Deep learning based structural pattern mining in tomograms -- several exploratory studies

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Systematic detection of macromolecular structures in cellular tomograms

Structural pattern mining / in silico purification: template-free detection of macromolecular structures

Challenges

- Imaging limits
  - Missing data (missing wedge effect)
  - Low signal-to-noise ratio
- High structural content complexity
  - Macromolecule structure highly diverse
  - High molecular crowding level
- Big data
  - Hundreds of tomograms
  - Millions of macromolecules

Deep learning

- Has become a mainstream approach for a wide range of computer vision tasks

- Automatic learning of a hierarchy of image features from large amount of data → learning very complex image composition rules

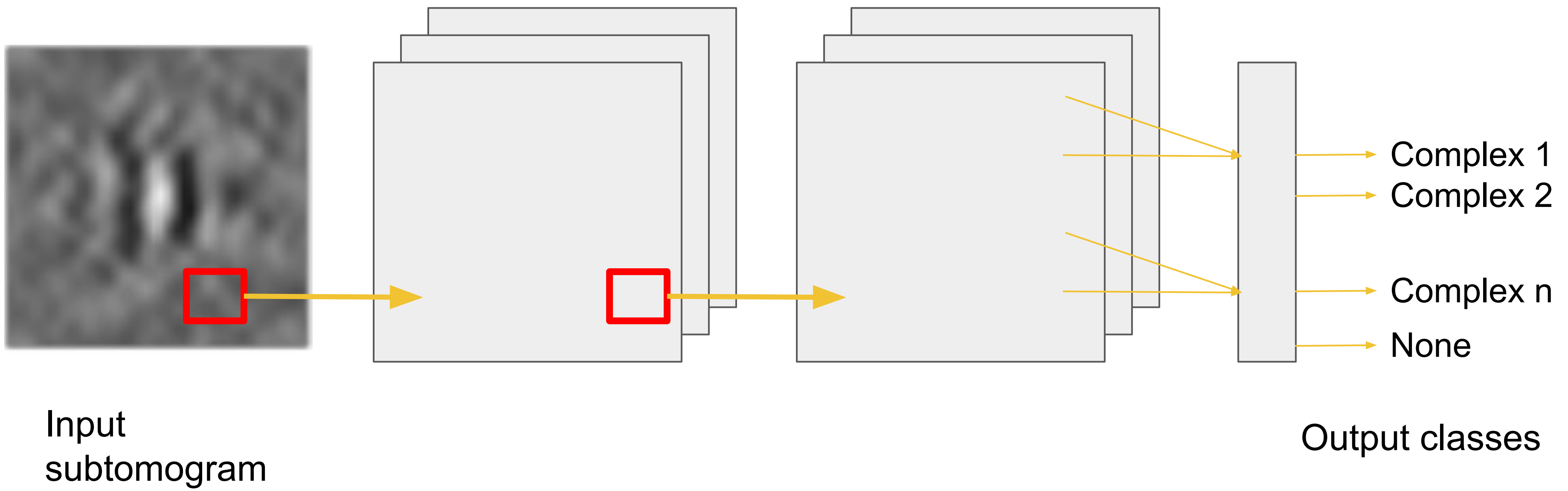
Exploratory projects

1. Macromolecule structure classification and subdivision
2. Autoencoder based pattern detection
3. Subtomogram segmentation
4. Simultaneous classification, segmentation, and density map inference
5. Visualization of CNN models
6. Learnable generative model of pseudo macromolecular structures

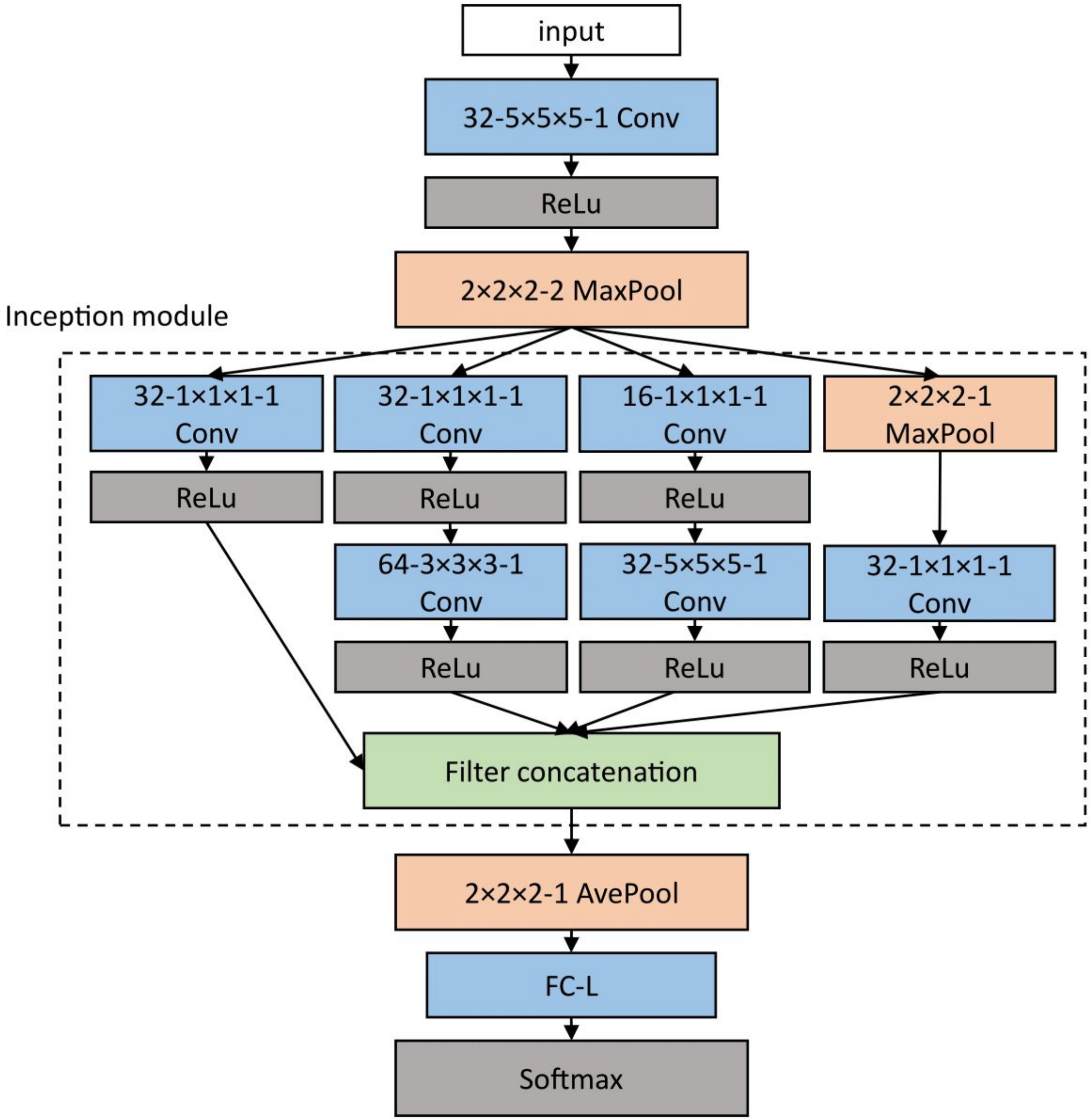
Supervised subtomogram classification

Xu et al. ISMB 2017

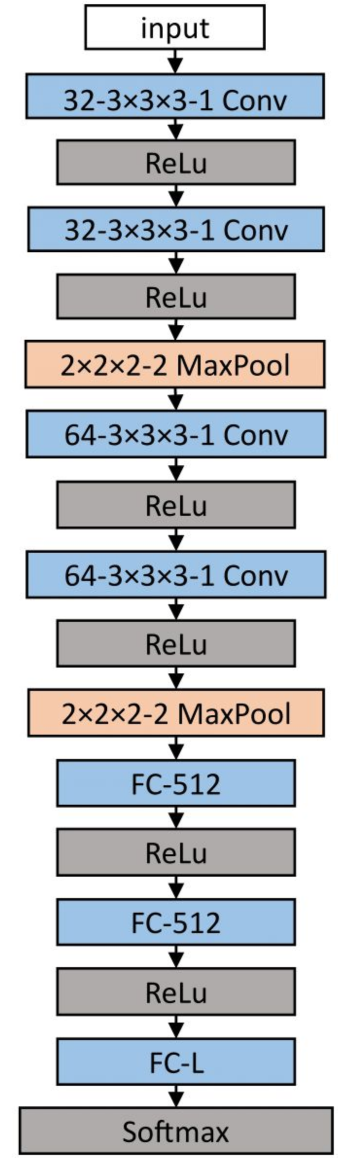
Supervised subtomogram classification



CNN classification models



(a) Inception3D network



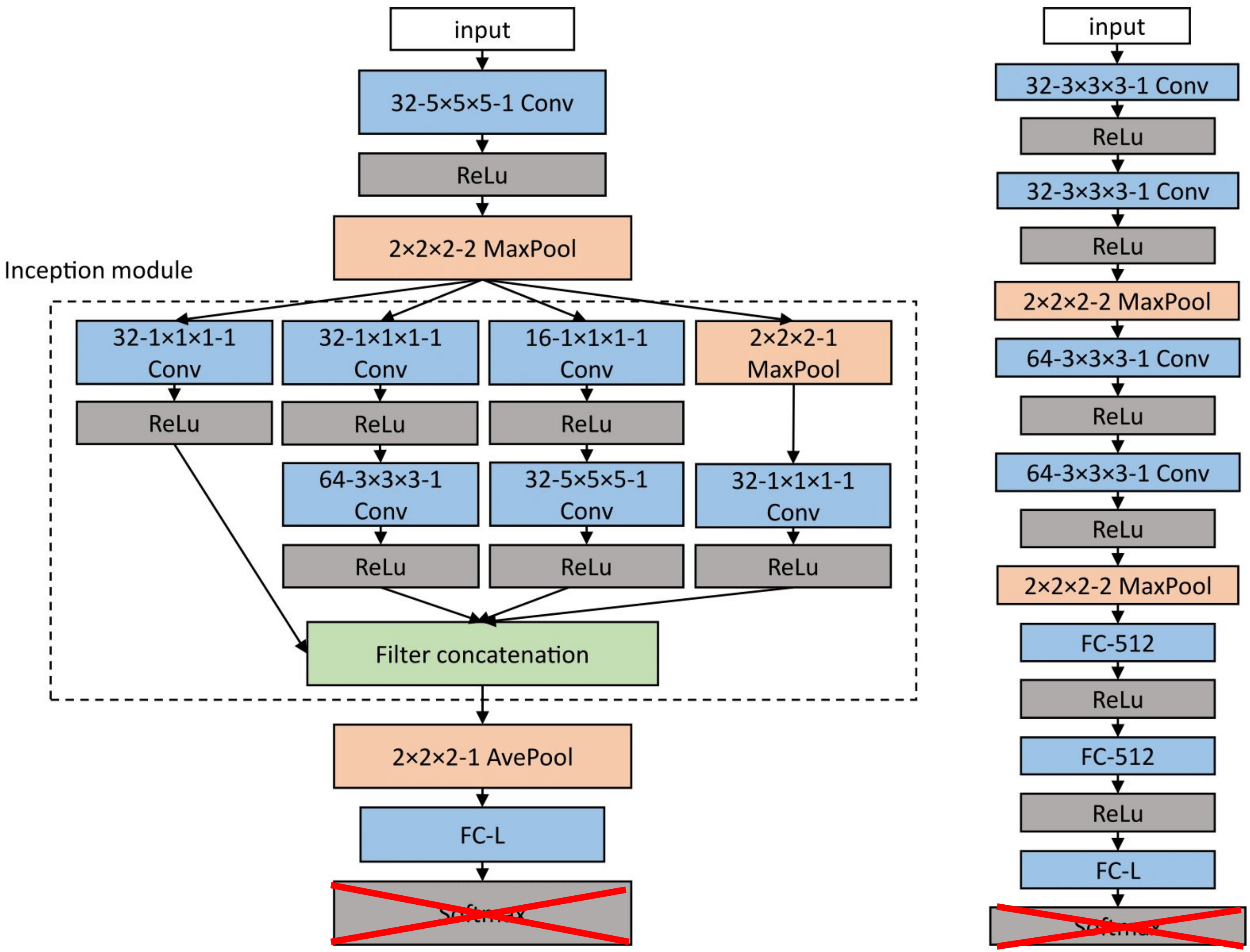
(b) DSRF3D network

Performance

- Classification accuracy significantly better than Rotational Invariant Features + Support Vector Machines

- Once trained, classifying 1M subtomograms take < 2 hours on a single GPU

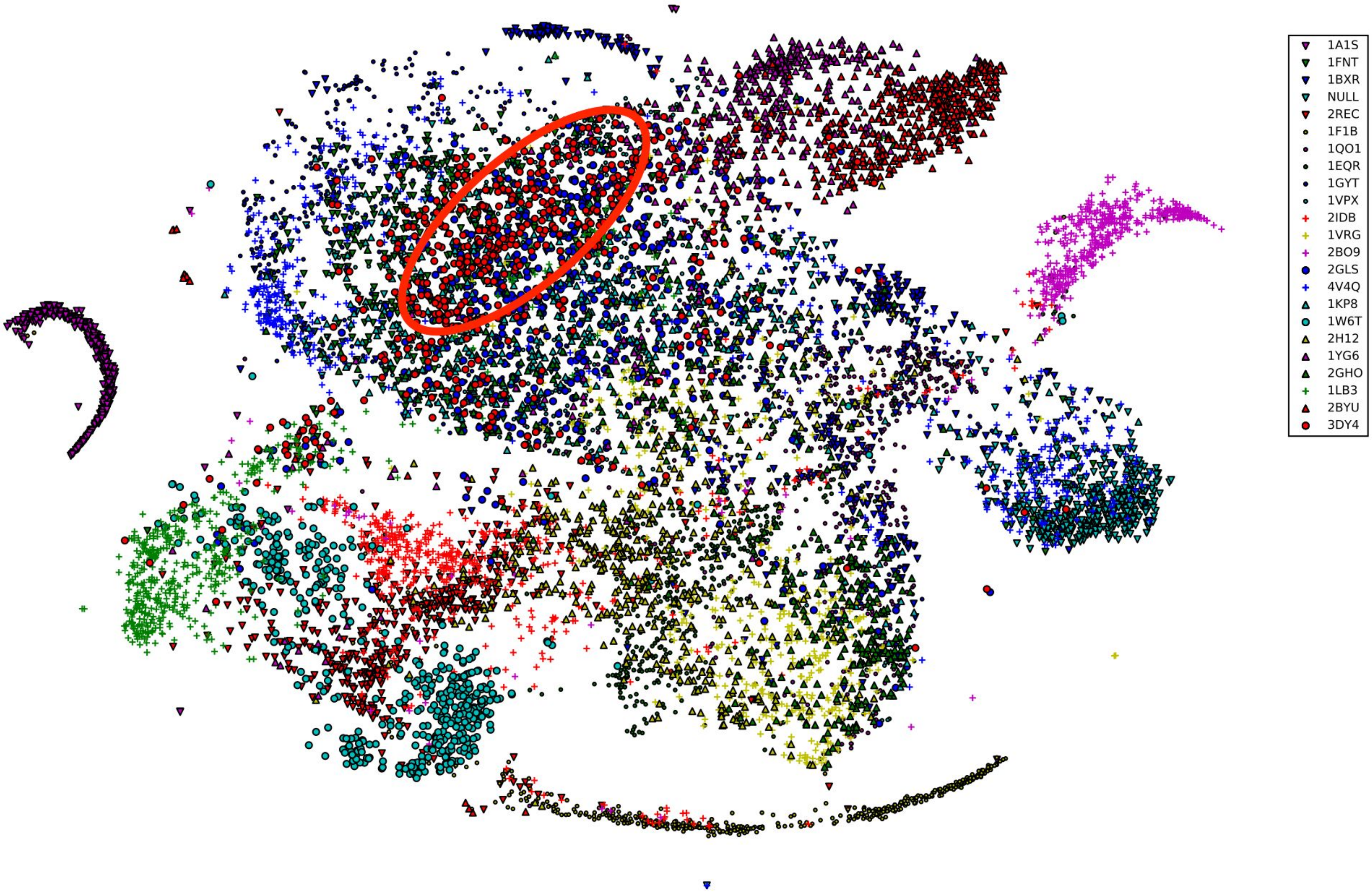
Supervised structural feature extraction



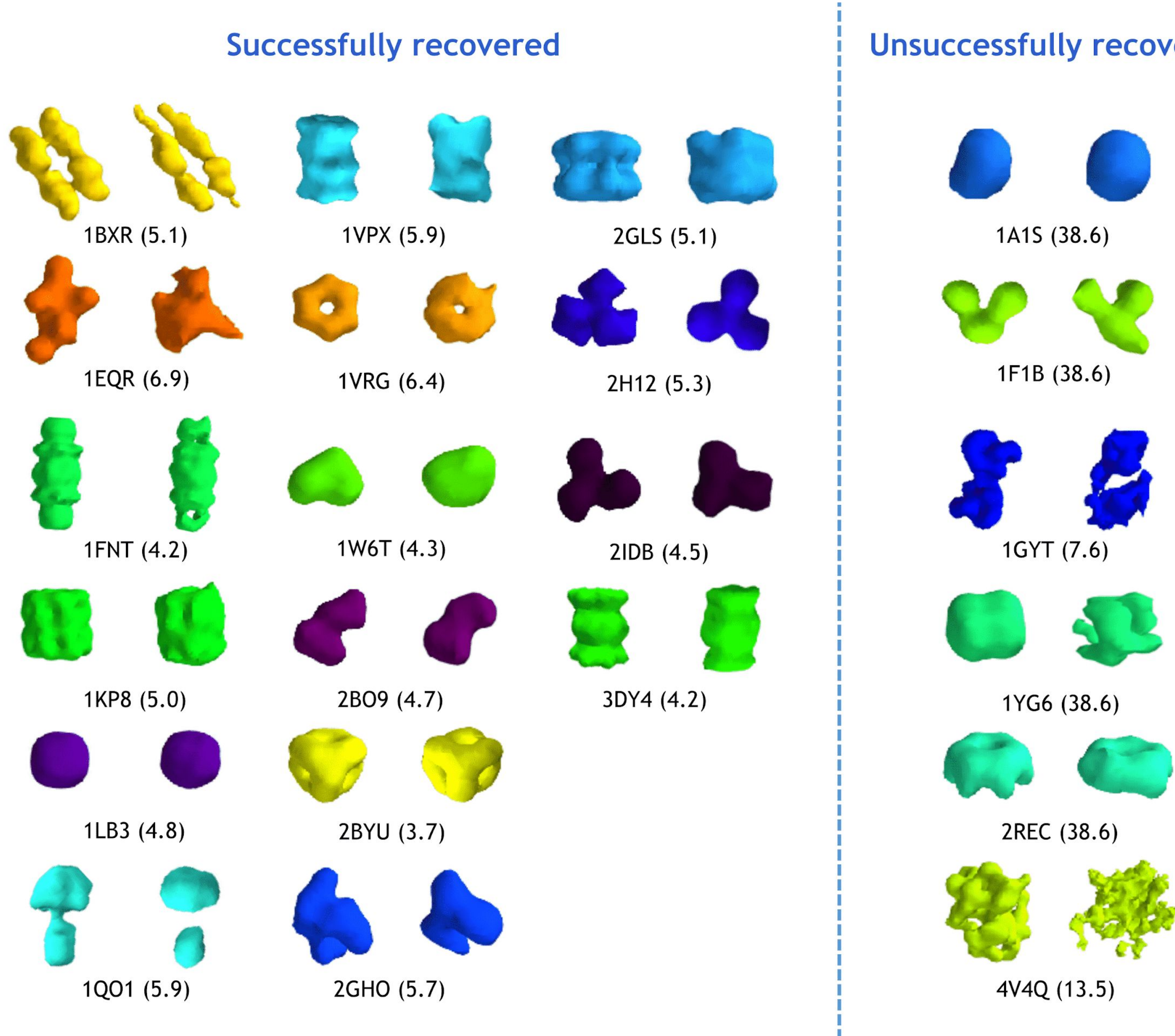
Supervised structural feature extraction

- Continuous representation of the likelihood of the class assignments
- Project the input subtomogram into a low dimensional structural feature space spanned by the training classes
- Invariant to
  - Rigid transformations
  - Missing wedge effects

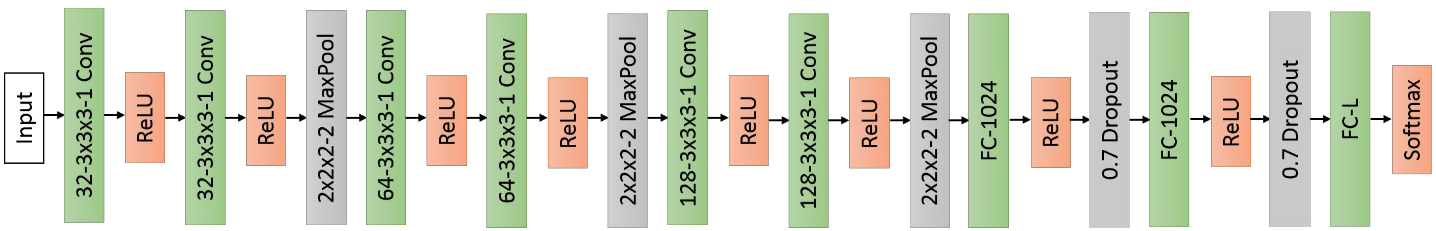
Detection of new structures



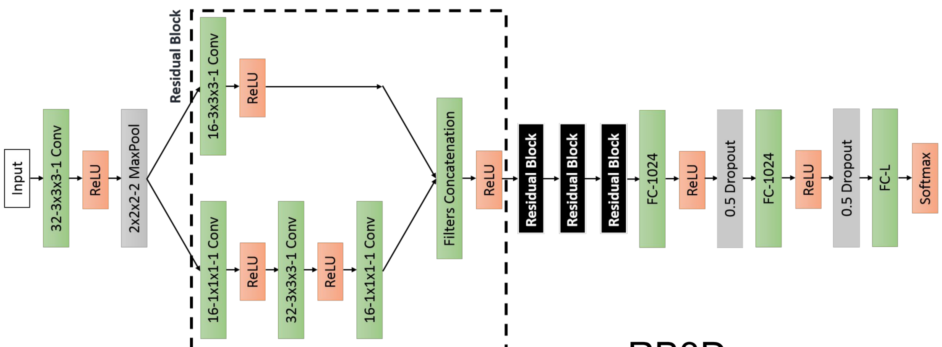
Detection of new structures: leave-one-out test



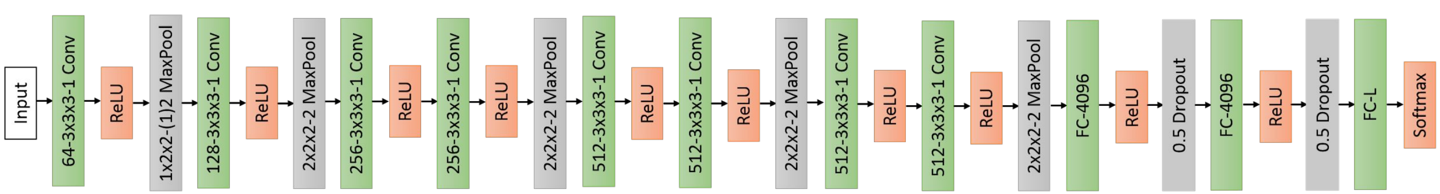
Improvements: deeper models for improved accuracy



DSRF3D-v2



RB3D

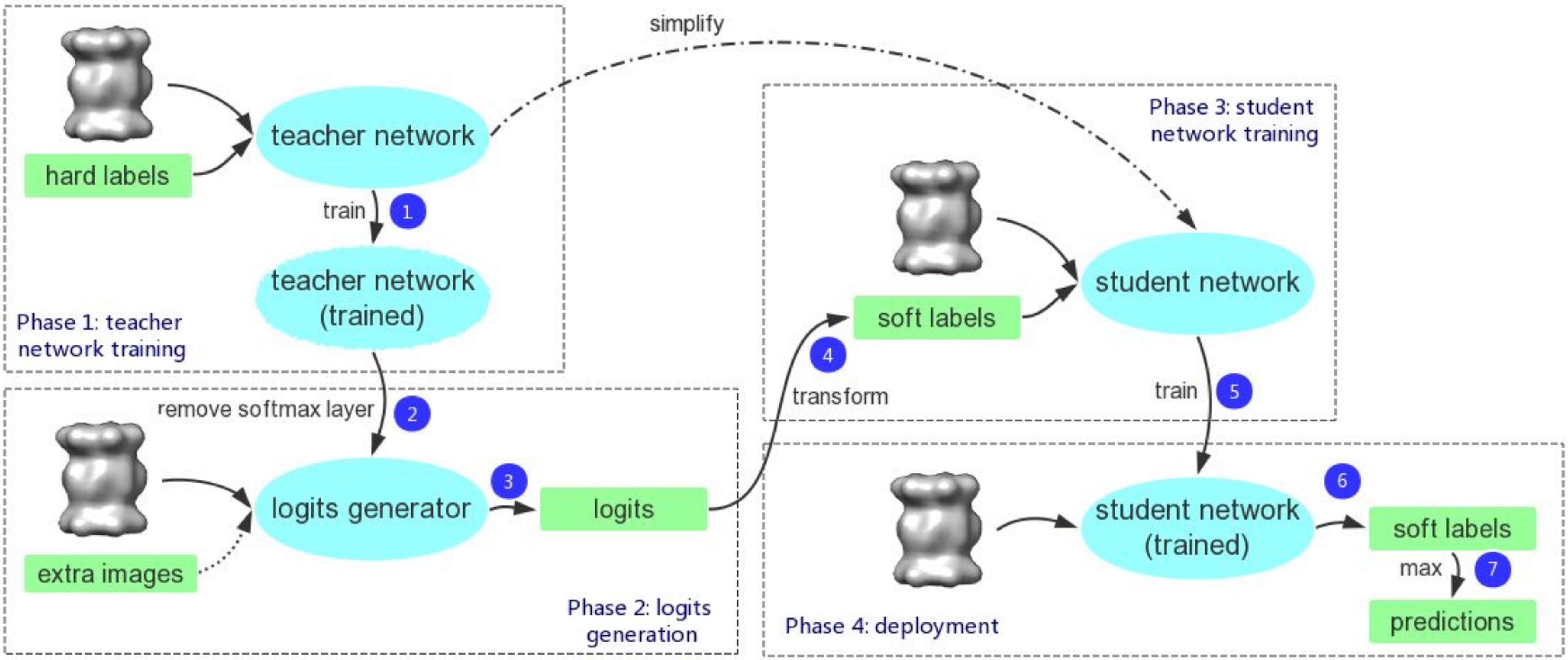


(Best performance)

CB3D

Che et al. arXiv:1707.04885

Improvements: model compression for increased speed

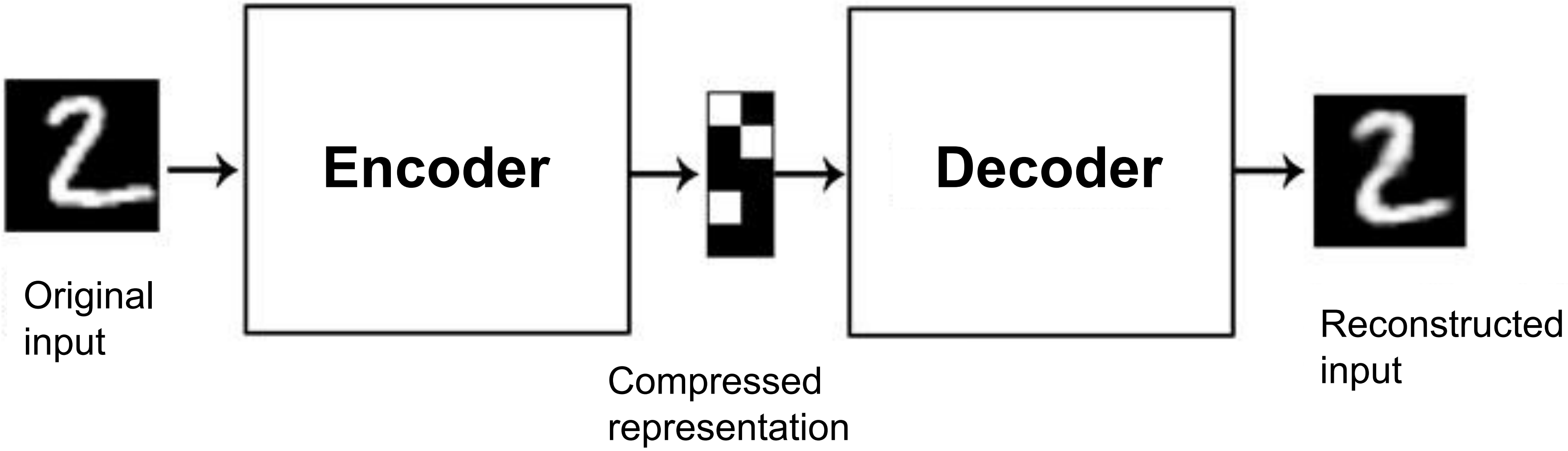


Guo et al. ICIAR 2018

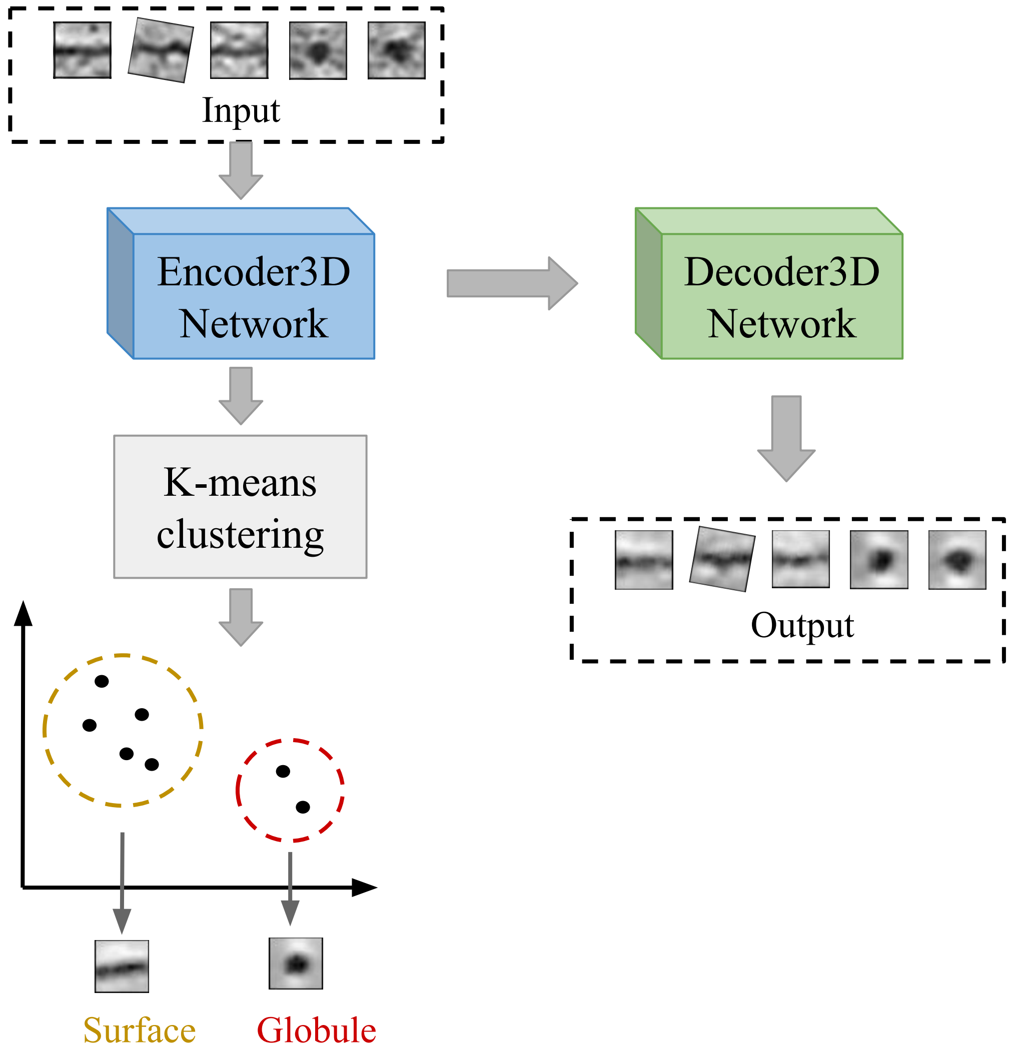
Autoencoder based pattern detection

Zeng et al. JSB 2017

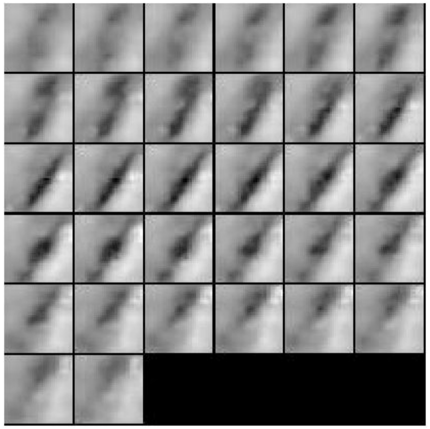
Autoencoder based pattern detection



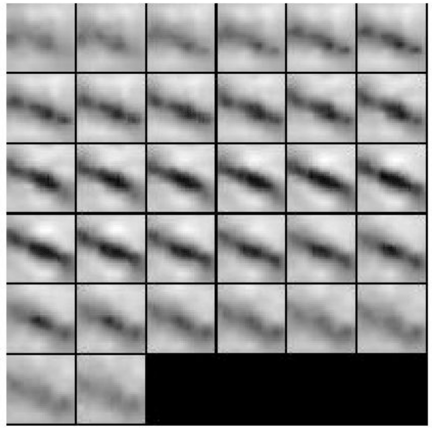
Autoencoder based pattern detection



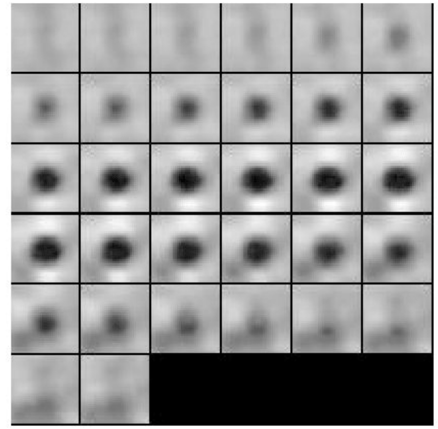
Autoencoder based pattern detection



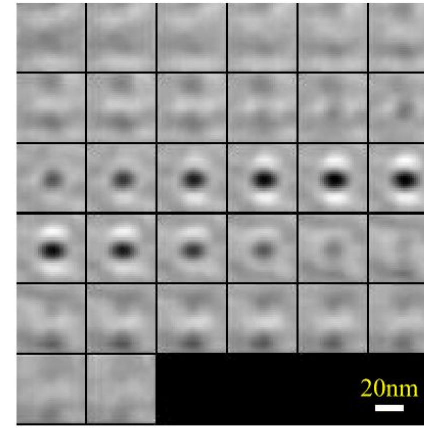
Surface patch



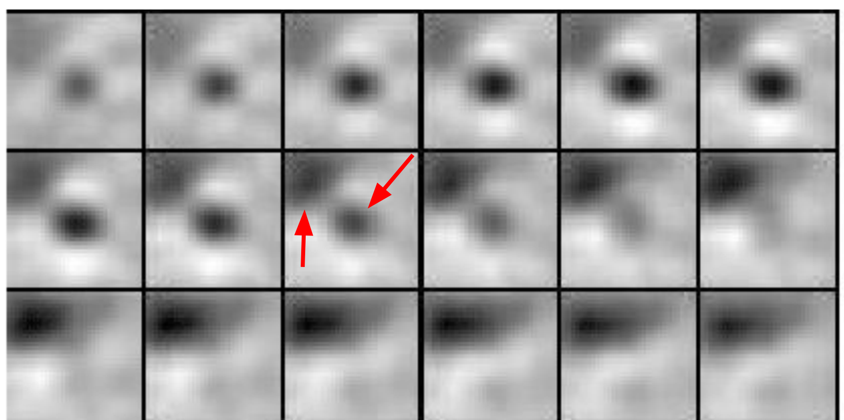
Surface patch



Large globule

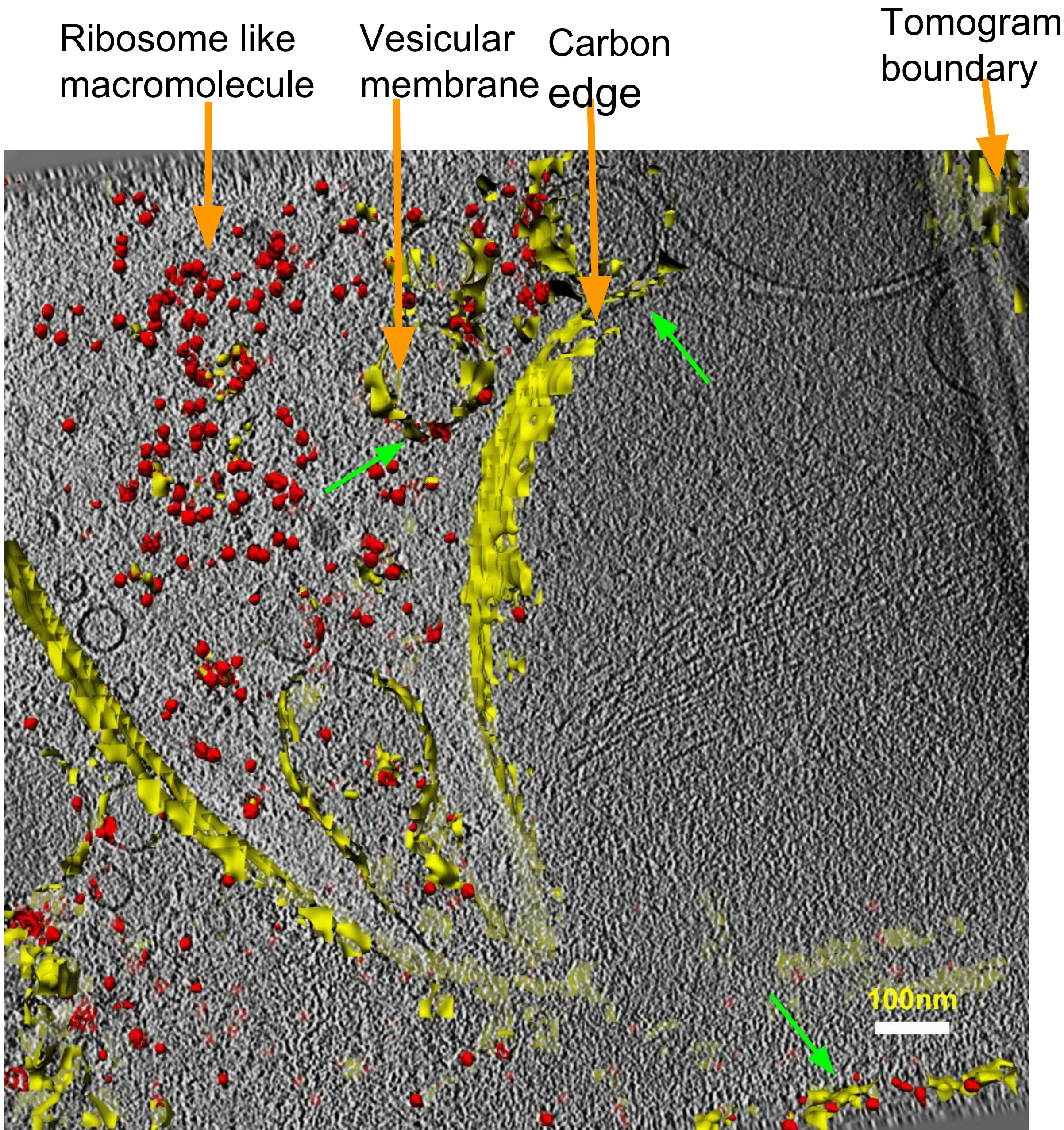


Small globule



Interaction between cellular components

Embedding of detected patterns



Subtomogram segmentation

Motivation: molecular crowding

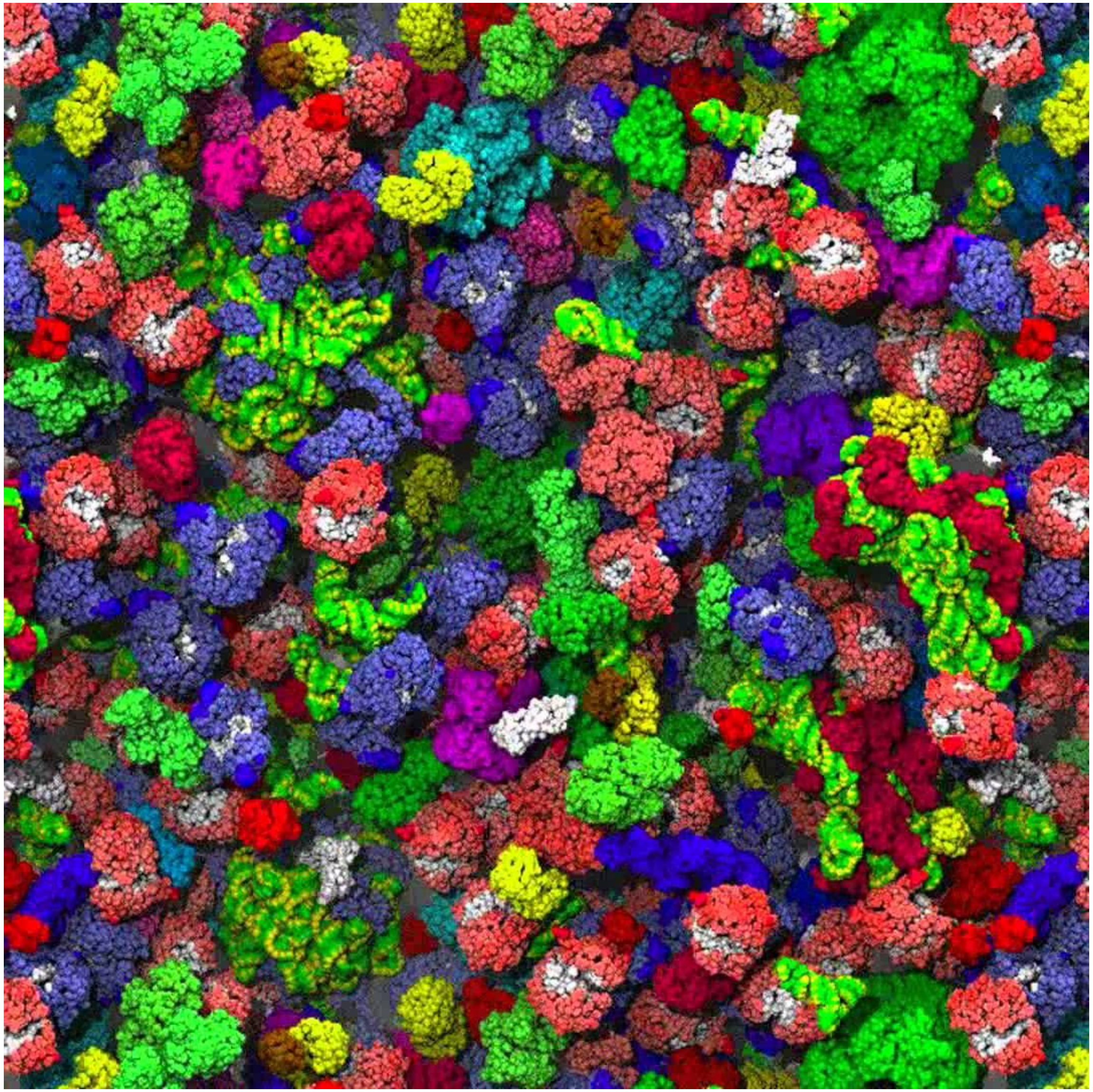
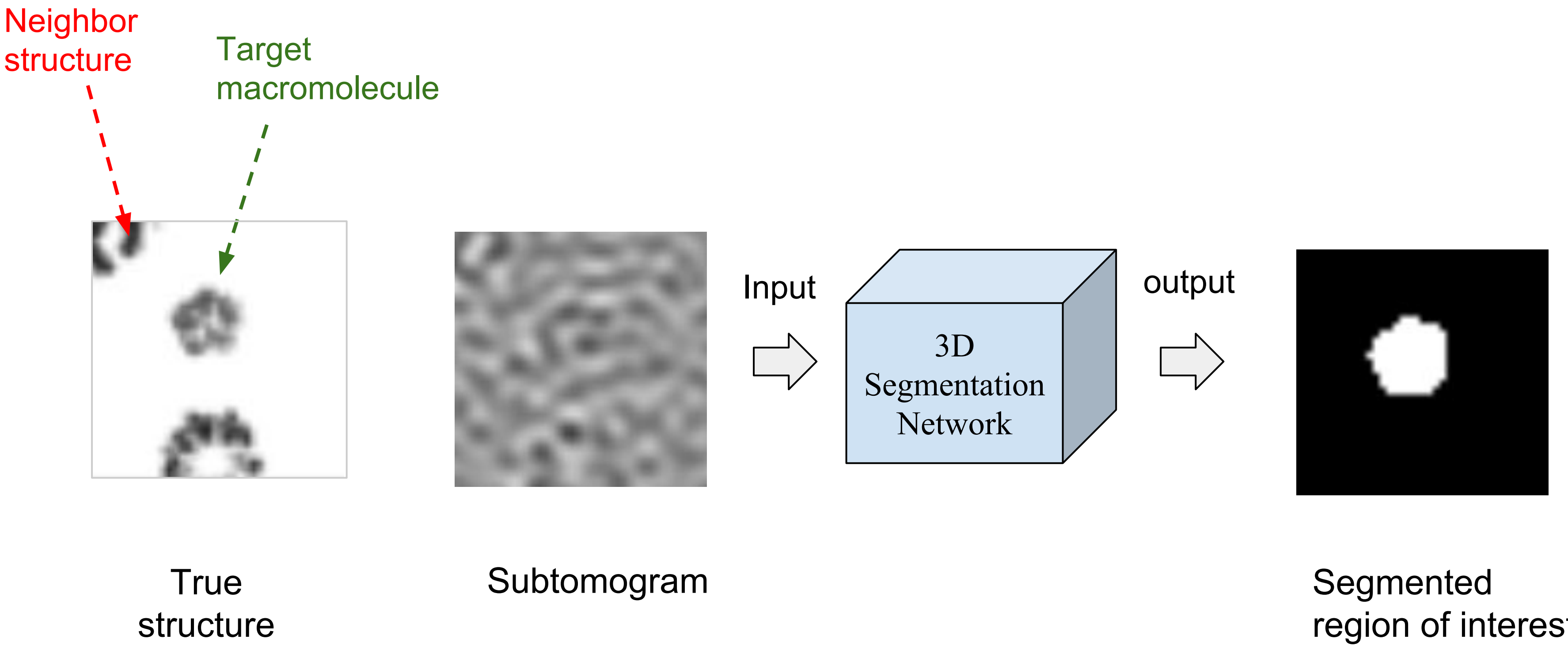


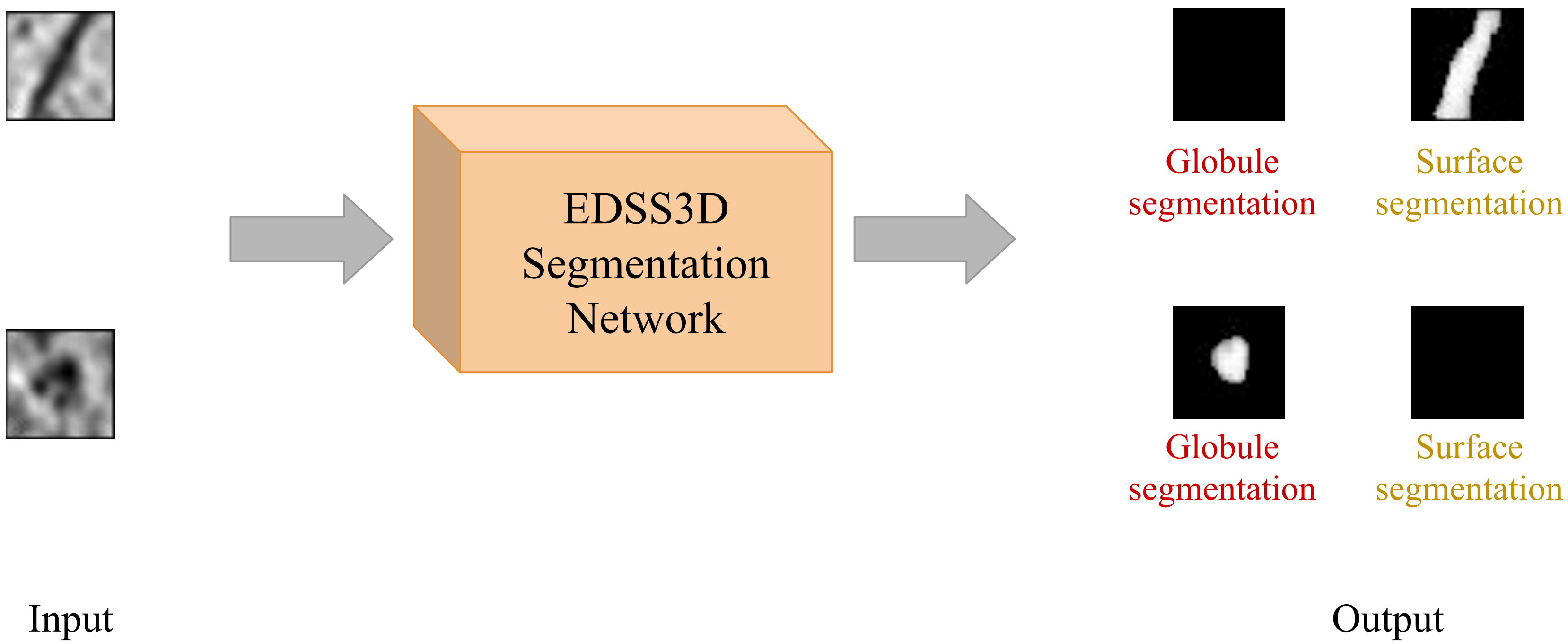
Image of simulated bacterial cytoplasm from McGuffee & Elcock, PLoS Comput Biol

Voxelwise binary classification based segmentation



Liu et al. arXiv:1802.04087

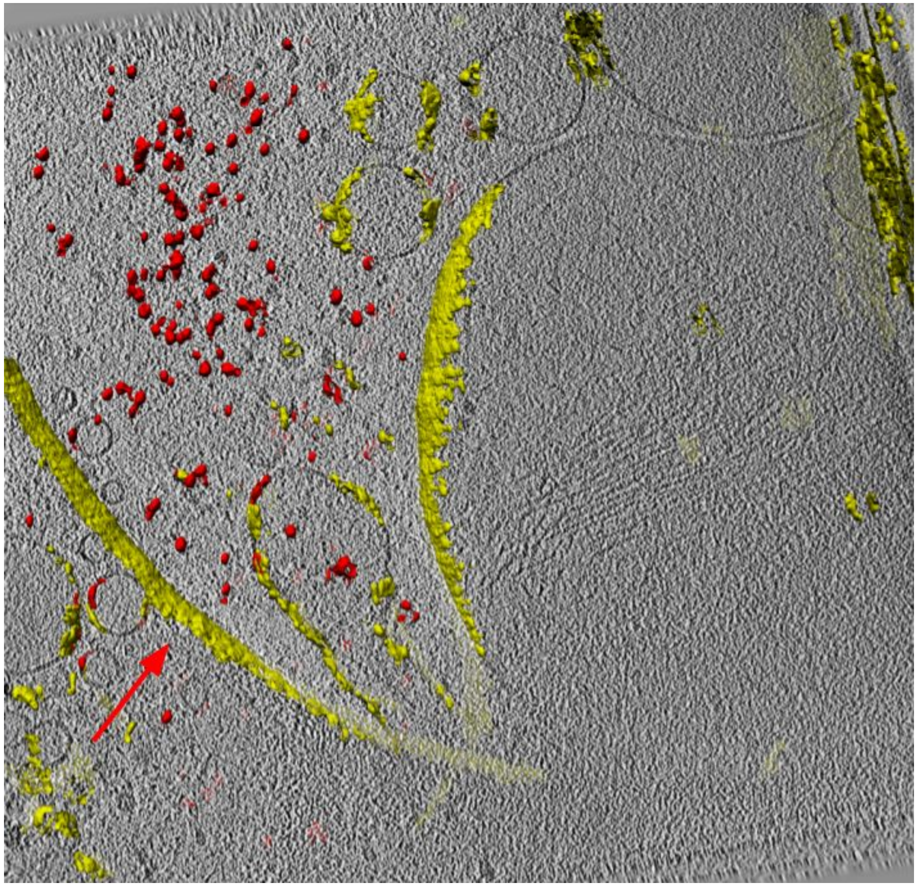
Voxelwise multiclass classification based segmentation



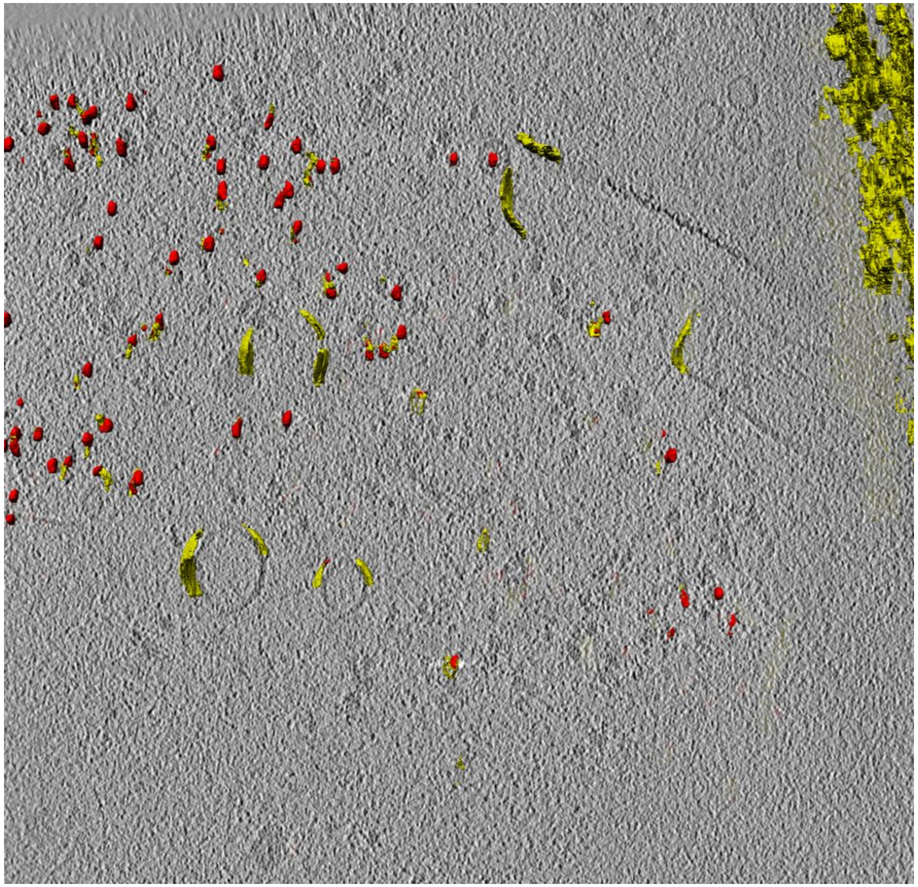
Zeng et al. JSB 2017

Weakly supervised segmentation

Training tomogram



Testing tomogram



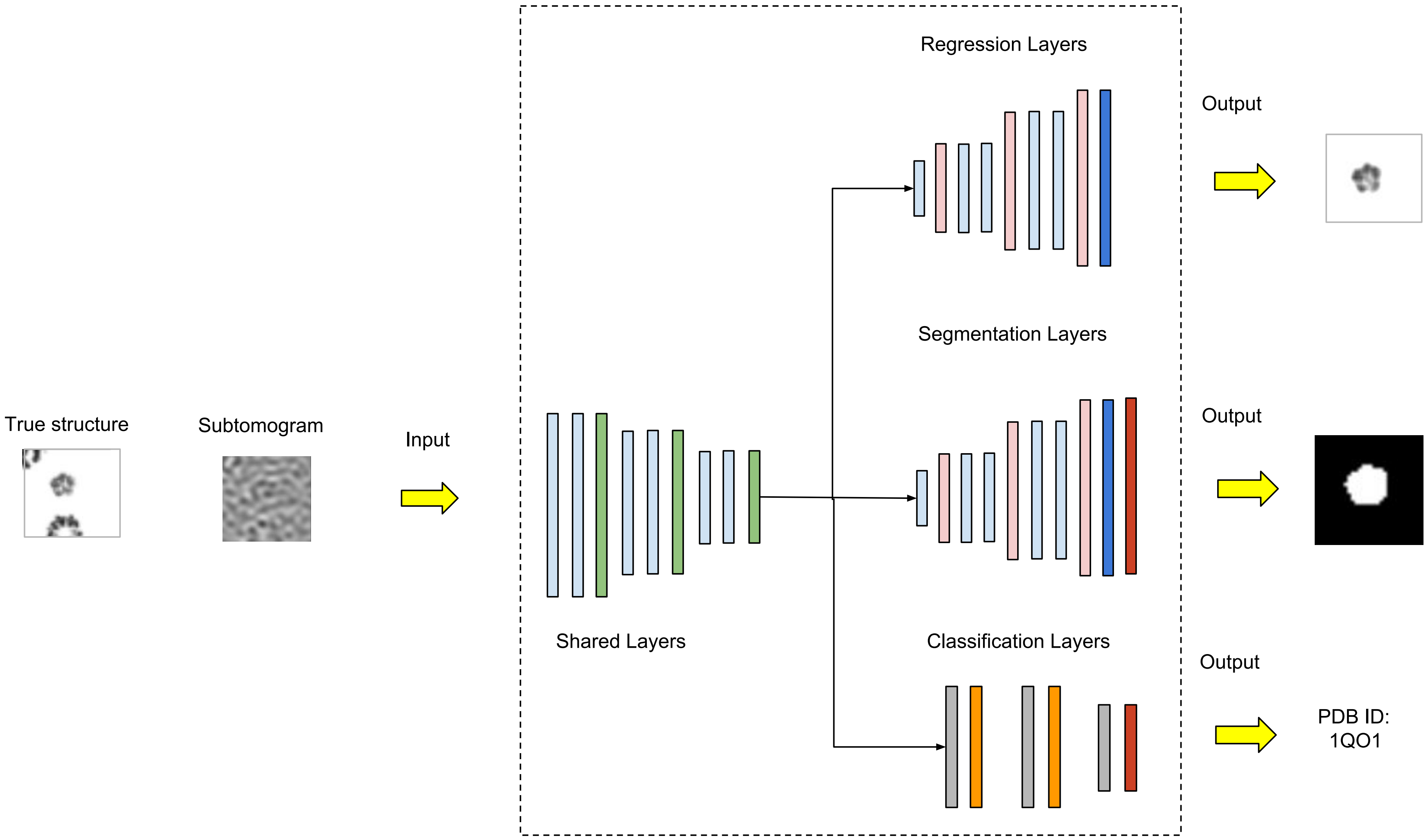
Autoencoder training → Segmentor training → Segmenter prediction

Zeng et al. JSB 2017

Simultaneous classification, segmentation, and density map inference

Liu et al. (under review)

Multi-task learning: concept



Liu et al. (under review)

Learnable generative model of pseudo macromolecular structures

Wang et al. (in progress)

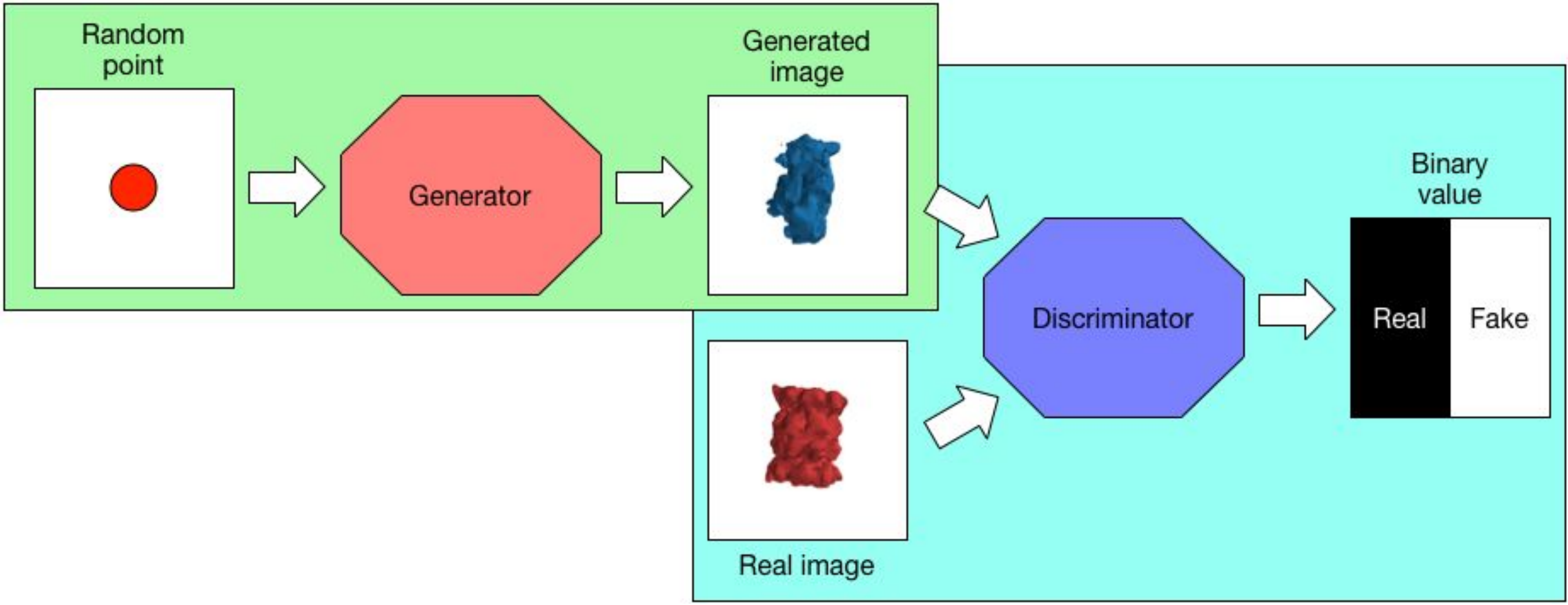
Motivation: hypothesis testing of template search

Given:

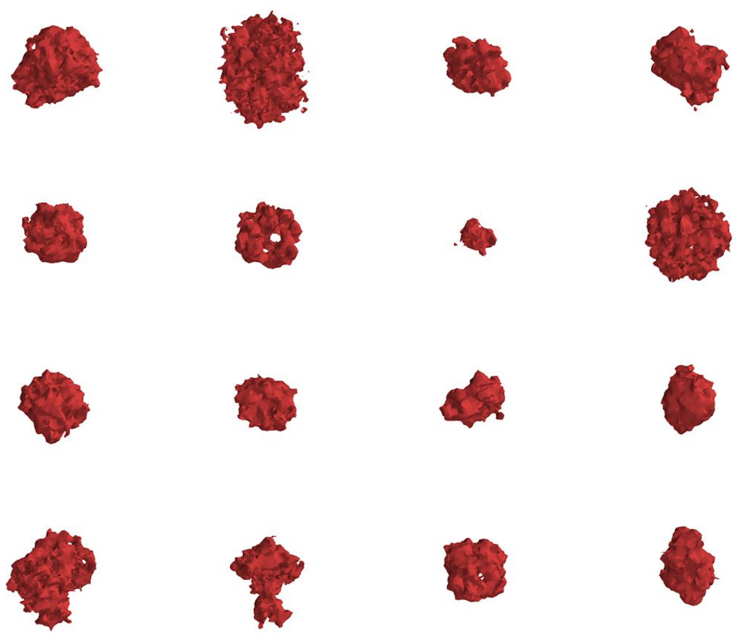
- a subtomogram S
- a structure T of interest
- a **random structure** T’ that is dissimilar to T
- a similarity measure p(S,T).

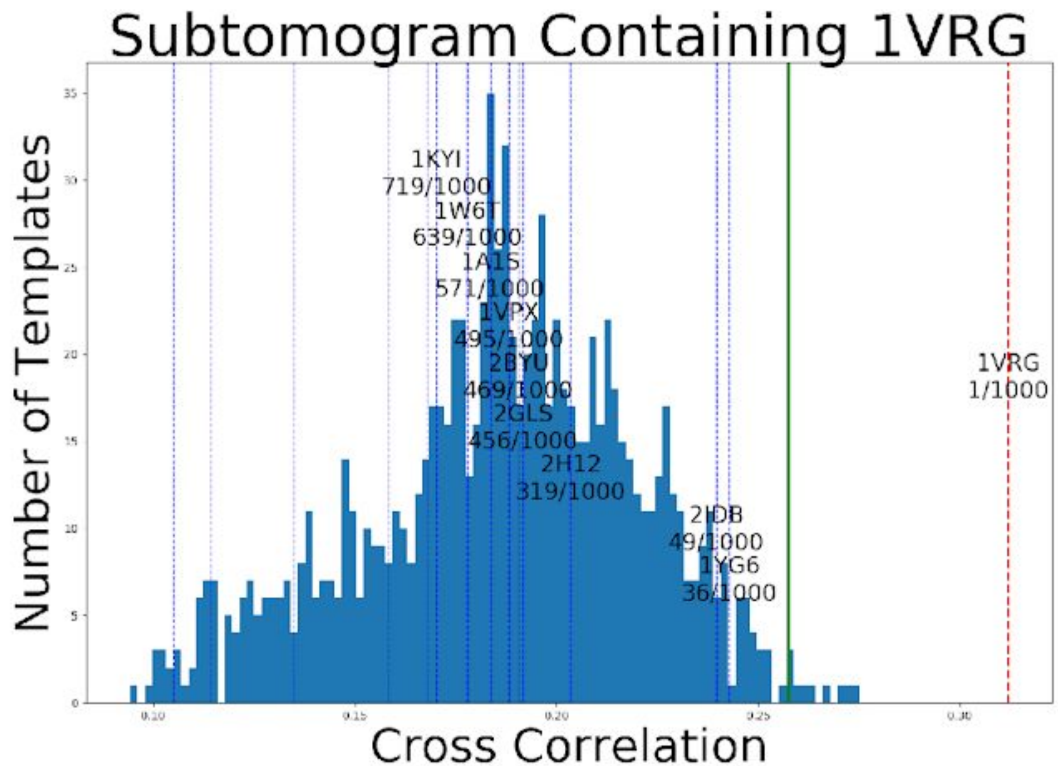
Question: How likely we will have p(S,T) > p(S, T’)?

3D generative adversarial network for sampling pseudo structure that "looks like" real ones



Learnable generative model of pseudo macromolecular structures





Summary

- Convolutional neural networks are potentially powerful tools for structural pattern mining
- Substantial further works needed to make supervised deep learning practically useful
  - Construction of good training data
  - Optimization of network models
  - Reduction of supervision

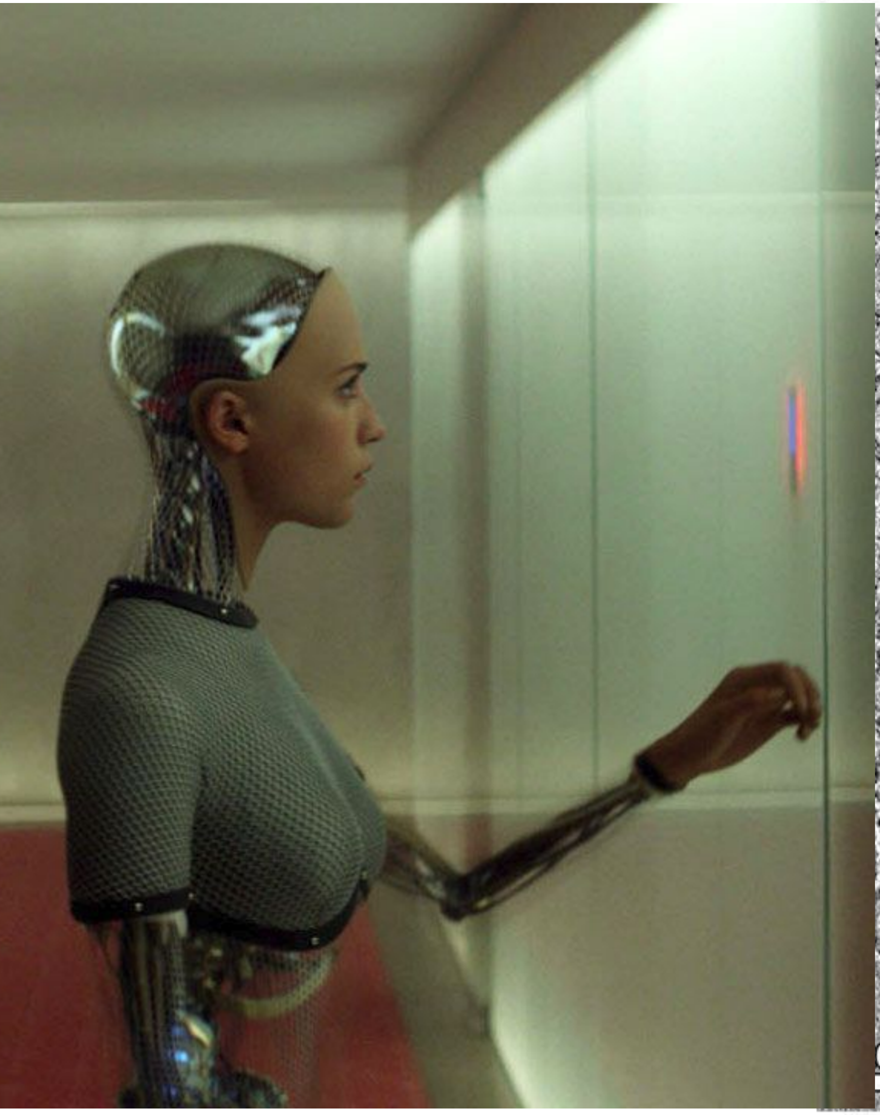
Proposal for the society: What's next?

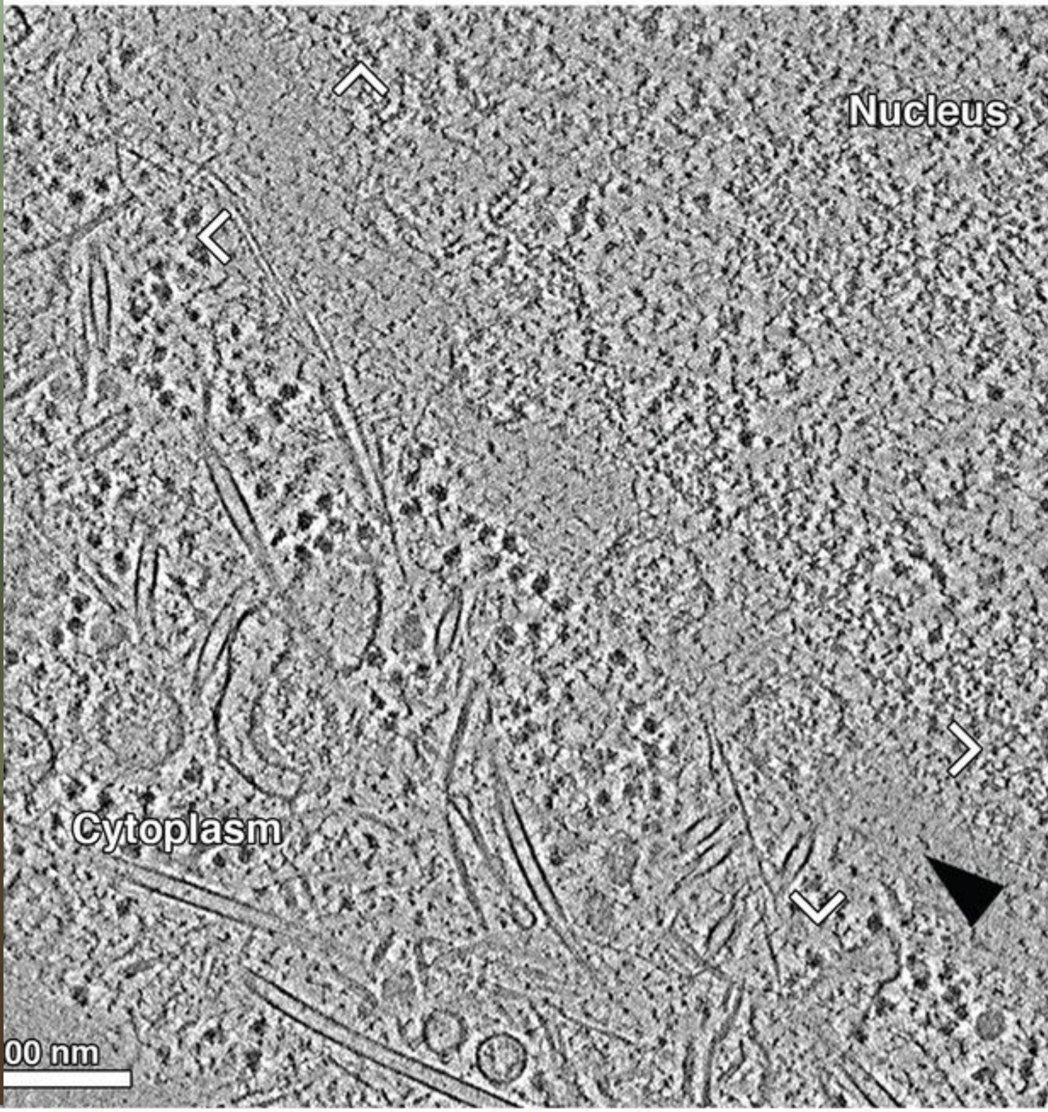
Construction of benchmark datasets and organize competitions

- Tomogram acquisition
- Manual annotation

- Object recognition, detection, segmentation, subtomogram classification & averaging etc.
- Accuracy, generalization ability etc.

AI for automatic understanding and analysis of tomogram





(Tomogram slice from Mahamid et al, 2016)

Thank you

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