Regularized Adversarial Training (RAT) for Robust Cellular Electron Cryo Tomograms Classification

Xindi Wu

Computational Biology Department
Carnegie Mellon University
Pittsburgh, USA
xindiw@andrew.cmu.edu

Yijun Mao

Institute of Artificial Intelligence and Robotics
Xi'an Jiaotong University
Xi'an, China
oraclemao@stu.xjtu.edu.cn

Haohan Wang

Language Technologies Institute
Carnegie Mellon University
Pittsburgh, USA
haohanw@cs.cmu.edu

Xiangrui Zeng

Computational Biology Department
Carnegie Mellon University
Pittsburgh, USA
xiangrui@andrew.cmu.edu

Xin Gao

Computational Bioscience Research Center
King Abdullah University of Science and Technology
Thuwal, Saudi Arabia
xin.gao@kaust.edu.sa

Eric P. Xing

Machine Learning Department
Carnegie Mellon University
Pittsburgh, USA
eping@cs.cmu.edu

Min Xu⁺

Computational Biology Department
Carnegie Mellon University
Pittsburgh, USA
mxu1@cs.cmu.edu

Abstract—Cellular Electron Cryo Tomography (CECT) 3D imaging has permitted biomedical community to study macromolecule structures inside single cells with deep learning approaches. Many deep learning-based methods have since been developed to classify macromolecule structures from tomograms with high accuracy. However, several recent studies have demonstrated the lack of robustness in these models against often-imperceptible, designed changes of input. Therefore, making existing subtomogram-classification models robust remains a serious challenge. In this paper, we study the robustness of the state-of-the-art subtomogram classifier on CECT images and propose a method called Regularized Adversarial Training (RAT) to defend the classifier against a wide range of designed threats. Our results show that RAT improves robustness for CECT image classification over the previous methods.

Index Terms—Cellular Electron Cryo Tomography, Classification, Robustness, Adversarial Training, Adversarial Attacks.

I. INTRODUCTION

A precise understanding of the structure and spatial organization of all macromolecules inside single cells is an essential step towards understanding macromolecule-governed cellular processes. Cellular Electron Cryo Tomography (CECT) [1], as an emerging technique, provides three-dimensional views of

macromolecules inside single cells in their native, frozen, hydrated state, thus, leading to an unprecedented era of applying statistical methods for systematic discovery of macromolecular structures. There are plenty of previous works devoted to separating structurally highly heterogeneous macromolecules captured by CECT data into structurally homogeneous subgroups, such as unsupervised subtomogram¹ [2]–[6] and deep learning based approaches for classification [7], [8].

Deep learning has become one of the most dominant classification methods, exhibiting impressive predictive performance in a variety of different biomedical applications [9]. Researchers nonetheless noticed an unsettling property of these deep models: a small perturbation of the sample may alter the prediction of a model dramatically [10], [11]. These perturbed examples are known as *adversarial examples* and the differences between original samples and adversarial examples may not even be perceivable to human [12]. This known vulnerability of neural networks may post serious robustness challenges of deep learning models in biomedical areas [13], [14], which naturally leads the follow-up questions such as whether these issues may affect the methods used on CECT data and how we can mitigate these issues if they exist.

In this paper, we first verify the vulnerability of the state-of-the-art deep learning models used on CECT data, then we propose a new efficient defense method called Regularized Adversarial Training (RAT) to improve the robustness of

⁺ Corresponding author.

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¹A *subtomogram* is a small cubic sub-image of a tomogram that contains a single macromolecule.

classifiers against adversarial examples, which the models have no knowledge of. Our experimental results show that our method improves robustness on an existing state-of-the-art subtomogram classification model and is consistently effective against a variety of differently generated adversarial examples. We compare our method with existing defense methods and observe the model trained with our method performs much better in both accuracy and robustness. In addition, we also explore how the regularization parameter in our method affects the performance of the model.

Our main contributions can be summarized as follows:

- We test the robustness of the current state-of-the-art deep learning methods for subtomogram classification, and reveal the vulnerability against adversarial examples.
- We propose a new method called Regularized Adversarial Training (RAT) that it can push the decision boundary, which is made by model from original training sample and adversarial training sample, away from the data while maximizing the natural accuracy during training.
- We show that our proposed method improves the robustness over the state-of-the-art model on subtomogram classification.

II. RELATED WORK

For a discussion of related work, we first introduce previous work for subtomogram classification; then, we briefly discuss related challenges in building robust models for biomedical applications; finally, we summarize the related topics for improving the adversarial robustness of general-purpose deep learning models, offering context for follow-up sections.

Subtomogram Classification Recently, unsupervised classification approaches for subtomograms have been developed [2], [3], [6] but have strictly limited computational scalability. In the work of [8], deep learning based methods have been applied to CECT images, and large-scale 3D subtomogram classification models such as DSRF3D-v2, RB3D, and CB3D have achieved solid results on subtomograms. However, we show that after applying adversarial attacks to cell images, they achieve only low classification accuracy.

Robust Biomedical Classification While deep learning has helped the models achieve unprecedentedly high prediction accuracy, the high-reliability requirement of biomedical application have created new challenges [15]. In particular, the heterogeneous nature of the biomedical data misleads the model to learn confounding factors rather than genuine signals [9]. Several solutions have been proposed to calibrate the learning process for deep learning methods in biomedical applications [16] or general vision applications [17], [18]. However, recent works have revealed the vulnerability of biomedical deep learning models towards delicately crafted adversarial examples [13], [14].

Adversarial Robustness of Deep Learning Ever since the discovery of adversarial examples [10], [11], the related research has progressed as a race between two groups: one group of researchers aims to deceive the model and invented powerful methods (known as *attack methods*) such as FGSM [11],

DeepFool [19], and many others [12], [20]–[24], while the other group aims to defend the model against the deception and proposed a wide range of methods (known as *defense methods*) [25]–[29]. For instance, Adversarial training [30] increases robustness using data augmentation for training data with adversarial examples. TRADES loss [31], which introduces regularization to loss function to push the decision boundary away from samples is another popular strategy to achieve robust learning system.

III. METHOD

In this section, we discuss the notation and current state-of-the-art model before introducing our proposed method.

A. Notation

Consider our subtomogram classification problem with the training set $\{\mathbf{x}_i, \mathbf{y}_i\}_{i=1}^N$ sampled from the distribution $\mathcal{D}$, where $\mathbf{x}_i$ denotes the i -th sample from subtomograms extracted from CECT images, $\mathbf{y}_i \in \{1, \dots, K\}$ is the label, N denotes the number of samples and K denotes the categories of labels. The network structure with parameters $\theta \in \mathbb{R}^p$ is denoted as $f(\mathbf{x}; \theta)$, and $f_l(\mathbf{x}; \theta)$ denotes the network $f(\mathbf{x}; \theta)$ but outputs the softmax instead of prediction. The loss function (e.g. cross-entropy) of the model on $(\mathbf{x}, \mathbf{y})$ corresponds to $\mathcal{L}(f(\mathbf{x}; \theta), \mathbf{y})$. A small adversarial perturbation is denoted by $\epsilon \in \mathbb{R}^d$. The adversarial sample is defined as $\mathbf{x}_{adv}$, while the perturbation is $\epsilon_1 = \mathbf{x}_{adv} - \mathbf{x}$ and $\epsilon_1 \in u_i$, where u_i represents the neighborhood of $\mathbf{x}$. Similarly, the perturbed adversarial sample generated by adding label-free perturbation to adversarial sample is defined as $\mathbf{x}'_{adv}$, while the perturbation is $\epsilon_2 = \mathbf{x}'_{adv} - \mathbf{x}_{adv}$ and $\epsilon_2 \in u'_i$, where u'_i represents the neighborhood of $\mathbf{x}_{adv}$. The ℓ_p norm for $1 \leq p < \infty$ of a vector $\mathbf{x}$ is denoted to be $\|\mathbf{x}\|_p = (\sum_{j=1}^d |\mathbf{x}_j|^p)^{1/p}$ and the ℓ_∞ norm is $\|\mathbf{x}\|_\infty = \max_i \{|\mathbf{x}_i|\}$. $\nabla_{\mathbf{x}} g(\mathbf{x}, \mathbf{y})$ is denoted to be the gradient of g with respect to the vector $\mathbf{x}$.

B. Convolution-based 3D Classification Model

Convolution-based 3D classification model (CB3D) [8] was proposed to achieve state-of-the-art deep learning based subtomogram classification performance. 3D CNN was used due to the structures of these macromolecules. We adopt CB3D model as the basic classifier module in our experiments. The CB3D network contains eight layers. The first two layers both have one 3D $3 \times 3 \times 3$ convolution layer with max pooling layer. The next three layers contain two 3D $3 \times 3 \times 3$ convolution layers with max pooling layer. The next two layers are fully connected layers and a softmax activation is appended to calculate the probabilities of each class. ReLU is applied as the activation function for all these layers except the last layer.

C. Regularized Adversarial Training (RAT)

Considerable efforts have been devoted to defense against adversarial samples, such as TRADES loss [31]. TRADES loss defines a loss function that contains two term: the natural loss encouraging the improvement of accuracy, and the robust loss encouraging the amelioration of robustness. However, directly

Fig. 1. A conceptual diagram of adversarial training subtomogram classification architecture. Note that those 2D-slice images are on behalf of 3D subtomograms. Also, the noise pattern is magnified 50 times in this picture in order to view it clearly in this conceptual diagram. This tomogram is from [32]

adopting TRADES loss seems not powerful enough to improve the robustness of the network as the effect of robust loss term, which can be regarded as a regularization, is limited by the requirement of accuracy and still faces the threat of overfitting. In order to make our model robust against various threats in addition to a wide variety of menacing attacks, inspired by adversarial training and TRADES loss, we propose a new defense method called Regularized Adversarial Training (RAT) which combines adversarial training and regularized discrepancy minimization to perform both high accuracy and strong robustness. Concretely, our method is in the form of

$$\min_{\mathbf{x}, \mathbf{y}} \mathbb{E}_{(\mathbf{x}, \mathbf{y}) \sim \mathcal{D}} \left(\max_{\mathbf{x}_{adv} \in \mathbb{B}(\mathbf{x}, \epsilon_1)} \left[\mathcal{L}(f(\mathbf{x}_{adv}; \theta); \mathbf{y}) + \gamma \max_{\mathbf{x}'_{adv} \in \mathbb{B}(\mathbf{x}_{adv}, \epsilon_2)} k(f_l(\mathbf{x}'_{adv}; \theta), f_l(\mathbf{x}_{adv}; \theta)) \right] \right), \quad (1)$$

where $k(\cdot, \cdot)$ is distance function and $\gamma > 0$ is the regularization parameter.

The first term in 1 mainly comes from adversarial training. The main idea of adversarial training is to increase the model's robustness using adversarial examples as the training data [33]–[35]. The classification model is trained on the adversarial distribution generated by projected gradient descent.

Following the most popular scheme, we use this objective:

$$\min_{\theta} \mathcal{L}(f(\mathbf{x}; \theta), \mathbf{y}) = \mathbb{E}_{(\mathbf{x}, \mathbf{y}) \sim \mathcal{D}} \min_{\theta} \left[\max_{\epsilon_1 \in u_i} \mathcal{L}(f(\mathbf{x} + \epsilon_1; \theta), \mathbf{y}) \right], \quad (2)$$

to formulate the aim of adversarial training. This objective function acts as an upper bound of the robust error. The main idea is to increase model's robustness by ensuring the model will predict the same class for perturbed examples as well as clean images. To be specific, we use Projected Gradient Descent (PGD) [23] to generate the perturbed examples.

For each batch of natural examples $\{\mathbf{x}_1, \dots, \mathbf{x}_m\}$, it starts from a random perturbation around the examples in a l^∞ ball around a data example as a seed and follows the gradient of

the current model weights regarding the input to generate a set of adversarial images $\{\mathbf{x}_{adv1}, \dots, \mathbf{x}_{advm}\}$ in each training iteration. The generation process comprises of several update process. The update rule can be formed as:

$$\mathbf{x}_{adv_{l+1}} = \text{Clip}_{[a,b]} \{ \mathbf{x}_{adv_l} + \mu_1 \text{sign}(\nabla_{\mathbf{x}_{adv_l}} \mathcal{L}(f(\mathbf{x}_{adv_l}, \theta), \mathbf{y})) \}, \quad (3)$$

where $\mathbf{x}_{adv_l}$ represents the adversarial samples after l -th update, μ_1 is the step size of perturbation in each update to form the adversarial examples and the outer clip function $\text{Clip}_{[a,b]}$ keeps $\mathbf{x}_{adv_l}$ in a perturbed range defined in advance. In general, it can be interpreted as an iterative algorithm to solve the following problem:

$$\max_{\mathbf{x}_{adv} \in \mathbb{B}(\mathbf{x}, \epsilon_1)} \mathcal{L}(f(\mathbf{x}_{adv}; \theta), \mathbf{y}). \quad (4)$$

To train a more robust model, we define a regularization measuring the discrepancy of decisions made by the model from adversarial examples, shown as the second term in 1. The primary concern is to minimizing the distance between the predictions of adversarial sample $\mathbf{x}_{adv}$ and the predictions of sample $\mathbf{x}'_{adv}$ generated from $\mathbf{x}_{adv}$ by a label-free algorithm. Like 4, the $\mathbf{x}'_{adv}$ is generated by solving the maximization problem:

$$\max_{\mathbf{x}'_{adv} \in \mathbb{B}(\mathbf{x}_{adv}, \epsilon_2)} k(f_l(\mathbf{x}'_{adv}; \theta), f_l(\mathbf{x}_{adv}; \theta)). \quad (5)$$

This algorithm is iterative and the update rule is like 3, which in l -th update is formulated as:

$$\mathbf{x}'_{adv_{l+1}} = \text{Clip}_{[a',b']} \{ \mathbf{x}'_{adv_l} + \mu_2 \text{sign}(\nabla_{\mathbf{x}'_{adv_l}} k(f_l(\mathbf{x}'_{adv_l}; \theta), f_l(\mathbf{x}_{adv}; \theta))) \}, \quad (6)$$

where $\mathbf{x}'_{adv_l}$ represents the perturbed adversarial samples generated from $\mathbf{x}_{adv}$ after l -th update.

Here we use *KullbackLeiblerdivergence* [36] to measure the distance between $f_l(\mathbf{x}'_{adv}; \theta)$ and $f_l(\mathbf{x}_{adv}; \theta)$. The softmax outputs computed by $f_l(\cdot; \cdot)$ are fed into the function as probability distribution. The regularization parameter γ is

critical of controlling the effect of regularization. The method tends to original adversarial training when $\gamma \rightarrow 0$ as the effort of regularization is almost eliminated, and tends to the all-one classifier when $\gamma \rightarrow +\infty$ as the effort of regularization almost dominates during optimization.

The regularization can be somehow regarded as an unsupervised process because it does not depend on label y . It first perturbs the adversarial samples only depending on adversarial sample by maximizing the “difference” between label determining adversarial samples $\mathbf{x}_{adv}$ and data determining adversarial samples $\mathbf{x}'_{adv}$.

By optimizing the network to get the similar prediction from $\mathbf{x}_{adv}$ and $\mathbf{x}'_{adv}$ in which the “difference” is large enough, the network can learn the robust features and ignore the easily been influenced features or features introduced by adversarial training from given images. Intuitively, since adversarial training can be viewed as the training set extension and augmentation and the first term in 1 can be regarded as minimizing the “distance” between $f(\mathbf{x}; \theta)$ and y while improving robustness, our method regularizes the adversarial training process by minimizing the “distance” between the prediction of $\mathbf{x}_{adv}$ and prediction of $\mathbf{x}'_{adv}$ to push the decision boundary of network away from the adversarial samples fed in the network, improving network robustness.

Algorithm 1 Regularized Adversarial Training

Input: $\{(\mathbf{x}_i, \mathbf{y}_i)\}_{i=1}^N$, learning rate η , batch size m , network parameter θ

Output: Robust network $f(\theta)$

Randomly initialize $f(\theta)$

while θ not converged **do**

for mini-batch $B = \{\mathbf{x}_1, \dots, \mathbf{x}_m\}$ from training set **do**

for $i = 1, \dots, m$ **do**

 Compute δ_1 using a single ascent step to approximate δ_1 via equation (4)

$\mathbf{x}_{adv_i} \leftarrow \mathbf{x}_i + \delta_1$

end for

for $i = 1, \dots, m$ **do**

 Compute δ_2 using a single ascent step to approximate δ_2 via equation (5)

$\mathbf{x}'_{adv_i} \leftarrow \mathbf{x}_{adv_i} + \delta_2$

end for

$\theta \leftarrow \theta - \eta \sum_{i=1}^m \nabla_{\theta} [\mathcal{L}(f(\mathbf{x}_{adv_i}; \theta), y_i) + \gamma k(f_l(\mathbf{x}'_{adv_i}; \theta), f_l(\mathbf{x}_{adv_i}; \theta))] / m$

end for

end while

IV. EXPERIMENT

A. Dataset

We use the dataset [37] which includes 7 structural classes, each with 400 subtomograms from EMPIAR. The SNR is 0.5 and missing wedge angle is 30 degrees. Each particle is consisted of 28^3 voxels, and the size of each voxel is 0.94 nm. For each tomogram downloaded from EMPIAR, we extracted potential structural regions using Difference of Gaussian with

parameters $s1 = 7.0$ and $k = 1.1$. Subvolumes of size $28 \times 28 \times 28$ were extracted and about 20 macromolecules were manually picked. The 20 subtomograms were averaged to generate the structural template. Structural template was aligned to all subvolumes extracted and produces cross-correlation scores. The top 1000 subvolumes were selected and we manually identified 400 subtomograms for each class.

B. Training Details

Our proposed model has been trained on a system with an NVIDIA GTX 1080 GPU for 100 epochs and the batch size is 16. We use TensorFlow to implement the proposed model. The entire dataset contains 2800 subtomograms. 80% images are sampled as the training set and the remaining ones are used as testing samples. We do not consider a validation set due to the small sample size. For every batch of data during training, we follow Equation 3 to perturb the original images. Both $[a, b]$ and $[a', b']$ are set as $[-0.01, 0.01]$. ϵ is set as 0.01 and step size μ is set to 0.001 for both $\mathbf{x}_{adv}$ and $\mathbf{x}'_{adv}$.

Consistent with the implementation in [30], we use both 10 steps to generate adversarial images $\mathbf{x}_{adv}$ and perturbed adversarial images $\mathbf{x}'_{adv}$. The hyperparameter γ is set to 1 for the attack against CB3D and attack against robustly trained CB3D experiments. We use cross-entropy as loss function at the first term in 1 and use ADAM for optimizing the parameters. The initial learning rate is 0.0001.

Besides, we also apply several techniques from recent works to stabilize the training procedure. Zero-mean normalization is applied to normalize both the training set and testing set. Dropout [38] is applied for reducing overfitting in neural network and the rate is set to 0.5.

C. Construction of adversarial attacks and defenses

We start the experiments to attack the state-of-the-art model and test the effectiveness of our defense method against a wide range of attack methods and compare with other methods, i.e. adversarial training and TRADES loss. The adversarial attack methods we used here include:

- **Fast Gradient Sign Attack (FGSM)** [11] considers the sign of the gradient of the model and perturbs the images along it to increase the prediction loss. We control the max ϵ of perturbation to control the performance.
- **DeepFool $L2/L\infty$ Attack** [19] approximates the model with a linear classifier and finds the closest projection of the original image onto the space of misclassification.
- **Carlini and Wagner Attack** [21] searches for the adversarial images that the disparity between these images and raw images is as small as possible while the adversarial samples are misclassified.
- **Additive Uniform Noise Attack** [39] The standard deviation of noise gradually increases until misclassified.
- **Salt and Pepper Noise Attack** [39] repeatedly adds the salt and pepper noise to the image until misclassified.

We also compare adversarial training and TRADES loss to demonstrate the efficiency of our method. We first apply attack against CB3D that we use the attack methods mentioned above

to attack the natural training CB3D network and generate the adversarial images. These attack methods are implemented using foolbox. We apply FGSM attack here with setting max ϵ to 0.03. We load different models and evaluate them on these adversarial images. The results are shown in Table I.

Furthermore, we verify the performance of our method against adversarial examples of robustly trained CB3D. We apply FGSM method to attack models training with our method, adversarial training and TRADES loss. Additive Uniform Noise Attack and Salt and Pepper Noise Attack are not applied because they are decision-based attacks [40] requiring neither gradients nor probabilities. To make our conclusion more convincing, we apply FGSM with setting max ϵ to 0.03, 0.06 and 0.12. The results are illustrated in Table II.

V. RESULTS AND DISCUSSIONS

A. Against Adversarial Examples of CB3D

We reported the experimental results in Table I. For the results that the adversarial images coming from natural training model, the vulnerability of existing state-of-art model for subtomogram classification can be revealed since the accuracy of natural training model is extremely low under all kind of attack methods. Then we can see our method makes a enormous progress to defend all these attack methods, especially on FGSM, DeepFool L_2 , DeepFool L_∞ and CW. All of them achieve high accuracy results (over 90%). The accuracy of model training with our method on Additive Uniform Noise Attack and Salt&Pepper Noise Attack is not as good as others. This is mainly because that these two attack methods are decision-based attacks, which are direct attacks that solely depend on the final decision made by the model, not the gradient. Thus, the gradient-based defense methods, e.g. ours, adversarial training and TRADES loss, are hard to optimize network to get the outstanding performance, though our proposed method still retains its dominant position. The defend performances of our method are much better than the other two methods on FGSM and Salt&Pepper Noise Attack methods. However, when applying Additive Uniform Noise Attack, the adversarial training method achieves the best result in the three methods. We can speculate that it is because of the regularization. The regularization aims to minimize the difference between adversarial images and its original images from the network perspective based on gradient. So when it comes to Uniform Noise, which randomly adds a stochastic number to every voxel, regularization is not embodied as the "difference" between adversarial images with uniform noise and original images is similar with the "difference" in regularization. Unlike uniform noise, Salt&Pepper Noise Attack method only randomly modifies part of voxel to either the maximum value or minimum value of the images, avoiding obscuring the effect of regularization.

B. Against Adversarial Examples of Robustly Trained CB3D

We summarized our results against adversarial examples of robustly trained CB3D in Table II. Although the accuracy on all attacks drops significantly from the natural accuracy,

which is result of evaluating on natural images, the model with our method still achieve the best results among these models. While applying FGSM attack method, the accuracy of our method is all more than 20% and the accuracy of other defense method is extremely low, which seems that the network randomly classifies the adversarial images completely.

VI. CONCLUSION

In this paper, we studied the robustness of the state-of-the-art deep learning model on CECT images (*i.e.* the CB3D model). We first verified the existing vulnerability of the model and then developed Regularized Adversarial Training (RAT) to improve the robustness of CB3D for one of the pioneering robust biomedical image classification models against adversarial corruptions. We experimented with a wide range of adversarial attack methods. Experimental results demonstrated that Regularized Adversarial Training can significantly improve robustness of the deep learning based subtomogram classification against a wide range of adversarial attacks effectively. This work represents a meaningful step towards robust classification and recovery of millions of macromolecules extracted from CECT images. We hope our method can help the biomedical community improve robustness of other biomedical image classification methods against adversarial attacks.

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TABLE I
AGAINST ADVERSARIAL EXAMPLES OF CB3D

Defense Model	Attacked Model	Natural Accuracy	Robust Accuracy					
			FGSM ^{0.03}	DeepFool L_2	DeepFool L_∞	CW	Salt&Pepper	Noise
Natural training	Natural training	97.32	14.29	0.36	0.18	0.00	1.96	14.29
Adversarial Training	Natural training	98.39	89.28	95.53	93.75	86.25	46.07	36.96
TRADES loss	Natural training	98.39	87.86	72.32	67.14	45.53	38.04	23.21
RAT	Natural training	99.46	96.07	97.32	97.86	90.18	70.54	23.21

TABLE II
AGAINST ADVERSARIAL EXAMPLES OF ROBUSTLY TRAINED CB3D

Defense Model	Under which Attack	L_∞ Distance ¹	Natural Accuracy (%)	Robust Accuracy (%)
Natural training	FGSM ^{0.03}	0.0356	97.32	14.29
Adversarial Training		0.0513	98.39	14.29
TRADES loss		0.0348	98.39	15.18
RAT		0.0686	99.46	27.50
Natural training	FGSM ^{0.06}	0.0358	97.32	14.29
Adversarial Training		0.0515	98.39	14.29
TRADES loss		0.0414	98.39	14.46
RAT		0.0705	99.46	27.32
Natural training	FGSM ^{0.12}	0.0359	97.32	14.29
Adversarial Training		0.0518	98.39	14.29
TRADES loss		0.0416	98.39	14.46
RAT		0.0708	99.46	27.32

¹The average L_∞ distance of all images.

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