

# CyTran: Cycle-Consistent Transformers for Non-Contrast to Contrast CT Translation

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**Abstract**—We propose a novel approach to translate unpaired contrast computed tomography (CT) scans to non-contrast CT scans and the other way around. Solving this task has two important applications: (i) to automatically generate contrast CT scans for patients for whom injecting contrast substance is not an option, and (ii) to enhance alignment between contrast and non-contrast CT by reducing the differences induced by the contrast substance before registration. Our approach is based on cycle-consistent generative adversarial convolutional transformers, for short, CyTran. Our neural model can be trained on unpaired images, due to the integration of a cycle-consistency loss. To deal with high-resolution images, we design a hybrid architecture based on convolutional and multi-head attention layers. In addition, we introduce a novel data set, Coltea-Lung-CT-100W, containing 3D triphasic lung CT scans (with a total of 37,290 images) collected from 100 female patients. Each scan contains three phases (non-contrast, early portal venous, and late arterial), allowing us to perform experiments to compare our novel approach with state-of-the-art methods for image style transfer. Our empirical results show that CyTran outperforms all competing methods. Moreover, we show that CyTran can be employed as a preliminary step to improve a state-of-the-art medical image alignment method. We release our novel model and data set as open source at: <https://github.com/ristea/cycle-transformer>.

**Index Terms**—Transformers, generative adversarial transformers, cycle-consistency, style transfer, image registration, image alignment, deep learning, computed tomography, triphasic CT, lung CT.

## I. INTRODUCTION

PATIENTS undergoing computed tomography (CT) screening may not be able to get intravenous injections with contrast agents due to allergies [1] or other medical conditions, e.g. muscular dystrophy, causing low blood creatinine levels. However, the contrast substance plays a very important role in helping doctors to detect and delimit certain lesions, e.g. malignant tumors [2]. For instance, radiotherapy heavily relies on the accurate segmentation of tumors.

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Certainly, the majority of patients are healthy enough to be injected with contrast agents, enabling doctors to obtain triple-phase CT scans which provide a significantly more clear picture of the malignant lesions. The triple-phase CT includes a native phase (before the contrast is injected), a portal venous phase (right after the contrast is injected), and a late arterial phase (when the contrast passes into the arteries). As the three phases are in successive temporal order, the corresponding CT scans are taken in different moments in time, inherently leading to a misalignment between scans caused by slight movements of the patient, e.g. due to breathing. In this scenario, some image registration method can be employed to align the CT scans. However, due to Hounsfield unit (HU) differences between contrast and non-contrast CT in certain types of tissue, the image alignment task becomes problematic, especially for the regions of interested, where tumors are located.

A method capable of translating between contrast and non-contrast CT scans, in both directions, is likely to solve the two problems presented above. Indeed, when patients are unable to undergo contrast CT screening, the doctors could simply employ the automated translation technique to generate contrast CT scans corresponding to the venous or arterial phases. When CT scans need to be aligned, the same translation technique can be applied prior to the alignment step to remove the effect of the contrast substance, thus allowing for a better alignment. Once the displacement field is generated, it can be applied on the unmodified contrast CT scan to obtain the final alignment result.

In this work, we present a novel deep learning model to translate between contrast and non-contrast CT scans. Our method relies on the success of generative adversarial networks (GANs) [3] in image-to-image translation [4], a class of vision tasks where the goal is to learn the mapping between an input image and an output image using a training set of paired or unpaired images from two different domains. Although GANs have been previously employed for medical image-to-image translation [5]–[8], we underline that the task of translating between contrast and non-contrast CT scans is very challenging due to the requirement of recognizing specific tissue types, anatomical structures, and even tumors, which exhibit significant HU changes between contrast phases. Failing to recognize such anatomical structures raises the possibility of introducing unrealistic information. This would evidently conduct to unreliable synthetic images, which cannot be used in diagnostic or treatment purposes. Convolutional neural networks fail to recognize the global structure of objects

in natural images [9], and, for the same reason, can fail to recognize anatomical structures in CT scans. To this end, we propose a cycle-consistent generative adversarial transformer, called *CyTran*, which has a higher capacity of recognizing global structure due to the incorporated transformer block. Since pure vision transformers cannot process high-resolution images due to the high number of learnable parameters involved, we design a hybrid architecture comprising both convolutions and multi-head attention, such that it can generate full-resolution CT scans.

To demonstrate applicability of CyTran on the important cases exemplified above, we introduce the *Coltea-Lung-CT-100W* data set formed of 100 3D anonymized triphasic lung CT scans of female patients. For each patient, there are three CT scans corresponding to the native, venous and arterial phases, respectively. We conduct a set of experiments to compare CyTran with other state-of-the-art style transfer methods, namely CycleGAN [4], pix2pix [10] and U-GAT-IT [11]. Both automatic and human evaluations indicate that our approach is consistently better than the competing methods. We perform another set of experiments to evaluate the applicability of style transfer methods in contrast to non-contrast CT alignment with a state-of-the-art 3D image registration method [12]. While the empirical results indicate that all style transfer methods are helpful, the highest performance improvements are brought by CyTran.

To the best of our knowledge, our contribution is threefold:

- We are the first to propose a cycle-consistent generative adversarial transformer in medical imaging, demonstrating state-of-the-art results in style transfer between contrast and non-contrast CT scans.
- We are the first to publicly release a data set containing triphasic lung CT scans.
- We are the first to use style transfer methods to enhance alignment between contrast and non-contrast CT scans.

## II. RELATED WORK

**1) Transformers:** Architectures based on self-attention, in particular transformers [13], have become the model of choice in natural language processing (NLP). Thanks to the computational power and scalability of transformers, it has become possible to train models of unprecedented size [14]. With the ever growing size of models and data sets, the performance improvements are constantly increasing. Considering the success of transformers in NLP [14], architectures based on multi-head self-attention have been adopted in the computer vision community, attaining superior results in various tasks [15]–[18]. Wu et al. [16] proposed a convolutional transformer that improves the Vision Transformer (ViT) [15] in terms of performance and efficiency by introducing convolutions into the model, in an attempt to take advantage of both designs. We further replace the multi-layer perceptron from the transformer block proposed by Wu et al. [16] with pointwise convolutional layers, allowing us to incorporate the resulting block into an efficient generative model that can produce high-resolution images. Zhang et al. [17] proposed a cycle-consistent attention mechanism for semantic segmentation. In

contrast, we introduce a novel generative model based on an efficient convolutional transformer backbone, where the cycle consistency is imposed at the output level, not at the latent feature level.

In medical imaging, the popularity of transformer architectures is rising [19]–[23], most likely because such models bring state-of-the-art results. For instance, Gao et al. [23] proposed an efficient self-attention mechanism which reduces computational complexity for cardiac magnetic resonance imaging (MRI) segmentation. In [22], the authors presented a zero-shot learning method employing a cross-attention transformer block to reconstruct MRI images. Luthra et al. [21] proposed an encoder-decoder network, which uses transformer blocks for CT image denoising. Different from the medical imaging methods based on transformers, we introduce a novel convolutional transformer architecture for style transfer between contrast and non-contrast CT images, which can be trained on unpaired data through the use of a cycle-consistency term in the loss. To our knowledge, this is the first work to propose cycle-consistent transformers in medical imaging.

**2) Image Translation:** Since the introduction of GANs [3] in 2014, a large body of research has focused on theoretical and architectural changes [4], [10], [24]–[26], giving rise to a wide adoption of GANs across various generation tasks, including image translation [4], [10], [11]. In 2016, the pix2pix framework [10] became one of the first GAN models to address the task of image-to-image translation from a source domain image, e.g. a springtime landscape, to a corresponding target domain image, e.g. a winter landscape, provided that paired images from the two different domains are available for training. To overpass the lack of paired data sets for style transfer, researchers have developed methods for unpaired image-to-image translation [4]. Zhu et al. [4] solved the problem by using two generators, one that translates a source image to the target domain, and the other to translate the translated image back to the source domain. The two generators are optimized such that the image passing through the two generators is close to the original input image, ensuring the cycle-consistency of the framework.

GANs have also been adopted in medical imaging, often being employed for medical image translation [7], [27]–[31]. For example, Seo et al. [27] proposed a two-stage algorithm to address style transfer between contrast and non-contrast CT images. The first stage removes the poor alignment effects, while the second stage relies on a GAN architecture to enhance the contrast of CT images. Other approaches used the pix2pix framework in applications where paired images are available, such as positron emission tomography (PET) to MRI translation [29], organ segmentation [32], MRI to CT translation [30], and low-dose CT denoising [28]. More recently, researchers started using CycleGANs [4] for various medical imaging tasks [7], [31]. For example, Kearney et al. [7] employed a CycleGAN [4] to translate between MRI and CT data. Modanwal et al. [31] proposed an algorithm that modifies CycleGAN by introducing two discriminators to translate between different MRI images. Closer to our task, Chandrashekhar et al. [5] proposed an algorithm which relies on CycleGAN to enhance the contrast of CT images. To the

best of our knowledge, none of the related methods are based on transformer architectures. We provide empirical evidence showing that cycle-consistent transformers outperform architectures based on pix2pix or CycleGAN when it comes to contrast to non-contrast CT translation and back.

**3) Image Registration:** Medical image registration is a fundamental problem that improves visual inspection, diagnostic, and treatment planning. It refers to the task of establishing spatial correspondences between points in a pair of fixed and moving images through a spatially varying deformation model. The state-of-the-art methods for medical image alignment are based on deep neural networks [33]–[39]. A recent registration approach proposed in [38] is based on a recursive cascade algorithm which assumes that, at each step, the neural model learns to perform a progressive deformation of the current warped image. Nevertheless, the trend of applying transformers has recently been adopted in medical image registration as well. However, Chen *et al.* [33] claimed that architectures based solely on transformers emphasize the low-resolution features because of the consecutive downsampling operations, resulting in a lack of detailed localization information that affects image registration performance. To alleviate this problem, the authors combined transformers with convolutional layers into an architecture called ViT-V-Net, which improves the recovery of localization information.

Different from other medical image registration approaches, we employ CyTran as a data augmentation method to improve alignment results. The augmentation consists of adding training examples of non-contrast CT scans that are synthetically generated by CyTran. As a secondary contribution, we extended ViT-V-Net [33] by employing multiple cascades at inference time, further improving the registration results by a considerable margin.

**4) Data Sets:** In recent years, the open-source access to large medical databases [40]–[44] has accelerated the development of deep learning methods in the medical imaging field. The organizers of the CHAOS challenge [45] released a medical data set containing CT and MRI data. The CT data was acquired from the upper abdomen area of 40 patients during the portal venous phase, after contrast agent injection. Moen *et al.* [46] developed a data set of CT scans from 299 patients for three types of clinical exams: non-contrast head CT scans, low-dose non-contrast chest scans and contrast-enhanced CT scans of the abdomen. Bilic *et al.* [47] released a data set which consists of 140 CT scans, each having five organs labeled: lung, bones, liver, kidneys and bladder. The data set blends examples from a wide variety of sources, including abdominal and full-body, contrast and non-contrast, low-dose and high-dose CT scans. The data sets of Moen *et al.* [46] and Bilic *et al.* [47] contain both contrast and non-contrast CT scans, but these are taken for different body sections. In contrast, our data set contains contrast and non-contrast CT scans of the same body section, the chest. To the best of our knowledge, Colteau-Lung-CT-100W is the first public data set formed entirely of triphasic lung CT scans, meaning that there are three 3D scans for each patient, corresponding to the native, early portal venous, and late arterial phases, respectively.

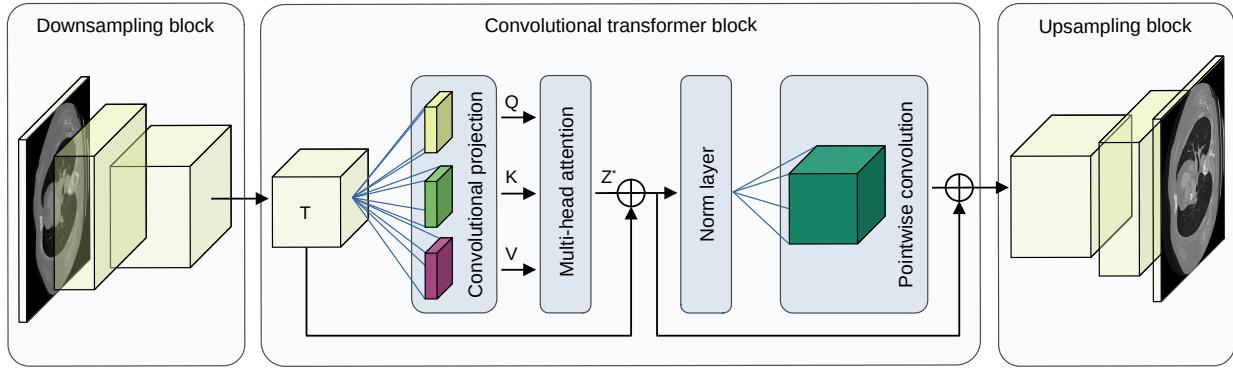
### III. IMAGE TRANSLATION METHOD

We propose a cycle-consistent generative adversarial transformer, which employs a generative visual transformer network to translate lung CT images between two different contrasts, e.g. native, venous or arterial. Our approach is inspired by the success of cycle-consistent GANs [4] in image-to-image translation for style transfer. Based on the assumption that style is easier to transfer than other aspects, e.g. geometrical deformations, cycle-GANs can replace the style of an image with a different style, while keeping its content. Our task involves style transfer between lung CT images acquired in different contrast phases. The contrast substance introduces HU changes for specific anatomical structures, such as tumors or blood vessels. However, the structures themselves should not exhibit geometrical changes between contrast phases, other than those caused by small movements of the patient, such as movements generated by respiration. While the changes between different contrast phases can be assimilated to style changes, we underline that the changes apply only to specific anatomical structures. Hence, to accurately mimic the contrast changes, the employed style transfer model should be capable of recognizing anatomical structures. We believe that models equipped with the power to extract and use global information have a higher capacity of recognizing anatomical structures. We thus conjecture that generative transformers can outperform convolutional generators at the task of learning to reproduce or unwind the changes caused by the contrast substance.

We propose a cycle-consistent architecture based on generative adversarial **transformers**, termed *CyTran*, to transfer CT scans between different contrast phases. Following the CycleGAN framework [4], CyTran is formed of two discriminators and two generators. The neural architecture of the discriminators is identical to the architecture used by Zhu *et al.* [4]. In a preliminary evaluation stage, we tried to replace the convolutional discriminators with transformers, but we observed that this change makes the discriminators too powerful with respect to the generative transformers. For this reason, we turned our attention to replacing the generative models only. We next describe in detail the proposed generative architecture as well as the entire optimization process.

#### A. Generative Convolutional Transformer Architecture

As we aim to benefit from the modeling power of transformers while being able to generate high-resolution CT images, we design a generative convolutional transformer with a manageable number of parameters. As illustrated in Figure 1, our generator is formed of a convolutional downsampling block, a convolutional transformer block, and a deconvolutional upsampling block. We underline that, without the convolutional downsampling block and the replacement of dense layers with convolutional layers inside the transformer block, the transformer would not be able to learn to generate images larger than  $64 \times 64$  pixels, due to memory overflow (measured on a Nvidia GeForce RTX 3090 GPU with 24GB of VRAM). In contrast, we need a model capable of generating CT slices of  $512 \times 512$  pixels. At this input resolution, our



**Fig. 1:** Our convolutional transformer for CT image generation, an essential part of CyTran. The model is formed of a downsampling block comprising convolutional layers, a convolution transformer block comprising a multi-head self-attention mechanism, and an upsampling block comprising transposed convolutions.

design changes significantly reduce the number of learnable parameters from 258 millions to 3.5 millions.

**1) Downsampling Block:** The downsampling block starts with a convolutional layer formed of 32 filters with a spatial support of  $7 \times 7$ , which are applied using a padding of 3 pixels to preserve the spatial dimension, while enriching the number of feature maps to 32. Next, we apply three convolutional layers composed of 32, 64 and 128 filters, respectively. All convolutional filters have a spatial support of  $3 \times 3$  and are applied at a stride of 2, using a padding of 1. Each layer is followed by batch-norm [48] and Rectified Linear Units (ReLU) [49]. Let  $\mathbf{T} \in \mathbb{R}^{h \times w \times c}$  denote the output tensor of the downsampling block. For an input CT slice of  $512 \times 512$  pixels, the dimensions of  $\mathbf{T}$  are  $64 \times 64 \times 128$ .

**2) Convolutional Transformer Block:** The downsampling block is followed by the convolutional transformer block, which provides an output tensor of the same size as the input tensor. Our convolutional transformer block is inspired by the block proposed by Wu et al. [16].

The input tensor  $\mathbf{T}$  is interpreted as a set of  $h \cdot w$  overlapping visual tokens. In our implementation, we have  $64 \cdot 64 = 4096$  tokens, where each token is a tensor of  $3 \times 3 \times 128$  components. The spatial dimensions of the visual tokens is determined by the receptive field of the filters in the next convolutional layer.

**Convolution projection.** In a vanilla transformer, a sequence of tokens is typically projected onto a set of weight matrices to obtain the queries  $\mathbf{Q}$ , the keys  $\mathbf{K}$ , and the values  $\mathbf{V}$ . Following Wu et al. [16], the projections typically implemented through matrix multiplication are replaced by depthwise separable convolution operations, referred to as *convolutional projection*. The convolutional projection is formed of three nearly identical projection blocks, with separate parameters. Each projection is a depthwise separable convolution block [50] formed of two convolutional layers and a batch-normalization layer in between.

The first layer in a projection block is a depthwise convolution with 128 filters, each having a receptive field of  $3 \times 3$ . The projection block producing the queries is configured with a stride of 1 (generating activation maps of  $64 \times 64$ ), while the other projection blocks use a stride of 2 (generating activation maps of  $32 \times 32$ ). The padding is 1 for all three blocks. The

output passes through a batch-norm, before going into the third layer. The third layer applies pointwise convolution with 64 filters. We hereby note that, in pointwise convolution, the filters always have a spatial support of  $1 \times 1$  and are applied at a stride of 1, without padding. Finally, the output tensors are reshaped into matrices by flattening the activation maps, while preserving the number of channels.

Let  $\mathbf{W}_Q$ ,  $\mathbf{W}_K$  and  $\mathbf{W}_V$  denote the learnable parameters of the three projection blocks. The query, key and value embeddings are computed as follows:

$$\begin{aligned} \mathbf{Q} &= \text{conv\_projection}(\mathbf{T}, \mathbf{W}_Q), \\ \mathbf{V} &= \text{conv\_projection}(\mathbf{T}, \mathbf{W}_V), \\ \mathbf{K} &= \text{conv\_projection}(\mathbf{T}, \mathbf{W}_K), \end{aligned} \quad (1)$$

where  $\mathbf{Q} \in \mathbb{R}^{n_q \times d_q}$ ,  $\mathbf{K} \in \mathbb{R}^{n_k \times d_k}$  and  $\mathbf{V} \in \mathbb{R}^{n_v \times d_v}$ . For the subsequent operation involving matrix multiplications, we need  $d_q = d_k$ , and  $n_k = n_v$ . In our implementation,  $n_q = 4096$  (obtained by flattening  $64 \times 64$  activation maps) and  $n_k = n_v = 1024$  (obtained by flattening  $32 \times 32$  activation maps). Due to the equal number of filters in the pointwise convolution in all three blocks,  $d_q = d_k = d_v = 64$ .

We underline that the goal of adding the convolutional projection is to achieve additional modeling power of the local spatial context from the output of the subsequent multi-head attention layer.

**Multi-head self-attention.** The convolutional projection layer is followed by a multi-head self-attention mechanism. The goal of self-attention is to capture the interaction among all tokens by encoding each entity in terms of the global contextual information. Given a sequence of items, the self-attention mechanism estimates the relevance of an item to other items, e.g. which visual token embeddings are likely to come together in a tensor. Basically, the self-attention layer updates each visual token by aggregating global information from the complete input tensor.

The output  $\mathbf{Z} \in \mathbb{R}^{n_q \times d_v}$  of the self-attention layer is given by:

$$\mathbf{Z} = \text{softmax} \left( \frac{\mathbf{Q}\mathbf{K}^\top}{\sqrt{d_q}} \right) \cdot \mathbf{V}, \quad (2)$$

where  $\mathbf{K}^\top$  is the transpose of  $\mathbf{K}$ . For a given token, the self-attention computes the dot product of the query with all keys,

which is then normalized using the softmax operator to get the attention scores. Each entity then becomes the weighted sum of all entities in the sequence, where the weights are given by the attention scores. At this point,  $Z$  is a matrix of  $4096 \times 64$  components. Upon reshaping the 4096-dimensional vectors back into activation maps, we obtain a tensor of  $64 \times 64 \times 64$  components. In order to encapsulate multiple complex relationships among different tokens in the tensor  $T$ , we employ a multi-head attention module [13]. Each head  $i \in \{1, \dots, n_h\}$  comprises a convolution projection and a self-attention mechanism, having a particular set of learnable parameters  $\{W_{Q_i}, W_{K_i}, W_{V_i}\}$ , where  $n_h$  is the number of heads. In our implementation, we set  $n_h = 6$ .

To form the output of the entire multi-head attention module, we concatenate the output tensors in the channel dimension, obtaining a tensor of  $64 \times 64 \times 384$  components. A pointwise convolution with 128 filters brings the dimension of the output tensor down to  $64 \times 64 \times 128$  components. Let  $Z^*$  denote the final output tensor of the multi-head self-attention module. We underline that the dimension of  $Z^*$  coincides with the dimension of the input tensor  $T$ , i.e.  $Z^* \in \mathbb{R}^{h \times w \times c}$ .

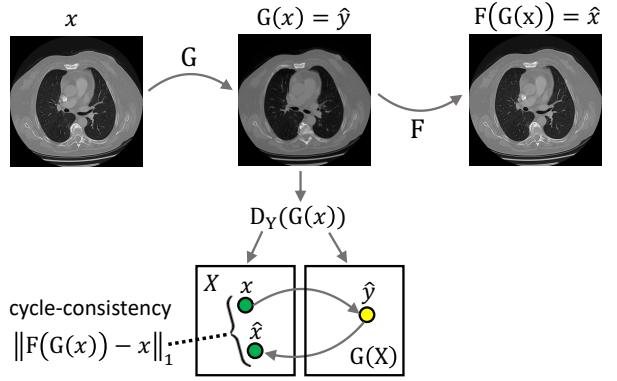
**Pointwise convolution.** After the multi-head attention layer, the output is summed up with the input of the convolutional projection and fed into a batch-normalization layer. Unlike the vast majority of transformers, we introduce a pointwise convolutional block instead of a multi-layer perceptron as the last processing step of the transformer block, further reducing the number of learnable parameters. Our convolutional block is formed of two consecutive pointwise convolutional layers, the first one being formed of 512 filters and the second one being formed of 128 filters. We use Gaussian Error Linear Units (GELU) [51] after the first pointwise convolutional layer.

Next, the input of the norm layer is added to the output of our pointwise convolutional block, resulting in the final output of our convolutional transformer block.

**3) Upsampling Block:** The last block of our convolutional transformer applies upsampling operations, being designed to revert the transformation of the downsampling block. The upsampling block is formed of three transposed convolutional layers comprising 128, 64 and 32 filters, respectively. All kernels have a spatial support of  $3 \times 3$ , being applied at a stride of 2, using a padding of 1. As for the downsampling block, we introduce batch-norm and ReLU activations after each transposed convolutional layer. Finally, we employ a convolutional layer with one filter to reduce the number of channels from 32 back to 1. The size of the receptive field of this final filter is  $7 \times 7$ . We use a padding of 3 to preserve the spatial dimensions, obtaining an output image of  $512 \times 512$  pixels.

## B. Learning on Unpaired CT Slices

We use the following notations throughout the remainder of this work. Let  $(X, Y)$  denote the pair of source and target domains. Since we are interested in translating contrast CT scans to non-contrast CT scans and vice versa, the pair  $(X, Y)$  can take one of the following values: (native, arterial), (native, venous), (venous, native), (arterial, native). For our application purposes, we are not interested in translating the (arterial,



**Fig. 2:** Translating CT images using cycle-consistent generative adversarial models from domain  $X$  to domain  $Y$ . The source CT image  $x$  is translated using the generative transformer  $G$  into the target CT image  $\hat{y}$ . The target CT image  $\hat{y}$  is translated back to the original domain  $X$  through the generative transformer  $F$ . The generative transformer  $G$  and the discriminator  $D_Y$  are optimized in an adversarial fashion, just as in any other GAN. In addition, the model is optimized with respect to the cycle-consistency loss between the original source CT image  $x$  and the fake CT image  $\hat{x}$ . Analogous steps are carried out for translating from  $Y$  to  $X$  (not represented in the image).

venous) and (venous, arterial) pairs. Let  $x$  denote a sample from domain  $X$  and  $y$  a sample from domain  $Y$ , respectively.

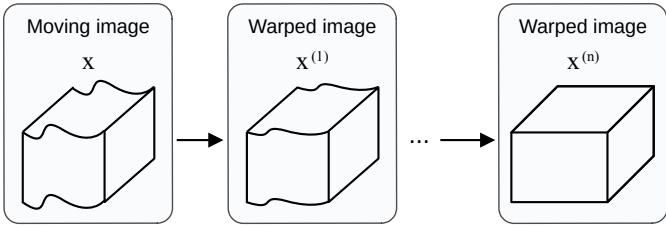
In Figure 2, we illustrate the generative process based on cycle-consistency for two CT images belonging to different contrast domains. The source CT image  $x$  is translated using the generative transformer  $G$  into  $\hat{y}$ , to make it seem that  $\hat{y}$  belongs to the target domain. The target CT image  $\hat{y}$  is translated back to the original domain  $X$  through the generative transformer  $F$ . The generative transformer  $G$  is optimized to fool the discriminator  $D_Y$ , while the discriminator  $D_Y$  is optimized to separate synthesized CT images from real samples, in an adversarial fashion. In addition, the network is optimized with respect to the reconstruction error computed between the original sample  $x$  and the cycle-generated CT sample  $\hat{x}$ . Adding the reconstruction error to the overall loss function ensures the cycle-consistency for domain  $X$ . An analogous training process is carried out to ensure cycle-consistency for domain  $Y$ . The complete loss function to optimize CyTran for contrast translation in both directions is:

$$L_{CyTran}(G, F, D_X, D_Y, x, y) = L_{GAN}(G, D_Y, x, y) + L_{GAN}(F, D_X, x, y) + \lambda \cdot L_{cycle}(G, F, x, y), \quad (3)$$

where,  $G$  and  $F$  are generative transformers,  $D_X$  and  $D_Y$  are convolutional discriminators,  $x$  is a CT slice from contrast phase  $X$ ,  $y$  is a CT slice from contrast phase  $Y$ , and  $\lambda$  is a parameter that controls the importance of cycle-consistency with respect to the two GAN losses. The first GAN loss is the least squares loss that corresponds to the translation from domain  $X$  to domain  $Y$ :

$$L_{GAN}(G, D_Y, x, y) = E_{y \sim P_{data}(y)} [(D_Y(y))^2] + E_{x \sim P_{data}(x)} [(1 - D_Y(G(x)))^2], \quad (4)$$

where  $E[\cdot]$  is the expect value and  $P_{data}(\cdot)$  is the probability



**Fig. 3:** Cascaded algorithm for volumetric image registration. The moving 3D CT scan  $\mathbf{x}$  is registered in a recursive cascade based on  $n$  steps. Thus,  $\mathbf{x}^{(i)}$  is the warped image at step  $i$ ,  $\forall i \in \{1, \dots, n\}$ .

distribution of data samples. Analogously, the second GAN loss is the least squares loss that corresponds to the translation from domain  $Y$  to domain  $X$ :

$$\begin{aligned} L_{GAN}(F, D_X, \mathbf{x}, \mathbf{y}) &= E_{\mathbf{x} \sim P_{data}(\mathbf{x})} [(D_X(\mathbf{x}))^2] \\ &\quad + E_{\mathbf{y} \sim P_{data}(\mathbf{y})} [(1 - D_X(F(\mathbf{y})))^2]. \end{aligned} \quad (5)$$

The cycle-consistency loss in Equation (3) is defined as the sum of cycle-consistency losses for both translations:

$$\begin{aligned} L_{cycle}(G, F, \mathbf{x}, \mathbf{y}) &= E_{\mathbf{x} \sim P_{data}(\mathbf{x})} [\|F(G(\mathbf{x})) - \mathbf{x}\|_1] \\ &\quad + E_{\mathbf{y} \sim P_{data}(\mathbf{y})} [\|G(F(\mathbf{y})) - \mathbf{y}\|_1], \end{aligned} \quad (6)$$

where  $\|\cdot\|_1$  is the  $l_1$  norm.

#### IV. IMAGE REGISTRATION METHOD

Unsupervised medical image registration can fail to properly align contrast CT scans to non-contrast CT scans, especially in the regions highlighted by the contrast agent, which are of primary interest. To alleviate such failure cases, we propose to employ CyTran on the contrast CT scans to eliminate differences induced by the contrast agent.

Let  $\mathbf{x} \in X$  denote a source 3D CT scan belonging to the contrast phase  $X$  (either venous or arterial), and  $\mathbf{y} \in Y$  a target 3D CT scan belonging to the non-contrast phase  $Y$  (native). Prior to the alignment of voxels in  $\mathbf{x}$  to  $\mathbf{y}$ , we translate all slices in the CT scan  $\mathbf{x}$  to the distribution  $Y$ , obtaining  $\hat{\mathbf{x}}$ . Then, we align  $\hat{\mathbf{x}}$  to  $\mathbf{y}$ , both belonging to the same distribution  $Y$ , and we obtain the displacement field  $M_{\hat{\mathbf{x}}}$ . Finally, we apply the displacement field  $M_{\hat{\mathbf{x}}}$  to  $\mathbf{x}$  in order to obtain the final alignment result.

To perform the alignment, we rely on the state-of-the-art ViT-V-Net model introduced by Chen et al. [33]. The model encodes the full-resolution input into high-level feature representations via a series of convolutional and max-pooling layers. Next, the resulting patches are fed into a transformer-based encoder, which consists of 12 alternating blocks of multi-head self-attention and dense layers. Finally, the result is decoded into a dense displacement field.

As another contribution, we extend ViT-V-Net [33] to a cascaded registration algorithm, which is intuitively illustrated in Figure 3. Let  $R$  be the registration model,  $\mathbf{x} \in \mathbb{R}^{h \times w \times d}$  the moving 3D image, and  $\mathbf{x}^{(1)} \in \mathbb{R}^{h \times w \times d}$  the warped image, such that  $R(\mathbf{x}) = \mathbf{x}^{(1)}$ . We propose to apply multiple cascades at inference time, by passing the output several times through the model:

$$R(\mathbf{x}^{(i-1)}) = \mathbf{x}^{(i)}, \forall i \in \{1, \dots, n\}. \quad (7)$$

**TABLE I:** The number of triphasic CT scans and individual slices from the Coltea-Lung-CT-100W data set.

	Training	Validation	Test	Total
#scans	70	15	15	100
#images	25,311	5,937	6,042	37,290

The recursive processing progressively reduces the alignment differences, leading to a superior result.

#### V. DATA SET

We release a novel data set entitled *Coltea-Lung-CT-100W*, which consists of 100 triphasic lung CT scans. The scans are collected from 100 female patients and represent the same body section. The slices are selected having as anatomical landmarks the 7th cervical vertebra cranially and the 12th thoracic vertebra caudally. A triphasic scan is formed of a native (non-contrast) scan, an early portal venous scan, and a late arterial scan. In our data set, the three CT scans forming a triphasic scan always have the same number of slices, but the number of slices may differ from one patient to another. The number of slices per scan ranges between 64 and 229, and the total number of slices is 37,290. The size of a CT slice is  $512 \times 512$  pixels and the slice thickness varies between 1.25 and 3 mm. The resolution of a pixel is  $1 \times 1 \text{ mm}^2$ .

We split our data set into three subsets, one for training (70 scans), one for validation (15 scans), and one for testing (15 scans). We report the number of slices in each subset in Table I. Our data set is stored as anonymized raw DICOM files and can be freely downloaded from <https://github.com/ristea/cycle-transformer.git>.

#### VI. EXPERIMENTS

We study two tasks on Coltea-Lung-CT-100W:

- style transfer between contrast and non-contrast CT slices, considering the following pairs of contrast phases: native → venous, venous → native, native → arterial, arterial → native.
- volumetric image registration of contrast CT scans to non-contrast CT scans, considering the following pairs: venous → native, arterial → native.

##### A. Style Transfer Experiments

**1) Baselines:** We compare CyTran with three state-of-the-art style transfer methods. Since our data set is suitable for paired style transfer, we consider pix2pix [10] as the first baseline. As CyTran is an approach capable of learning from unpaired images, we select two more baselines from the same category of methods, namely CycleGAN [4] and U-GAT-IT [11]. We note that GAN-based style transfer methods can introduce visual artifacts during the generation process, which could be problematic in medical practice. We thus consider important comparing the generative models with a *no-transfer* baseline, which simply outputs the unprocessed input image. If this baseline outperforms a generative model, it indicates the respective model is unreliable, introducing too many artifacts.

**TABLE II:** Style transfer results for the native→venous, venous→native, native→arterial and arterial→native contrast pairs. Our model is compared with several state-of-the-art baselines on the test set, in terms of MAE, RMSE and SSIM. The symbol  $\uparrow$  means higher values are better, while  $\downarrow$  means lower values are better. The best results are highlighted in bold.

Method	native→venous			venous→native			native→arterial			arterial→native		
	MAE $\downarrow$	RMSE $\downarrow$	SSIM $\uparrow$	MAE $\downarrow$	RMSE $\downarrow$	SSIM $\uparrow$	MAE $\downarrow$	RMSE $\downarrow$	SSIM $\uparrow$	MAE $\downarrow$	RMSE $\downarrow$	SSIM $\uparrow$
no-transfer	0.072	0.160	0.656	0.072	0.160	0.656	0.072	0.163	0.664	0.072	0.163	0.664
pix2pix [10]	0.070	0.165	0.729	0.076	0.180	0.646	0.064	0.157	0.738	0.075	0.174	0.648
U-GAT-IT [11]	0.066	0.150	0.720	0.074	0.162	0.642	0.066	0.152	0.734	0.073	0.160	0.651
CycleGAN [4]	0.066	0.150	0.724	0.071	0.160	0.660	0.065	0.154	0.729	0.072	0.160	0.662
CyTran (ours)	<b>0.063</b>	<b>0.147</b>	<b>0.739</b>	<b>0.070</b>	<b>0.157</b>	<b>0.664</b>	<b>0.063</b>	<b>0.149</b>	<b>0.742</b>	<b>0.070</b>	<b>0.156</b>	<b>0.668</b>

**TABLE III:** Subjective human evaluation results based on 50 cases randomly selected from the test set for each of the following contrast pairs: native→venous, venous→native, native→arterial and arterial→native. The reported numbers represent votes awarded by three doctors for each generative model.

Contrast pair	Doctor #1				Doctor #2				Doctor #3			
	pix2pix [10]	U-GAT-IT [11]	CycleGAN [4]	CyTran (ours)	pix2pix [10]	U-GAT-IT [11]	CycleGAN [4]	CyTran (ours)	pix2pix [10]	U-GAT-IT [11]	CycleGAN [4]	CyTran (ours)
native→venous	3	9	14	24	1	4	10	35	4	9	4	33
venous→native	8	6	5	31	6	3	4	37	4	4	3	39
native→arterial	5	8	11	26	2	6	4	38	2	2	4	42
arterial→native	5	5	8	32	6	4	10	30	2	5	5	38
Overall votes	21	28	38	113	15	17	28	140	12	20	16	152
Overall percentage	10.5%	14%	19%	56.5%	7.5%	8.5%	14%	60%	6%	10%	8%	76%

**2) Performance evaluation:** We report the mean absolute error (MAE), root mean square error (RMSE) and structure-similarity index measure (SSIM) between the  $i$ -th translated image in a source scan and the slice at the same index  $i$  in the corresponding target scan. The SSIM measures the capability of keeping original structures unchanged, while the MAE and RMSE measure the ability of transferring the desired style, e.g. the ability of raising HU levels of a tumor in native→venous style transfer.

Furthermore, we asked three doctors (two radiotherapists and one oncologist) to independently vote for the best among four style transfer methods: pix2pix, CycleGAN, U-GAT-IT and CyTran. The doctors evaluated a total of 200 cases, randomly picked from the test set. We selected 50 cases for each of the four contrast pairs. The annotators were instructed to analyze the translated images in order to observe structural deformations, the correctness of contrast change with respect to the target image, and the occurrence of visual artifacts with respect to the input CT image. During the annotation, we did not disclose the matching between models and translated images to the doctors. With each presented case, the translated images were randomly shuffled, so it would be impossible for the doctors to know which translation method produced a certain image. As evaluation measures, we report the number of votes and the corresponding percentage for each method.

**3) Data preprocessing:** To avoid working with high values and ensure the stable training of deep learning models, we shifted the raw voxel values to the HU scale by subtracting the intercept, and we divided the resulting values by 1000. We apply this preprocessing for all the models, including the baselines.

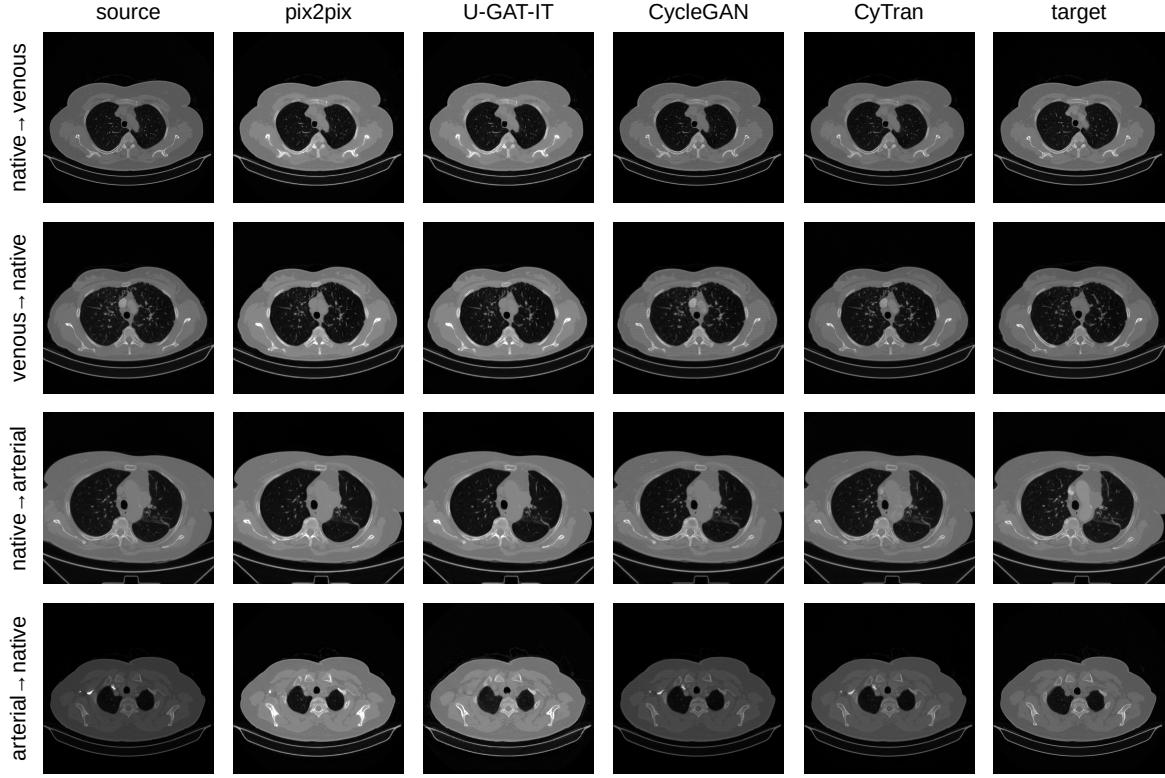
**4) Hyperparameter tuning:** We train all generative models from scratch using Adam [52] for 70 epochs, on mini-batches of two examples. For the baseline methods, we set

all hyperparameters as indicated by the authors introducing the respective models [4], [10], [11]. For our approach, we set the learning rate to  $10^{-4}$ , keeping the default values for the other parameters of Adam. Following Zhu *et al.* [4], we set the weight that controls the importance of cycle-consistency in Equation (3) to  $\lambda = 1$ . We provide the code to reproduce our results at: <https://github.com/ristea/cycle-transformer.git>.

**5) Quantitative results:** We conducted style transfer experiments on four contrast pairs, comparing our approach against three state-of-the-art methods and the *no-transfer* baseline. The corresponding results are shown in Table II. First of all, we observe that CyTran is the only approach that consistently surpasses the *no-transfer* baseline across all contrast pairs and evaluation metrics. For instance, our approach is the only one able to surpass the *no-transfer* baseline for the arterial→native transfer. Although pix2pix [10] can leverage the paired nature of the data set, it seems to produce the lowest performance levels, being surpassed by CycleGAN [4], U-GAT-IT [11] and CyTran. All in all, our method attains the highest performance levels in each and every experiment, always outperforming the baselines. This conclusion supports our conjecture that CyTran is a more suitable method for style transfer between contrast and non-contrast CT images.

**6) Subjective human evaluation results:** While the MAE, RMSE and SSIM metrics show that our method is the clear winner, the performance improvements with respect to the second-best model seem rather small. To better assess the performance differences among the generative models, we turn our attention to the subjective evaluation study based on the annotations (votes) provided by three independent doctors. The corresponding results are presented in Table III.

The study shows that our approach was voted as the winner by all three doctors, in all style transfer experiments.



**Fig. 4:** Examples of images translated by pix2pix, U-GAT-IT, CycleGAN and CyTran, respectively. The input (source) and target images are displayed for reference.

Remarkably, even if the doctors did not know which method produced which image, CyTran gathered more than 50% of the votes from each doctor. The lowest percentage recorded by CyTran is for Doctor #1, who rated our solution as being the most convenient in 113 of 200 (56.5%) cases. Still, CyTran outperforms CycleGAN, the second-best model, by a considerable margin of 37.5%. Doctor #3 was most favorable towards our model, voting for CyTran in 152 of 200 (76%) cases. In contrast, U-GAT-IT, the second-best model in opinion of Doctor #3, obtained only 20 of 200 (10%) votes. In conclusion, all doctors agree that CyTran is significantly better than the other state-of-the-art translation models.

**7) Qualitative analysis:** In Figure 4, we present a randomly-sampled case for each of the four contrast pairs. We observe that pix2pix suffers from visual artifacts such as discontinuity in the scapula or erasure of the cortex of the rib, as seen in the native→arterial translation. Moreover, soft tissues have an increase in noise and there is no additional useful information regarding the vessel contrast. When converting from arterial to native using pix2pix, the structure appears severely altered: the rib is completely dissociated, muscle margins are modified, vessel differentiation is difficult. Similar to the pix2pix method, U-GAT-IT creates a false warping aura around the bones. The quality of the pulmonary parenchyma is not significantly altered and the appearance of the vessels and soft tissues are harder to differentiate. CycleGAN increases noise especially around high contrast areas, as seen in the native→arterial translation. The soft tissues adjacent to bony structure, such as the scapula or the ribs, have a halo of structural deformation. This method also creates a grid-like

texture on top of the CT image, which distorts both the structural integrity and increases the number of visual artifacts. In contrast, CyTran does not suffer from loss of information regarding the structures, tissue consistency and margins, as seen in the venous→native translation of the right breast tumor. The true benefit of CyTran lies in the conversion from native CT scans into generated arterial or venous CT scans, because of the fair amount of information acquired with respect to the native image, even if the vessels do not get as bright as in the reference image.

### B. Volumetric Registration Experiments

**1) Baselines:** As baselines, we consider three state-of-the-art unsupervised medical image registration methods: a 1-cascade Volume Tweening Network (VTN) [38], a 3-cascade VTN [38], and ViT-V-Net [33].

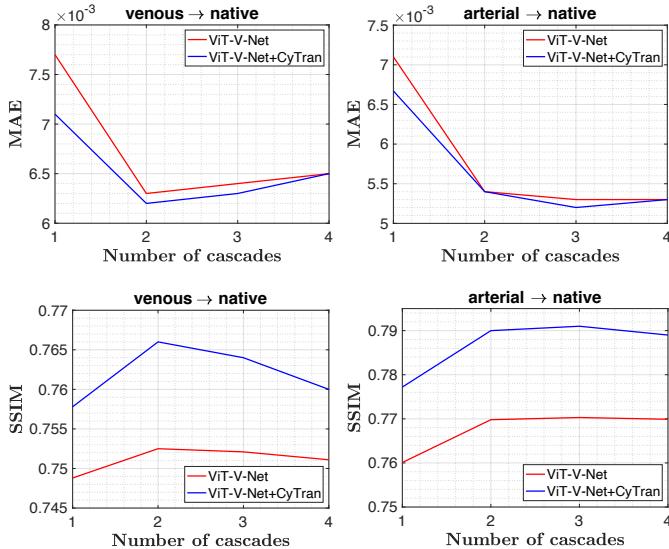
**2) Performance measures:** Since our data set does not contain any labeled segmentation maps, we consider performance measures suitable for evaluating unsupervised registration methods, which quantify the ability to align moving structures, without damaging the integrity of CT scans. Therefore, we report the MAE and SSIM between the warped scan (the alignment result) and the reference scan.

**3) Data preprocessing:** We apply the same data preprocessing steps as for the style transfer experiments.

**4) Hyperparameter tuning:** We train all networks from scratch with the hyperparameters indicated by the authors of cascaded VTNs [38] and ViT-V-Net [33], except for the mini-batch size, which we reduce to two data samples such that we can train each model on a single GPU.

**TABLE IV:** Volumetric registration results for the venous→native and arterial→native contrast pairs. Our model is compared with several state-of-the-art methods and ablated versions of itself on the test set, in terms of MAE and SSIM. The symbol  $\uparrow$  means higher values are better, while  $\downarrow$  means lower values are better. The best results are highlighted in bold.

Method	venous→native		arterial→native	
	MAE $\downarrow$	SSIM $\uparrow$	MAE $\downarrow$	SSIM $\uparrow$
1-cascade VTN [38]	0.0098	0.6883	0.0094	0.6894
3-cascade VTN [38]	0.0083	0.7010	0.0081	0.7041
ViT-V-Net [33]	0.0077	0.7488	0.0071	0.7601
ViT-V-Net+pix2pix [10]	0.0093	0.7210	0.0090	0.7312
ViT-V-Net+U-GAT-IT [11]	0.0074	0.7501	0.0070	0.7602
ViT-V-Net+CycleGAN [4]	0.0075	0.7498	0.0069	0.7641
ViT-V-Net+CyTran (ours)	0.0071	0.7578	0.0066	0.7772
3-cascade ViT-V-Net (ours)	0.0064	0.7521	0.0053	0.7703
3-cascade ViT-V-Net+CyTran (ours)	<b>0.0063</b>	<b>0.7640</b>	<b>0.0052</b>	<b>0.7910</b>



**Fig. 5:** Results for cascaded ViT-V-Net [33] and ViT-V-Net+CyTran models with various cascade steps. Models without recursive cascade are equivalent to models with one cascade step.

For our approach, we introduce two hyperparameters: the augmentation rate and the number of cascade steps. The augmentation rate represents the percentage of training data processed with a style transfer method and added to training set. We consider augmentation rates ranging from 10% to 100%, at a set of 10%. For the number of cascade steps, we consider all values between 1 and 4. We tune these hyperparameters on the validation set, reporting the test results for the optimal configuration found on the validation set.

**5) Quantitative results:** In Table IV, we present the comparative results between our 3-cascade ViT-V-Net framework trained on images translated by CyTran and the three state-of-the-art methods based on cascaded VTNs [38] and ViT-V-Net [33]. In addition, we show ablation results obtained by removing either the cascade or CyTran from our model. We also report results for the ViT-V-Net model trained on

images translated by our competitors: pix2pix, U-GAT-IT and CycleGAN.

First, we observe that training ViT-V-Net on images translated by pix2pix [10] damages performance, leading to worse results for both venous→native and arterial→native pairs, in comparison with vanilla ViT-V-Net [33]. In contrast, U-GAT-IT [11], CycleGAN [4] and CyTran bring performance gains, indicating that our idea of transferring the style of source CT scans to target CT scans before registration is useful. Among these three models, CyTran gives the highest performance gains, once again showing its superiority over pix2pix, U-GAT-IT and CycleGAN.

Interestingly, our idea of introducing ViT-V-Net in a recursive cascade is also useful. This observation is confirmed by the fact that the 3-cascade ViT-V-Net outperforms ViT-V-Net, as well as the fact that the 3-cascade ViT-V-Net+CyTran outperforms ViT-V-Net+CyTran. To further confirm our observation, we present results for ViT-V-Net and ViT-V-Net+CyTran with various numbers of cascade steps in Figure 5. We observe that having more than one cascade brings considerable improvements over the baselines. For both approaches, the highest gains are obtained with 3 cascades for the arterial→native pair, and 2 cascades for the venous→native pair.

In summary, the empirical results show that our recursive cascaded ViT-V-Net based on CyTran style transfer is the best approach for non-contrast to contrast CT scan registration, surpassing all baselines and ablated models.

## VII. CONCLUSIONS

In this paper, we introduced cycle-consistent convolutional transformers in medical imaging. We employed our approach to transfer the style between contrast and non-contrast CT scans, showing that it outperforms state-of-the-art methods such as pix2pix, U-GAT-IT and CylenGAN. Moreover, we showed that CyTran brings significant improvements for a state-of-the-art medical image registration method. An important contribution of our work is Coltea-Lung-CT-100W, a new data set of triphasic CT scans comprising a total of 37,290 images. In future work, we aim to apply our registration results to improve multi-image super-resolution and lesion segmentation.

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