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Hongmei Yuan (✉ yuan.hm@neusoft.com)

Neusoft Research of Intelligent Healthcare Technology,Co.Ltd.

MingLei Yang

Neusoft Research of Intelligent Healthcare Technology,Co.Ltd.

Shan Qian

Neusoft Research of Intelligent Healthcare Technology,Co.Ltd.

WenXin Wang

Neusoft Medical System,Co.Ltd.

XiaoTian Jia

Shenyang Advanced Medical Equipment Technology Incubation Center,Co.Ltd.

Feng Huang

Neusoft Medical System,Co.Ltd.

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Brain CT Registration Using Hybrid Supervised Convolutional Neural Network

YUAN Hong-mei^{1,2*}, YANG Ming-lei^{1,2}, QIAN Shan^{1,2}, WANG Wen-xin², JIA Xiao-tian³, HUANG Feng²

Abstract:

Background: Brain computed tomography (CT) image registration is an essential step in the image evaluation of acute cerebrovascular disease (ACVD). Due to the complexity of human brain morphology, low brain CT soft-tissue resolution, low gray/white matter contrast, and the large anatomy variation across individuals, it is still a great challenge to perform brain CT registration accurately and rapidly. This study developed a hybrid supervised convolutional neural network (HSCN-Net) which may be used for assessment of ACVD in brain CT.

Method: HSCN-Net generates synthetic deformation fields by a simulator to solve the lack of registration gold standard. The simulator are used to generate multi-scale deformation fields to overcome the registration challenge of large deformation. HSCN-Net adopts a hybrid loss function constituted by deformation field and image similarity to improve registration accuracy and generalization ability. In this work, one hundred and one brain CT images were included for HSCN-Net training and evaluation, and the results were compared with Demons and VoxelMorph. Qualitative analysis by visual evaluation, as well as quantitative analysis by Endpoint Error (EPE) between deformation fields, image Normalized Mutual Information (NMI), and Dice coefficient were carried out to access the model performance.

Results: Qualitative analysis of HSCN-Net was similar to that of Demons, and both were superior to that of VoxelMorph. Moreover, HSCN-Net was more competent for large and smooth deformations. For quantitative evaluation, the EPE mean of HSCN-Net (3.29 mm) was lower than that of Demons (3.47 mm) and VoxelMorph (5.12 mm); the Dice mean of HSCN-Net was 0.96, which was better than that of Demons (0.90) and VoxelMorph (0.87); and the NMI mean of HSCN-Net (0.83) was slightly lower than that of Demons(0.84) but higher than that of VoxelMorph (0.81). In addition, the mean registration time of HSCN-Net (17.86 s) was lower than that of VoxelMorph (18.53 s) and Demons (147.21 s).

Conclusion: The proposed hybrid supervised convolution registration network can achieve accurate and rapid brain CT registration. It is helpful for improving image evaluation of ACVD, thereby assisting clinicians in diagnosis and treatment decision-making.

Keywords: Image registration; Brain CT; Deep learning; Hybrid supervision;

1. Background

Over the past several decades, the incidence and mortality of acute cerebrovascular disease (ACVD) is increasing in China, especially acute ischemic stroke (AIS). It is of great importance for favorable outcome to perform proper treatment at acute stage^[1]. Computed Tomography (CT) has become one of the important and routine examination for ACVD because of its convenience and quickness^[2]. CT also has significant advantages in terms of hospital deployment rate and clinical utilization rate^[3]. CT is routinely adopted to evaluate brain early ischemic change in clinic, where Alberta Stroke Program Early CT Score (ASPECTS) is commonly recommended. The middle cerebral artery (MCA) blood supply area is the main quantitative area of ASPECTS. Brain CT registration is an important step to perform ASPECTS. However, brain CT registration is still a great challenge mainly due to the following reasons: Firstly, the human brain morphology is very complex. Secondly, soft-tissue resolution of brain CT image is relatively low. Thirdly, the structure contrast of gray/white matter in brain CT image is also relatively low. Lastly, there may be exist large anatomical structure variations across individuals.

Most traditional brain registration algorithms can be summed up as iterative optimization problems. High-dimensional optimization may lead to heavy computation burden and slow convergence speed. In three-dimensional (3D) brain CT images, the common registration time is generally as high as tens of minutes^[4-11]. For example, the registration methods using B-spline as the elastic deformation model, they grid the image firstly, then use B-spline to control the grid changes to fit the whole image transformation^[12]. These algorithms can accurately simulate the local deformation^[13], but they run very slowly, which are difficult to meet the needs of clinical acute brain CT image evaluation. The Demons-based registration methods are another type of brain non-rigid registration algorithms. They use optical flow field to model the image elastic deformation and iteratively optimize the deformation field. This type of algorithms base on gray information, which can avoid the manual interference in the feature extraction process. However, they are only suitable for small deformations and sensitive to the image gray changes^[14].

Deep learning-based registration methods have been proposed for accurate and fast registration in the last few years^[15-17]. The existing brain registration networks are often used between magnetic resonance (MR) images or between multimodal images (such as magnetic resonance imaging (MRI) and CT), the registration between brain CT images are rarely reported. For example, VoxelMorph^[18], a deep learning framework for brain MRI proposed by dalca et al., uses convolutional neural networks (CNN) to achieve unsupervised image registration. Full convolution neural network registration method^[19] proposed by Fan et al. uses double supervised training method. Deep diffusion MRI registration (DDMReg) proposed by fan Zhang et al. can simultaneously apply the whole brain and specific fiber orientation information^[20]. R. Han et al. proposed a deformable MR-CT registration method^[21], which synthesizes a CT image from MRI firstly and then registers the synthetic CT to the intraoperative CT using an inverse-consistent registration network.

Researches showed that compared with the traditional algorithms, deep learning-based registration algorithms have improved the registration speed, but registration result is slightly poor, and it is difficult to overcome the large deformation challenge ^{[22][23]}. In addition, there are few registration algorithms specifically for brain CT images. Moreover, although the supervised learning-based neural network can theoretically improve the registration accuracy, it is hard to obtain high-quality registration gold standard ^[24]. To solve all of these problems, a fully automatic registration method based on Hybrid Supervised Convolutional Neural Network (HSCN-Net) was proposed in this work to achieve accurate and fast brain CT registration. The contributions of HSCN-Net are as follows:

- (1) To solve the problem of lacking registration gold standard, HSCN-Net uses the simulator to generate synthetic deformation fields and images during the training process as gold standards to realize supervised training, better improve the registration accuracy.
- (2) To overcome the challenge of large deformation fields between images to be registered, large deformations of appropriate proportion are added to the deformation fields generated by simulator. Through continuous optimization learning, HSCN-Net increased its ability to handle large deformation.
- (3) In order to improve the registration accuracy and generalization ability of the model, HSCN-Net adopts a hybrid supervised loss function constituted by the alignment accuracy of the deformation fields as the supervised target and the image similarity as the self-supervised target.
- (4) HSCN-Net can be applied to brain CT image registration and provides an excellent algorithm for the brain CT image registration.

2. Results

2.1 Qualitative Analysis

Fig. 1 demonstrates cross-section visualization of registration results from a typical case. (a) is the reference image, (b) is the moving image, (c) - (e) are the registration results of HSCN-Net, Demons and VoxelMorph algorithms, respectively. The main part of the rectangular box is the ventricle structure. It can be seen that compared with the moving image (b), the ventricular structures in images (c), (d), (e) were more consistent spatially to that in reference image (a). It indicates that all the three registration methods can achieve the spatial matching purpose. Moreover, compared with the ventricle in (e), both size and shape of the ventricle in (c) and (d) were more similar, and more closer to the corresponding region in reference image (a), which shows that (c) and (d) had a better spatial matching. In addition, the deformations between voxels in image (e) were relatively small. (f) - (h) are the local enlarged images corresponding to the same parts in (c)-(e) in turn. As indicated by the arrow, the deformations in figures (f) and (h) were smoother than these in figure (g), and also more consistent with the smooth characteristics of tissue deformation.

Fig. 1 Registration results of CT brain image. (a) is the reference image, (b) is the moving image, (c) - (e) are the registration results of HSCN-Net, Demons and VoxelMorph algorithms, respectively. (f) - (h) are the local enlarged images corresponding to the same parts in (c)-(e) in turn. It can be seen that all the three registration methods can achieve the spatial matching purpose. Compared with the ventricle in (e), (c) and (d) had a better spatial matching. The deformations in figures (f) and (h) were smoother than these in figures (g), and also more consistent with the smooth characteristics of tissue deformation.

2.2 Quantitative Analysis

The results of EPE, NMI, Dice, and the running time of the three algorithms were shown in Table 1.

Table 1 Registration error and performance quantification table (mean $\pm$ sd)

Method	EPE(mm)	NMI	Dice (%)	Time(s)
Demons	3.47 $\pm$ 1.03	0.84$\pm$0.02	0.90 $\pm$ 0.03	147.21 $\pm$ 27.46

VoxelMorph	5.12±1.72	0.81±0.02	0.87±0.05	18.53±0.25
HSCN-Net	3.29±0.98	0.83±0.01	0.96±0.04	17.86±0.23

Table 1 demonstrates that the three algorithms' EPE mean values sort as ascending order were HSCN-Net, Demons, and VoxelMorph, which indicating that the deformation field error of HSCN-Net was the smallest among these algorithms. More specifically, the EPE mean value of HSCN-Net was 1.83 (mm) less than VoxelMorph, strongly stating that the registration accuracy of HSCN-Net was much higher than that of VoxelMorph ($p<0.05$). For NMI metric, the mean of HSCN-Net (0.83) was slightly lower than that of Demons algorithm (0.84) ($p>0.05$), but slightly higher than that of VoxelMorph algorithm (0.81) ($p<0.05$), which shows that the registration results of Demons had the highest correlation with the reference image among the three registration methods, and followed by HSCN-Net. Furthermore, the Dice coefficient of the MCA blood supply area between the HSCN-Net registration result and the reference image was quantified as 0.96, which was higher than Demons' 0.90 ($p<0.05$) and VoxelMorph's 0.87 ($p<0.05$). Only the Dice metric of HSCN-Net was 0.01 higher than that of Demons, and the standard deviations of other metrics of HSCN-Net were the lowest among three methods. It indicates HSCN-Net has high robustness and generalization ability. Finally, Table 1 also shows that Demons took 147.21 ± 27.46 (s), VoxelMorph 18.53 ± 0.25 (s), and HSCN-Net 17.86 ± 0.23 (s) for one case. It demonstrates that the registration speed of HSCN-Net was slightly higher than that of classic registration network VoxelMorph ($p>0.05$), and much higher than that of traditional registration algorithm Demons ($p<0.05$).

3. Discussion

In this work, a non-rigid brain CT image registration algorithm based on hybrid supervised convolutional neural network (HSCN-Net) was proposed. To overcome the difficulty in obtaining the high-quality deformation fields as gold standard in supervised learning, HSCN-Net uses the simulator to generate multi-scale virtual deformation fields during the training. Aiming at the challenge of large deformation fields between images to be registered, large deformations with appropriate proportion are added to the deformation fields generated by simulation. Moreover, HSCN-Net proposes a hybrid supervised loss function combines multiple information of deformation field and image, which significantly improves the accuracy and generalization ability of the network.

Since the supervised learning-based registration network can provide the deformation fields corresponding to the registration images, the network can learn the information of the prediction deformation field directly and supervised. Compared with the unsupervised learning-based network, the supervised learning-based registration network could simplify the network training and improve the registration accuracy in theory. However, it is difficult to accurately annotate the displacement of corresponding pixel points in the images. In addition, there are large numbers of pixels in medical images. So it is difficult for even senior doctors to complete the tedious and time-consuming annotation work. An alternative method is to use traditional method to generate the deformation fields as the gold standard, but the accuracy of the gold standard will be limited by the registration accuracy of the traditional method.

Therefore, in the network training, it is difficult to obtain accurate and large amount of deformation field gold standard. It is the main reason why the most registration results from supervised learning-based network are not very ideal^[15-17]. In order to solve this problem, the proposed HSCN-Net first uses the simulator to generate virtual deformation field, then applies the produced deformation field to the moving image to generate virtual deformed image, and finally the accurate deformation field between the moving image and reference image is obtained during the training process. Compared with the unsupervised registration network VoxelMorph, the EPE mean of HSCN-Net was reduced by 1.83 mm ($p<0.05$), which also verifies that HSCN-Net significantly improves the registration accuracy.

Since many possible transformations of moving images in unsupervised network will yield close similarity measurement value, the gradient of the similarity measurement is not very accurate in the representation of the transformation type and scale in the process of obtaining the optimal solution of the network. In addition, the optimization problem without the initialized transformation at the finest resolution is difficult due to the large degrees of freedom in the transformation parameters. Therefore, the existing network is easy to fall into the local minimum value and prone to get inaccurate deformation^[27]. Especially when the deformation is large, the prediction accuracy will be reduced obviously^[27]. To address this challenge, large deformations produced by HSCN-Net were used in the training process directly. Iterative learning of multi-scale deformation makes HSCN-Net's prediction of deformation field between images more realistic and more suitable for the large deformation. Moreover, the simulated deformation field includes a variety of transformations such as affine and elasticity. The diversity of transformations was more consistent with the transformation characteristics of real image pairs, which further improves the registration accuracy of HSCN-Net. Besides, the EPE standard deviation of HSCN-Net was 0.74 lower than that of VoxelMorph ($p<0.05$), also demonstrates that the generalization ability of HSCN-Net has been effectively improved.

The neural network optimizes parameters by minimizing the loss function, so the loss function is one of the key factors that affect the performance of neural network. In this paper, a new loss function combining the deformation field EPE and data similarity was proposed. EPE measure directly quantifies the alignment accuracy of the deformation field generated by the simulator and the predicted deformation field, which can improve the accuracy of the predicted deformation field. As a self-supervised training target, image similarity reflects the similarity between the reference image and the prediction image, which is a powerful feedback of the registration visualization results and can better ensure the generalization ability of the model. Table 1 shows that, the NMI mean of HSCN-Net's correlation metric was improved by 0.02 compared with VoxelMorph ($p<0.05$), and the overlap degree (Dice coefficient) of MCA blood supply area between reference image and prediction image was improved by 0.09 ($p<0.05$). Finally, the standard deviation of EPE and NMI were the lowest among the three algorithms, which indicates that HSCN-Net has higher robustness and generalization ability.

Most traditional registration algorithms have slow convergence speed because they involve high-dimensional optimization. Compared with the traditional registration method Demons, the average registration time of HSCN-Net reduced from 147.21s to 17.86s, which

greatly improves the registration speed ($p < 0.05$). Compared with the neural network VoxelMorph, the average registration time of HSCN-Net was also reduced by 0.67s ($p < 0.05$). The above two points show that HSCN-Net has certain advantages in running speed. Therefore, HSCN-Net has greater clinical application value for ACVD which requires image registration rapidly.

There still exist some limitations in this study. Firstly, all brain CT cases involved in training and validation are all from the same hospital, while CT images from multi-manufacturer and multi-equipment cannot be collected at present. In the future, we will pay more attention to the diversity of data sources, continue to collect more brain CT data for the optimization and validation of HSCN-Net, and further improve the accuracy, robustness and generalization ability of HSCN-Net. Secondly, due to the limited memory resources on the GPU, HSCN-Net cannot be very deep and random pairs among training set were selected with a batch size limited to 1. Besides, we will attempt to apply HSCN-Net to the CT data from the other body parts such as heart, liver, etc. for the image interpretation.

4. Conclusion

In summary, a non-rigid brain CT image registration algorithm based on hybrid supervised convolution neural network was proposed. It can achieve accurate and fast brain CT registration with high generalization ability including large deformations. The method could help rapid image evaluation and interpretation of ACVD, so as to provide reference for the neurologist to perform diagnosis and treatment decision-making.

5. Method

5.1 Data Set and Experiment Configuration

Because there are no published standard datasets for brain CT registration, we use data continuously collected from hospitals in this study. We ask senior neuroradiologist manually annotate the MCA blood supply area on all validation data set. One hundred and one brain non-enhanced CT images were collected as the data set, of which fifty-seven cases were used for HSCN-Net network training, fourteen cases were used for testing, and thirty cases were used for performance validation. The data size is $512 \times 512 \times 64$ and the voxel spacing is $0.36 \times 0.36 \times 2$ mm. All the data were preprocessed by skull removal and Z-score normalization. Our experiment is running on win10, 64-bit operating system and GeForce RTX 2080 Ti, and the virtual environment is configured in Python 3.6 + TensorFlow 2.0.0.

5.2 Network Design

This study proposes a Unet-based^[25] neural network structure which mainly consists of two parts: encoding path and decoding path. The encoding path follows the typical architecture of a convolutional network. It is mainly composed of convolution and max pooling operations repeated. The core function of the encoding path is to learn the deep

semantic features of image. The decoding part fuses the semantic feature layers obtained in the encoding stage and every step in the decoding path consists of an up-sampling of the feature map. Moreover, the network adds dilated convolution inside the encoding and decoding module, which can expand the receptive field to improve the feature extraction ability without increasing parameters number. The framework of proposed network is shown in Fig. 2. More importantly, a deformation field simulation generator is integrated into the network structure, the simulator simulates and generates the gold standards of deformation field during training, which can alleviate the difficulty of high-quality gold standards obtaining in supervised learning. Intentionally, the deformation fields are configured with a certain proportion of large deformation, which is intended to improve the larger deformation processing ability of HSCN-Net. On the other hand, the moving image and the fixed image deformed from the moving image by the simulated deformation field are defined as the first set of input images. Next, leaving the moving image unchanged, another fixed image is randomly selected from the training set, these two images are defined as the second set of input images. Then, these two sets of images are input into the network for training at the same time. Finally, deformation field information and image information are obtained simultaneously to optimize the network.

The network adopts both self-supervised learning and supervised learning to optimize network parameters. Training images are divided into self-supervised group and supervised group. The two images in self-supervised group, which denoted as the first reference image I^1 and moving image M , are randomly selected from the training set. For supervised group, the simulator generates deformation field F_g^0 to warp the image M to the second reference image I^0 . The two sets of images are simultaneously input into the network for training. Then the two predicted deformation fields are obtained: F_p^0 and F_p^1 , respectively. Till now, three sub-loss functions need to be calculated: the similarity measure L_F between the random deformation field F_g^0 and the predicted deformation field F_p^0 , the similarity measure L_{M0} between the reference image I^0 and the predicted image I_p^0 in supervised group, and the similarity measure L_{M1} between the reference image I^1 and the predicted image I_p^1 in self-supervised group. Furthermore, three sub-loss functions are multiplied by the corresponding weight coefficients and added together to get the hybrid supervised loss function. Subsequently, the hybrid supervised loss function is fed back to the network backward propagation process to optimize the parameters until converged. Specifically, the hybrid loss function is computed as follows:

Fig. 2. Framework of HSCN-Net. We use a simulator to generate synthetic deformation fields and images during training to solve the problem of lacking registration gold standard. Large deformations of appropriate proportion are added to the synthetic deformation fields to overcome the challenge of large deformation fields between images to be registered. And HSCN-Net adopts a hybrid supervised loss function constituted by the alignment accuracy of the deformation fields and the image similarity to improve the registration accuracy and generalization ability of the model.

$$L_{reg}(F_p^0, F_g^0, I^0, I^1, I_p^0, I_p^1; \theta) = \alpha L_F(F_p^0, F_g^0; \theta) + \beta L_{M0}(I^0, I_p^0; \theta) + \gamma L_{M1}(I^1, I_p^1; \theta) \quad (1)$$

where I_p^0 represents the predicted registration image generated by the deformation field F_p^0 acting on the moving image M , I_p^1 represents the predicted registration image generated by the deformation field F_p^1 acting on the moving image M , θ is the parameters of the neural network. The hybrid supervised loss $L_{reg}(F_p^0, F_g^0, I^0, I^1, I_p^0, I_p^1; \theta)$ combines multiple information of deformation field alignment accuracy and image similarity and α, β, γ are the hyper-parameters to balance the three sub-losses.

$$L_F(F_p^0, F_g^0; \theta) = \frac{1}{|\Omega|} \sum_{p \in \Omega} \|F_p^0(p) - F_g^0(p)\|_{L_2} \quad (2)$$

where p is the voxel position in the image coordinate space Ω . $|\Omega|$ represents the voxel number in registration image. The supervised learning-based loss function L_F quantifies the deviation error between the gold standard deformation field F_g^0 and the predicted deformation field F_p^0 , so as to improve the alignment accuracy of the two deformation fields.

$$L_{M0}(I^0, I_p^0; \theta) = -\frac{1}{|\Omega|} \sum_{p \in \Omega} \frac{(\sum_{p_i} (I^0(p_i) - \overline{I^0(p)})) (I_p^0(p_i) - \overline{I_p^0(p)})^2}{\sum_{p_i} (I^0(p_i) - \overline{I^0(p)})^2 \sum_{p_i} (I_p^0(p_i) - \overline{I_p^0(p)})^2} \quad (3)$$

where p_i is the voxel coordinate in the neighborhood centered on the voxel $f(x, y, z)$. $\overline{I^0(f(x, y, z))}$ and $\overline{I_p^0(f(x, y, z))}$ are local means within the window around voxel position $f(x_i, y_i, z_i)$ in I^0 and I_p^0 respectively.

$$L_{M1}(I^1, I_p^1; \theta) = -\frac{1}{|\Omega|} \sum_{p \in \Omega} \frac{(\sum_{p_i} (I^1(p_i) - \overline{I^1(p)})) (I_p^1(p_i) - \overline{I_p^1(p)})^2}{\sum_{p_i} (I^1(p_i) - \overline{I^1(p)})^2 \sum_{p_i} (I_p^1(p_i) - \overline{I_p^1(p)})^2} \quad (4)$$

where p_i is the voxel coordinate in the neighborhood centered on the voxel $f(x, y, z)$. $\overline{I^1(f(x, y, z))}$ and $\overline{I_p^1(f(x, y, z))}$ are local means within the window around voxel position $f(x_i, y_i, z_i)$ in I^1 and I_p^1 respectively.

The experiment shows that when $\alpha = 1/13$, $\beta=\gamma=0.4$, the contribution of the three sub-loss functions $L_F(F_p^0, F_g^0; \theta)$, $L_{M0}(I^0, I_p^0; \theta)$, $L_{M1}(I^1, I_p^1; \theta)$ for the network parameter optimizing is relatively balanced. The supervised learning-based deformation field similarity loss functions L_F directly reflect the deviation of gold standard deformation field and predict the deformation field, which is beneficial to improve the accuracy of the network. The self-supervised learning-based image similarity loss functions L_{M0} and L_{M1} can reduce the dependence of registration network on the diversity of training set, and help to improve the generalization ability of the model.

To fully model various transformations (indicating the anatomical variations across individuals), the simulator randomly generates deformation field F_g^0 including affine and elastic. F_g^0 is applied to moving image M to generate the reference image I^0 , so F_g^0 can be the gold standard for warping M to I^0 . As the gold standard, F_g^0 overcomes the problems of low accuracy and poor consistency of the training gold standard in supervised learning. Besides, some large deformations are randomly generated in the deformation field F_g^0 , thereby alleviating the problem that the existing registration methods cannot adapt to large deformations.

5.3 Network Performance Evaluation Method

To assess the performance of HSCN-Net in brain CT image registration, comparative experiment was conducted with Demons^[26], a traditional deformable registration method, and VoxelMorph^[18], a typical unsupervised deep learning network. Firstly, all the cases in the validation set were defined as moving images. Then, random deformation fields generated by the simulator were applied to moving images to generate reference images. The corresponding deformation field was used as the deformation field gold standard between the moving image and the reference image. Next, the moving image and the reference image were paired and fed into the network. Finally, in order to evaluate the registration accuracy, robustness and efficiency of HSCN-Net, qualitative and quantitative analysis were carried out. Qualitative analysis was performed by visually assess the registered images, including the anatomical structure consistence with reference image and the smoothness of the registered image. Quantitative analysis included metrics such as Endpoint Error (EPE), image Normalized Mutual Information (NMI)^[29], Dice^[28] coefficient and registration time. EPE is used to measure the alignment accuracy between the predicted deformation field and the gold standard deformation field. NMI is used to quantify the correlation between the predicted image and the reference image. Its value ranges from 0 to 1. The larger the value, the stronger the correlation between the predicted image and reference image, and vice versa. Dice coefficient quantifies the degree of overlap between the MCA blood supply areas in the predicted image and the reference image. The gold standards of MCA blood supply areas are annotated by senior neuroradiologist. Also, the running time of the three algorithms were statistically analyzed. Paired t -test was used to compare the registration accuracy and running

time of different registration methods, and a p -value less than 0.05 was considered statistically significant. See Eq.2 for the definition of EPE.

Declarations

Corresponding Author: YUAN Hong-mei, E-mail: yuan.hm@neusoft.com

Author details:

1. Neusoft Research of Intelligent Healthcare Technology, Co. Ltd, Shengyang 110179, China

2. Neusoft Medical System, Co. Ltd, Shengyang 110167, China

3. Shenyang Advanced Medical Equipment Technology Incubation Center, Co. Ltd, Shengyang 110167, China

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication: Not applicable.

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