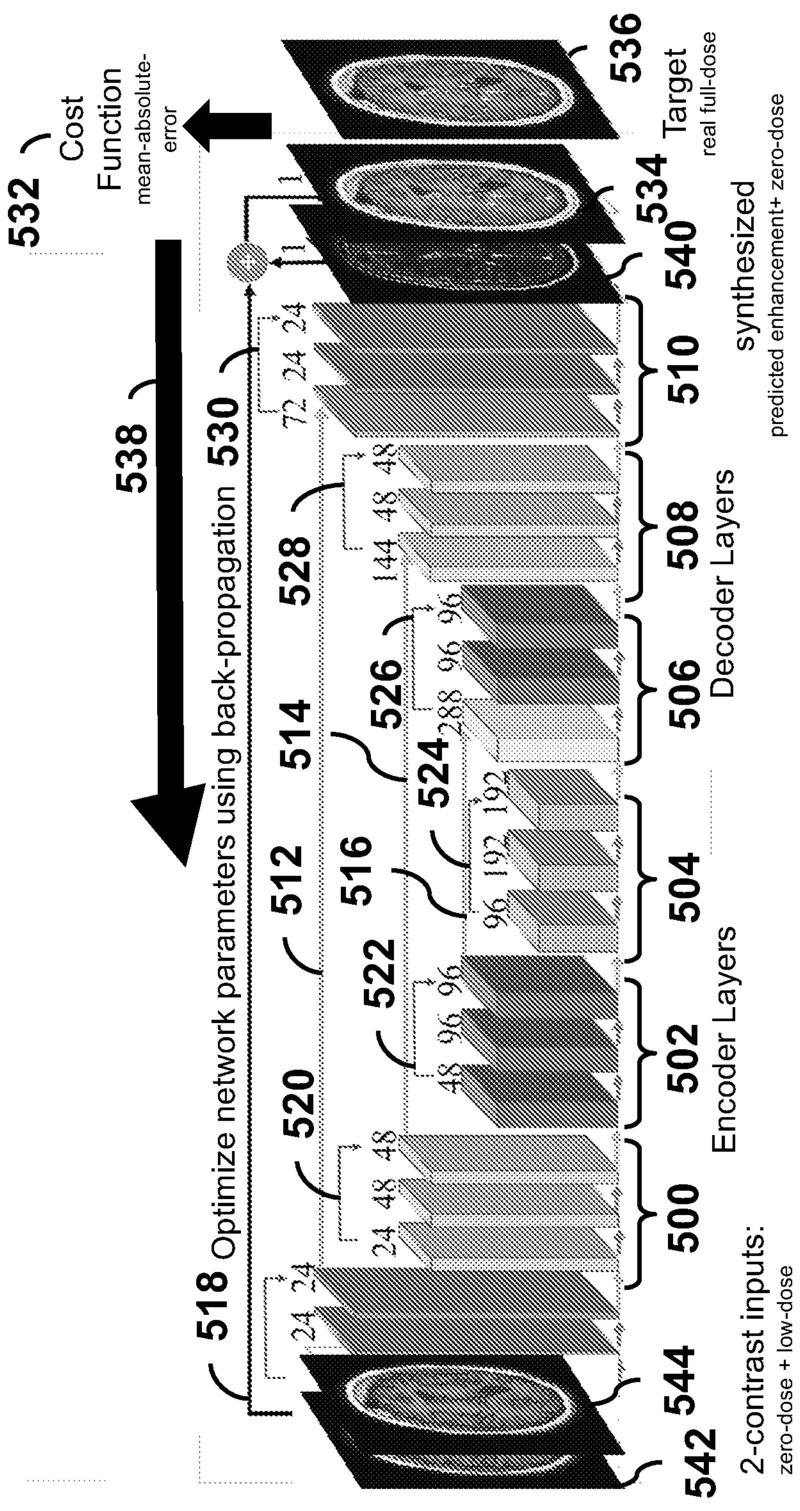

532
Cost Function
mean-absolute-error
536
Target
real full-dose
534
540
synthesized
predicted enhancement+ zero-dose
538
530
Optimize network parameters using back-propagation
528
514
512
520
518
526
524
516
522
72 24 24
144 48 48
288 96 96
96 192 192
48 96 96
24 48 48
24 24
510
508
506
504
502
500
Decoder Layers
Encoder Layers
544
542
2-contrast inputs:
zero-dose + low-dose

Fig. 5

Fig. 6

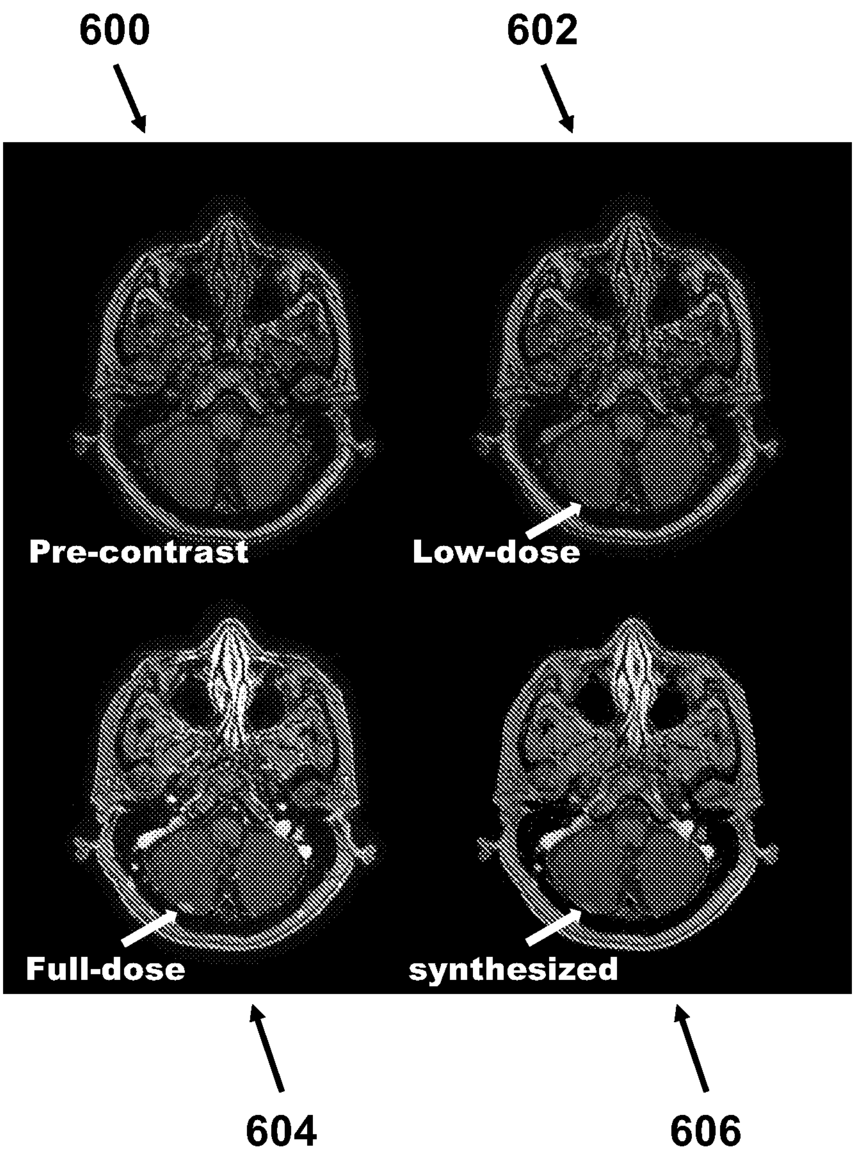
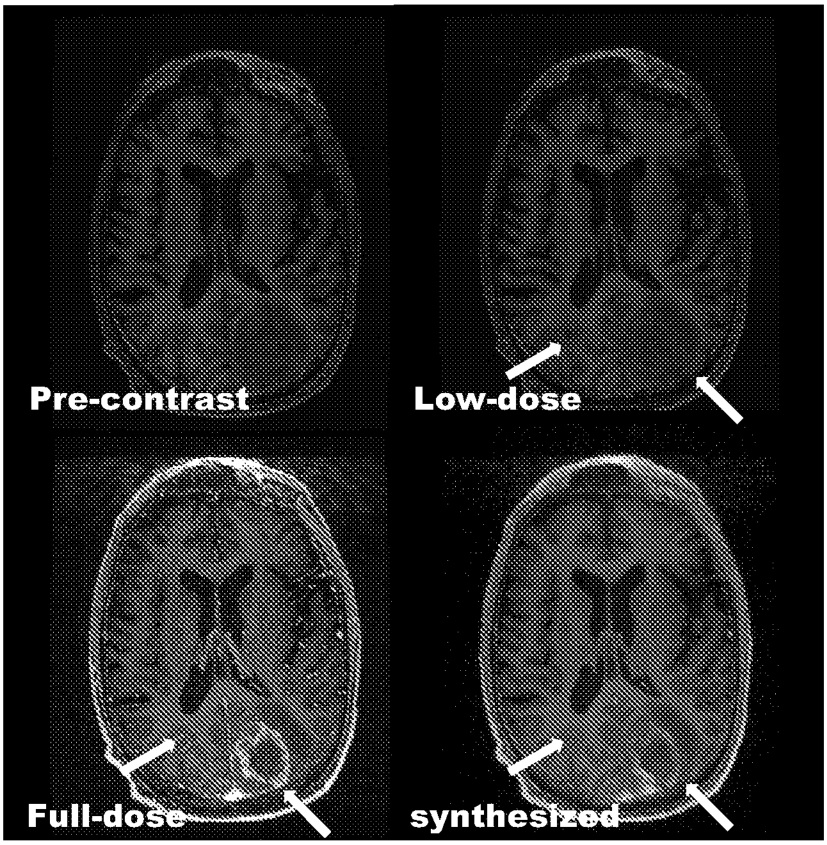


Fig. 7

700

702



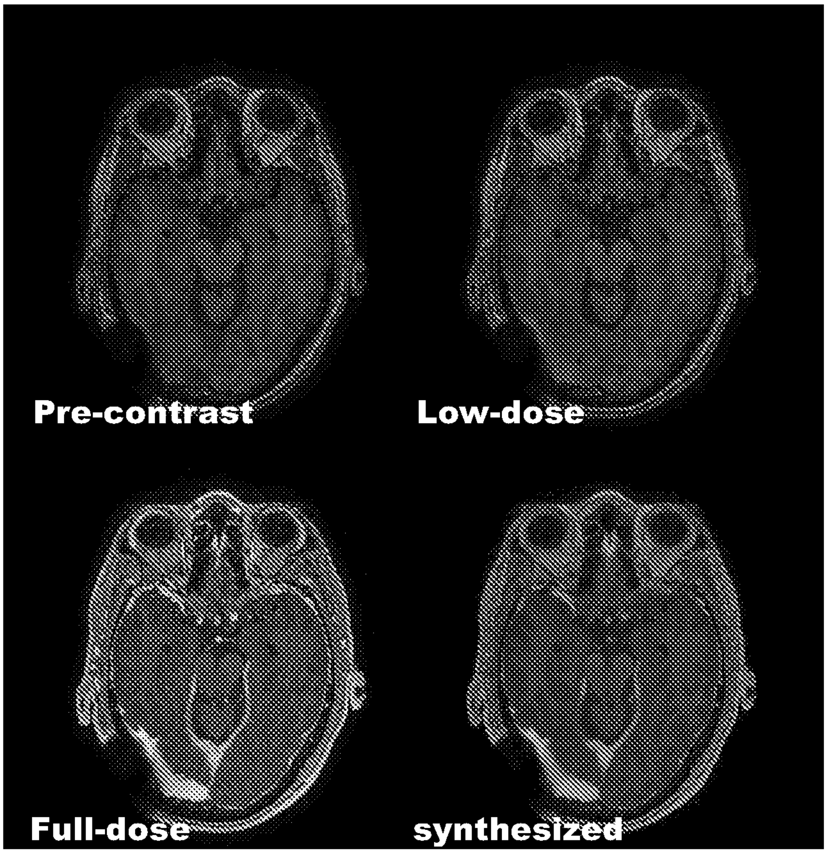
704

706

Fig. 8

800

802



804

806

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/55034

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61B 6/00; G06K 9/62, 9/64, 9/66; G06T 3/40, 5/50 (2019.01)
CPC - A61B 6/52, 6/5211, 6/5217, 6/5229, 6/5252, 6/5258, 6/545; G06K 9/62, 9/64, 9/66; G06T 3/4046, 5/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0201895 A1 (THE UNIVERSITY OF CHICAGO) 23 July 2015; abstract; paragraphs [0016-0028]	1-8
A	MARDANI, M. et al. "Deep Generative Adversarial Networks for Compressed Sensing (GANCS) Automates MRI"; 31 May 2017 [retrieved 6 February 2019]. Retrieved from the Internet: <URL: https://arxiv.org/pdf/1706.00051.pdf>; abstract; page 2, first full paragraph	1-8
A	US 2016/0106321 A1 (SIEMENS AKTIENGESELLSCHAFT) 21 April 2016; paragraphs [0040-0041, 0066]	1-8
A	WO 2016/175755 A1 (SIEMENS HEALTHCARE GMBH) 03 November 2016; paragraphs [0017-0020]	1-8
A	US 2005/0171409 A1 (ARIMURA, H. et al.) 04 August 2005; paragraphs [0046-0049, 0080-0084]	1-8
P, Y	US 2018/0018757 A1 (SUZUKI, K.) 18 January 2018; entire document	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 February 2019 (06.02.2019)	26 FEB 2019

Name and mailing address of the ISA/	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/55034

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

-***-Continued from Box III-***-
The application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fee must be paid.

Group I: Claims 1-2 are directed towards a method comprising: training a deep learning network DLN with the pre-processed set of images by applying zero-contrast images from the set of images and low-contrast images from the set of images as input to the DLN and using a cost function to compare the output of the DLN with full-contrast images from the set of images to train parameters of the DLN using backpropagation.

Group II: Claims 3-8 are directed towards a method comprising: applying the low-contrast image and the zero-contrast image as input to a deep learning network DLN to generate as output of the DLN a synthesized full-dose contrast agent image of the subject; wherein the DLN has been trained by applying zero-contrast images and low-contrast images as input and full-contrast images as reference ground-truth images.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. Group I has at least training a deep learning network DLN with the pre-processed set of images by applying zero-contrast images from the set of images and low-contrast images from the set of images as input to the DLN and using a cost function to compare the output of the DLN with full-contrast images from the set of images to train parameters of the DLN using backpropagation that Group II does not have. Group II has at least applying the low-contrast image and the zero-contrast image as input to a deep learning network DLN to generate as output of the DLN a synthesized full-dose contrast agent image of the subject; wherein the DLN has been trained by applying zero-contrast images and low-contrast images as input and full-contrast images as reference ground-truth images that Group I does not have.

The common technical features of Groups I and II are a method for training a diagnostic imaging device to perform medical diagnostic imaging with reduced contrast agent dose, the method comprising: a) performing diagnostic imaging of a set of subjects to produce a set of images comprising, for each subject of the set of subjects, i) a full-contrast image acquired with a full contrast agent dose administered to the subject, ii) a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than the full contrast agent dose, and iii) a zero-contrast image acquired with no contrast agent dose administered to the subject; b) pre-processing the set of images to co-register and normalize the set of images to adjust for acquisition and scaling differences between different scans.

These common features are disclosed by US 2015/0201895 A1 to THE UNIVERSITY OF CHICAGO (hereinafter "Chicago") which discloses a method for training a diagnostic imaging device to perform medical diagnostic imaging with reduced contrast agent dose (machine learning dose contrast reduction technique for CT imaging; abstract; paragraphs [0024-0025]), the method comprising: a) performing diagnostic imaging of a set of subjects to produce a set of images comprising, for each subject of the set of subjects (CT imaging is performed on patients producing a series of images of patient; abstract; paragraph [0016]), i) a full-contrast image acquired with a full contrast agent dose administered to the subject (high contrast image associated with high dose to patient; paragraphs [0017, 0024]), ii) a low-contrast image acquired with a low contrast agent dose administered to the subject, where the low contrast agent dose is less than the full contrast agent dose (low contrast image associated with low dose to patient; paragraphs [0022, 0024]), and iii) a zero-contrast image acquired with no contrast agent dose administered to the subject (CT images may be input with overlapping edge regions providing zero contrast; paragraphs [0016, 0018]); b) pre-processing the set of images to co-register and normalize the set of images to adjust for acquisition and scaling differences between different scans (pixel/voxel values may be spatially associated and normalized to construct the output CT image from the set of input images; paragraphs [0021, 0025-0026, 0028]).

Since the common technical features are previously disclosed by the Chicago reference, these common features are not special and so Groups I and II lack unity.