

1 CycleGAN for style transfer in X-ray angiography

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4
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6 Abstract

7 *Purpose* We aim to perform generation of angiograms for various vascular struc-
8 tures as a mean of data augmentation in learning tasks. The task is to enhance
9 the realism of vessels images generated from an anatomically-realistic cardio-
10 respiratory simulator to make them look like real angiographies.

11 *Methods* The enhancement is performed by applying the CycleGAN deep network
12 for transferring the style of real angiograms acquired during percutaneous inter-
13 ventions into a data set composed of realistically simulated arteries.

14 *Results* The cycle-consistency was evaluated by comparing an input simulated
15 image with the one obtained after two cycles of image translation. An average
16 structural similarity (SSIM) of 0.948 on our data sets has been obtained. The ves-
17 sel preservation was measured by comparing segmentations of an input image and
18 its corresponding enhanced image using Dice coefficient.

19 *Conclusions* We proposed an application of the CycleGAN deep network for en-
20 hancing the artificial data as an alternative to classical data augmentation tech-
21 niques for medical applications, particularly focused on angiogram generation. We
22 discussed success and failure cases, explaining conditions for the realistic data aug-
23 mentation which respects both the complex physiology of arteries and the various
24 patterns and textures generated by X-ray angiography.

25 1 Introduction

26 Deep learning methods have quickly gained acceptance in the field of medical
27 image analysis. However, in order to provide satisfying results, machine learning

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1 techniques require a large amount of significant data. In the medical community,
 2 it is difficult to obtain medical data for a number of reasons. First of all, the large
 3 resource needed to collect and manage a database is a major hurdle. Secondly,
 4 obtaining expert annotations of imaging data for supervised and semi-supervised
 5 learning is a rather expensive and time-consuming process. Thirdly, legal consider-
 6 ations regulate the sharing of medical data, which varies from country to country
 7 and are subject to ethical committees and patient’s approval.

8 For natural images research, data augmentation is widely used to increase the
 9 number of samples. However, standard data augmentation (mainly data warp-
 10 ing) should be used with caution in a medical context. Indeed, in the case of
 11 angiographies, vessels must not be unrealistically wide or narrow, as structural
 12 and anatomical information could be used for further analysis and diagnosis of a
 13 patient [7]. This is achieved by regulating the maximum amounts of translation,
 14 rotation and non-rigid deformation applied to obtain plausible physical variations
 15 of the medical images [11]. However, this often comes down as a lengthy and costly
 16 process that requires a medical expert’s intervention.

17 In this paper, we are proposing a new approach to address the problem of
 18 an insufficient amount of training data in medical image analysis applications,
 19 such as vessel segmentation, detection, and classification from X-ray angiography.
 20 Such method has already been proven successful for the enhancement of realism
 21 of synthetic eye images [13], where the authors show an improvement of learning
 22 accuracy. We propose a solution of the given problem by applying CycleGAN [15]
 23 to perform a style transfer from real images obtained using X-ray based techniques
 24 to artificial images generated by the simulator [12] (Figure 1). The proposed ap-
 25 proach has the potential to become a more affordable and convenient way of gener-
 26 ating more training data while conserving the anatomical integrity of arteries and
 27 realistic X-ray patterns. Furthermore, because the generation process is entirely
 28 controlled, the annotations of those images can also be easily generated.

29 The contributions of this work are the following:

- 30 1. Proposition of an anatomy-based data-augmentation technique for X-ray an-
 31 giography.
- 32 2. Evaluation of the CycleGAN method for images containing low contrast and
 33 a high amount of noise.

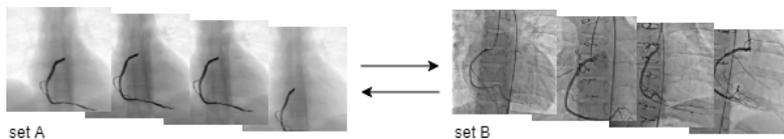


Fig. 1 Image translation between two domains: simulated data (set A) and real angiograms (set B).

2 Related work

2.1 Standard data augmentation

Deep learning approaches require a large amount of data to train a model that not only provides good results on the test at hand but also avoids over-fitting. However, many domains, such as medical imaging, suffer from a shortage of data. A common approach is to take a smaller but labeled data set and augment it in a way that improves the effectiveness of models [9]. Amongst them, image augmentation [4, 5, 8, 14] and data augmentation guided by expert knowledge [14] are some of the most popular techniques. The most generic approach for image augmentation is data warping. It consists of performing geometric transformations such as translation, reflection, and cropping, as well as changing its color scheme.

In [4] elastic deformations are the main source of variation in mammography at a lesion level. In [5, 28] data warping is used to obtain more data samples of fundus images depicting retinal blood vessels for further segmentation. Same is applied in [8] for augmenting datasets of brain tumors. Tumors do not have a definite shape and therefore may exhibit large spatial and structural variability, which is not the case for other objects, such as heart vessels which have definite unchangeable structure.

In [14] geometric and color augmentation is combined with specialist knowledge about skin lesion symmetry (anti-symmetry). Lesion segmentation is approximated to ellipse whose axes are then used for controlling varied distortions of the original lesion sample. The segmentation mask is used so that symmetry is preserved and further classification of lesions could be done.

2.2 GAN-based methods for data augmentation

Another approach is to synthesize new data using generative adversarial networks (GANs) [2]. The idea is to use two competing neural networks: a generator and a discriminator (or adversary). A generator is generating a sample learning from the distribution of training data. A discriminator is evaluating how similar is the output of the generator to true data samples, by calculating the adversarial loss and acting like a two-class classifier: generated image either belongs to a target distribution or it does not. For medical image synthesis, GANs have become a more generic solution [45] as they allow creating more variety of data (appearance of a specific pathology, different imaging protocols) comparing to traditional data augmentation. GAN-based methods include unconditional and conditional medical image synthesis.

The first group of methods implies that image is generated from noise without any additional information. Liver lesions [16], lung nodules [1], and brain MR images [17] generation are some of many successful cases. In [29], unconditional GANs are used for obtaining synthetic fundus patches to obtain more data for segmentation task.

The second group (conditional GANs) are methods where additional information is provided to generate images with desired properties. An image is the most common condition used for such supervision, which was first offered in “pix2pix” framework [3]. The task of mapping is done using paired examples for training

1 when every image from a source domain A has a corresponding pair from a target
2 domain B . During training, a generator takes an input image, $realA$ and tries to
3 map it to target domain B , measuring success by comparing a generated image,
4 $fakeB$, to ground truth, $realB$, which serves as a strict condition. Successful appli-
5 cations of conditional GANs for vessels include those for synthesizing retinal fundus
6 images, all using vessel map as conditional information for generator [18–21].
7 In [22] a task of generating synthetic X-rays of the lumbar spine is tackled using
8 conversion from sagittal to coronal radiographic projections of the trunk.

9 2.3 Data augmentation for vessels

10 Mentioned applications of both standard and GAN-based approaches for data
11 augmentation of vessels images come down to tasks done on publicly available
12 datasets: retinal fundus imaging (datasets DRIVE [23], STARE on which most
13 of the vessels computer vision tasks are trained and tested so far); lung vessels
14 CT imaging (VESSEL12 challenge [24] for vessel segmentation); coronary arteries
15 (CAVAREV [25], CoronARe challenge [26] for 3-D reconstruction, this dataset has
16 projections of thorax with left coronary tree only; IVUS dataset [27] of ultrasound
17 images for vessel segmentation). In recent work [30], cerebral vasculatures data is
18 synthesized and coupled with real clinical data to achieve a state-of-the-art perfor-
19 mance of a deep learning model. To our best knowledge, there are no solutions for
20 tackling the problem of insufficient data when it comes to computation of biophys-
21 ical measurements in pediatric interventional cardiology where a little amount of
22 data is available. With this work, we, therefore, want to start closing this gap and
23 initiate further research into generating cardiac angiography data.

24 2.4 Enhancing realism of angiograms

25 While standard data augmentation techniques imply producing more data by
26 warping given samples to achieve variety, our idea is to first simulate varied cardiac
27 angiograms and then to enhance them for obtaining realistic images. This puts our
28 approach closer to GAN-based methods which allow generating data with addi-
29 tional conditions. For our work, we wish to generate realistic images from simulated
30 images, where the vessel’s geometry is properly preserved, while also introducing
31 radiographic noise and angiography-related artifacts. An input image is artificial
32 data and an output image is realistic-looking data.

33 This modification can be interpreted as an image-to-image translation task and
34 is a core of many cross-modality image synthesis applications of GANs. Some of
35 them require paired data, like in the “pix2pix” framework [3]: PET (positron emis-
36 sion tomography) to MR (magnetic resonance) translation of brain images [31], T1-
37 and T2-weighted MRI to MRA (magnetic resonance angiography) translation of
38 brain images [32], CT (computed tomography) to PET translation of thorax [33]
39 and liver images [34]. Paired data is obtained by co-registering different image
40 modalities.

41 We want to avoid expensive and time-consuming labeling. Frameworks like
42 CycleGAN [15] and similar methods [35, 36] relax this labeling constrain. Cycle-
43 GAN does not use any labeled examples and instead of building image-to-image

1 mapping, creates a translation between domains. In order to maintain a meaning-
 2 ful mapping between images from source and target domains, a second GAN is
 3 introduced which maps an output of the first generator back to the original input.
 4 The intuition behind this is similar to language translation: to check whether a
 5 French sentence has been correctly translated to Spanish we can translate it back
 6 to French and compare with the initial sentence to evaluate the "quality" of the
 7 translation. In CycleGAN model (Figure 2), this role is performed by an addi-
 8 tional component in the loss function called cycle-consistency-loss, which ensures
 9 forward and backward cycle consistencies:

$$L_{cyc}(G, D_A, B, A) = E_{a \sim p_{data}(a)}[|F(G(a)) - a|_1] + E_{b \sim p_{data}(b)}[|G(F(b)) - b|_1].$$

10 Other two components are adversarial losses for two generators. Thus, the
 11 objective of CycleGAN includes three losses: adversarial loss for the first generator,
 12 adversarial loss for the second generator and cycle-consistency loss.

$$L(G, F, D_A, D_B) = L_{GAN_1} + L_{GAN_2} + \lambda_{cyc}(G, D_A, B, A),$$

13 where λ controls the relative importance of the objectives.

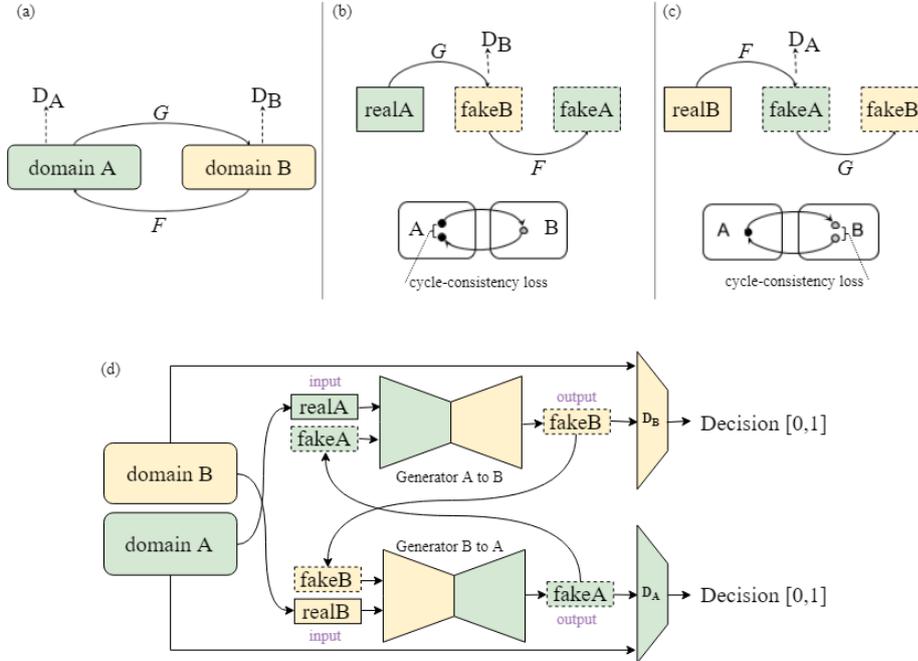


Fig. 2 (a) CycleGAN model contains two mapping functions $G: A \rightarrow B$ and $F: B \rightarrow A$, and associated adversarial discriminators D_B and D_A . D_B encourages G to translate A into outputs indistinguishable from domain B , and vice versa for F . (b) forward cycle-consistency loss: for each image from the domain A : $realA \rightarrow fakeB = G(realA) \rightarrow fakeA = F(G(realA)) \approx realA$; (c) backward cycle-consistency loss: for each image from domain B : $realB \rightarrow fakeA = F(realB) \rightarrow fakeB = G(F(realB)) \approx realB$. (d) CycleGAN architecture which includes two generator and two discriminator neural networks.

1 CycleGAN framework, within the last years, became already widely used for
 2 various cross-modality translations tasks, such as: MR to CT translation of my-
 3 ocardium [37], cardio-vascular volumes [38], musculoskeletal [39], brain [40] im-
 4 ages; T1 to T2 translation of brain images [41–43]; Real to Synthetic translation
 5 of endoscopy images for monocular depth estimation [44].

6 Theoretical ability to do cross-domain translations in an unsupervised fashion,
 7 empirical proofs of accomplishing this task for various medical image applications
 8 encouraged us to refer to CycleGAN model. We, therefore, have an objective of
 9 expanding the quality of simulated cardiac angiography data by enhancing its
 10 realism using CycleGAN framework.

11 3 Methodology

12 3.1 Data description

13 X-ray angiography sequences - or angiograms, are two-dimensional X-ray moving
 14 sequences. They are used in percutaneous interventions for the treatment of vas-
 15 cular disease. 2D X-ray angiography allows for the visualization of the arteries in
 16 real-time during the intervention [7] and the guidance of catheters.

17 **Data acquisition.** The angiographies used in our proposed work were ac-
 18 quired from different patients with congenital heart disease from the Sainte-Justine’s
 19 Hospital (Montreal, Canada). These data were collected offline and anonymized
 20 after approval by the Sainte-Justine’s Institutional Ethics Review Board. The an-
 21 giograms were acquired by a C-arm Infinix-CFI BP (Toshiba Medical). Samples
 22 are given in Figure 3. The angiograms comprise different vascular structures such
 23 as pulmonary, aorta, right coronary artery (RCA) and left coronary artery (LCA).

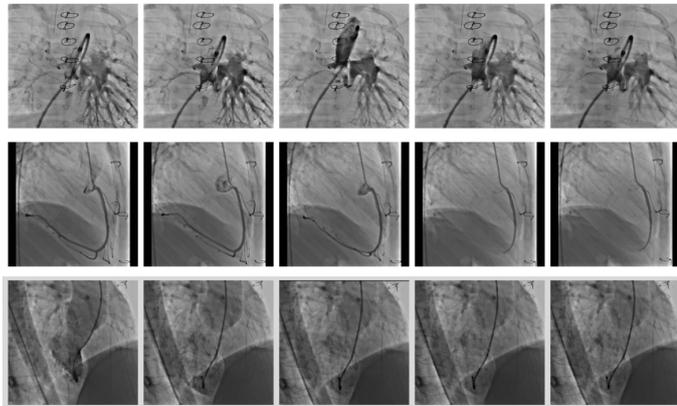


Fig. 3 Examples of angiograms (5 frames of each sequence only).

24 **Grouping the data.** To prove the proposed approach works, we needed to
 25 experiment first with smaller data sets, separating X-ray scans of different vessels.
 26 Thus, we grouped all angiography sequences into two categories: RCA and LCA.
 27 Frames of different sequences of each category can be seen in Figure 4.

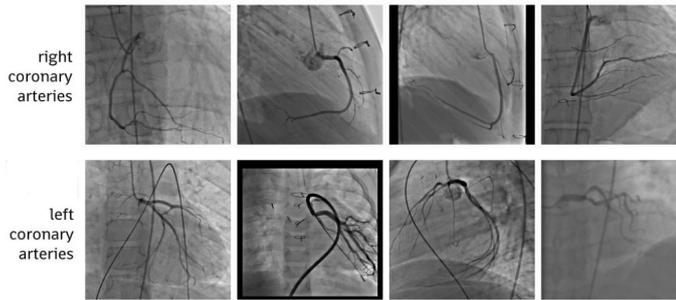


Fig. 4 Result of grouping angiographies into two different categories (4 randomly selected frames of each category only): right coronary arteries, left coronary arteries.

1 **Analyzing the data.** X-ray angiography is known for different imaging ar-
 2 tifacts. Some sequences depict sternal sutures which means the patient had pre-
 3 vious operations. While this can alter the result of segmentation, for our goal
 4 it is a realistic-looking-data style we want to achieve. We can see guiding wires
 5 and catheter as these are tools used during catheterization to introduce the con-
 6 trast agent. Visibility of vessels depends on the diffusion of the contrast agent
 7 in the blood flow. Therefore, the vessels are not always entirely visible on the
 8 angiograms [7]. This results in many *empty* frames containing only background
 9 information which are not useful for our applications. Hence, we removed these
 10 frames from sequences.

11 3.2 Simulating artificial data

12 The data domain set is composed of artificial data which we want to modify in
 13 order to make it look like the target domain, i.e. real angiograms.

14 **XCAT simulator.** Artificial images were obtained using *XCAT 2.0* motion
 15 simulator [12]. It is a CT simulation tool based on the 4D extended cardiac-torso
 16 phantom, a whole-body computer model of the human anatomy and physiology
 17 based on NURBS surfaces. XCAT provides an accurate representation of the com-
 18 plex human anatomy and has the advantage, that the shape of its organs can
 19 be altered to realistically model anatomical variations and patient motion [12].
 20 Those biological constraints make this tool particularly adapted to our process
 21 of obtaining more realistic data. Using XCAT, we obtained projection images of
 22 different vessel types. They already can be directly used as training data e.g. for
 23 segmentation and reconstruction tasks [6]. However, despite realistic anatomy, the
 24 textures of projections are still not realistic enough and a learning model trained
 25 solely on simulated data might fail when applied to real data during validation or
 26 testing, given all the artifacts present in real data which the simulator does not
 27 create.

28 **Simulator parameters.** The main advantage of XCAT is its ability to sim-
 29 ulate anatomically diverse patient models as we choose the gender of a patient,
 30 indicate whether a patient is healthy or has any (e.g. heart) lesions, change the
 31 motion mode (respiratory, cardiac motion, or both), etc. For our proposed work,
 32 we used only one set of parameters (default), as the calculation of CT projections

1 is time-consuming due to mathematical complexities behind the simulator [12].
 2 Apart from the simulator parameters, we can modify the projection parameters
 3 which affect the acquisition process, e.g. the angle of projection. Even though the
 4 shape of the vessel is preserved when rotating, the final images will serve as com-
 5 pletely different samples for training any model. Examples of simulated images are
 6 presented in Figure 5.

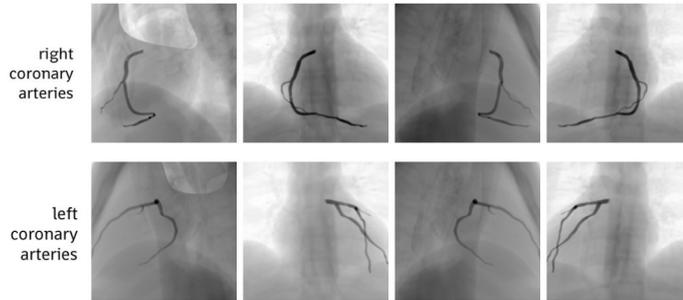


Fig. 5 Examples of simulated images of two vessel types: first frames of right coronary arteries and left coronary arteries sequences, with different angiographic views (lateral, cranial,caudal,left anterior oblique, right anterior oblique).

7 3.3 Data sets and training details

8 The CycleGAN framework requires two data sets: set A and set B . In our case, set
 9 A , or source domain, is the artificial data from the simulator and set B , or target
 10 domain, is real, clinical, data.

11 We formed small data sets by grouping together sequences of real data com-
 12 prising up to three angiographic view projections, and sequences of artificial data
 13 from similar views, e.g. 0-40 degree angulation for RCA and 0-20 degree angulation
 14 for LCA. As we can see in Figures 4 and 5, real and simulated images have many
 15 differences in textures. Additionally, real data contain specific structures such as
 16 catheters, wires, balloons, and stents unseen in simulations. We limited our data
 17 sets by choosing RCA and LCA with fewer objects in images. We first grouped
 18 together training data: $trainA$, $trainB$, and then selected a few images from each
 19 of the sets as testing data: $testA$ and $testB$ accordingly, and removed them from
 20 training data. RCA data set: the training set size was 130 for simulated, 154 for
 21 real data. LCA data set: 138 for simulated, 16 for real.

22 We used the implementation of CycleGAN by X. Hu ¹. All the networks were
 23 trained from scratch with a learning rate of 0.0002. The weight for the cycle
 24 consistency loss λ was 20 for RCA and 30 for LCA (default is 10). Each model
 25 was trained for 200 epochs. After every 10 epochs, we launched the testing phase,
 26 i.e. translating of testing images into real style and back, and saved the results.

¹ Xiaowei Hu, "Tensorflow implementation for learning an image-to-image translation with-
 out input-output pairs", <https://github.com/XHUJOY/CycleGAN-tensorflow>, 2017

1 4 Results and discussion

2 4.1 Visual examination

3 Based on the convergence of losses, we chose the optimal number of epochs for
 4 training each model: for RCA it was 50, for LCA it was 160 epochs. Each model
 5 was still trained for 200 epochs (Figure 6) for further analysis of how this and
 6 other hyper-parameters (e.g. λ coefficient) are influencing training.

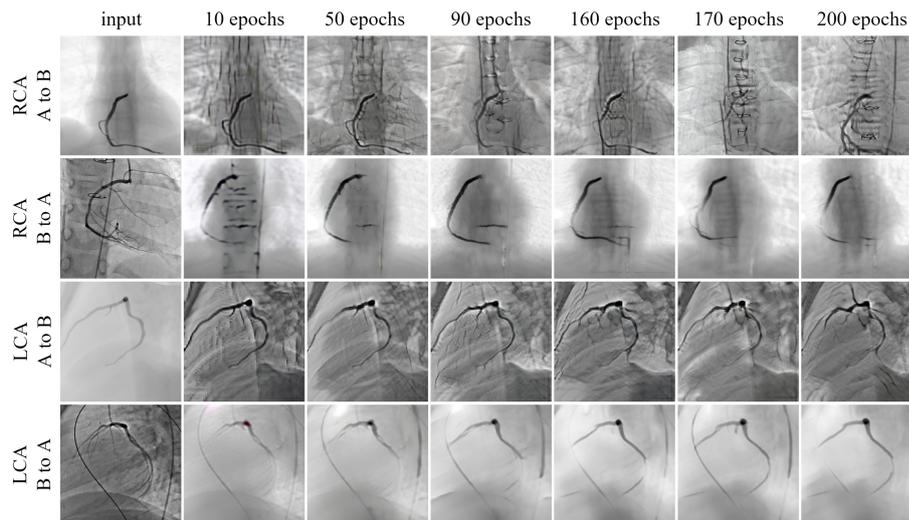


Fig. 6 Results of tests after different number of epochs.

7 Firstly, we observe that the longer the training is, the better is the quality of
 8 output images, i.e. they are more smooth and don't have chalkboard artifacts like
 9 outputs on early stages of training (Figure 7).

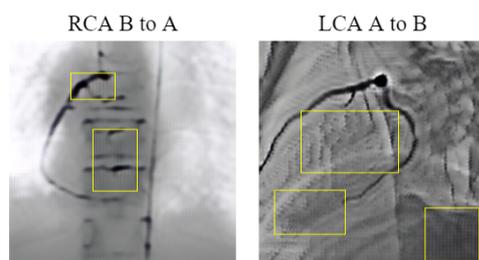


Fig. 7 Chalkboard artifacts that are especially visible on images produced by models trained for a small amount of epochs.

10 Furthermore, we see that over the time of training the RCA model starts
 11 deforming vessel shapes, while LCA model displays only slight distortion. This is

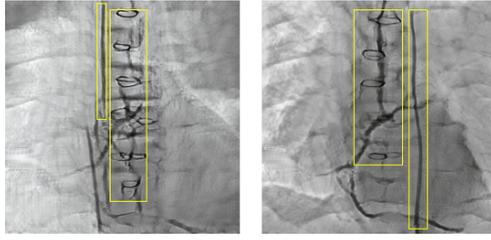


Fig. 8 Clinical objects that are visible in the later RCA results: models trained for 150 and 170 epochs. Highlighted are wires and catheters generated by CycleGAN trained on RCA dataset.

1 due to λ which is a key hyperparameter for preserving the structure of vessels.
 2 A small λ would fail to prevent big distortions, while a too large value would
 3 suppress fine details in the resulting image. Additionally, we see more various
 4 clinical objects, such as catheters and wires (Figure 8), appearing in RCA results
 5 (even if a vessel shape itself may get deformed). This is possible because the number
 6 of available training images from domain B (real angiographies) is much larger for
 7 RCA data set than the one for LCA (154 against 16). Therefore, the more variety
 8 in training data, the more variety is possible in resulting images (given, domains
 9 are still corresponding).

10 We observe that CycleGAN model is able to transfer radiographic noise and
 11 texture of real X-ray angiography images onto simulated ones, often together with
 12 additional clinical objects (if they are present in training data). Quality of transla-
 13 tion depends on the amount of training data available, the number of epochs and
 14 λ weight of cycle-consistency loss.

15 4.2 Quantitative evaluation

16 Quantitative evaluation of generative models is often a challenging task, especially
 17 when experimental setting doesn't imply having ground truth images for testing
 18 and validation. So, for analyzing the performance of our model beyond the vi-
 19 sual judgments, we utilized two ideas: cycle-consistency and vessel segmentation
 20 (Figure 9).

21 During its training, CycleGAN model is using cycle-consistency loss as the dif-
 22 ference between *realA* and *fakeA* which it aims to minimize. To evaluate quanti-
 23 tatively and show which level of cycle consistency our model reached, we measured
 24 the similarity between input images and output images after one cycle of trans-
 25 lations, as shown in Figure 9. We used NRMSE (normalized root mean squared
 26 error), SSIM (structure similarity), and PSNR (peak signal-to-noise ratio) met-
 27 rics, which are the most common metrics for measuring image similarity. Results
 28 are given in Table 1. According to all the metrics, RCA performs better at A to
 29 B translation than LCA, having lower error (average of 0.029), higher structural
 30 similarity (average of 0.960) and higher PSNR value (31.303). LCA, on the other
 31 hand, has the highest error (0.27) while for other models this metric is almost
 32 equal to 0.1 (and even less, 0.03, for RCA).

33 Second criteria we used for quantitative evaluation of the obtained model is
 34 segmentation of input and output images to measure how well vessel shapes are

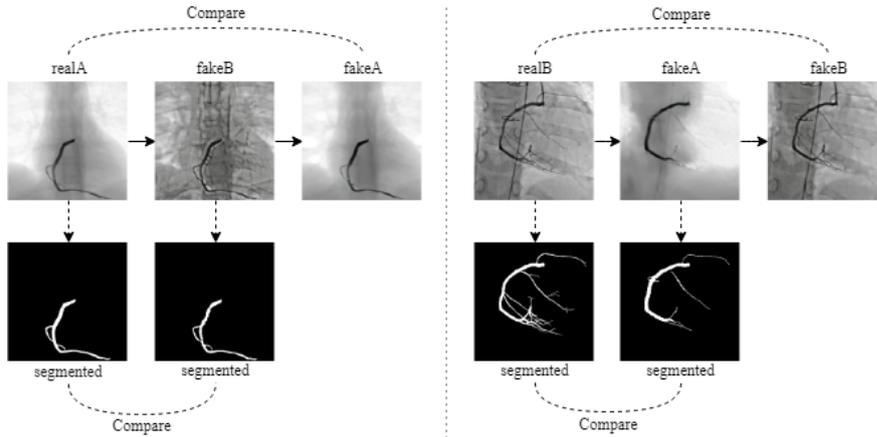


Fig. 9 Visual representation of our evaluation approach. (a) in translation $A \rightarrow B \rightarrow A$ we compare *simulated* (*realA*) with *fake_simulated* (*fakeA*) images for measuring cycle consistency, and compare segmented *simulated* (*realA*) with segmented *enhanced* (*fakeB*) images for measuring shape preservation; (b) vice versa for translation $B \rightarrow A \rightarrow B$

DATASET and translation direction	NRMSE		SSIM		PSNR		DICE	
	mean	st.dev	mean	st.dev	mean	st.dev	mean	st.dev
RCA A->B	0,029	0,010	0,960	0,003	31,303	2,927	0,718	0,015
RCA B->A	0,088	0,028	0,738	0,018	21,960	2,787	0,589	0,032
LCA A->B	0,270	0,192	0,935	0,022	17,474	7,200	0,637	0,074
LCA B->A	0,085	0,008	0,761	0,007	21,486	0,795	0,454	0,030

Table 1 Different similarity metrics (NRMSE, SSIM, PSNR) for evaluation of cycle-consistency loss, and Dice scores for evaluation of vessel preservation given for each data set and each translation direction.

1 preserved (Figure 9). First, manual segmentation of vessels was done for input
 2 testing images and corresponding output images produced by CycleGAN (with
 3 the white color marking vessels, and black color marking background). Then, an
 4 overlap of obtained binary images was calculated using the Dice metric. Results of
 5 segmentation evaluation are presented in Table 1 (last column) and examples of
 6 segmentation are given in Figure 10. Both images of overlays and Dice scores values
 7 display that RCA and LCA models are performing better at A to B translation
 8 (RCA A to B, LCA A to B) than at the opposite one. In the enhanced images,
 9 original physiology of vessels is preserved, though their shapes seem to be slightly
 10 thinner which have caused Dice scores to be 0.718 and 0.637 for RCA and LCA
 11 data sets, respectively.

12 *Recommendations.* Based on the different results explored above, authors ad-
 13 vise to take into consideration the following:

- 14 1. Sizes of training sets for GANs. The number of 100-150 real images should be
 15 sufficient for training a good model, while a small number (10-50) may lead to
 16 slow convergence and overfitting.
- 17 2. Weight of the cycle-consistency component in the loss function (λ). A large λ
 18 (e.g. 30) suppresses fine details as well as extra variations in the resulting image,
 19 while a too small value (e.g. 10) fails to prevent deformations. An average value
 20 (e.g. 20, as used for RCA data set) should be optimal for our task.

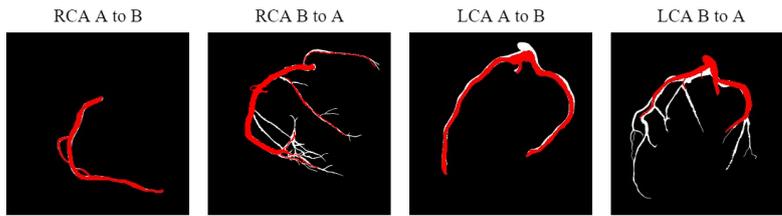


Fig. 10 Segmented images overlaid on top of each other for visual comparison. White color marks segmentations of original input images, and red color marks segmentations of images produced by CycleGAN.

- 1 3. Number of epochs. As we see on Figure 6, the more epochs we train our model
- 2 with, the fewer image artifacts we obtain (chalkboard ones, white spots, found
- 3 at early stages), but the more overfitting to a training set our models are.
- 4 Providing this, we recommend evaluating results obtained after a different
- 5 number of epochs to choose the best model for further style transfer.

6 5 Conclusions and future works

7 We introduced a new application of unsupervised image translation for generat-
 8 ing realistic-looking angiograms from simulated ones. Our approach can be used
 9 with the purpose of obtaining more data for training and evaluating medical im-
 10 age processing methods for vessels specifically. We used CycleGAN and tuned its
 11 parameters to achieve the best results for RCA and LCA data sets.

12 *One of the promising applications of our pipeline is generating more data and*
 13 *compiling it into a public dataset of coronary artery 2D images with corresponding*
 14 *annotation information.*

15 *Another application of the method is implementing a cross-modality translation*
 16 *but specifically for angiograms.* The objective is to train models that learn style
 17 (e.g. noise and artifacts distribution) specific to different acquisition systems so
 18 that available angiography data could be used together for training and testing of
 19 other learning models.

20 *Finally, results of B to A translation (real \rightarrow simulated) suggested another*
 21 *area of application: unsupervised vessel segmentation where source domain is real*
 22 *angiograms and target domain is segmentation masks of simulated images, which*
 23 *can be obtained by applying Hessian-based filters.*

24 Future works include experimenting with more data sets (other angiographic
 25 views, types of vessels i.e. aorta and pulmonary, bones, etc.); using obtained mod-
 26 els as pre-trained models for other data sets; keeping *empty* background frames in
 27 training data; adding catheters, wires as a style; improving evaluation of method
 28 by implementing a "real vs fake" perceptual study with human observers; training
 29 similar models with different modality vessel images and with segmented images.

30 Disclosure of potential conflicts of Interest

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33 Conflict of interest: The authors declare that they have no conflict of interest.
 34

Research involving Human Participants and/or Animals

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.

Informed consent

Informed consent: Informed consent was obtained from all individual participants included in the study.

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