Active Generative Models for Out-of-Distribution Discovery: from Theory to Molecules

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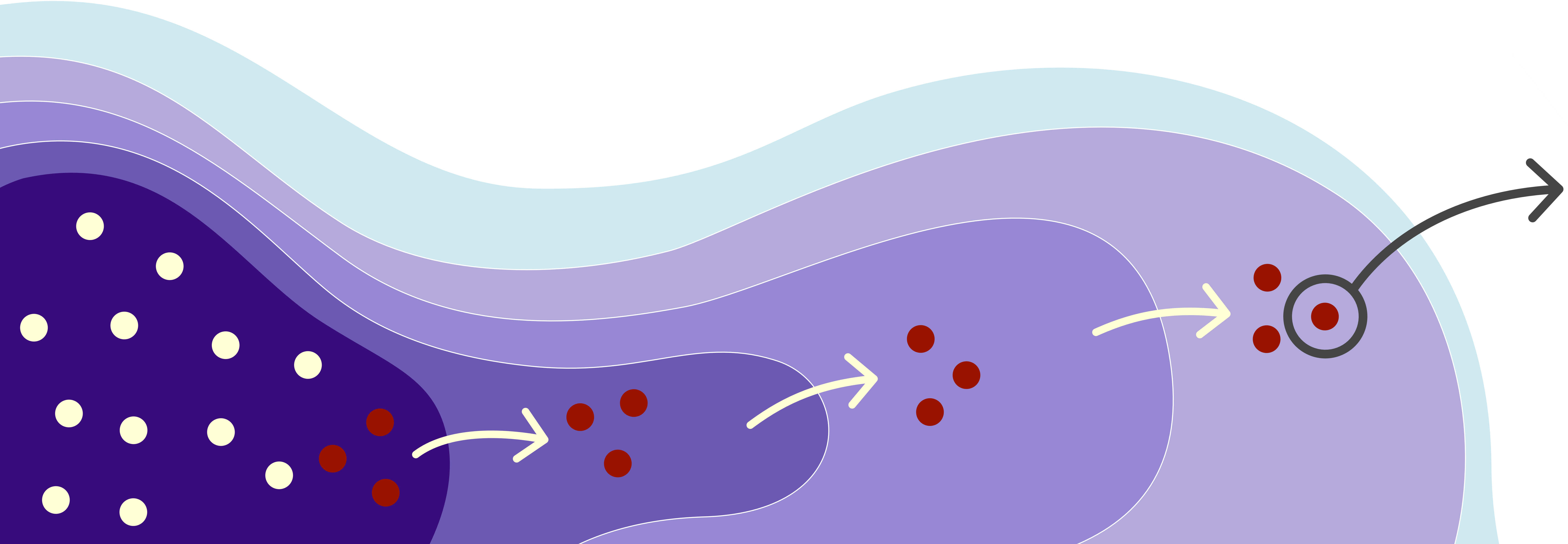
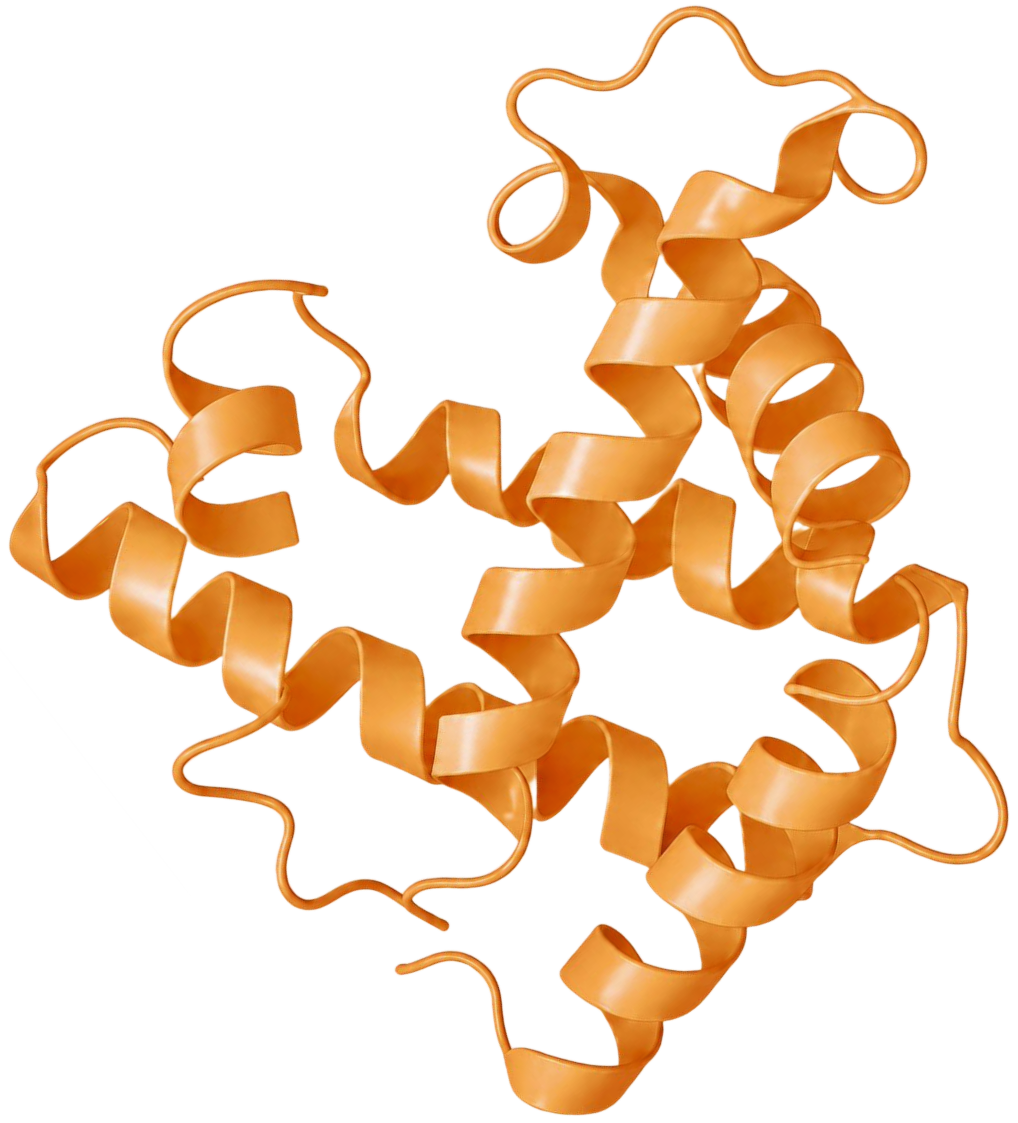




UNIST, July 13th, 2026

Team

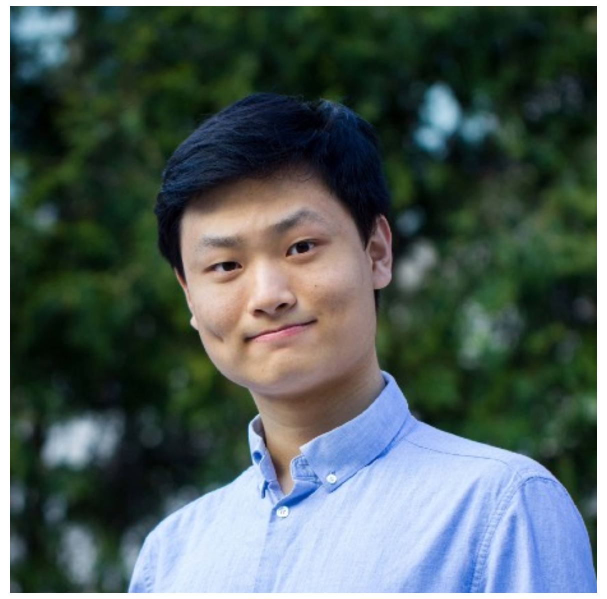

Riccardo De Santi


Bruce Lee


Cristian P. Jensen


Kimon Protopapas


Sophia Tong


Chenghao Liu


Pranam Chatterjee

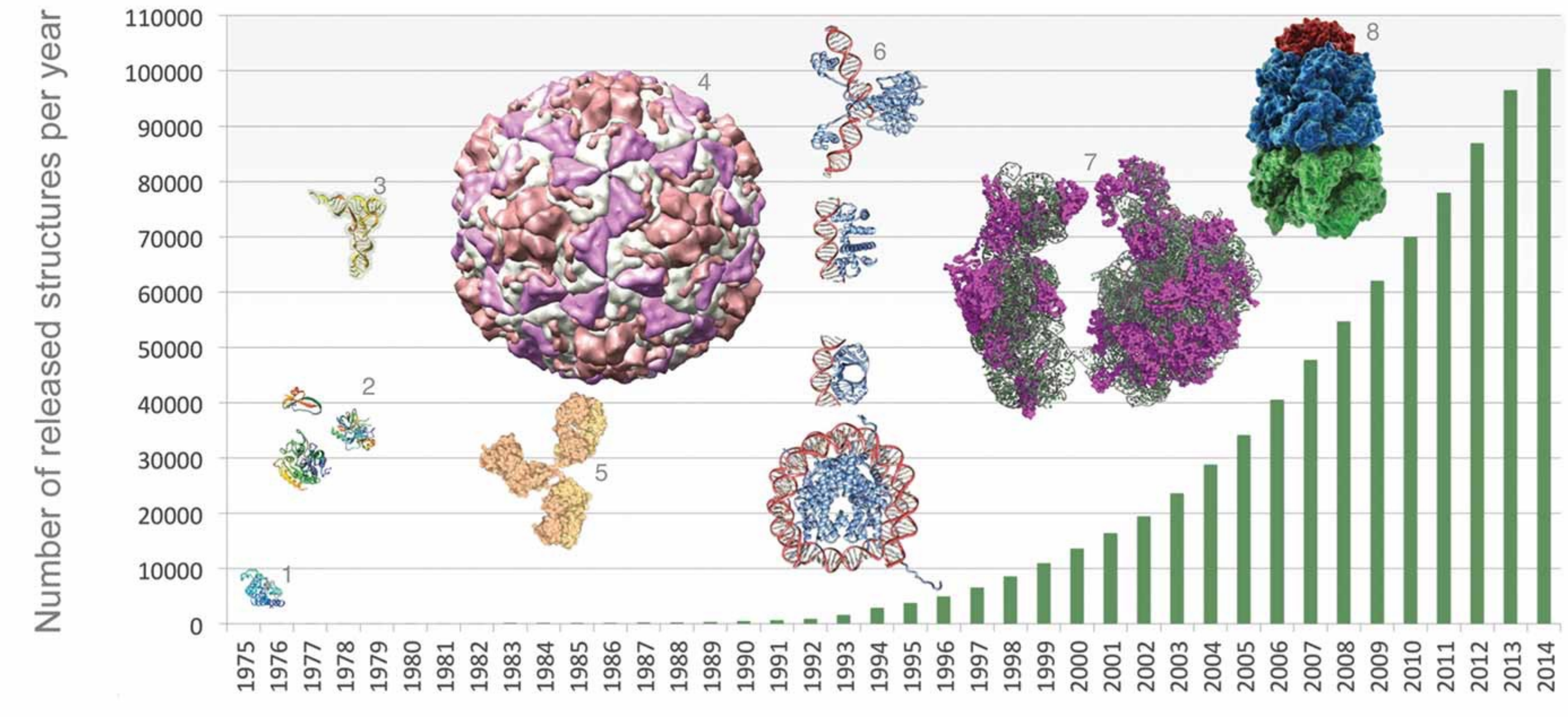

Yisong Yue


Andreas Krause

Generative Models

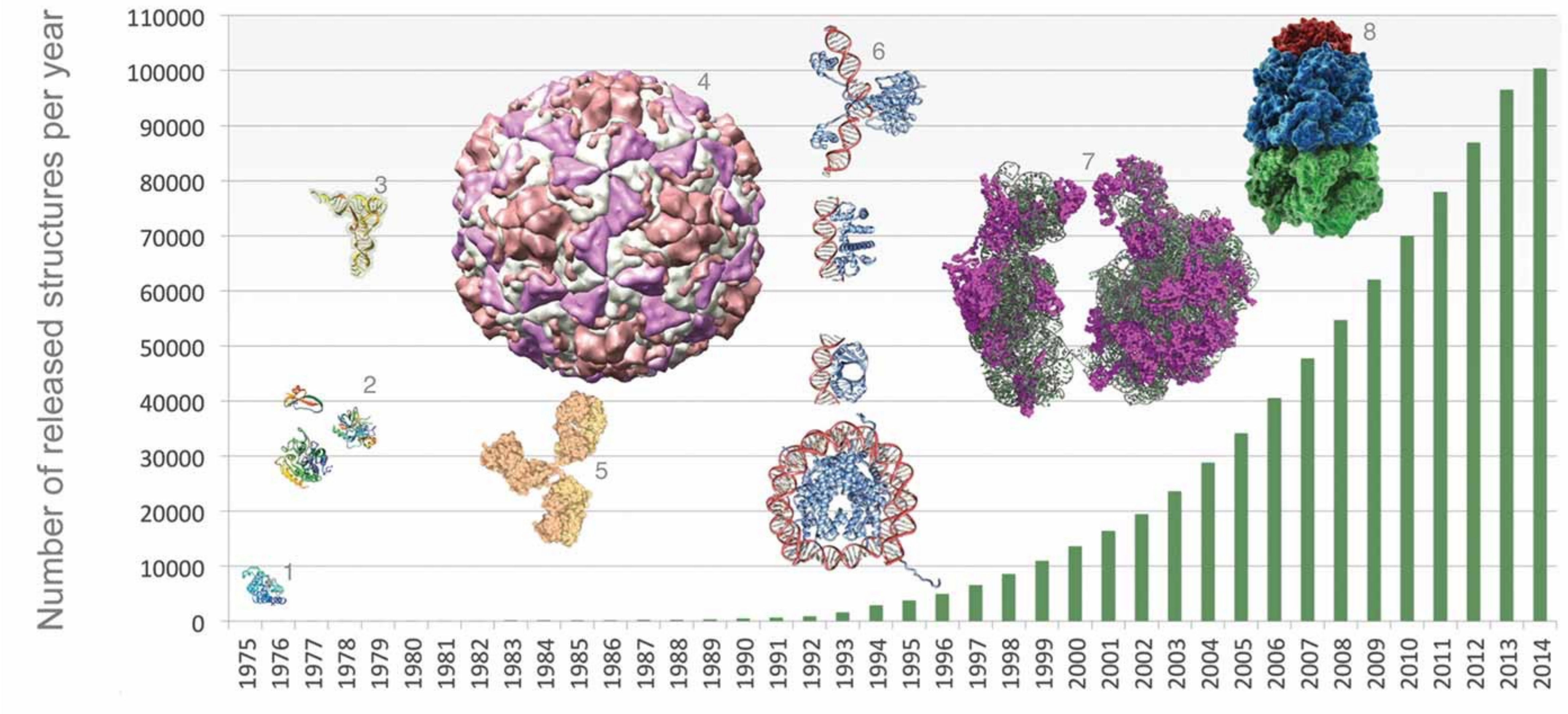
[Steven Wommack]

Generative Models for Science



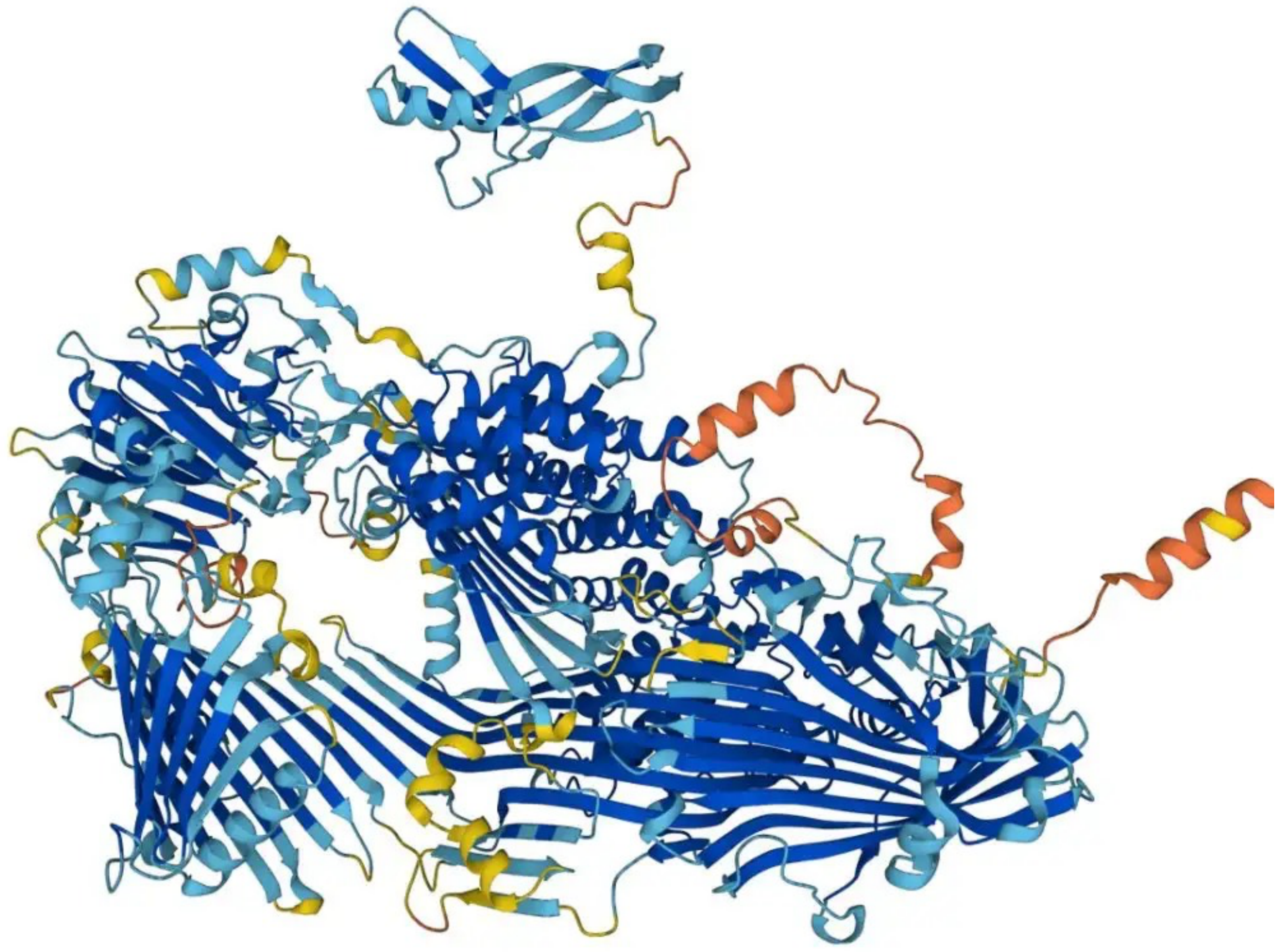
Protein Data Databank **(PDB)**

Generative Models for Science

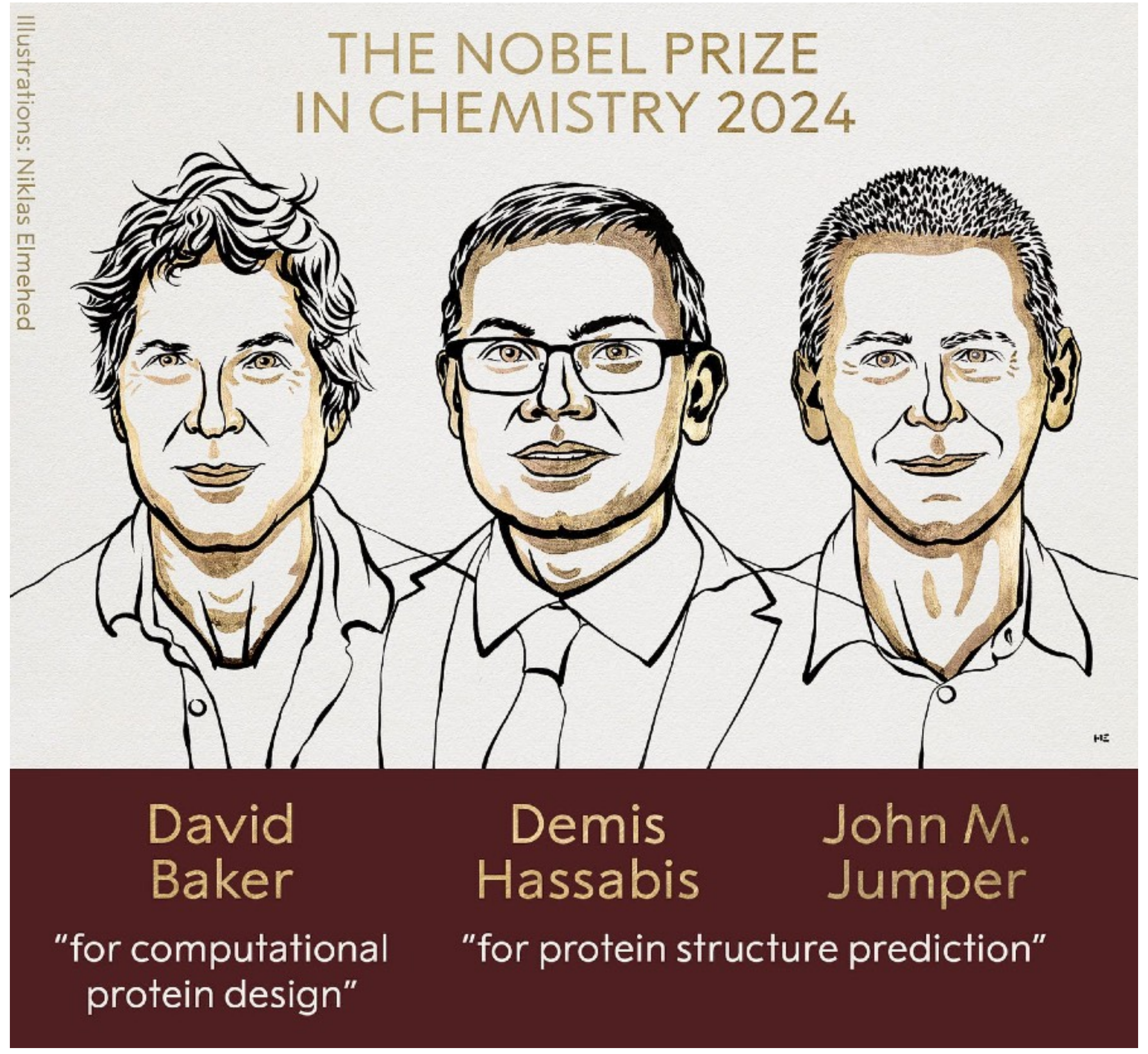


Protein Data Databank **(PDB)**

Protein structure prediction and design



2024 Chemistry Nobel Prize



Generative ~~Modeling~~ Discovery?

What is Discovery?

black-box function (reward)

$$\underset{x \in \Omega}{argmax}\; f(x)$$

valid design space (e.g., drugs, materials)

(or **action space**)

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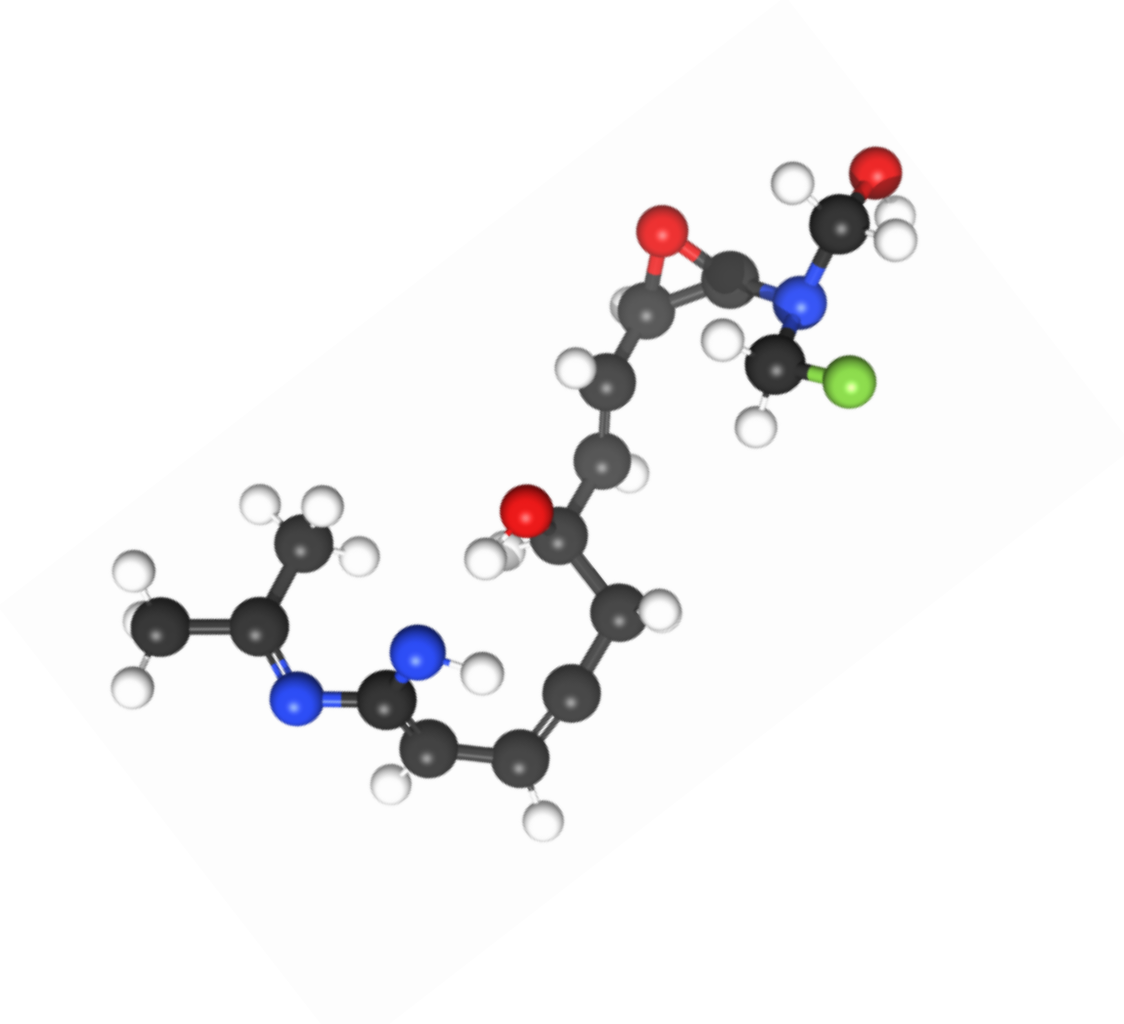
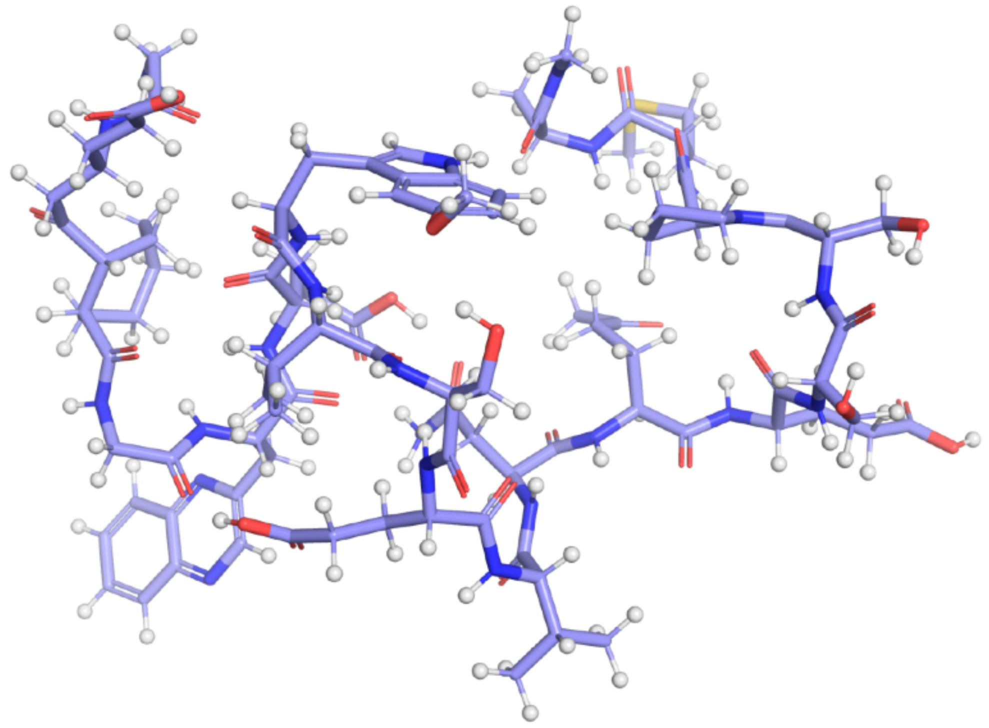
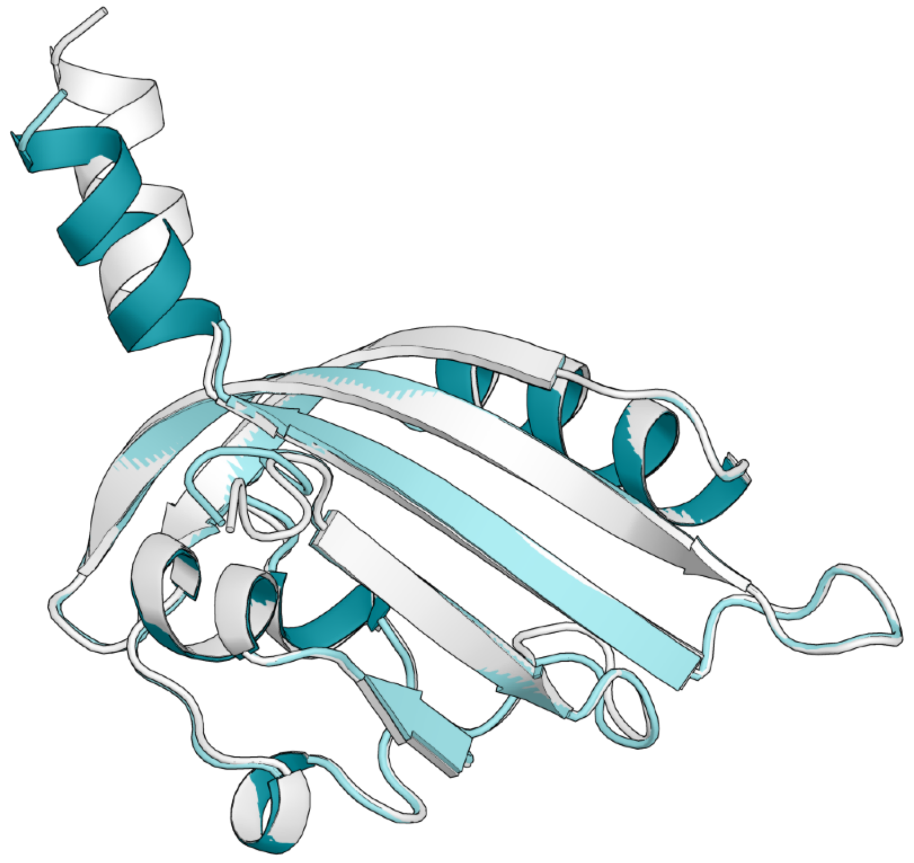
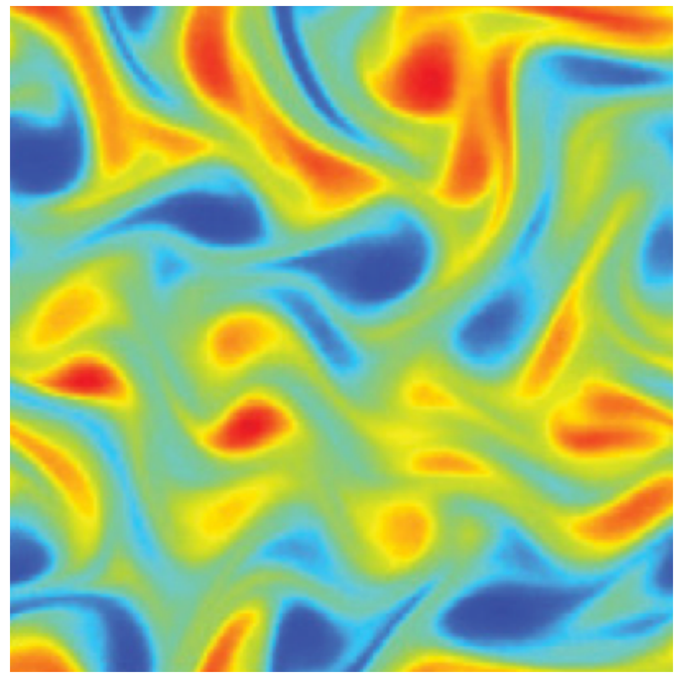
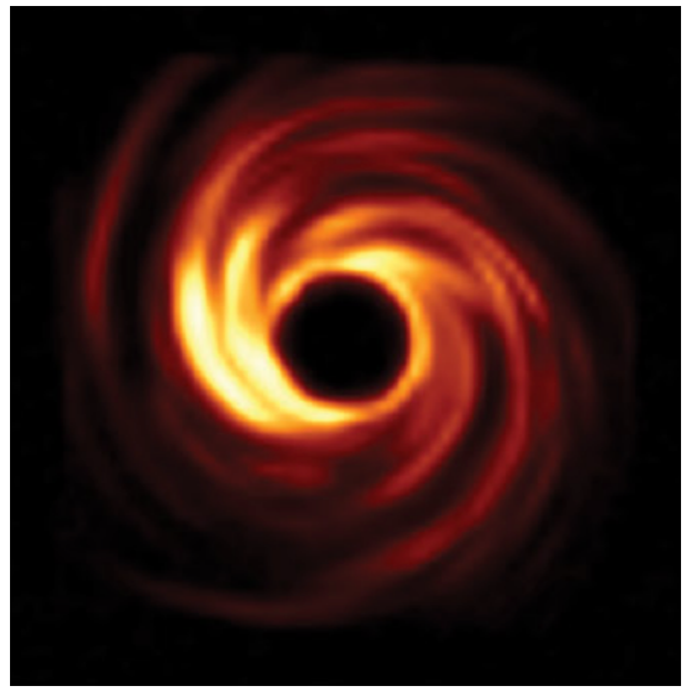

[Zheng et al., 2025]

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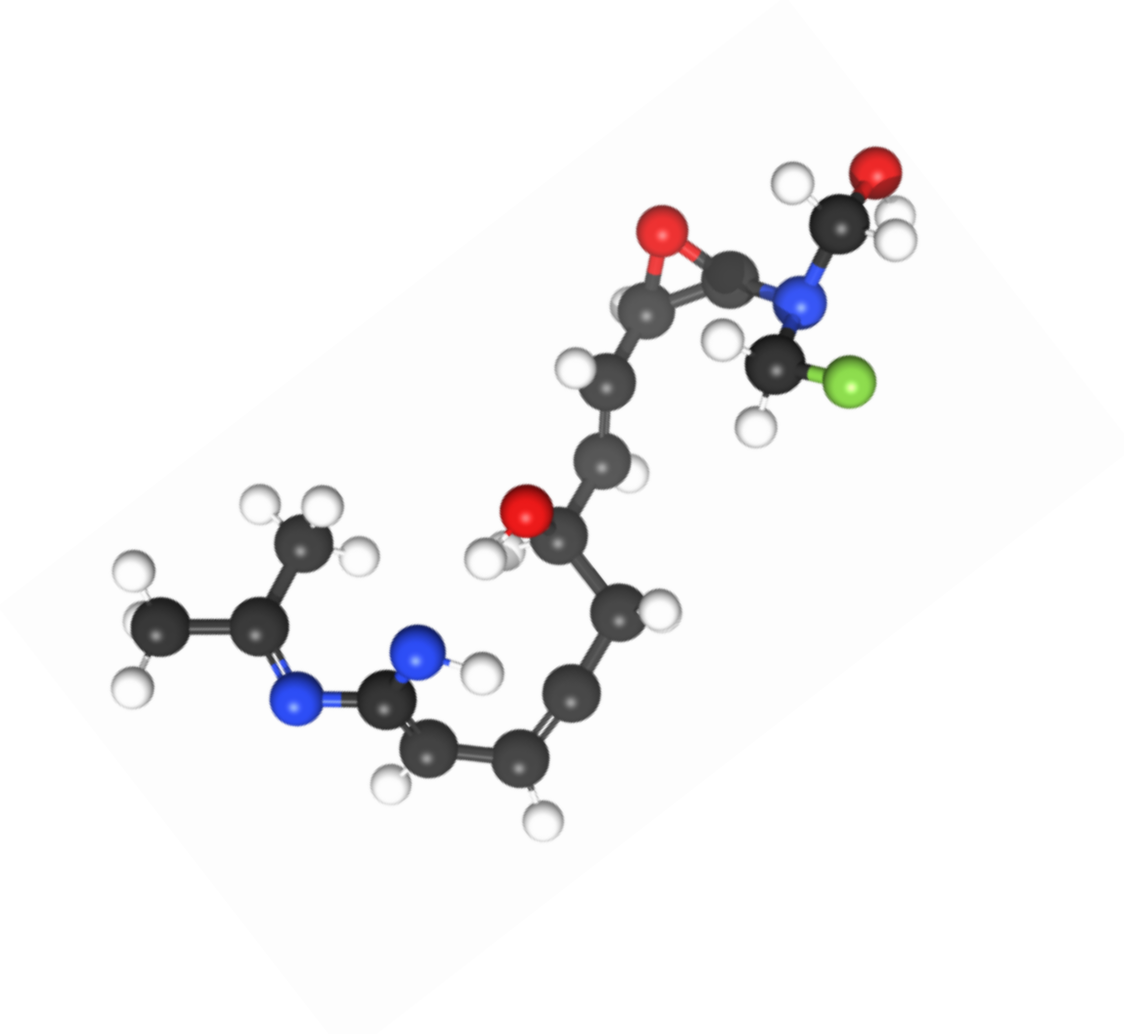
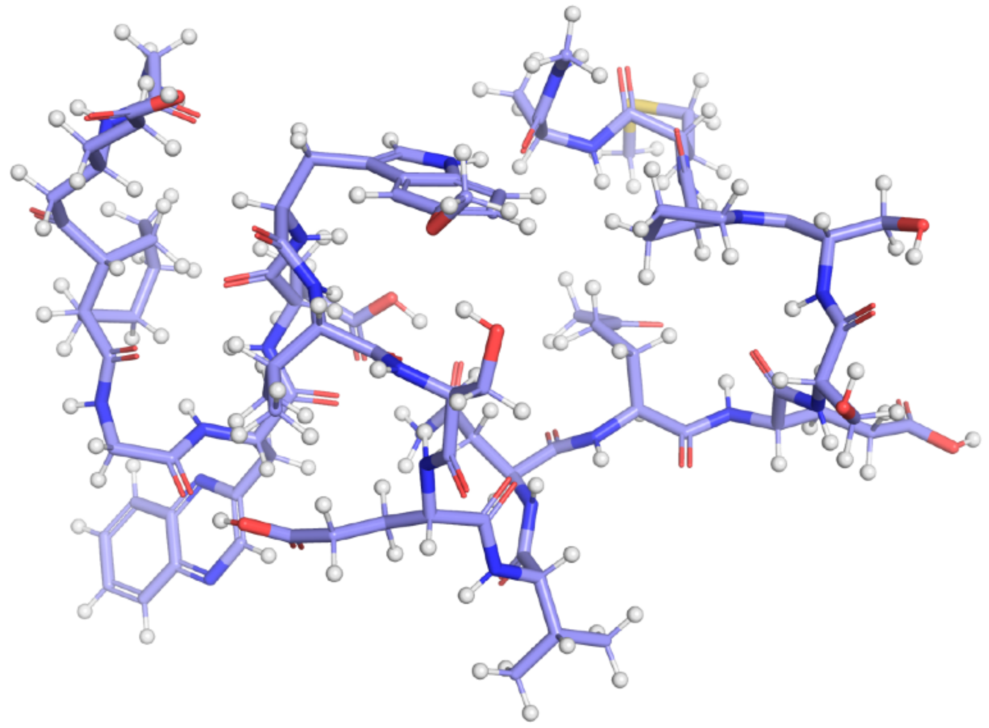
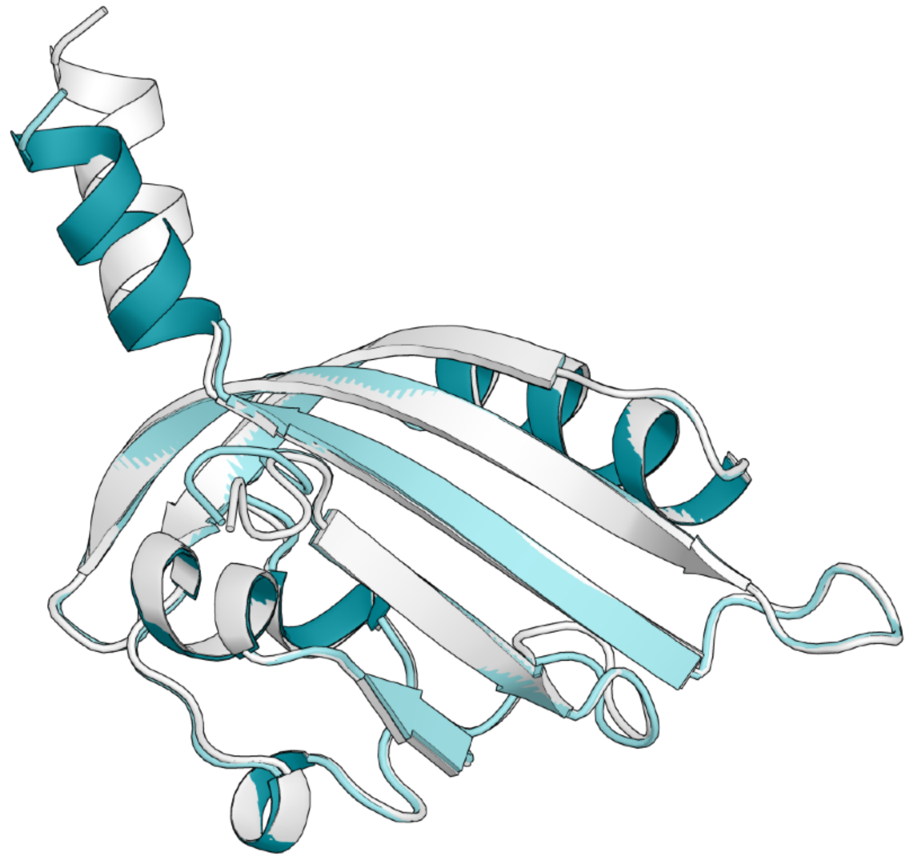
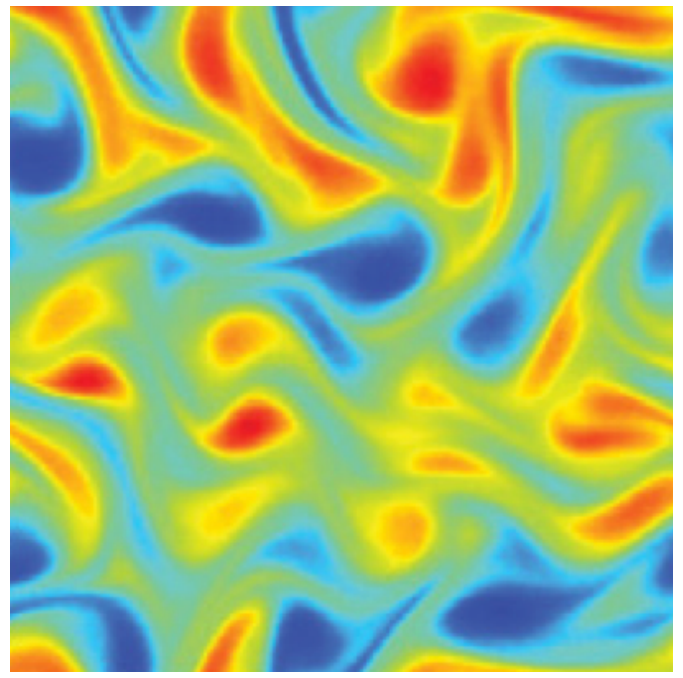
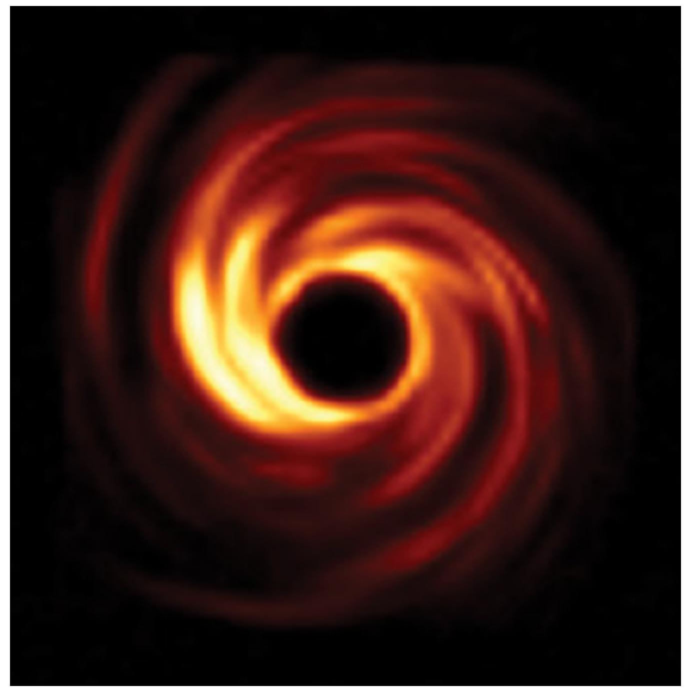
$\approx 10^{60}$ drug discovery

$\approx 10^{80}$ material design

unknown or **hard to represent** and **search**

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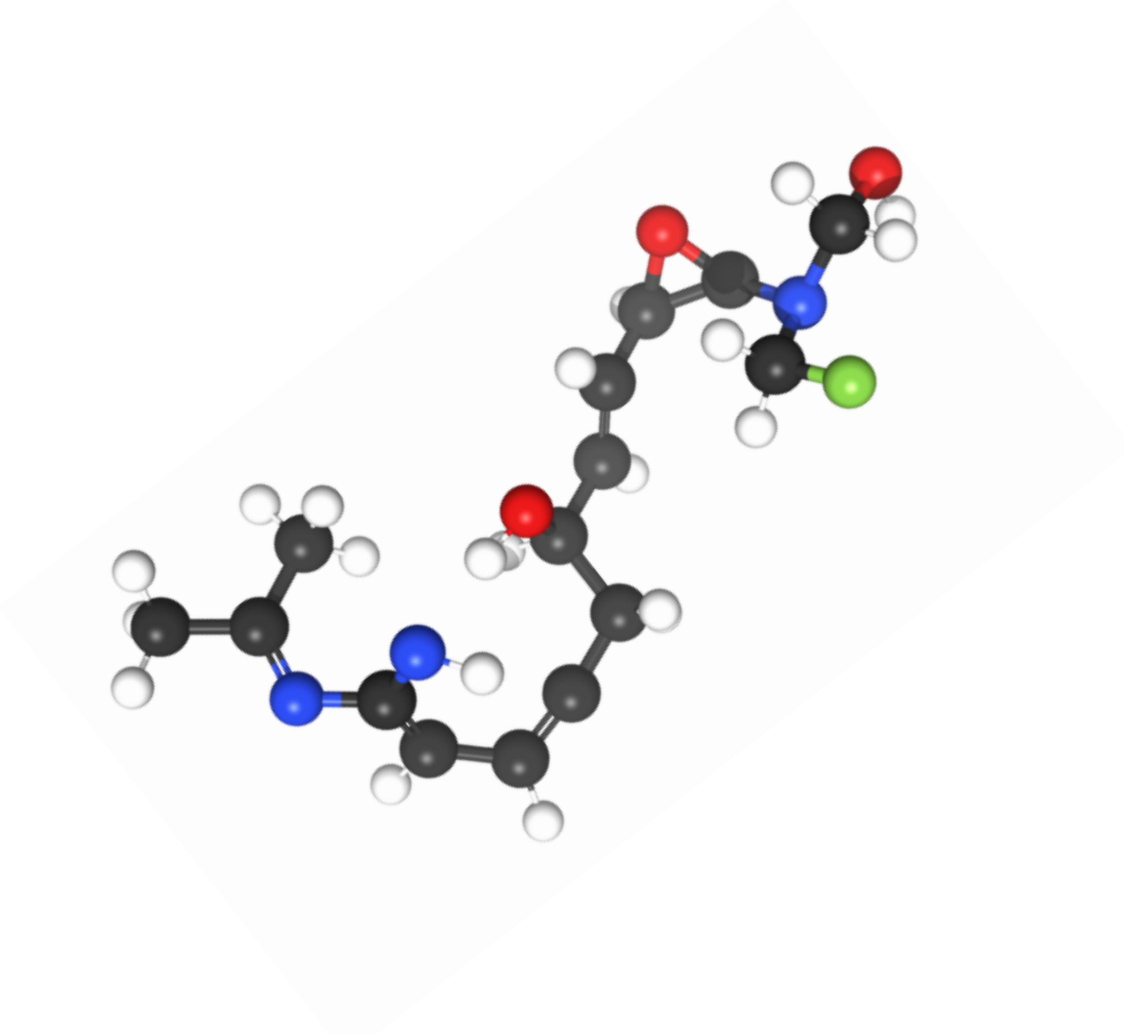
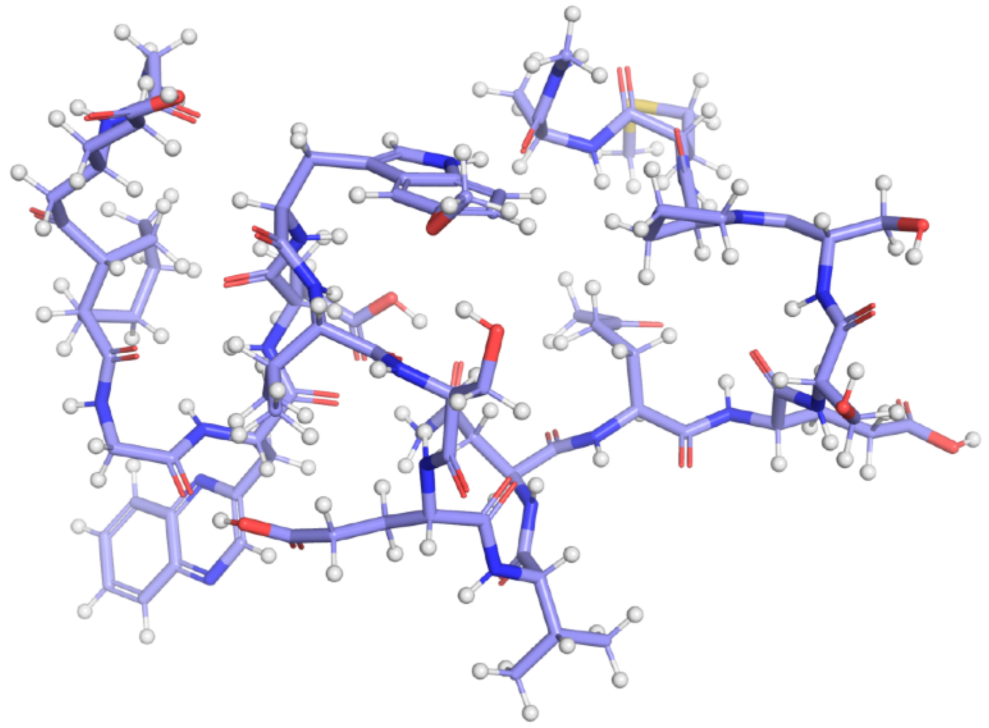
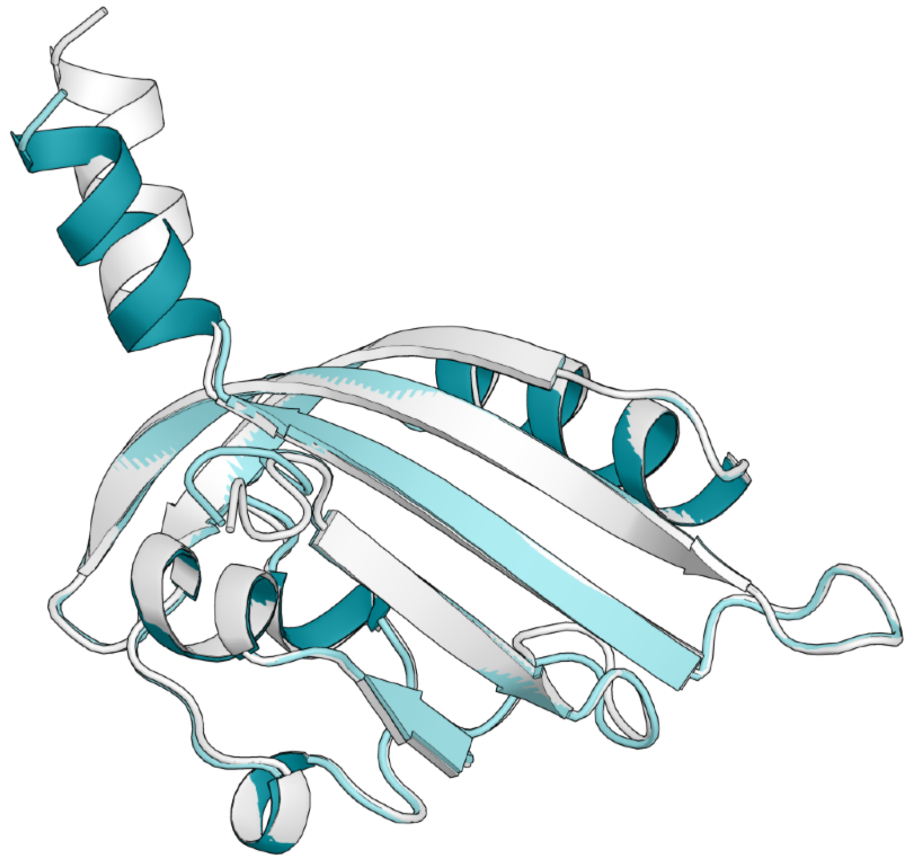
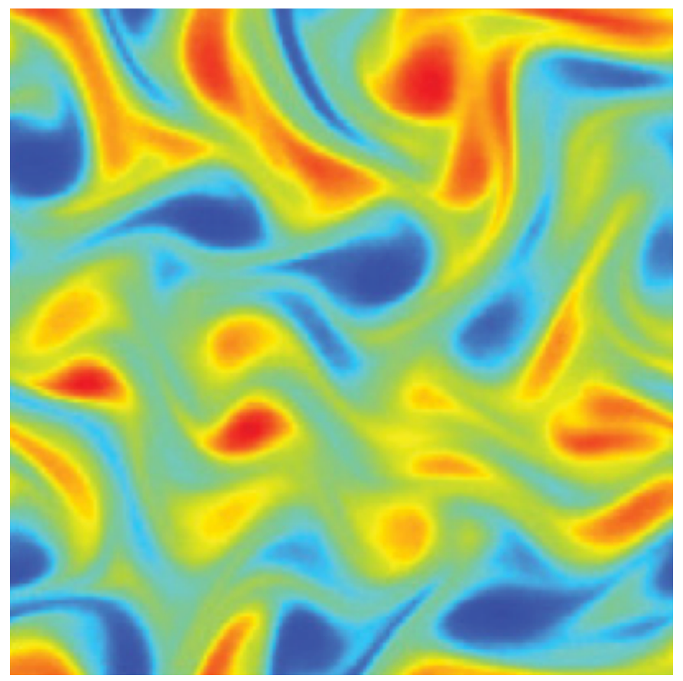
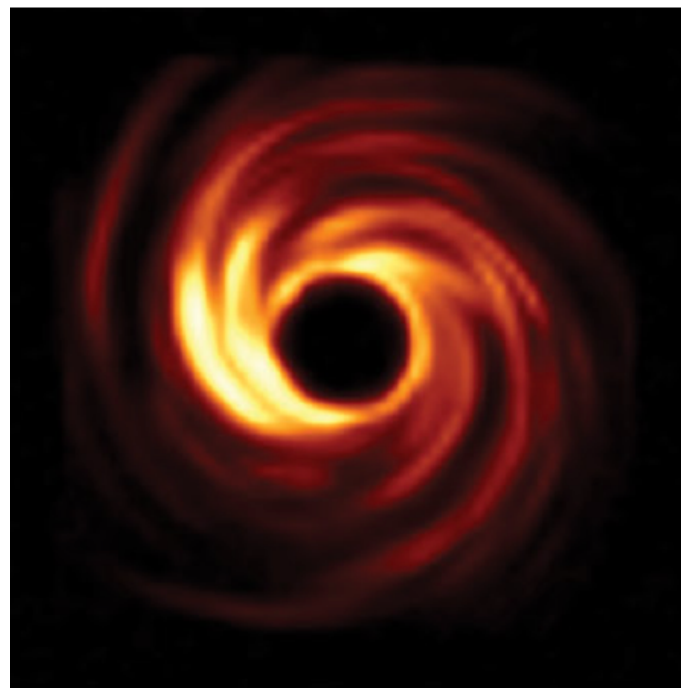
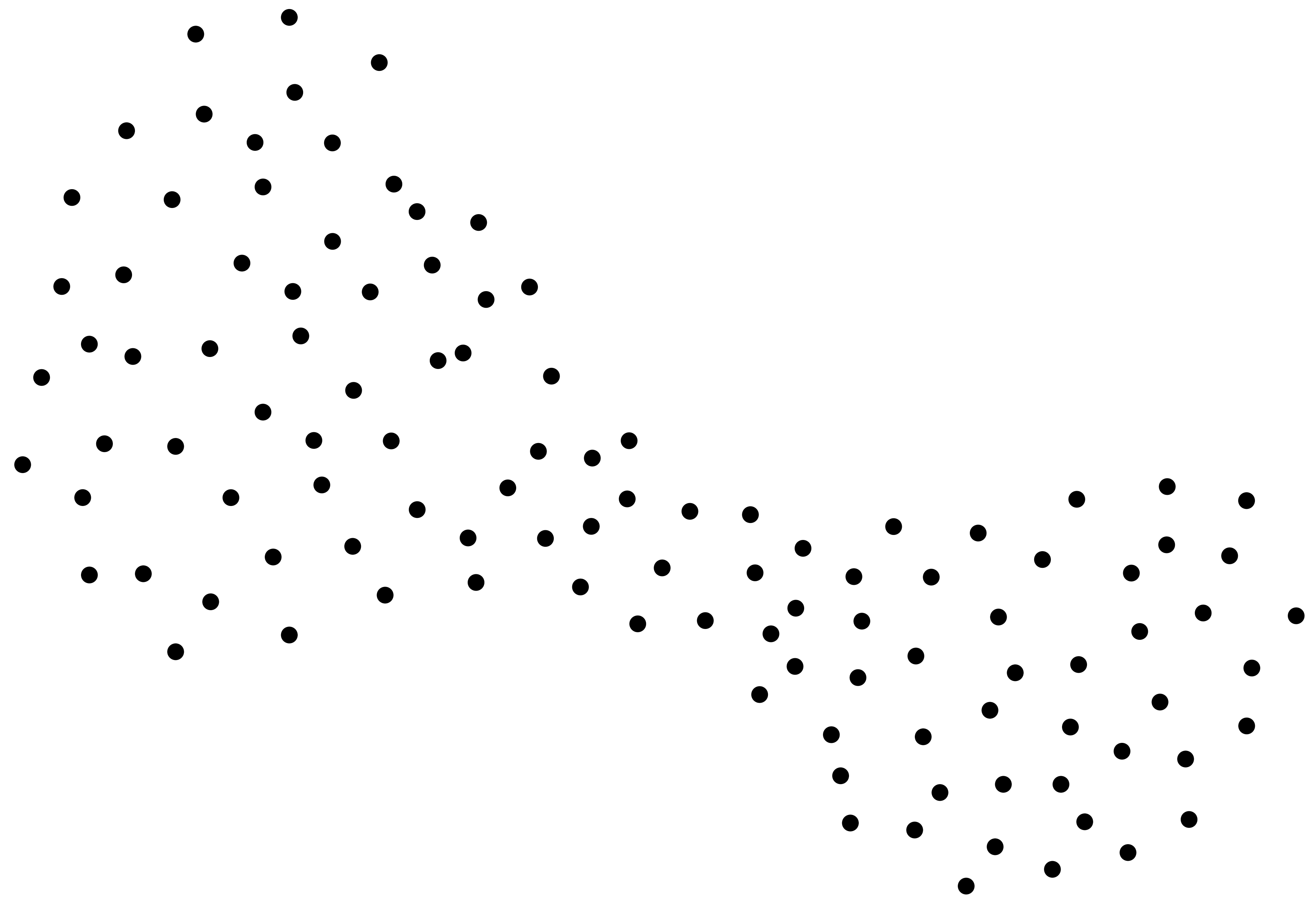
→ Generative Discovery

[Zheng et al., 2025]

Generative Discovery Paradigm

Data $D = \{x_i\}_{i=1}^n$



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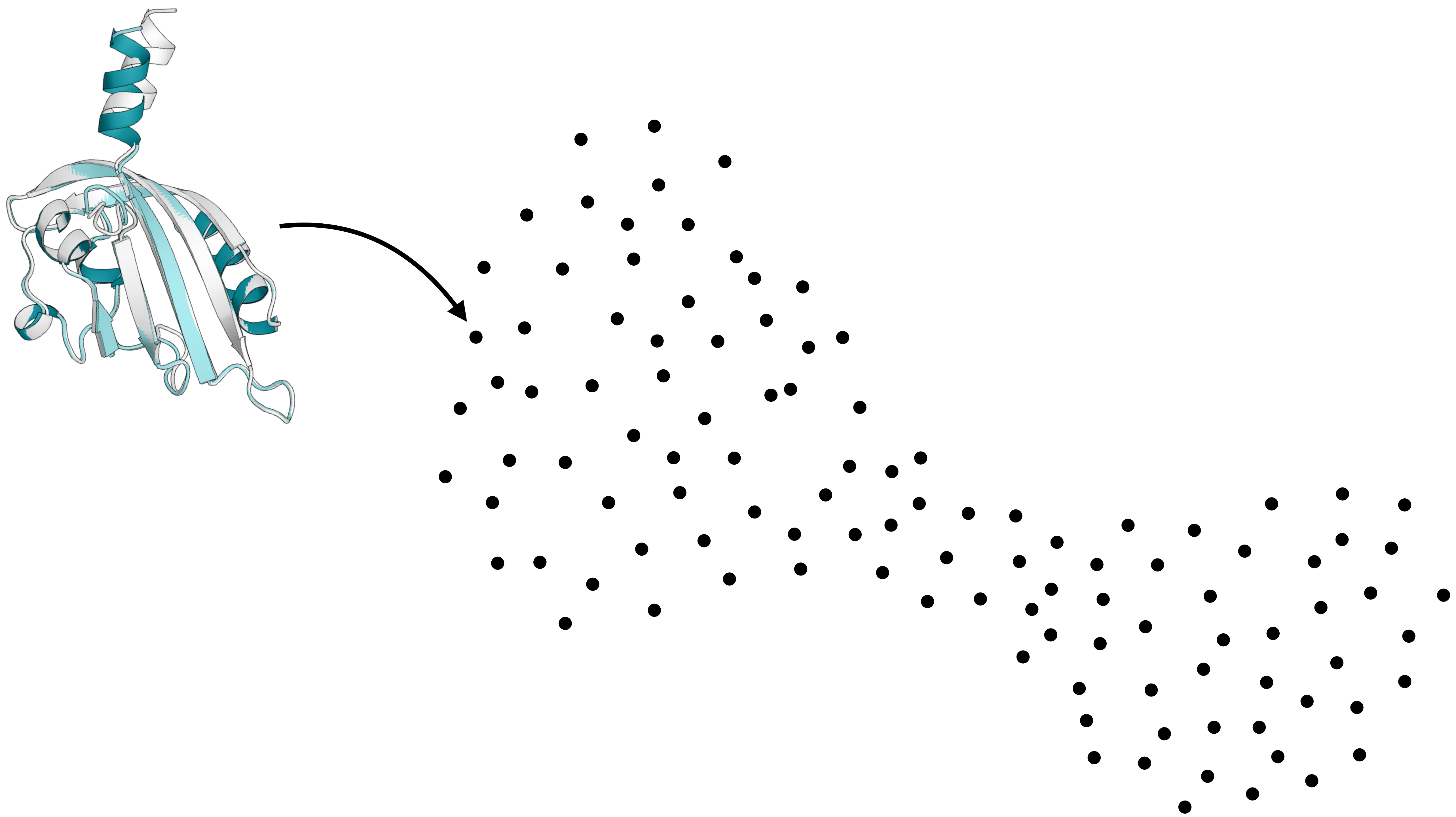
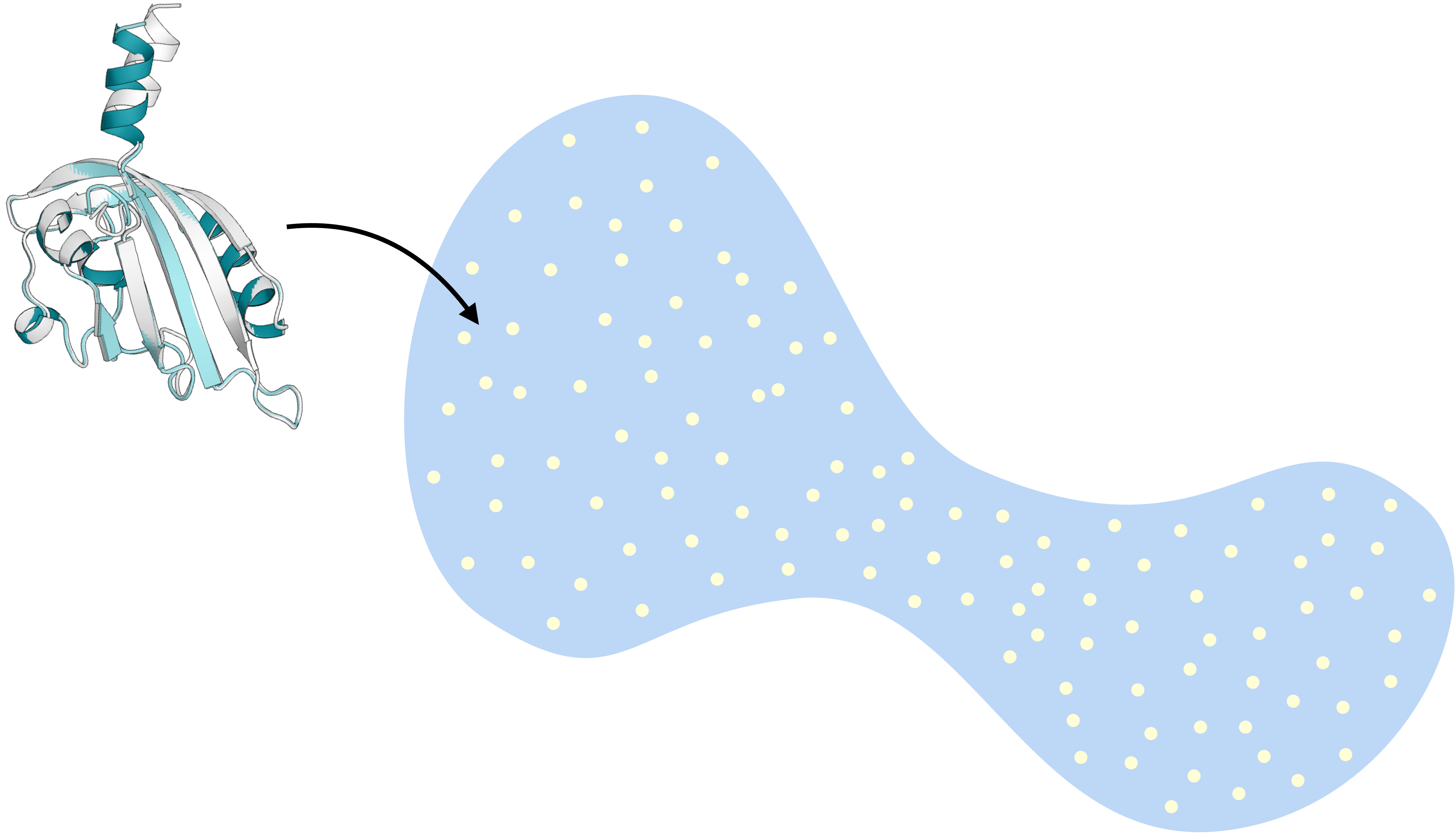


Generative Discovery Paradigm

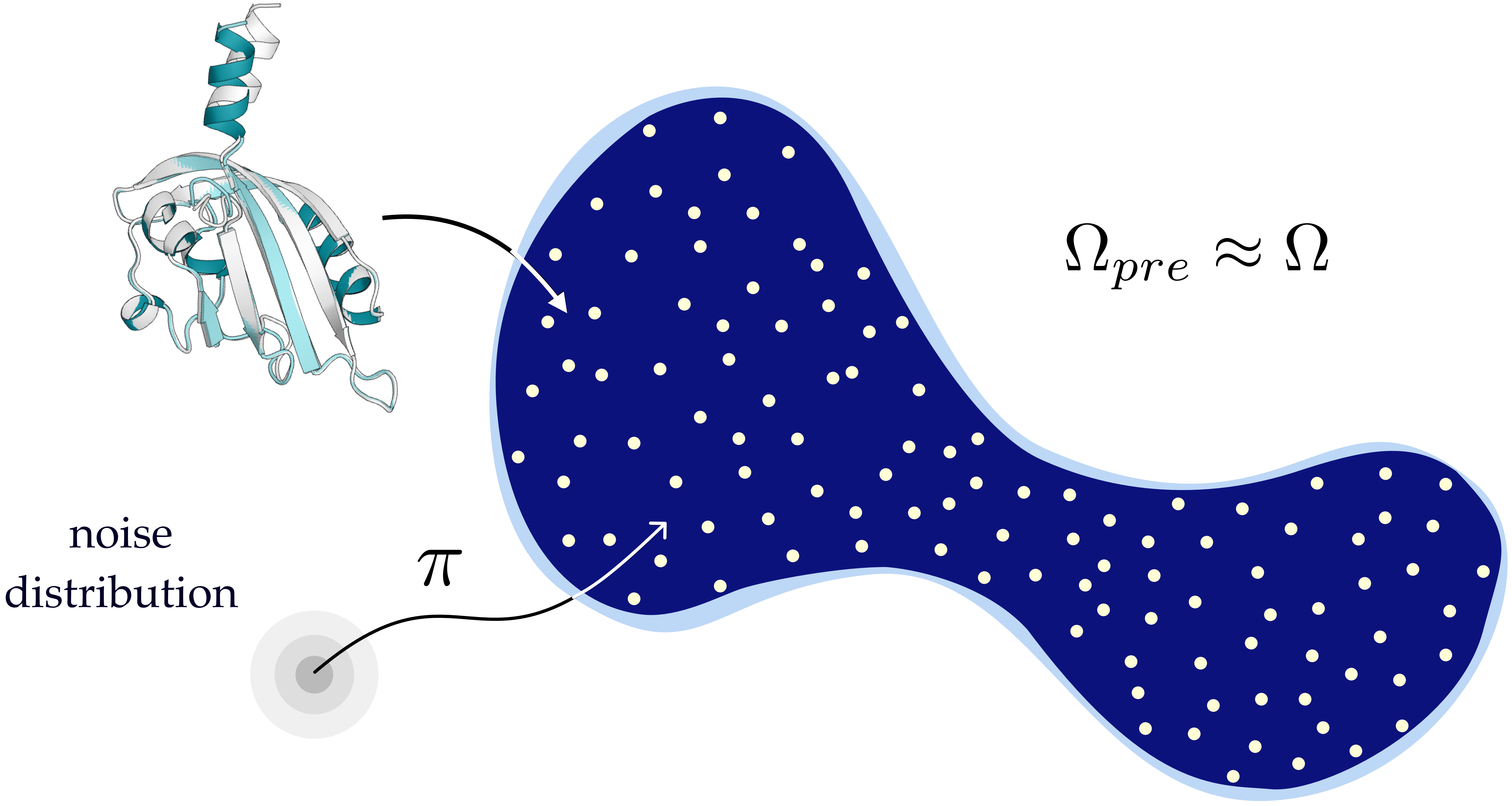
valid design space Ω (e.g., protein structures)

Data $D = \{x_i\}_{i=1}^n$



Generative Discovery Paradigm

valid design space Ω — generable set of pre-trained gen. model Ω_{pre}



$\Omega_{pre} \approx \Omega$

Data $D = \{x_i\}_{i=1}^n$

$\downarrow$

Pre-trained generative model π

The Dream: Discovery via Generative Optimization

valid design space Ω

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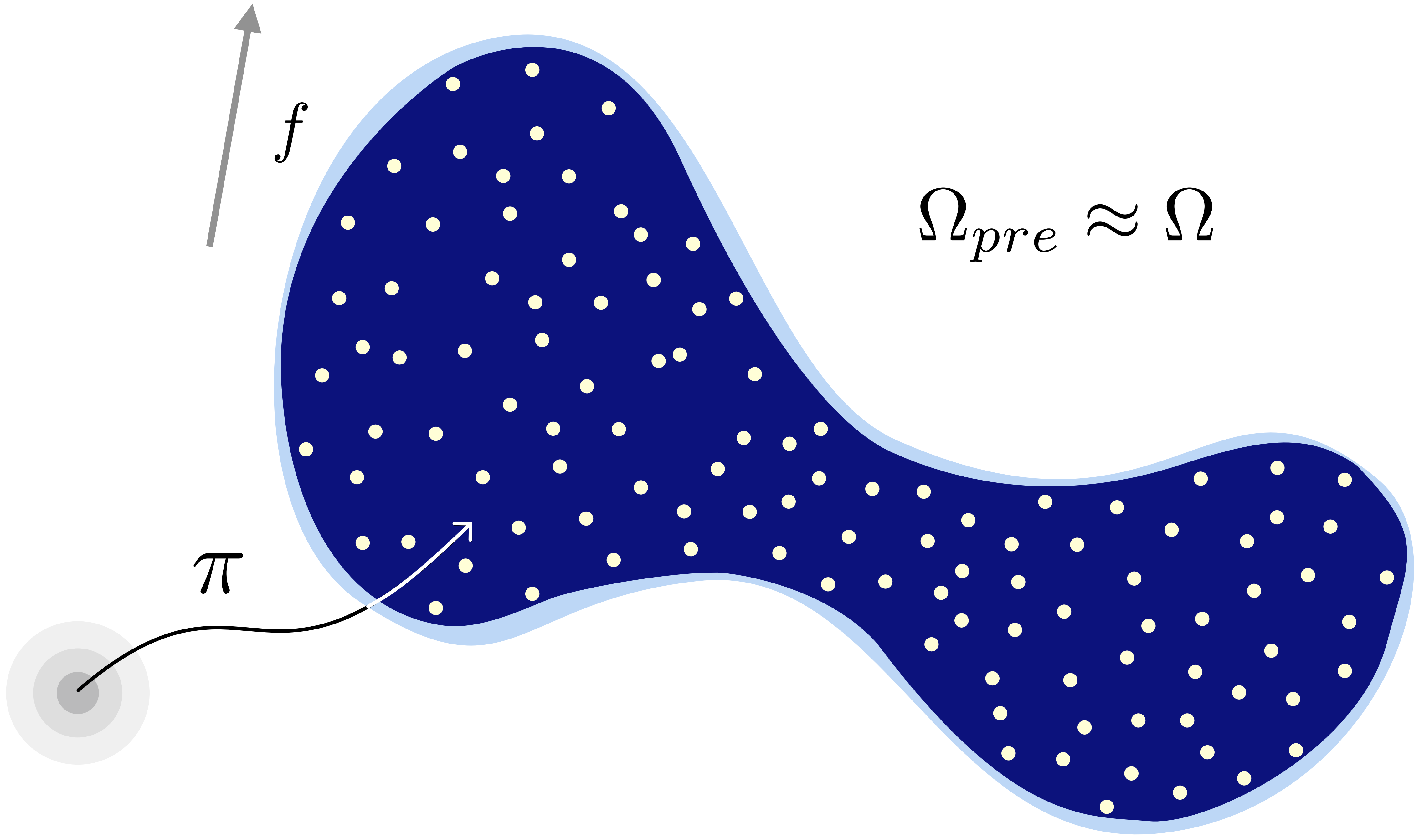
Data $D = \{x_i\}_{i=1}^{n}$

$\downarrow$

Pre-trained generative model π



Discovery problem

$$\underset{x \in \Omega}{argmax}\ f(x)$$

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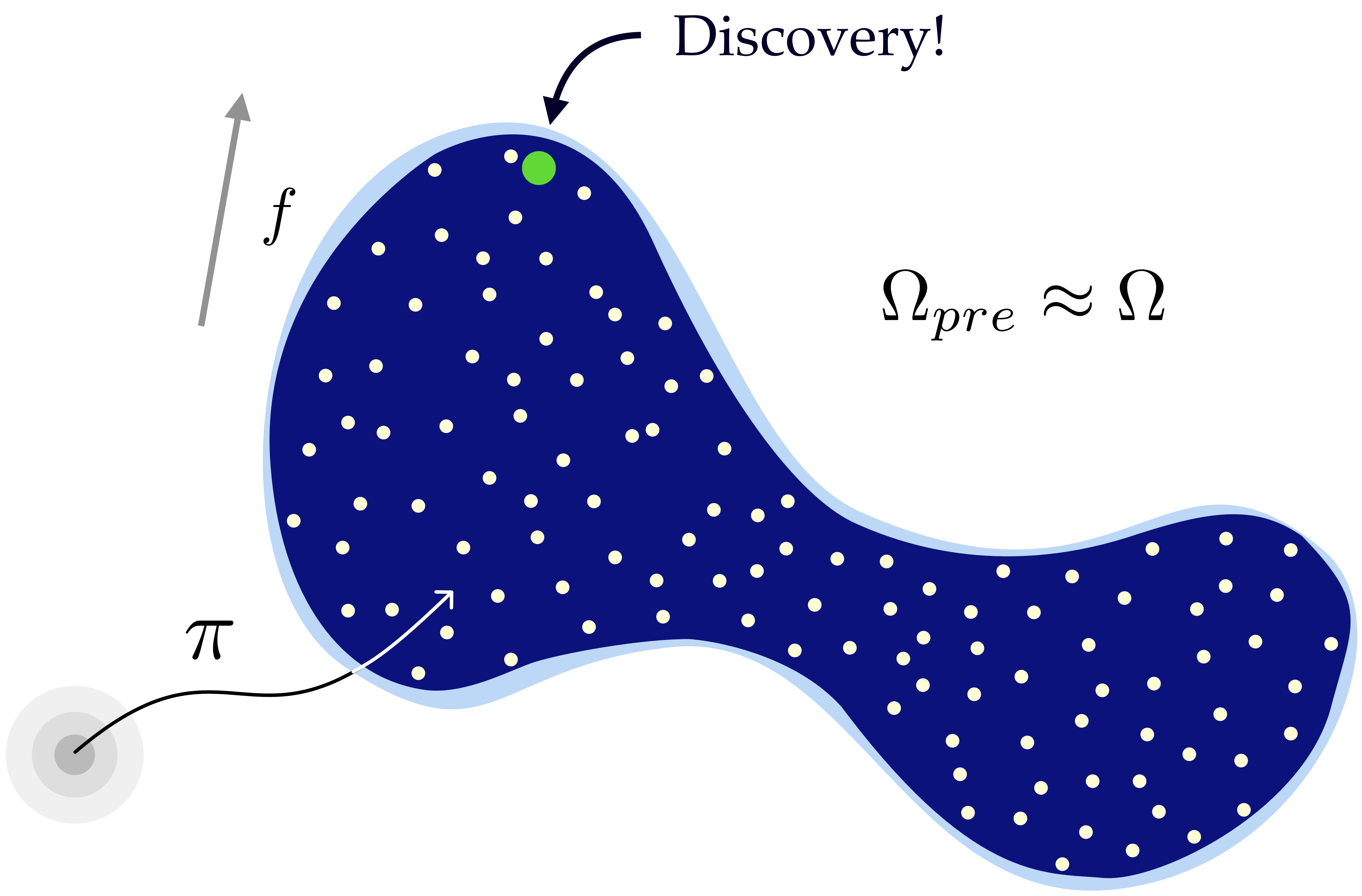


Data $D = \{x_i\}_{i=1}^n$

↓

Pre-trained generative model π

↓

Adapt π to optimize f

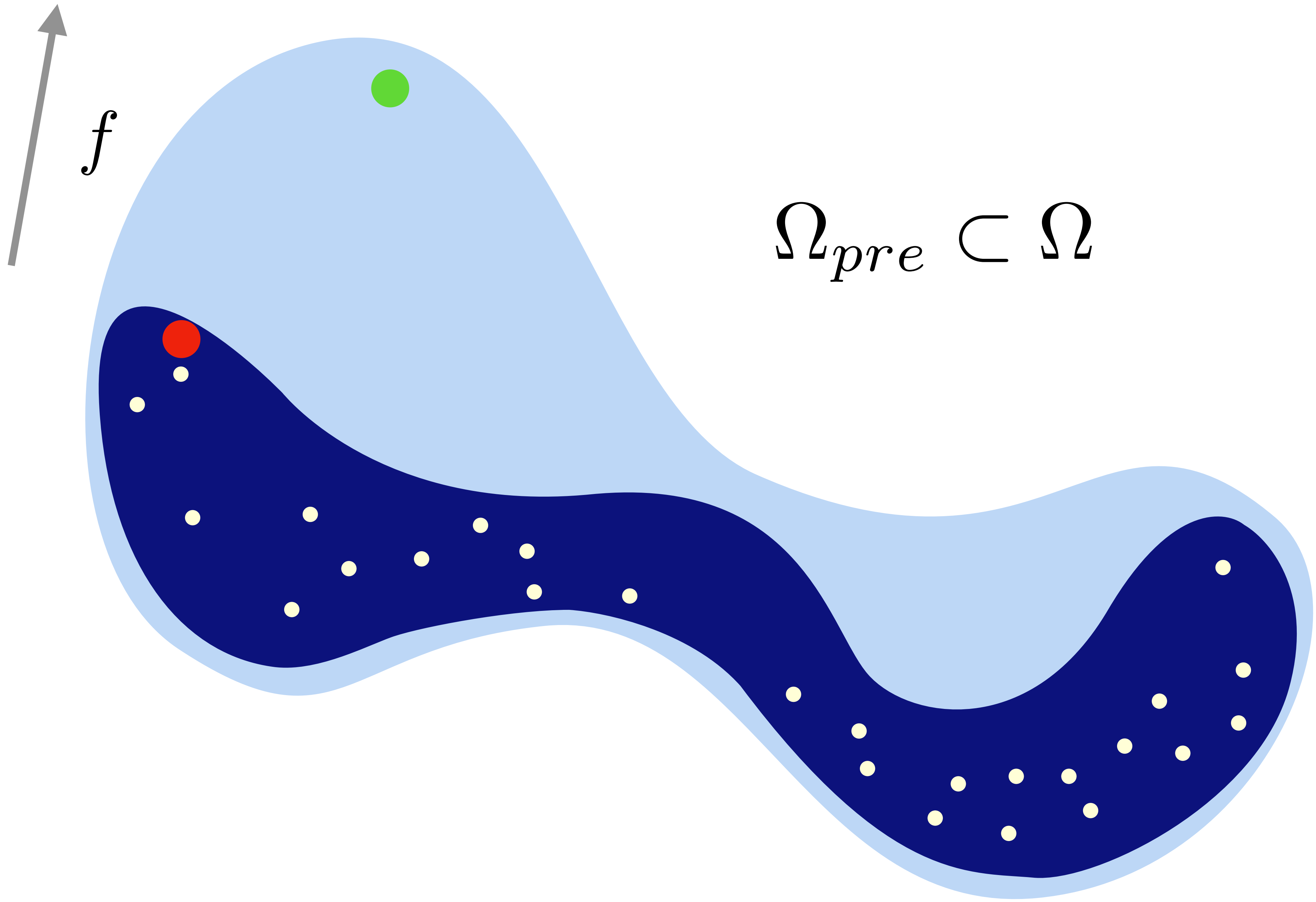
Discovery problem

$$\underset{x \in \Omega}{argmax}\ f(x)$$

The Reality: Generative Optimization Limitation

valid design space Ω

generable set of pre-trained gen. model Ω_{pre}



$\Omega_{pre} \subset \Omega$

Generative models generalize locally over training data.

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The Reality: Generative Optimization Limitation

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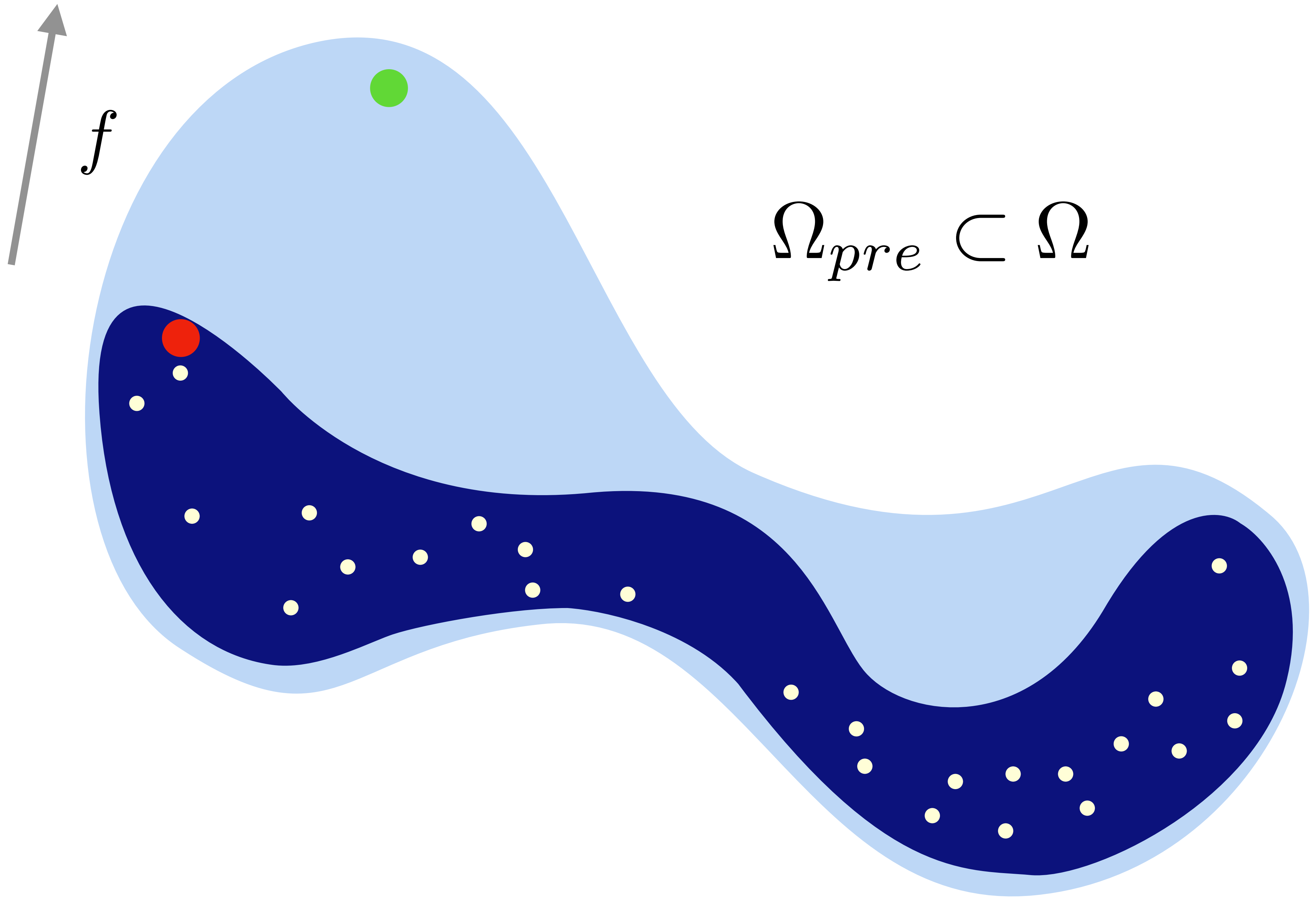

$\Omega_{pre} \subset \Omega$

Generative models generalize locally over training data.

↓

Especially in natural sciences:

E.g.,
- Chemistry
- Biology
- Physics

Discovery problem

$$\underset{x \in \Omega}{argmax}\ f(x)$$

The Reality: Generative Optimization Limitation

valid design space Ω

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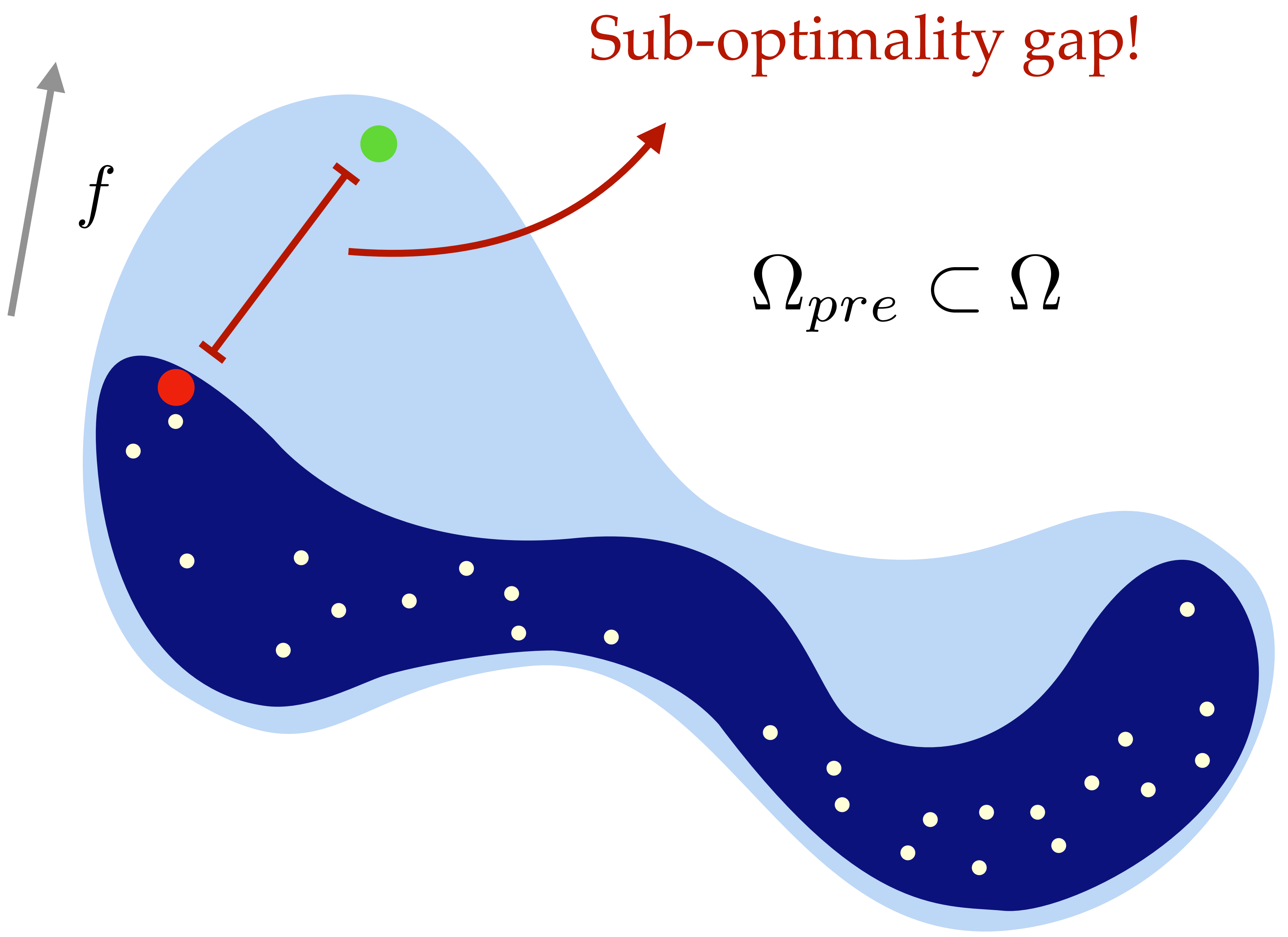

Discovery problem

$$\underset{x \in \Omega}{argmax}\ f(x)$$

Generative discovery entails a new exploration problem

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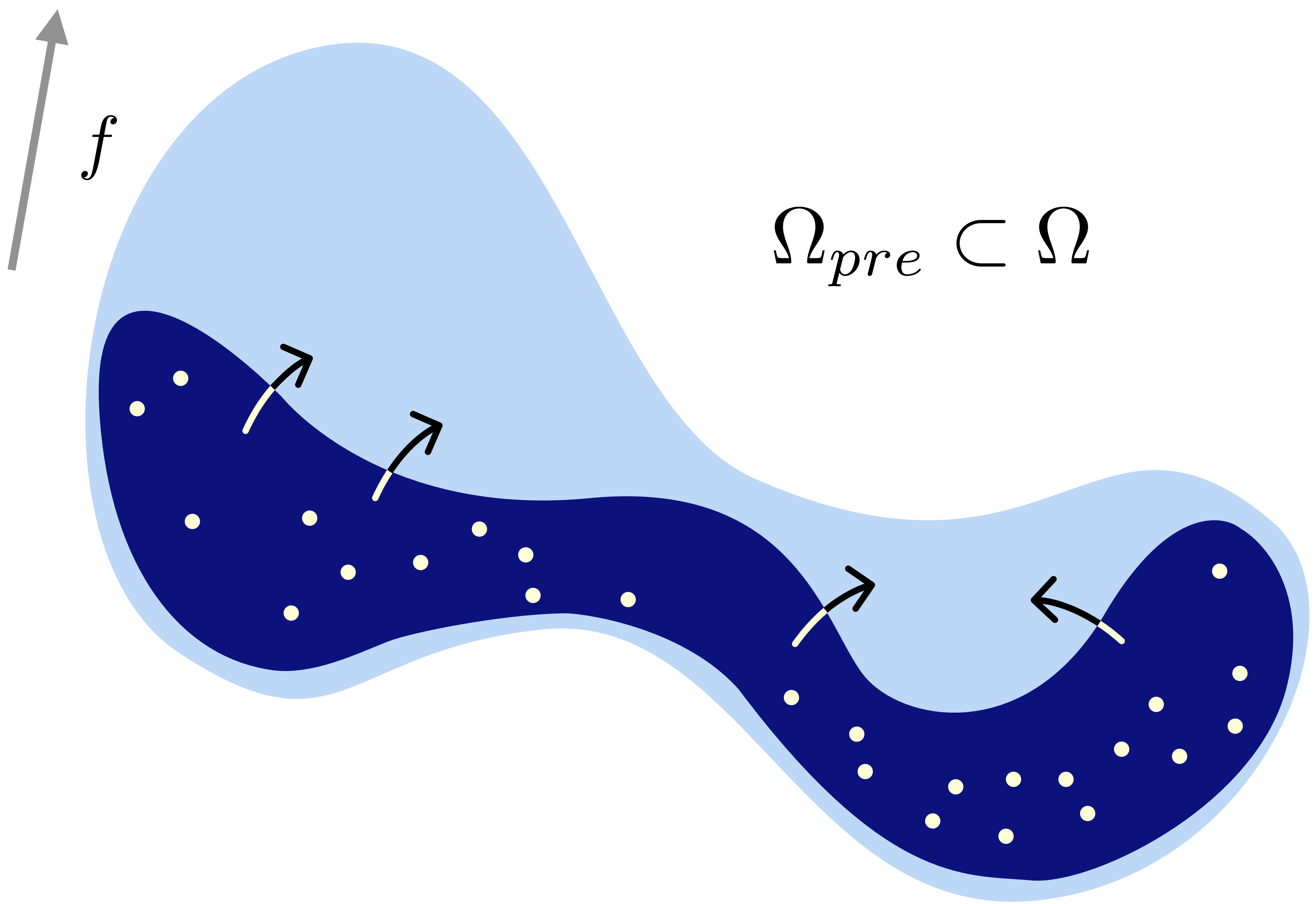

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Generative discovery entails a new exploration problem

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classic optimization
(e.g., convex optimization)

f known

Ω known

Generative discovery entails a new exploration problem

$$\underset{x \in \Omega}{argmax} \; f(x)$$

classic optimization (e.g., convex optimization)		**decision-making** (e.g., bandits, BO, RL)	
f	known	f	learned
Ω	known	Ω	known

Generative discovery entails a new exploration problem

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Generative discovery entails a new exploration problem

$$\underset{x \in \Omega}{argmax}\ f(x)$$

classic optimization (e.g., convex optimization)		**decision-making** (e.g., bandits, BO, RL)		**generative discovery** (e.g., drug design)	
f	known	f	learned	f	learned
Ω	known	Ω	known	Ω	learned

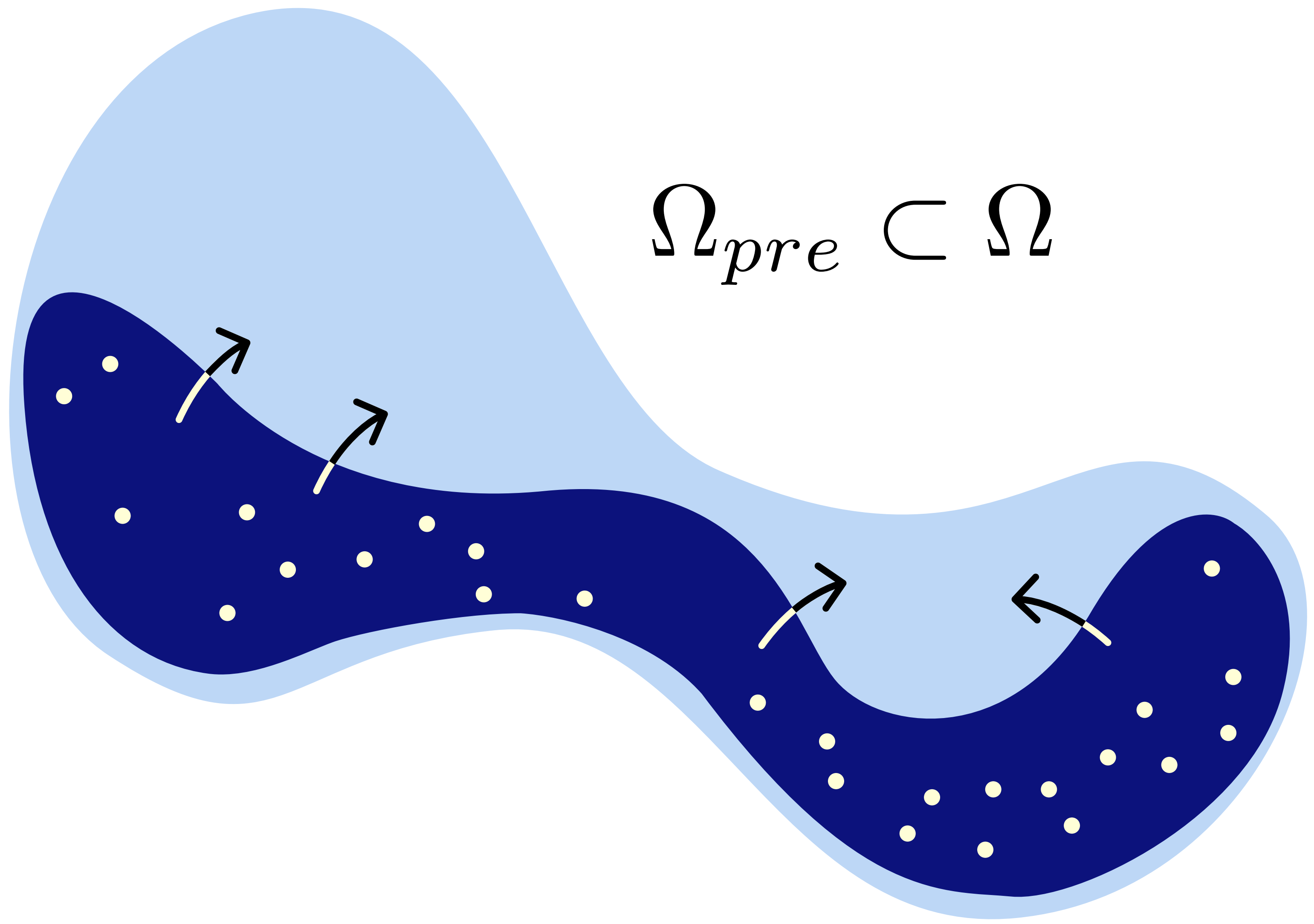
Takeaway

Discovery requires the machine to **expand its action space** (i.e., **learn what actions are possible**)

How? Out-of-Distribution Flow Modeling

valid design space Ω

generable set of pre-trained gen. model Ω_{pre}



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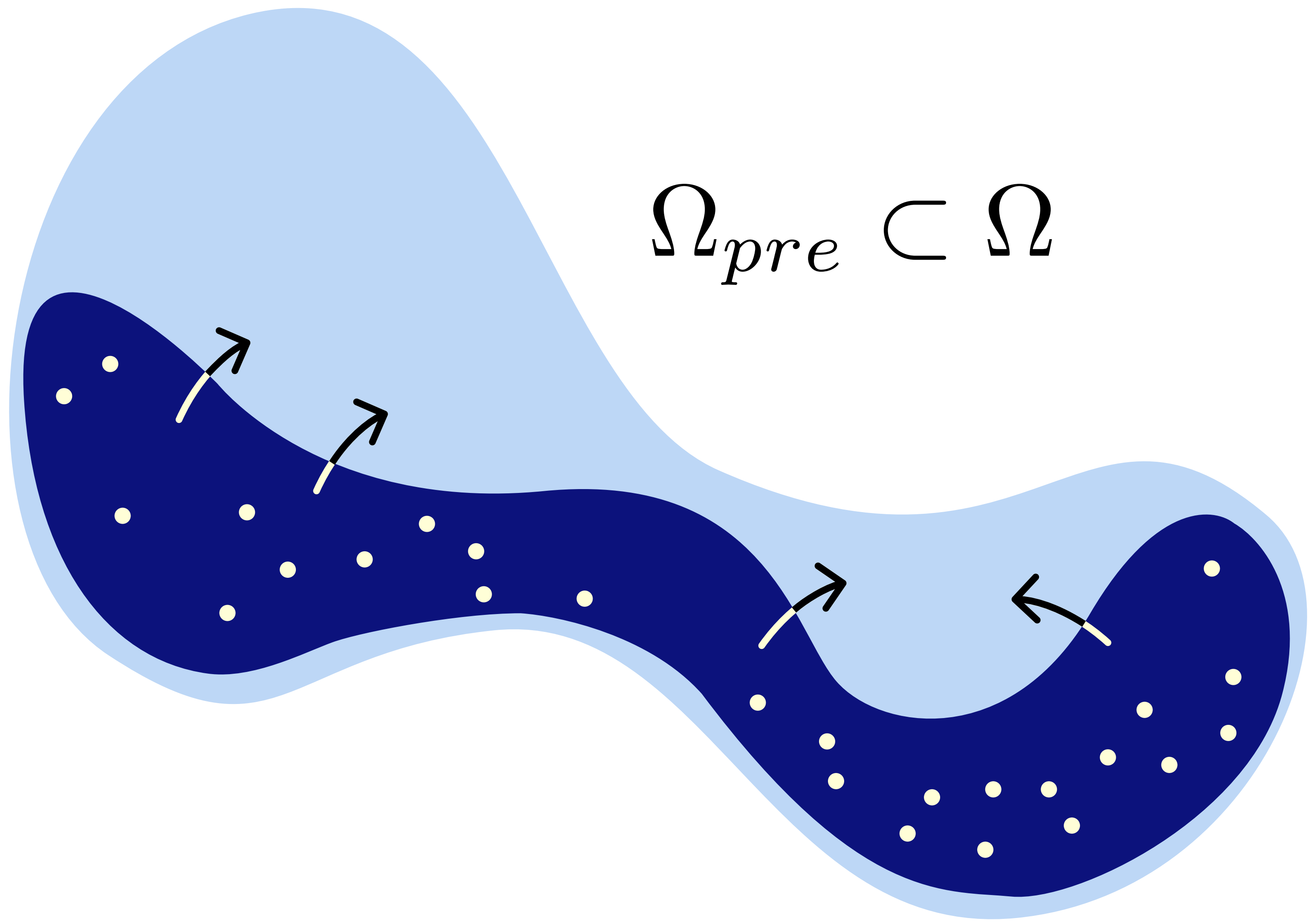
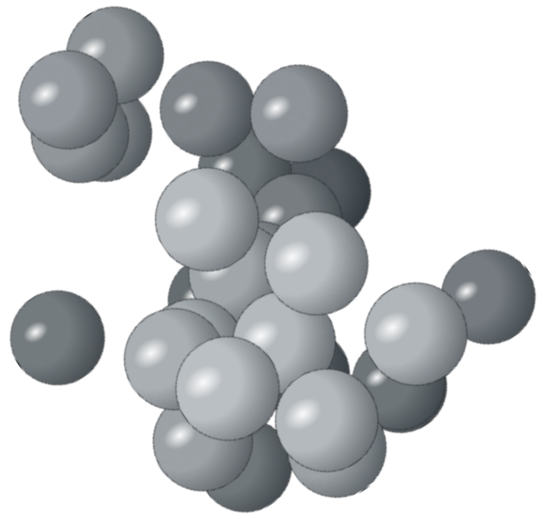


$\Omega_{pre} \subset \Omega$

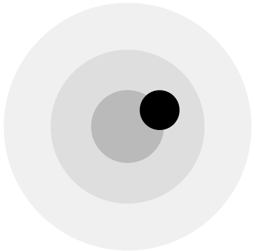
1. Formalize OOD generative modeling
2. How? Active Flow Expansion (ActFlow)
3. Guarantees for OOD generative modeling
4. Results on chemical and biological data

Discovery requires the machine to **expand its action space** (i.e., **learn what actions are possible**)

Diffusion and Flow Modeling: Generation



noise
distribution

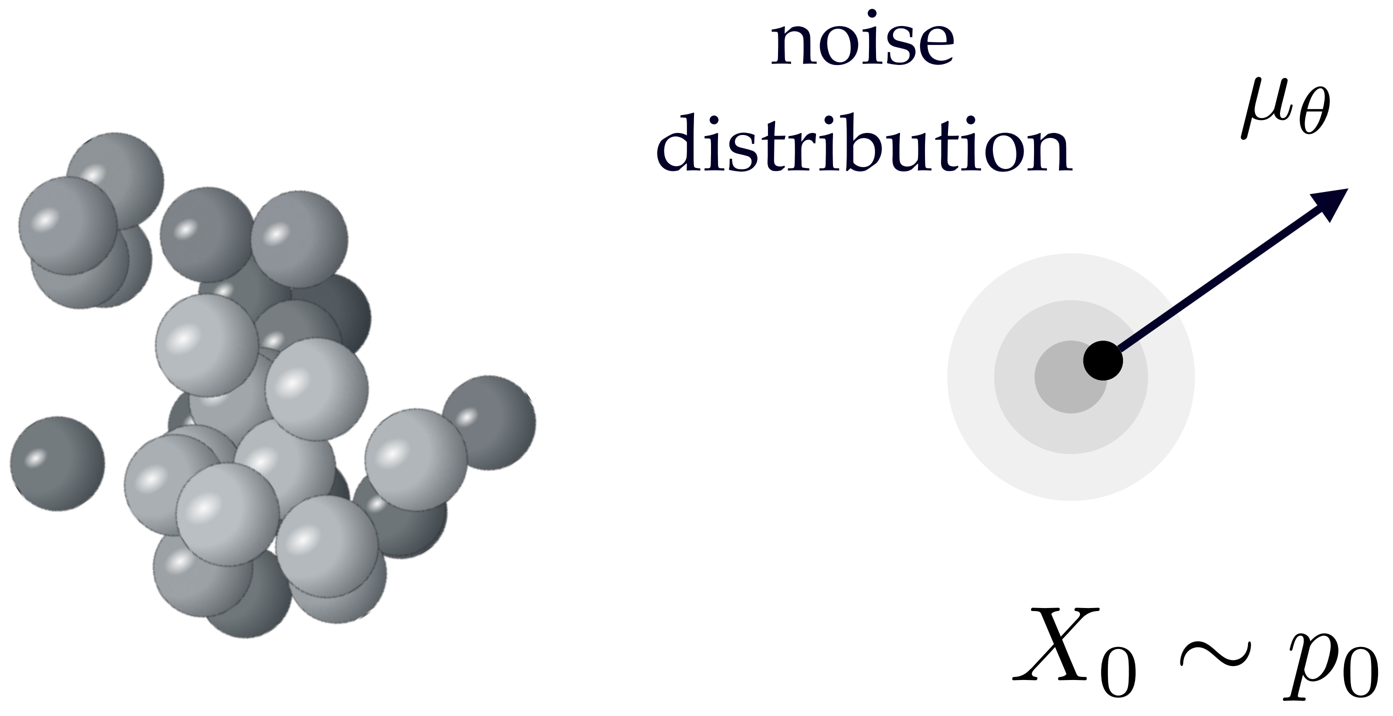


$X_0 \sim p_0$

Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field μ_θ

Diffusion and Flow Modeling: Generation



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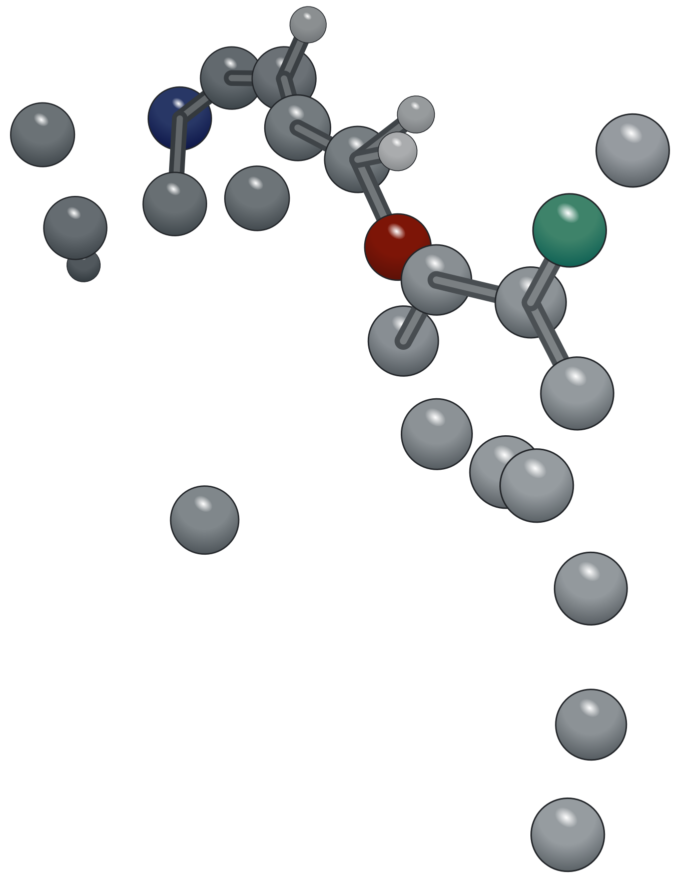

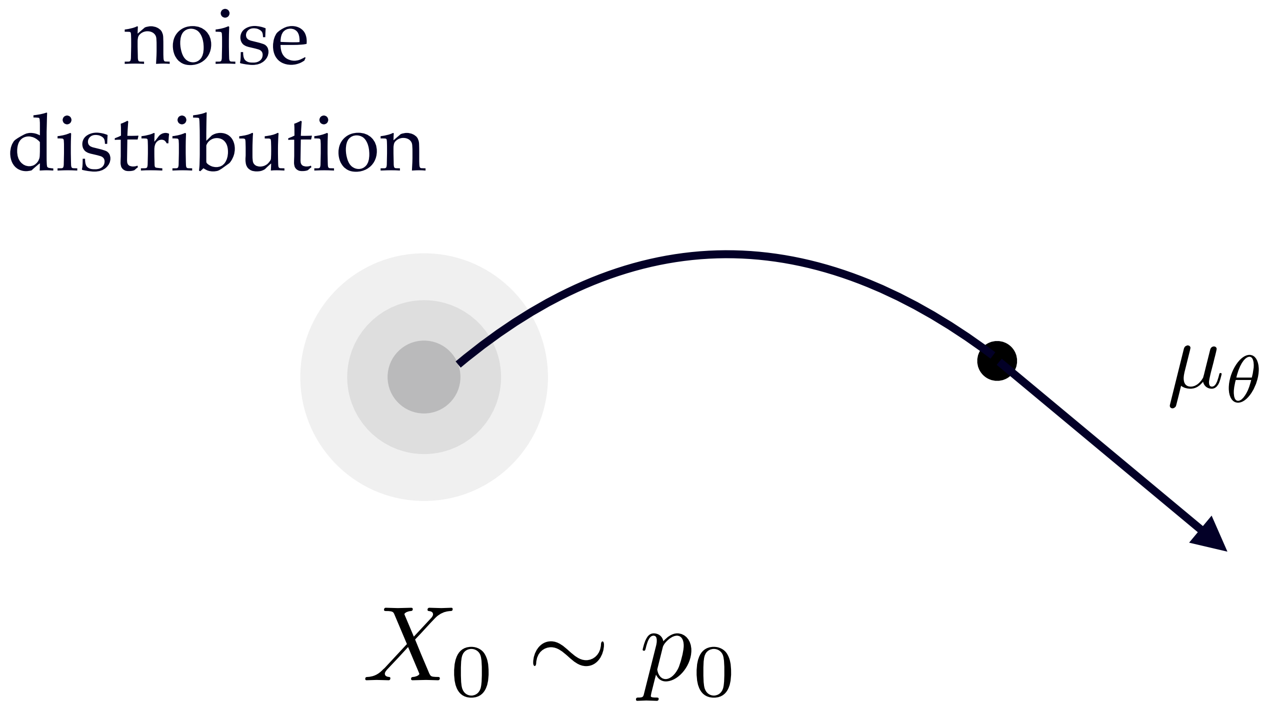

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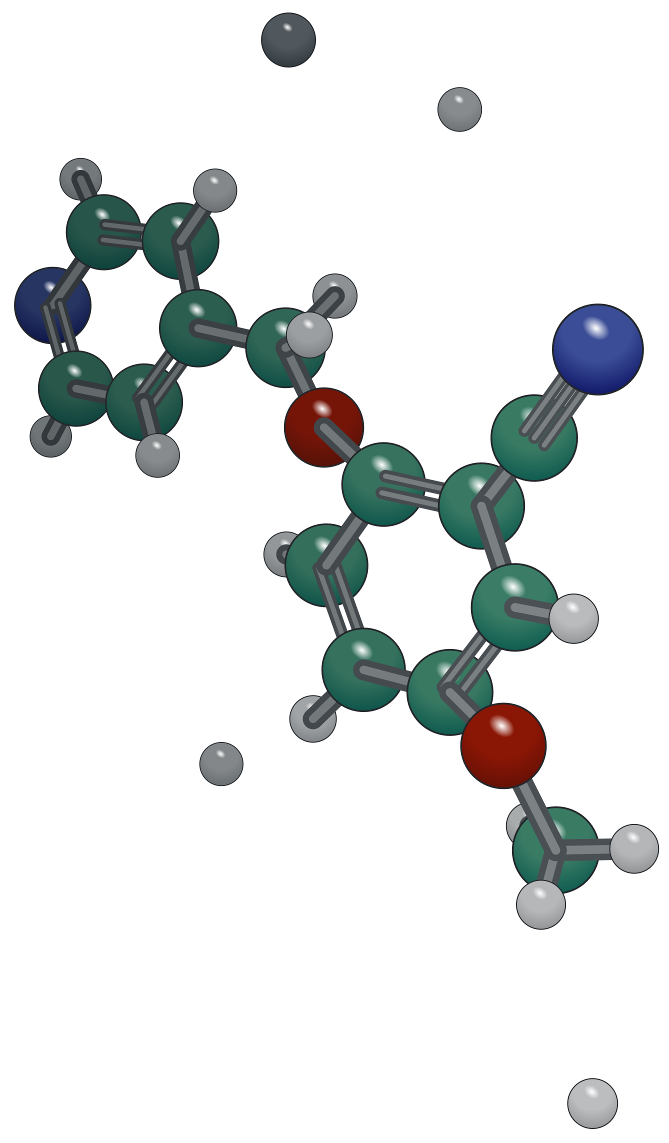

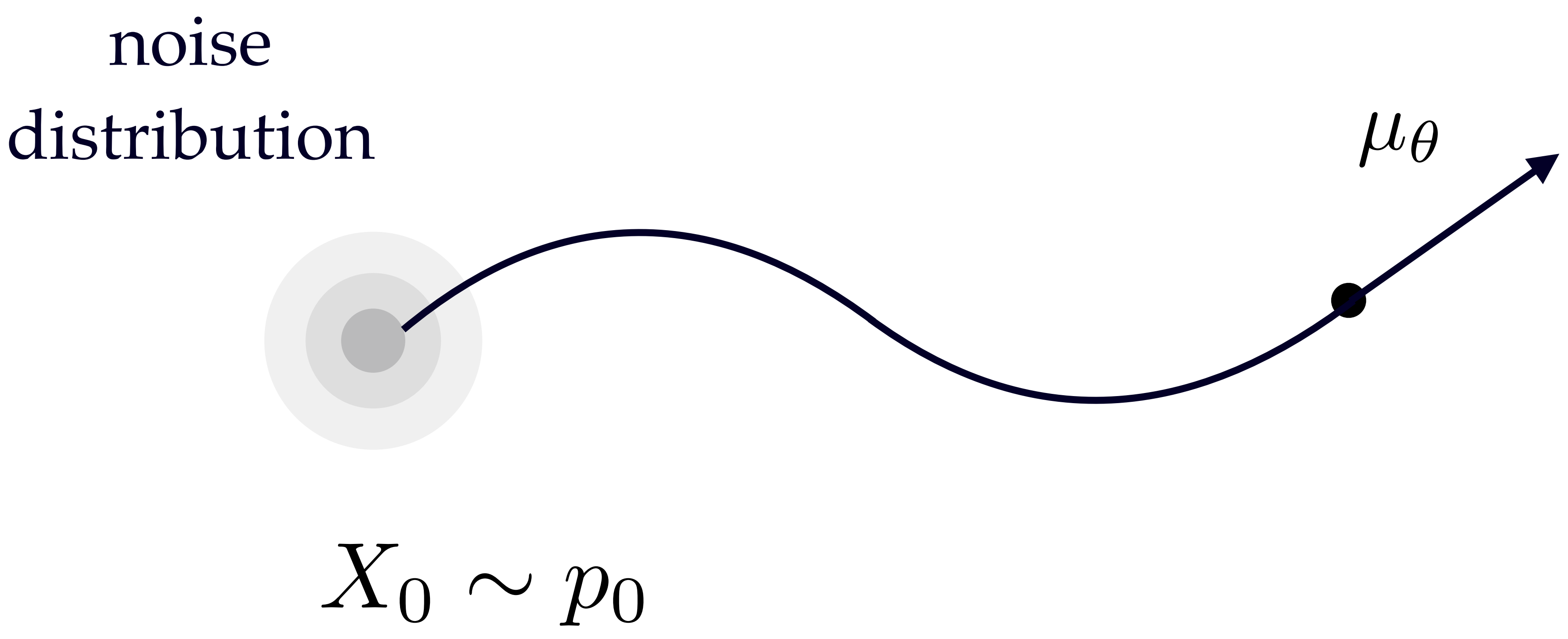

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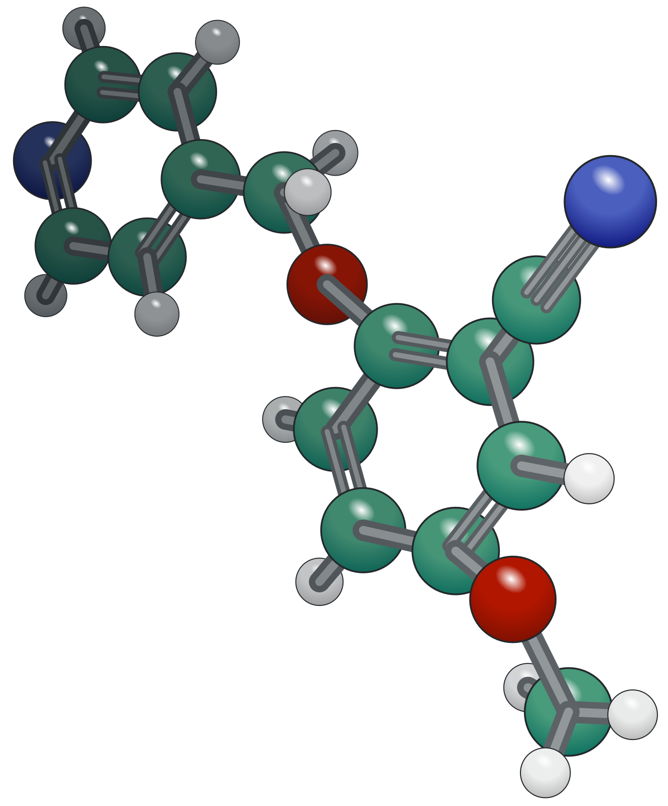

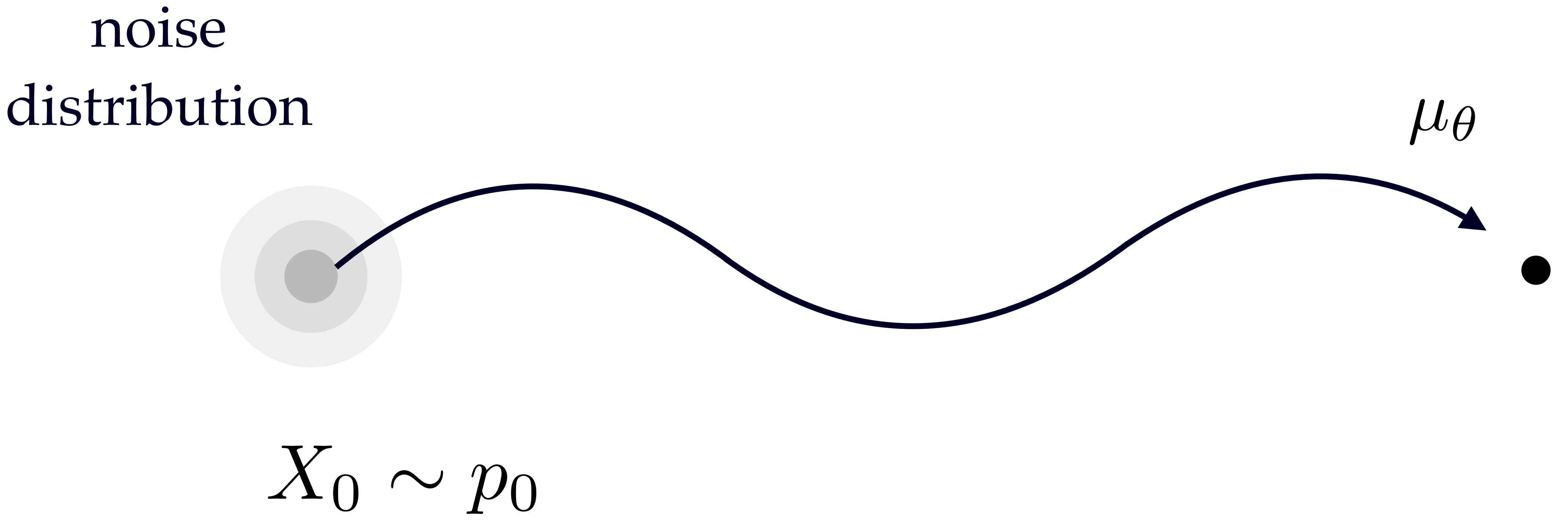

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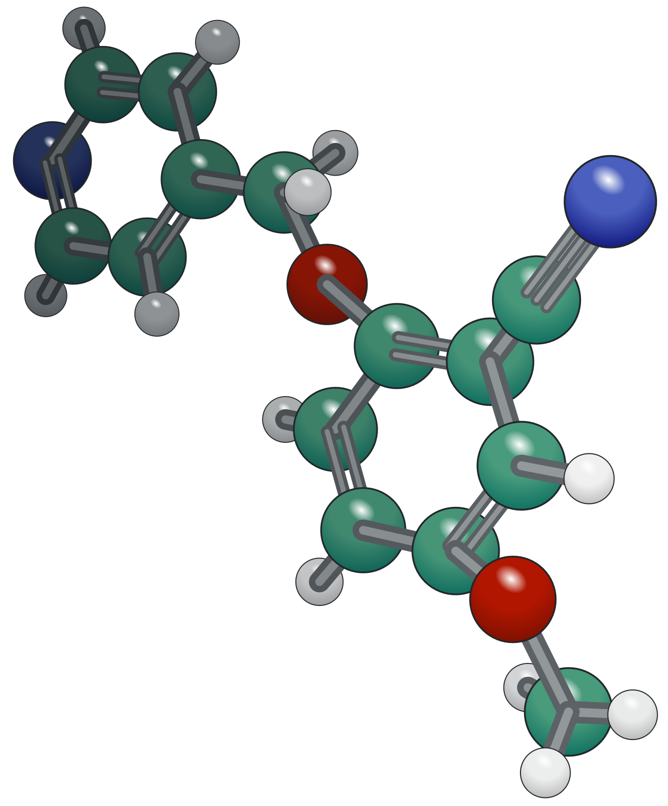

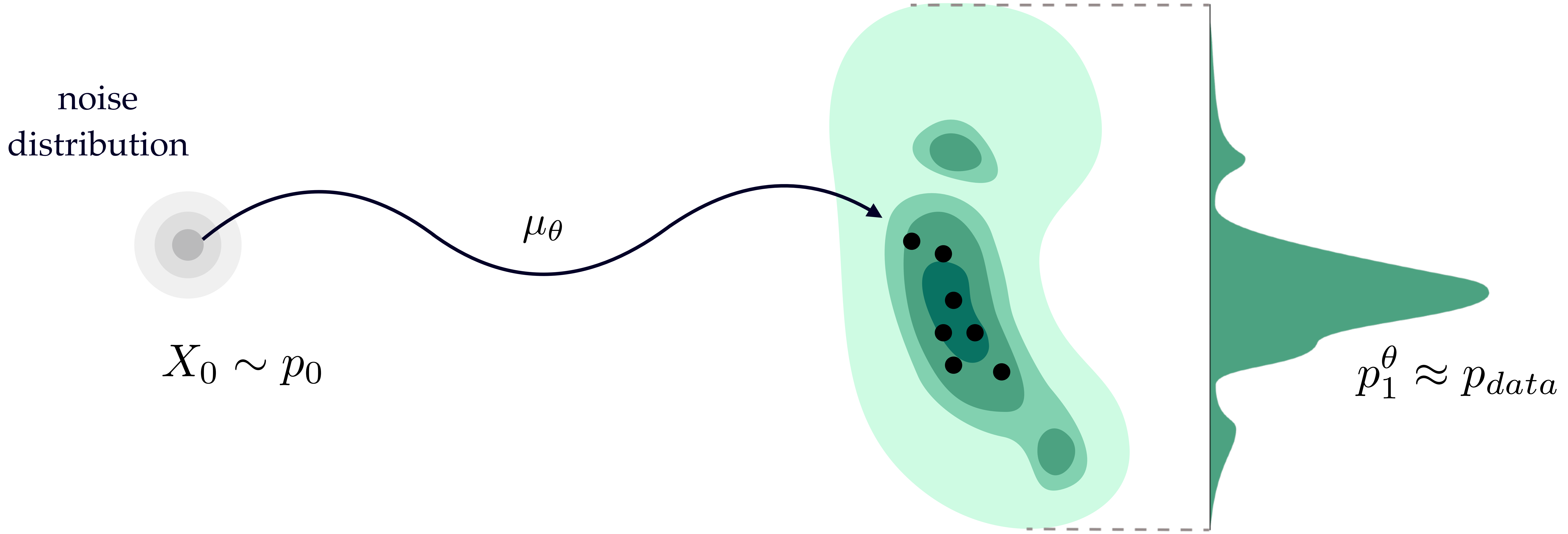

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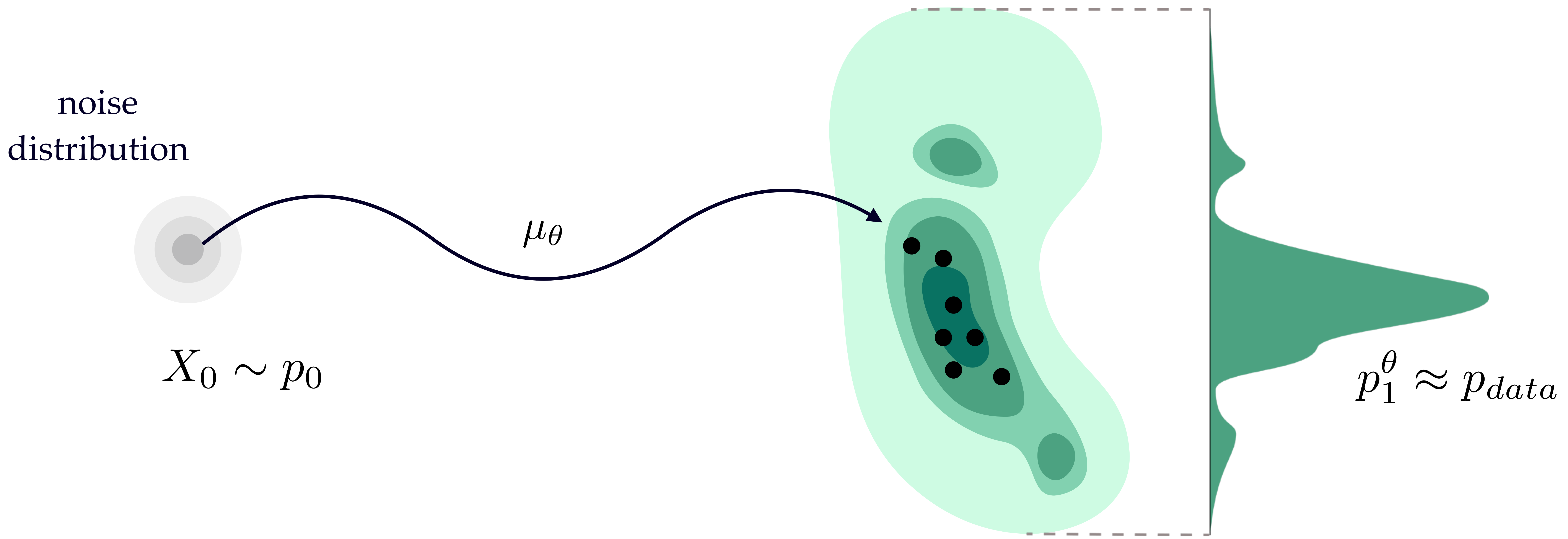
Diffusion and Flow Modeling: Pre-Training

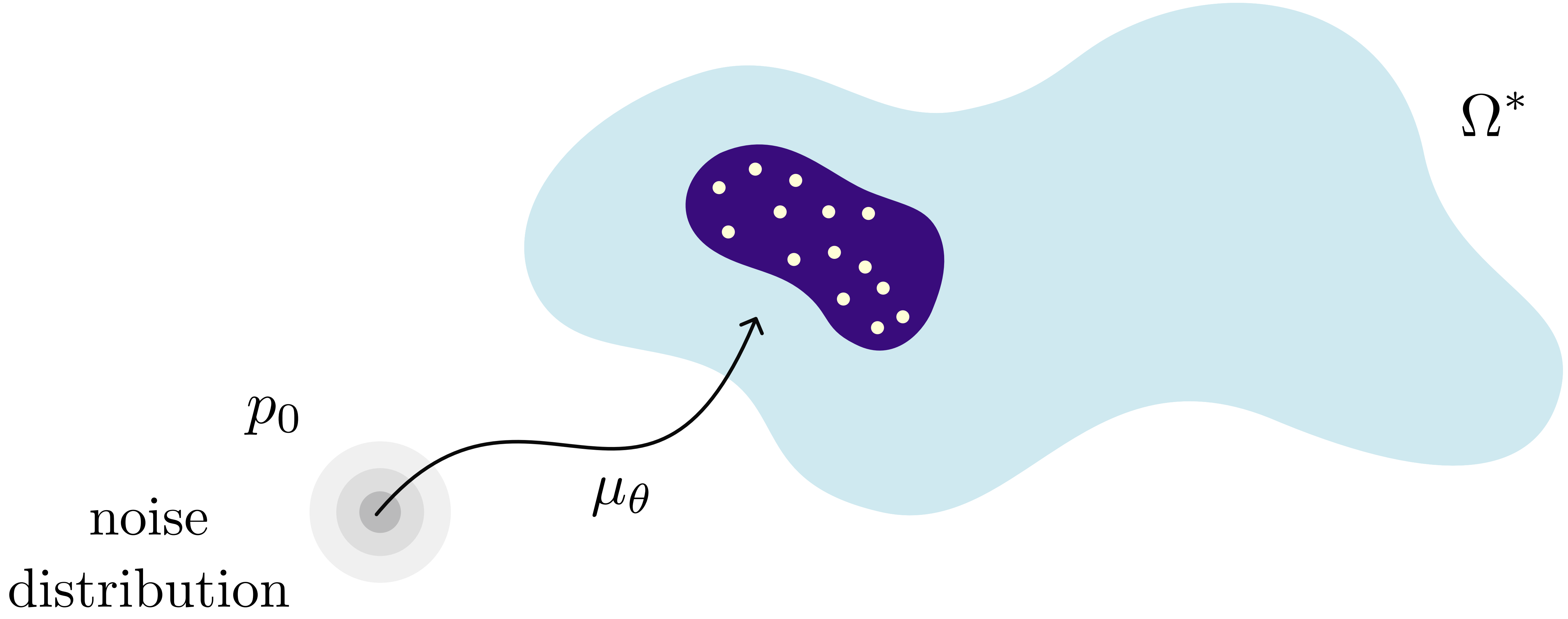


Distribution Matching: Standard Flow Pre-training

learn θ s.t. $p_1^\theta \approx p_{data}$

Implement via e.g., Flow/Score Matching

Flow Pre-training for Discovery: Key Limitation



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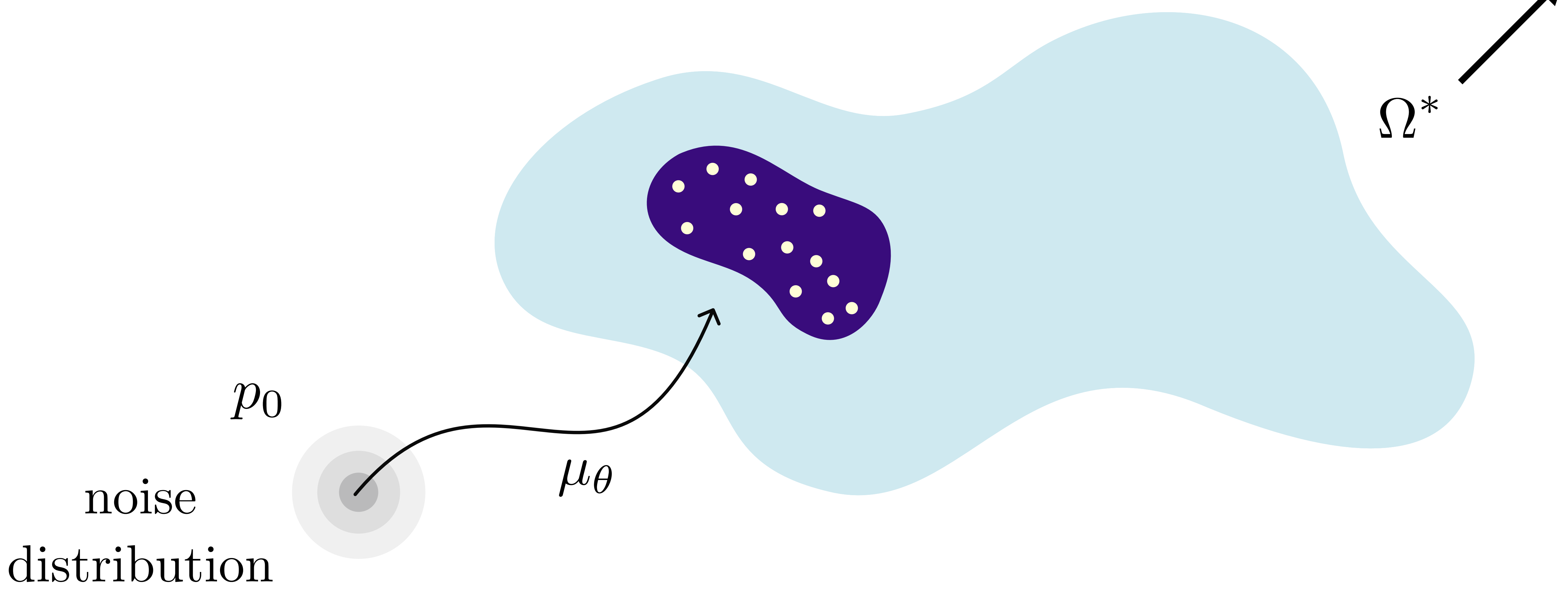
Flow Pre-training for Discovery: Key Limitation

Valid design space

$$\Omega^* := \{x \in \mathcal{X} : v(x) = 1\}$$

Unknown laws of nature (e.g., chemistry, biology)



Distribution Matching: Standard Flow Pre-training

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Flow Pre-training for Discovery: Key Limitation

How to formalize limited coverage?

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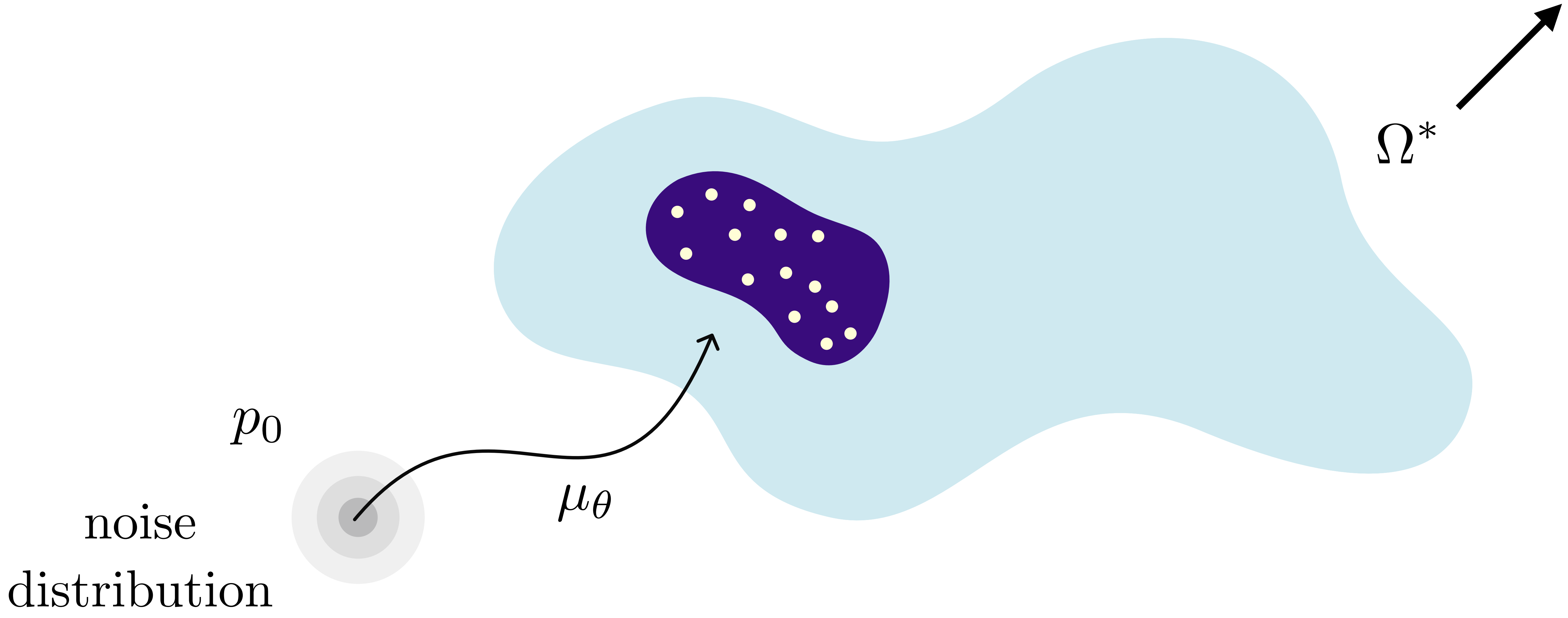

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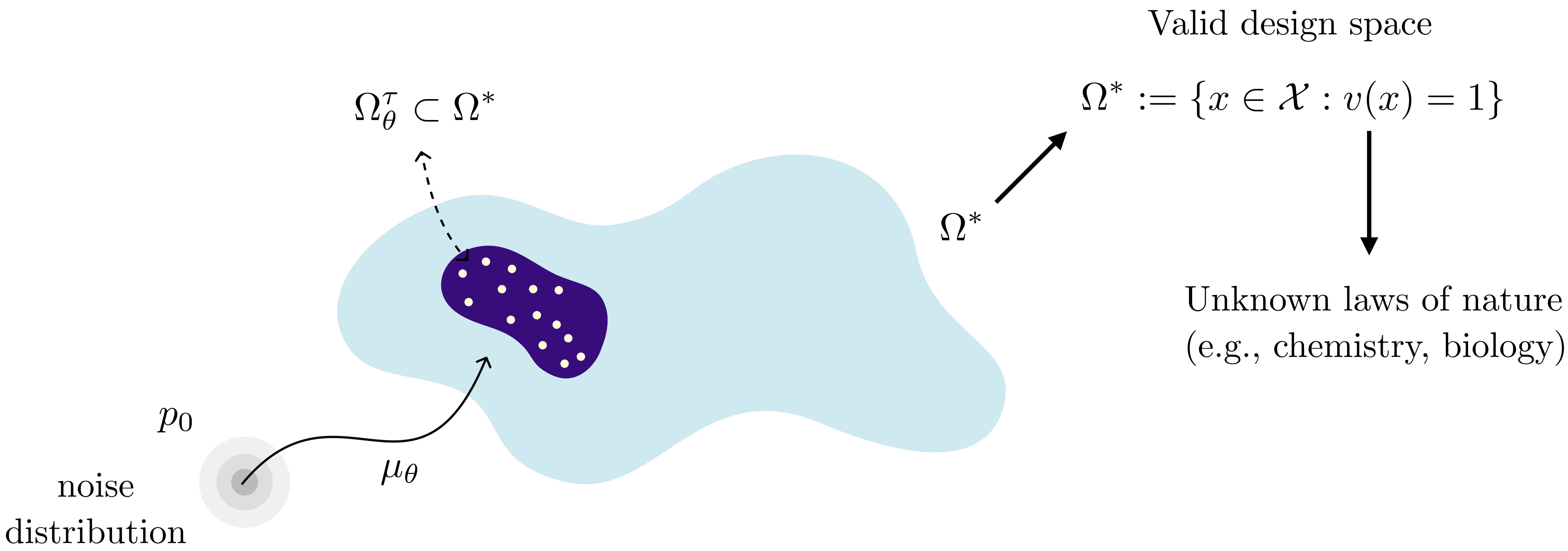
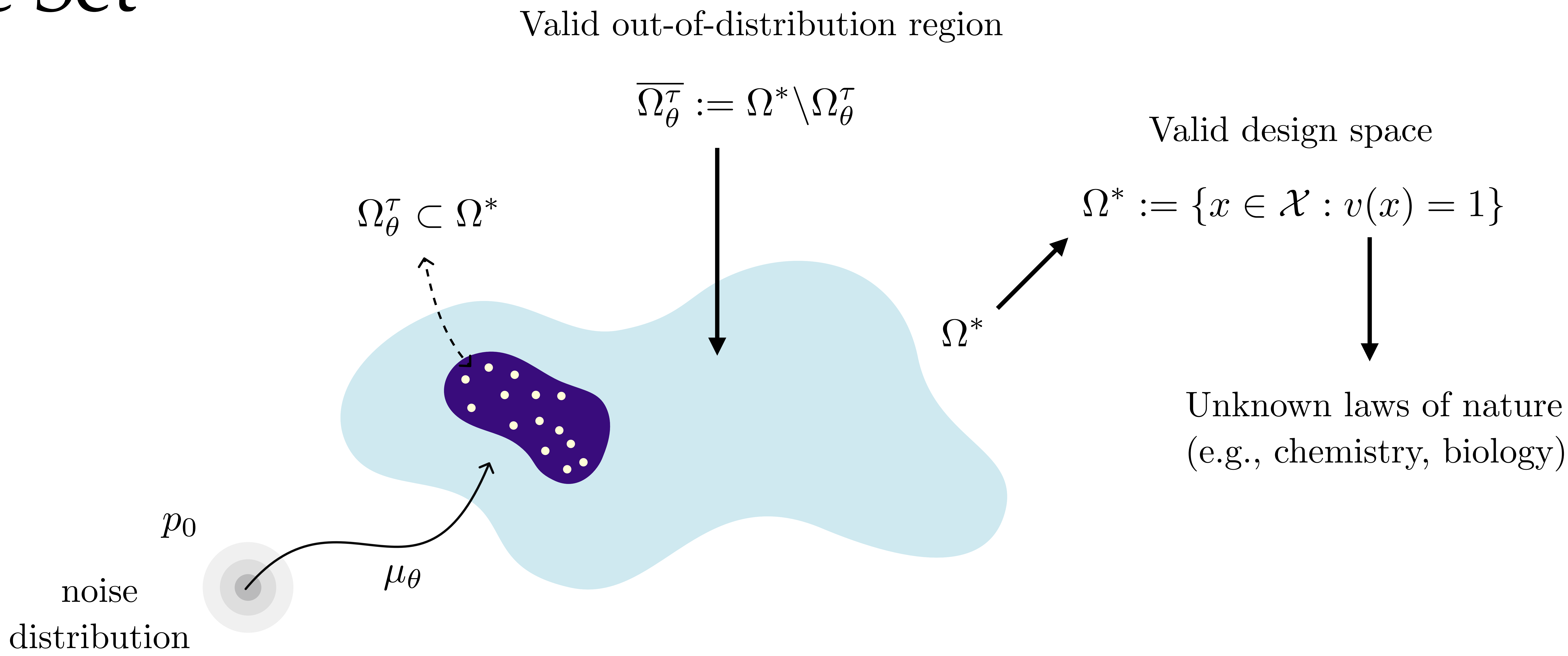
Generable Set



Definition (Generable Set). Let μ_θ inducing density p_1^θ. For $\tau > 0$, we define its τ-level generable set as:

$$\Omega_\theta^\tau := \{x \in \mathcal{X} : p_1^\theta(x) \geq \tau\}$$

Generable Set



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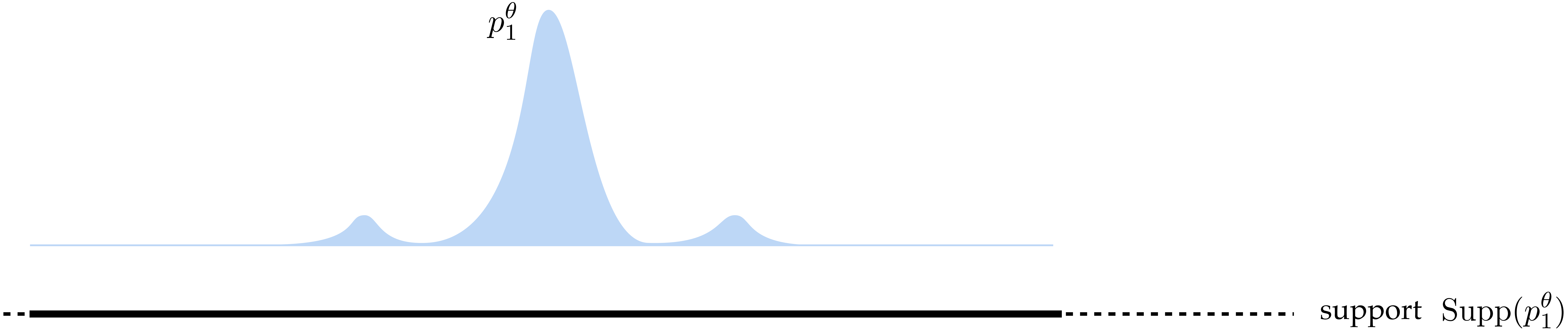
Generable Set vs Support



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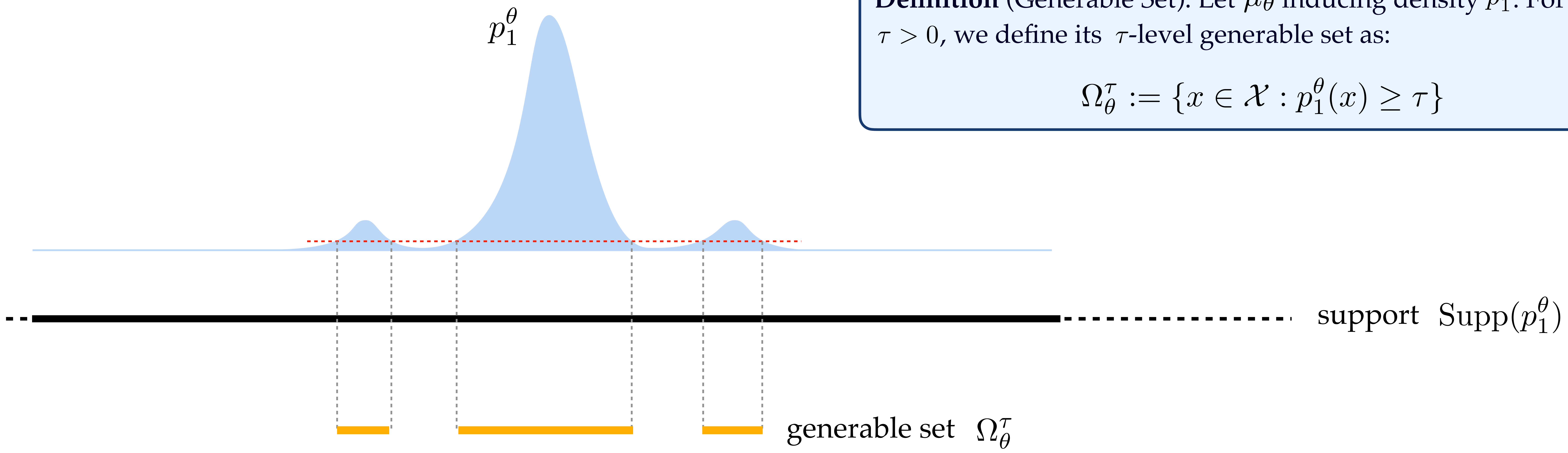

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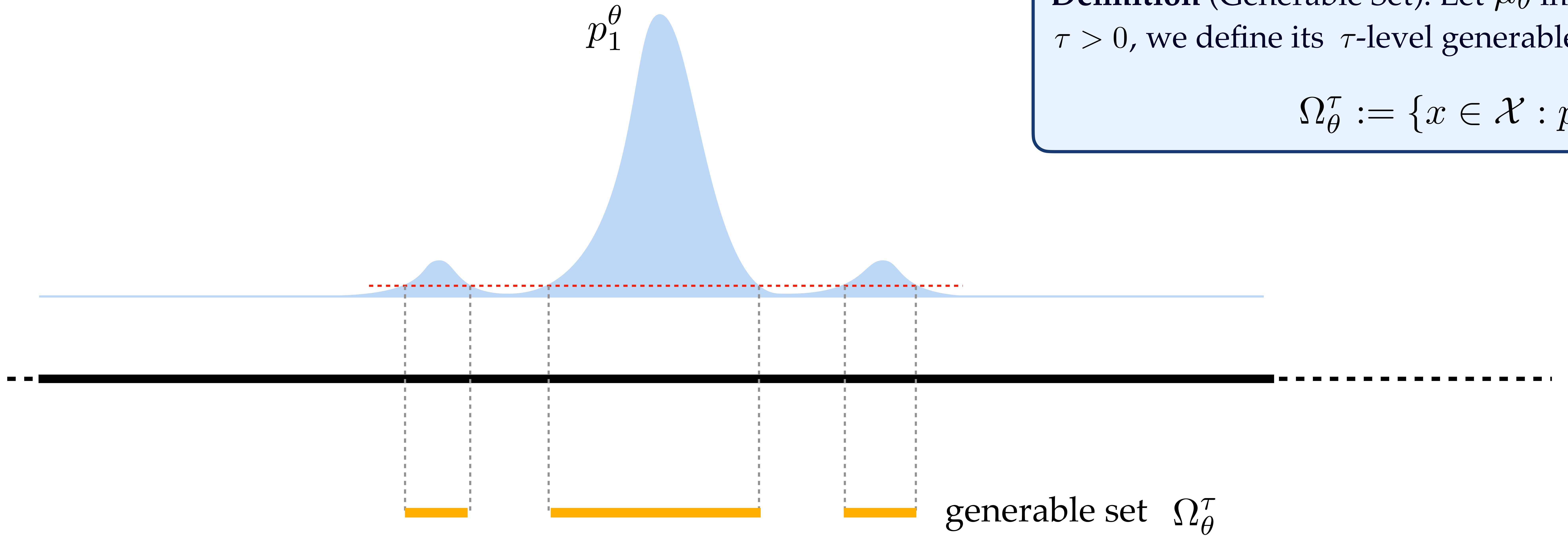
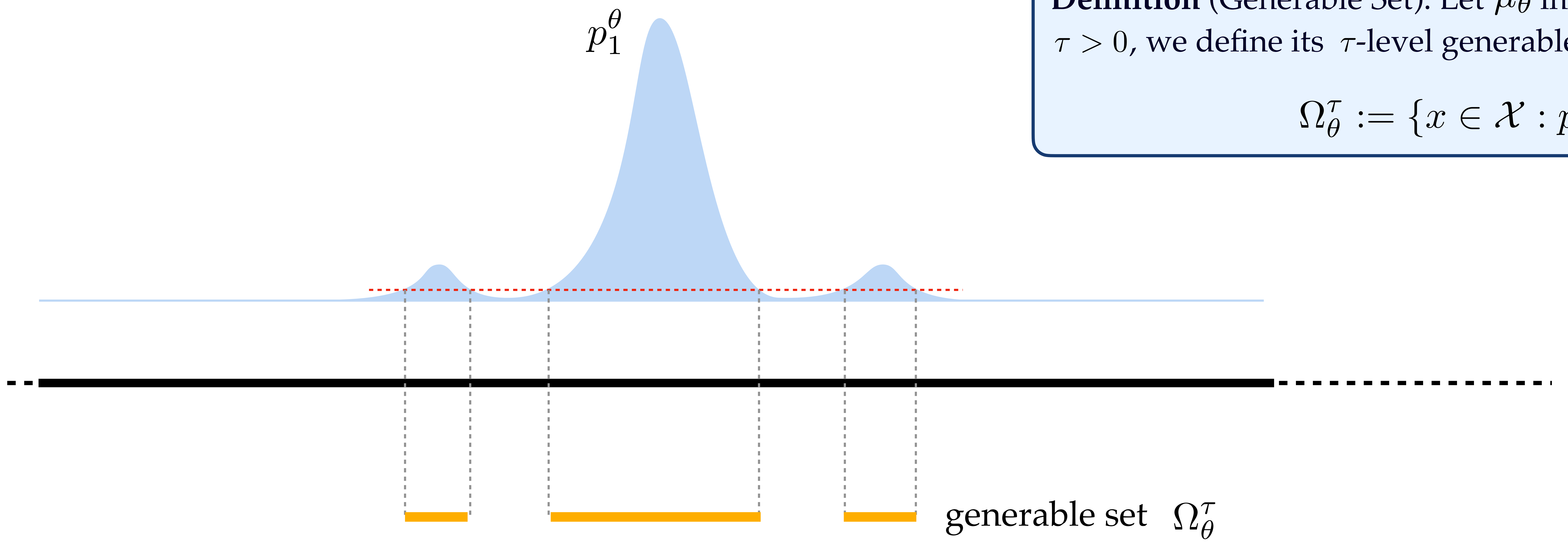


$$\Omega_\theta^\tau \xrightarrow{\tau \to 0} \mathrm{Supp}(p_1^\theta)$$

Generable Set vs Support



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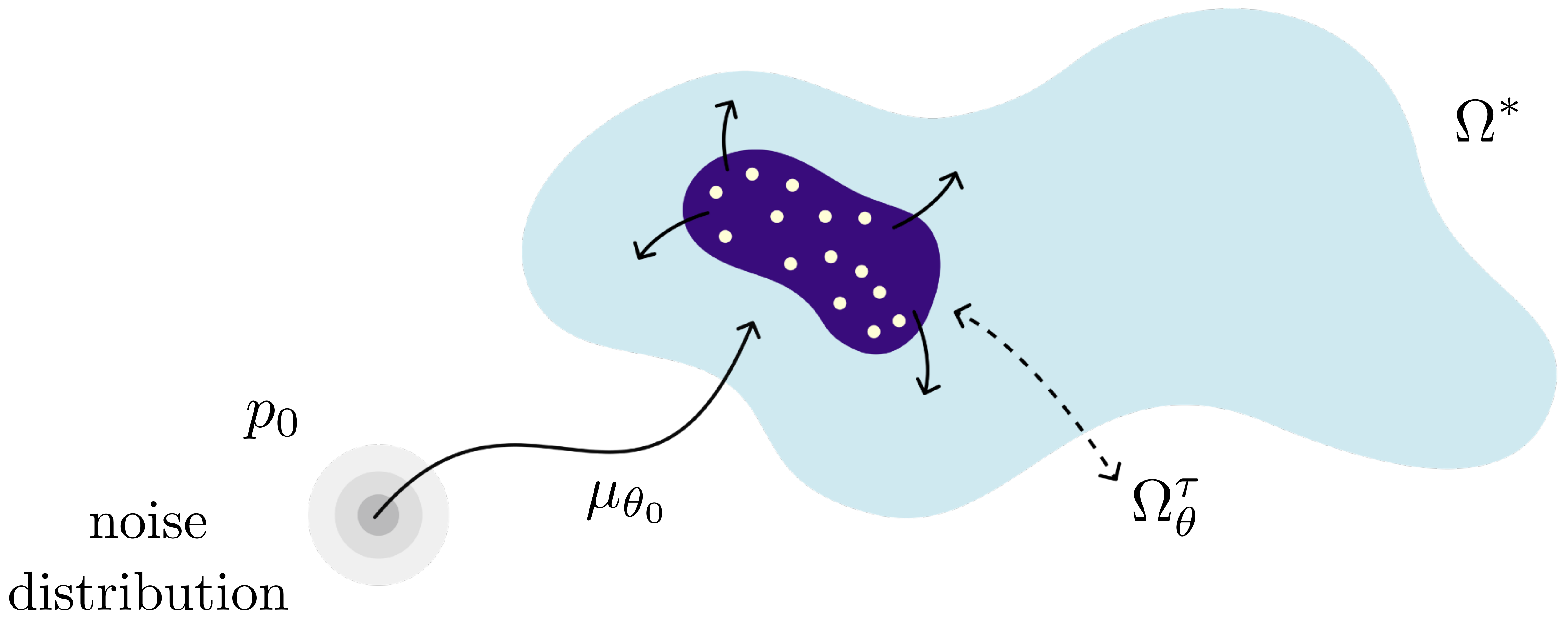
generable set
- region likely to be covered by a finite draw
- region where the generative model is reliable (e.g., sufficient validity signal)

Generable Set Expansion for OOD Flow Modeling

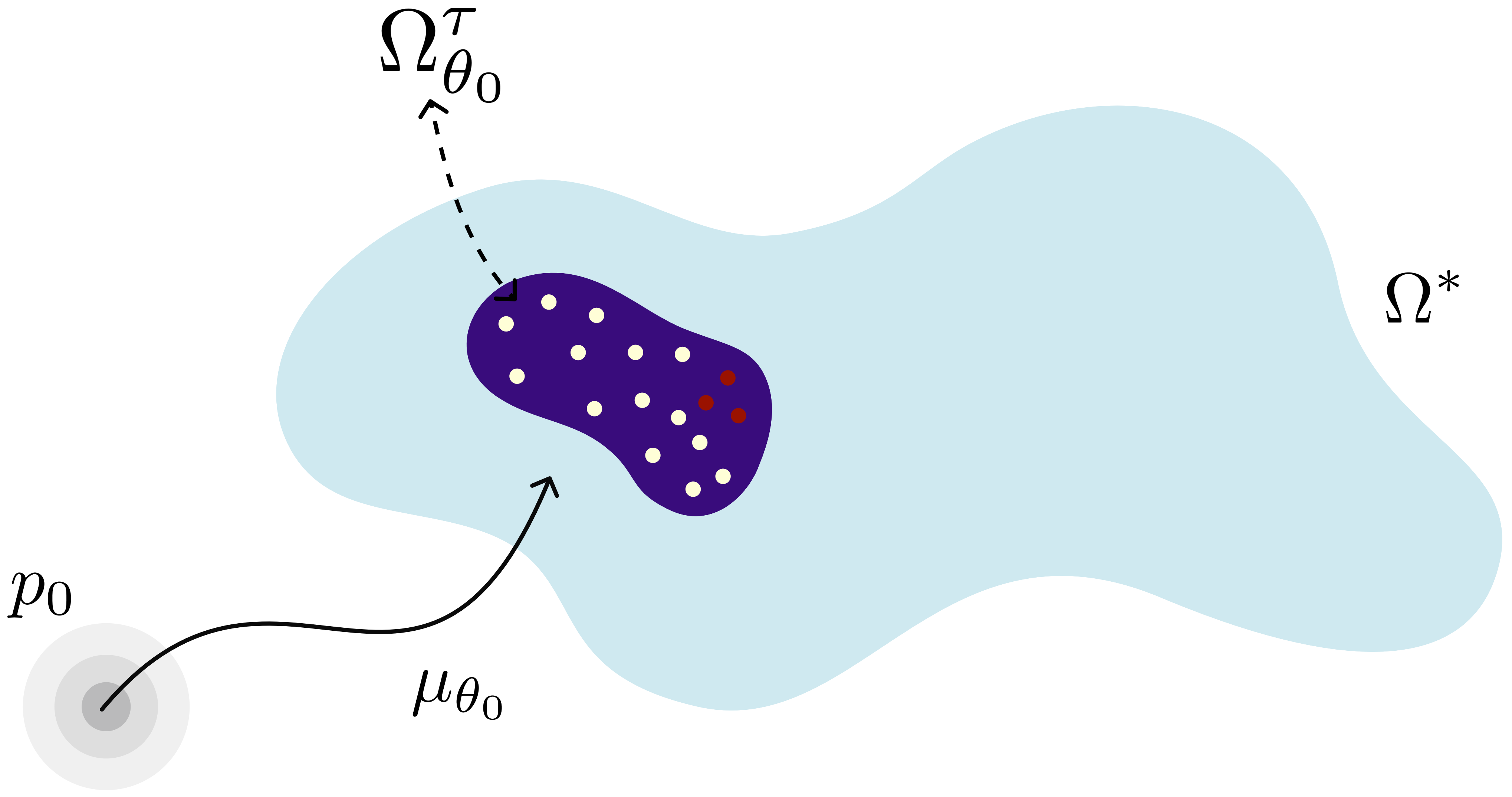


Requires acquiring information about Ω^* beyond the data

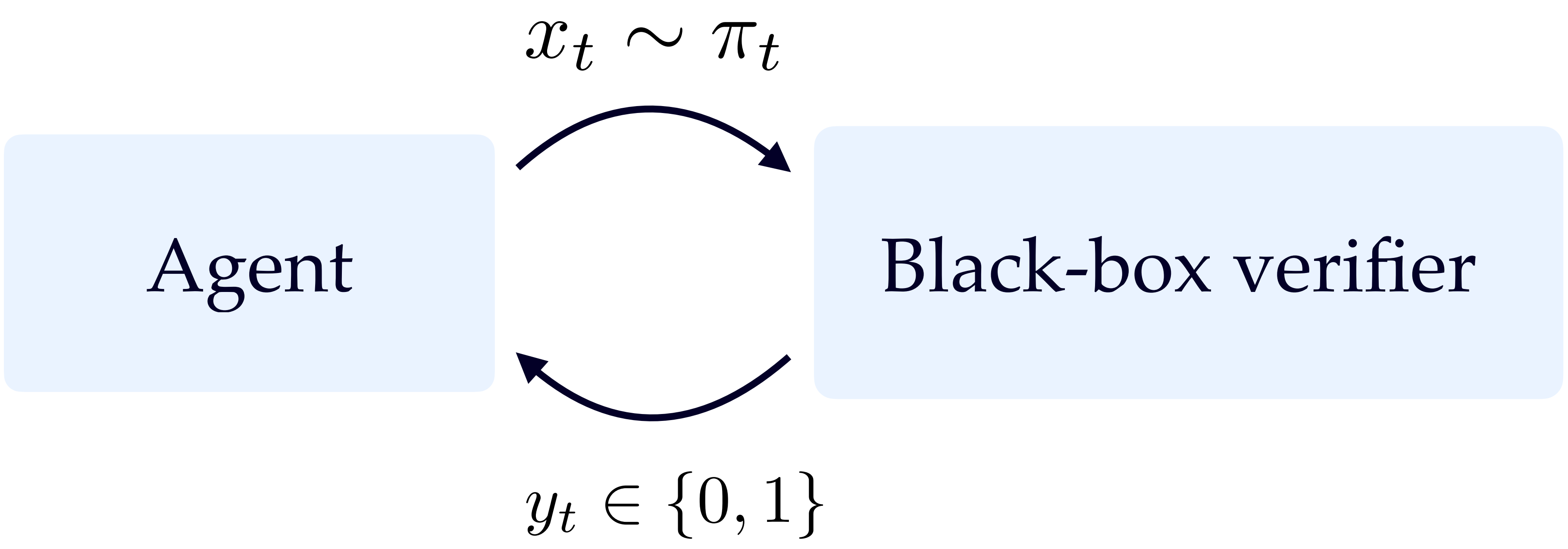
Generable Set Expansion: Out-of-Distribution Flow Modeling

learn θ s.t. $\Omega_\theta^\tau \approx \Omega^*$

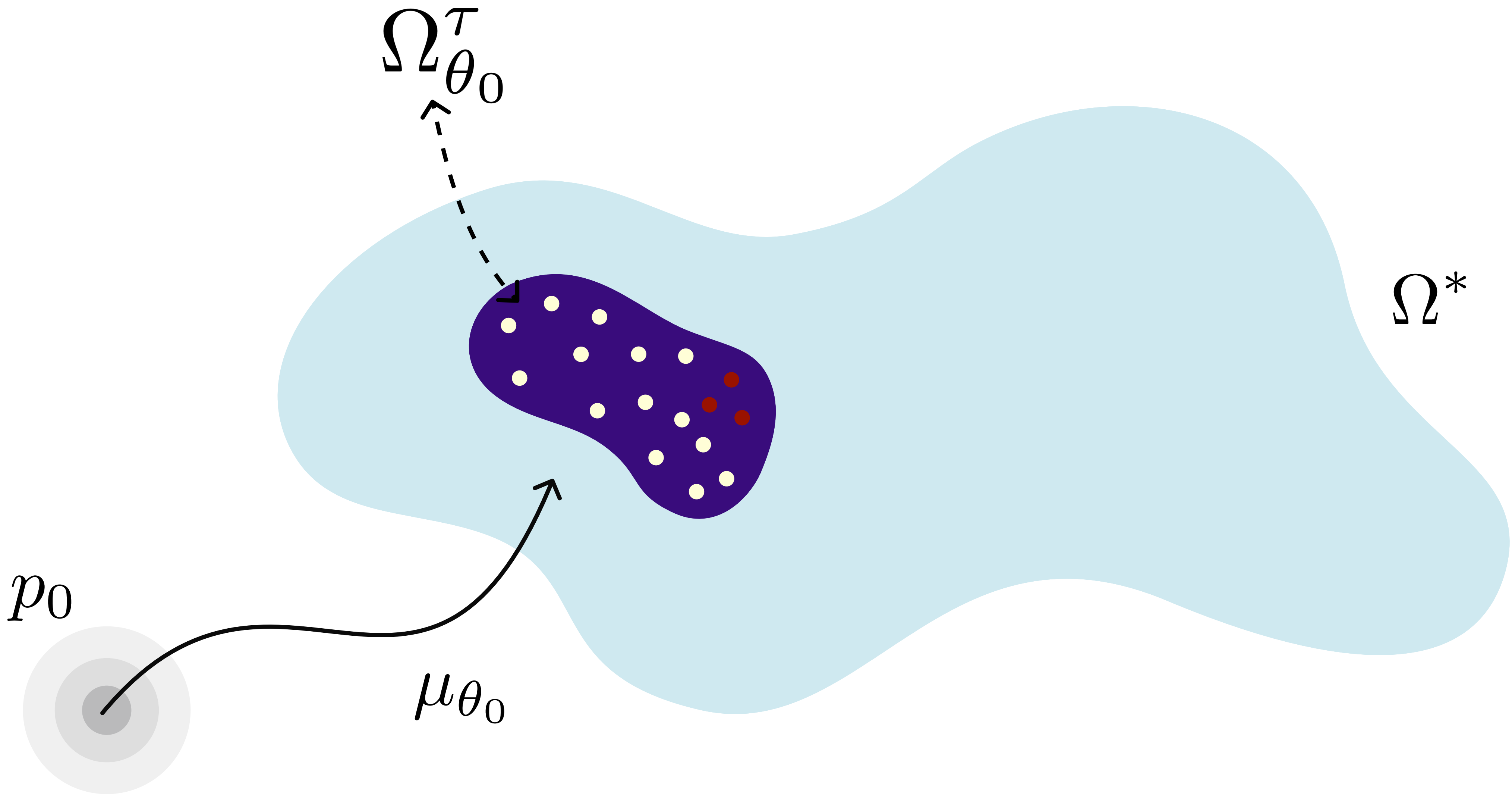
Generable Set Expansion for OOD Flow Modeling



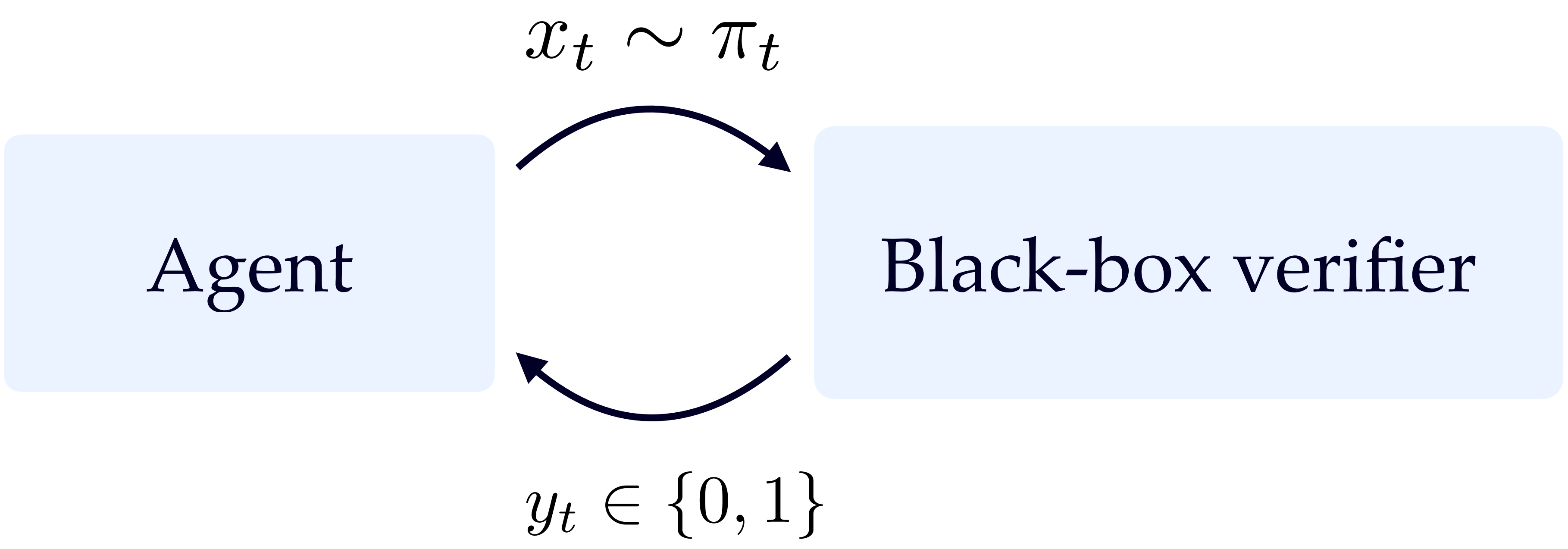
Black-box noisy binary verifier feedback



Generable Set Expansion for OOD Flow Modeling



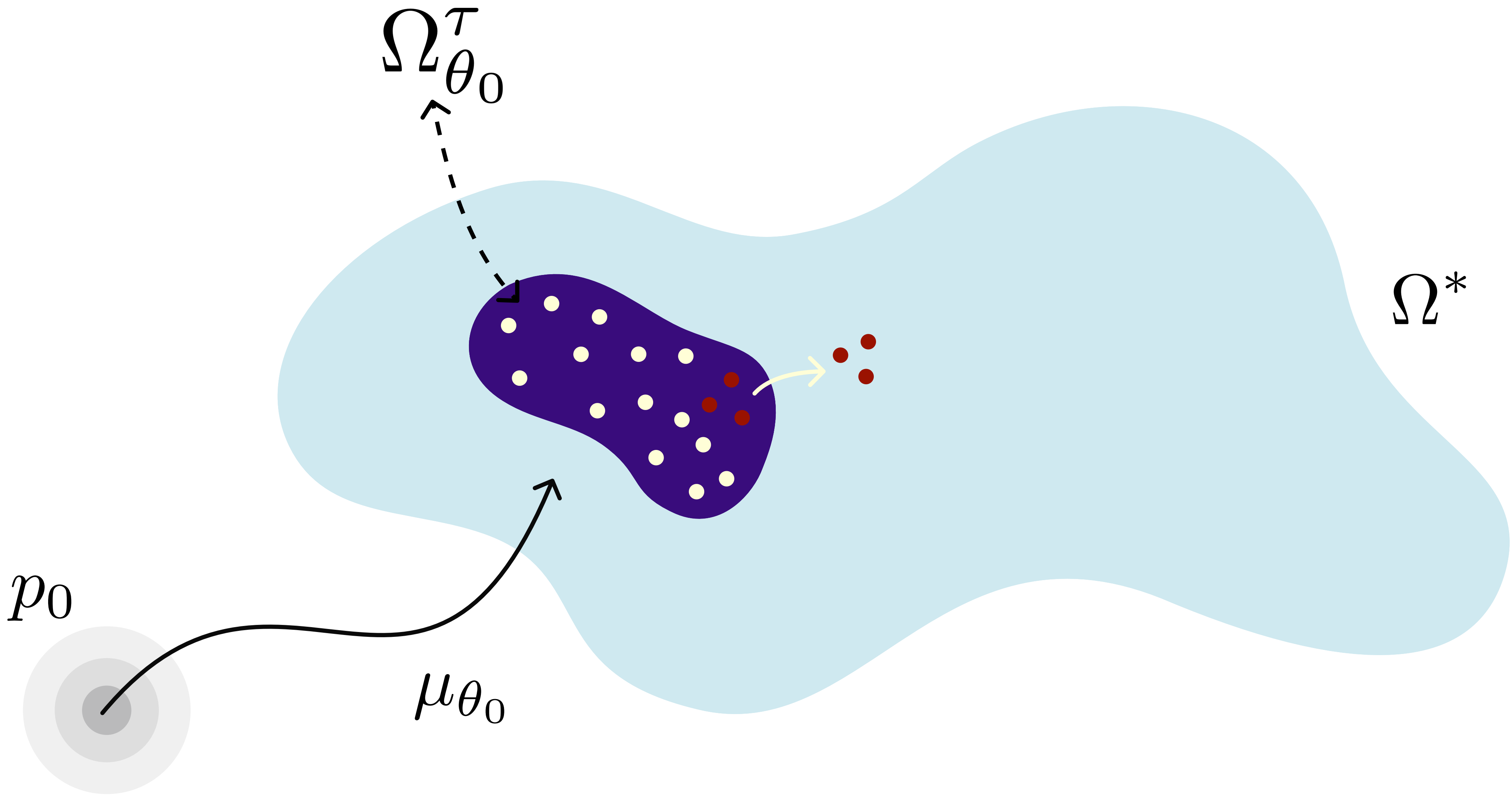
Black-box noisy binary verifier feedback



$$\theta^{\text{pre}} = \theta_0$$

$$\Omega_{\theta_0}^{\tau}$$

Generable Set Expansion for OOD Flow Modeling



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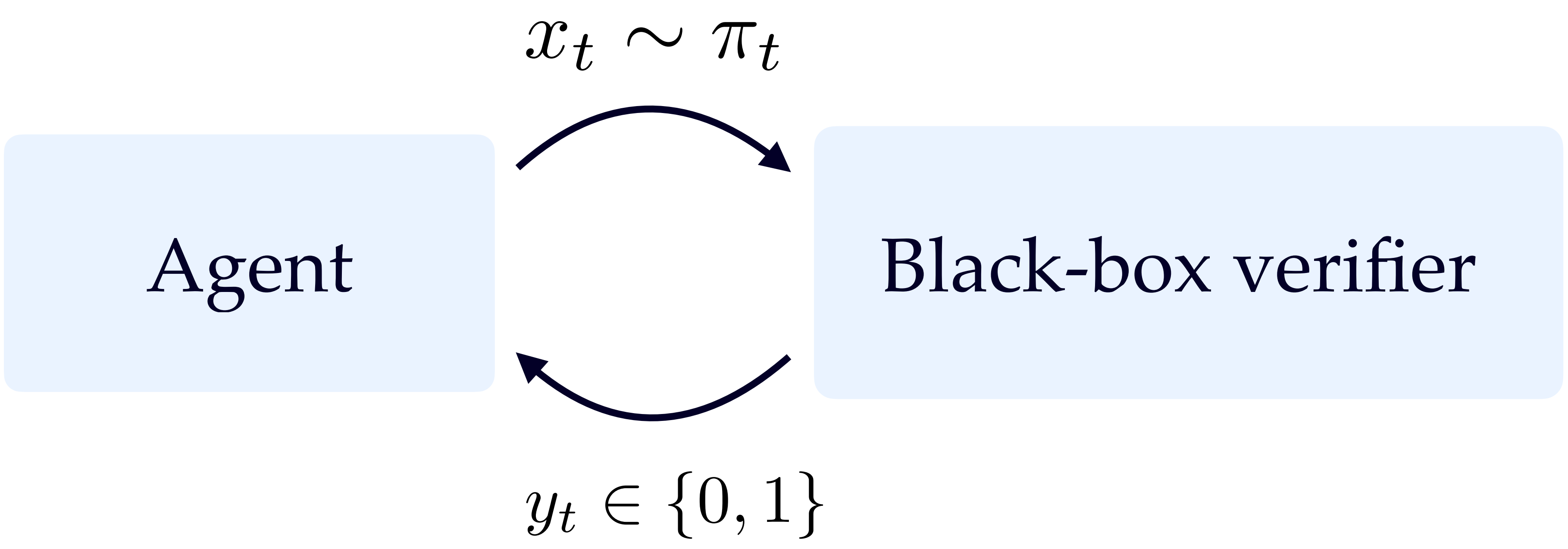
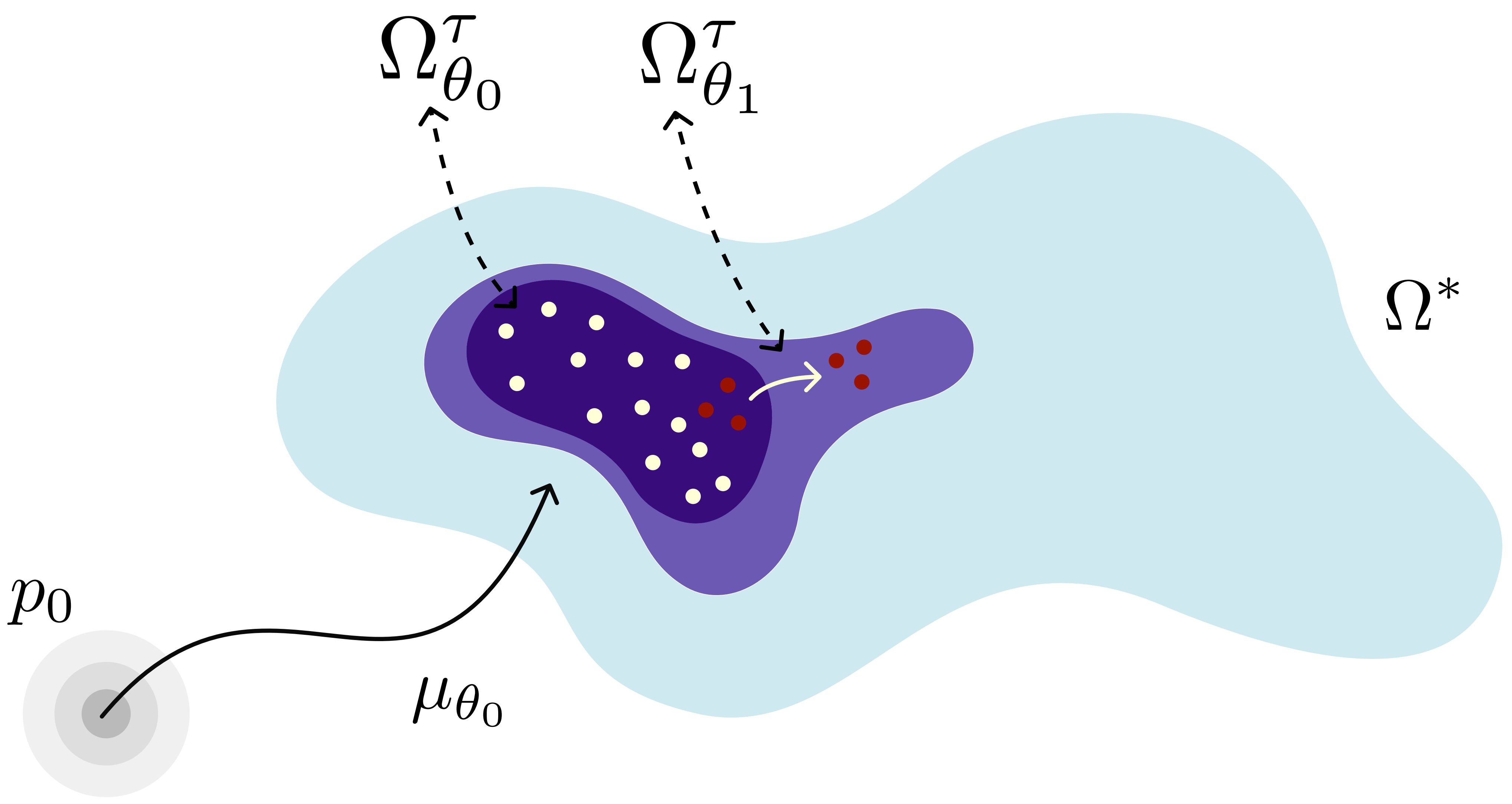


$$\theta^{\text{pre}} = \theta_0$$

$$\Omega^{\tau}_{\theta_0}$$

Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



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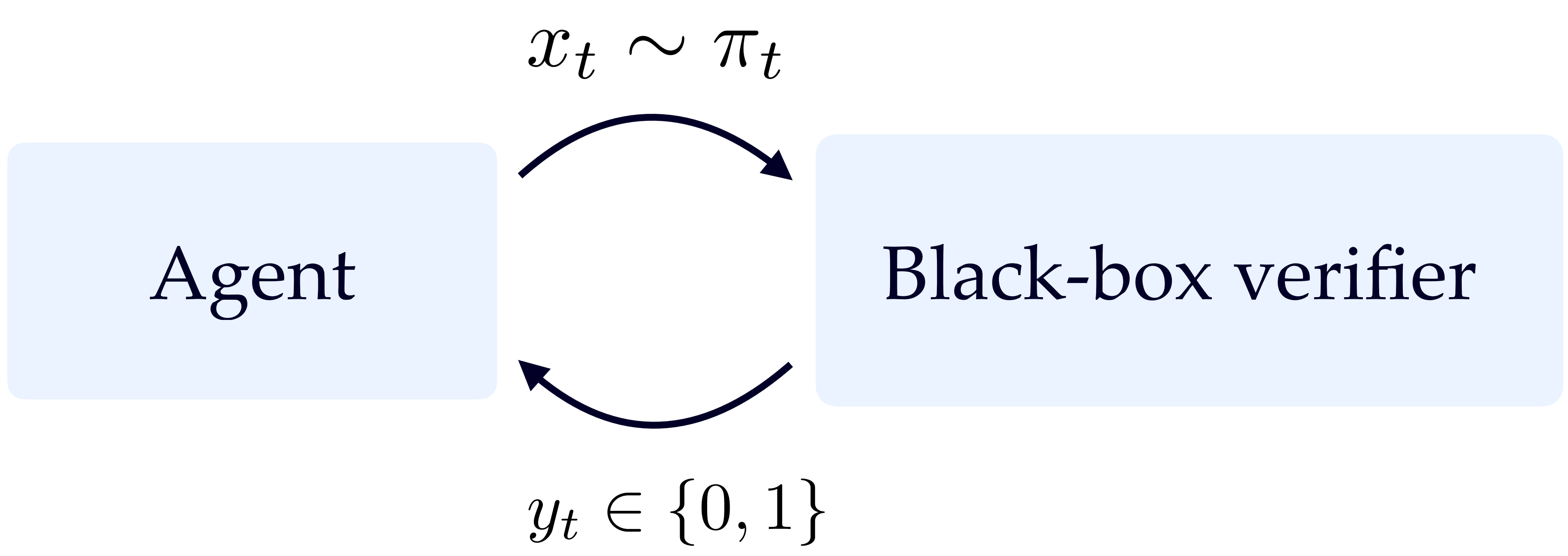
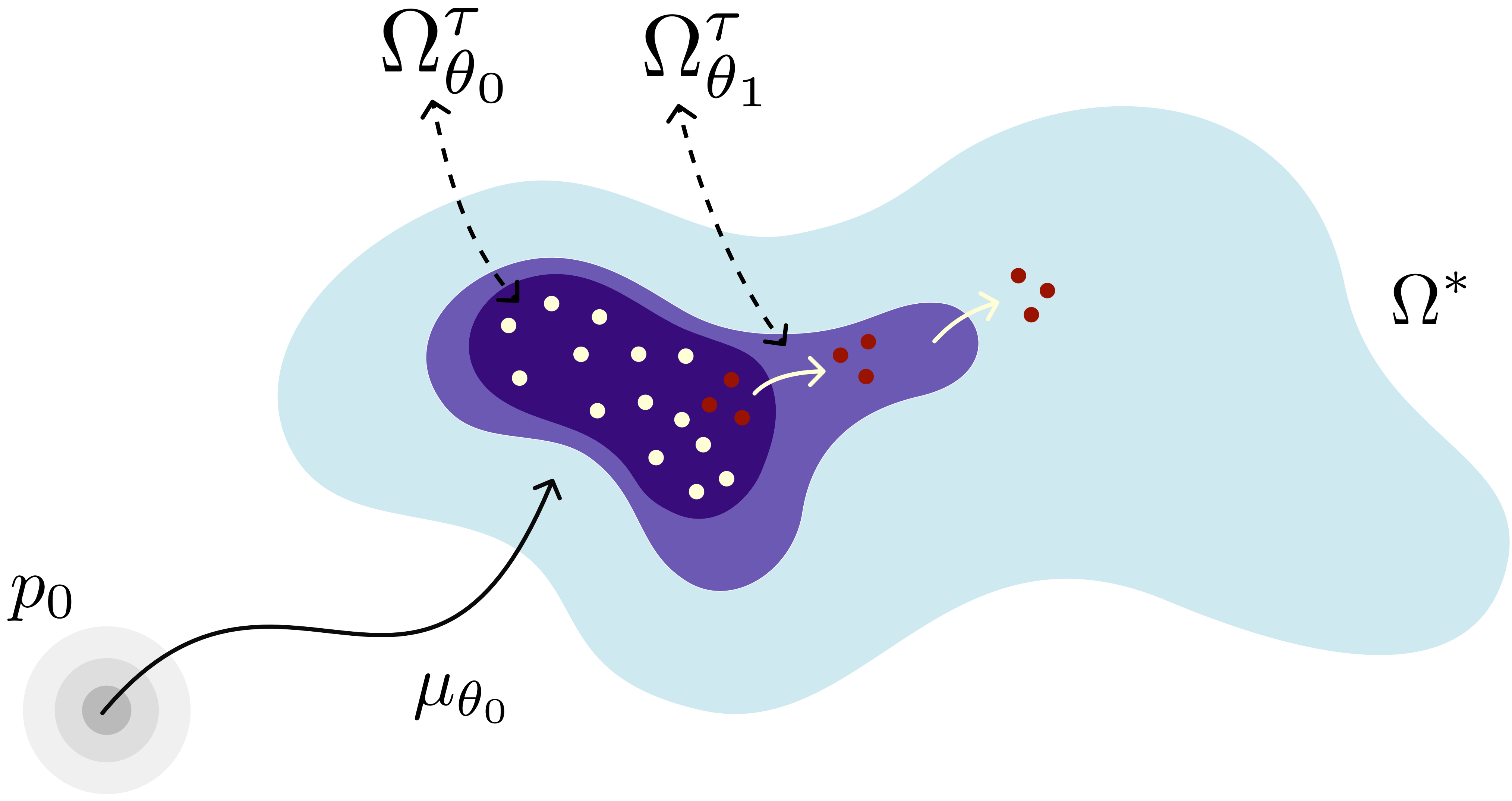


$$\theta^{\text{pre}} = \theta_0 \to \theta_1$$

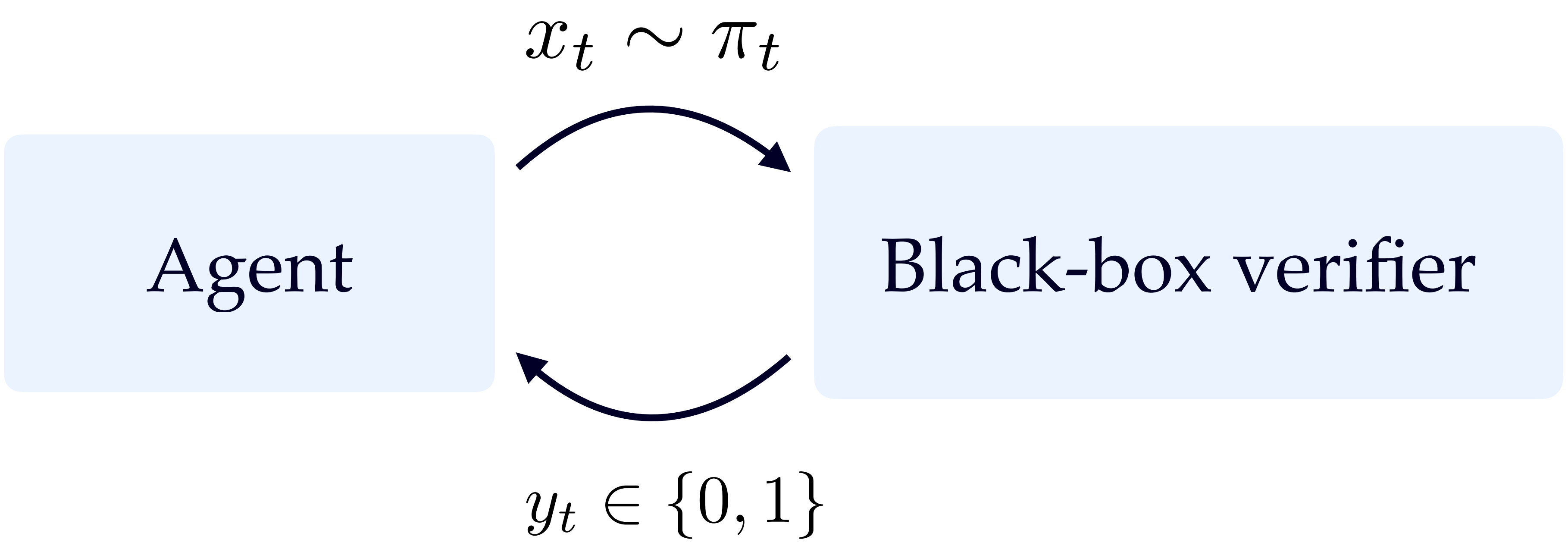
$$\Omega^{\tau}_{\theta_0} \subseteq \Omega^{\tau}_{\theta_1}$$

Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



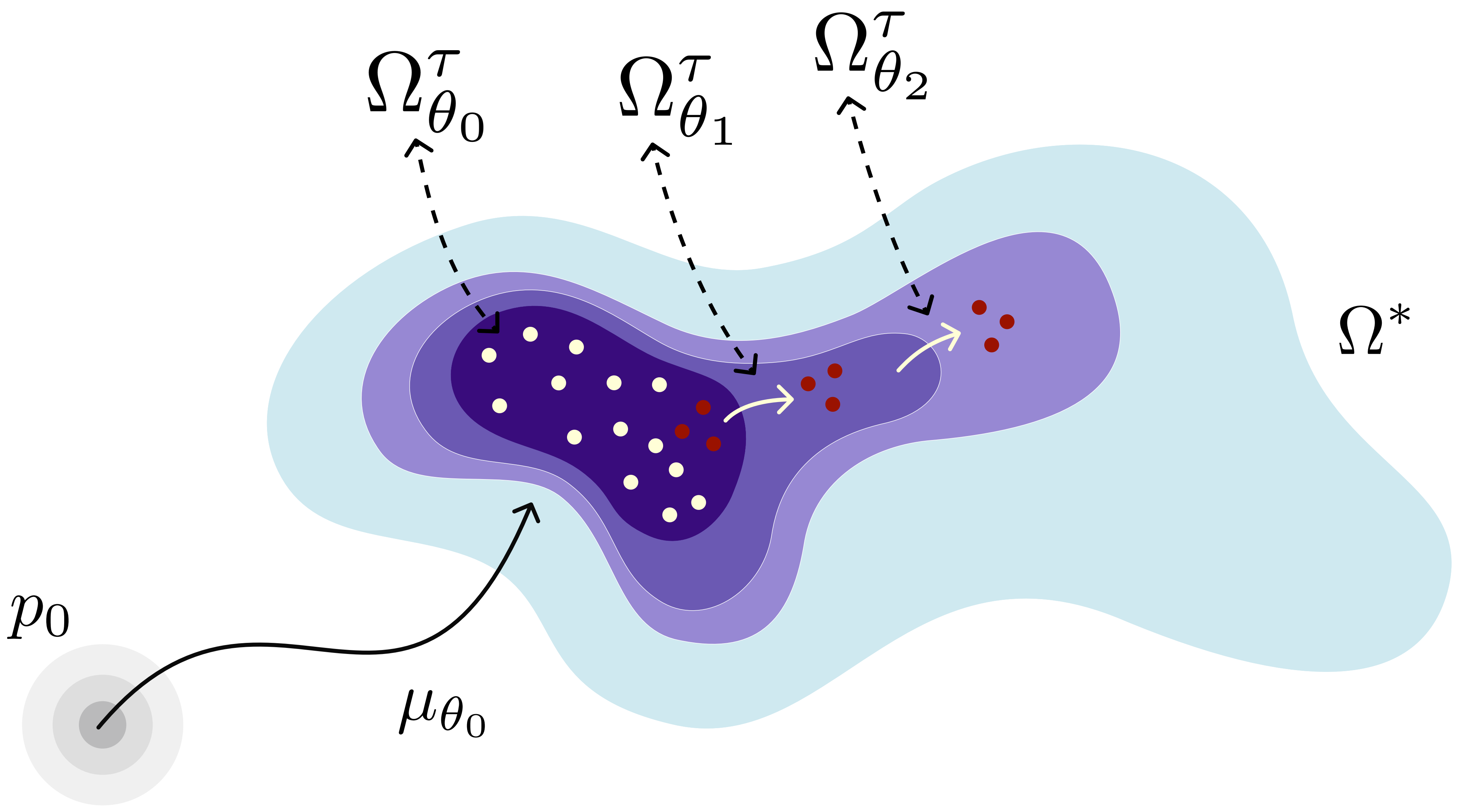
Black-box noisy binary verifier feedback



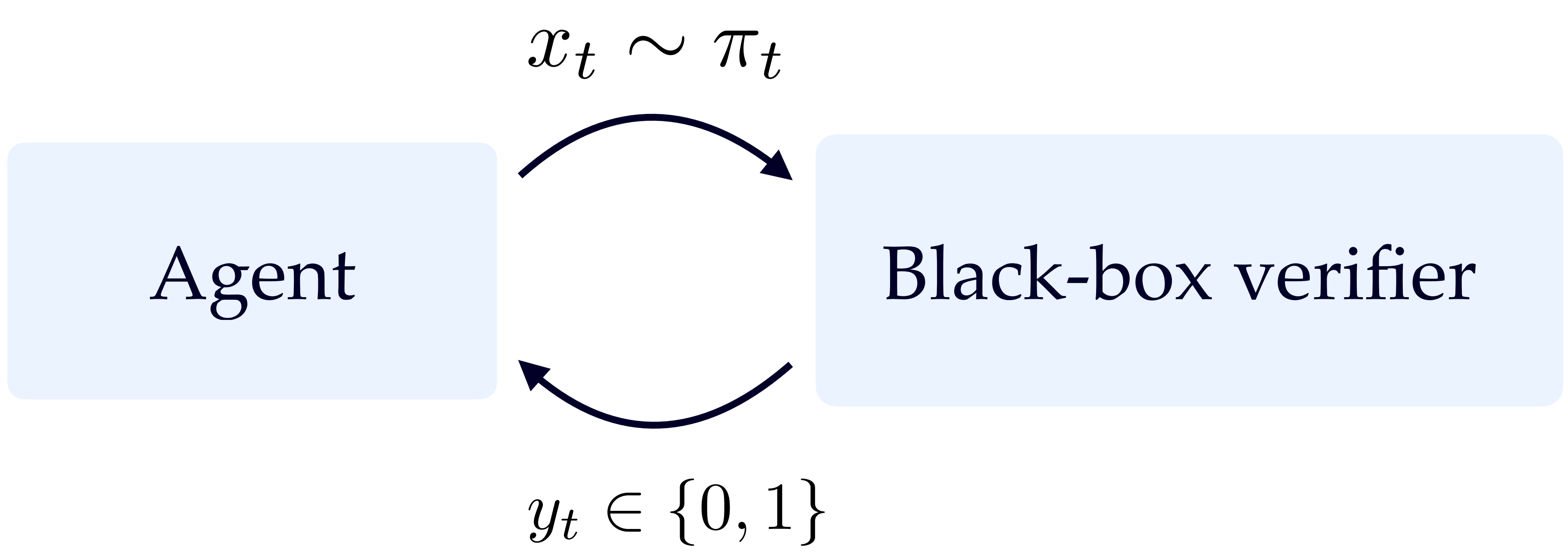
$$\theta^{\text{pre}} = \theta_0 \rightarrow \theta_1 \rightarrow \qquad \Omega^{\tau}_{\theta_0} \subseteq \Omega^{\tau}_{\theta_1} \subseteq$$

Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



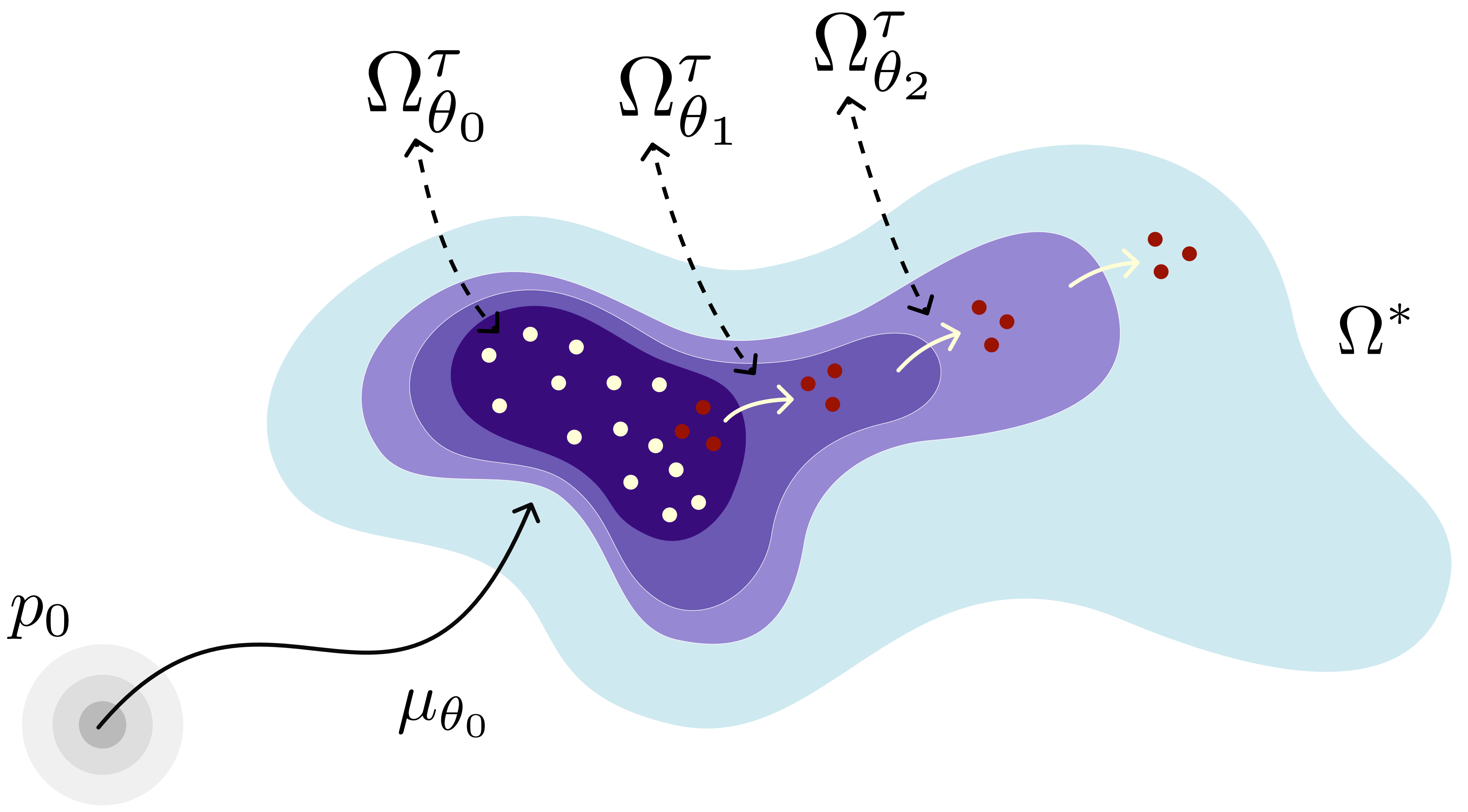
Black-box noisy binary verifier feedback



$$\theta^{\text{pre}} = \theta_0 \to \theta_1 \to \cdots \qquad \Omega^\tau_{\theta_0} \subseteq \Omega^\tau_{\theta_1} \subseteq \cdots$$

Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



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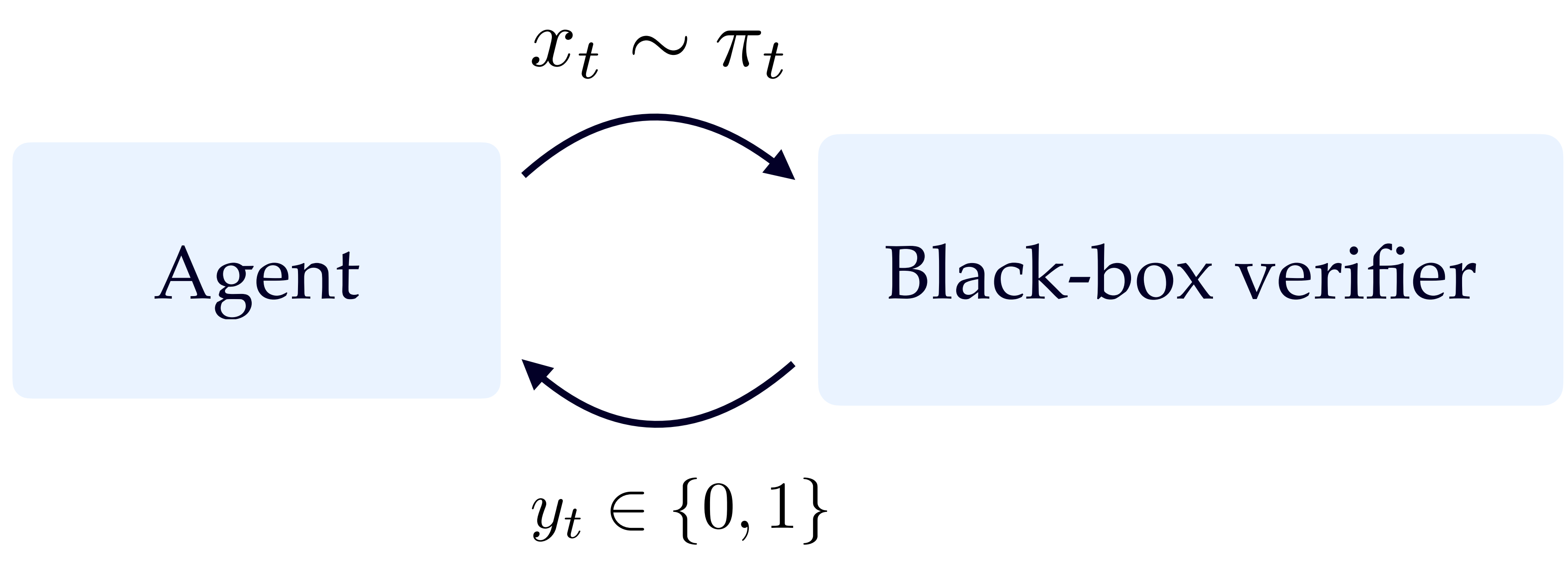

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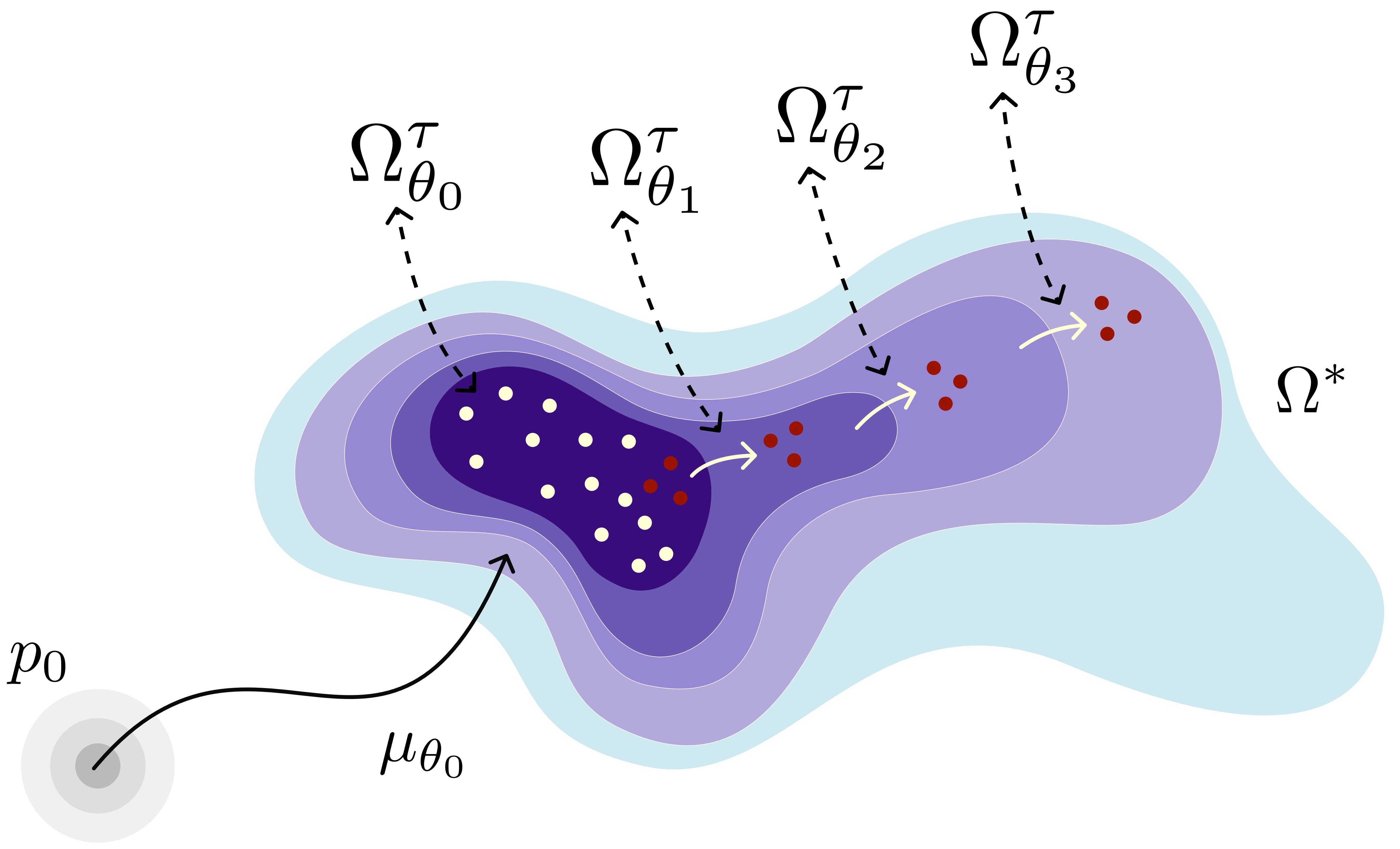
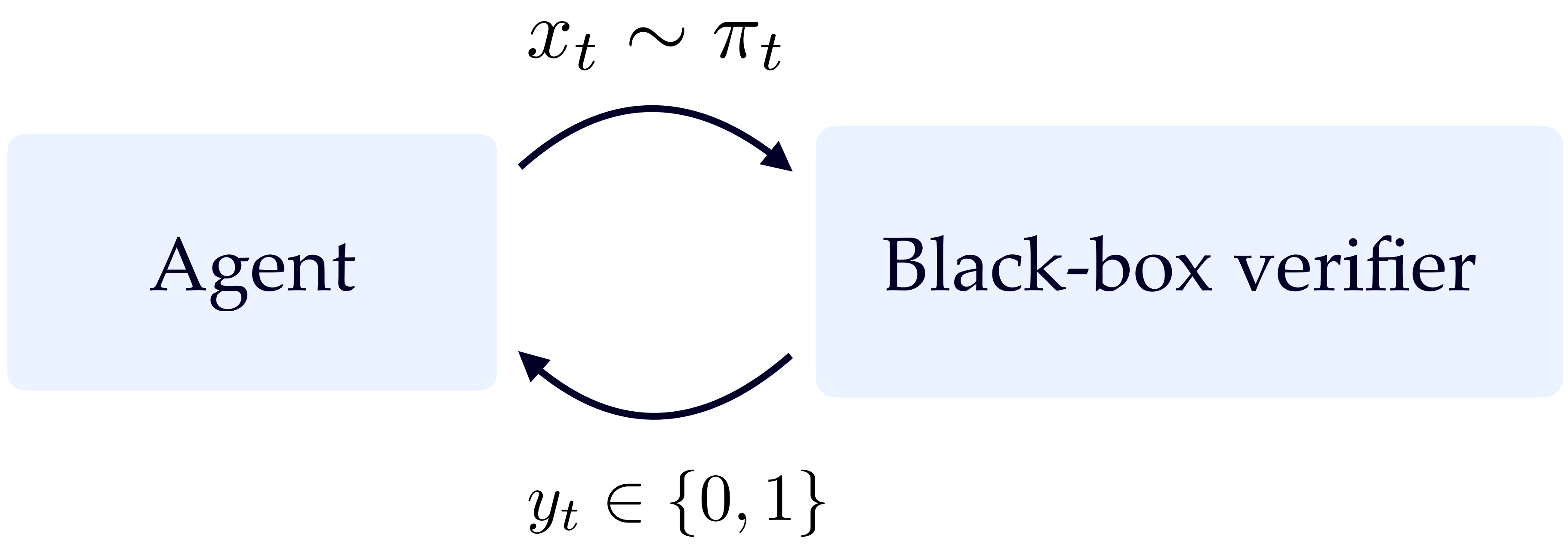
Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



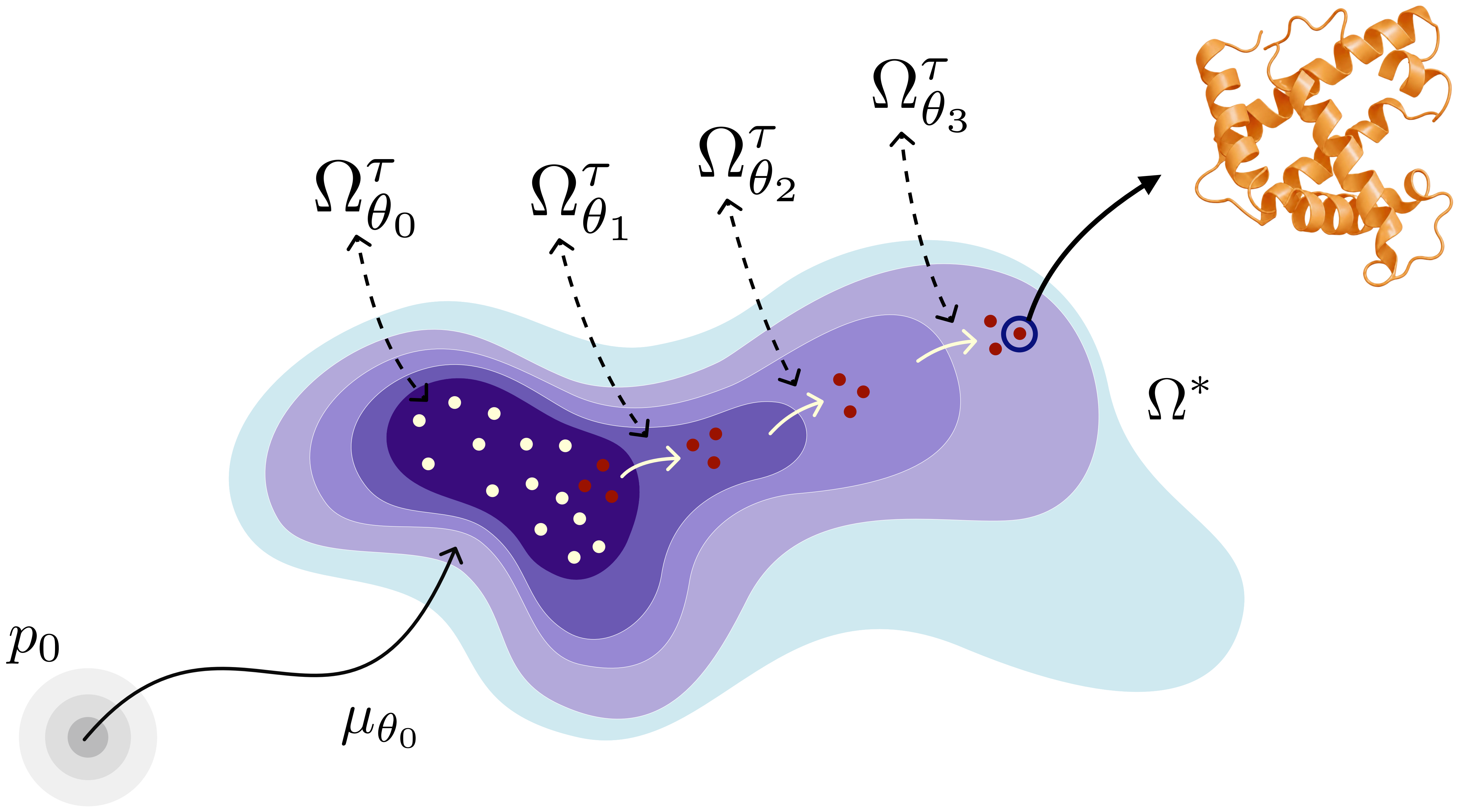
Black-box noisy binary verifier feedback



$$\theta^{\text{pre}} = \theta_0 \to \theta_1 \to \cdots \to \theta_T \qquad \Omega^\tau_{\theta_0} \subseteq \Omega^\tau_{\theta_1} \subseteq \cdots \subseteq \Omega^\tau_{\theta_T}$$

Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



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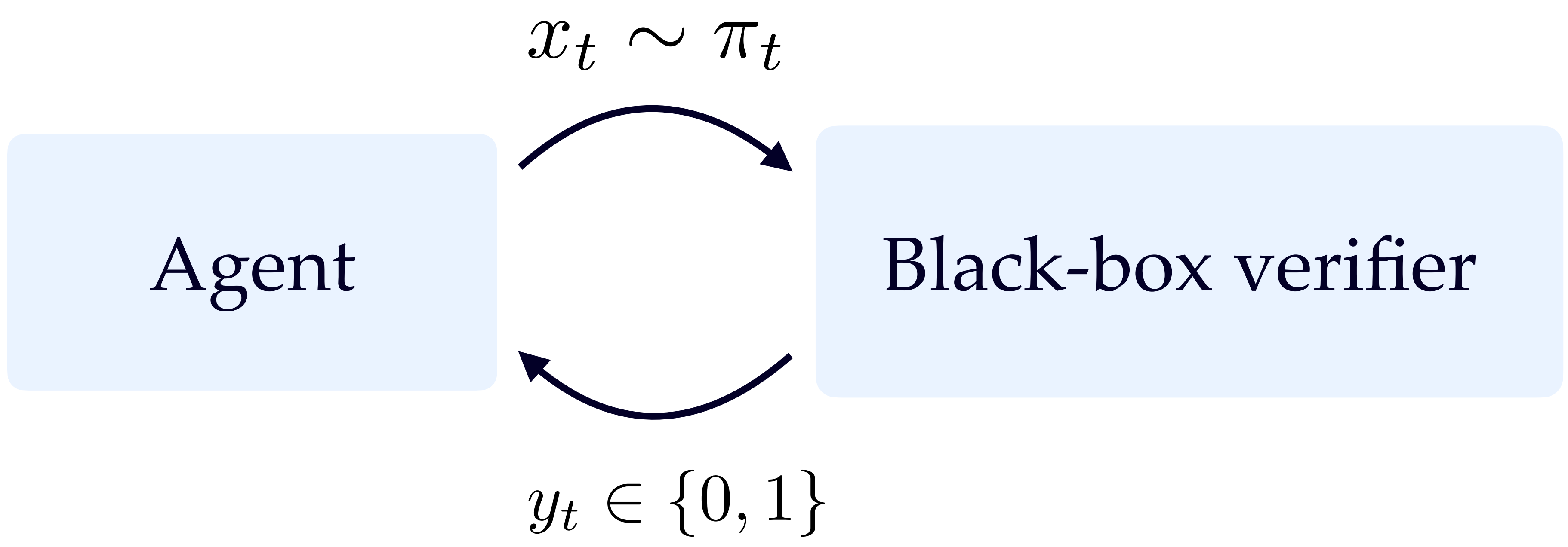

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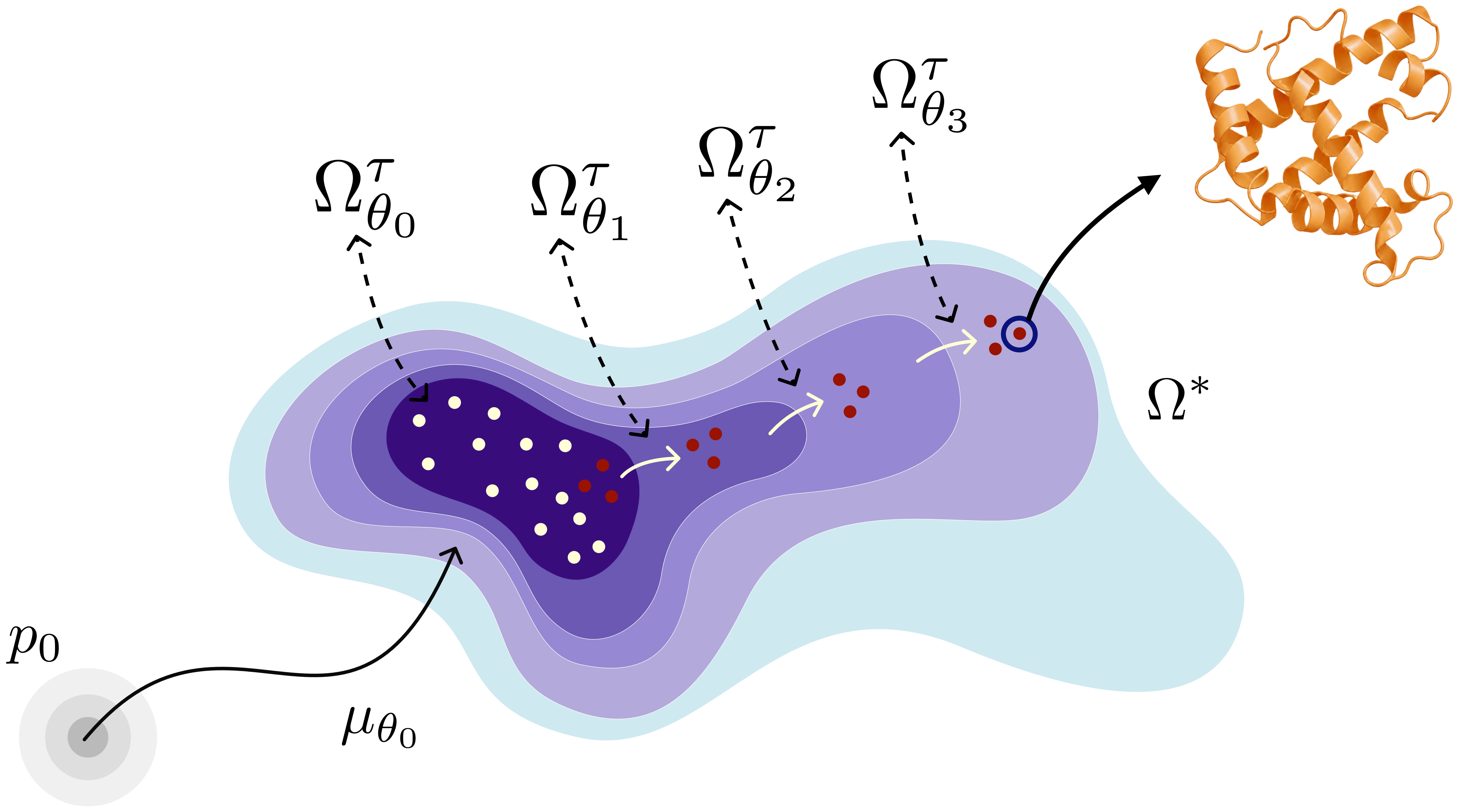
Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



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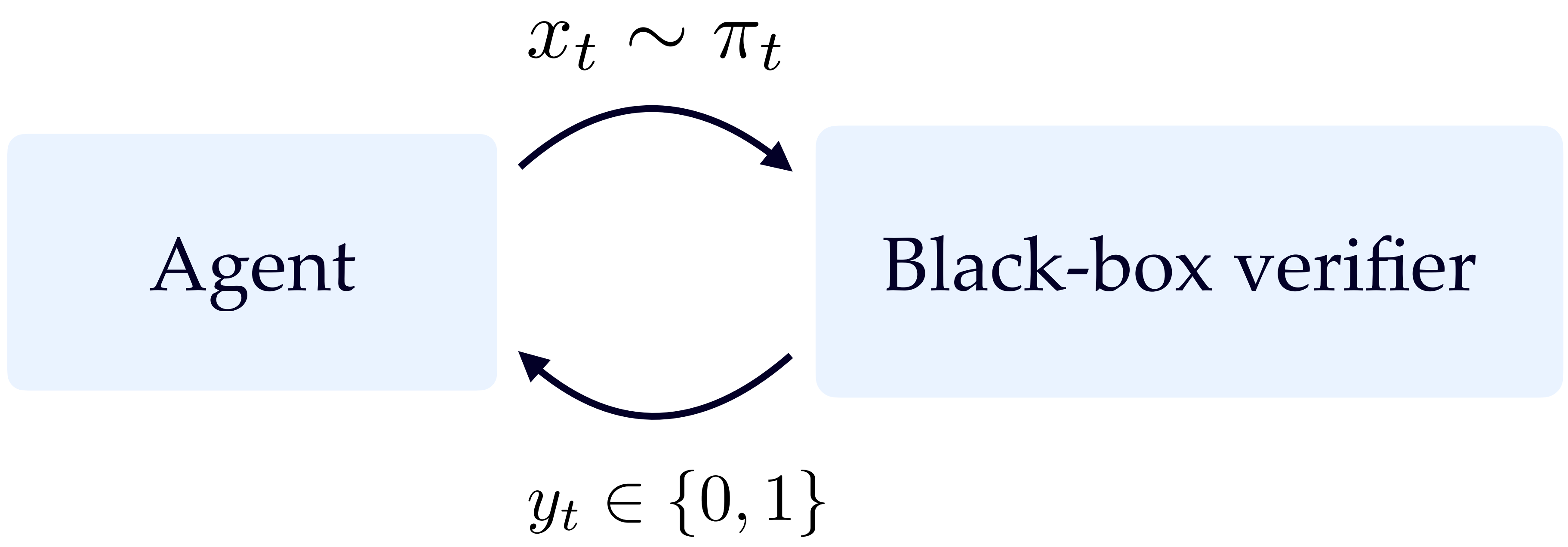

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Continual expansion via adaptation on valid **frontier samples**

How to self-generate frontier samples? Generative Uncertainty Sampling

inference-time distribution

$$x_{t+1} \sim \tilde{p}_t \in \arg\max_{q}$$

next data point

generates data

How to self-generate frontier samples? Generative Uncertainty Sampling

verifier uncertainty estimate on $\mathcal{Z}_s^t$

inference-time distribution

$$x_{t+1} \sim \tilde{p}_t \in \arg\max_q \mathbb{E}_{x \sim q}\left[\sigma_t\left(\phi_s^t(x)\right)\right]$$

next data point

noised flow representation

$$\mathcal{Z}_s^t = \phi_s^t(\mathcal{X})$$

generates data with **high verifier (i.e., laws of nature) uncertainty**

How to self-generate frontier samples? Generative Uncertainty Sampling

verifier uncertainty estimate on $\mathcal{Z}_s^t$

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$$x_{t+1} \sim \tilde{p}_t \in \arg\max_q \mathbb{E}_{x \sim q}\left[\sigma_t\left(\phi_s^t(x)\right)\right] - \beta \, \mathrm{KL}\left(q \,\|\, p_1^{\theta_t}\right)$$

next data point

noised flow representation
$\mathcal{Z}_s^t = \phi_s^t(\mathcal{X})$

current-model (i.e., prior)
regularization

generates data with **high verifier (i.e., laws of nature) uncertainty**, yet with **sufficient validity prior**

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verifier uncertainty estimate on $\mathcal{Z}_s^t$

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$\longrightarrow$ highly informative **frontier samples**

ActFlow: Active Flow Expansion

$$x_{t+1} \sim \tilde{p}_t \in \arg\max_q \mathbb{E}_{x\sim q}\left[\sigma_t\left(\phi_s^t(x)\right)\right] - \beta\,\mathrm{KL}\left(q \,\|\, p_1^{\theta_t}\right)$$

ActFlow: Active Flow Expansion

Init: Initial flow model μ_{θ_0}, black-box verifier $\tilde{v}$, iterations T, $\mathcal{D}_0 \leftarrow \emptyset$

For $t = 0, 1, \ldots, T-1$:

Update surrogate uncertainty σ_t from $\mathcal{D}_t$

Self-generate:

$$x_{t+1} \sim \tilde{p}_t \in \arg\max_q \mathbb{E}_{x\sim q}\left[\sigma_t\left(\phi_s^t(x)\right)\right] - \beta\,\mathrm{KL}\left(q \,\|\, p_1^{\theta_t}\right)$$

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Query verifier $y_{t+1} \leftarrow \tilde{v}(x_{t+1})$

$\mathcal{D}_{t+1} \leftarrow \mathcal{D}_t \cup \{(x_{t+1}, y_{t+1})\}$

$\theta_{t+1} \leftarrow \textsc{UpdateFlow}(\theta_t, \mathcal{D}_{t+1})$

Return μ_{θ_T}

Theoretical Guarantees for Out-of-Distribution Flow Modeling

Distribution matching

$$p_1^\theta \approx p_{data}$$

$\longrightarrow$

Design space coverage

$$\Omega_\theta^\tau \approx \Omega^*$$

Generative modeling beyond data distribution matching

Theoretical Guarantees for Out-of-Distribution Flow Modeling

Theorem (Informal, generable representation set covers reachable set).
Fix $\epsilon > 0$ and an integer $H \geq 1$. Then, with

$$T^\star \gtrsim \left(\frac{\alpha \gamma_{HT^*}^{\Omega_\star}}{\epsilon} \right)^2$$

By running ActFlow, it holds with probability at least $1 - \delta$ that after T^* verified samples:

$$R_\epsilon^H(S_0) \subseteq \Omega_{T^\star}^\tau$$

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generable representation set

reachable set given **H-fold** recursive application of **one-step reachability operator** over flow representation:

$$R_\epsilon(S) := \{z \in \mathcal{Z} : \exists z' \in S \text{ s.t. } s(g(z')) - L_s L_g d(z, z') - \epsilon \geq h\}$$

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$$R_\epsilon^H(S_0) \subseteq \Omega_{T^\star}^\tau$$

maximum information gain

$$\gamma_t^A \triangleq \max_{z_1,\ldots,z_t \in A} \frac{1}{2} \log\det\Big(I_t + (\lambda\kappa)^{-1} K_t\Big)$$

captures laws of nature complexity

generable representation set

reachable set given **H-fold** recursive application of **one-step reachability operator** over flow representation:

$$R_\epsilon(S) := \{z \in \mathcal{Z} : \exists z' \in S \text{ s.t. } s(g(z')) - L_s L_g d(z, z') - \epsilon \geq h\}$$

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By running ActFlow, it holds with probability at least $1 - \delta$ that after T^* verified samples:

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Allows to identify **structural conditions** and **statistical complexity** for:

$$\Omega^\star \subseteq \Omega_{T^\star}^{X,\tau_X}$$

valid design space

generable set on $\mathcal{X}$

Theoretical Guarantees for Out-of-Distribution Flow Modeling

Theorem (Informal, generable representation set covers reachable set).
Fix $\epsilon > 0$ and an integer $H \geq 1$. Then, with

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By running ActFlow, it holds with probability at least $1 - \delta$ that after T^* verified samples:

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Takeaway

ActFlow allows to build (generable) **set-theoretic guarantees** for **out-of-distribution flow modeling**.

Distribution matching

$$p_1^{\theta} \approx p_{data}$$

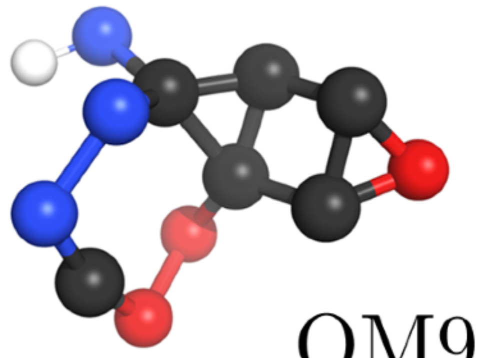
$$\longrightarrow$$

Design space coverage

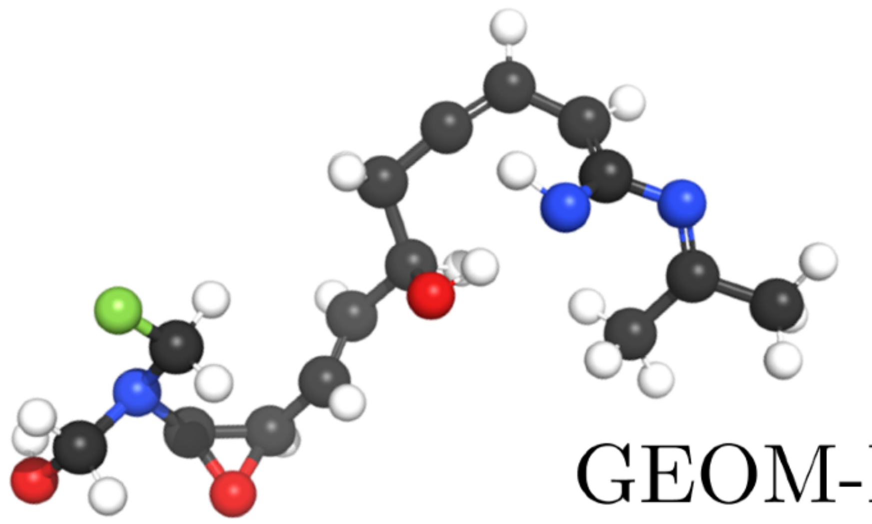
$$\Omega_{\theta}^{\tau} \approx \Omega^{*}$$

Toward a (learning) **theory of** (generative) **discovery**

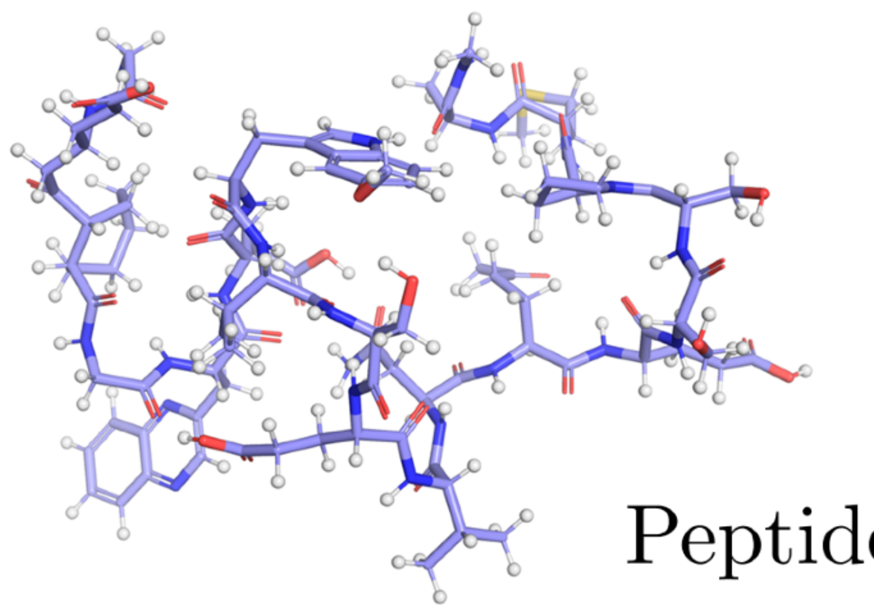
ActFlow for Chemical and Biological Generative Discovery



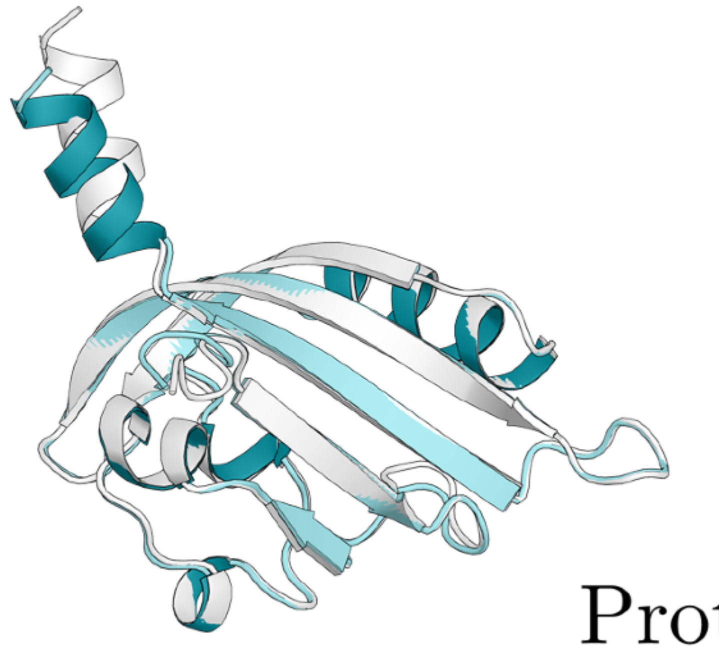
QM9 small
organic molecule



GEOM-Drugs
drug-like molecule

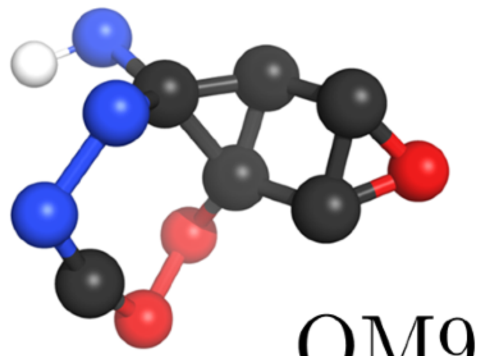


Peptide

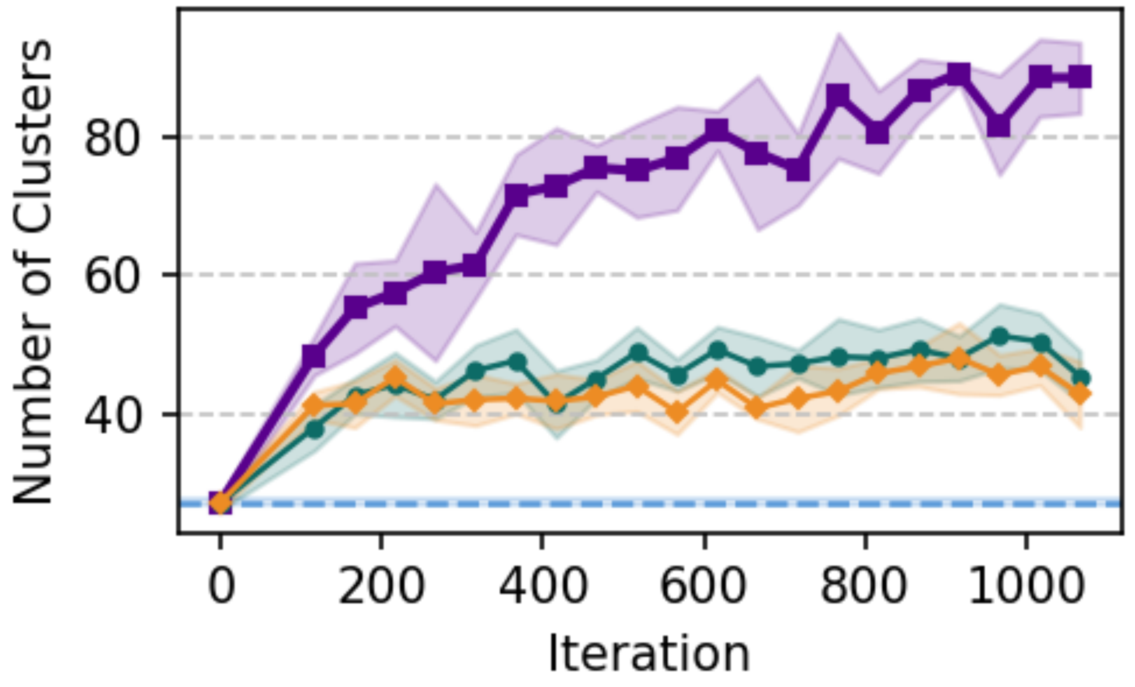


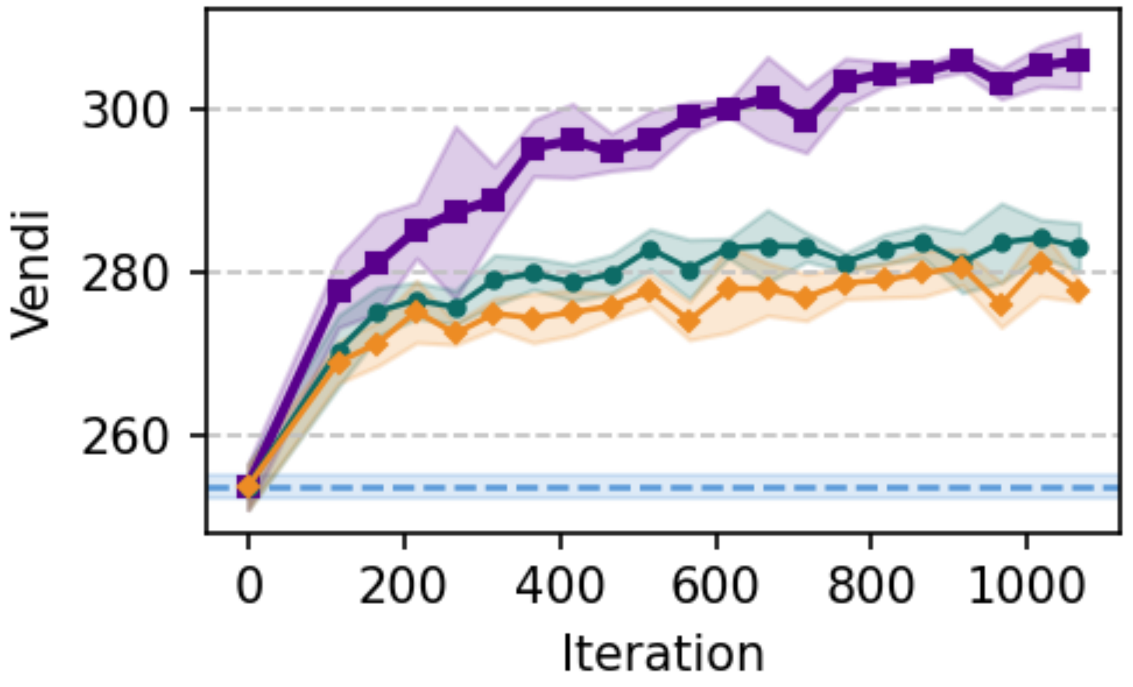
Protein

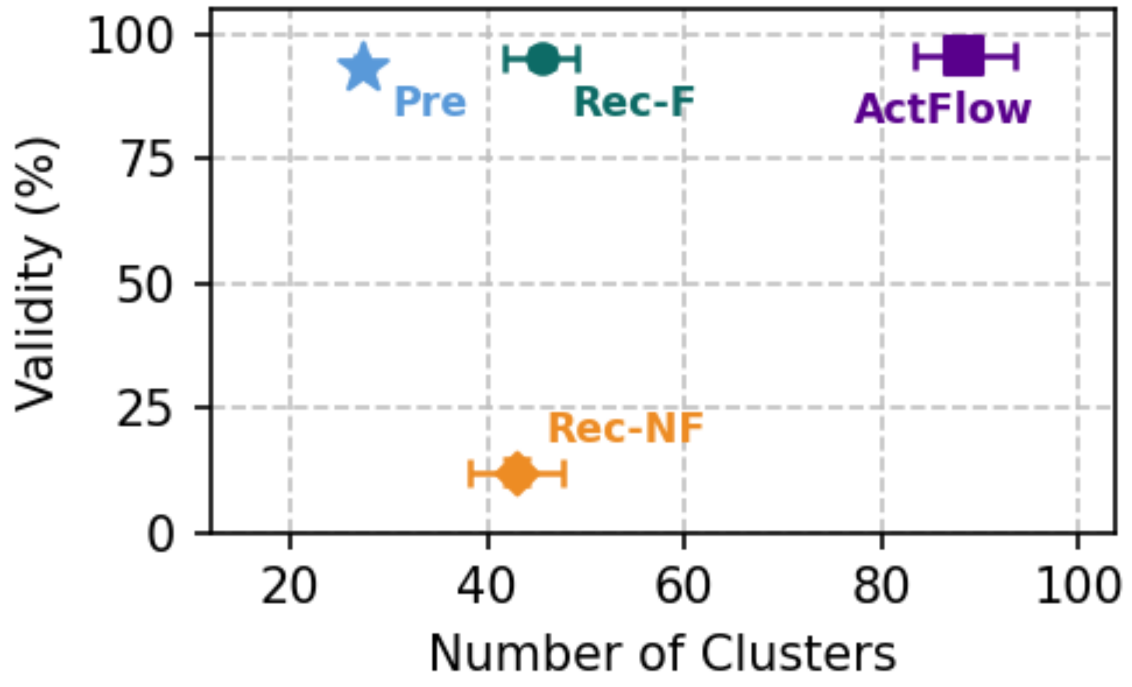
ActFlow for Small Organic and Drug-like Molecules

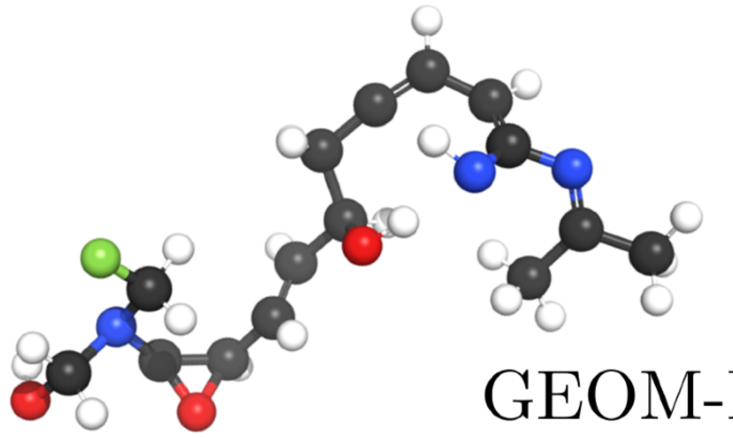


QM9 small organic molecule

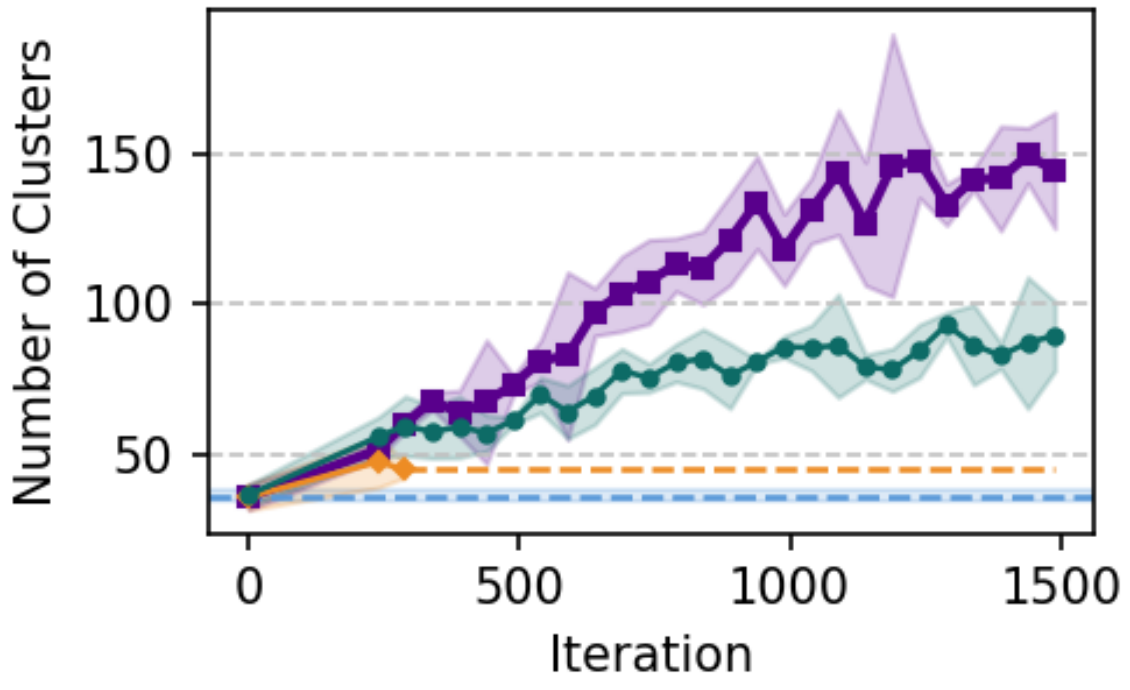


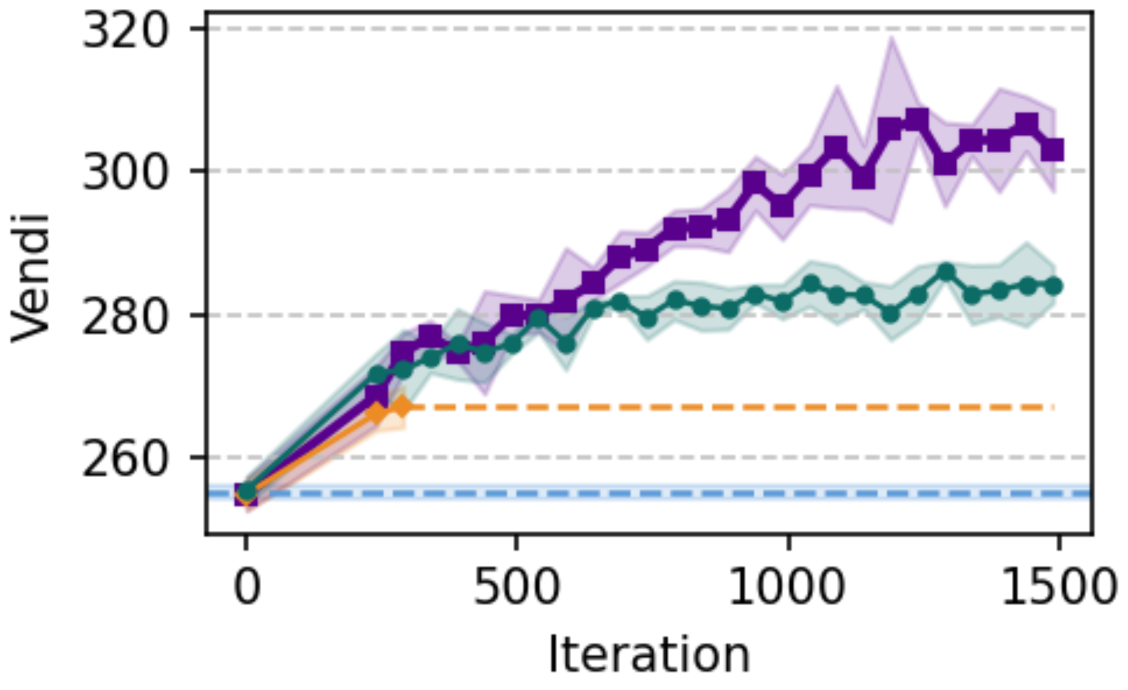


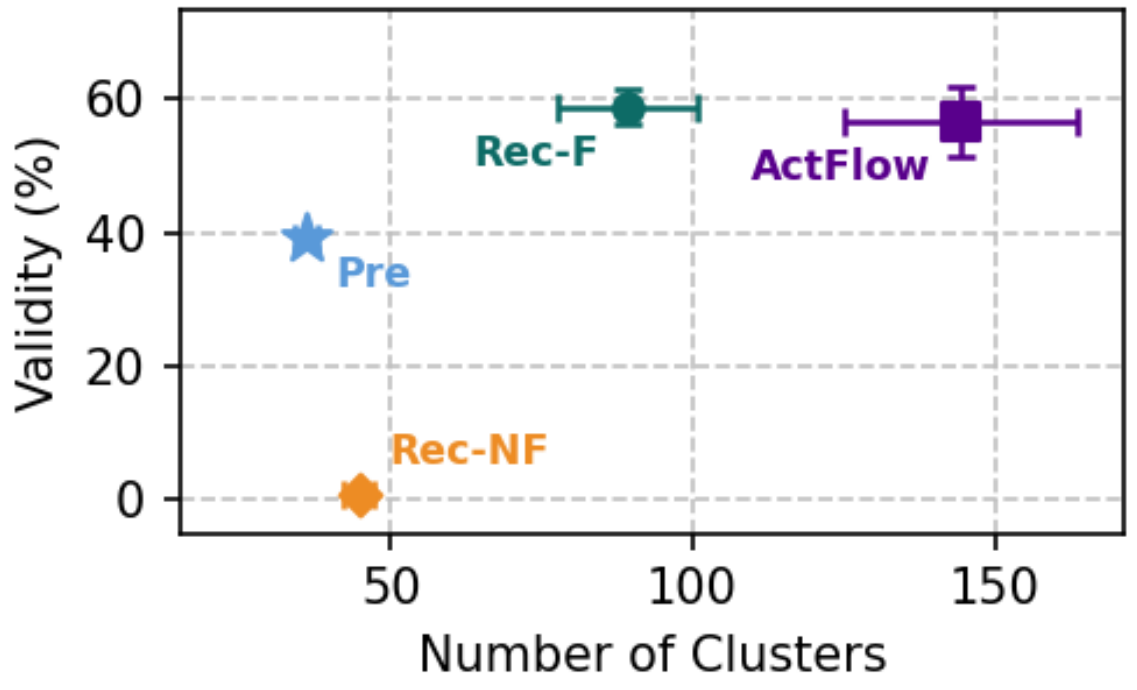




GEOM-Drugs drug-like molecule

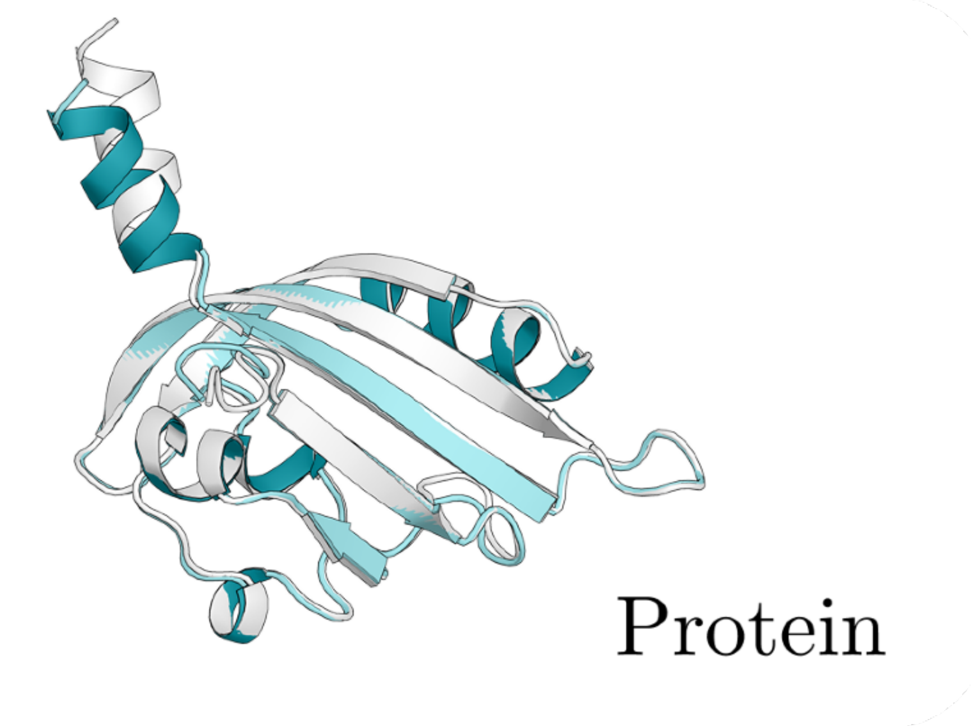


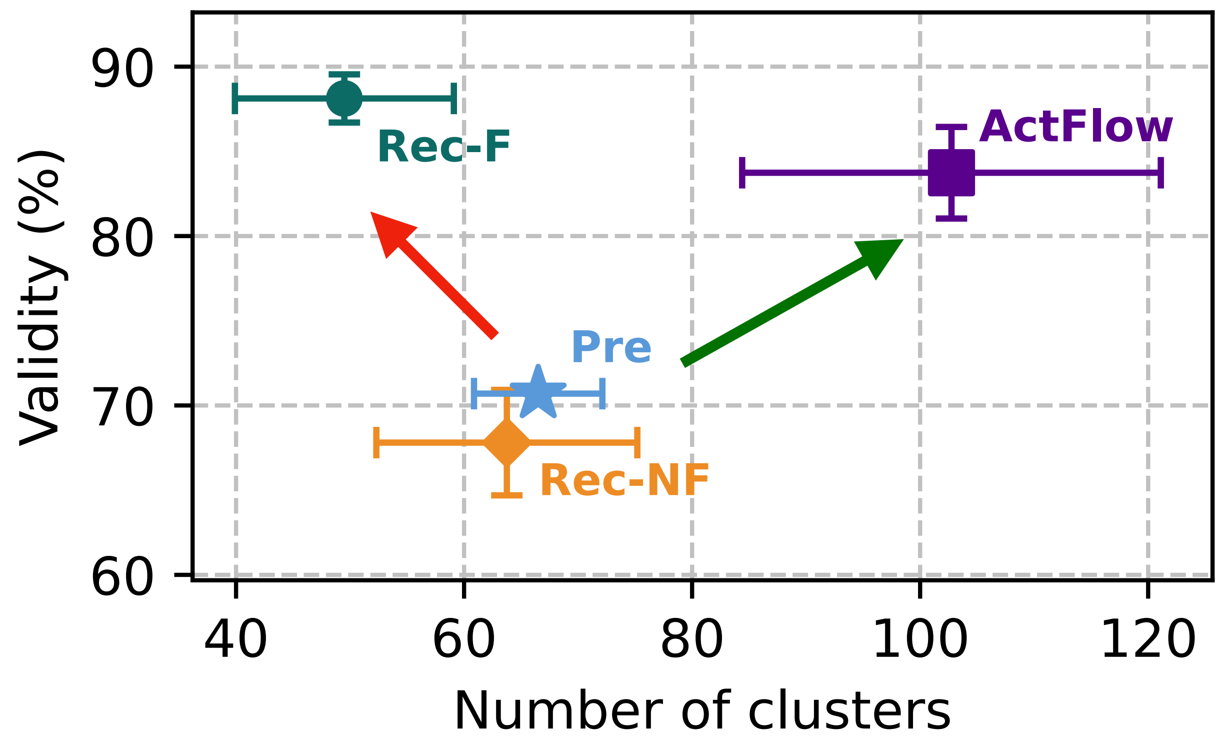




ActFlow for Therapeutic Peptides and Protein Design

	Therapeutic Peptide Design				Protein Sequence Design			
Method	Coverage ↑	Diversity ↑	FID	Validity (%) ↑	Coverage ↑	Diversity ↑	FID	Validity (%) ↑
Pre	61.00 ± 0.00	13.73 ± 0.00	0.00 ± 0.00	40.12 ± 0.00	66.50 ± 5.63	12.87 ± 0.63	0.05 ± 0.01	70.81 ± 1.12
REC-NF	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	63.75 ± 11.45	11.85 ± 0.34	0.27 ± 0.06	67.81 ± 3.11
REC-F	59.67 ± 17.97	13.62 ± 4.34	3.18 ± 1.77	71.16 ± 5.22	49.50 ± 9.60	11.67 ± 0.40	0.25 ± 0.04	88.12 ± 1.42
ACTFLOW	358.33 ± 95.45	58.87 ± 25.98	59.15 ± 44.31	41.59 ± 10.06	102.75 ± 18.36	42.14 ± 10.85	5.45 ± 3.34	83.74 ± 2.70





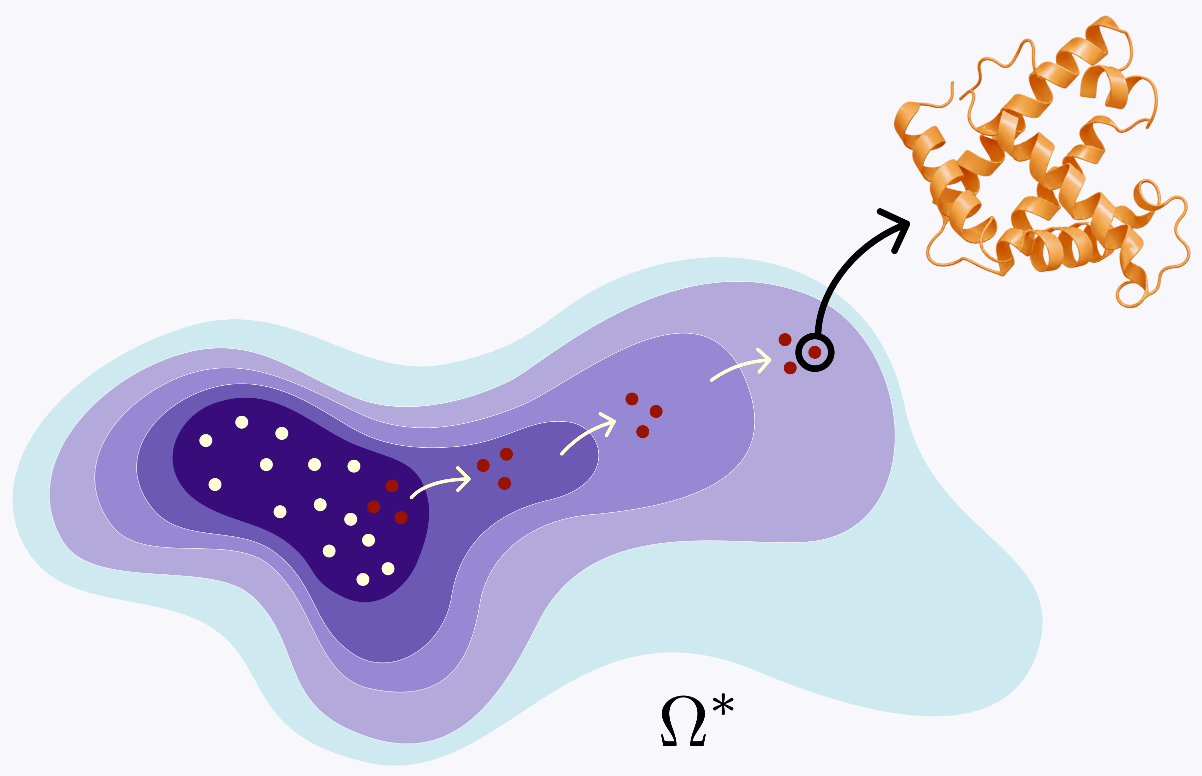
Takeaway

ActFlow allows to **actively expand** pre-trained biochemical flow and diffusion models **over OOD regions**.

Research Program

Foundations of Generative Discovery Beyond the Data

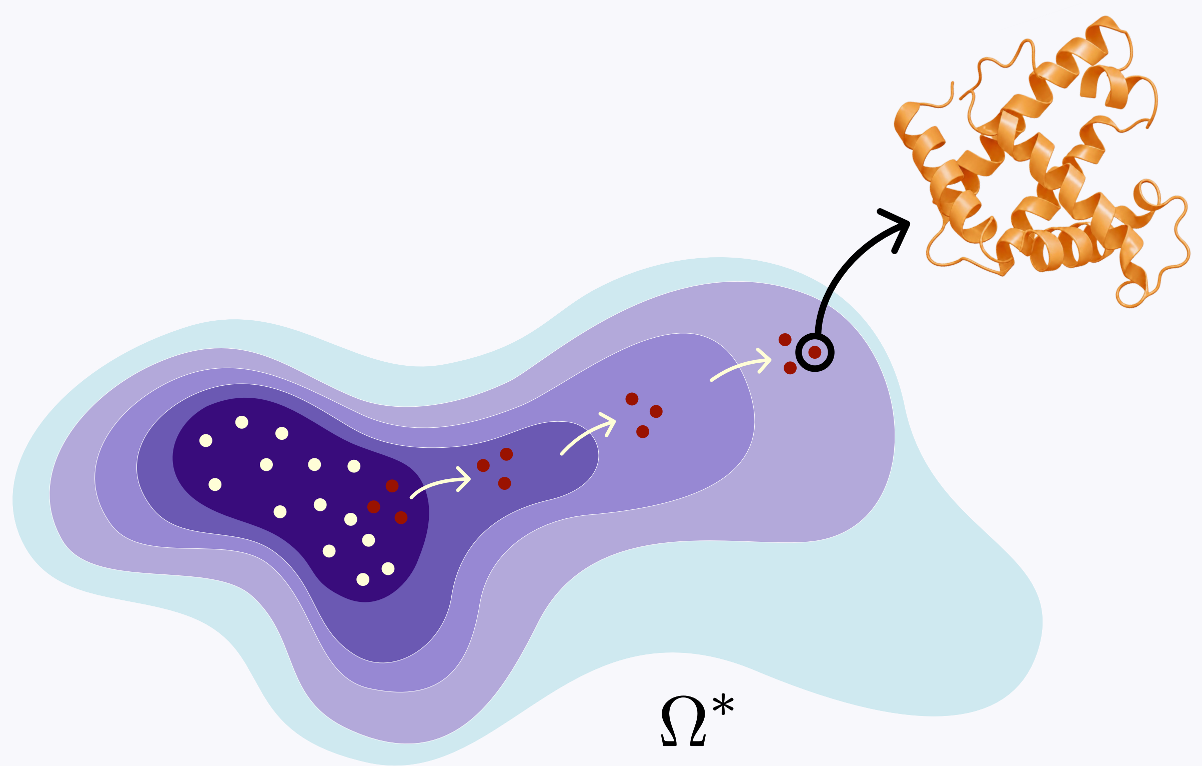
Out-of-Distribution
Flow Modeling



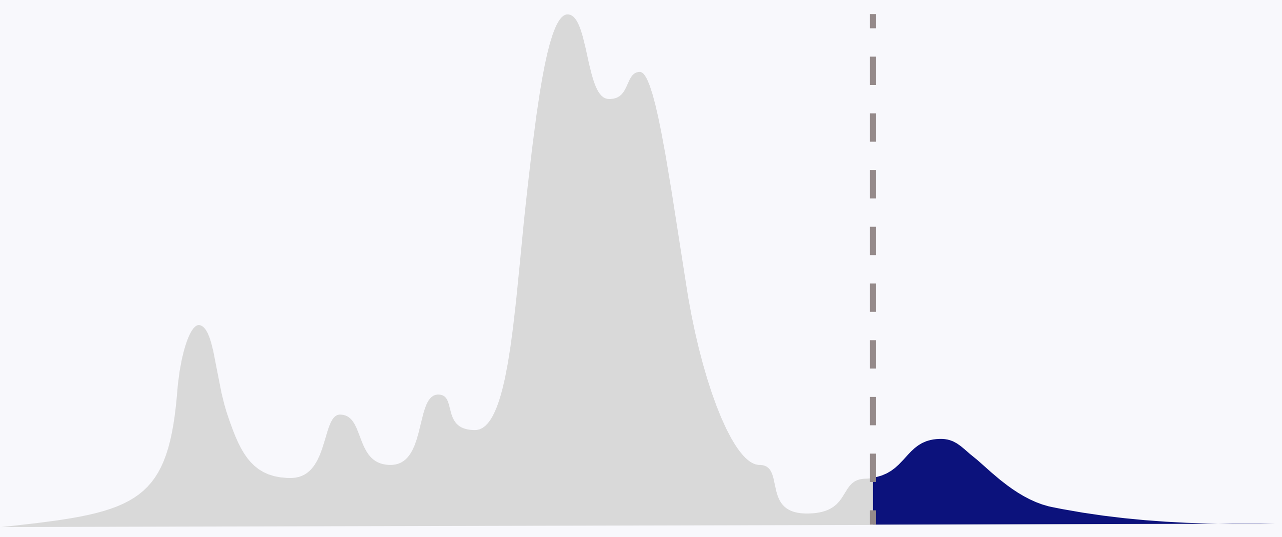
Research Program

Foundations of Generative Discovery Beyond the Data

Out-of-Distribution Flow Modeling

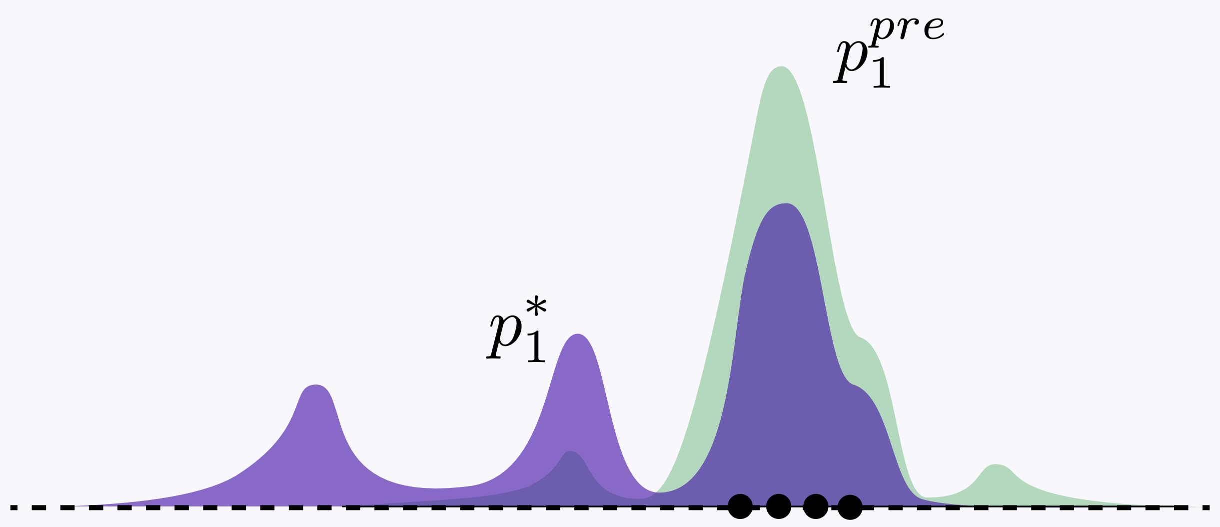


High-value rare structure generation



$\mathrm{CVaR}^{f}_{1-\beta}(p^{\pi}_1)$

Data Debiasing and Hidden Mode Discovery



Thanks!

Collaborators

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Funding

NCCR Catalysis

NCCR Automation

ETH AI CENTER

Thanks!

Paper + Code

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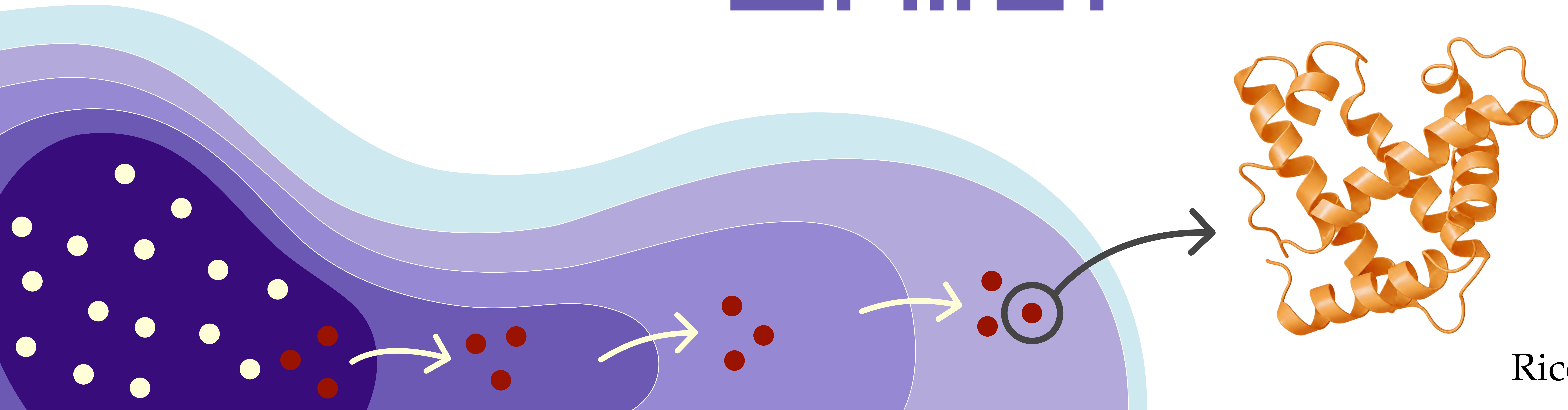

Riccardo De Santi