Multi-CryoGAN:
Reconstruction of Continuous Conformations in Cryo-EM without pose nor conformation estimation

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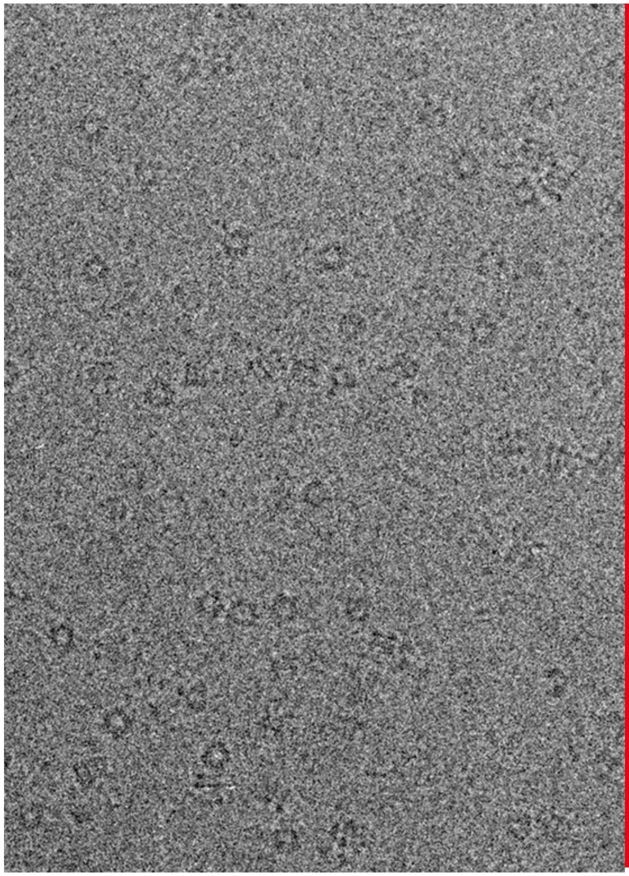
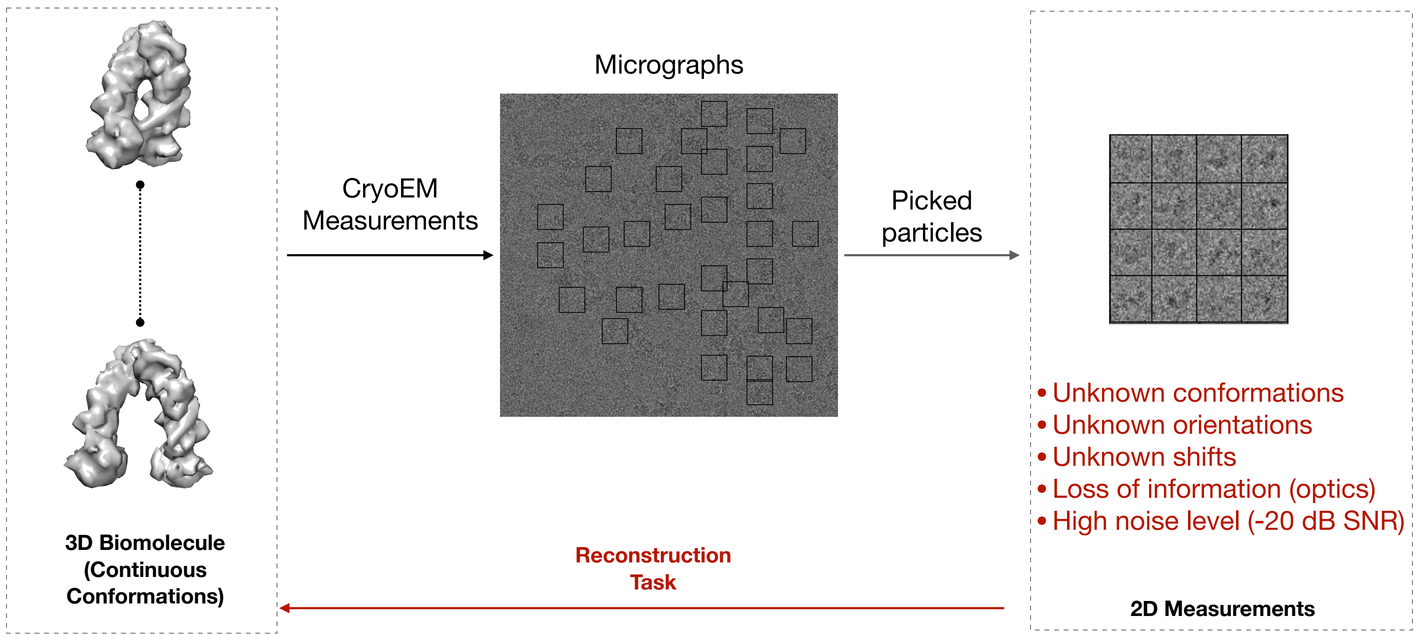
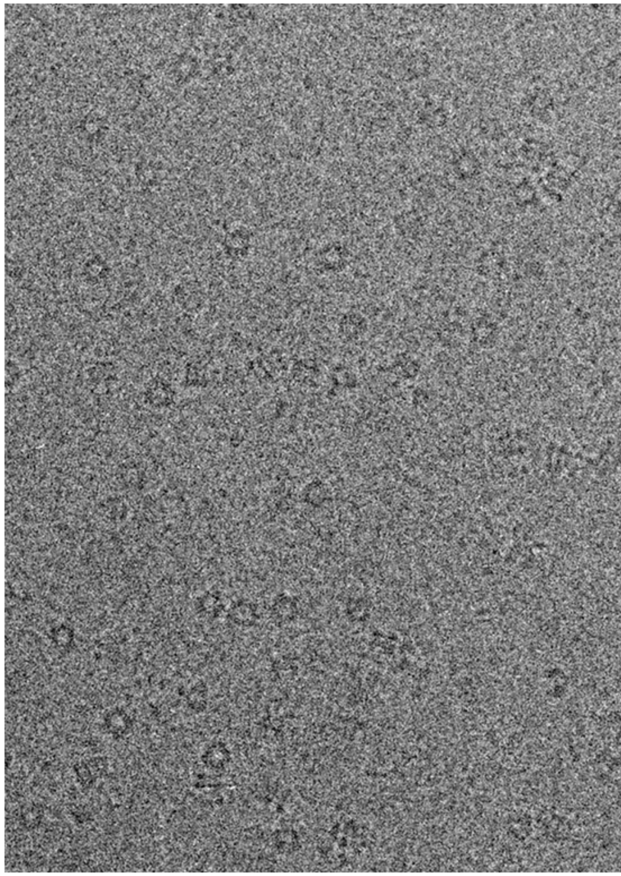
- Multi-CryoGAN for continuous conformations
  - Results



Challenges

Cryo-EM reconstruction problem

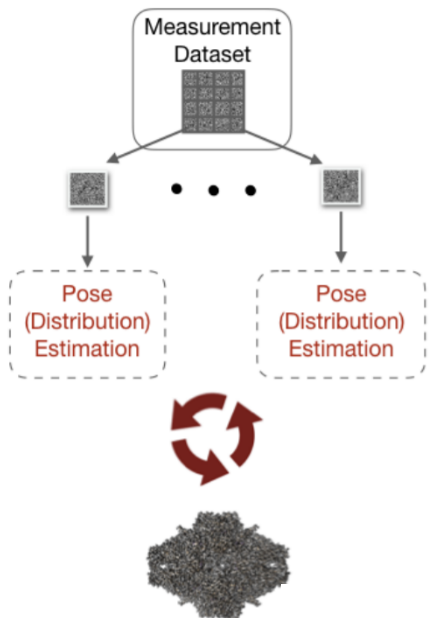




Current Methods

Current Methods

- Use complicated routines to estimate pose (or distribution) for each projection.

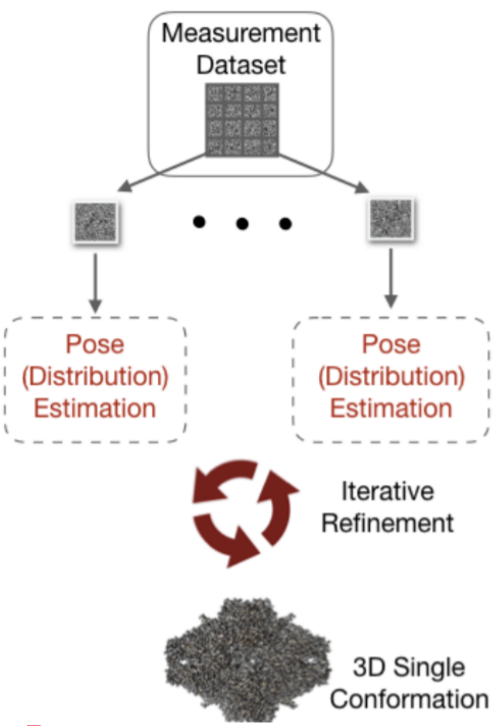


- Number of variables to estimate grow with the data size.

Standard reconstruction method in Cryo-EM

Standard techniques

(Likelihood-based)



Single Conformation

$$\mathbf{x}_{\text{rec}} = \arg\max_{\mathbf{x}} \sum_{n=1}^{N} \log p(\mathbf{y}_{\text{data}}^{n} | \mathbf{x})$$

Pose (distribution) estimation for each projection

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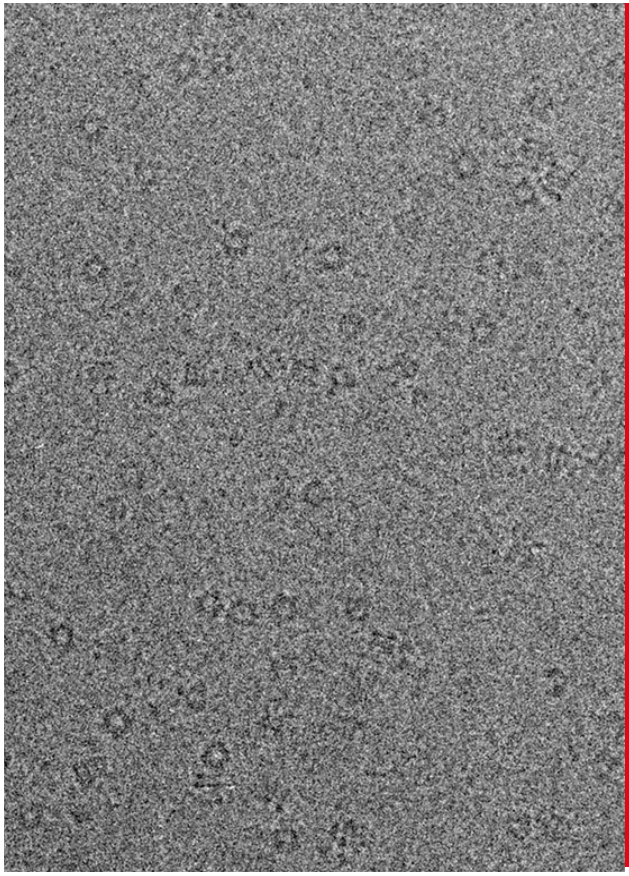
Multiple Conformation

Pose (distribution) estimation for each projection

Conformation estimation for each projection

[Dashti et al., 2014, Anden et al. 2015 Moscovich et al., 2020, Lederman et al. 2020, Seitz et al. 2019, Sorzano et al. 2020, Zhong et a. 2020]

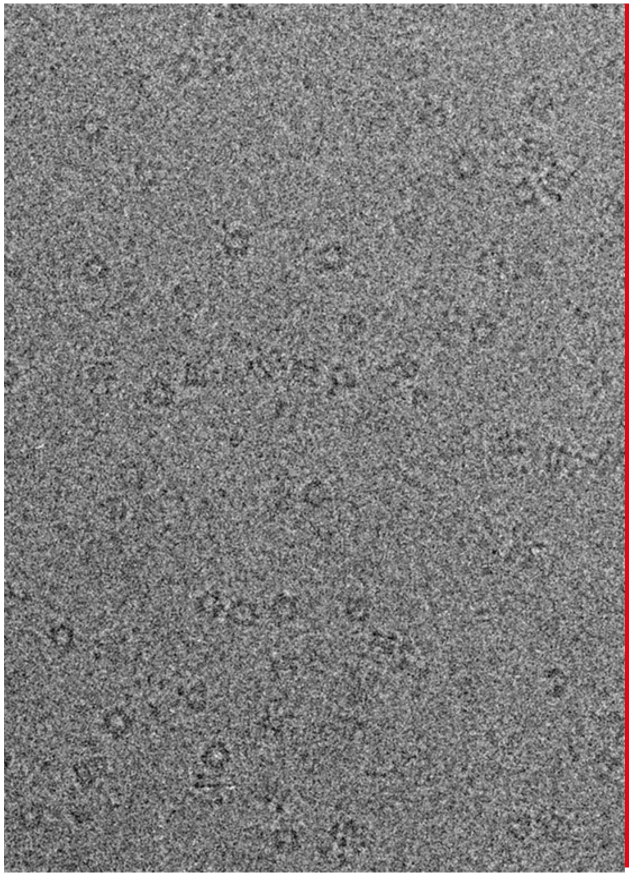
How about no pose or conformation estimation routine?



CryoGAN for single conformation

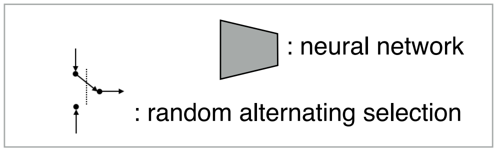
Intuition

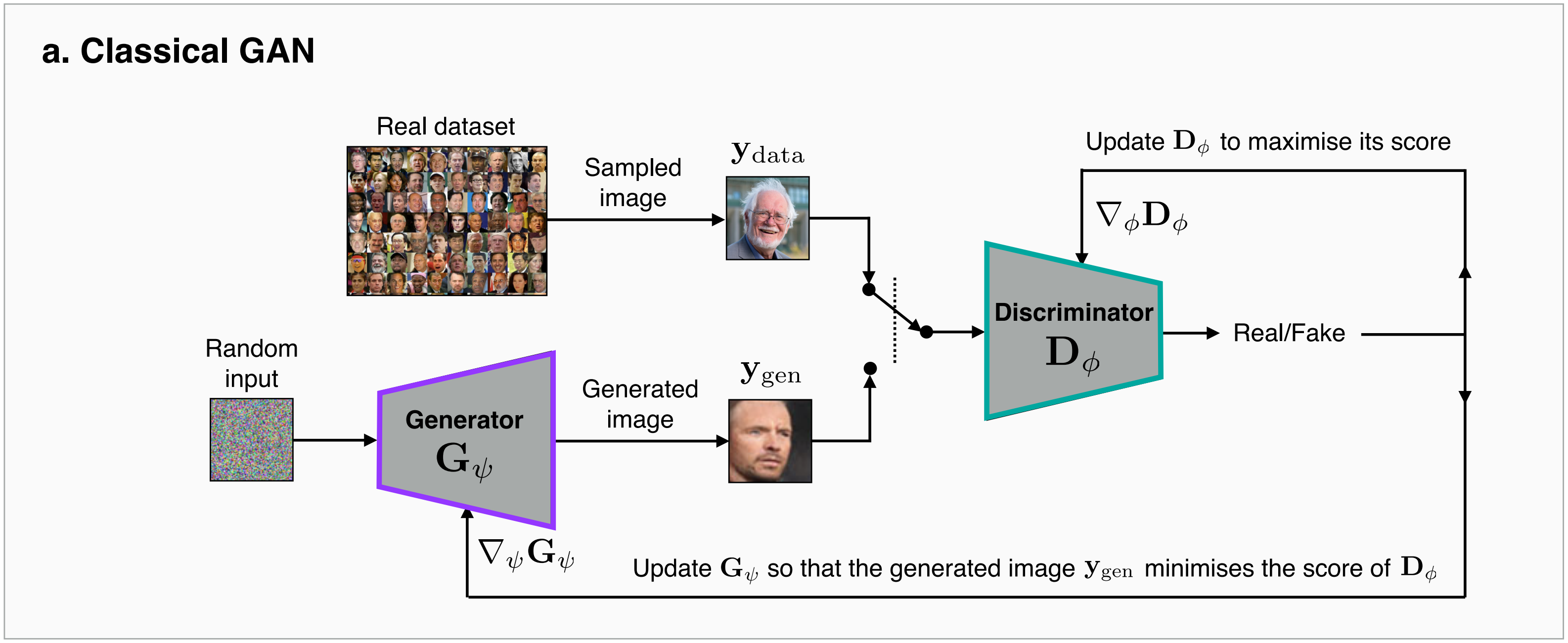
Reconstruct the structure whose
“set of projections from random poses”
looks similar to
“acquired data”



Top-Bottom View

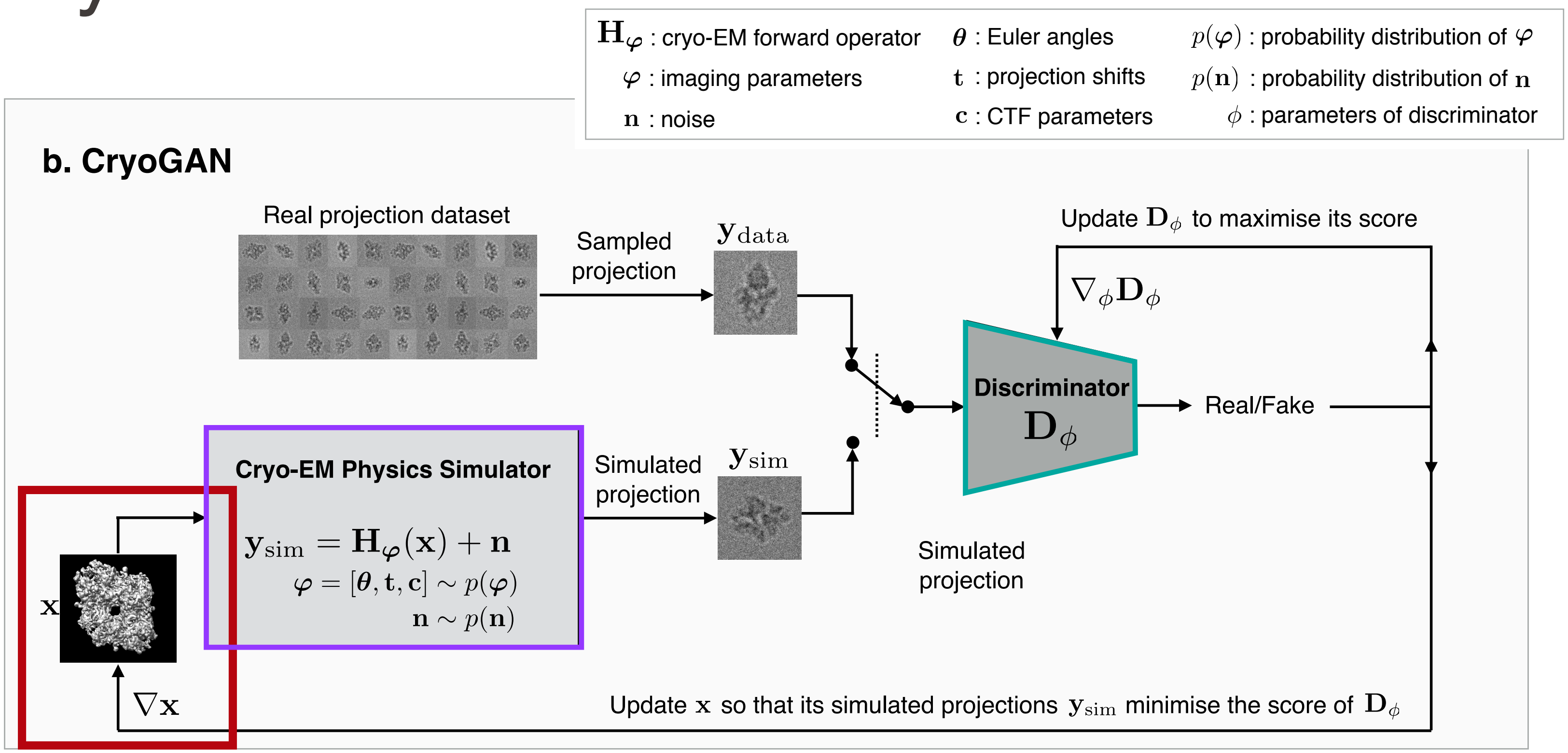
Classical GAN



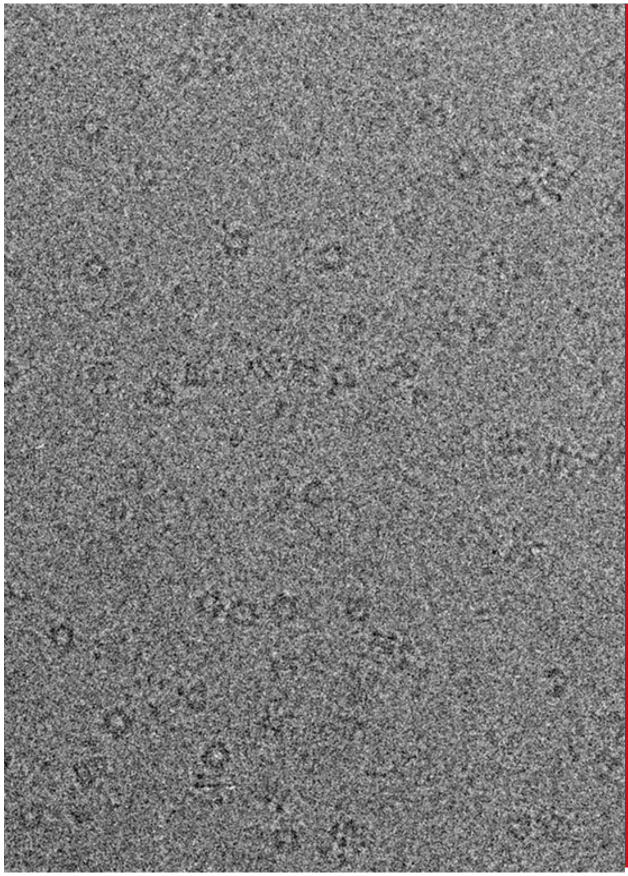


- **Discriminator** Learns to **discriminate** between real and fake (=synthetic) faces
- **Generator** Learns to **generate** fake (=synthetic) faces that fool the discriminator
- **Adversarial** **Captures the distribution of the real dataset** https://thispersondoesnotexist.com/

CryoGAN

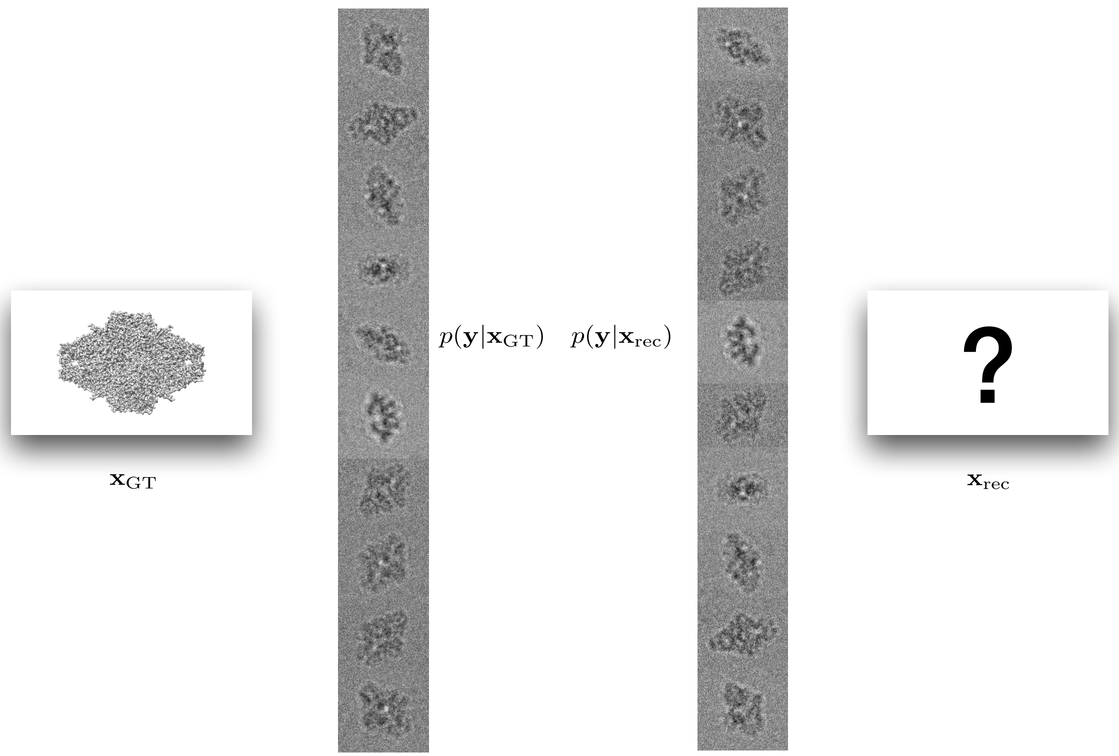


- **Discriminator** — Learns to **discriminate** between real and fake (=synthetic) projections
- **Cryo-EM Simulator** — **Generate** fake (=synthetic) projections from a given 3D volume
- **Adversarial** — **Learns a volume whose fake projections fool the Discriminator**



Bottom-Top View

Distribution Matching



Distribution Matching

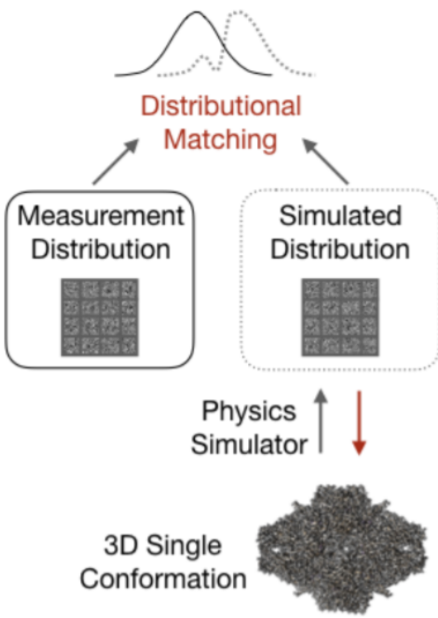
- Why?

- With some assumptions on forward model.

Theorem 1. $p(\mathbf{y}|\mathbf{x}_1) = p(\mathbf{y}|\mathbf{x}_2) \Leftrightarrow \mathbf{x}_1 = G(\mathbf{x}_2)$,
where G is some rotation-reflection operation.

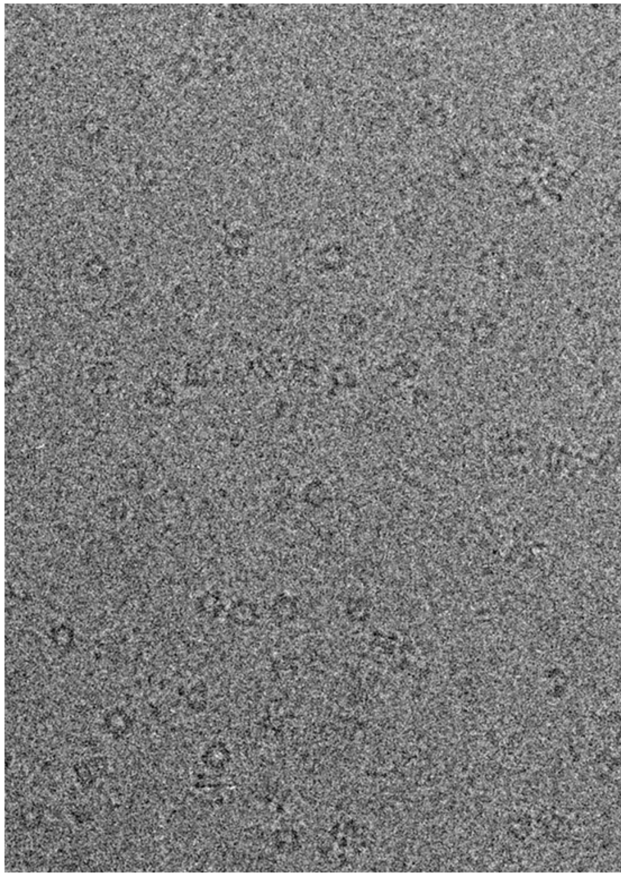
[G., 2020]

Distribution Matching



- Learn a 3D volume whose **simulated projection distribution** matches **data distribution**

- Use GAN
- No pose estimation
- No required good initial volume
- End-to-end



Algorithm

Distances

- Wasserstein Distance

$$WD(p_1, p_2) = \inf_{\gamma \in \Pi(p_1, p_2)} \mathbb{E}_{(\mathbf{y}_1, \mathbf{y}_2) \sim \gamma} [\|\mathbf{y}_1 - \mathbf{y}_2\|]$$

$$\mathbf{x}_{\text{rec}} = \underset{\mathbf{x}}{\operatorname{argmin}} \inf_{\gamma \in \Pi(p_{\mathbf{x}}, p_{\text{data}})} \mathbb{E}_{(\mathbf{y}_1, \mathbf{y}_2) \sim \gamma} [\|\mathbf{y}_1 - \mathbf{y}_2\|]$$

- Dual form

$$\mathbf{x}_{\text{rec}} = \underset{\mathbf{x}}{\operatorname{argmin}} \max_{s : \|s\|_L < 1} \left(\mathbb{E}_{\mathbf{y} \sim p_{\text{data}}} [s(\mathbf{y})] - \mathbb{E}_{\mathbf{y} \sim p_{\mathbf{x}}} [s(\mathbf{y})] \right)$$

- Using Neural Network : universal approximation property

$$\mathbf{x}_{\text{rec}} = \underset{\mathbf{x}}{\operatorname{argmin}} \max_{\mathbf{D}_\phi : \|\mathbf{D}_\phi\|_L < 1} \left(\mathbb{E}_{\boxed{\mathbf{y} \sim p_{\text{data}}}} [\mathbf{D}_\phi(\mathbf{y})] - \mathbb{E}_{\boxed{\mathbf{y} \sim p_{\mathbf{x}}}} [\mathbf{D}_\phi(\mathbf{y})] \right)$$

Acquired Measurements

Simulated measurements

Optimization

- Min max loss

$$\mathbf{x}_{\mathrm{rec}} = \operatorname*{argmin}_{\mathbf{x}} \max_{\mathbf{D}_\phi} \left(\mathbb{E}_{\mathbf{y}\sim p_{\mathrm{data}}}[\mathbf{D}_\phi(\mathbf{y})] - \mathbb{E}_{\mathbf{y}\sim p_{\mathbf{x}}}[\mathbf{D}_\phi(\mathbf{y})] + \lambda \cdot \mathbb{E}_{\mathbf{y}\sim p_{\mathrm{int}}}[(\|\nabla_{\mathbf{y}}\mathbf{D}_\phi(\mathbf{y})\| - 1)^2] \right)$$

- Sample a batch

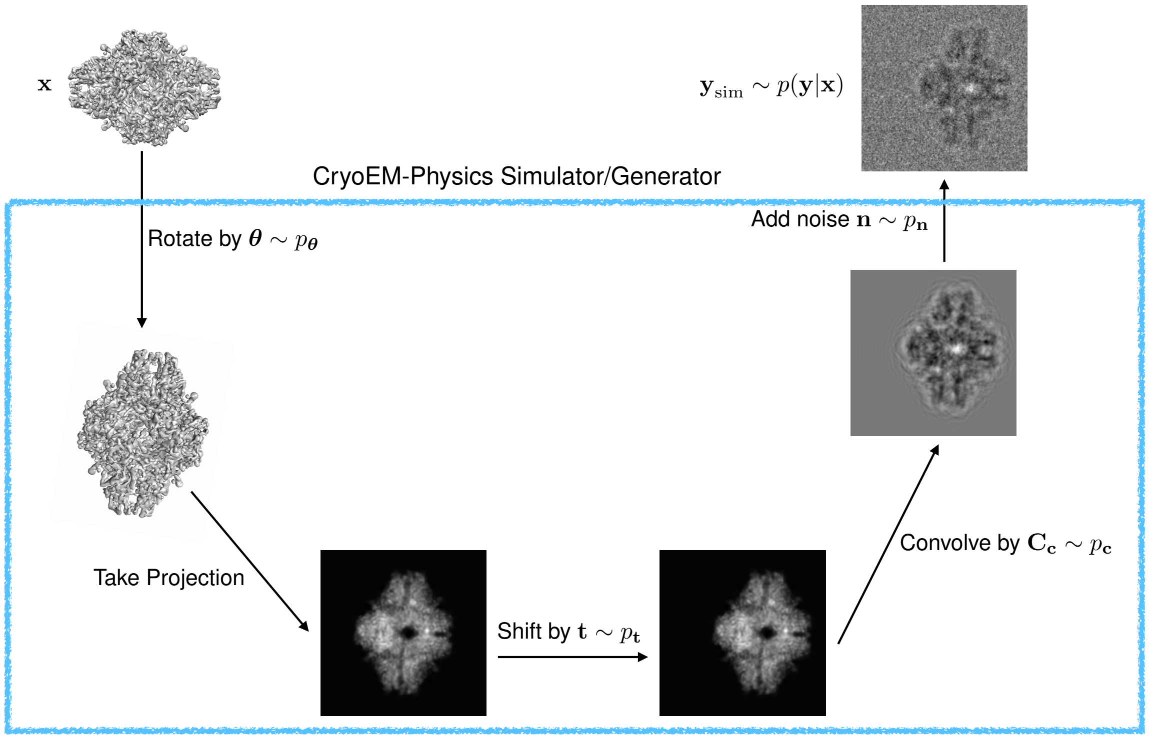
$$\mathbf{y}^b_{\mathrm{data}} \sim p_{\mathrm{data}} \qquad \mathbf{y}^b_{\mathrm{sim}} \sim p_{\mathbf{x}} \qquad \mathbf{y}^b_{\mathrm{int}} \sim p_{\mathrm{int}}$$

- Empirical

$$L_S(\mathbf{x}, \mathbf{D}_\phi) = \sum_{b=1}^{B} \mathbf{D}_\phi(\mathbf{y}^b_{\mathrm{data}}) - \sum_{b=1}^{B} \mathbf{D}_\phi(\mathbf{y}^b_{\mathrm{sim}}) + \lambda \sum_{b=1}^{B} (\|\nabla_{\mathbf{y}}\mathbf{D}_\phi(\mathbf{y}^b_{\mathrm{int}})\| - 1)^2)$$

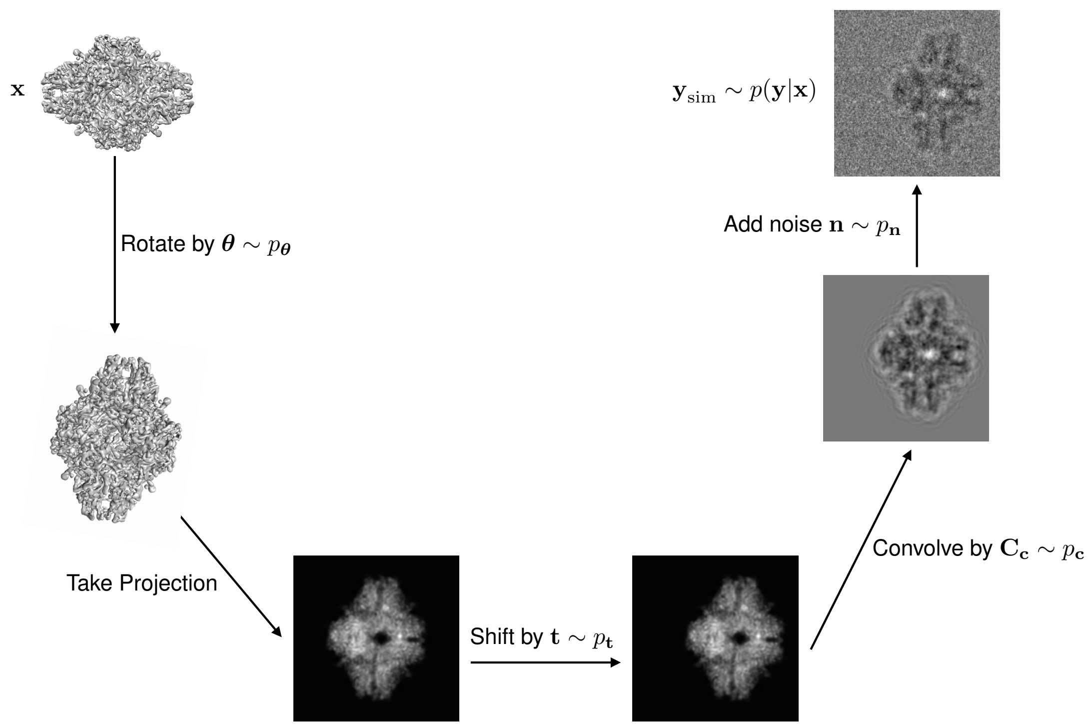
Sampler/Simulator/Generator/

- CryoEM physics simulator



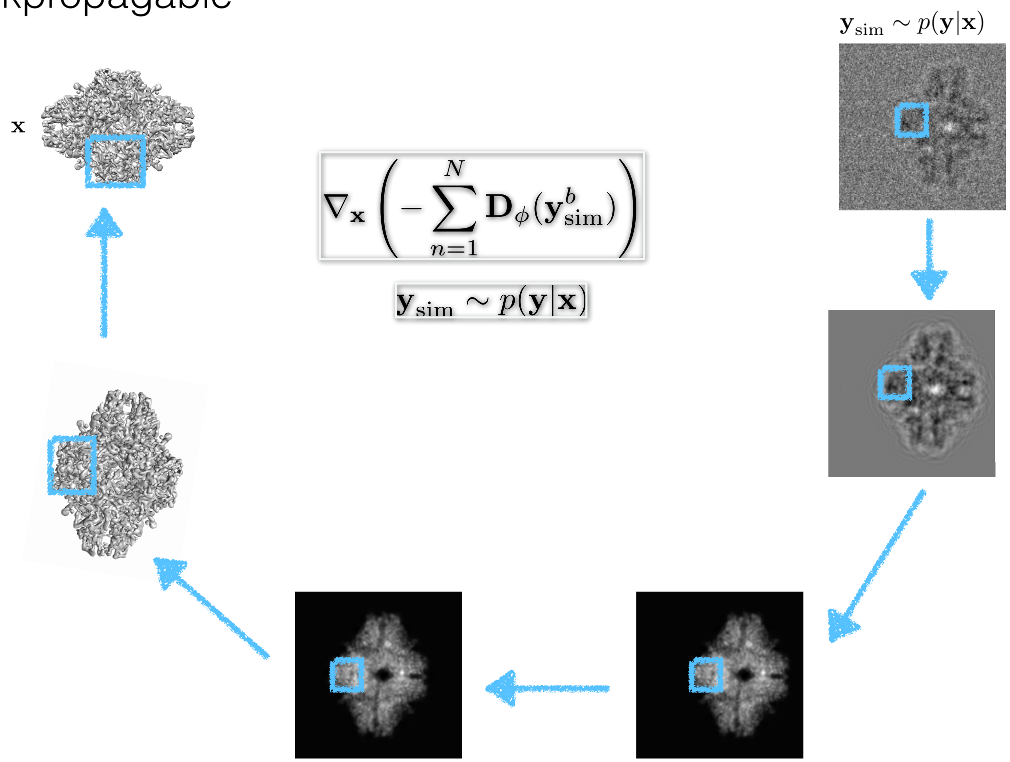
Simulator/Generator

- Sample $\mathbf{y}_{\text{sim}} \sim p(\mathbf{y}|\mathbf{x})$



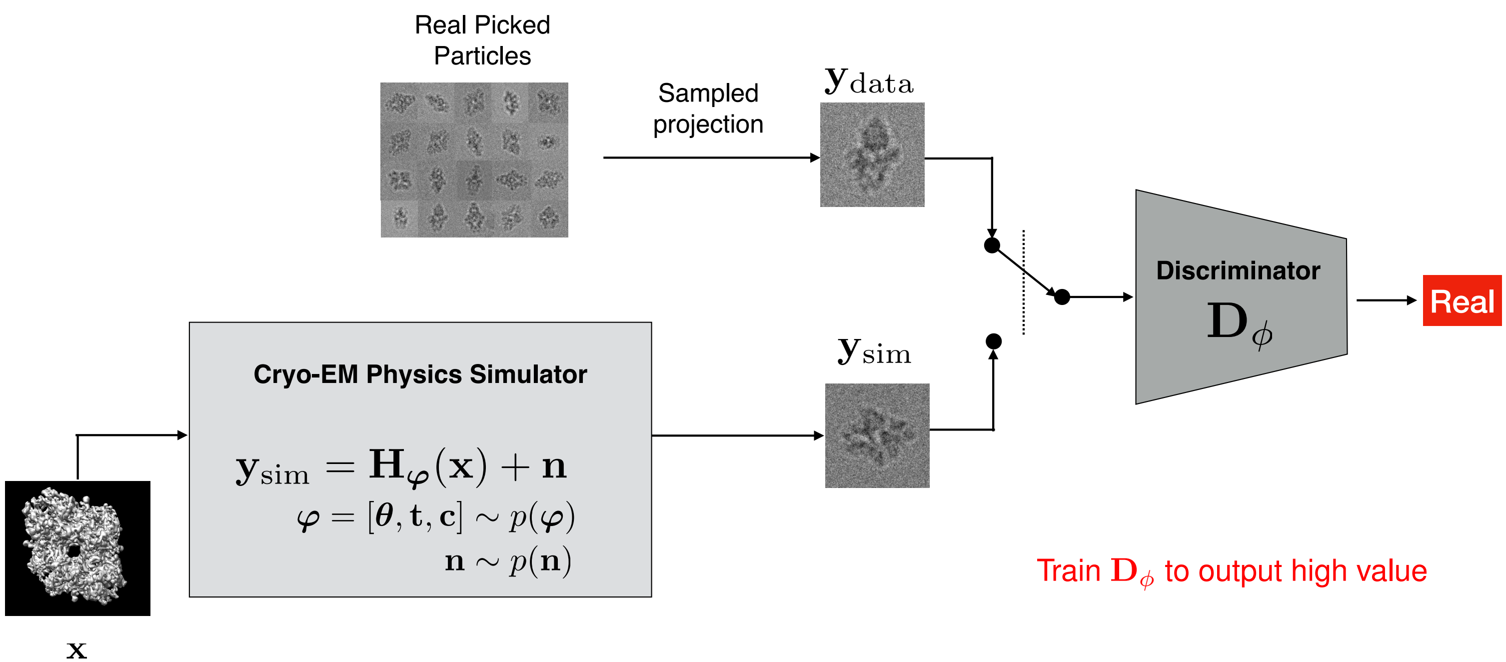
Simulator/Generator

- Backpropagable



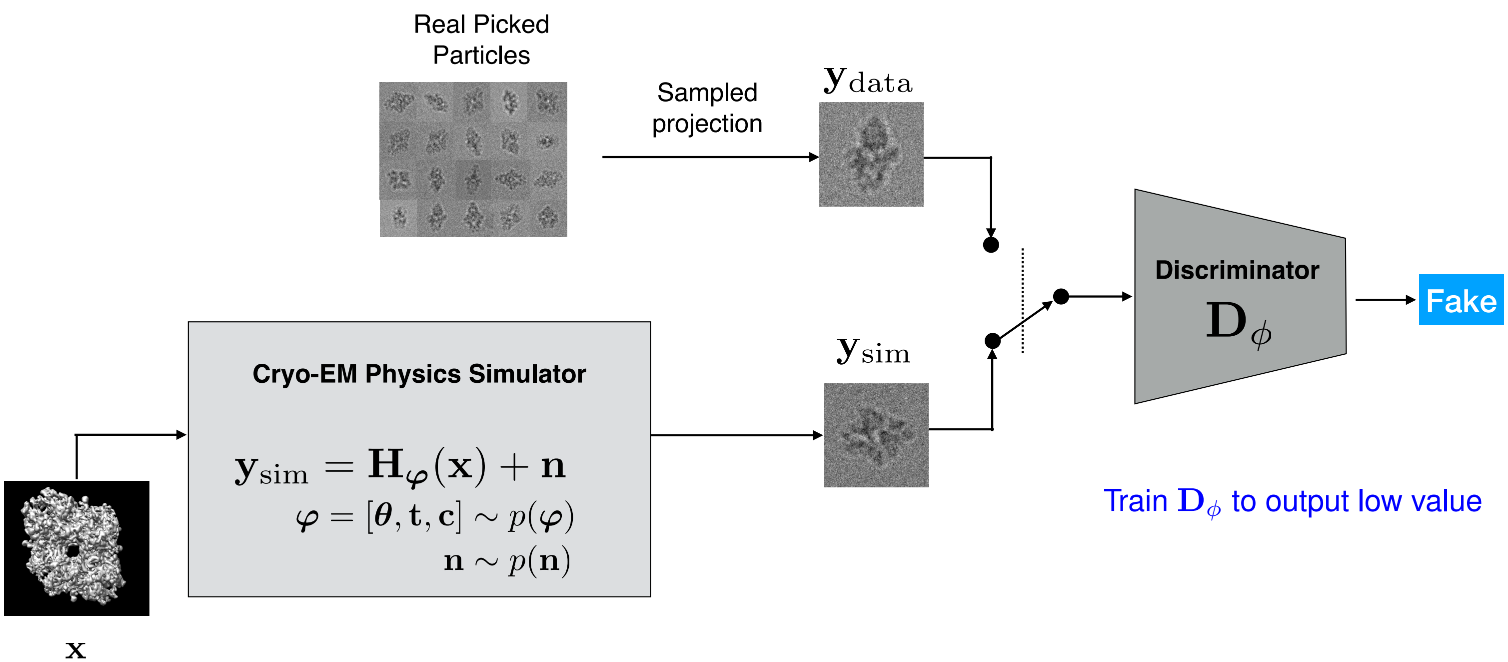
CryoGAN

- Discriminator



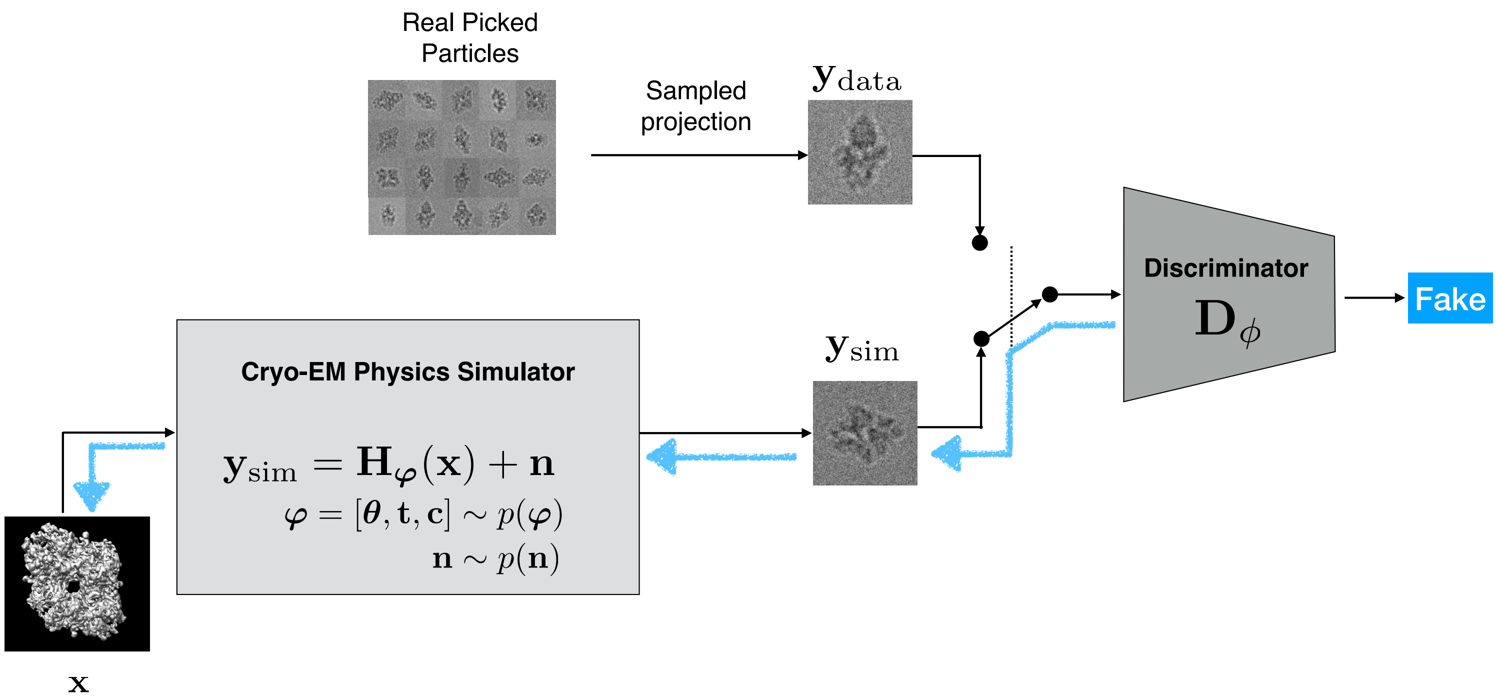
CryoGAN

- Discriminator

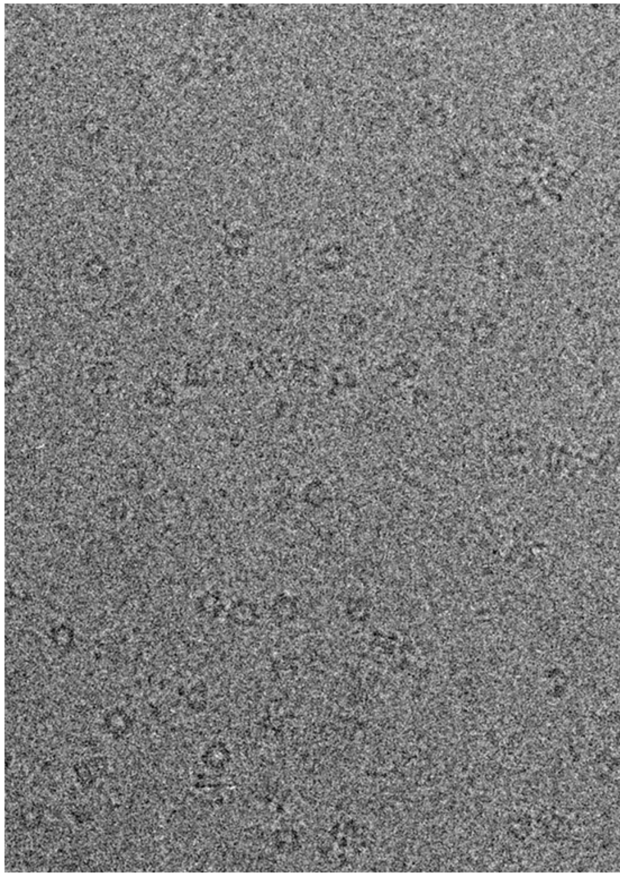


CryoGAN

- Generator



Change $\mathbf{x}$ to output high value



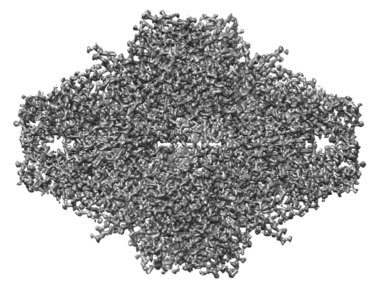
Experiments & Results

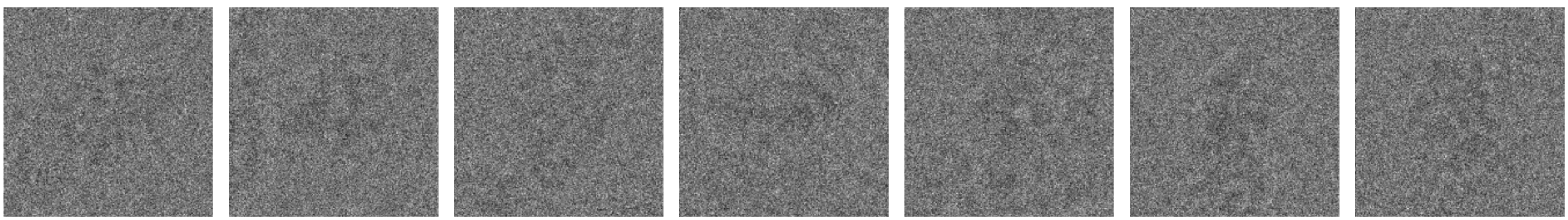
Synthetic experiments

Real experiments

Synthetic Experiment (-20 dB Noise)

- Synthetic beta-gal. volume
- Density map fitted on atomic model (2.5 A)
- 41,000 projections, uniformly distributed
- Realistic CTF and noise conditions
- Noise extracted from experimental micrographs





41000 projections

Results (Structure)