FakET: Simulating Cryo-Electron Tomograms with Neural Style Transfer

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Article

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FakET: Simulating Cryo-Electron Tomograms with Neural Style Transfer

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Abstract

Particle localization and -classification constitute two of the most fundamental problems in computational microscopy. In recent years, deep learning based approaches have been introduced for these tasks with great success. A key shortcoming of these supervised learning methods is their need for large training data sets, typically generated from particle models in conjunction with complex numerical forward models simulating the physics of transmission electron microscopes. Computer implementations of such forward models are computationally extremely demanding and limit the scope of their applicability. In this paper we propose a simple method for simulating the forward operator of an electron microscope based on additive noise and Neural Style Transfer techniques. We evaluate the method on localization and classification tasks using one of the established state-of-the-art architectures showing performance on par with the benchmark. In contrast to previous approaches, our method accelerates the data generation process by a factor of 750 while using 33 times less memory and scales well to typical transmission electron microscope detector sizes. It utilizes GPU acceleration and parallel processing. It can be used as a stand-alone method to adapt a training data set or as a data augmentation technique. The source code is available at https://gitlab.com/deepet/faket.

Keywords— Machine Learning, Deep Learning, CryoET, Cryo-Electron Tomography, Neural Style Transfer, CryoEM, Deep Finder, Synthetic Data, Data Augmentation, Pre-training, Domain Adaptation, Classification, Localization

Acknowledgement— The IMP and D.H. are generously funded by Boehringer Ingelheim. We thank Julius Berner from the Mathematical Data Science @ UniVie, Ilja Gubins and Marten Chaillet from the SHREC team, and the members of the Haselbach lab for helpful discussions.

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1 Introduction

Recent developments in cryo-electron tomography (cryoET) allow to obtain high resolution representations of macromolecular complexes in their native cellular environment showing molecular interactions that are hardly accessible with other methods Turk and Baumeister [2020]. In cryoET, the imaged sample is in most cases a 100-200 nm thick slice of a frozen cell. From this slice, projection images are taken in a transmission electron microscope (TEM) from different rotation (tilt) angles. An artifact free reconstruction would require measurements using tilt angles, that would complete the half circle. However, this is not feasible, due to limitations of the specimen holder, and only a range of 140° can be recorded. The missing tilt images later on result in a so-called missing-wedge in the 3D reconstruction (cryo-electron tomogram). In addition, the electron beam severely damages the sample during imaging, so only a low electron dose can be used to image a biological specimen. The low dose in combination with the presence of ice in the sample results in the acquired data being very noisy. Consequently, the identification of molecules within these reconstructions is a daunting task. Particle identification is however necessary as the particles need to be classified and averaged to determine high resolution structures. While cryoET has led to a large number of breakthroughs, providing hitherto unseen detail in the molecular architecture of cells Zimmerli et al. [2021], O'Reilly et al. [2020], Mahamid et al. [2016], the aforementioned challenges still hinder the widespread use of cryoET in the larger cell biology and structural biology community. In this context, the development of new reliable software tools is of paramount importance, which is however obstructed by the lack of sufficient accessible and annotated data to develop the software tools on.

1.1 SHREC simulator

To overcome the problem with the lack of data, in 2019, the annual *SHREC – 3D Shape Retrieval Contest* included a new track titled *Classification in Cryo-Electron Tomograms*. The organizers of this track proposed a task of localization and classification of biological particles in cryo-electron tomograms. Every year since, experts from

Motivation

- particle localization and classification are important challenges
- supervised deep learning methods have been successfully introduced
- large amounts of training data is required (usually manually labeled)
- some small and/or scarce particles are impossible to manually label

Main Contributions

We propose FakET:

- an efficient method for **simulating projections** from a TEM
- based on **neural style transfer**
- generates data of comparable quality to state-of-the-art methods
- **much faster, requires less memory, and scales well** to standard tomogram sizes
- valuable tool for researchers in structural biology

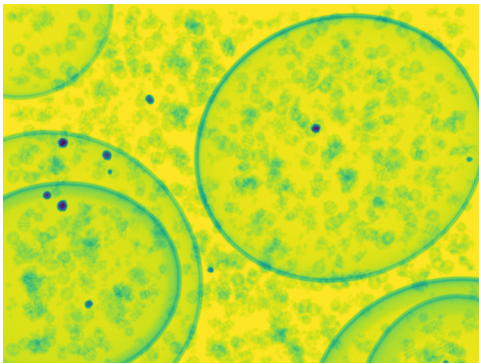
Style-transferred image (output)

Content image (input)

Style image (input)

*figure from Gatys et al. 2016

Simulated projection (output)



Noiseless projection (input)

TEM projection (input)

Related literature

Neural Style Transfer

2016 IEEE Conference on Computer Vision and Pattern Recognition

Image Style Transfer Using Convolutional Neural Networks

Leon A. Gatys
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Bernstein Center for Computational Neuroscience, Tübingen, Germany
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Baylor College of Medicine, Houston, TX, USA

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Max Planck Institute for Biological Cybernetics, Tübingen, Germany

Abstract

Rendering the semantic content of an image in different styles is a difficult image processing task. Arguably, a major limiting factor for previous approaches has been the lack of image representations that explicitly represent semantic information and, thus, allow to separate image content from style. Here we use image representations derived from Convolutional Neural Networks optimised for object recognition, which make high level image information explicit. We introduce A Neural Algorithm of Artistic Style that can separate and recombine the image content and style of natural images. The algorithm allows us to produce new images of high perceptual quality that combine the content of an arbitrary photograph with the appearance of numerous well-known artworks. Our results provide new insights into the deep image representations learned by Convolutional Neural Networks and demonstrate their potential for high level image synthesis and manipulation.

1063-6919/16 $31.00 © 2016 IEEE
DOI 10.1109/CVPR.2016.265

Image Style Transfer Using Convolutional Neural Networks, Gatys, Leon A., et al. CVPR (2016).

- Seminal paper proposing Neural Style Transfer
- for separation and recombination of content and style
- uses CNN as image representation extractor
- VGG19 net pre-trained on Imagenet data set

SHREC Challenge

Computers & Graphics 91 (2020) 279–289

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/cag

Special Section on 3DOR 2020

SHREC 2020: Classification in cryo-electron tomograms

Ilja Gubins[a,1,*], Marten L. Chaillet[b,1], Gijs van der Schot[b,1], Remco C. Veltkamp[a,1], Friedrich Förster[b,1], Yu Hao[c], Xiaohua Wan[c], Xuefeng Cui[d], Fa Zhang[c], Emmanuel Moebel[e], Xiao Wang[f], Daisuke Kihara[f,g], Xiangrui Zeng[h], Min Xu[h], Nguyen P. Nguyen[i], Tommi White[j], Filiz Bunyak[i]

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[g] Department of Biological Sciences, Purdue University, USA
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ABSTRACT

Cryo-electron tomography (cryo-ET) is an imaging technique that allows us to three-dimensionally visualize both the structural details of macro-molecular assemblies under near-native conditions and its cellular context. Electrons strongly interact with biological samples, limiting electron dose. The latter limits the signal-to-noise ratio and hence resolution of an individual tomogram to about 50 (5 nm). Biological molecules can be obtained by averaging volumes, each depicting copies of the molecule, allowing for resolutions beyond 4 (0.4 nm). To this end, the ability to localize and classify components is crucial, but challenging due to the low signal-to-noise ratio. Computational innovation is key to mine biological information from cryo-electron tomography.

To promote such innovation, we provide a novel simulated dataset to benchmark different methods of localization and classification of biological macromolecules in cryo-electron tomograms. Our publicly available dataset contains ten tomographic reconstructions of simulated cell-like volumes. Each volume contains twelve different types of complexes, varying in size, function and structure.

In this paper, we have evaluated seven different methods of finding and classifying proteins. Six research groups present results obtained with learning-based methods and trained on the simulated dataset, as well as a baseline template matching, a traditional method widely used in cryo-ET research. We find that method performance correlates with particle size, especially noticeable for template matching which performance degrades rapidly as the size decreases. We learn that neural networks can achieve significantly better localization and classification performance, in particular convolutional networks with focus on high-resolution details such as those based on U-Net architecture.

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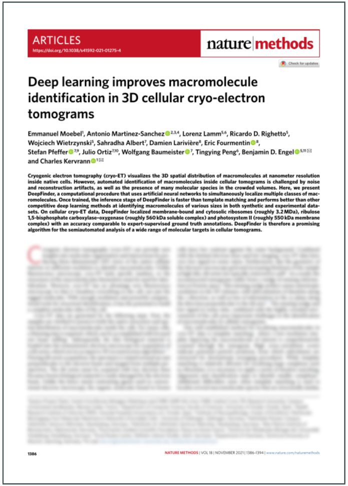
E-mail address: i.gubins@uu.nl (I. Gubins).
1 Track organizers

https://doi.org/10.1016/j.cag.2020.07.010

SHREC 2020: Classification in cryo-electron tomograms, Gubins, Ilja, et al. Computers & Graphics (2020).

- SHREC Challenge (active in 2019, 2020, 2021)
- particle localization and classification tasks
- simulates a set of 10 cryo-electron tomograms
- DeepFinder was one of the most successful methods

Deep Finder



ARTICLES
https://doi.org/10.1038/s41592-021-01275-4
nature methods

Check for updates

Deep learning improves macromolecule identification in 3D cellular cryo-electron tomograms

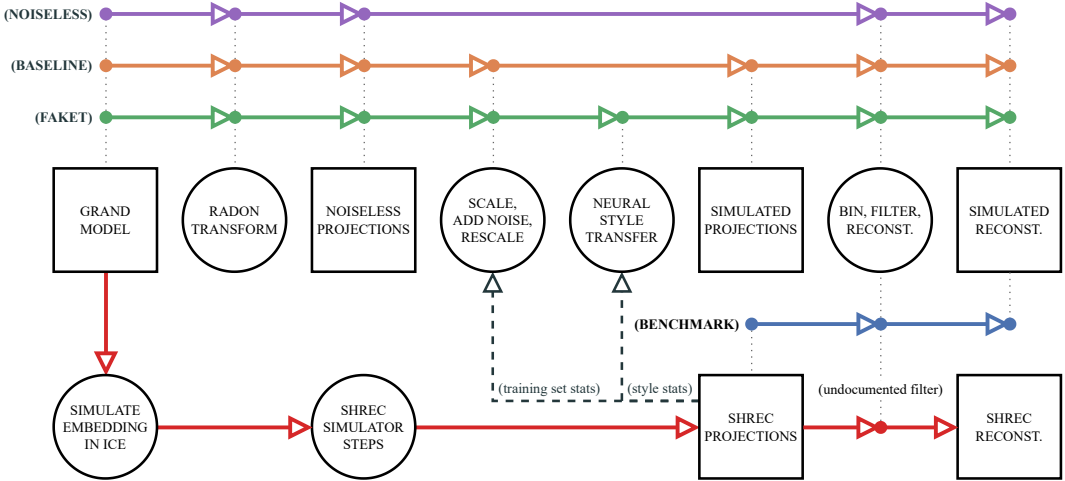
Emmanuel Moebel[1], Antonio Martinez-Sanchez[2,3,4], Lorenz Lamm[5,6], Ricardo D. Righetto[5], Wojciech Wietrzynski[5], Sahradha Albert[7], Damien Larivière[8], Eric Fourmentin[8], Stefan Pfeffer[7,9], Julio Ortiz[7,10], Wolfgang Baumeister[7], Tingying Peng[6], Benjamin D. Engel[5,11] ✉ and Charles Kervrann[1] ✉

Cryogenic electron tomography (cryo-ET) visualizes the 3D spatial distribution of macromolecules at nanometer resolution inside native cells. However, automated identification of macromolecules inside cellular tomograms is challenged by noise and reconstruction artifacts, as well as the presence of many molecular species in the crowded volumes. Here, we present DeepFinder, a computational procedure that uses artificial neural networks to simultaneously localize multiple classes of macromolecules. Once trained, the inference stage of DeepFinder is faster than template matching and performs better than other competitive deep learning methods at identifying macromolecules of various sizes in both synthetic and experimental datasets. On cellular cryo-ET data, DeepFinder localized membrane-bound and cytosolic ribosomes (roughly 3.2 MDa), ribulose 1,5-bisphosphate carboxylase–oxygenase (roughly 560 kDa soluble complex) and photosystem II (roughly 550 kDa membrane complex) with an accuracy comparable to expert-supervised ground truth annotations. DeepFinder is therefore a promising algorithm for the semiautomated analysis of a wide range of molecular targets in cellular tomograms.

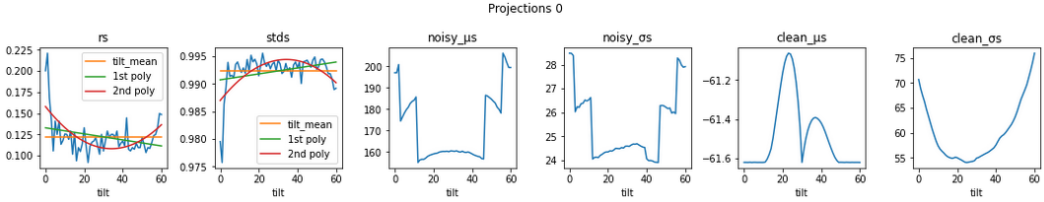
Deep learning improves macromolecule identification in 3D cellular cryo-electron tomograms, Moebel, Emmanuel, et al. Nature methods (2021).

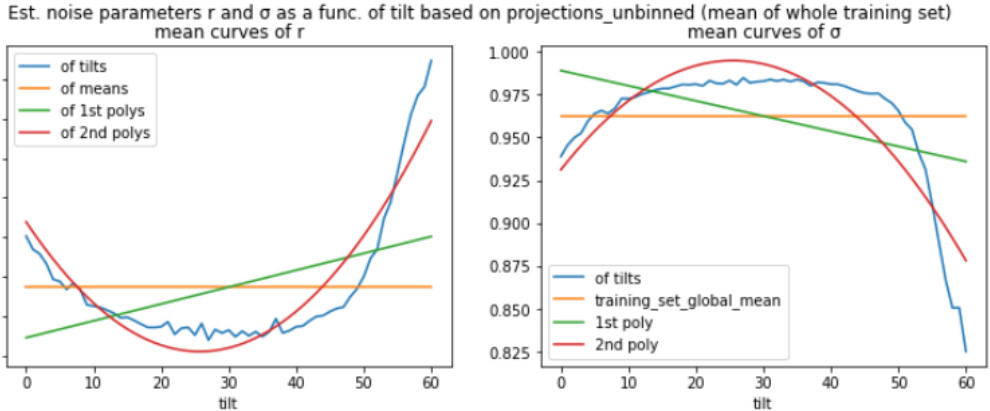
- Proposes DeepFinder neural network
- for particle localization and classification
- evaluates on SHREC Challenge data set
- evaluates also on experimental data set

Methods


(NOISELESS)
(BASELINE)
(FAKET)
GRAND MODEL
RADON TRANSFORM
NOISELESS PROJECTIONS
SCALE, ADD NOISE, RESCALE
NEURAL STYLE TRANSFER
SIMULATED PROJECTIONS
BIN, FILTER, RECONST.
SIMULATED RECONST.
(BENCHMARK)
(training set stats)
(style stats)
(undocumented filter)
SIMULATE EMBEDDING IN ICE
SHREC SIMULATOR STEPS
SHREC PROJECTIONS
SHREC RECONST.

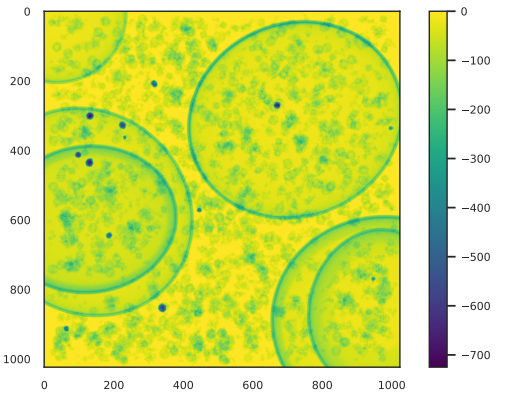
Tilt-dependent noise estimation

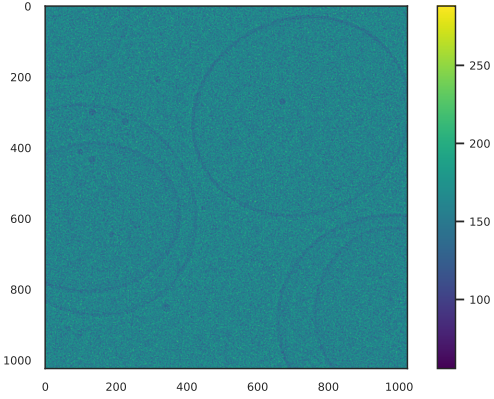

Projections 0
rs
stds
noisy_μs
noisy_σs
clean_μs
clean_σs
tilt_mean
1st poly
2nd poly
tilt
Projections 1
rs
stds
noisy_μs
noisy_σs
clean_μs
clean_σs
tilt_mean
1st poly
2nd poly
tilt


Est. noise parameters r and σ as a func. of tilt based on projections_unbinned (mean of whole training set)
mean curves of r
of tilts
of means
of 1st polys
of 2nd polys
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0
10
20
30
40
50
60
tilt
mean curves of σ
1.000
0.975
0.950
0.925
0.900
0.875
0.850
0.825
of tilts
training_set_global_mean
1st poly
2nd poly
0
10
20
30
40
50
60
tilt

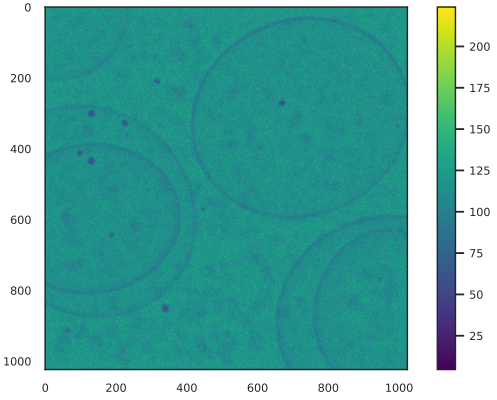
Simulating Projections

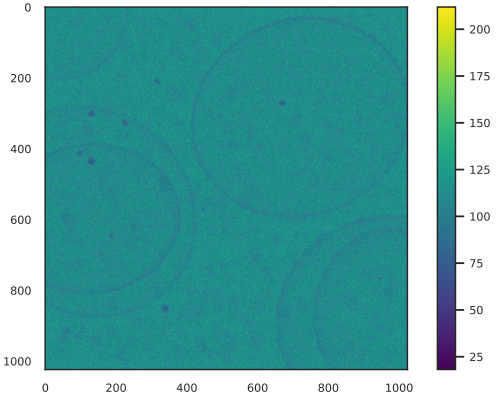
Projections *noiseless* & SHREC



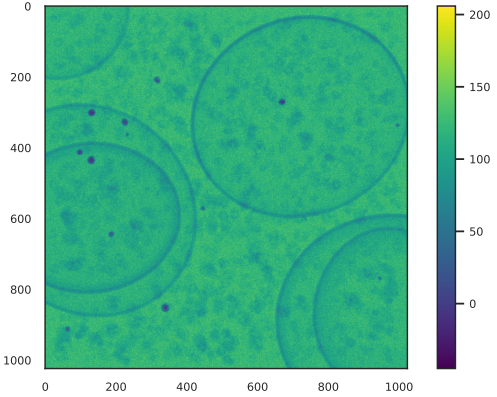


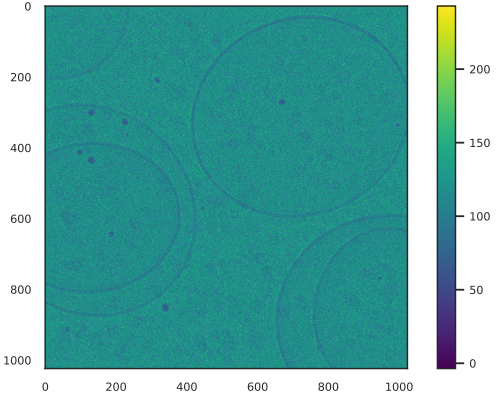
Projections BASELINE & *noisy*





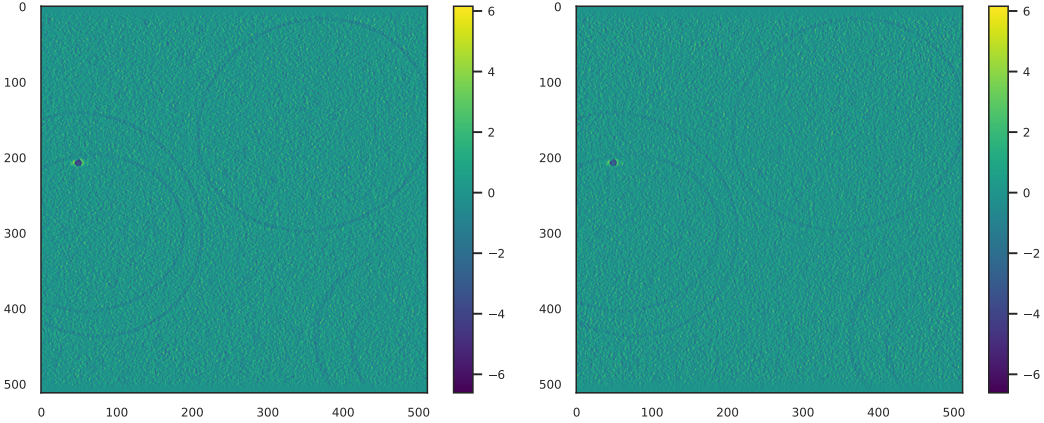
Projections *content* & FAKET



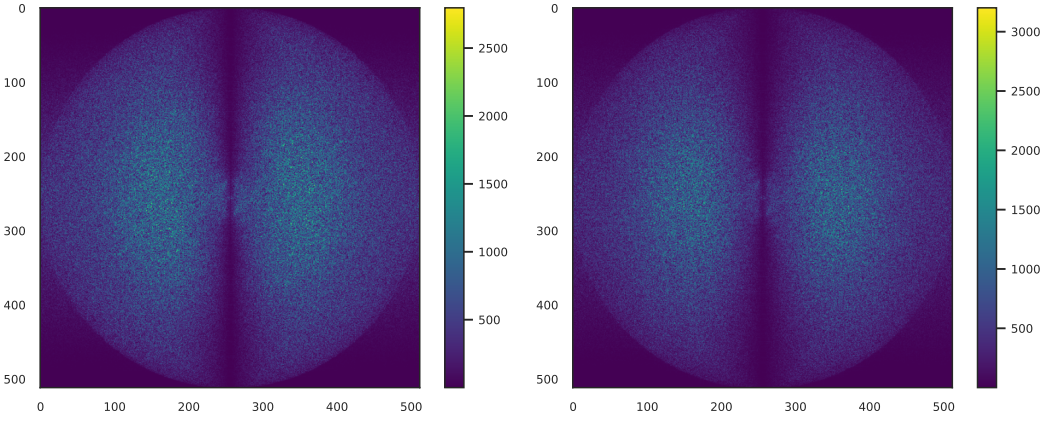


Reconstructions

Reconstruction SHREC vs. BENCHMARK



Reconstruction SHREC vs. BENCHMARK



Experiments & Results

Experiments

BENCHMARK → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)
FAKET → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)
BASELINE → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)

*9 training tomograms equals to 688 batches

Experiments

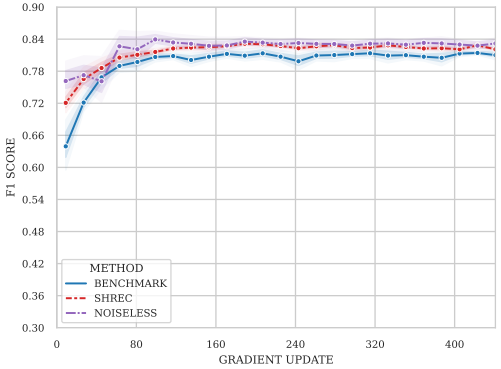
BENCHMARK → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)
FAKET → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)
BASELINE → DeepFinder (train 70 ep.) → test on SHREC 10^{th} (segm., clust., eval.)

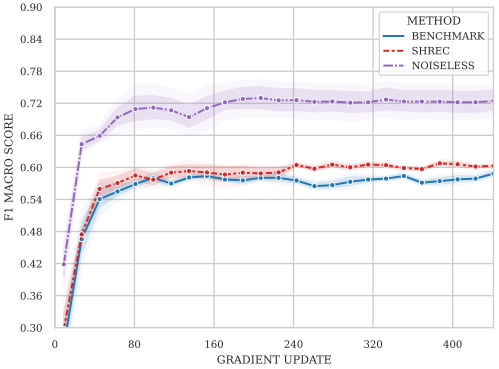
We also computed:

noiseless → DeepFinder (train 50 ep.) → test on *noiseless* 10^{th} (segm., clust., eval.)
SHREC → DeepFinder (train 50 ep.) → test on SHREC 10^{th} (segm., clust., eval.)

*9 training tomograms equals to 688 batches

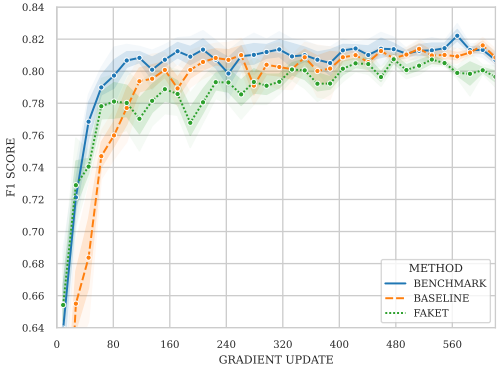
Results - DeepFinder Limits

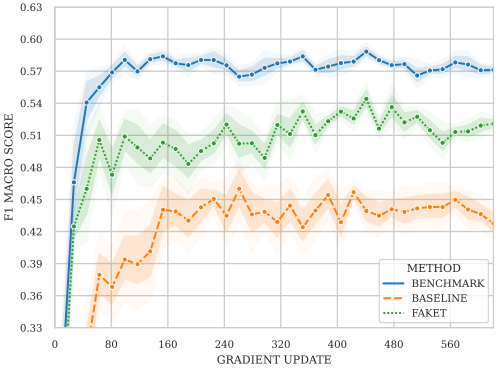




*One gradient update on x axis actually stands for 688 updates. Localization task (left) & classification task (right).

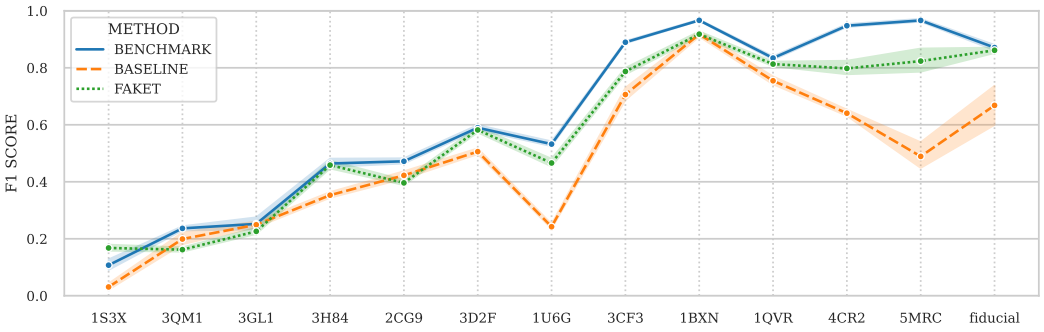
Results





*One gradient update on x axis actually stands for 688 updates. Localization task (left) & classification task (right).

Results



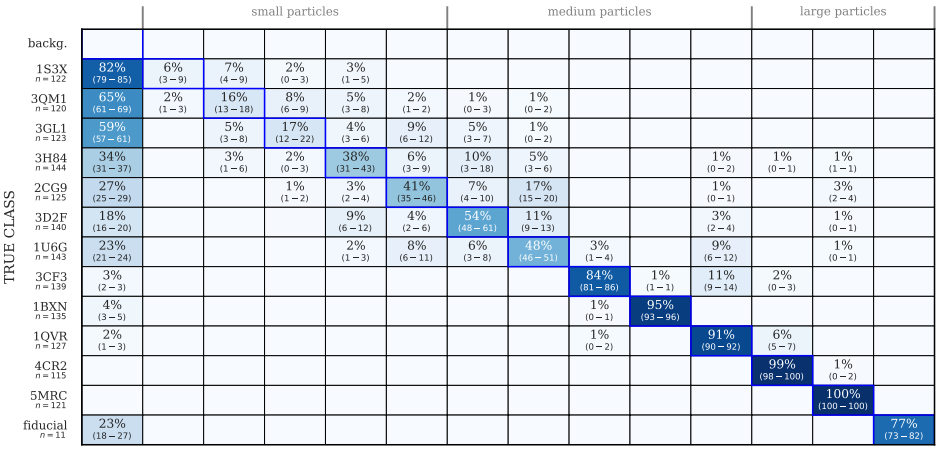
*Particles are ordered from smallest to largest.

Results

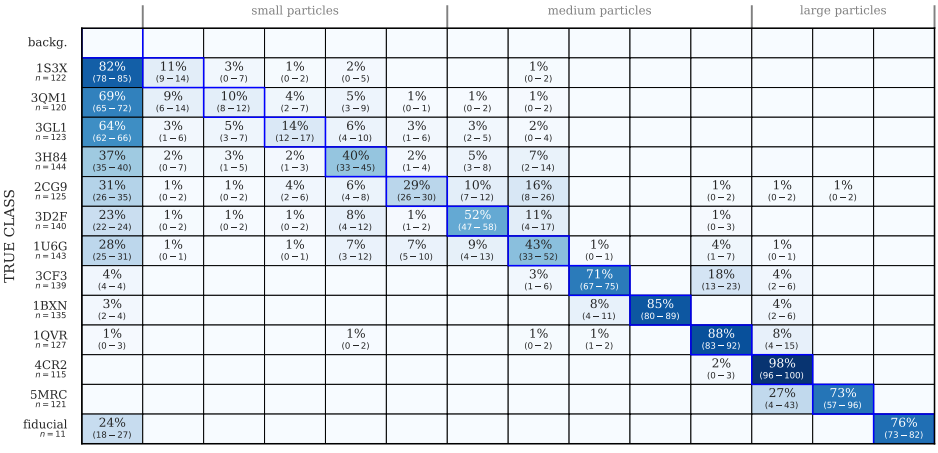
Model	Train data	Data cost	Localization F1	Classification F1
DF	benchmark	$\approx 150\,h$ (3×CPU, 114 GB RAM)	0.815	0.581 (100 %)
DF	faket	$\approx 12\,m$ (1×GPU, 40 GB VRAM)	0.800	0.533 (92 %)
DF	baseline	$\approx 20\,s$ (1×CPU, 1 GB RAM)	0.813	0.441
TM-F			0.576	0.446
TM			0.372	0.470

*All models are tested on SHREC 10^{th} tomogram.

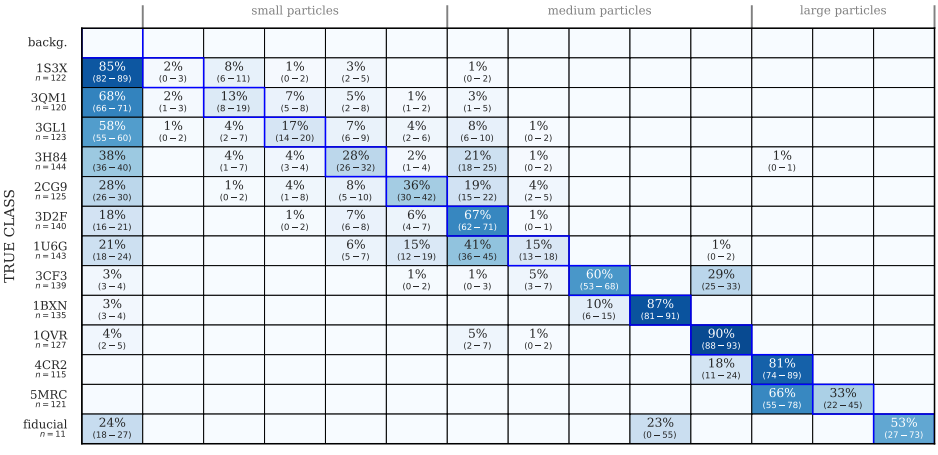
Confusion Matrix BENCHMARK



Confusion Matrix FAKET



Confusion Matrix BASELINE



Conclusions

- FAKET, a novel method for simulating the forward operator of TEM
- FAKET combines additive noise and neural style transfer (NST)
- allows practitioners to generate synthetic cryo-electron tilt series
- 750× faster and uses 33× less memory than SHREC simulator
- GPU accelerated but can be also computed only using CPUs
- provides practitioners with annotated data to train neural networks
- provides annotated data for particles that are hard to manually label
- useful among other things in particle localization and classification
- capable of simulating large tilt series common in experimental environments
- open-source

Outlook

- validation on real experimental data
- fine-tuning the NST network on tomographic data
- making user-friendly CLI interface

The Goal

Happy structural biologists who use FakET to solve their problems. Laboratory, emotional, excited, happy, hyperrealistic, portrait, male and female, there is an electron microscope in the background, they are looking at a computer display showing a detail of a cell.

Image generated using: https://midjourney.com

Pavol Harar

pavol.harar.eu

HararPavol

Received an MSc in System Engineering and Informatics and a PhD in Machine Learning from Brno University of Technology. Gained experience in predictive modeling, signal processing, and parallel computing as a member of Brain Diseases Analysis Laboratory and Numerical Harmonic Analysis Group. At the time of presentation a postdoc at the Data Science Research Network @UniVie and a visiting postdoc at the Institute of Molecular Pathology in Vienna.