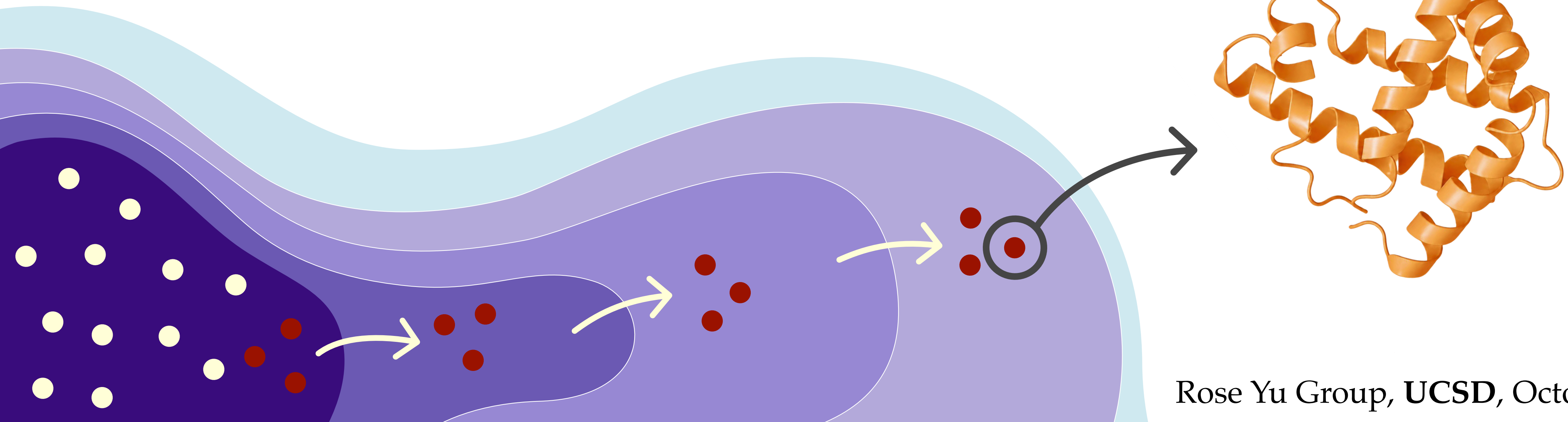


Generative Discovery Beyond the Data

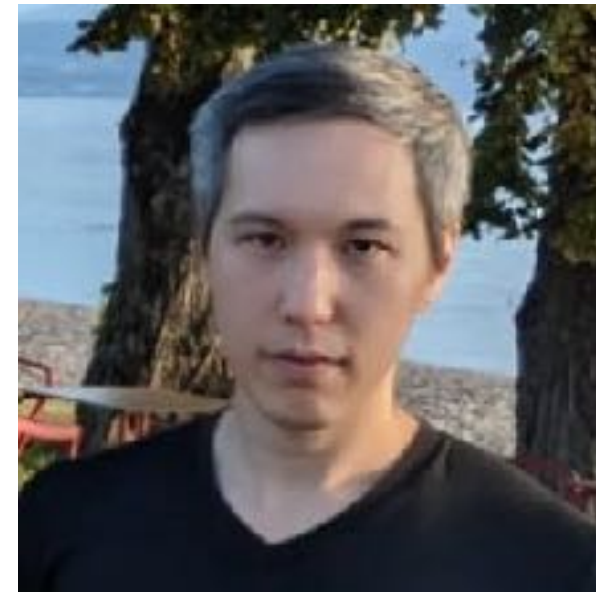
Riccardo De Santi

Doctoral Fellow at ETH AI Center
@r_de_santi rdesanti@ethz.ch





Riccardo De Santi



Ya-Ping Hsieh



Kimon Protopapas



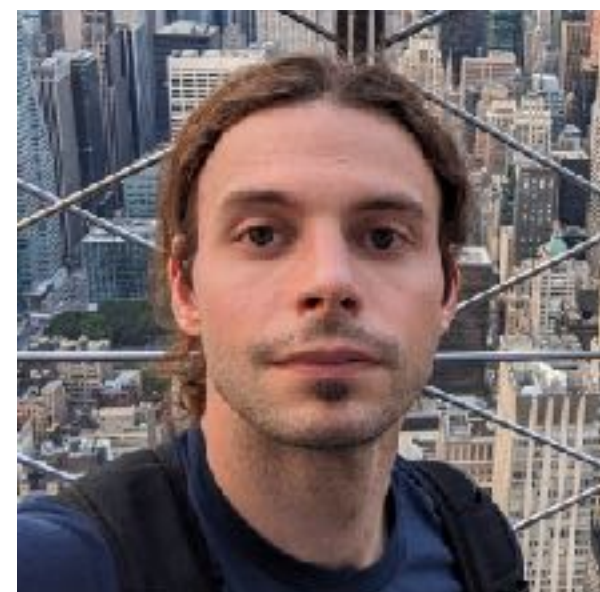
Bruce Lee



Cristian P. Jensen



Zebang Shen



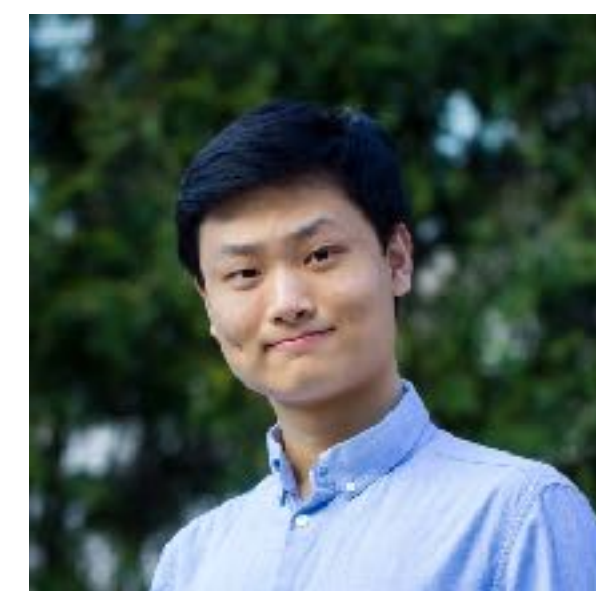
Marin Vlastelica



Zifan Wang



Sophia Tong



Chenghao Liu



Federico Di Gennaro



Angelo Gnazzo



Pranam Chatterjee



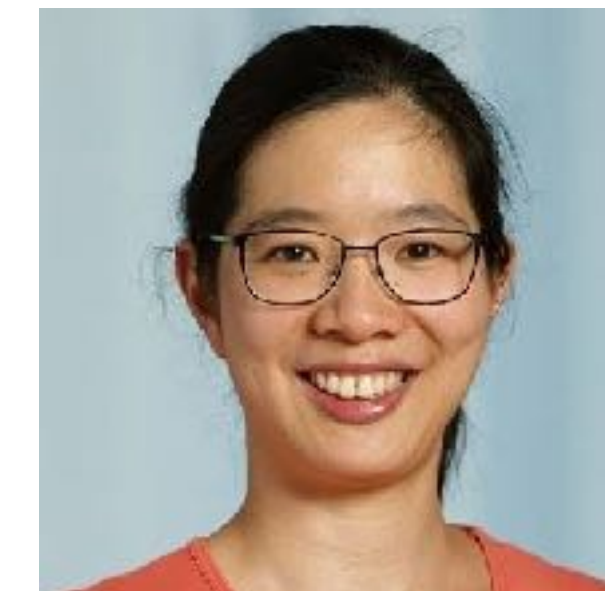
Niao He



İsmail İlkan Ceylan



Michael M. Zavlanos



Fanny Yang



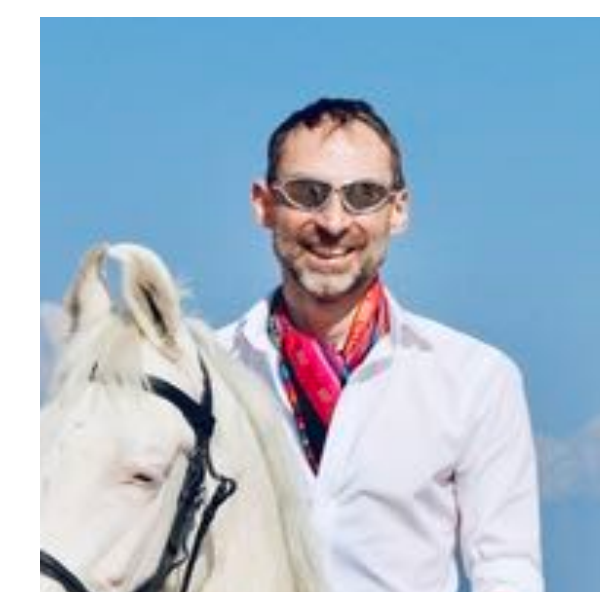
Karl H. Johansson



Frances H. Arnold



Yisong Yue



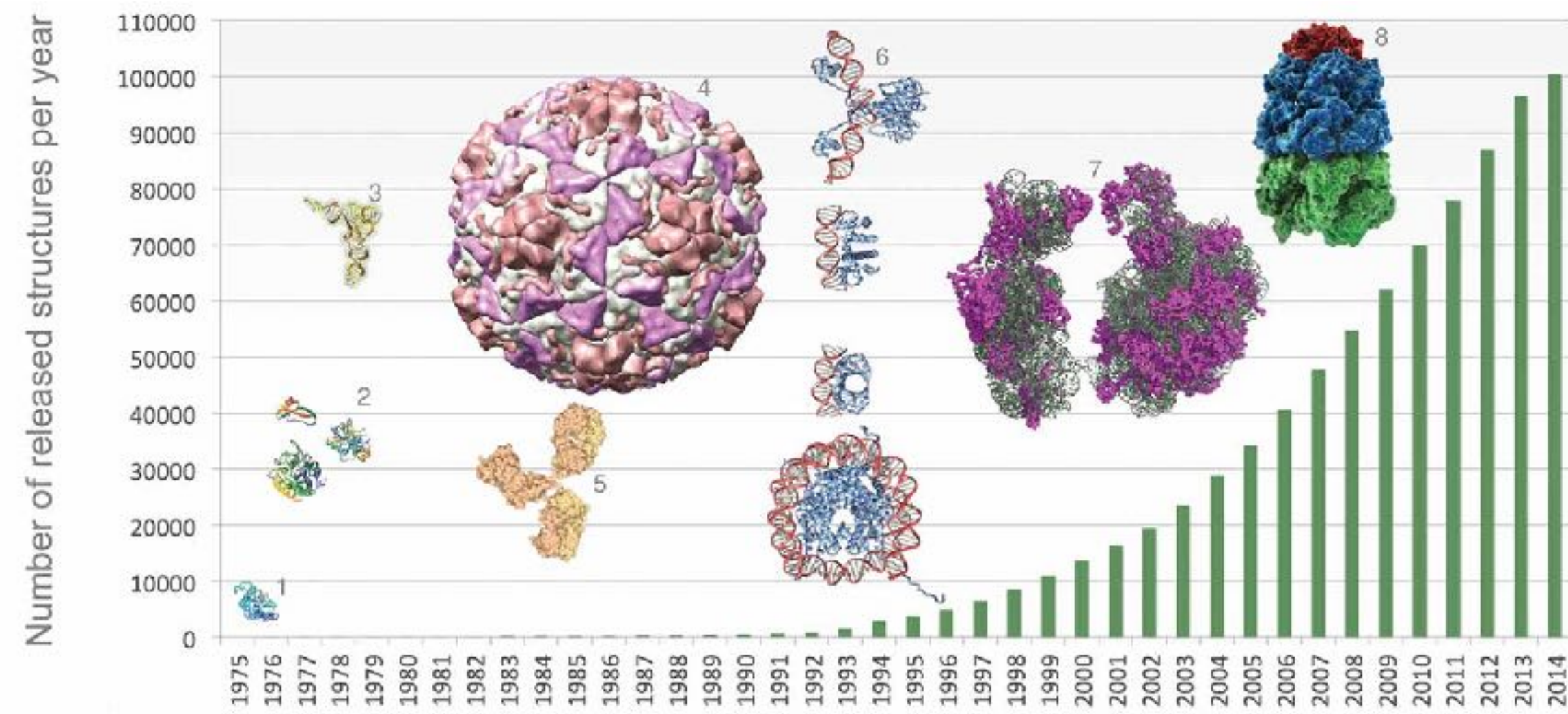
Michael M. Bronstein



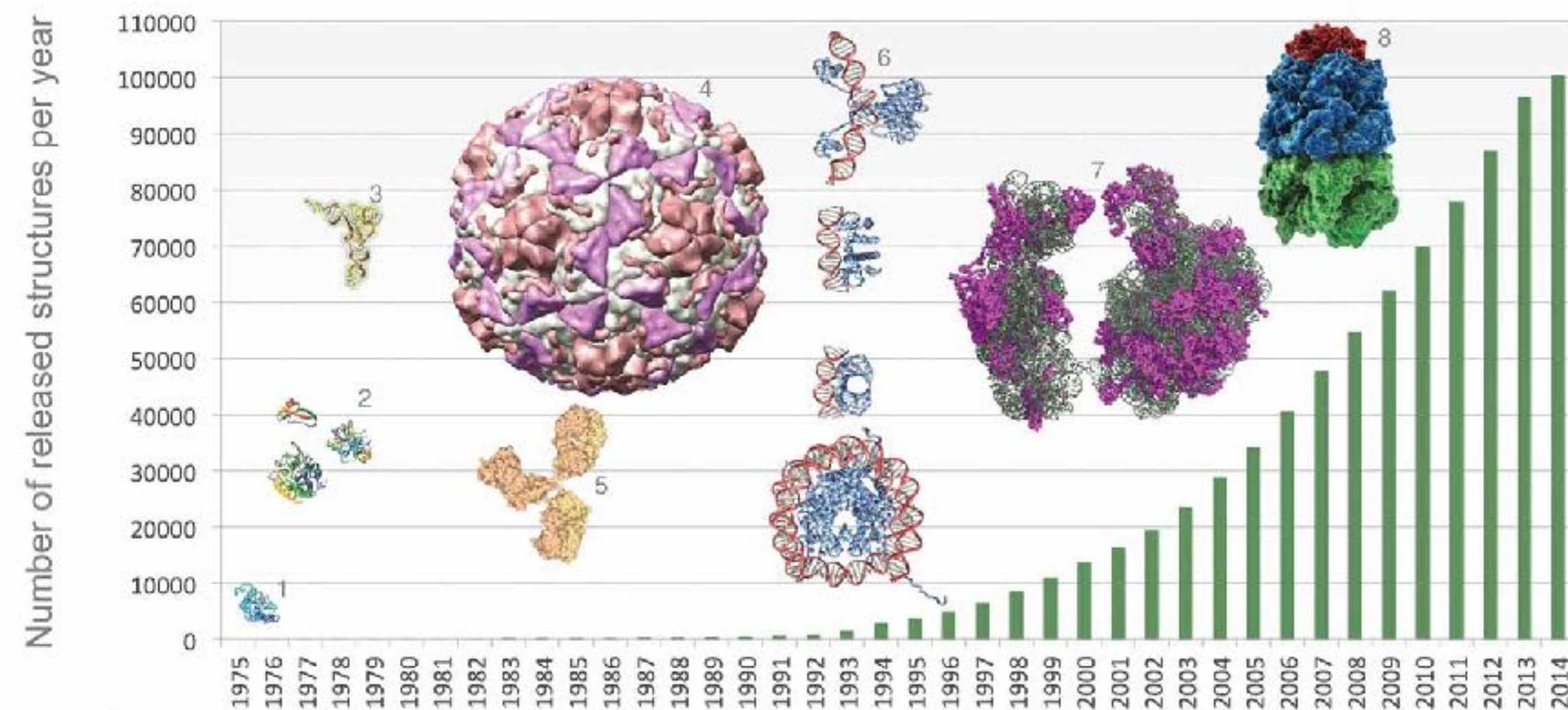
Andreas Krause



[Steven Wommack]

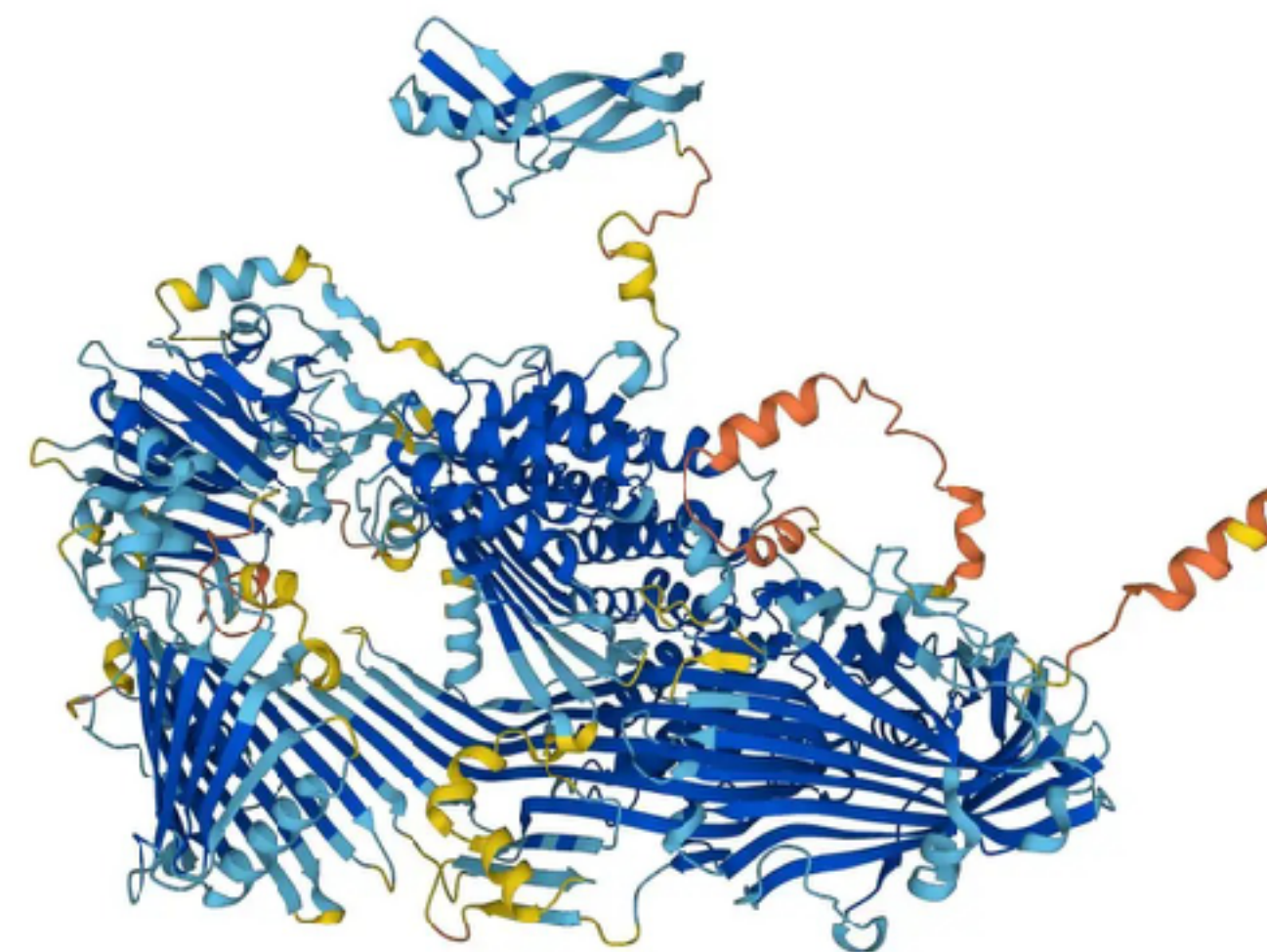


Protein Data Databank (PDB)

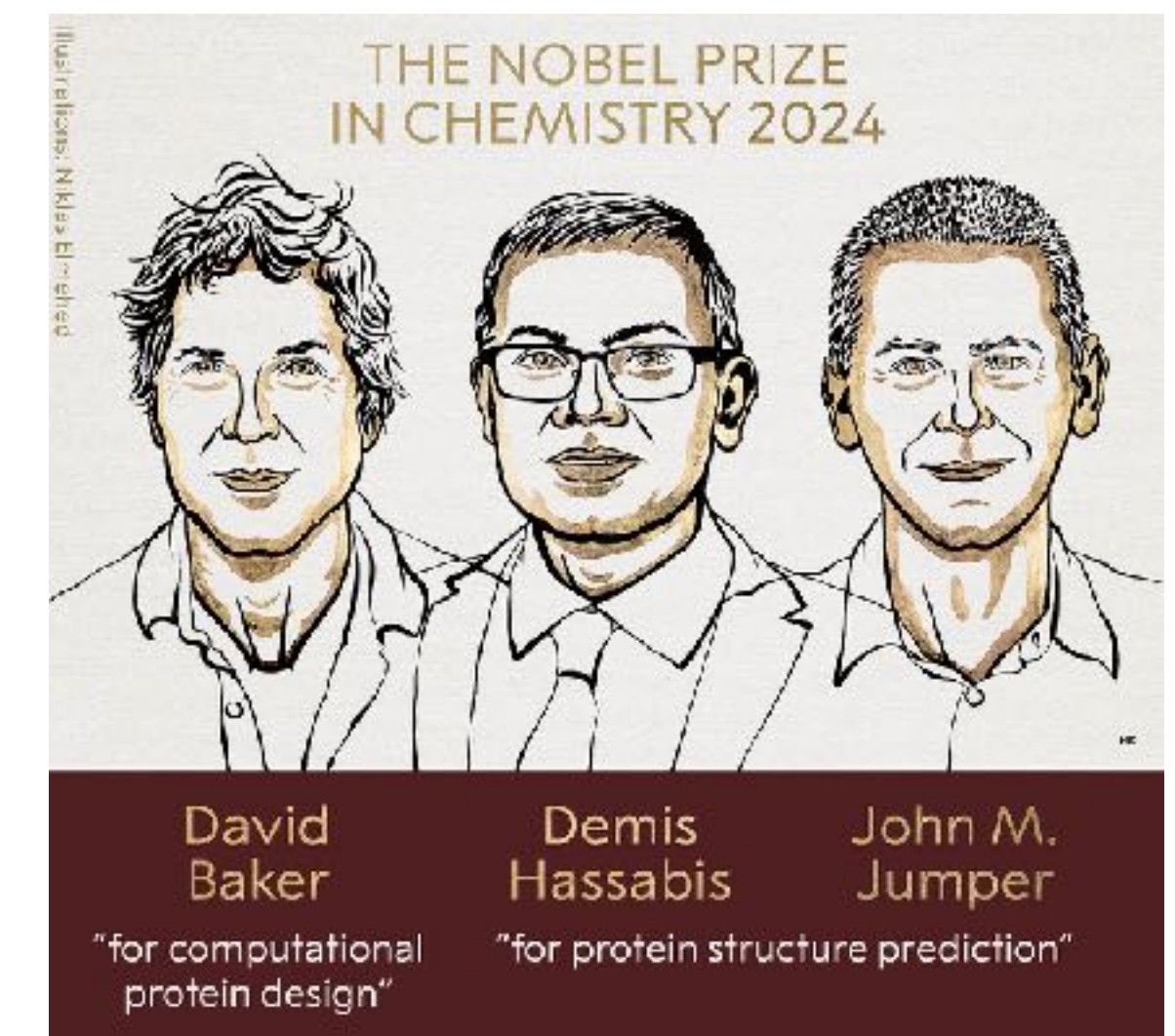


Protein Data Databank (PDB)

Protein structure prediction and design



2024 Chemistry Nobel Prize



Generative ~~Modeling~~ Discovery?

What is Discovery?

black-box function (reward)

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

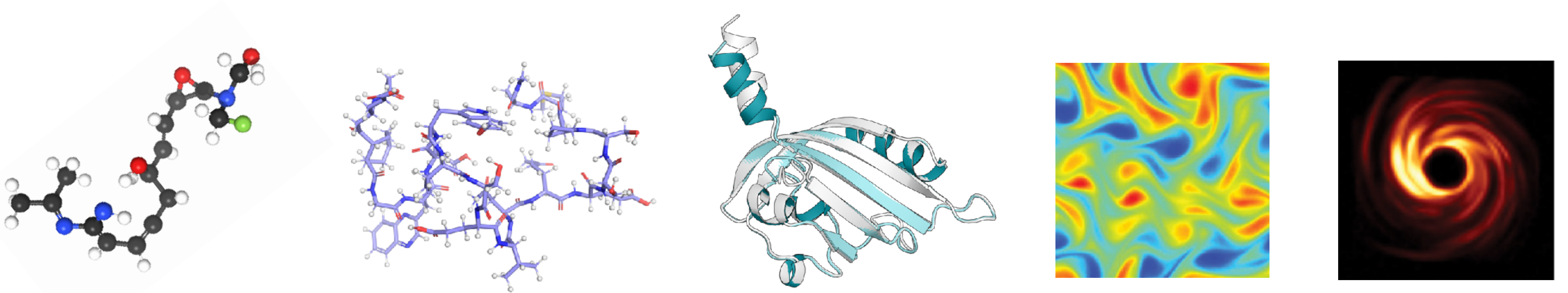
valid design space (e.g., drugs, materials)
(or action space)

What is Discovery?

black-box function (reward)

$$\operatorname{argmax}_{x \in \Omega} f(x)$$

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



[Zheng et al., 2025]

What is Discovery?

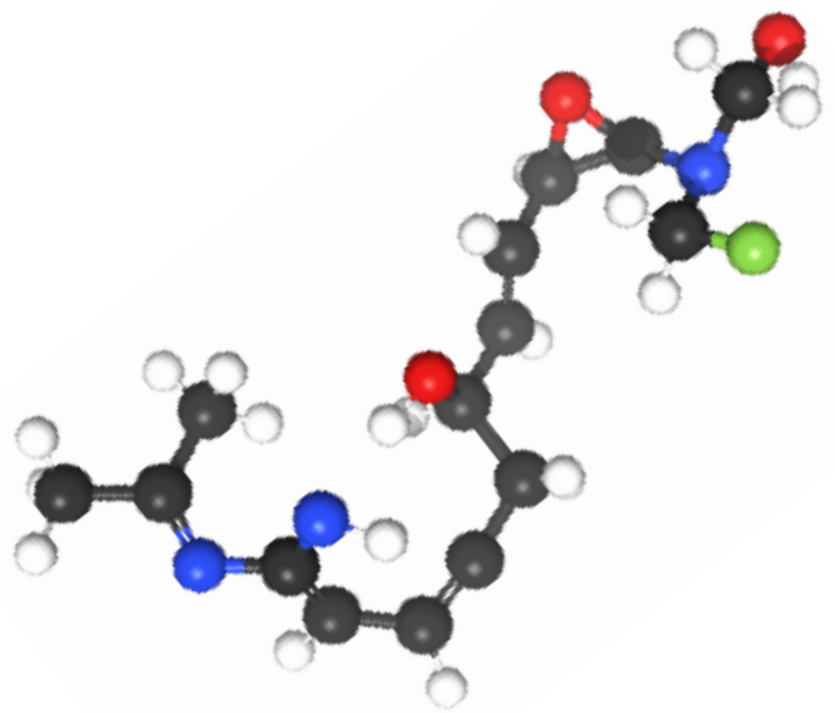
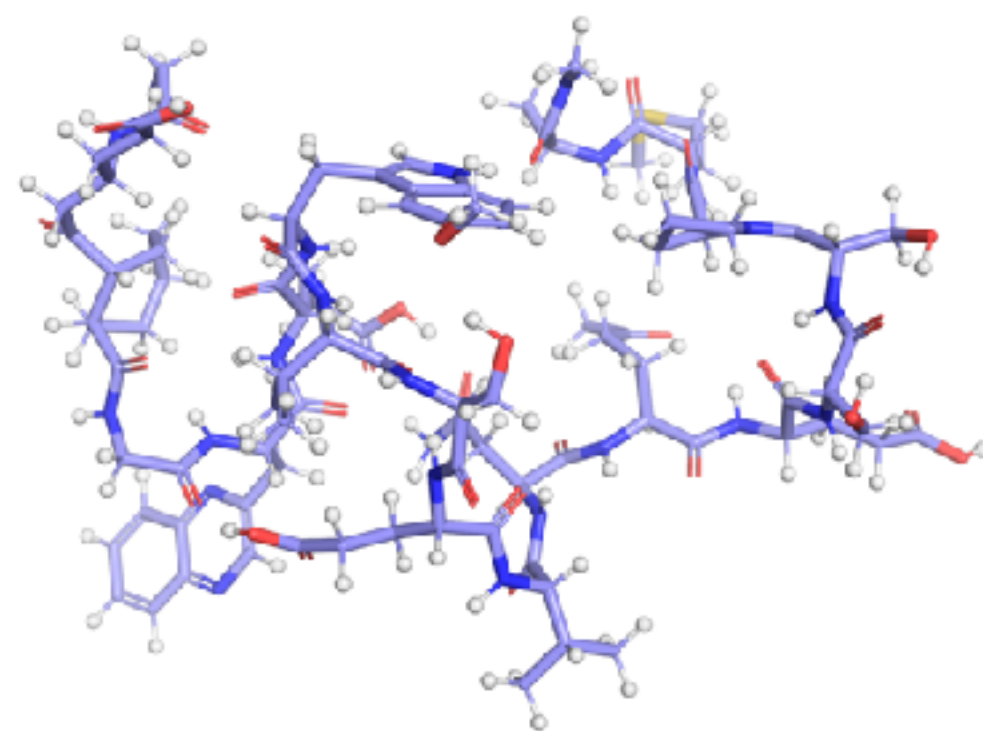
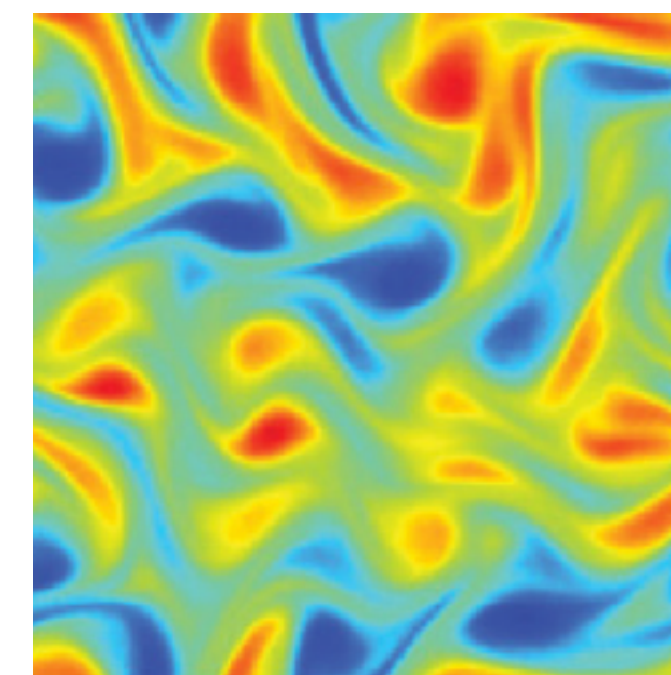
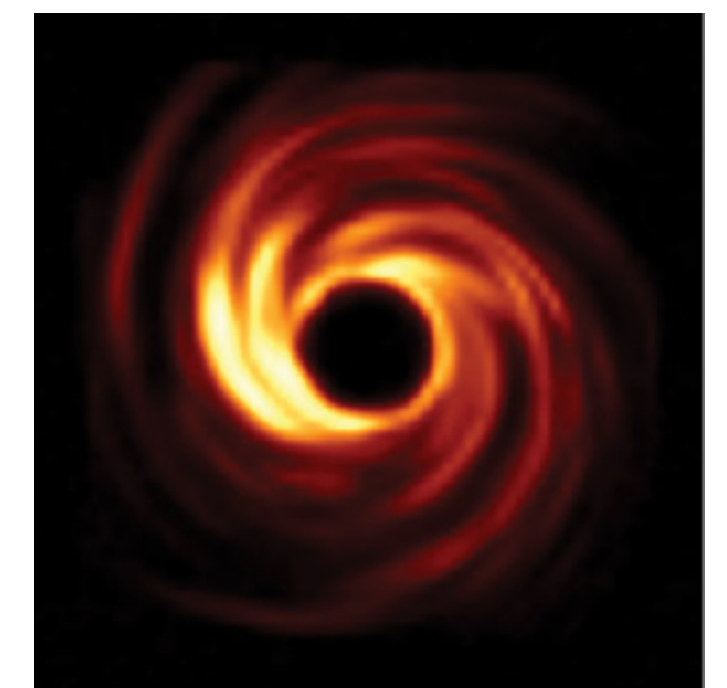
black-box function (reward)

$\approx 10^{60}$ drug discovery
 $\approx 10^{80}$ material design

$$\operatorname{argmax}_{x \in \Omega} f(x)$$

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

unknown or hard to represent and search



What is Discovery?

black-box function (reward)

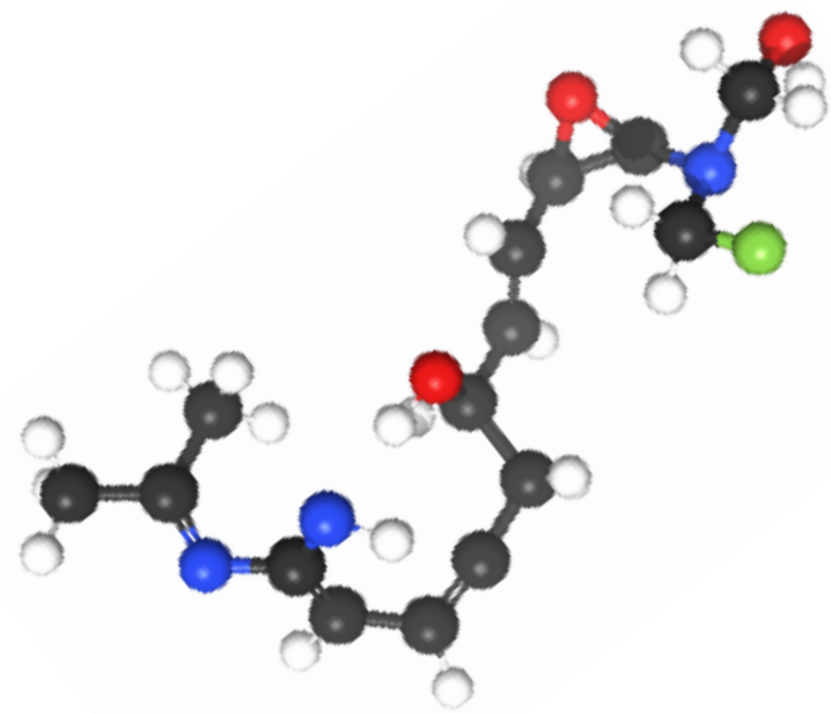
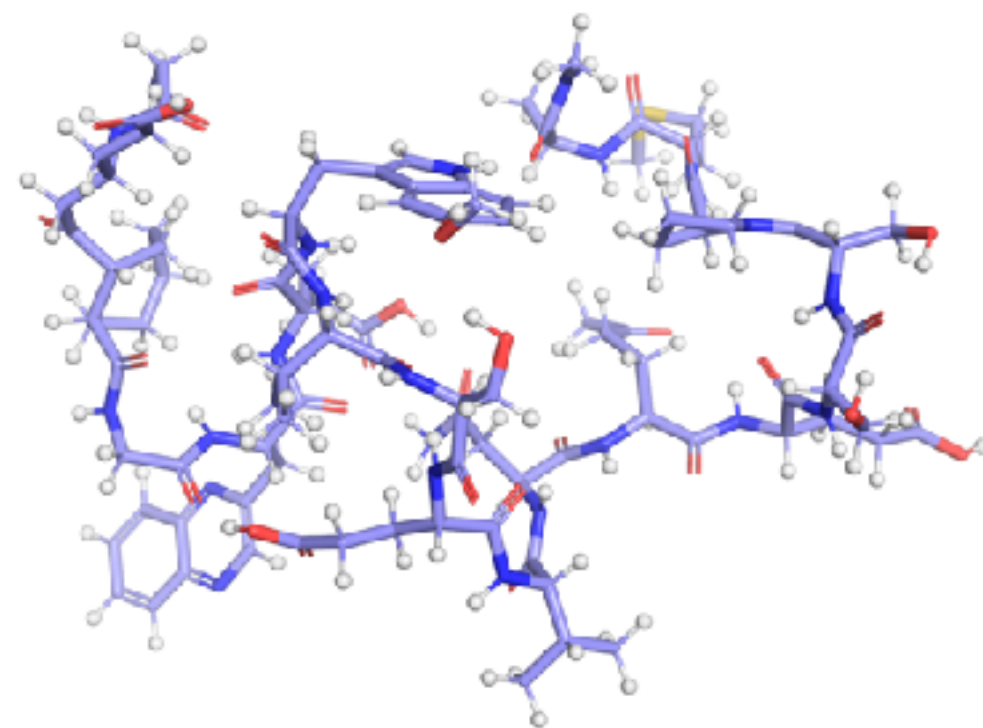
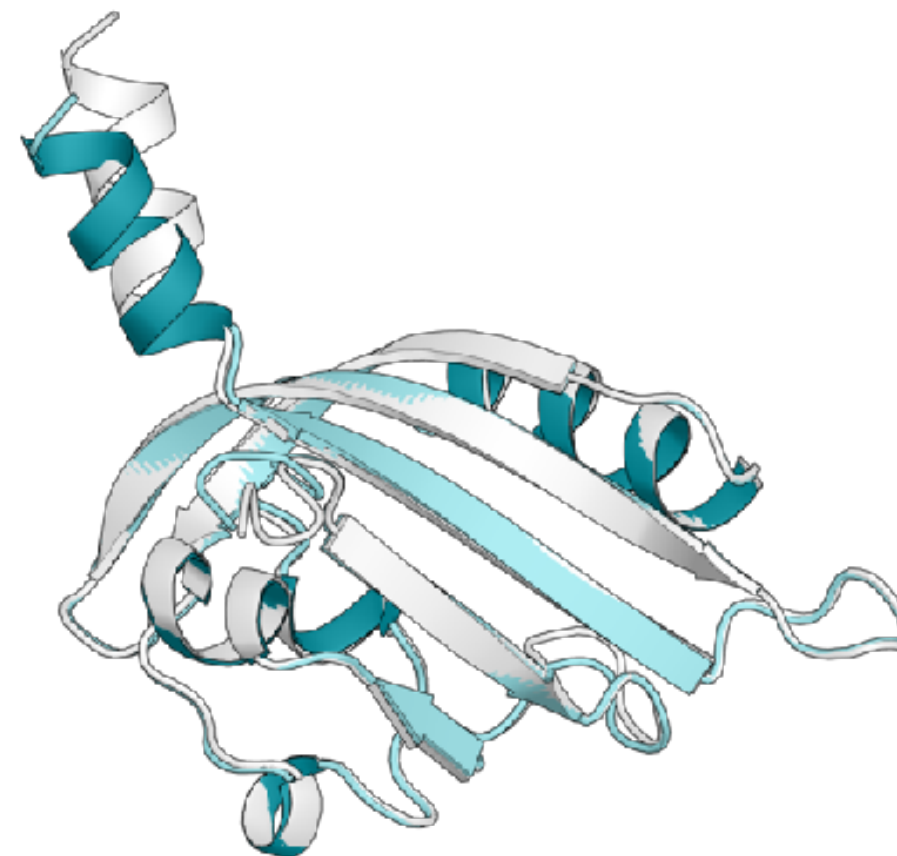
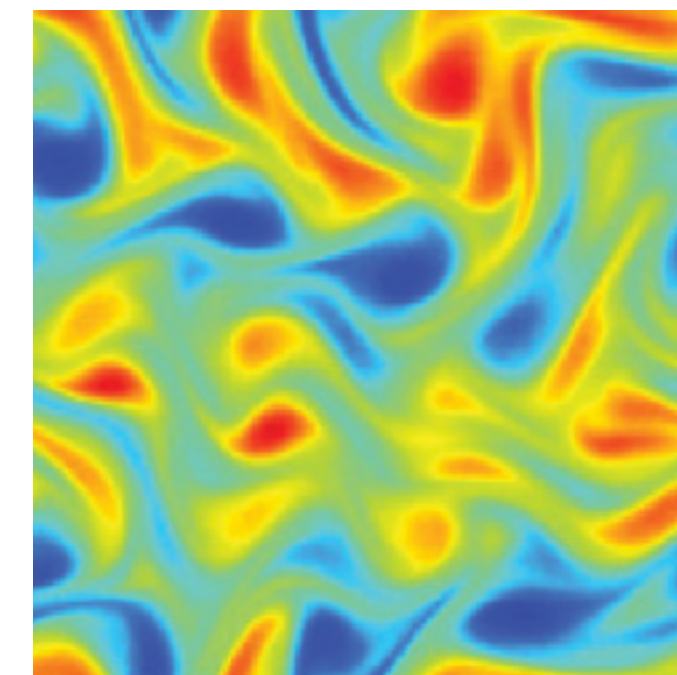
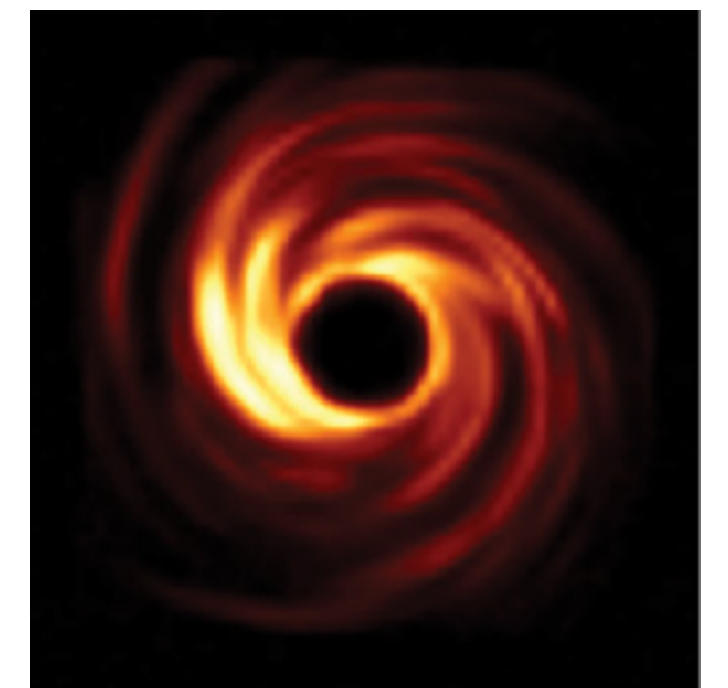
$\approx 10^{60}$ drug discovery
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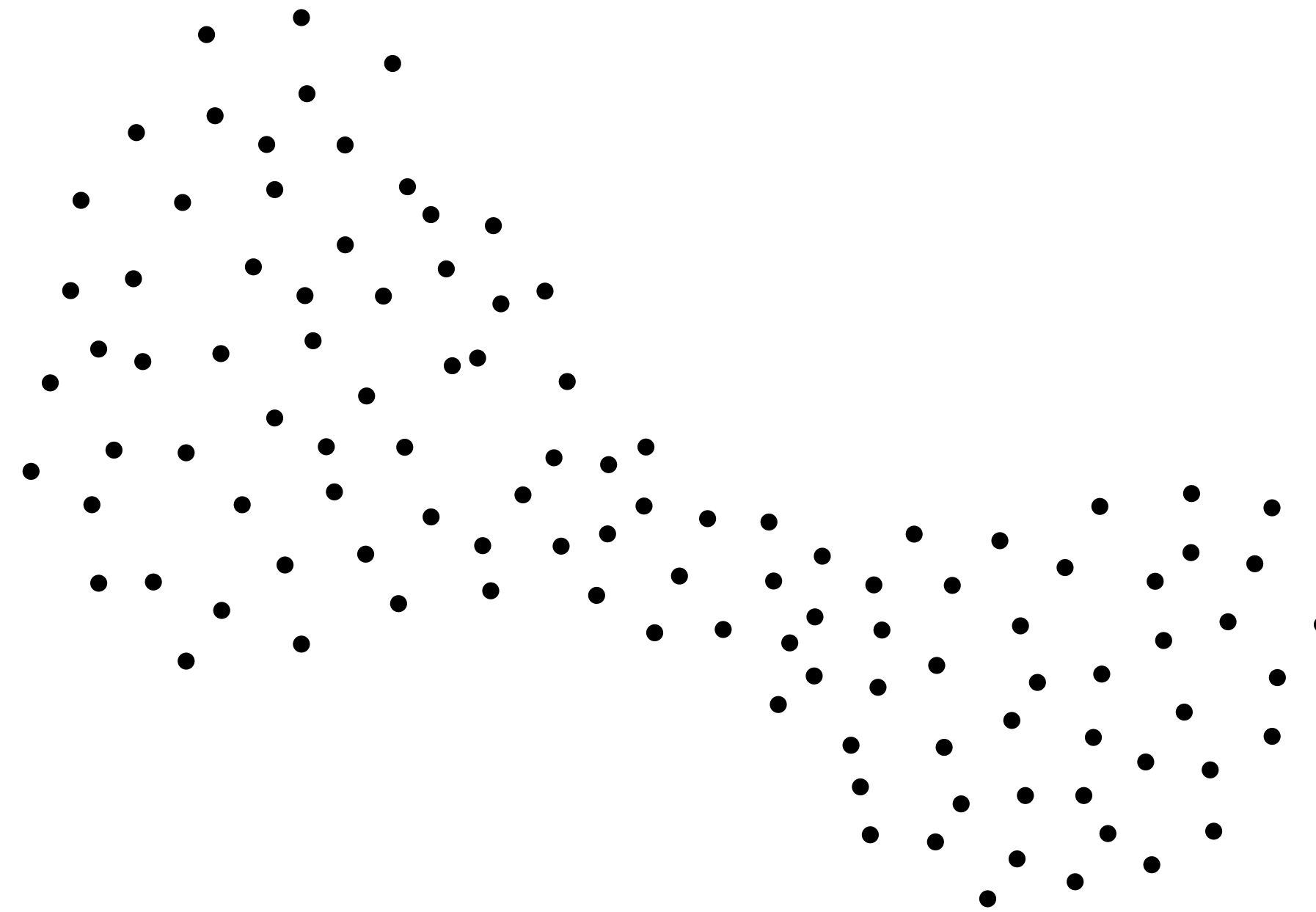
unknown or hard to represent and search

→ Generative Discovery

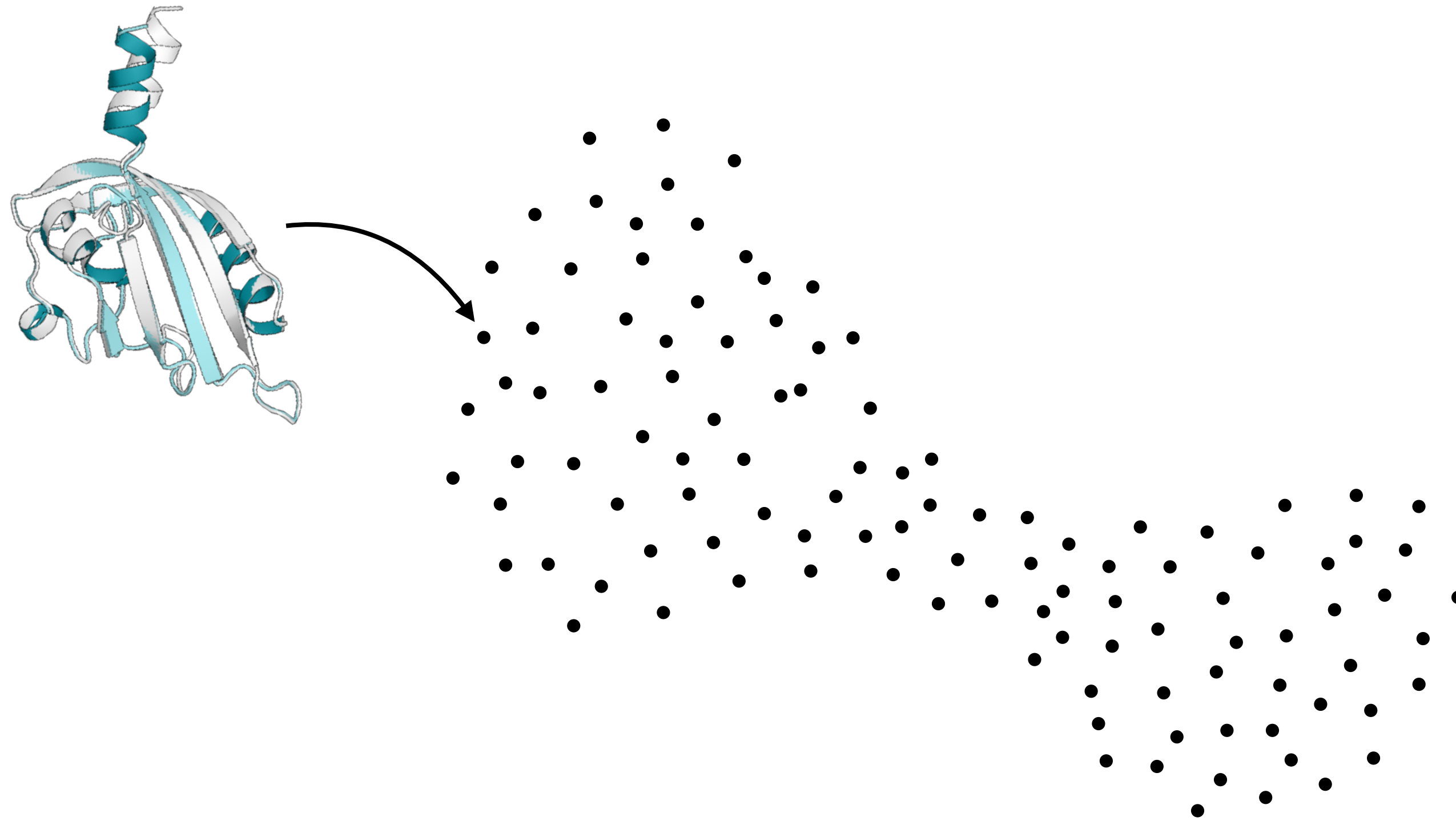


Generative Discovery Paradigm

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



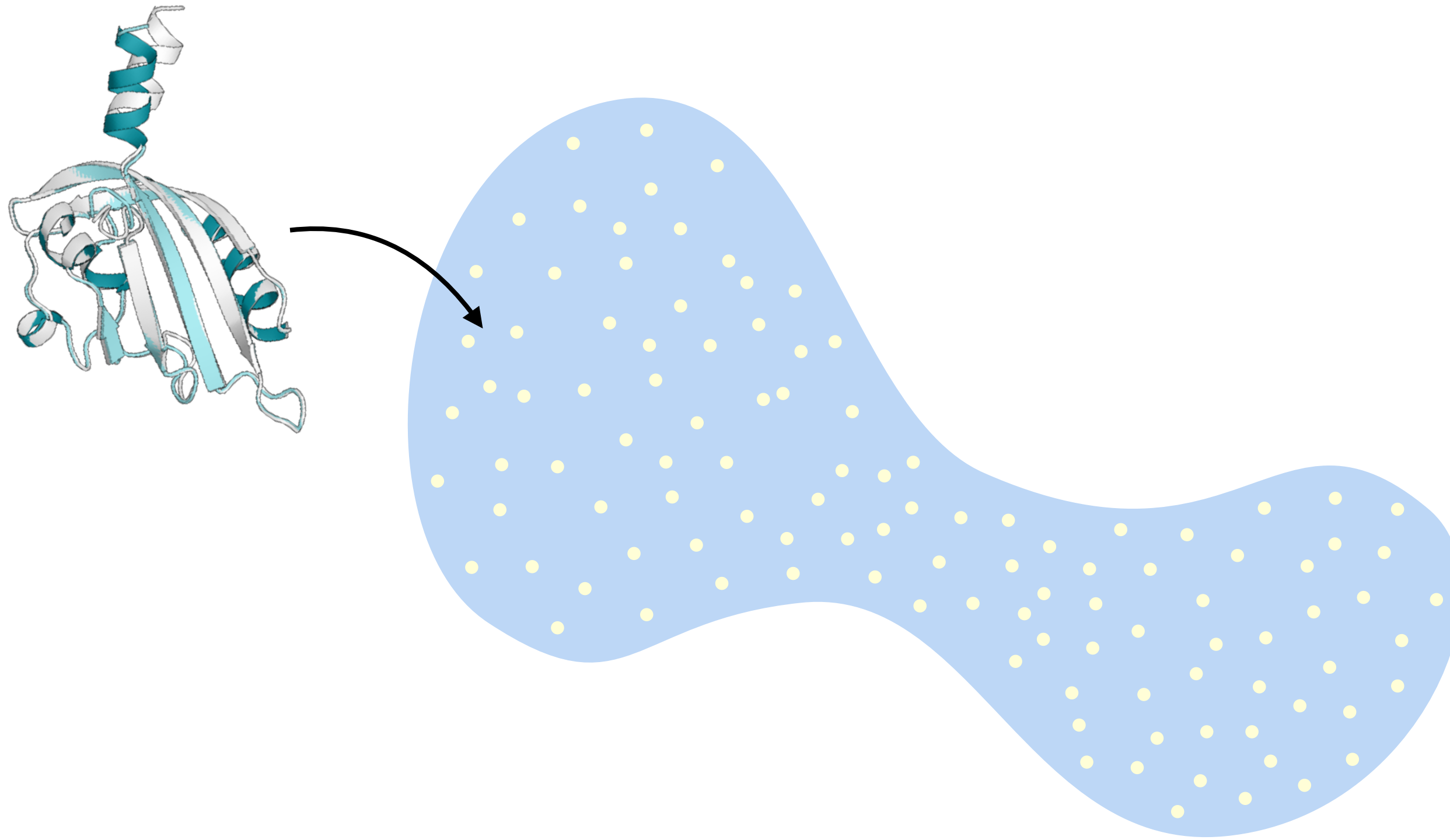
Generative Discovery Paradigm



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

Generative Discovery Paradigm

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

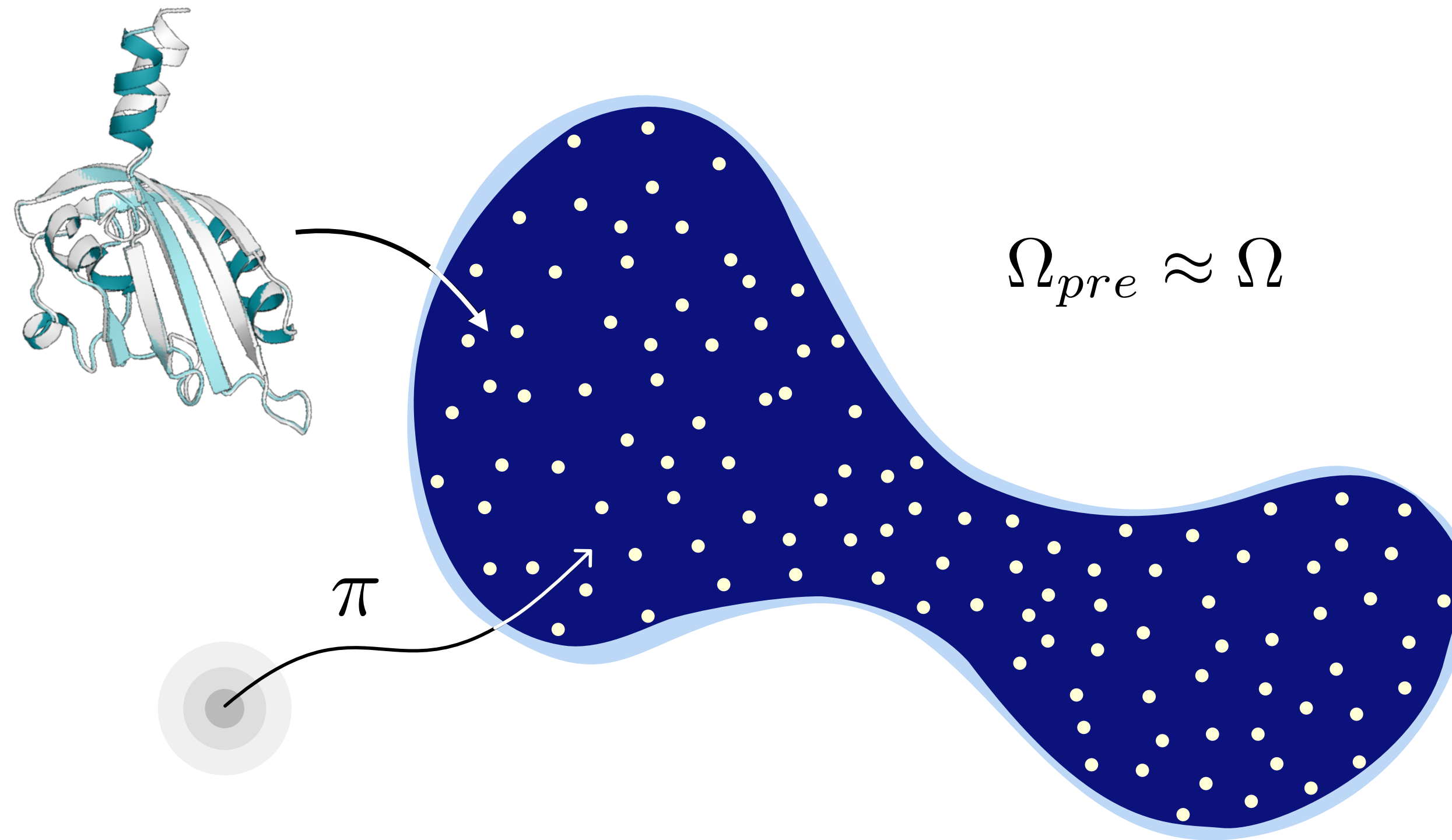


Data $D = \{x_i\}_{i=1}^n$

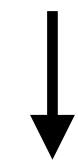
Generative Discovery Paradigm

● valid design space Ω

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



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

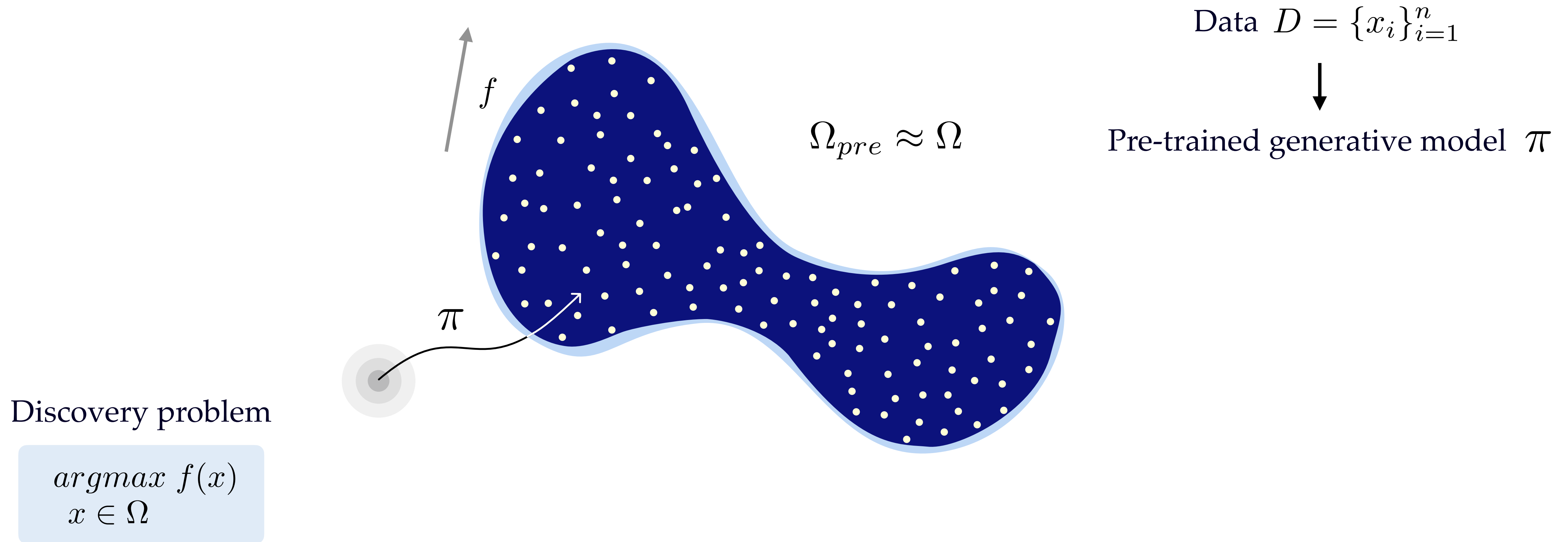


Pre-trained generative model π

The Dream: Discovery via Generative Optimization

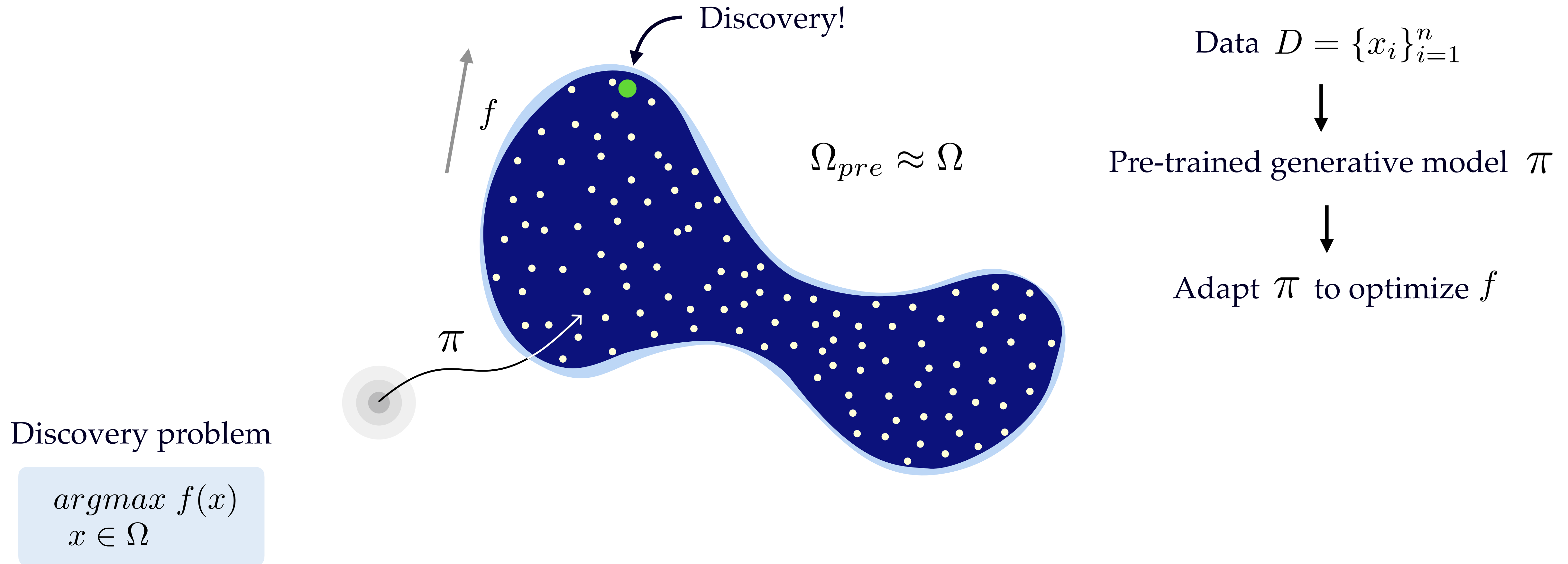
● valid design space Ω

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



The Dream: Discovery via Generative Optimization

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



Generative Modeling

Learn generative prior from data

Generative Modeling

Learn generative prior from data



Current Status

Generative model **in-distribution** reward-adaptation to improve **average behavior**

Generative Modeling

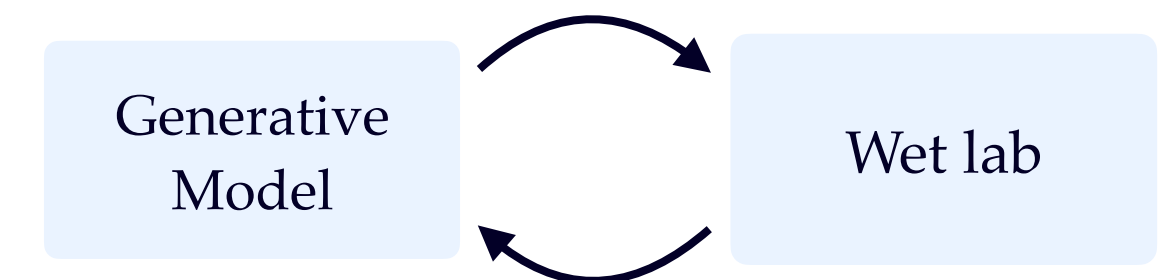
Learn generative prior from data



Current Status

Generative model **in-distribution** reward-adaptation to improve **average behavior**

'discover novel peptides with promising anticancer activity'



Generative Modeling

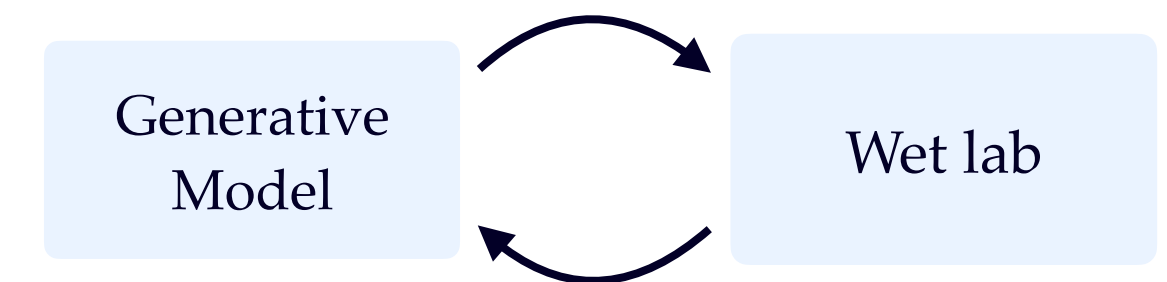
Learn generative prior from data



Current Status

Generative model **in-distribution** reward-adaptation to improve **average behavior**

'discover novel peptides with promising anticancer activity'



not about **in-distribution** samples or **average behavior** and with **limited budget** of experiments

Generative Modeling

Learn generative prior from data



Current Status

Generative model **in-distribution** reward-adaptation to improve **average behavior**



This talk

Generative Discovery

Generation of **rare and diverse structures**, potentially **far beyond available data** and **sample-efficiently**

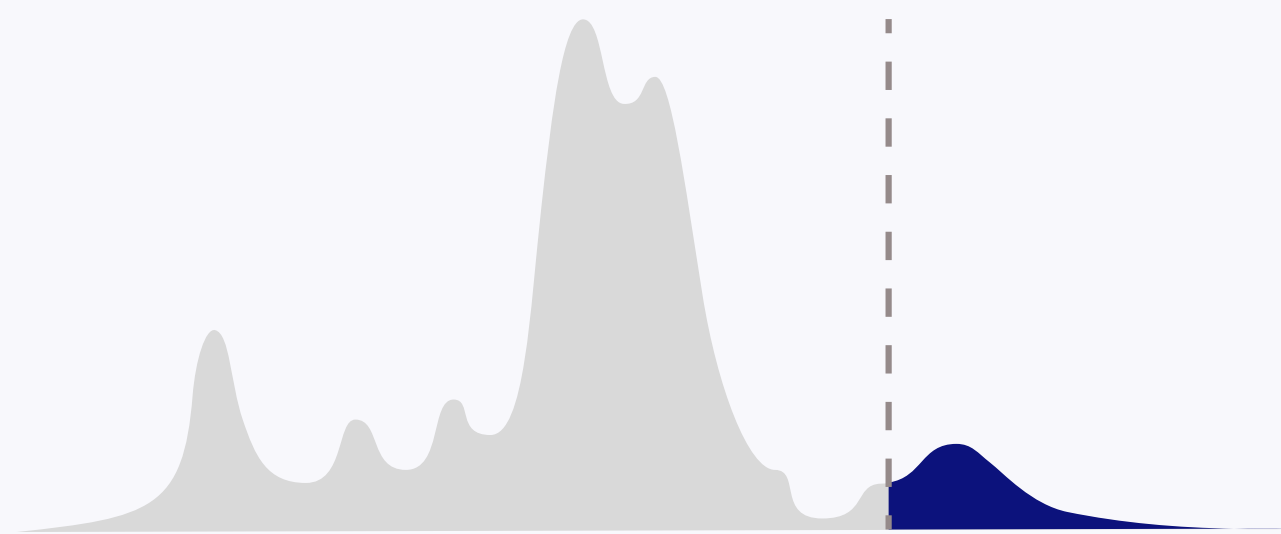
Generative Discovery

Generation of **rare and diverse structures**, potentially **far beyond available data** and **sample-efficiently**

Part I

Rare and Diverse
Generation

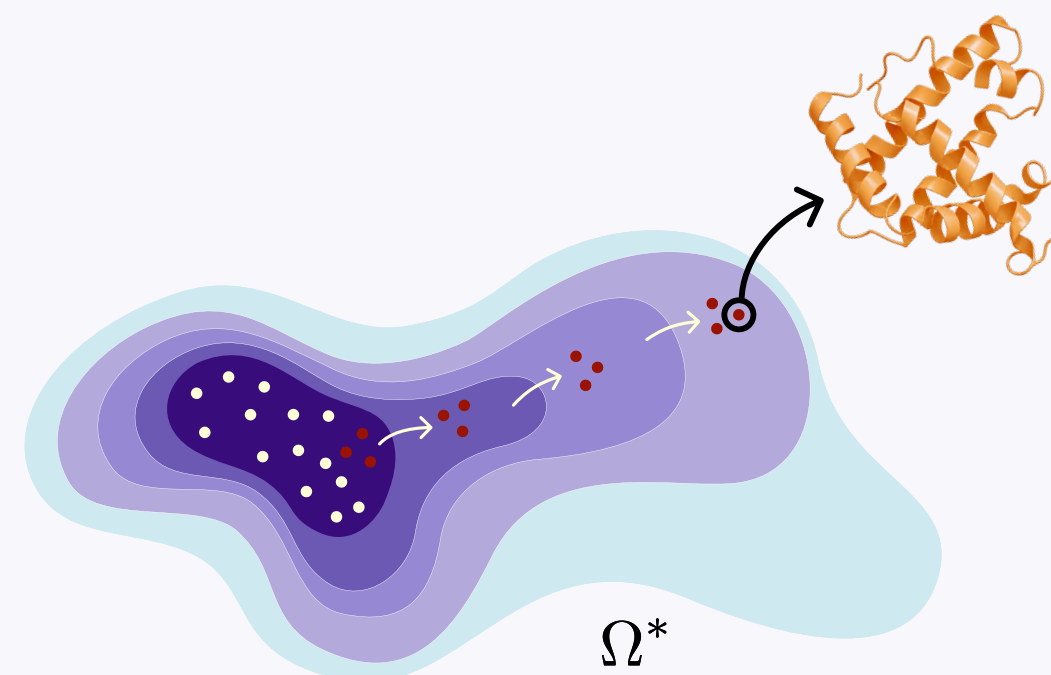
Which candidates matter?



Part II

Out-of-Distribution Flow
Modeling

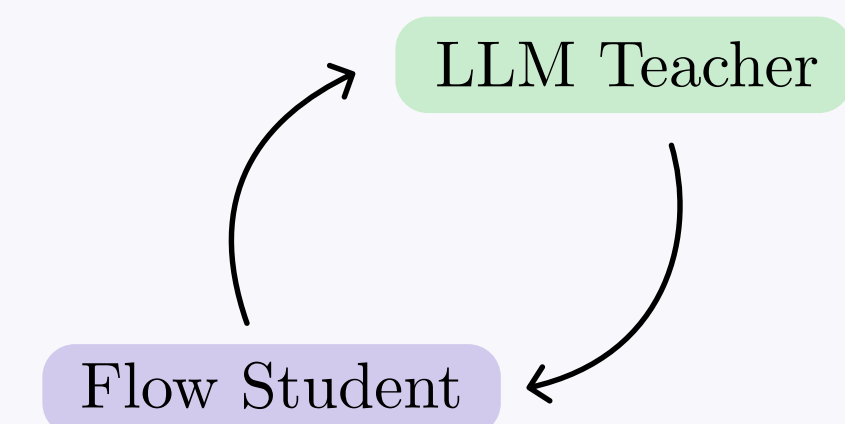
Which regions can we reach?



Part III

Sample-Efficient Discovery
via LLM Feedback

What feedback guides us there?



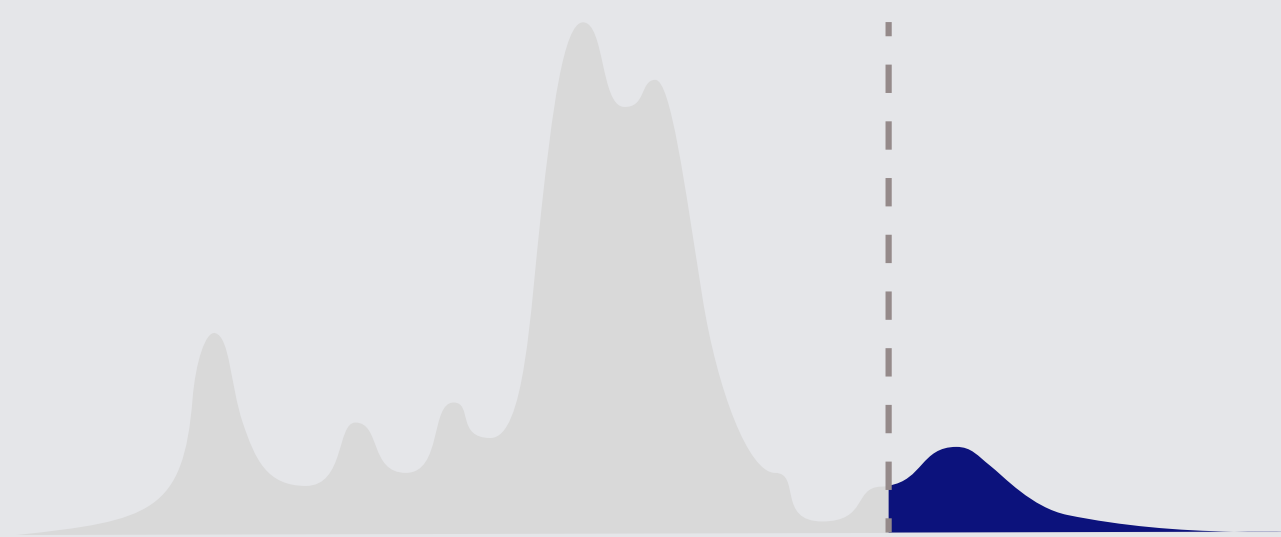
This talk:

Generative Discovery Beyond the Data

Part I

Rare and Diverse
Generation

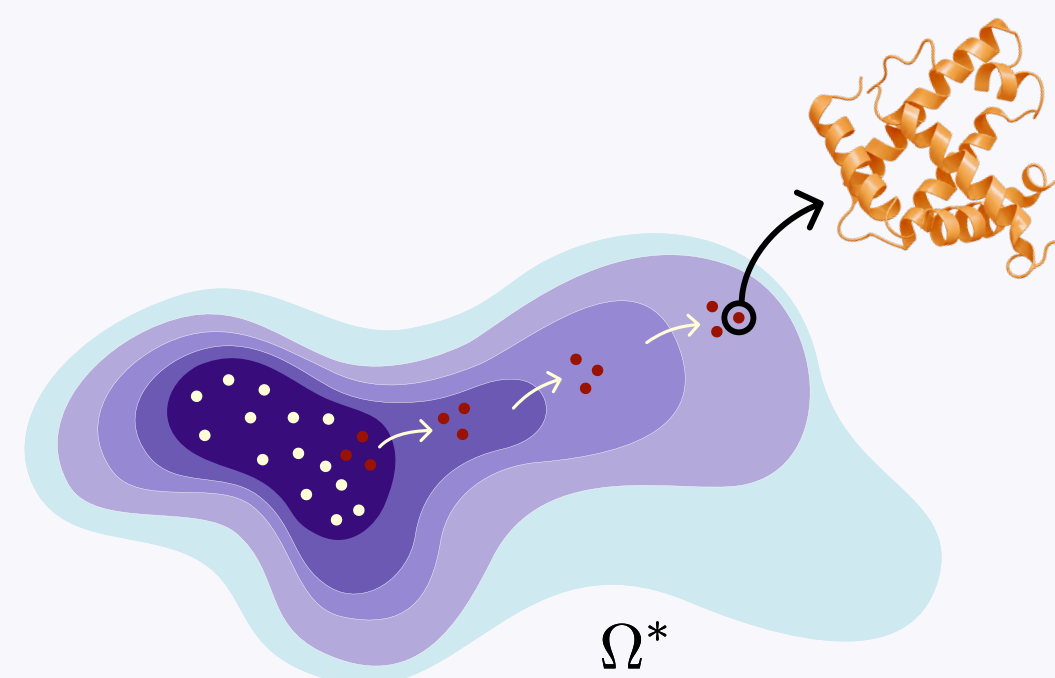
Which candidates matter?



Part II

Out-of-Distribution Flow
Modeling

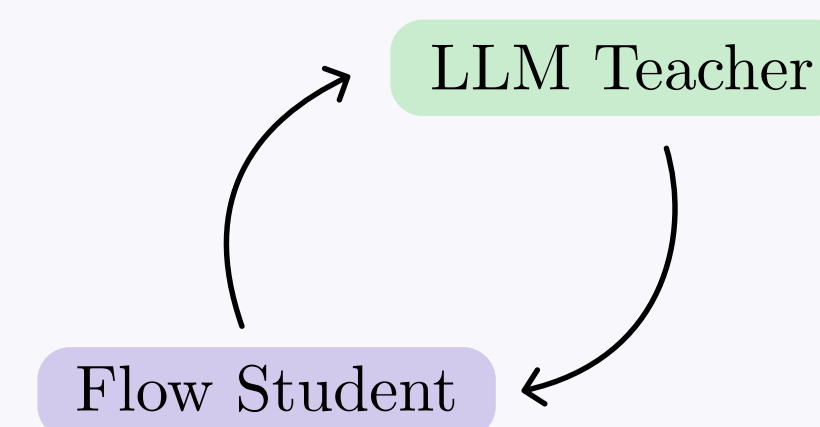
Which regions can we reach?



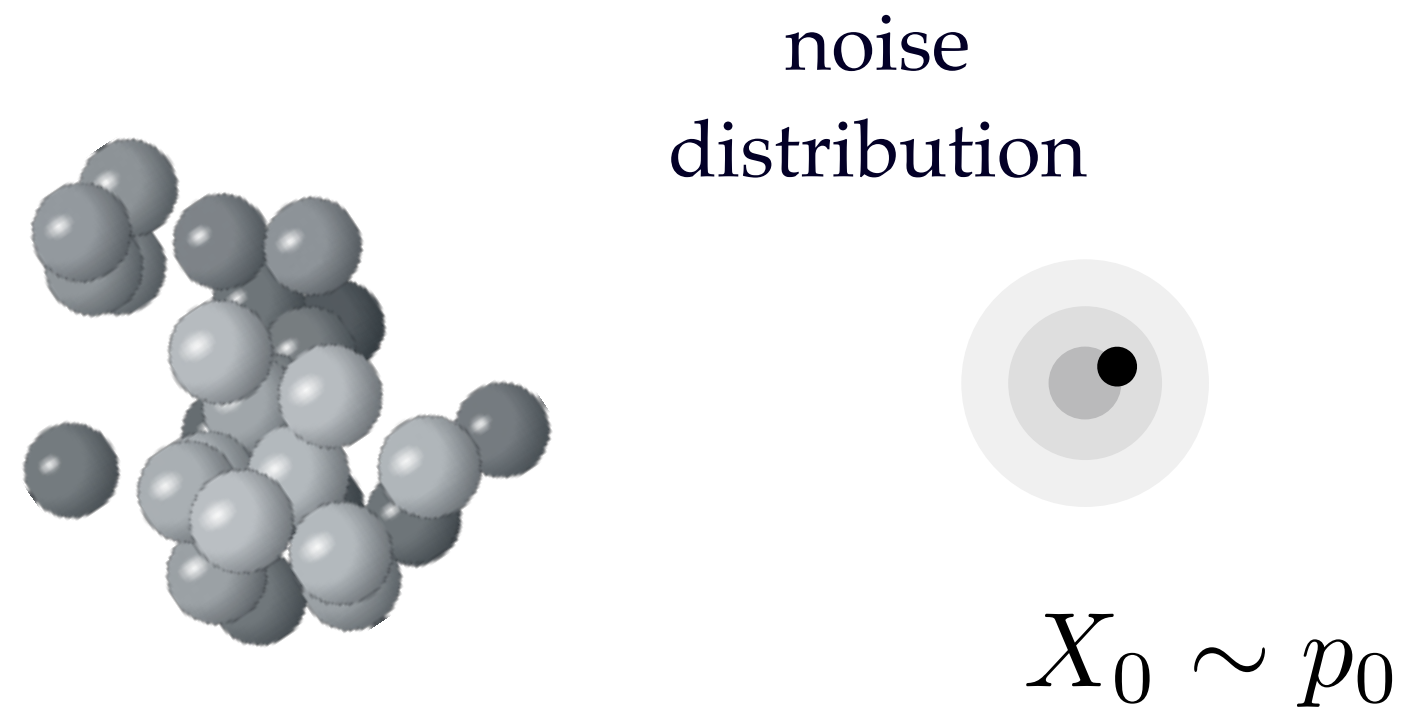
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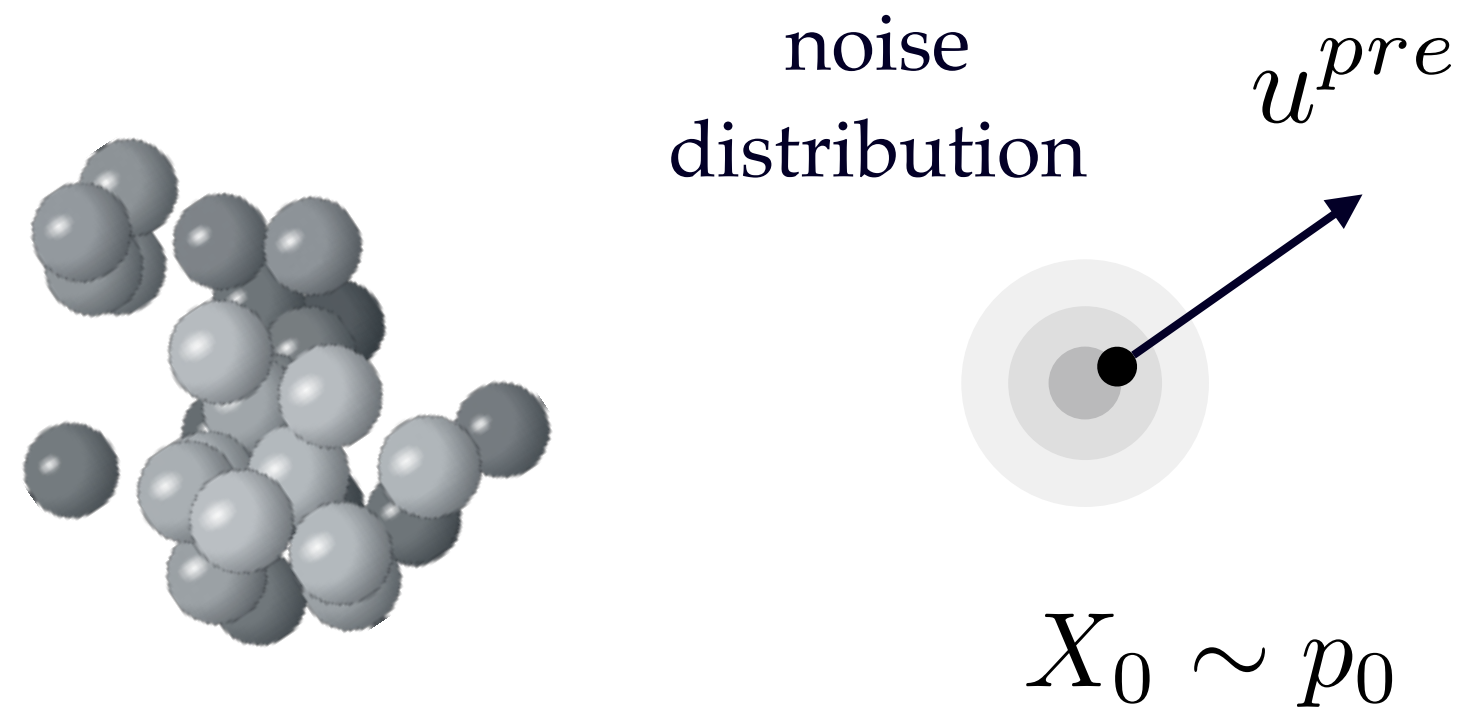
Diffusion and Flow Modeling



Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field u^{pre}

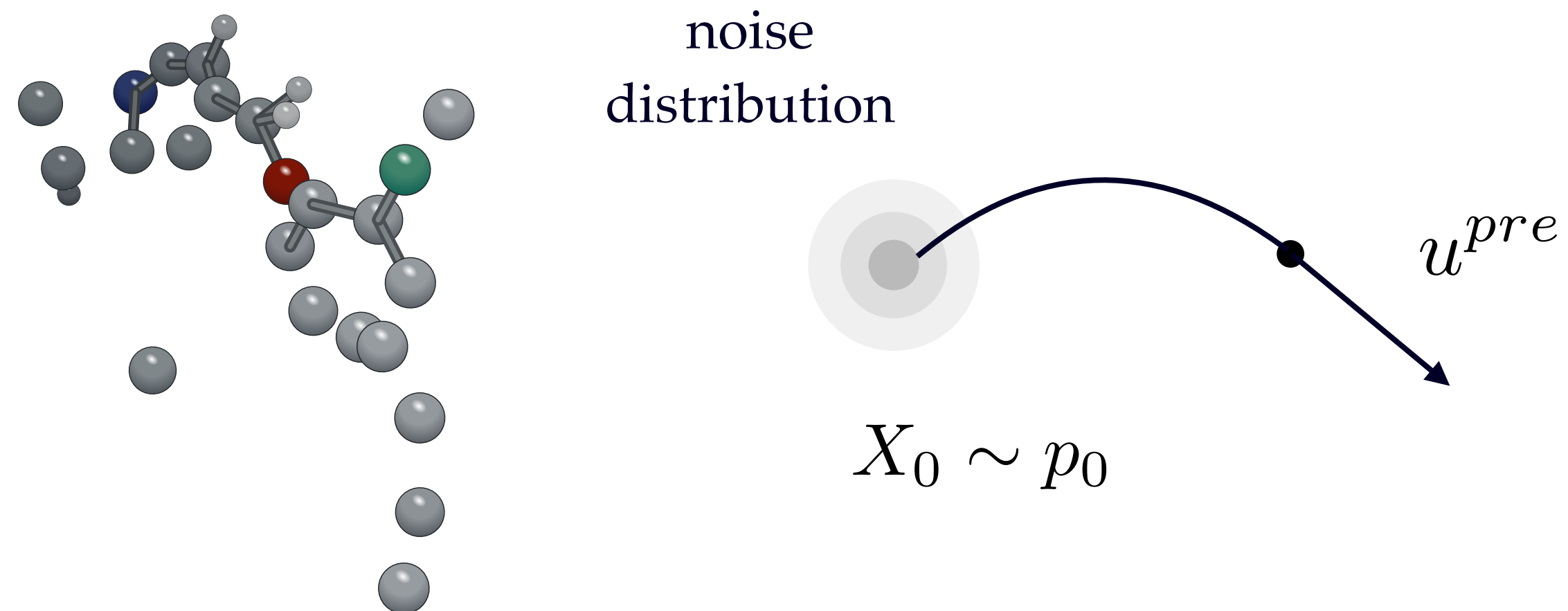
Diffusion and Flow Modeling



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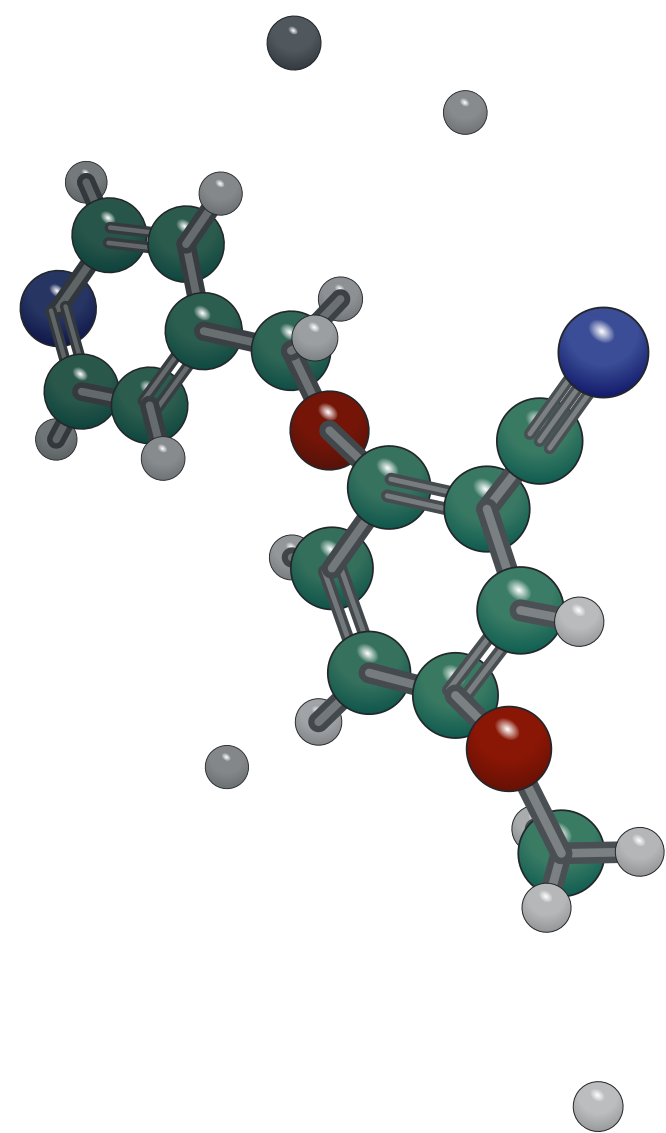
Diffusion and Flow Modeling



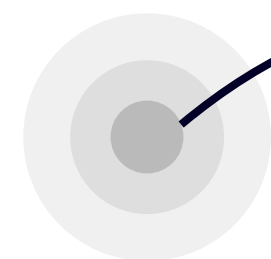
Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field u^{pre}

Diffusion and Flow Modeling



noise
distribution



$$X_0 \sim p_0$$

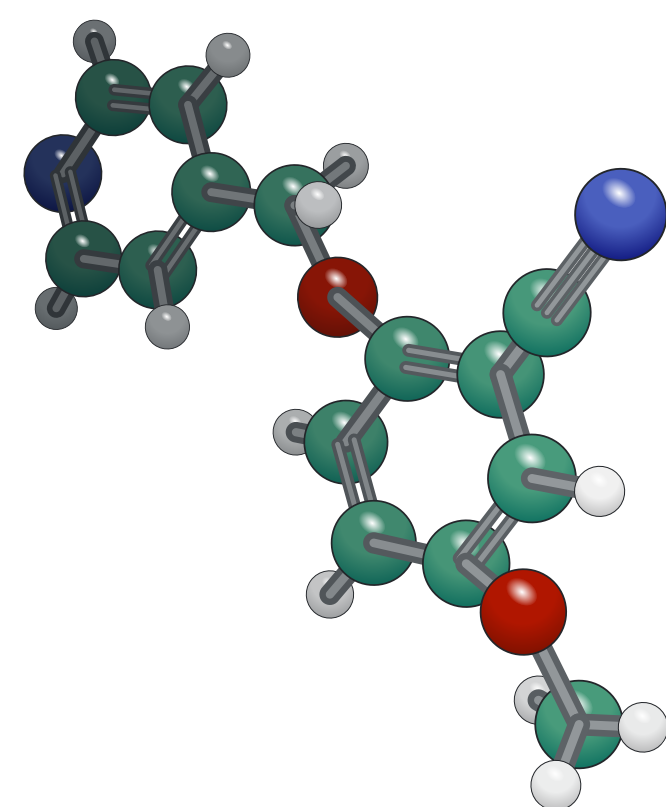
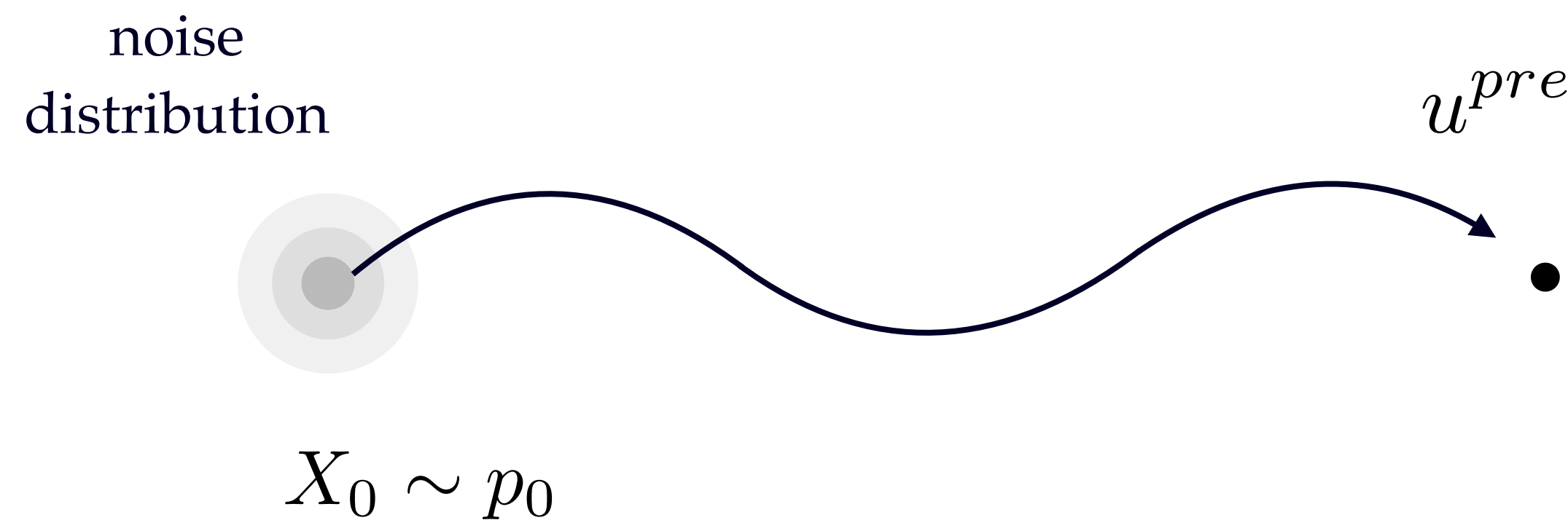
u^{pre}



Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field u^{pre}

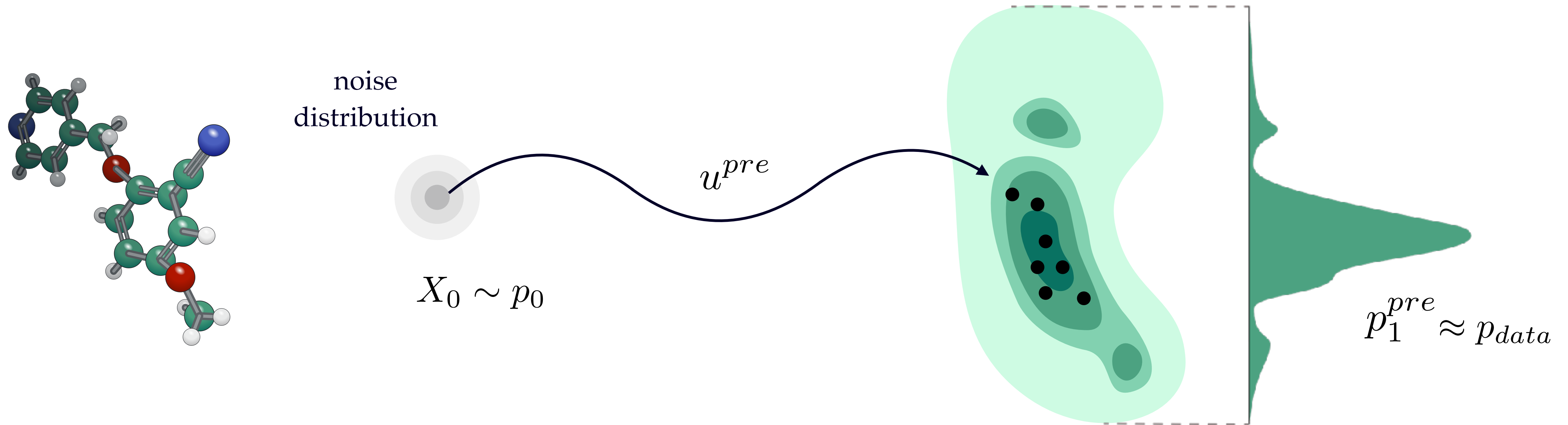
Diffusion and Flow Modeling



Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field u^{pre}

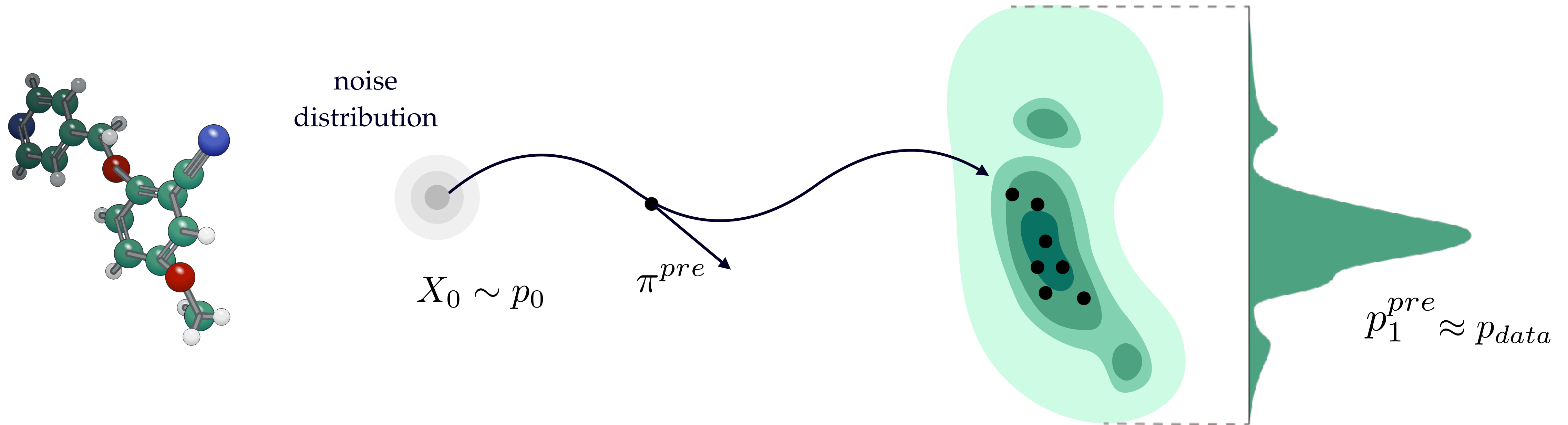
Diffusion and Flow Modeling



Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned vector field u^{pre}

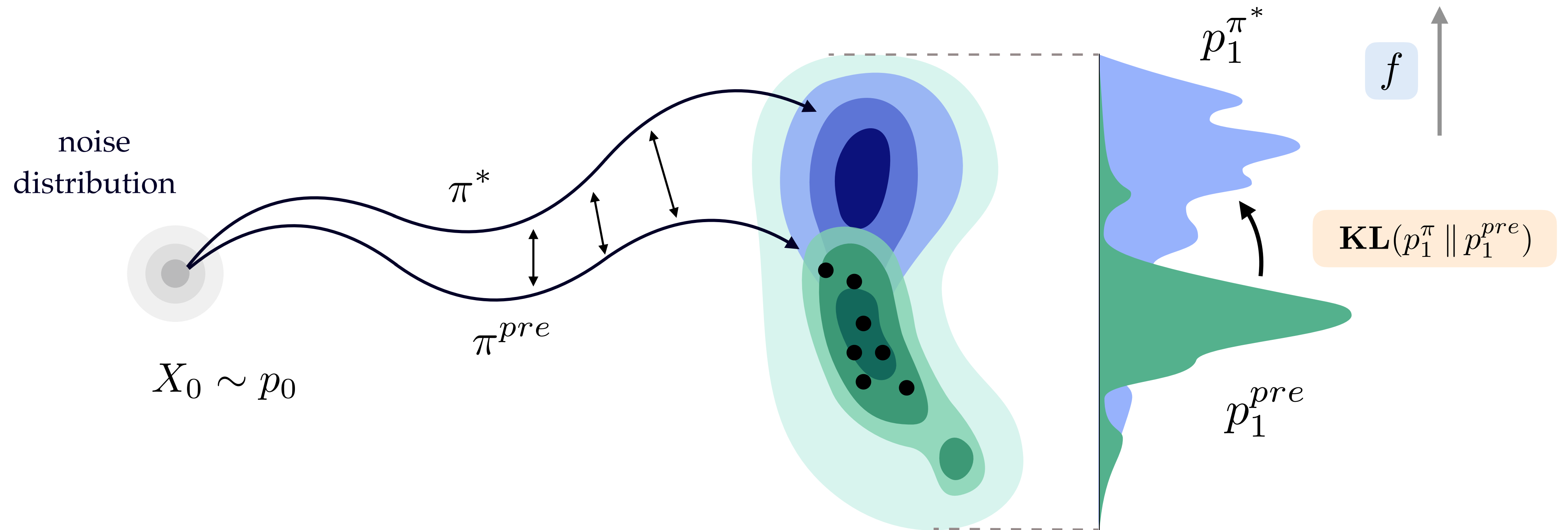
Diffusion and Flow Modeling



Generation via learned vector field

Sample noise $X_0 \sim p_0$ $\longrightarrow$ Follow learned policy π^{pre}

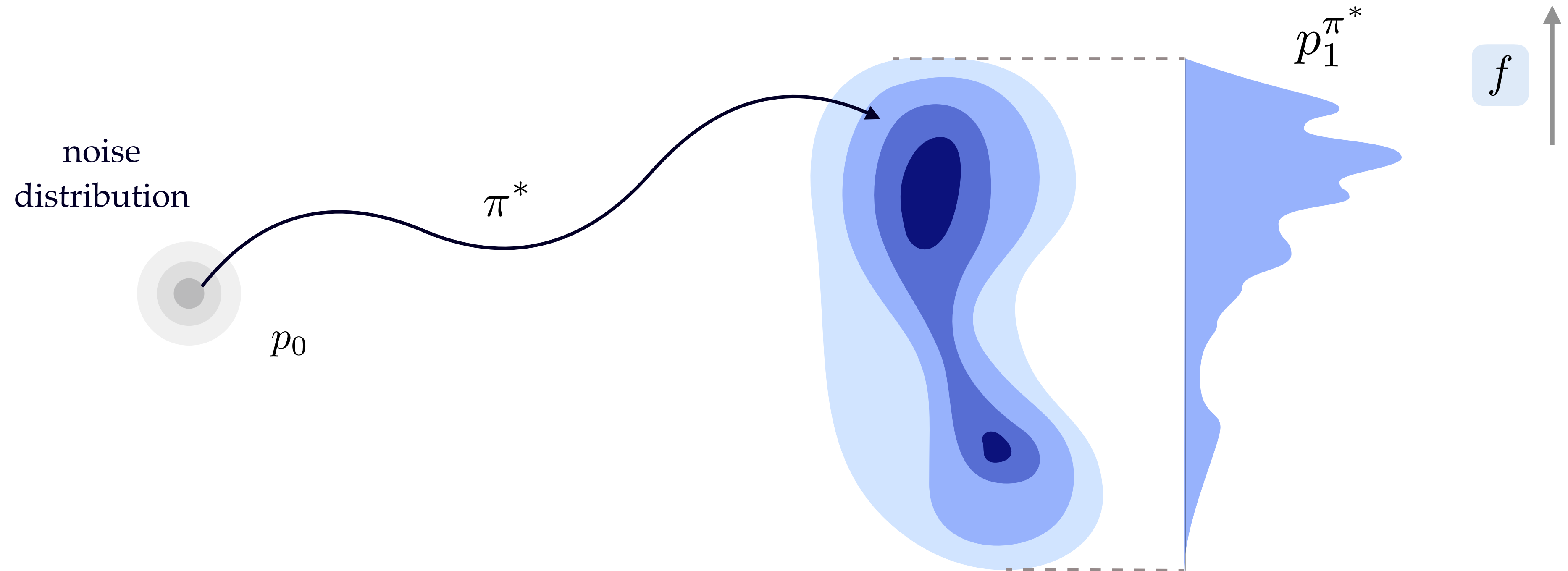
Generative Optimization via Flow Adaptation



Flow Reward-Guided Adaptation

$$\pi^* \in \operatorname{argmax}_{\pi} \mathbb{E}_{x \sim p_1^{\pi}} [f(x)] - \alpha \text{KL}(p_1^{\pi} \parallel p_1^{pre})$$

Generative Optimization via Flow Adaptation



Flow Reward-Guided Adaptation

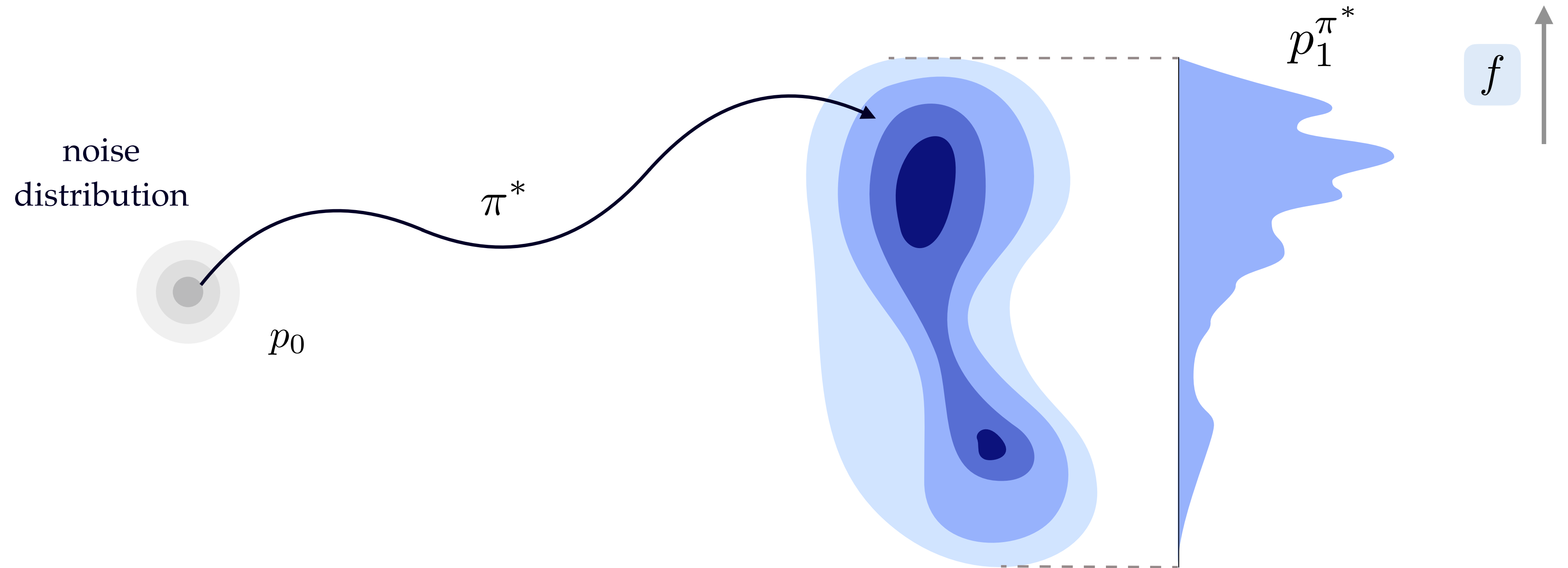
$$\pi^* \in \operatorname{argmax}_{\pi} \mathbb{E}_{x \sim p_1^{\pi}} [f(x)] - \alpha \mathbf{KL}(p_1^{\pi} \parallel p_1^{pre})$$

Closed form *reward tilted distribution*

$$p_1^{\pi^*}(x) \propto \exp\left(\frac{f(x)}{\alpha}\right) \cdot p_1^{pre}(x)$$

in-distribution density reweighing

Generative Optimization via Flow Adaptation



Flow Reward-Guided Adaptation

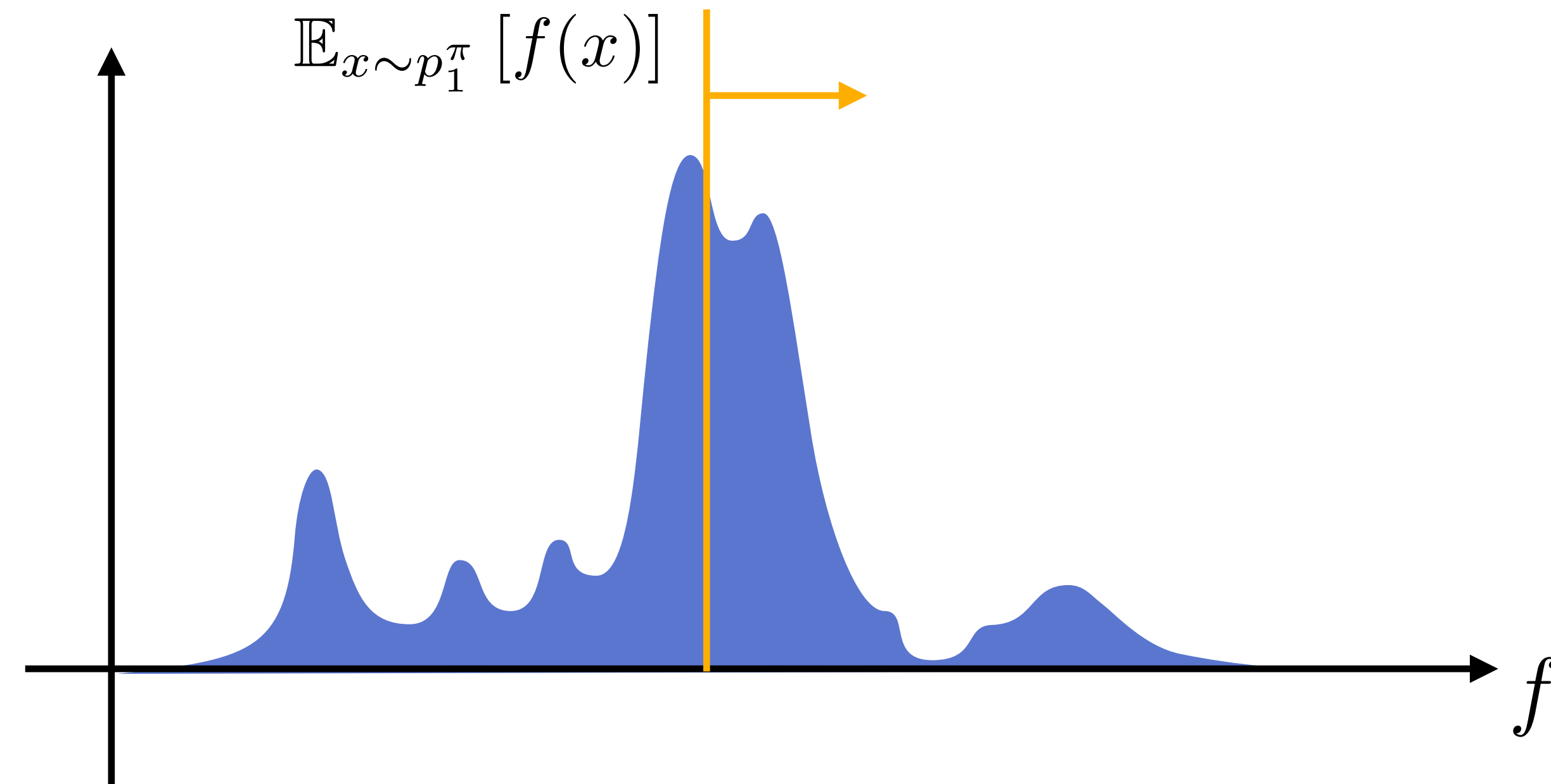
$$\pi^* \in \operatorname{argmax}_{\pi} \mathbb{E}_{x \sim p_1^{\pi}} [f(x)] - \alpha \mathbf{KL}(p_1^{\pi} \parallel p_1^{pre})$$

E.g.,

FlowGRPO (RL, **gradient-free**)

Adjoint Matching (Control, **gradient-based**)

Is Expended Reward Maximization Good for Discovery?

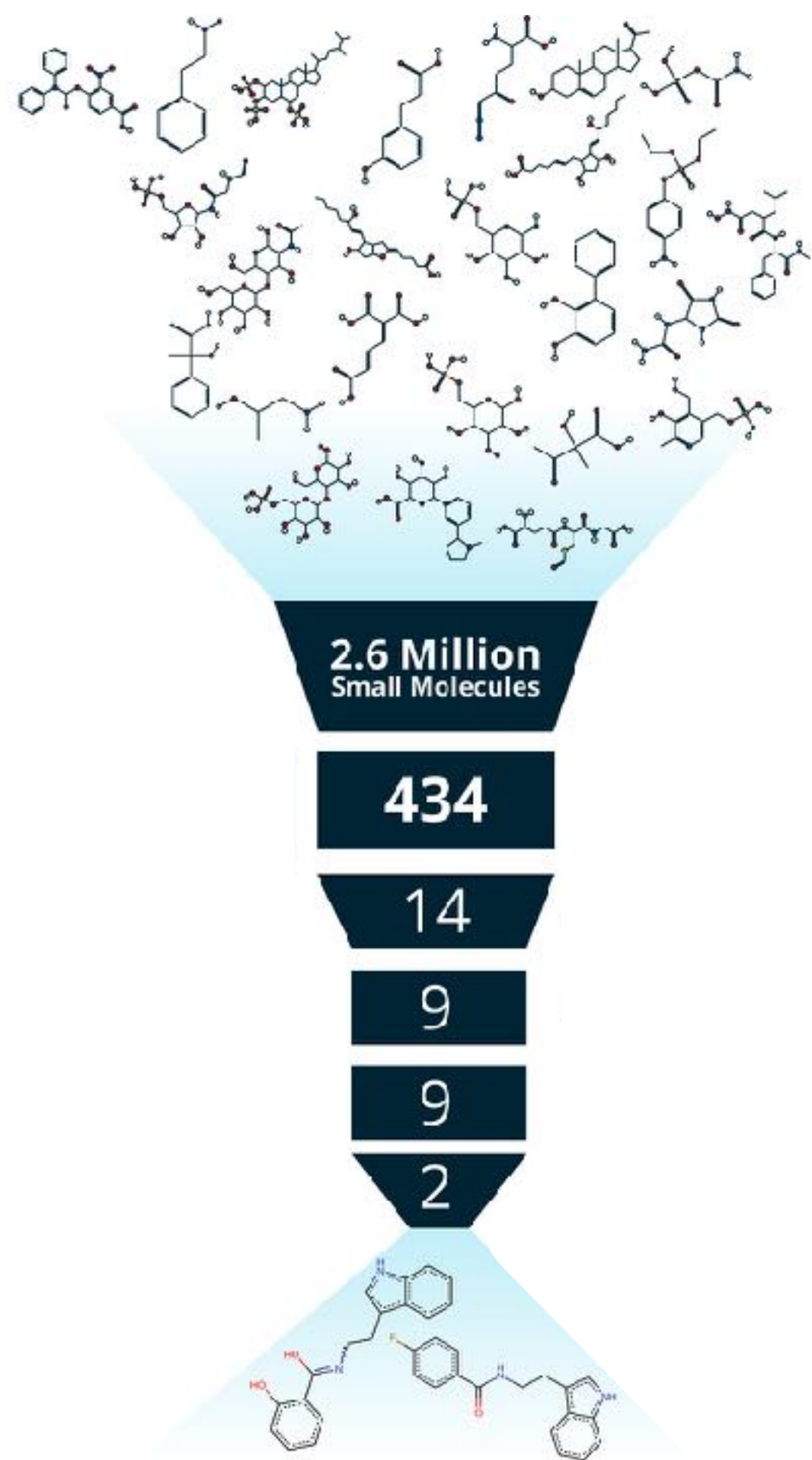


Flow Reward-Guided Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \mathbb{E}_{x \sim p_1^\pi} [f(x)] - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

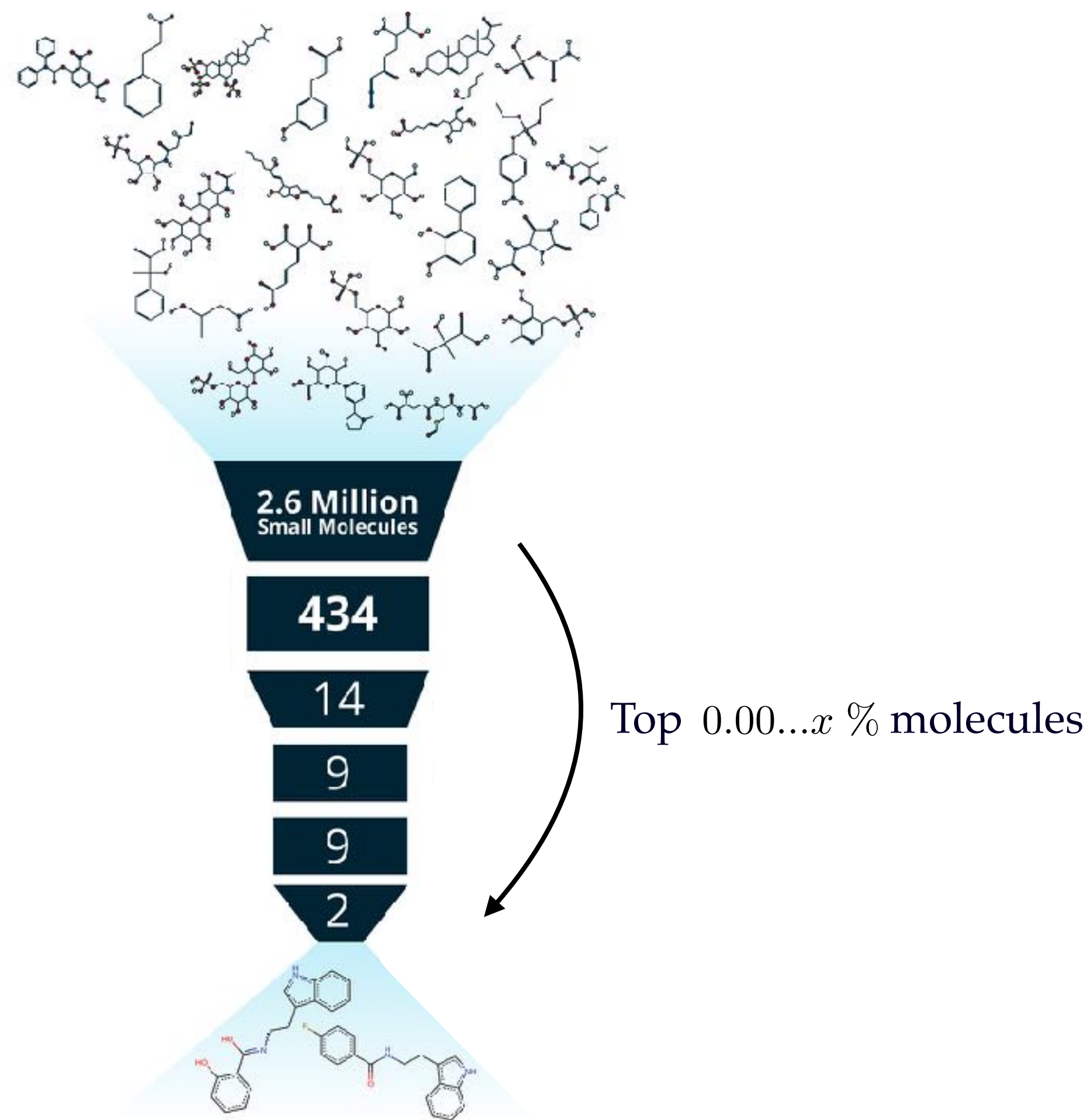
Optimizes average sample quality

Discovery Pipeline in Chemistry and Biology



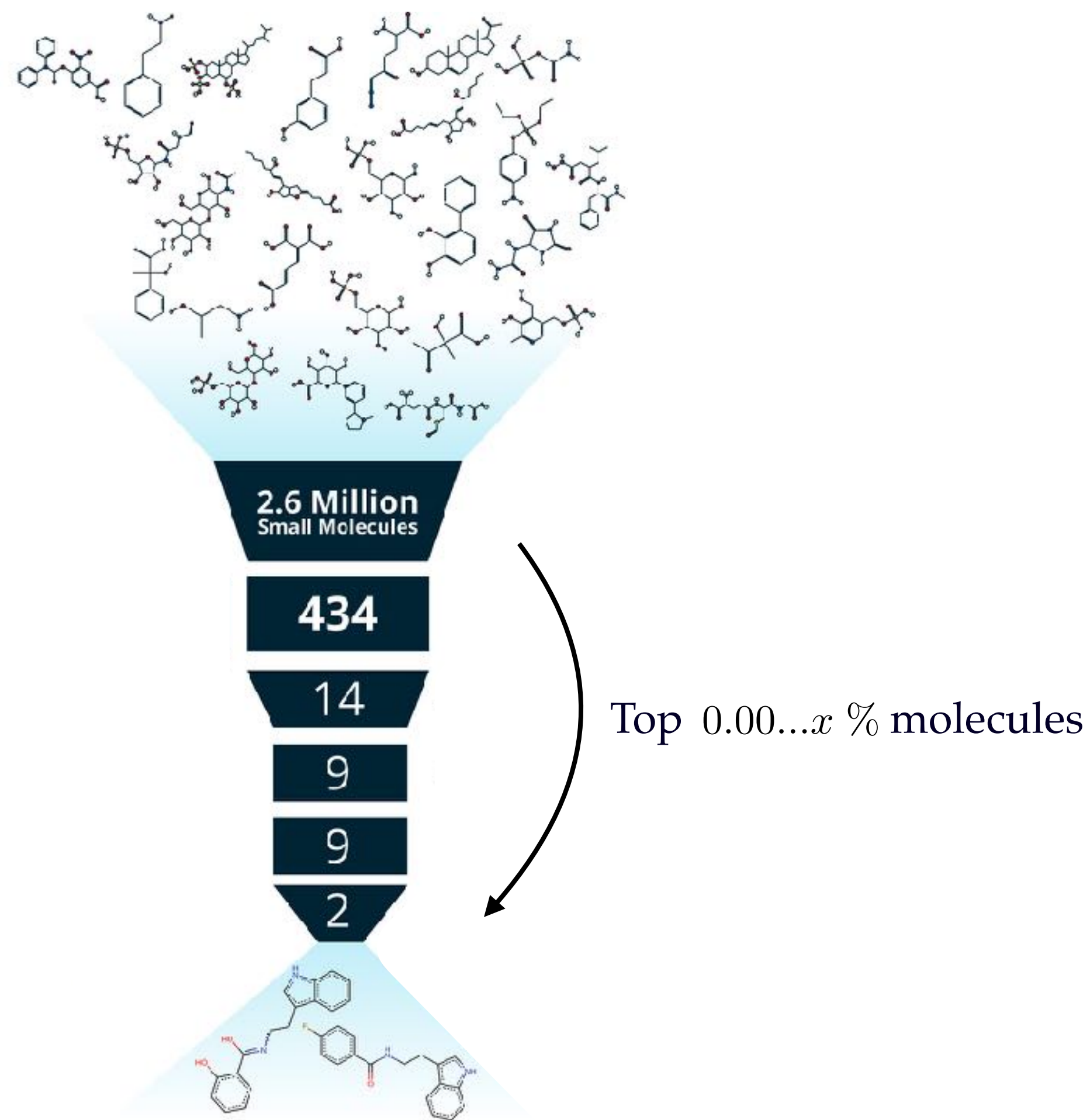
[Anastasiia Gryniukova et al., 2023]

Discovery Pipeline in Chemistry and Biology



[Anastasiia Gryniukova et al., 2023]

Discovery Pipeline in Chemistry and Biology

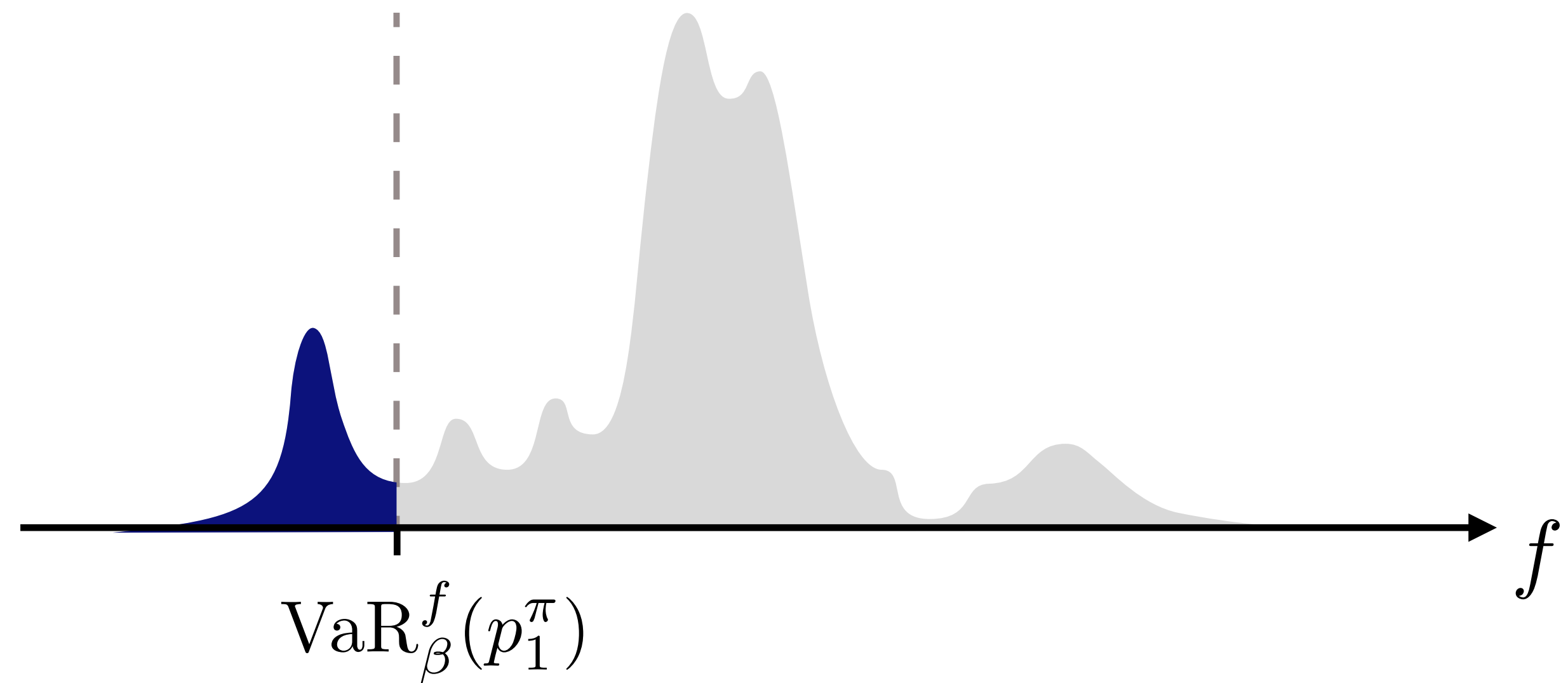


Takeaway

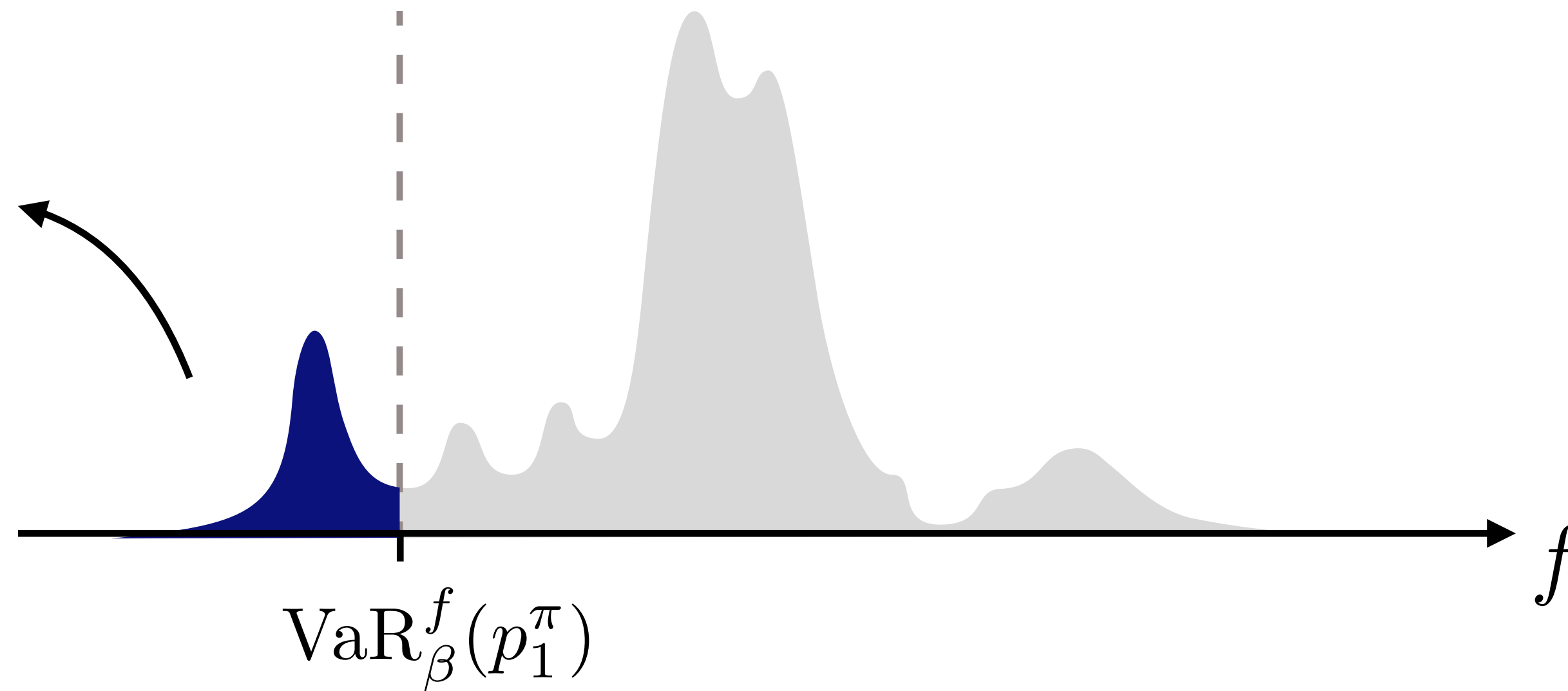
Average reward adaptation is often a bad objective for discovery.

[Anastasiia Gryniukova et al., 2023]

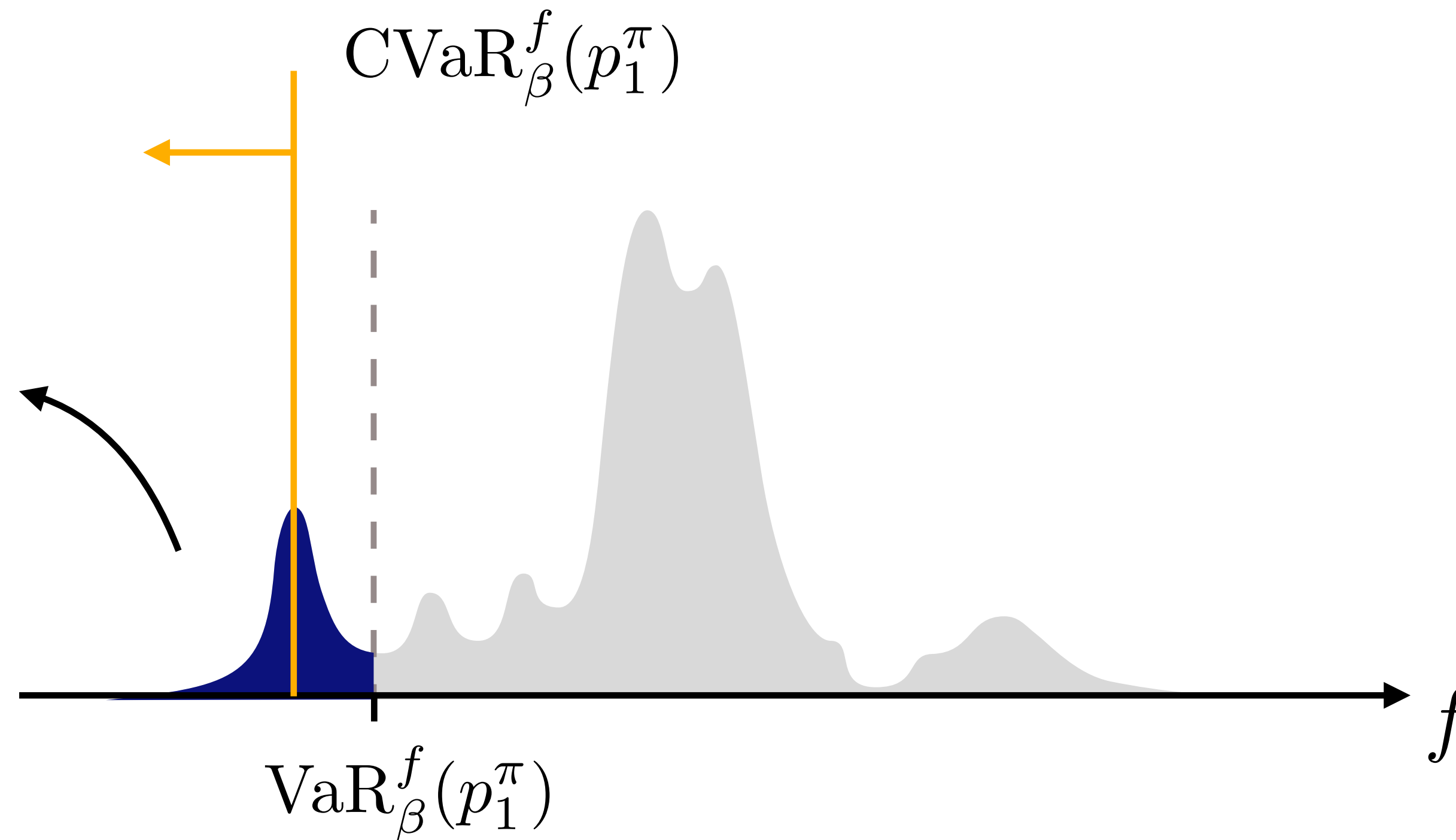
Risk-sensitivity for Quantitative Finance



Risk-sensitivity for Quantitative Finance



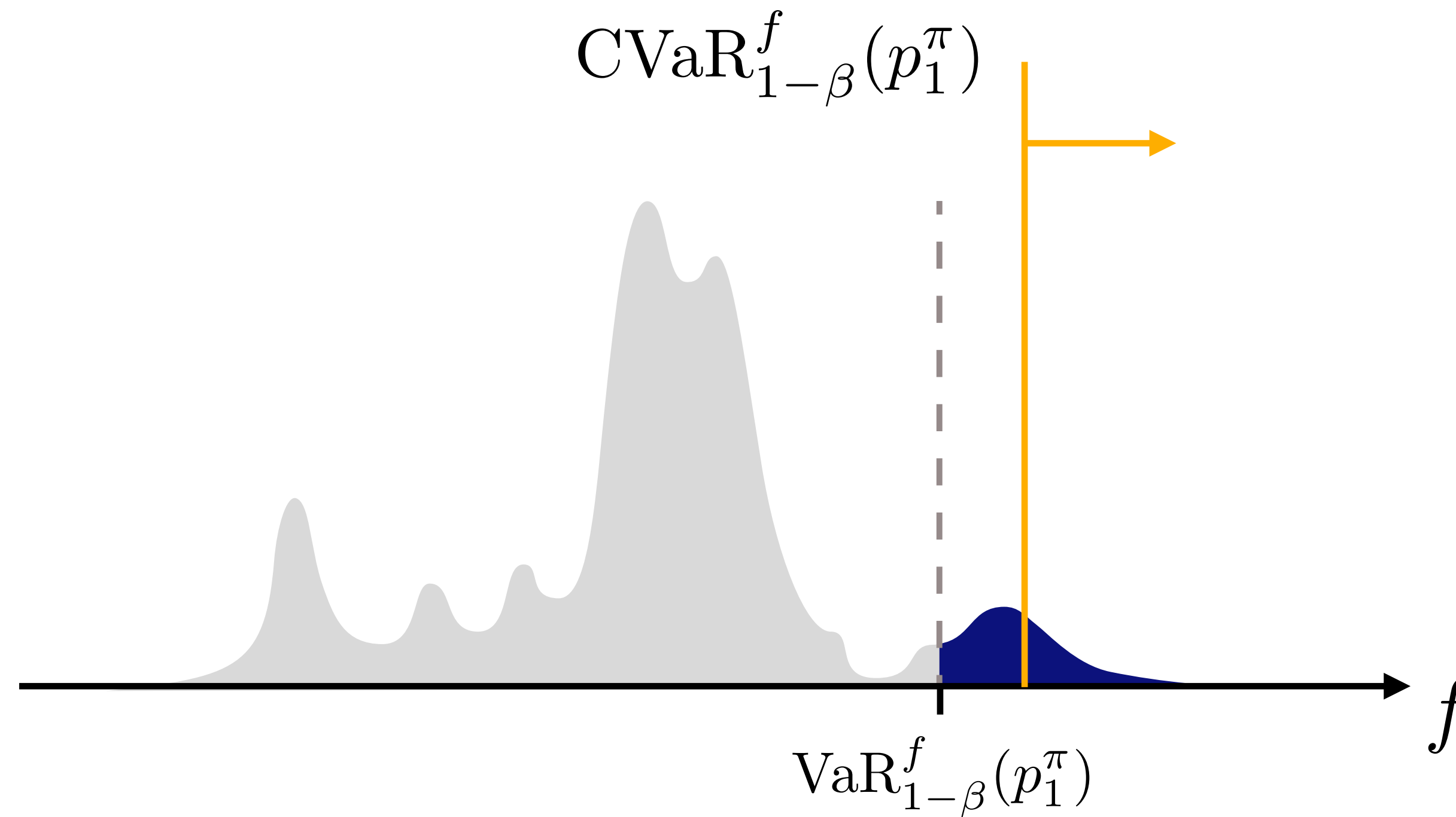
Risk-sensitivity for Quantitative Finance



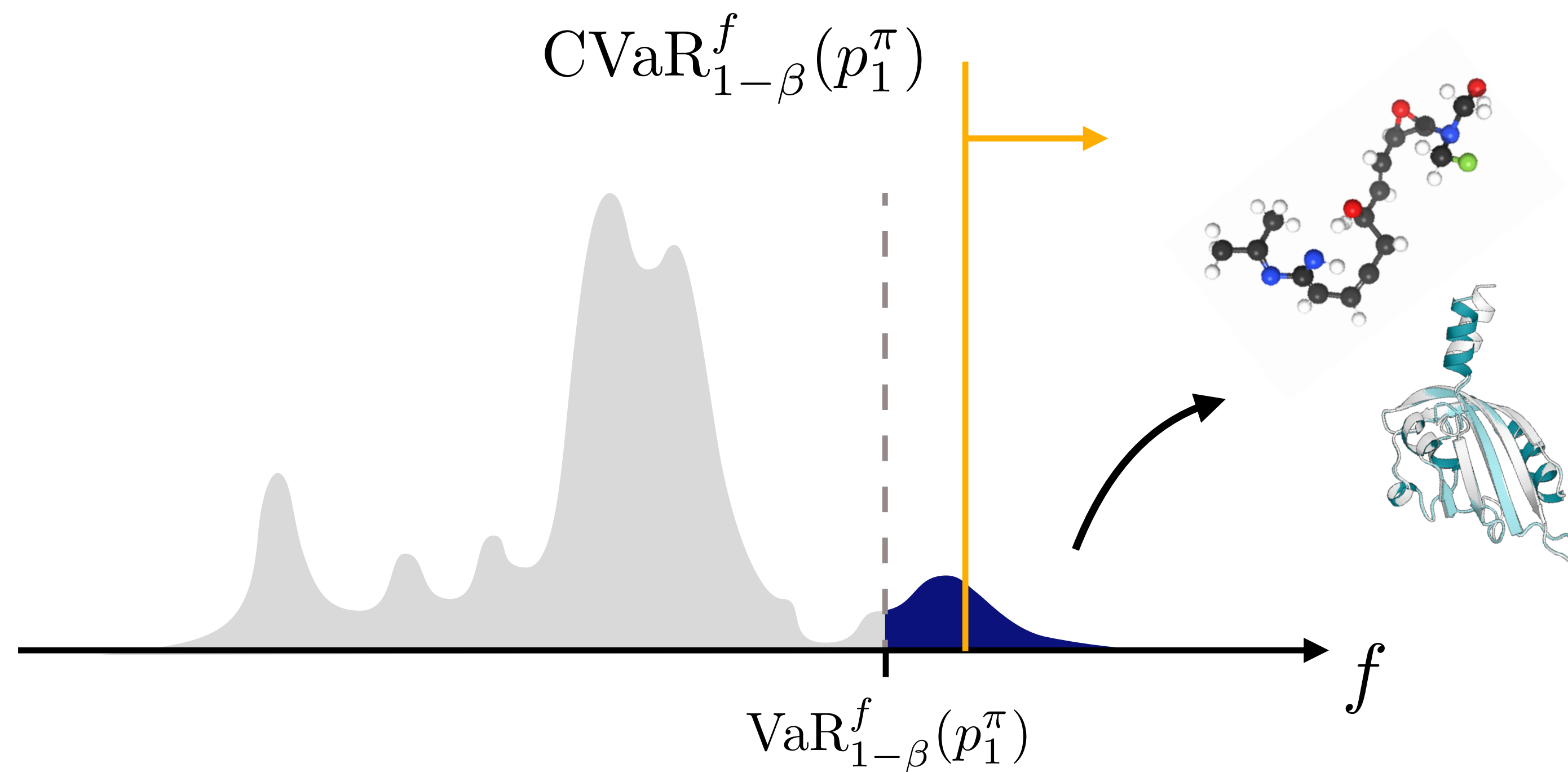
$$\text{CVaR}_\beta^f(p_1^\pi) := \mathbb{E}_{x \sim p_1^\pi} [f(x) \mid f(x) \leq \text{VaR}_\beta^f(p_1^\pi)]$$

Expected value of **left (bottom) β quantile**

Risk-Sensitive Flow Steering for Discovery

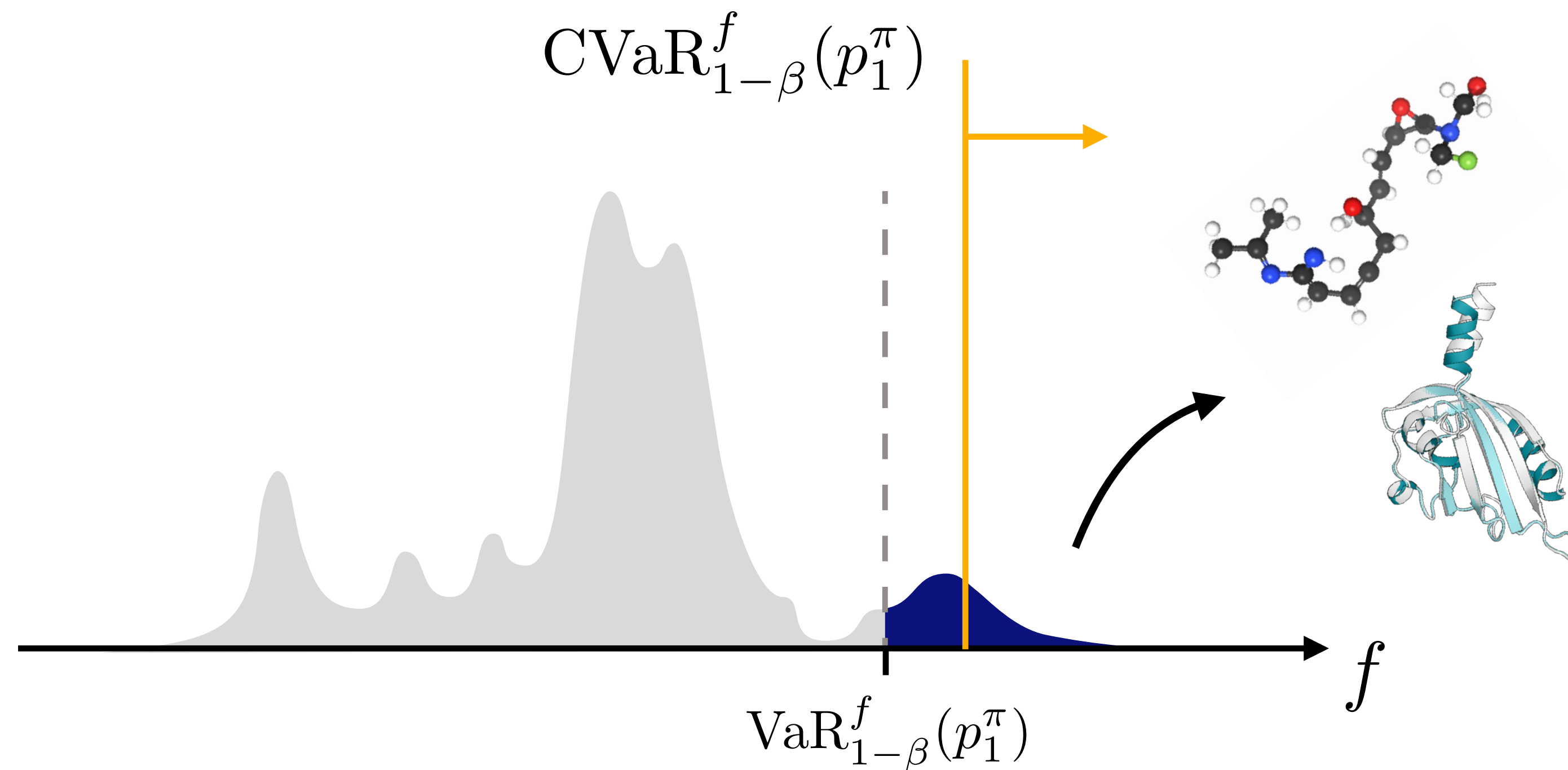


Risk-Sensitive Flow Steering for Discovery



Valid high-value rare events $\approx$ (potential) discoveries

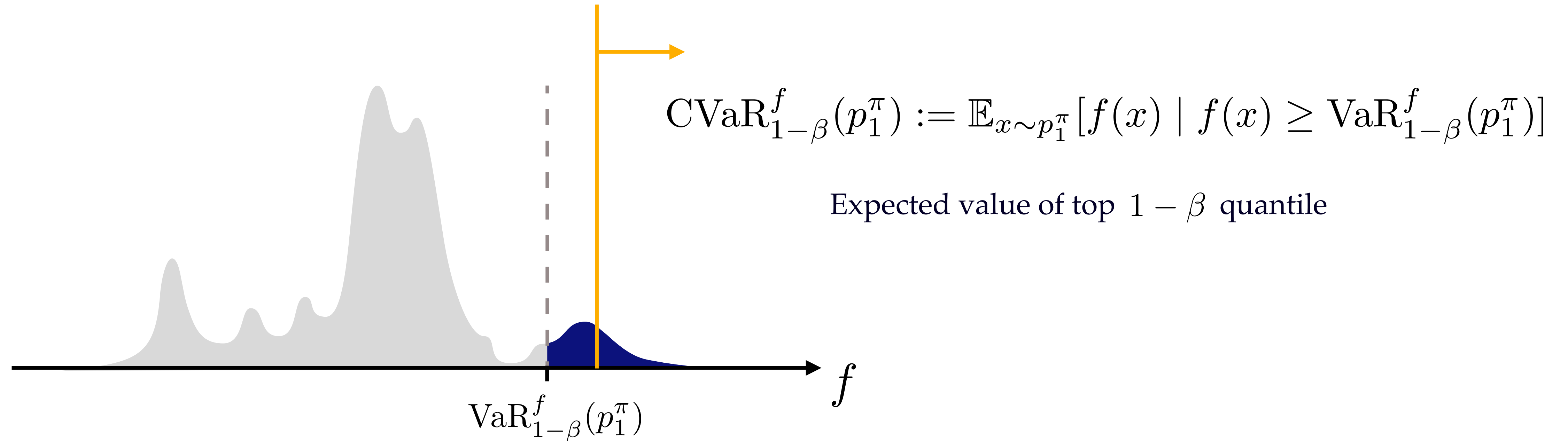
Risk-Sensitive Flow Steering for Discovery



$$\text{CVaR}_{1-\beta}^f(p_1^\pi) := \mathbb{E}_{x \sim p_1^\pi} [f(x) \mid f(x) \geq \text{VaR}_{1-\beta}^f(p_1^\pi)]$$

Expected value of **right (top) $1 - \beta$ quantile**

Tail-Aware Flow Adaptation for Discovery

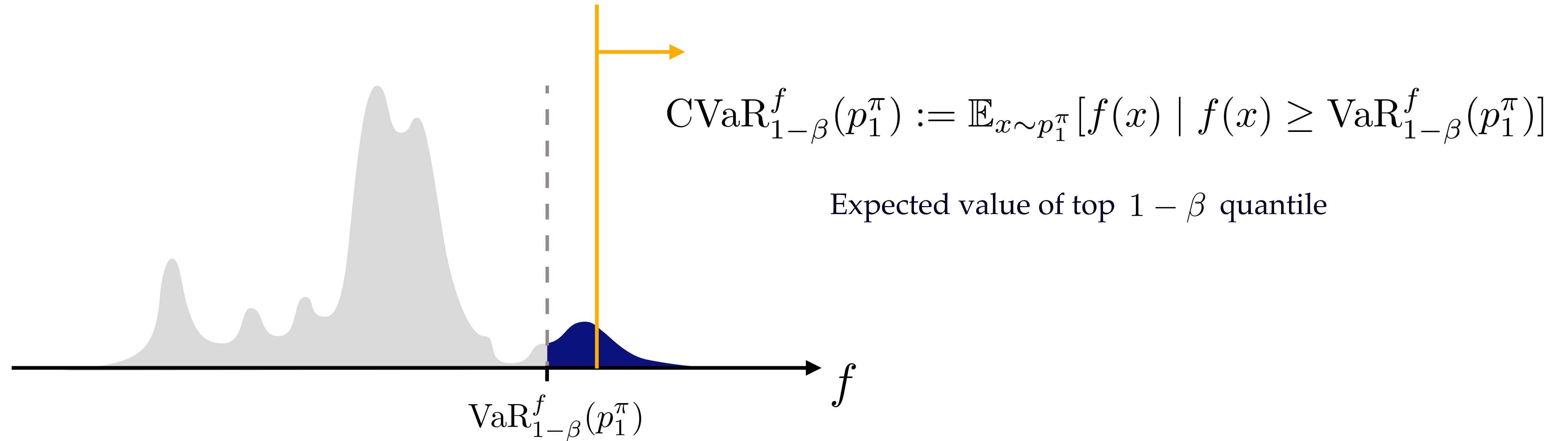


Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \text{CVaR}_{1-\beta}(p_1^\pi) - \alpha \text{KL}(p_1^\pi \parallel p_1^{pre})$$

**Prior regularization to
generate valid structures**

Tail-Aware Flow Adaptation for Discovery



Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \text{CVaR}_{1-\beta}(p_1^\pi) - \alpha \text{KL}(p_1^\pi \parallel p_1^{pre})$$

**Prior regularization to
generate valid structures**

CVaR is a non-linear functional. How to optimize?

CVaR Fine-Tuning in One Step

Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \operatorname{CVaR}_{1-\beta}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

CVaR Fine-Tuning in One Step

Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \operatorname{CVaR}_{1-\beta}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

$$\operatorname{CVaR}_{1-\beta}(p_1^\pi) = \min_{t \in \mathbb{R}} \left\{ t + \frac{1}{\beta} \mathbb{E}_{x \sim p_1^\pi} [(f(x) - t)_+] \right\} \quad \text{CVaR variational formulation}$$

CVaR Fine-Tuning in One Step

Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \operatorname{CVaR}_{1-\beta}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

$$\operatorname{CVaR}_{1-\beta}(p_1^\pi) = \min_{t \in \mathbb{R}} \left\{ t + \frac{1}{\beta} \mathbb{E}_{x \sim p_1^\pi} [(f(x) - t)_+] \right\} \quad \text{CVaR variational formulation}$$

First solve a scalar threshold problem:

$$t^* = \arg \min_{t \in \mathbb{R}} \left\{ t + \alpha \log \mathbb{E}_{x \sim p_1^{pre}} \left[\exp \left(\frac{(f(x) - t)_+}{\alpha \beta} \right) \right] \right\} \quad \begin{array}{l} \text{1-dim opt. problem} \\ \text{(e.g., GD / line-search)} \end{array}$$

CVaR Fine-Tuning in One Step

Tail-Aware Reward-Guided Flow Fine-Tuning

$$\pi^* \in \operatorname{argmax}_{\pi} \operatorname{CVaR}_{1-\beta}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

$$\operatorname{CVaR}_{1-\beta}(p_1^\pi) = \min_{t \in \mathbb{R}} \left\{ t + \frac{1}{\beta} \mathbb{E}_{x \sim p_1^\pi} [(f(x) - t)_+] \right\} \quad \text{CVaR variational formulation}$$

First solve a scalar threshold problem:

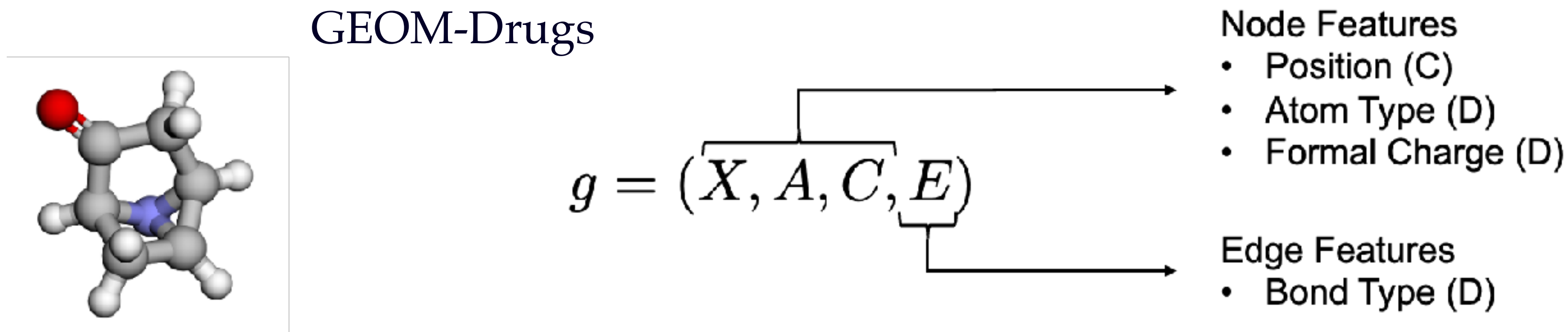
$$t^* = \arg \min_{t \in \mathbb{R}} \left\{ t + \alpha \log \mathbb{E}_{x \sim p_1^{pre}} \left[\exp \left(\frac{(f(x) - t)_+}{\alpha \beta} \right) \right] \right\} \quad \begin{array}{l} \text{1-dim opt. problem} \\ \text{(e.g., GD / line-search)} \end{array}$$

Then fine-tune flow once:

$$r^*(x) = \frac{(f(x) - t^*)_+}{\beta} \quad \longrightarrow \quad \pi^* \in \operatorname{argmax}_{\pi} \mathbb{E}_{x \sim p_1^\pi} [r^*(x)] - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

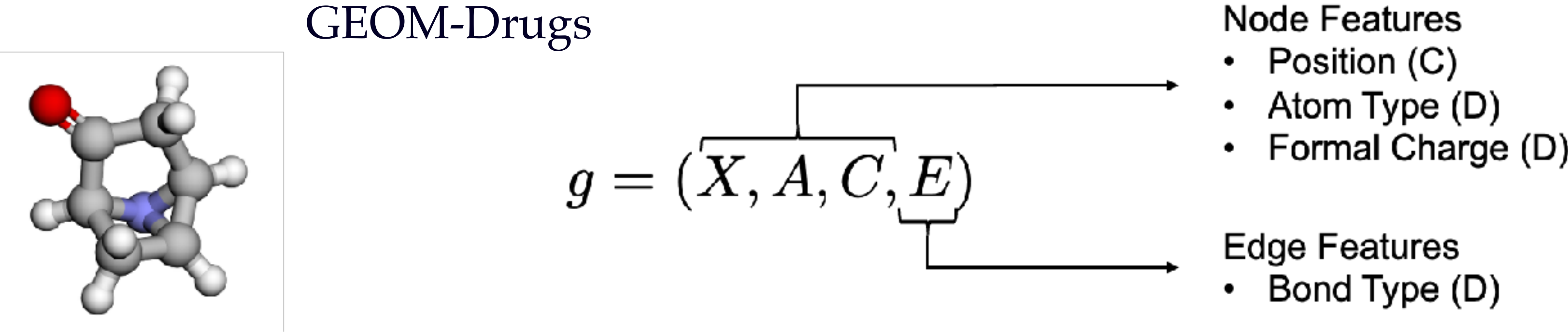
~ 2 lines of code!

CVaR Flow Fine-Tuning for De Novo Molecular Design



Flow over 3D molecular conformers

CVaR Flow Fine-Tuning for De Novo Molecular Design



Flow over 3D molecular conformers

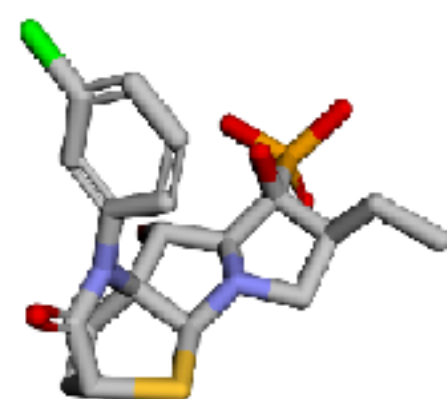
	Training time	FT calls	$\mathbb{E}[r]$	$\text{CVaR}_{0.9}[r]$	Validity	SA score
Pre-trained	0	0	$21.9_{\pm 1.21}$	$161.5_{\pm 10.6}$	$87.4\%_{\pm 0.12\%}$	$7.64_{\pm 0.02}$
Adjoint M.	T	1	$29.8_{\pm 0.58}$	$167.1_{\pm 7.22}$	$78.3\%_{\pm 1.01\%}$	$7.66_{\pm 0.02}$
TFFT	$\approx T$	1	$27.1_{\pm 2.29}$	$183.4_{\pm 15.8}$	$85.7\%_{\pm 0.59\%}$	$7.70_{\pm 0.04}$

[Dunn and Koes, 2024] [Axelrod and Bombarelli, 2022]

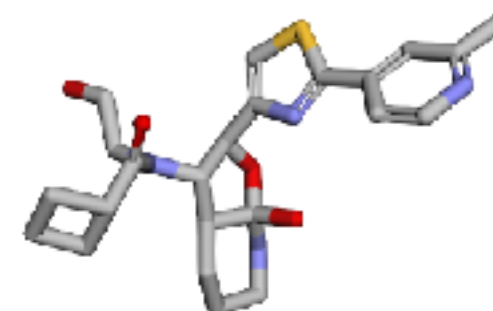
Reward = Negative energy via GFN1-xTB, Validity = RDKit Sanitizer

Top-Samples via CVaR Flow Fine-tuning: GEOM-Drugs

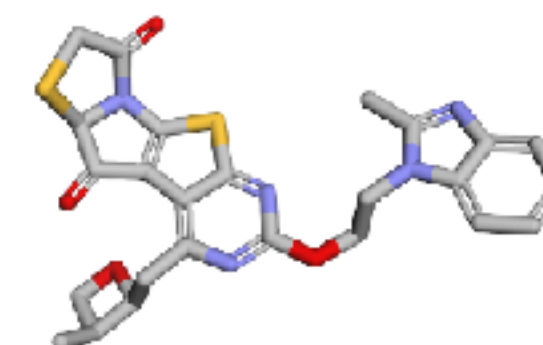
Pre-trained



840



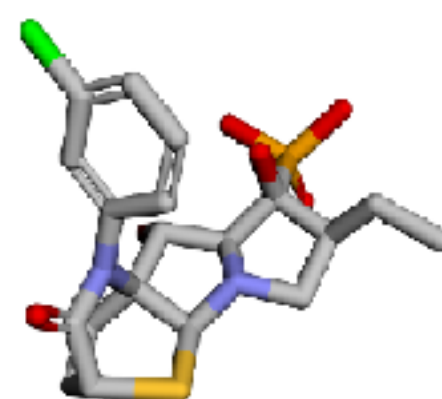
826



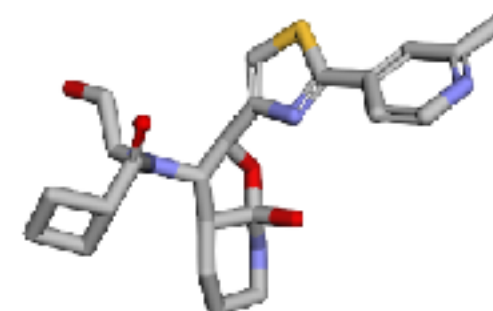
755

Top-Samples via CVaR Flow Fine-tuning: GEOM-Drugs

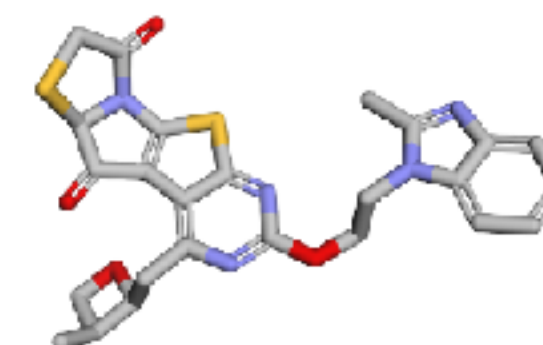
Pre-trained



840

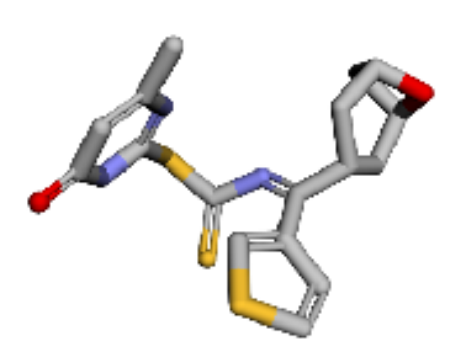


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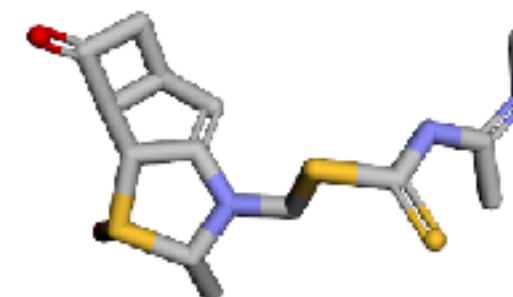


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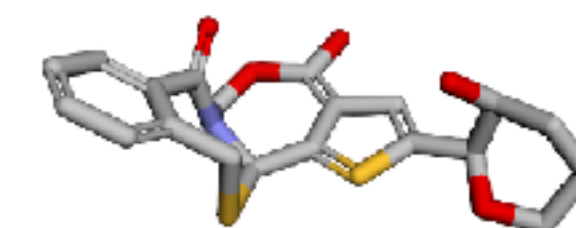
Adjoint Matching



1069



891

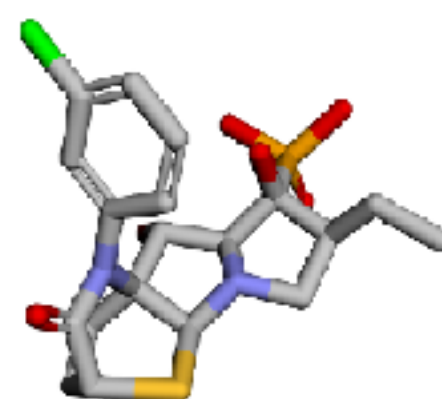


852

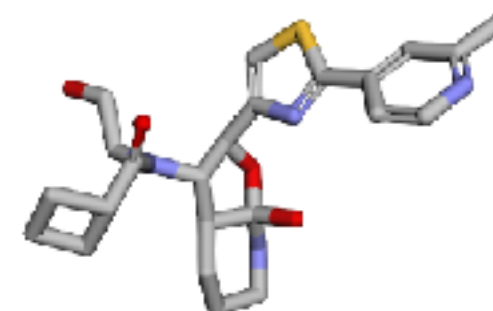
**~1.3x
higher-rewards**

Top-Samples via CVaR Flow Fine-tuning: GEOM-Drugs

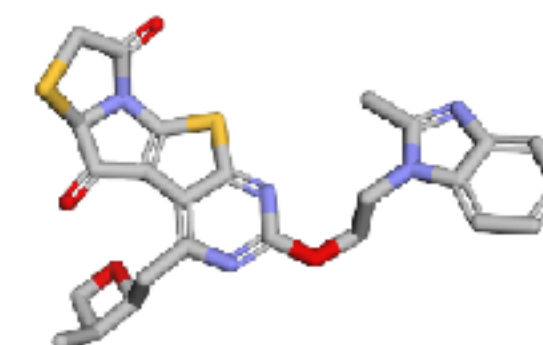
Pre-trained



840

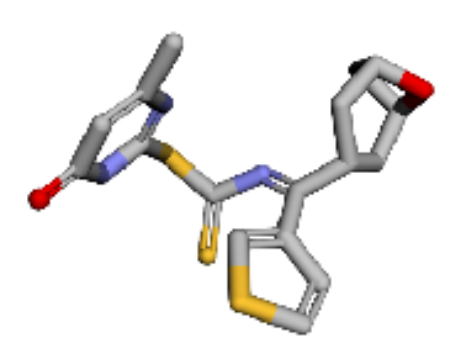


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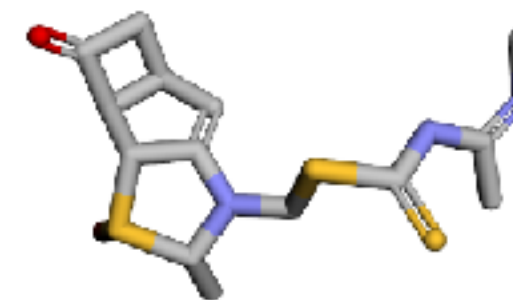


755

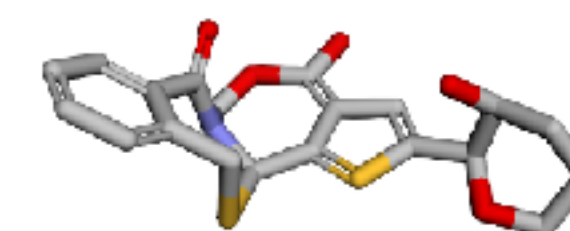
Adjoint Matching



1069



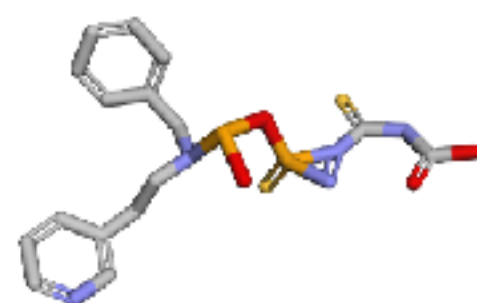
891



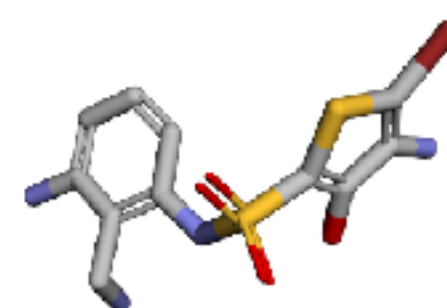
852

**~1.3x
higher-rewards**

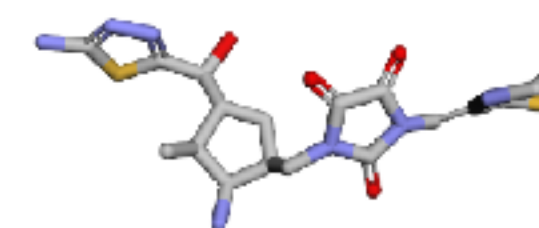
TFFT



5059



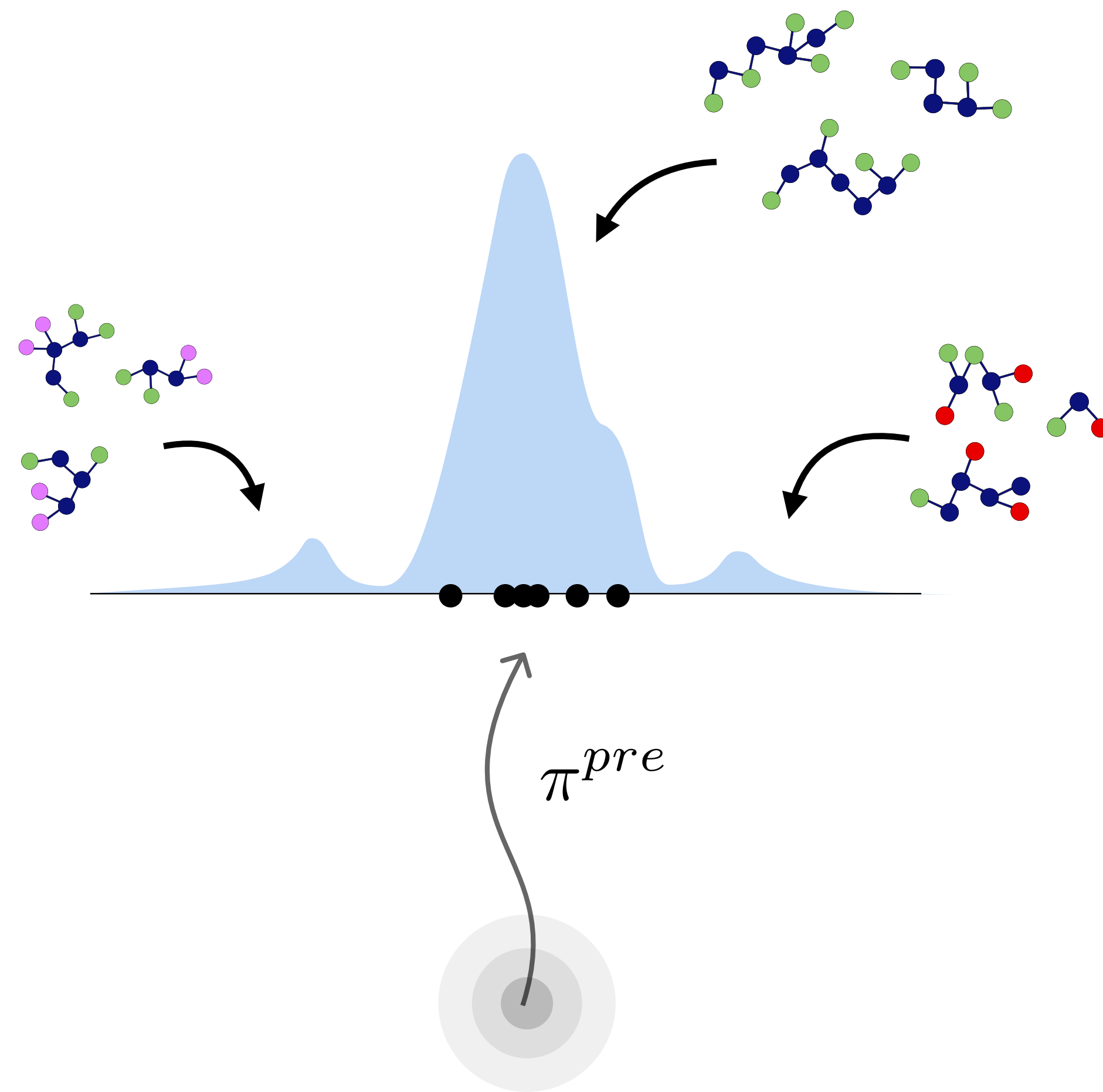
3237



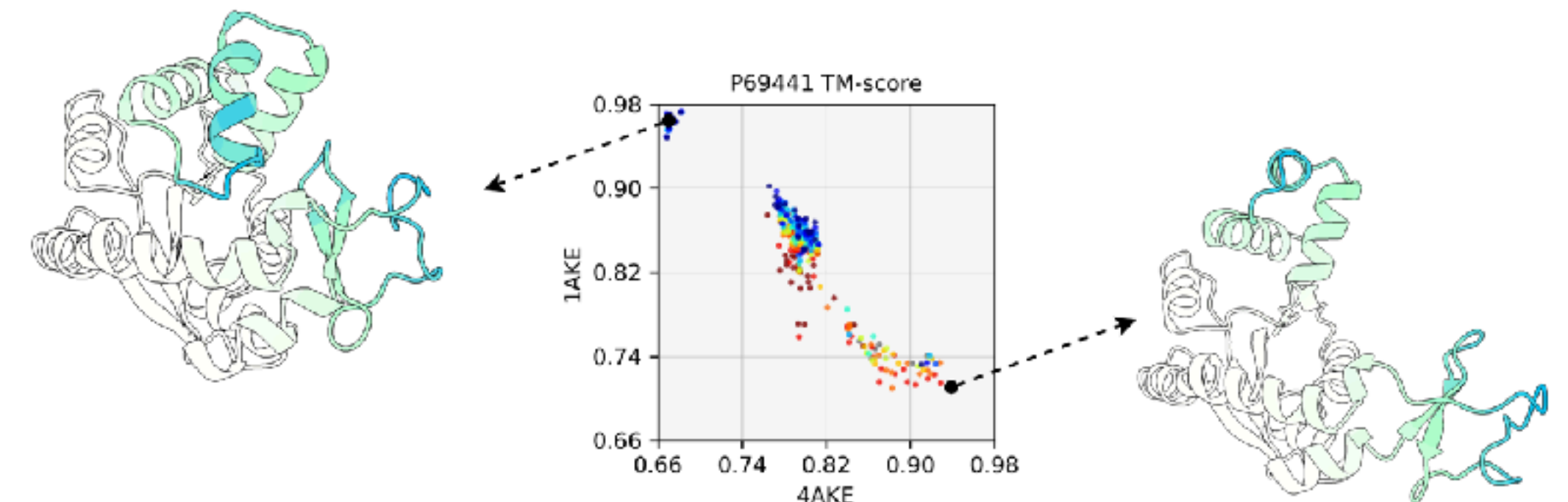
1032

**~5x
higher-rewards**

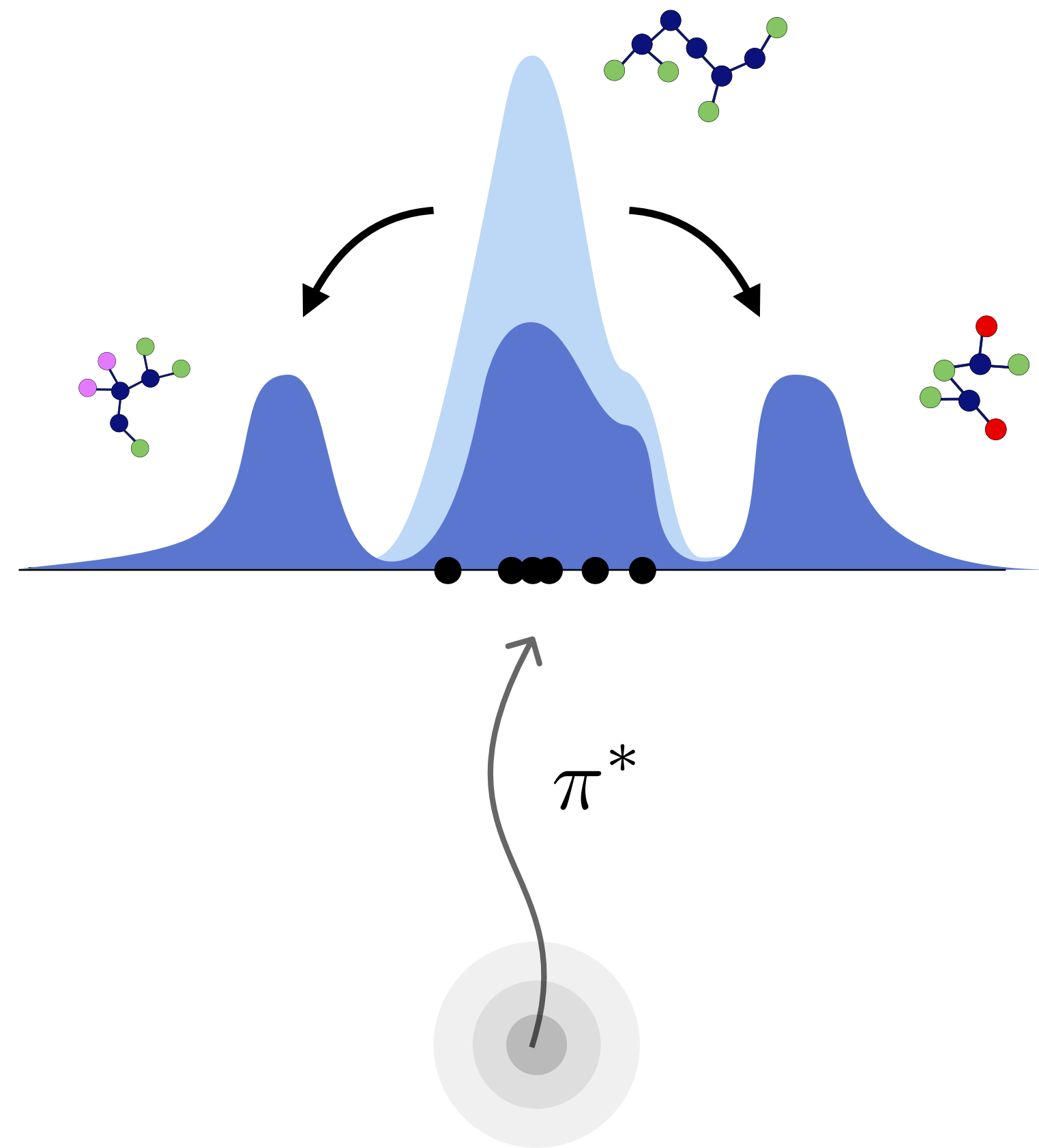
How to Adapt a Flow to Cover Diverse Modes?



Key Hypothesis: protein generative models learn valid low-probability modes often hidden under finite samples.



Flow Density Control for Entropic Expansion



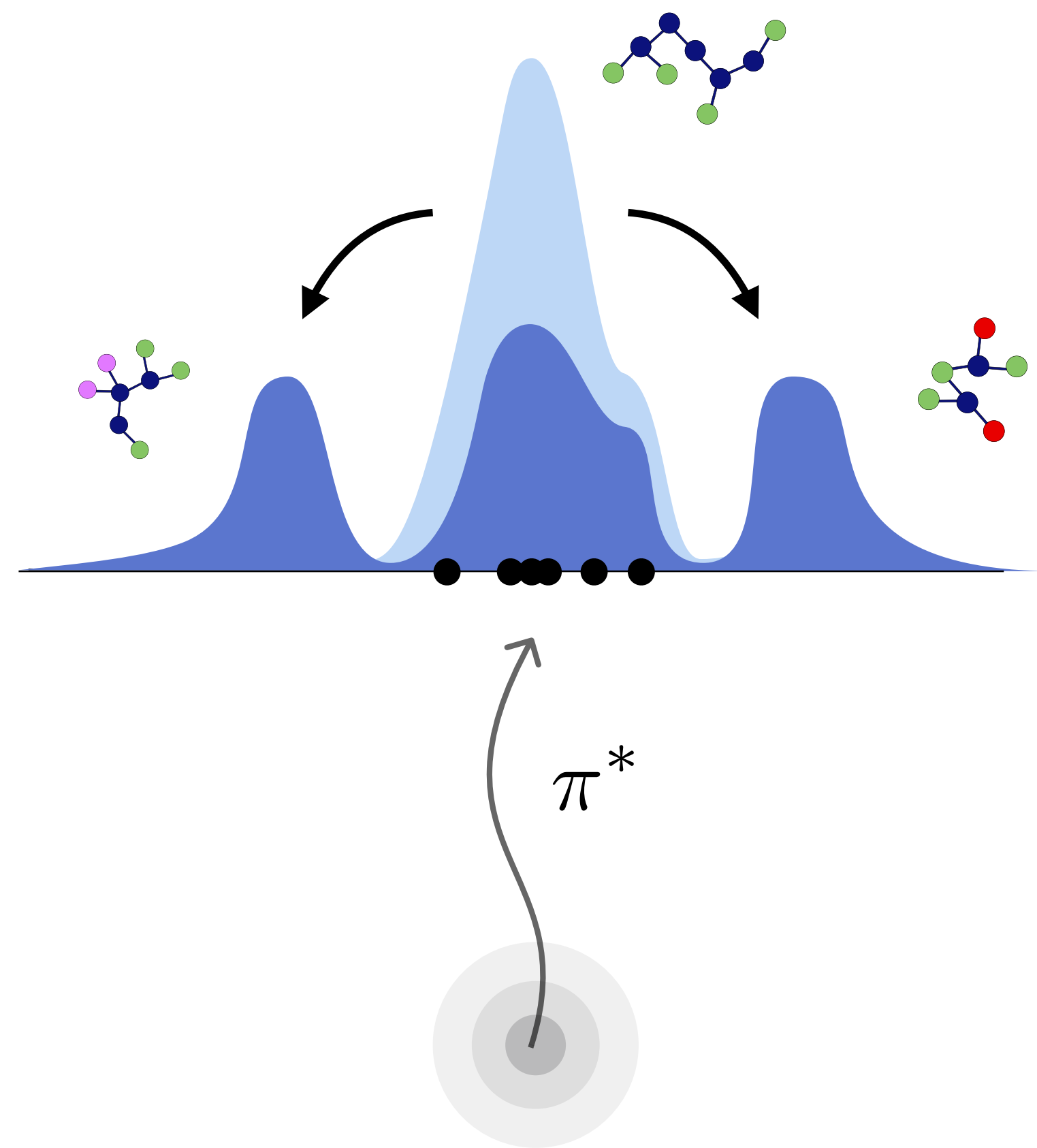
KL-regularized Entropic Expansion

$$\pi^* \in \operatorname{argmax}_{\pi} \mathcal{H}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

Increases diversity

Avoid invalid regions

Flow Density Control for Entropic Expansion



KL-regularized Entropic Expansion

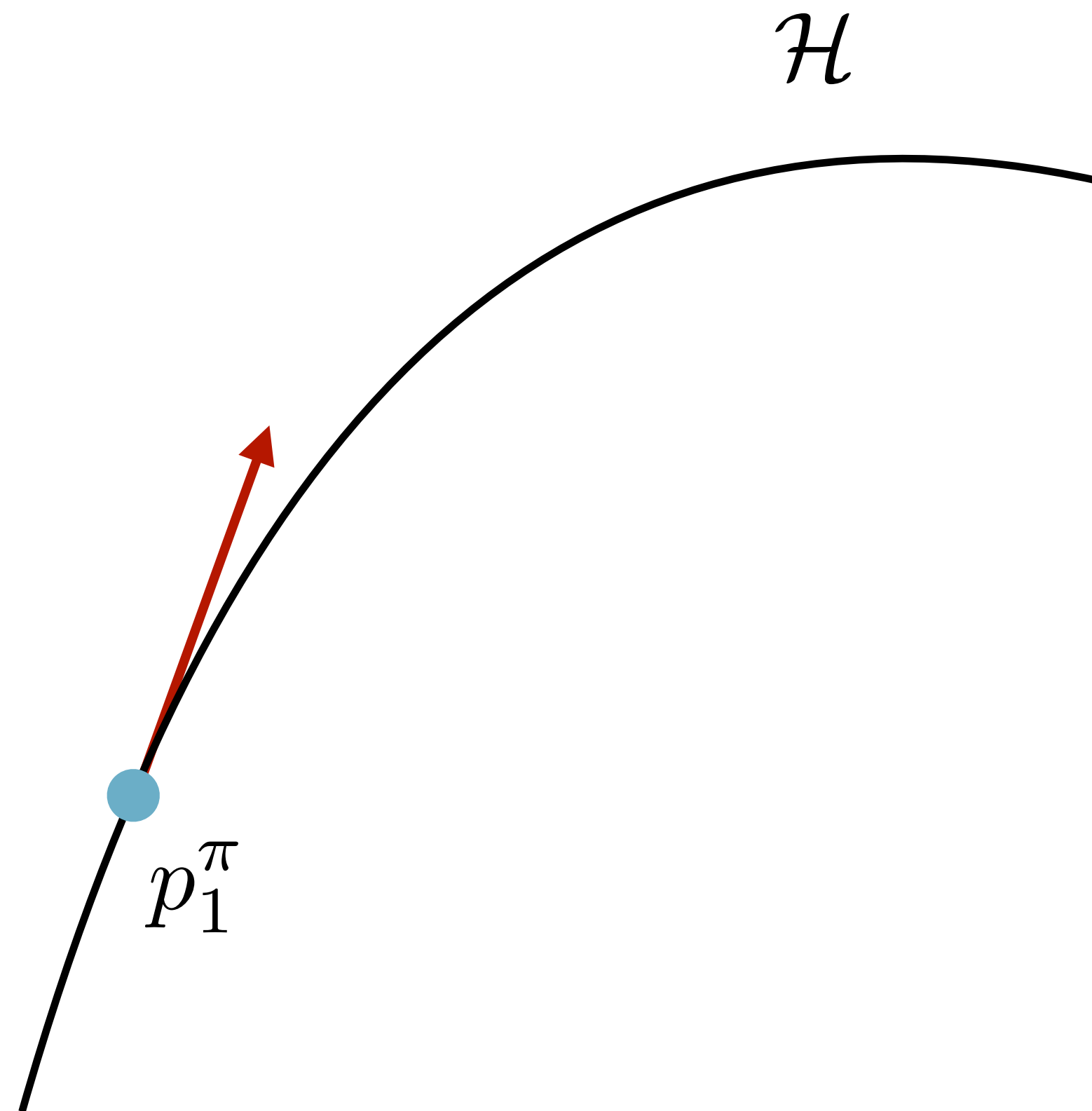
$$\pi^* \in \operatorname{argmax}_{\pi} \mathcal{H}(p_1^\pi) - \alpha \mathbf{KL}(p_1^\pi \parallel p_1^{pre})$$

Increases diversity

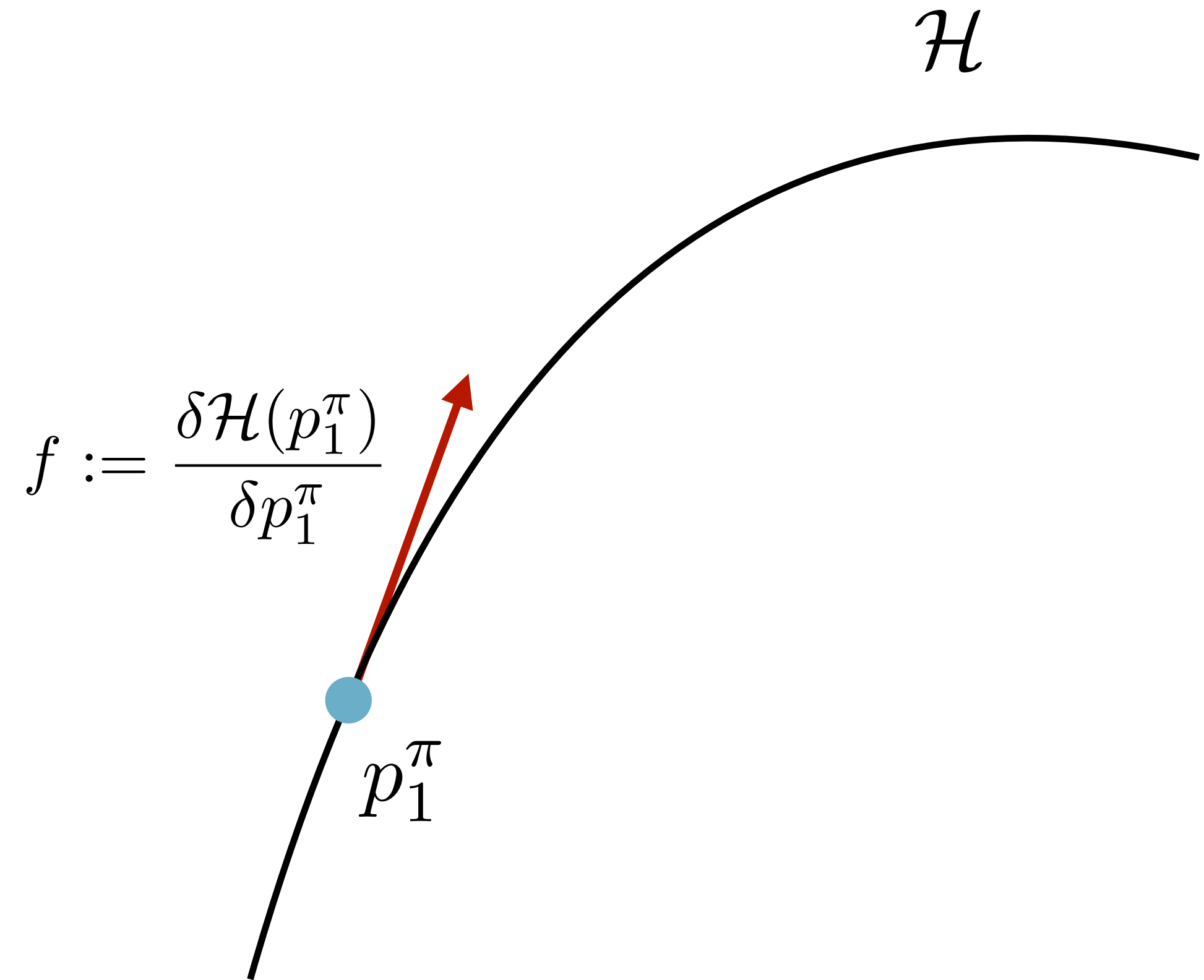
Avoid invalid regions

Entropy is a **non-linear** functional. **How to optimize?**

Flow Density Control (FDC)



Flow Density Control (FDC)

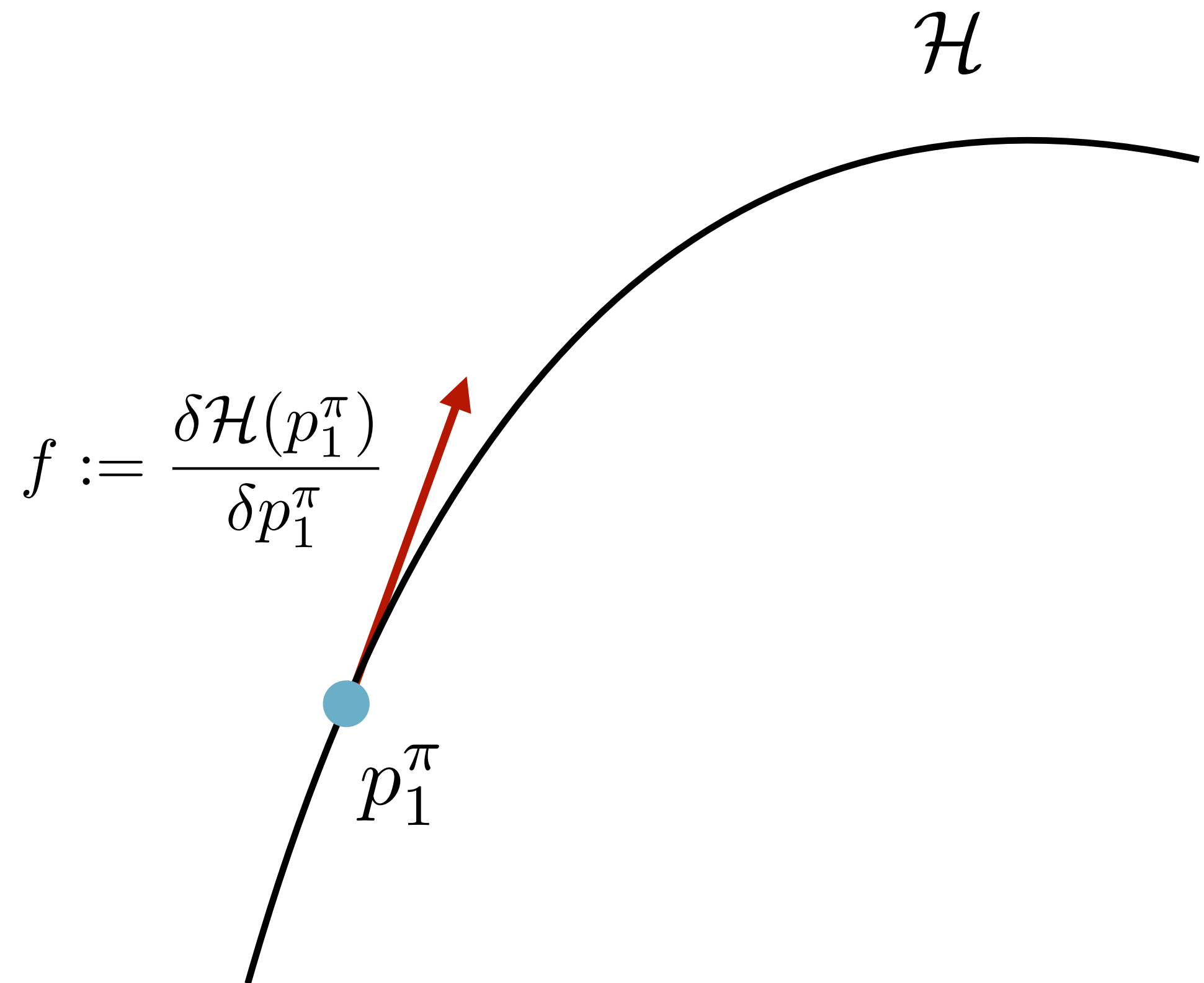


Entropy First Variation (Surprise)

$$f := \frac{\delta \mathcal{H}(p_1^\pi)}{\delta p_1^\pi} = -\log(p_1^\pi)$$

**surprise as intrinsic
reward function**

Flow Density Control (FDC)



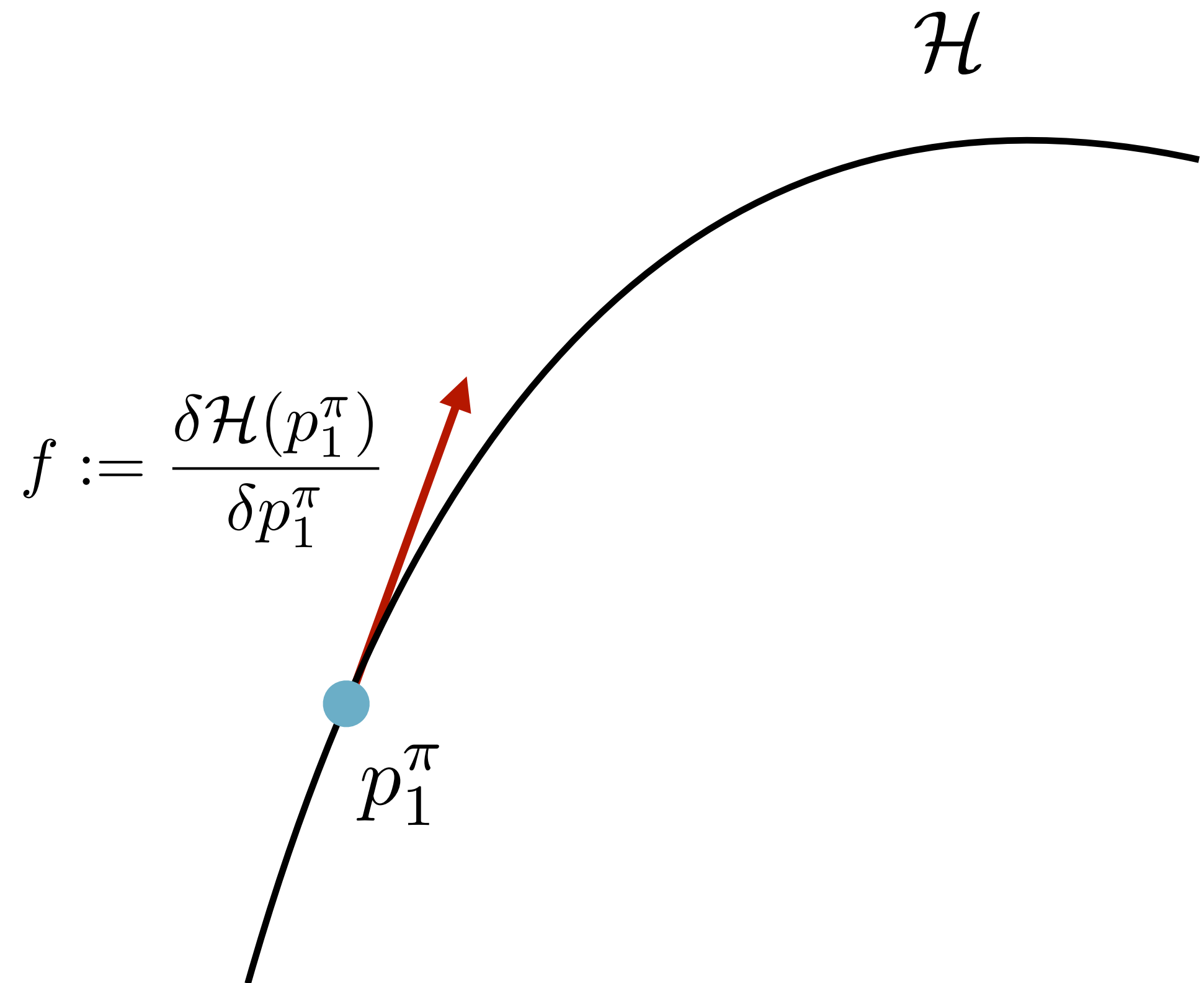
Entropy First Variation (Surprise)

$$f := \frac{\delta \mathcal{H}(p_1^\pi)}{\delta p_1^\pi} = -\log(p_1^\pi)$$

surprise as intrinsic
reward function

Log likelihoods are hard to estimate!
(currently does not scale)

Flow Density Control (FDC)



Entropy First Variation (Surprise)

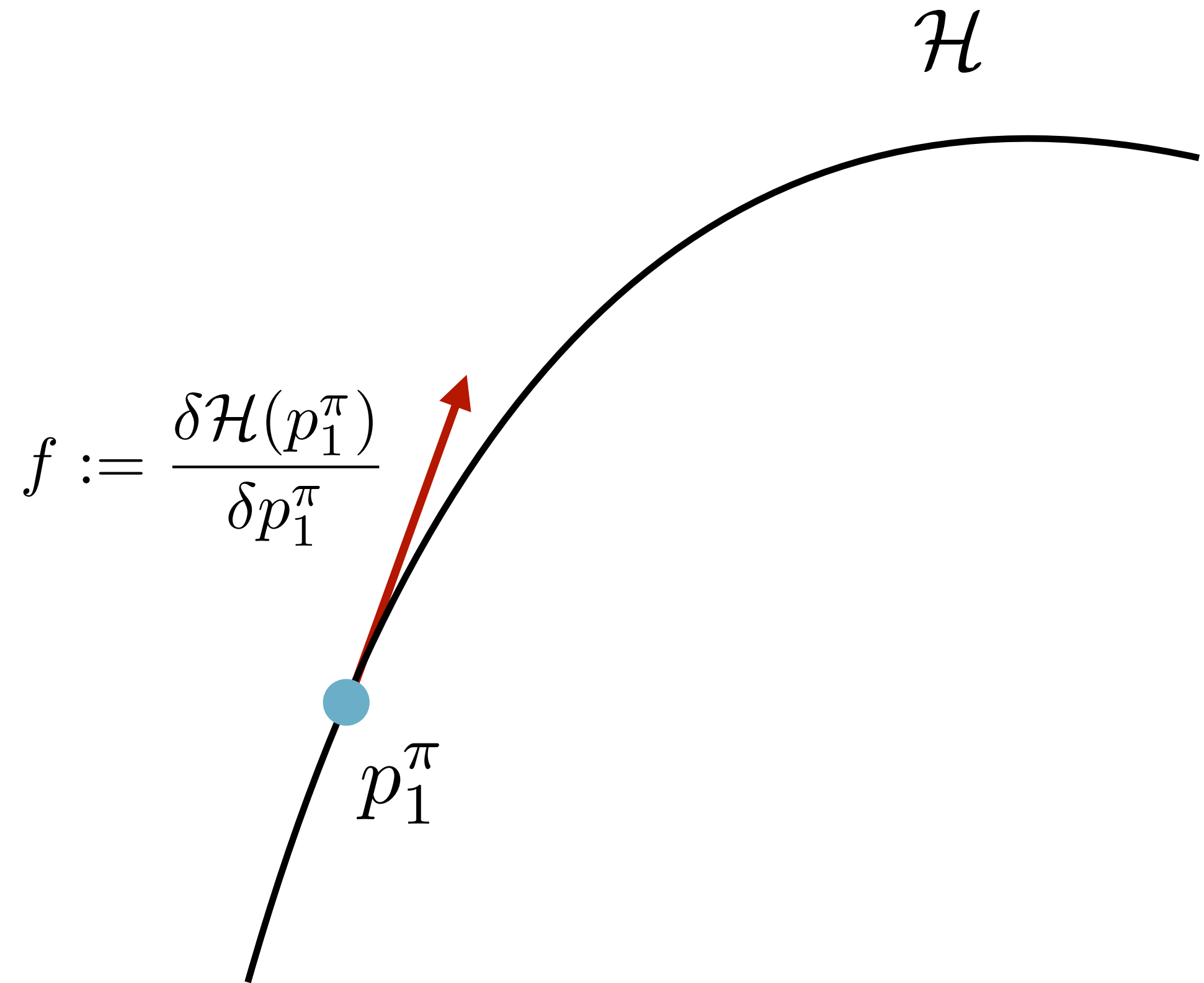
$$f := \frac{\delta \mathcal{H}(p_1^\pi)}{\delta p_1^\pi} = -\log(p_1^\pi)$$

surprise as intrinsic
reward function

Log likelihoods are hard to estimate!
(currently does not scale)

We can fully bypass log-likelihood estimation!

Flow Density Control (FDC)



Entropy First Variation (Surprise)

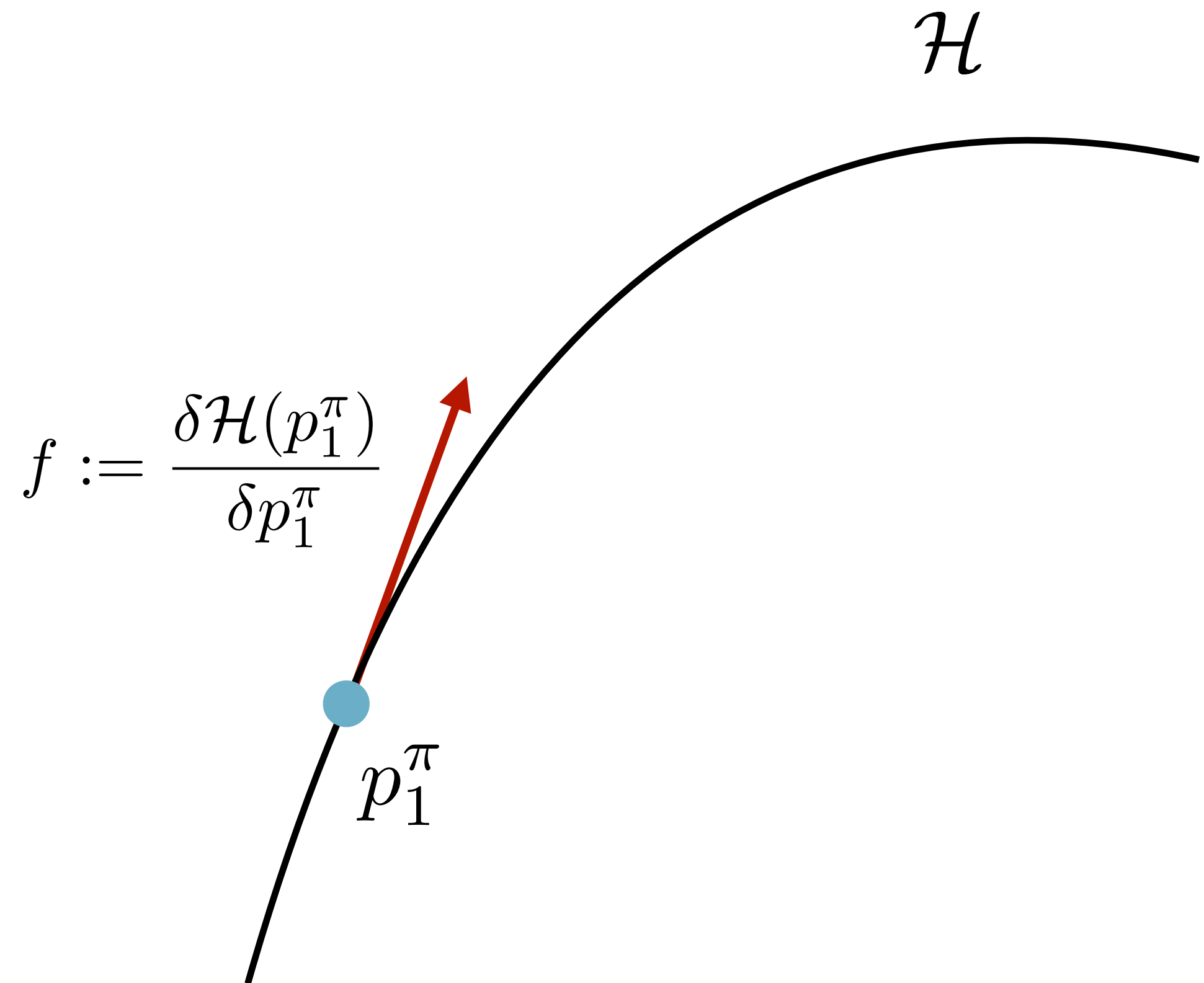
$$f := \frac{\delta \mathcal{H}(p_1^\pi)}{\delta p_1^\pi} = -\log(p_1^\pi)$$

**surprise as intrinsic
reward function**

Closed-form Gradient of Surprise

$$\nabla f = -\nabla \log(p_1^\pi)$$

Flow Density Control (FDC)



Entropy First Variation (Surprise)

$$f := \frac{\delta \mathcal{H}(p_1^\pi)}{\delta p_1^\pi} = -\log(p_1^\pi)$$

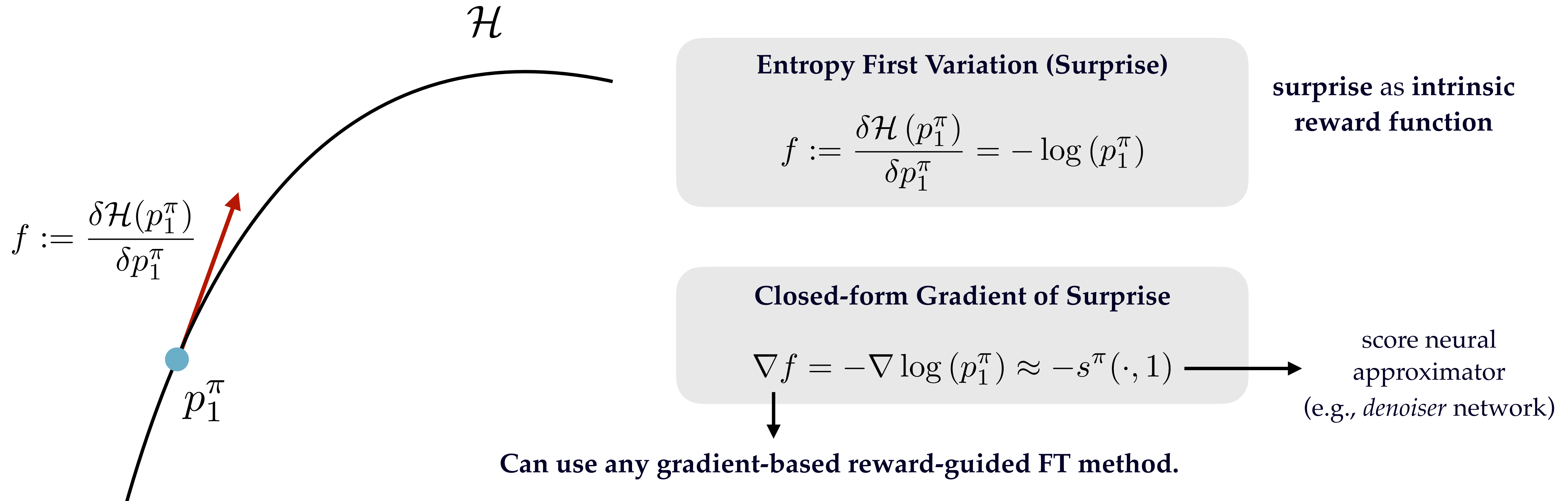
**surprise as intrinsic
reward function**

Closed-form Gradient of Surprise

$$\nabla f = -\nabla \log(p_1^\pi) \approx -s^\pi(\cdot, 1)$$

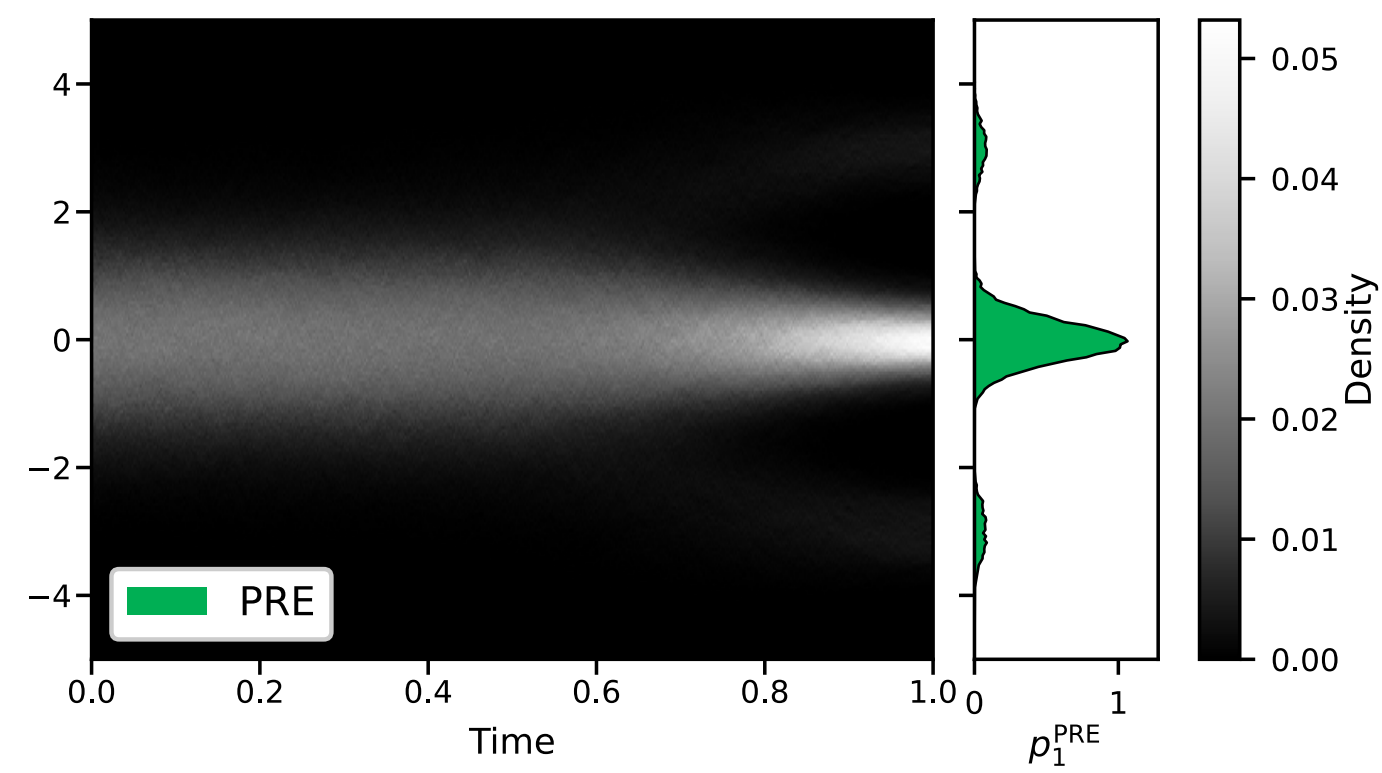
score neural
approximator
(e.g., *denoiser* network)

Flow Density Control (FDC)



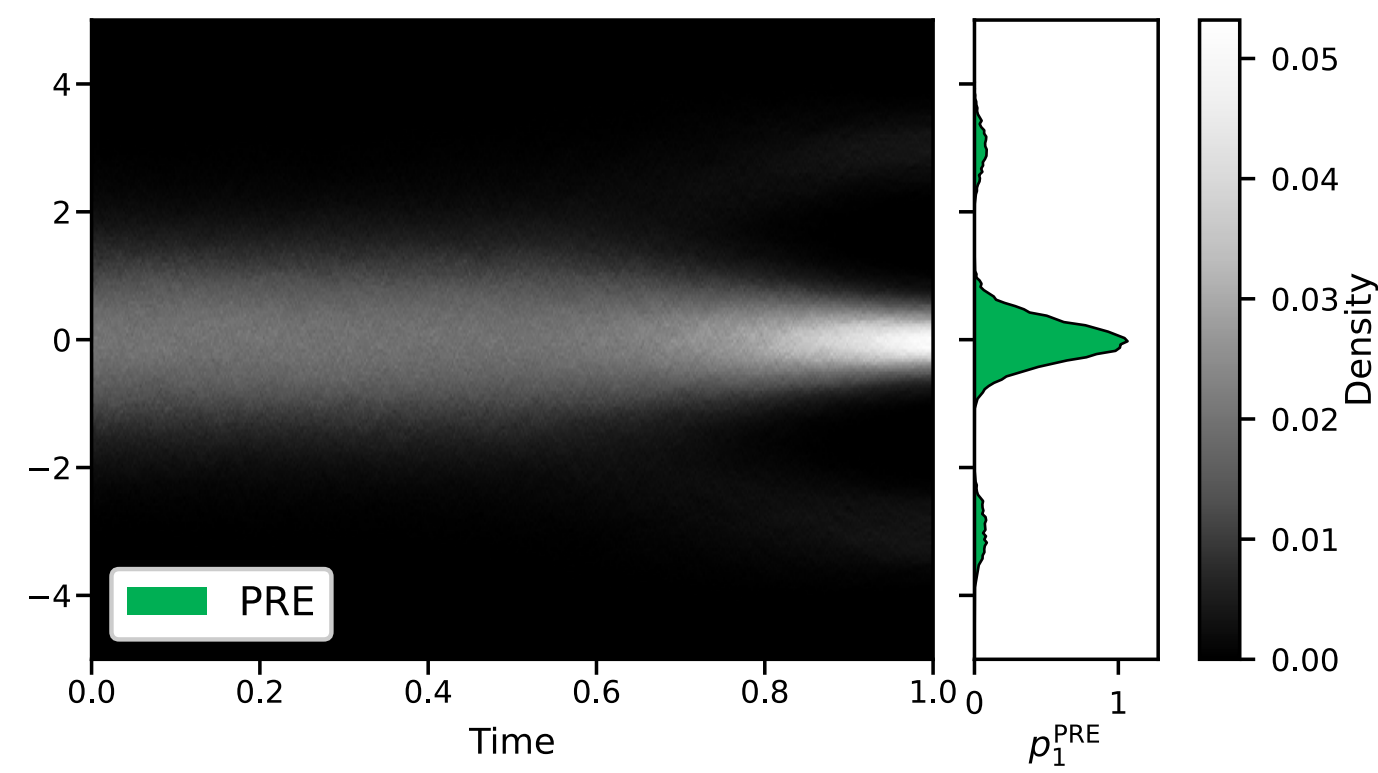
Key: linearizing entropy leads to intrinsic reward f (i.e. surprise) for standard RL fine-tuning

Pre-trained generative model



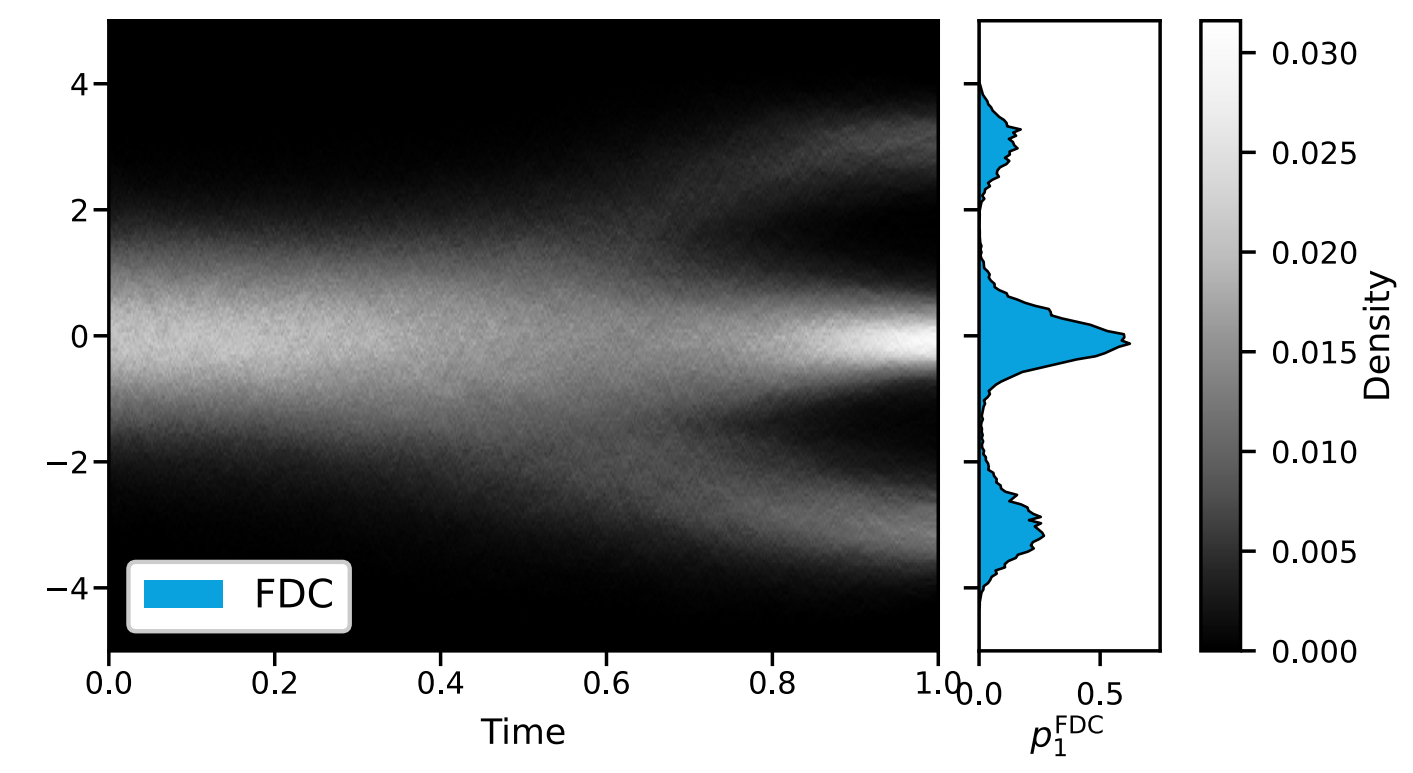
$$\mathbb{P}(\text{sample } x \text{ in main mode}) \approx 1$$

Pre-trained generative model



FDC

Expanded generative model

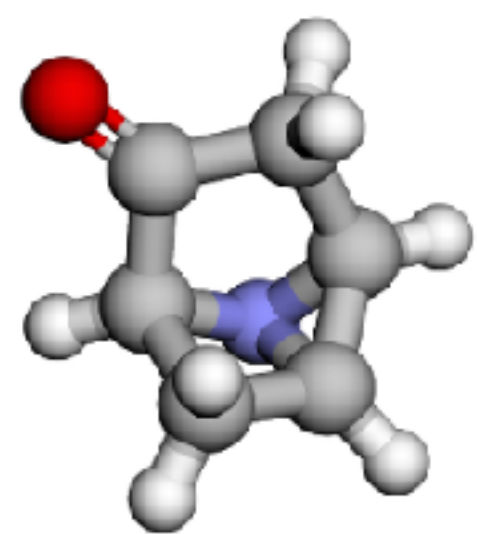
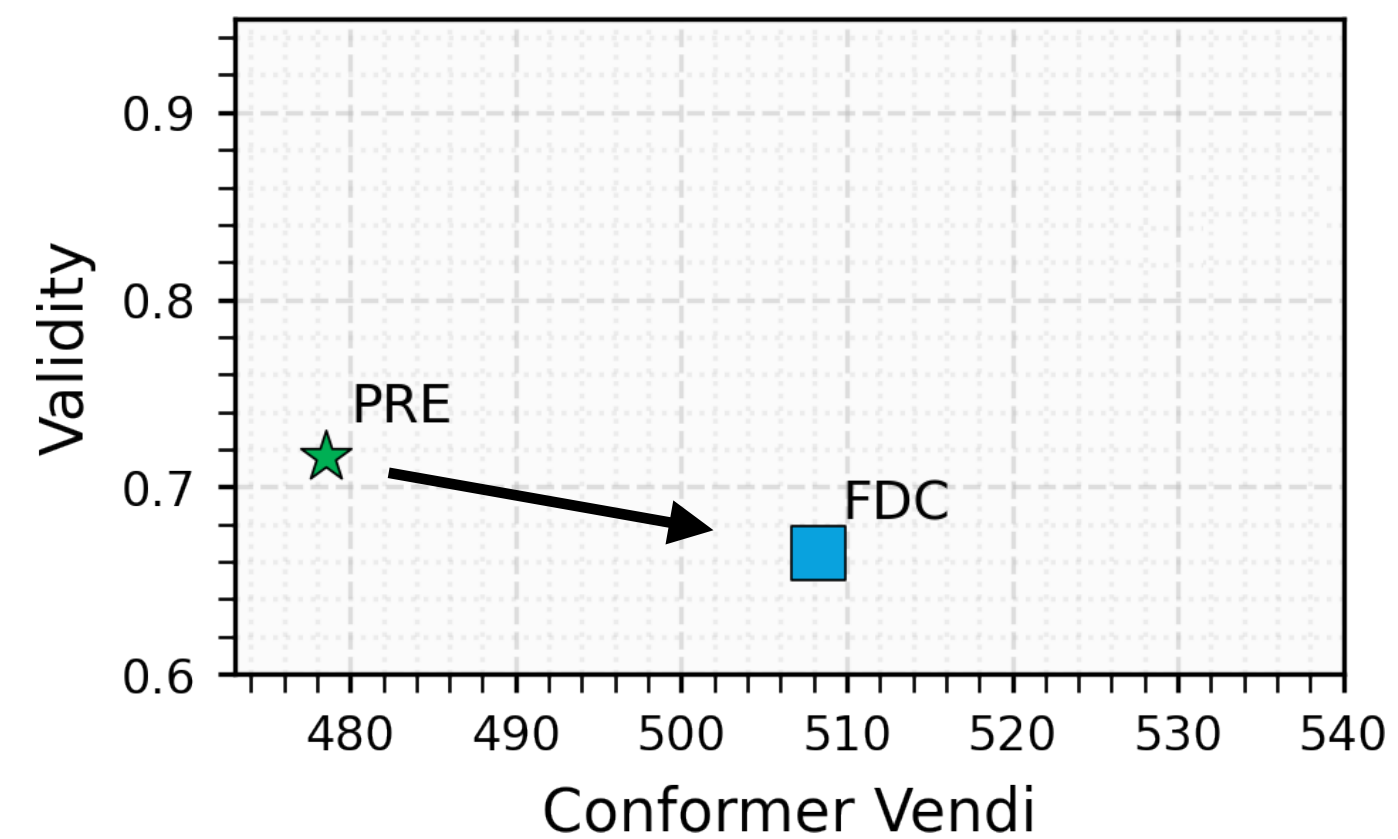


$$\mathbb{P}(\text{sample } x \text{ in main mode}) \approx 1$$

$$\mathbb{P}(\text{sample } x \text{ in main mode}) \approx 0.5$$

FDC for Molecule and Protein Design

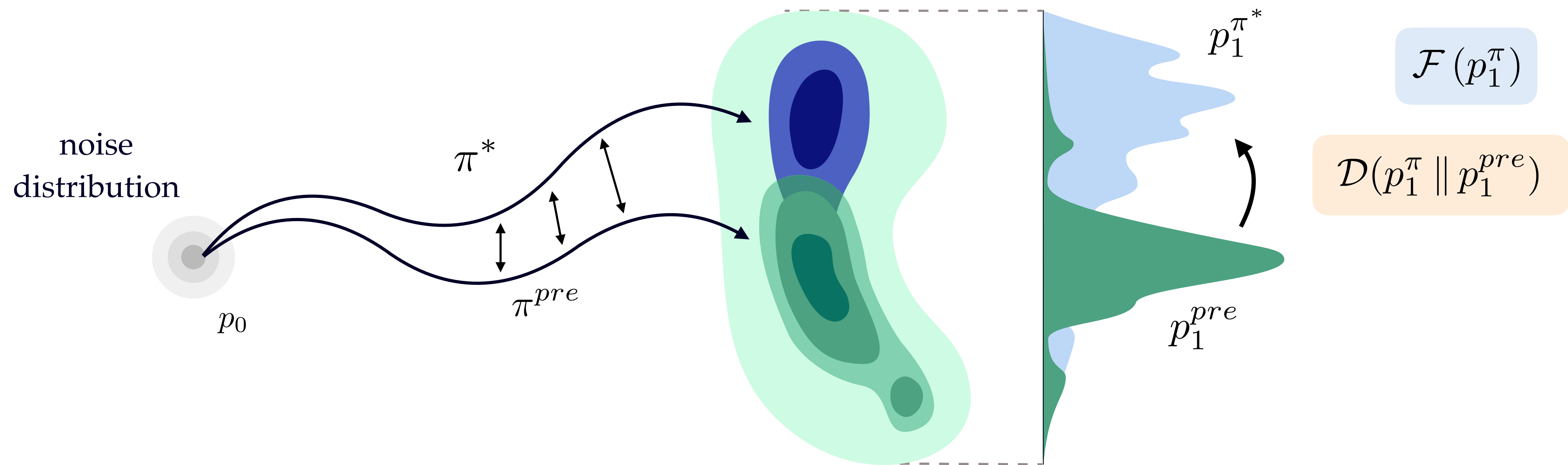
GEOM-Drugs



FDC achieves higher conformer diversity
of drug-like molecules

Flow Density Control for Distributional Fine-Tuning

Control of tail behavior is essential for discovery (e.g., diversity, tail-aware optimization)



How to represent new task?

$\mathcal{F}$

How to preserve prior information?

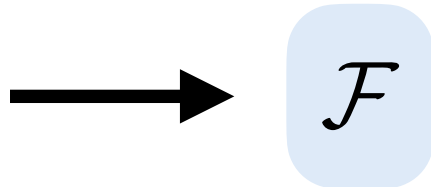
$\mathcal{D}$

Distributional Generative Optimization

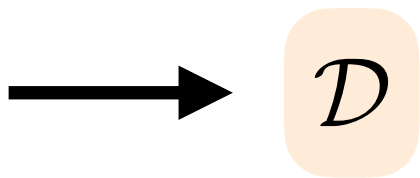
$$\pi^* \in \operatorname{argmax}_{\pi} \mathcal{F}(p_1^{\pi}) - \alpha \mathcal{D}(p_1^{\pi} || p_1^{pre})$$

Flow Density Control for Distributional Fine-Tuning

How to represent new task?



How to preserve prior information?



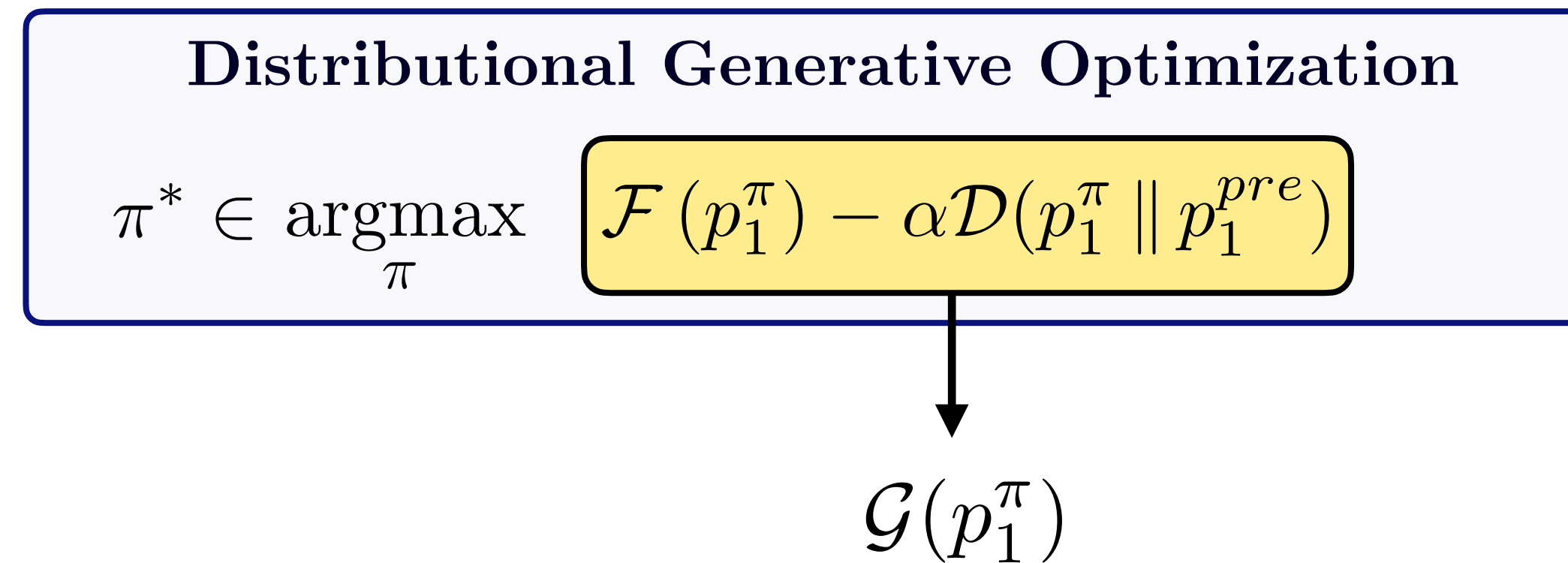
APPLICATION	FUNCTIONAL $\mathcal{F} / \mathcal{D}$	LINEAR GO	NON-LINEAR GO	
			CONVEX	GENERAL
REWARD OPTIMIZATION [14, 55]	$\mathbb{E}_{x \sim p^\pi} [r(x)]$	✓	✓	✓
MANIFOLD EXPLORATION [12] GEN. MODEL DE-BIASING	$\mathcal{H}(p^\pi) := - \mathbb{E}_{x \sim p^\pi} [\log p^\pi(x)]$	✗	✓	✓
RISK-AVERSE OPTIMIZATION	$\text{CVaR}_\beta^r(p^\pi) := \mathbb{E}_{x \sim p^\pi} [r(x) \mid r(x) \leq q_\beta^r(p^\pi)]$	✗	✓	✓
	$\mathbb{E}_{x \sim p^\pi} [r(x)] - \text{Var}(p^\pi)$	✗	✗	✓
NOVELTY-SEEKING OPTIMIZATION	$\text{SQ}_\beta^r(p^\pi) := \mathbb{E}_{x \sim p^\pi} [r(x) \mid r(x) \geq q_\beta^r(p^\pi)]$	✗	✗	✓
OPTIMAL EXPERIMENT DESIGN	$s \left(\mathbb{E}_{x \sim p^\pi} [\Phi(x) \Phi(x)^\top - \lambda \mathbb{I}] \right)$	✗	✓	✓
	$s(\cdot) \in \{\log \det(\cdot), -\text{Tr}(\cdot)^{-1}, -\lambda_{\max}(\cdot)\}$			
DIVERSE MODES DISCOVERY	$-\mathbb{E}_z [D_{KL}(p^{\pi,z} \parallel \mathbb{E}_k p^{\pi,k})]$	✗	✗	✓
LOG-BARRIER CONSTRAINED GENERATION	$\mathbb{E}_{x \sim p^\pi} [r(x)] - \beta \log (\langle p^\pi, c \rangle - C)$	✗	✓	✓
KULLBACK-LEIBLER DIVERGENCE [14, 55]	$D_{KL}(p^\pi \parallel p^{pre}) = \int p^\pi(x) \log \frac{p^\pi(x)}{p^{pre}(x)} dx$	✓	✓	✓
RÉNYI DIVERGENCES	$D_\beta(p^\pi \parallel p^{pre}) := \frac{1}{\beta - 1} \log \int (p^\pi(x))^\beta (p^{pre})^{1-\beta} dx$	✗	✗	✓
OPTIMAL TRANSPORT DISTANCES	$W_p(p^\pi \parallel p^{pre}) := \inf_{\gamma \in \Gamma(p^\pi, p^{pre})} \mathbb{E}_{(x,y) \sim \gamma} [d(x,y)^p]^{\frac{1}{p}}$	✗	✗	✓
MAXIMUM MEAN DISCREPANCY	$\text{MMD}_k(p^\pi \parallel p^{pre}) := \ \mu_{p^\pi} - \mu_{p^{pre}}\ , \mu_p := \mathbb{E}_{x \sim p} [k(x, \cdot)]$	✗	✓	✓

Flow Density Control: Theoretical Guarantees

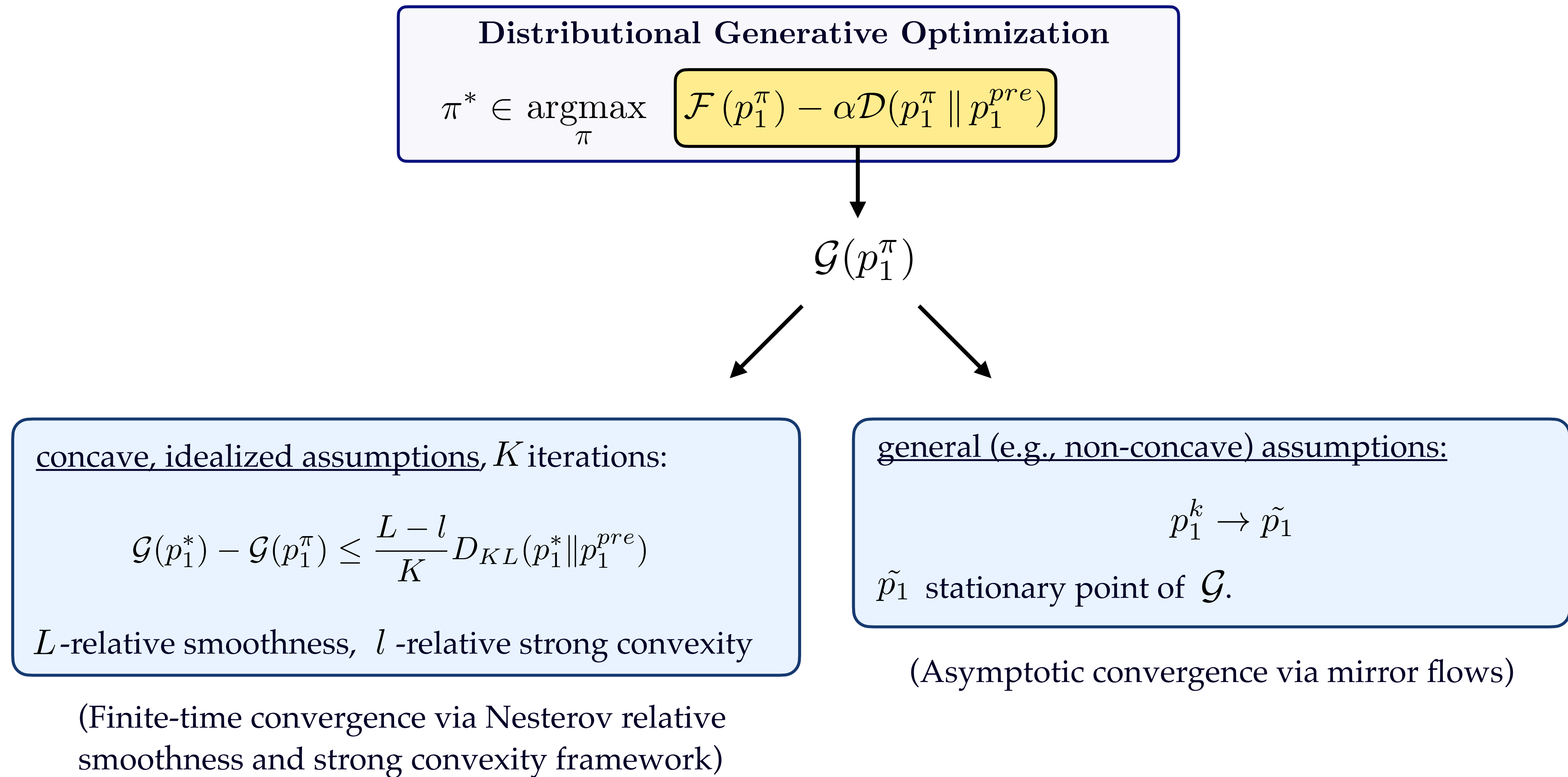
Distributional Generative Optimization

$$\pi^* \in \operatorname{argmax}_{\pi} \mathcal{F}(p_1^\pi) - \alpha \mathcal{D}(p_1^\pi \parallel p_1^{pre})$$

Flow Density Control: Theoretical Guarantees



Flow Density Control: Theoretical Guarantees



Flow Density Control: Generative Optimization Beyond Entropy-Regularized Fine-Tuning

[Riccardo De Santi, Marin Vlastelica, Ya-Ping Hsieh, Zebang Shen, Niao He, Andreas Krause]

Spotlight NeurIPS 2025 **Oral** at ICML 2025 BioGen Workshop

Efficient Tail-Aware Generative Optimization via Flow Model Fine-Tuning

[Zifan Wang, Riccardo De Santi, Xiaoyu Mo, and Michael M. Zavlanos, Andreas Krause, Karl H. Johansson]

ICML 2026

Provable Maximum Entropy Manifold Exploration via Diffusion Models

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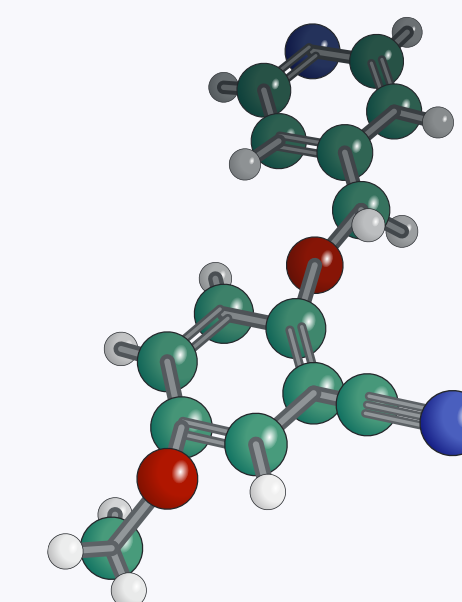
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ICML 2026

Provable Maximum Entropy Manifold Exploration via Diffusion Models

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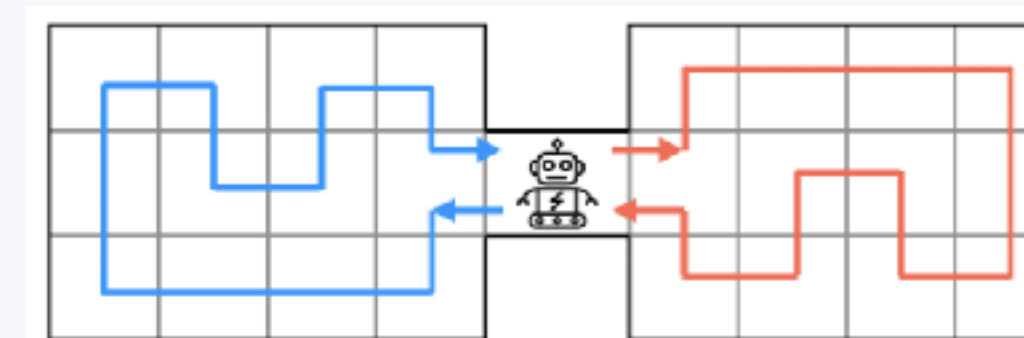
ICML 2025



The Importance of Non-Markovianity in Maximum State Entropy Exploration

[Mirco Mutti*, Riccardo De Santi*, and Marcello Restelli]

Outstanding Paper Award at ICML 2022



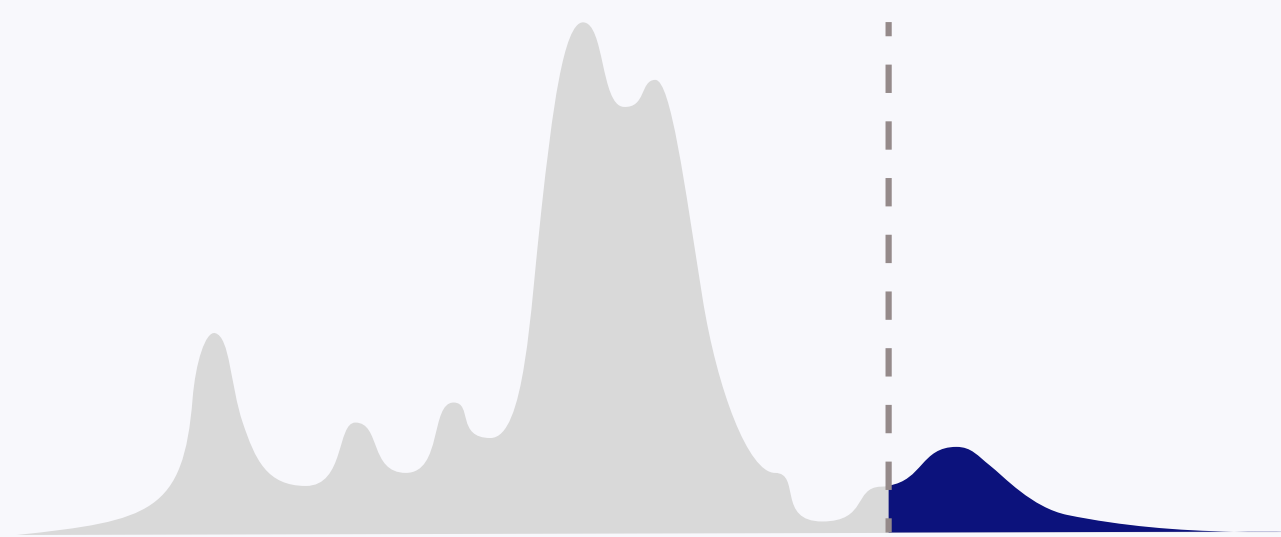
This talk:

Generative Discovery Beyond the Data

Part I

Rare and Diverse
Generation

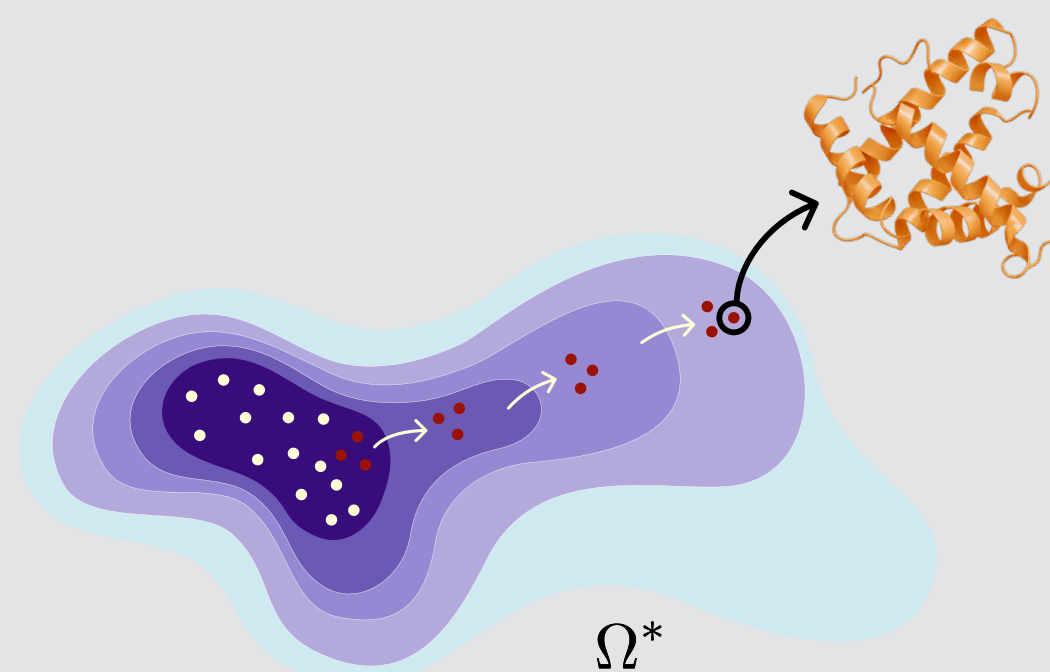
Which candidates matter?



Part II

Out-of-Distribution Flow
Modeling

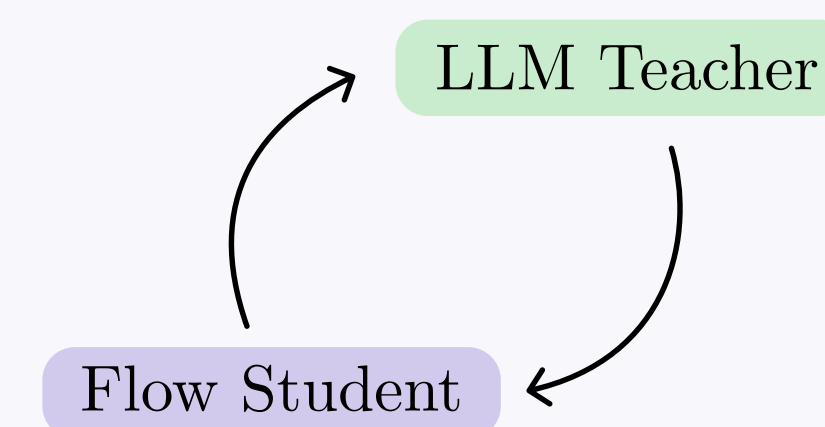
Which regions can we reach?



Part III

Sample-Efficient Discovery
via LLM Feedback

What feedback guides us there?



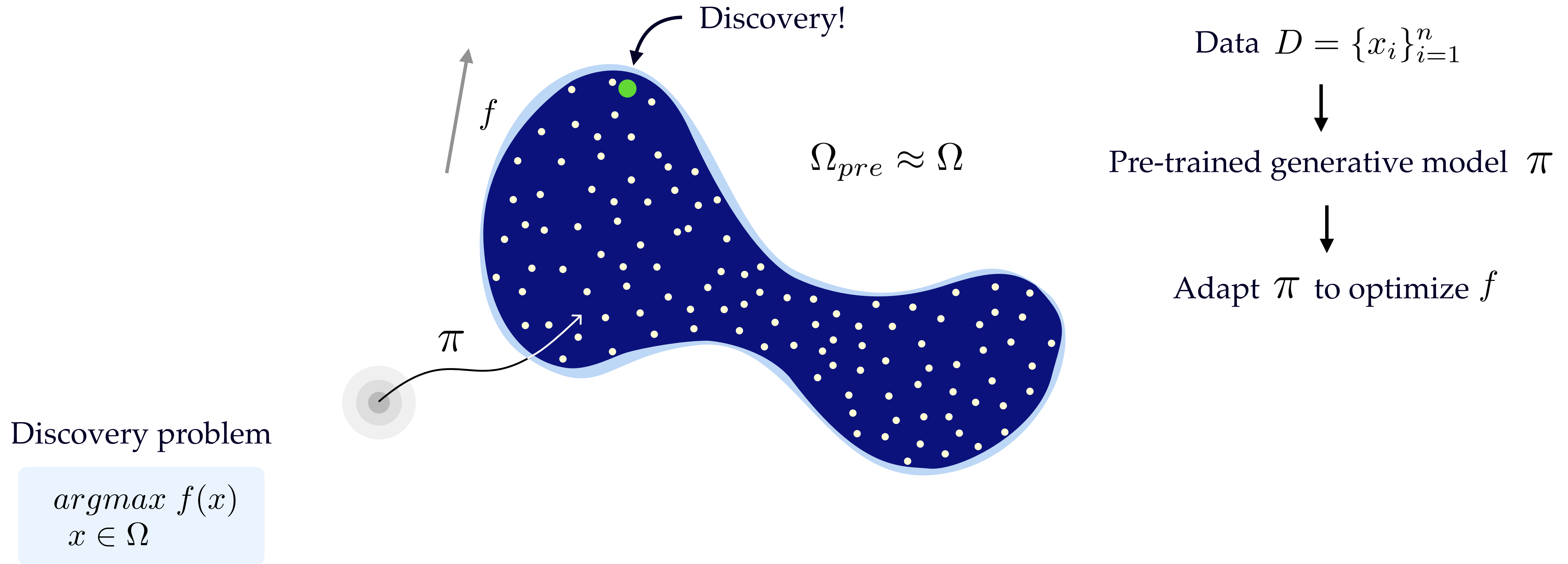
Active Flow Expansion for Out-of-Distribution Discovery: from Theory to Molecules

[Riccardo De Santi, Bruce Lee, Cristian Perez Jensen, Kimon Protopapas, Sophia Tang, Cheng-Hao Liu, Pranam Chatterjee, Yisong Yue, Andreas Krause]

NeurIPS 2026

The Dream: Discovery via Generative Optimization

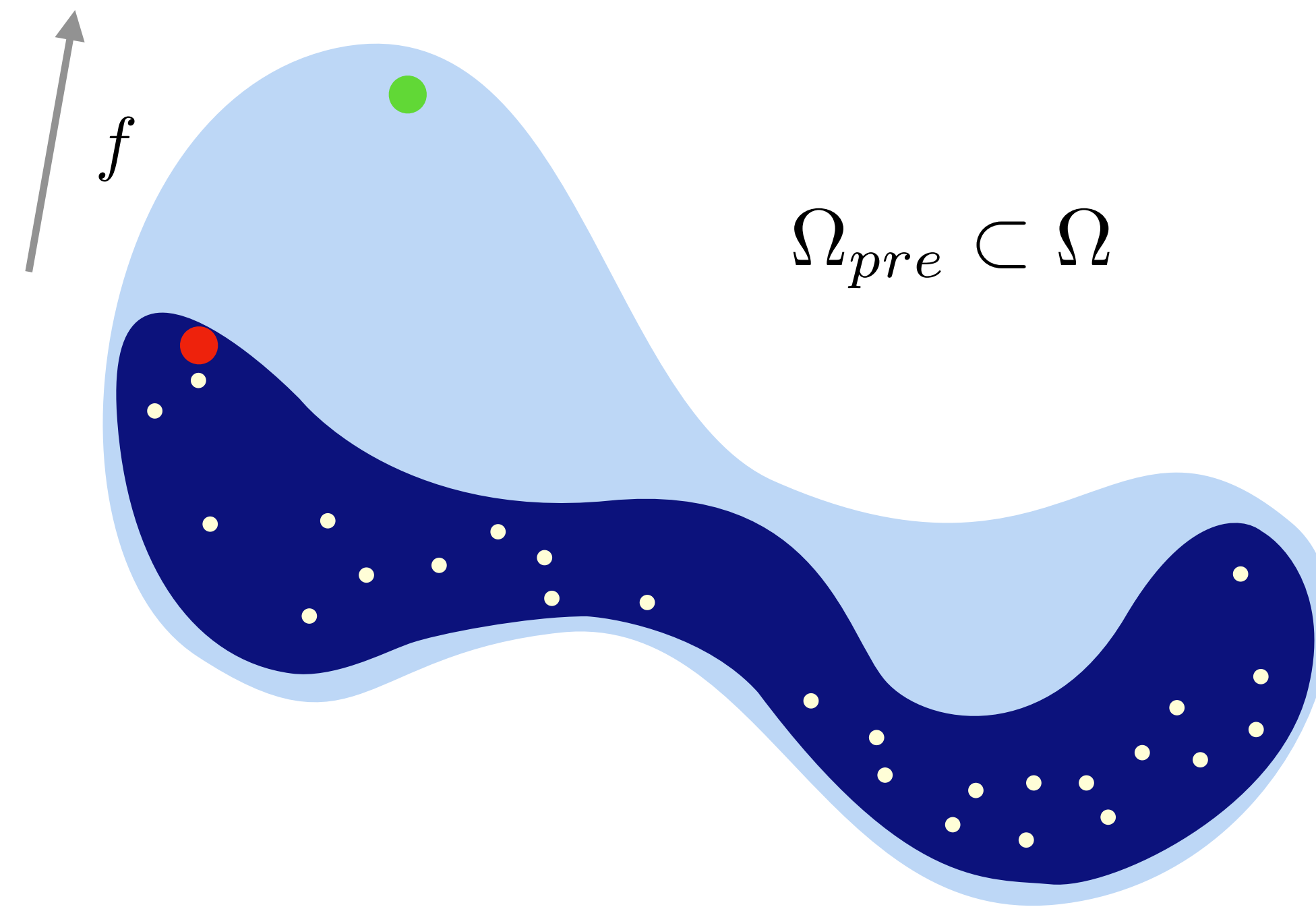
● valid design space Ω ● generable set of pre-trained gen. model Ω_{pre}



The Reality: Generative Optimization Limitation

● valid design space Ω

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



Generative models
generalize locally over
training data.

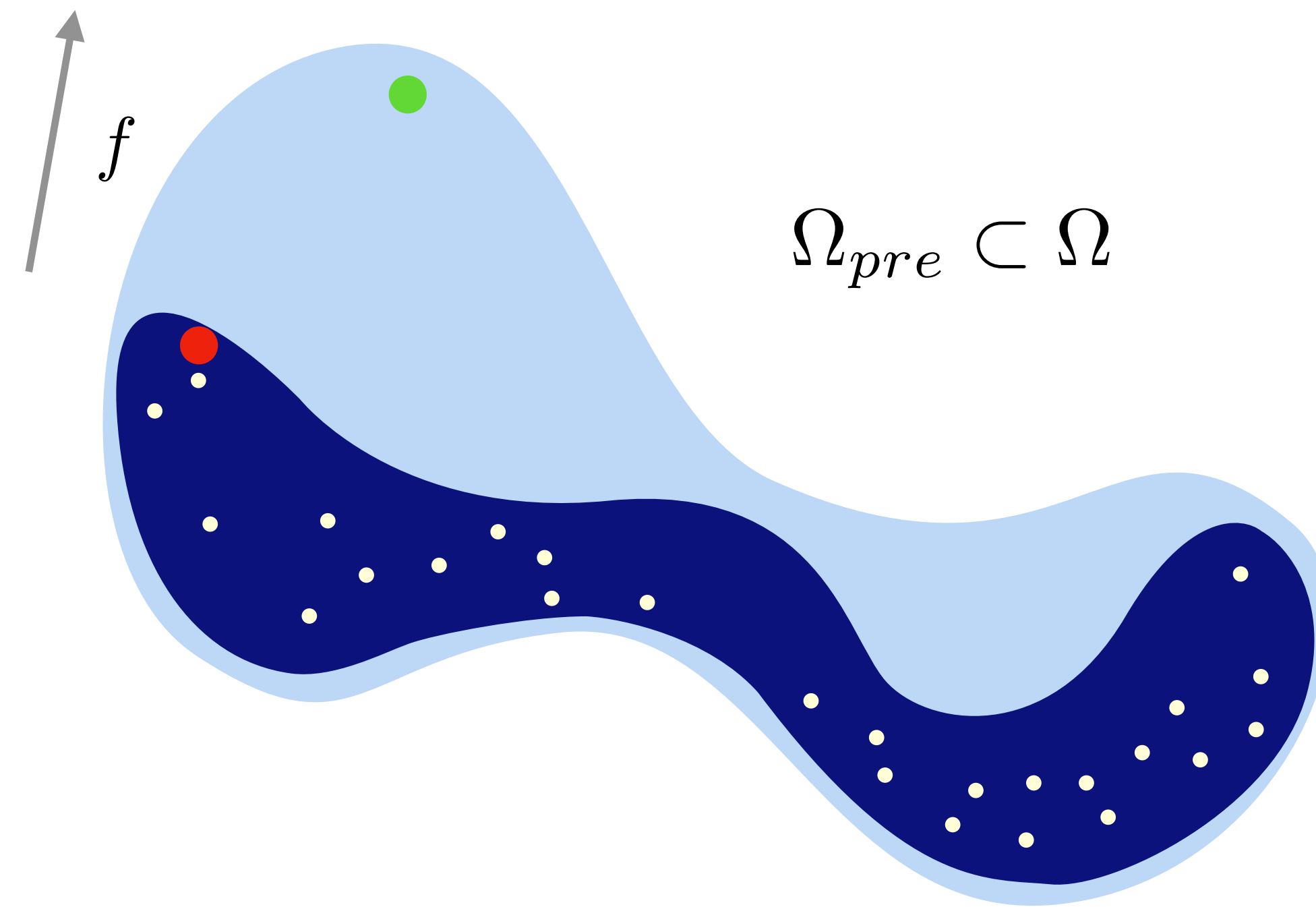
Discovery problem

$$\begin{aligned} & \operatorname{argmax} f(x) \\ & x \in \Omega \end{aligned}$$

The Reality: Generative Optimization Limitation

● valid design space Ω

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



Discovery problem

$$\begin{aligned} \operatorname{argmax} \quad & f(x) \\ \text{s.t.} \quad & x \in \Omega \end{aligned}$$

Generative models
generalize locally over
training data.

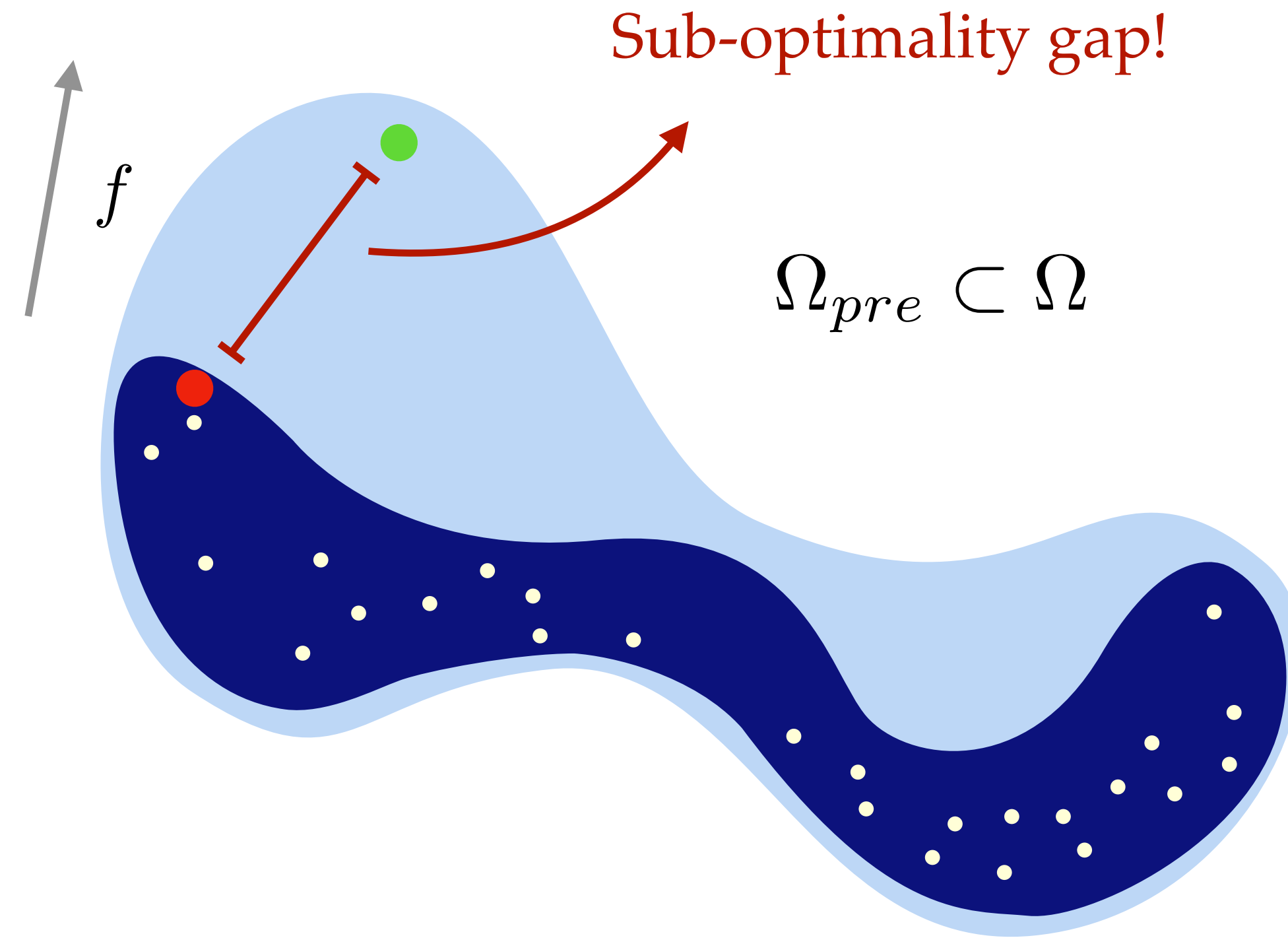
Especially in natural sciences:

E.g.,

- Chemistry
- Biology
- Physics

The Reality: Generative Optimization Limitation

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

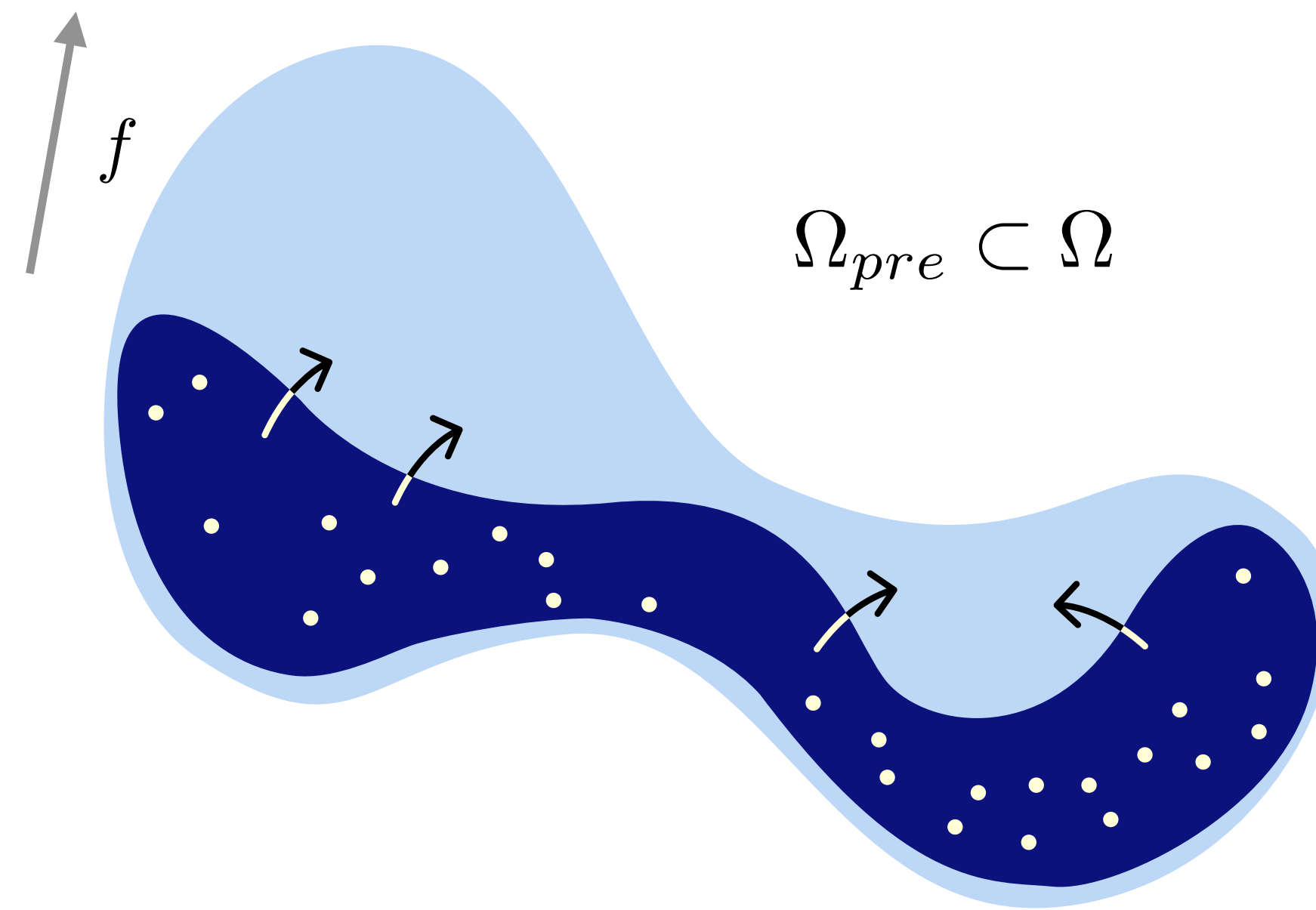


Discovery problem

$$\begin{aligned} & \operatorname{argmax} f(x) \\ & x \in \Omega \end{aligned}$$

Generative discovery entails a new exploration problem

$$\operatorname{argmax}_{x \in \Omega} f(x)$$



Generative discovery entails a new exploration problem

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

Generative discovery entails a new exploration problem

$$\operatorname{argmax}_{x \in \Omega} f(x)$$

classic optimization
(e.g., convex optimization)

f known

Ω known

Generative discovery entails a new exploration problem

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

classic optimization
(e.g., convex optimization)

f known

Ω known

decision-making
(e.g., bandits, BO, RL)

f learned

Ω known

Generative discovery entails a new exploration problem

$$\operatorname{argmax}_{x \in \Omega} f(x)$$

classic optimization
(e.g., convex optimization)

f known

Ω known

decision-making
(e.g., bandits, BO, RL)

f learned

Ω known

generative discovery
(e.g., drug design)

f learned

Ω learned

Generative discovery entails a new exploration problem

$$\operatorname{argmax}_{x \in \Omega} f(x)$$

classic optimization
(e.g., convex optimization)

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Ω known

decision-making
(e.g., bandits, BO, RL)

f learned

Ω known

generative discovery
(e.g., drug design)

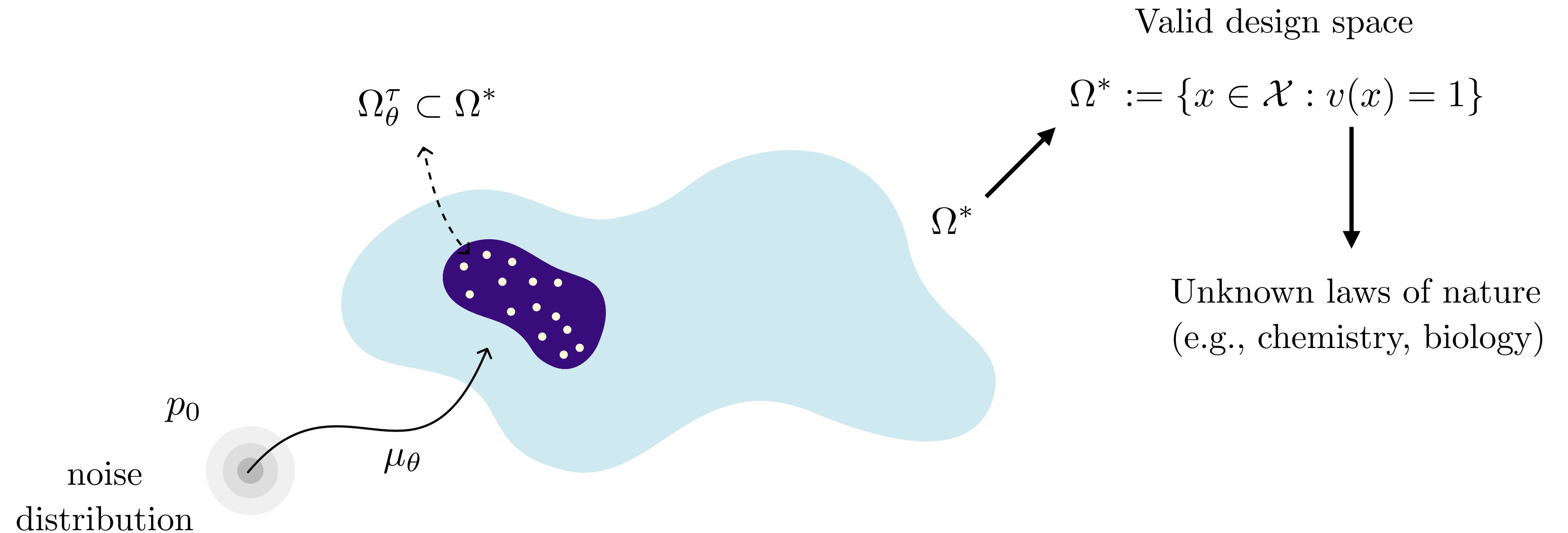
f learned

Ω learned

Takeaway

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

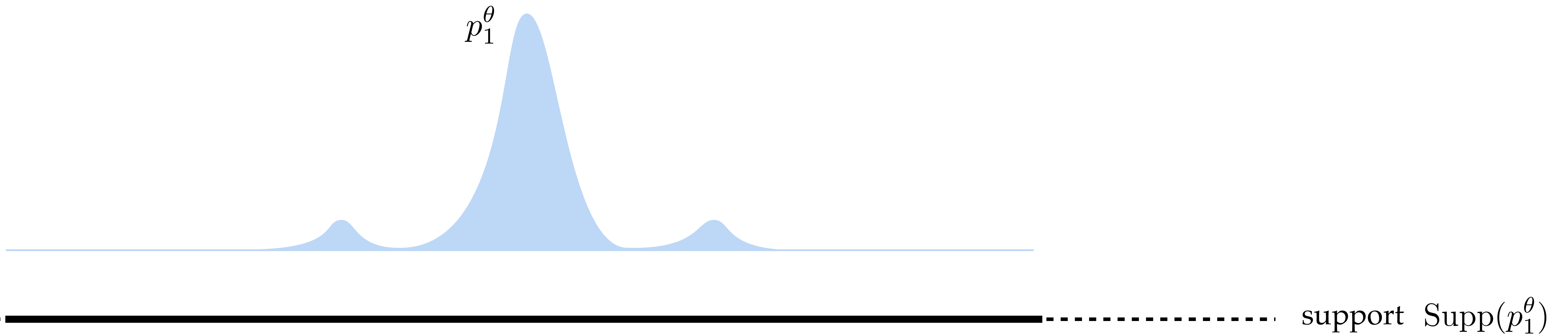
Out-of-Distribution Flow Modeling



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

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

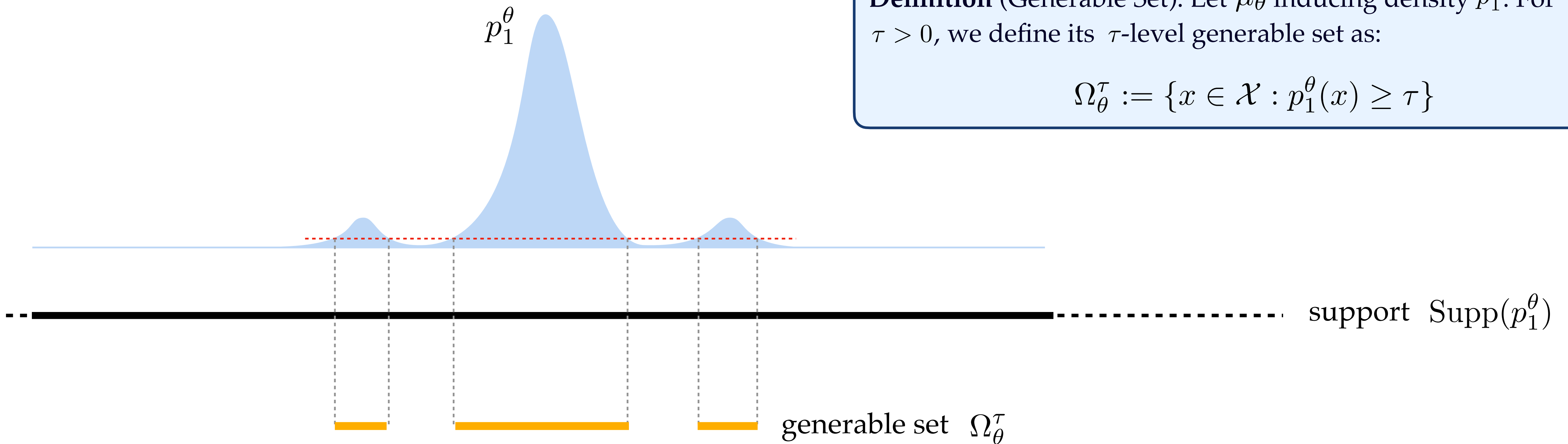
Generable Set vs Support



Generable Set vs Support

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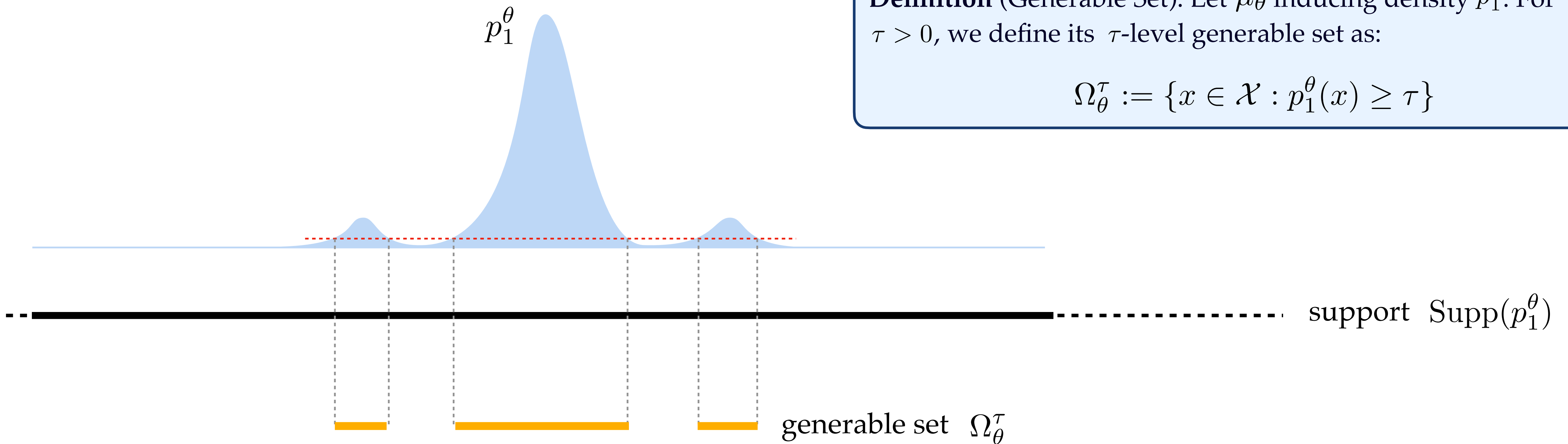
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Generable Set vs Support

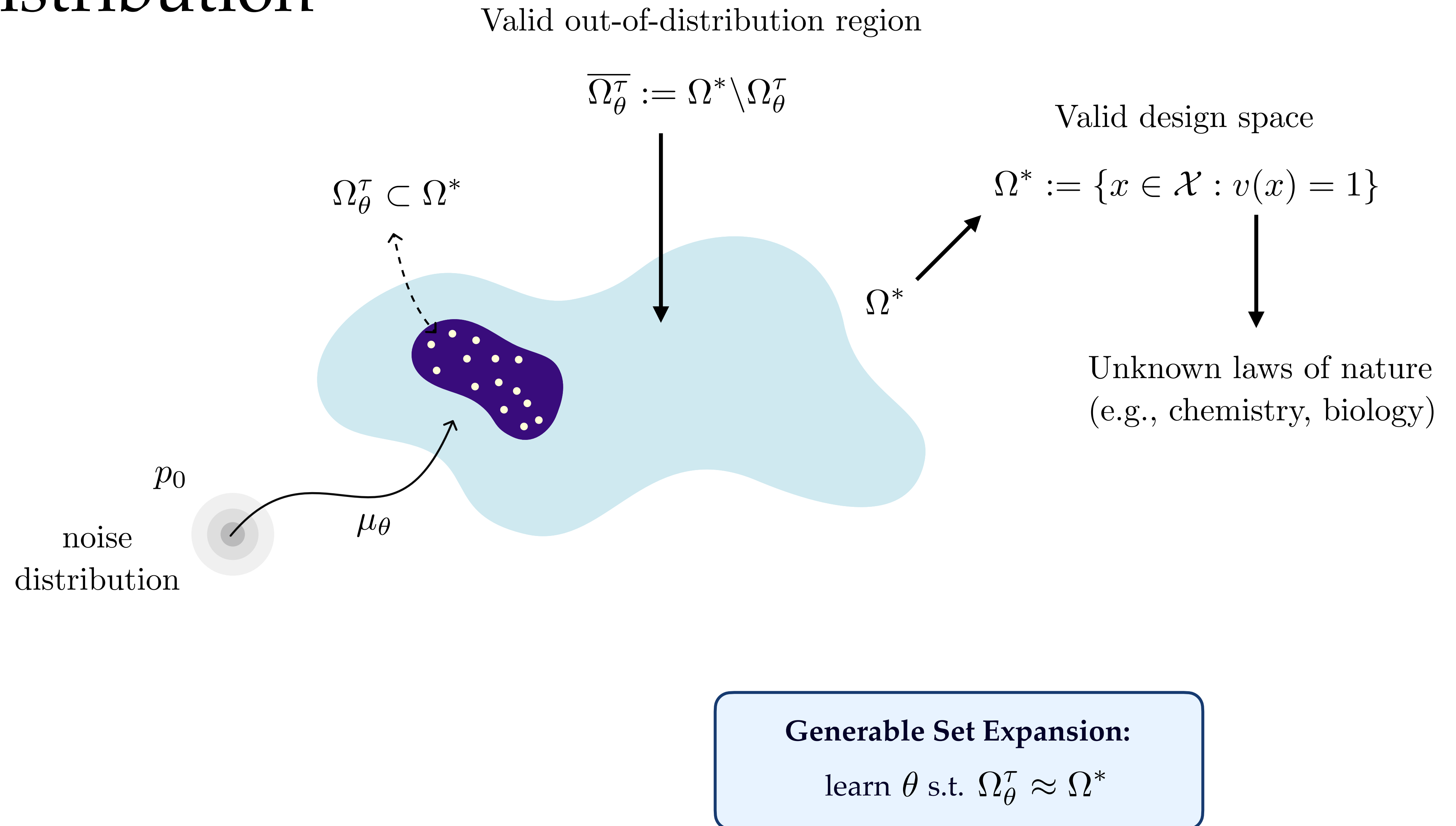
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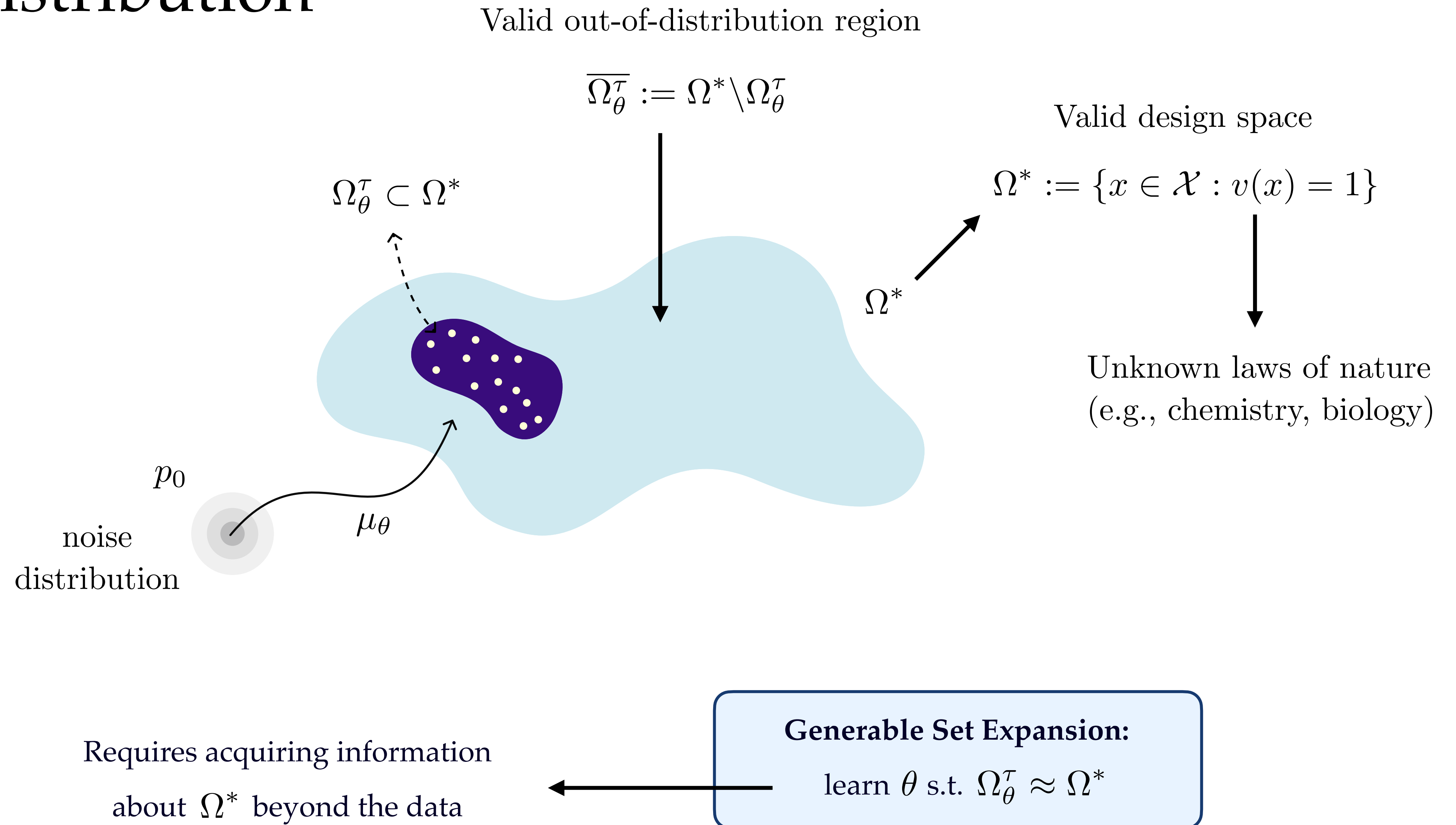


generable set $\rightarrow$ region likely to be covered by a finite draw
 $\rightarrow$ region where the generative model is reliable (e.g., sufficient validity signal)

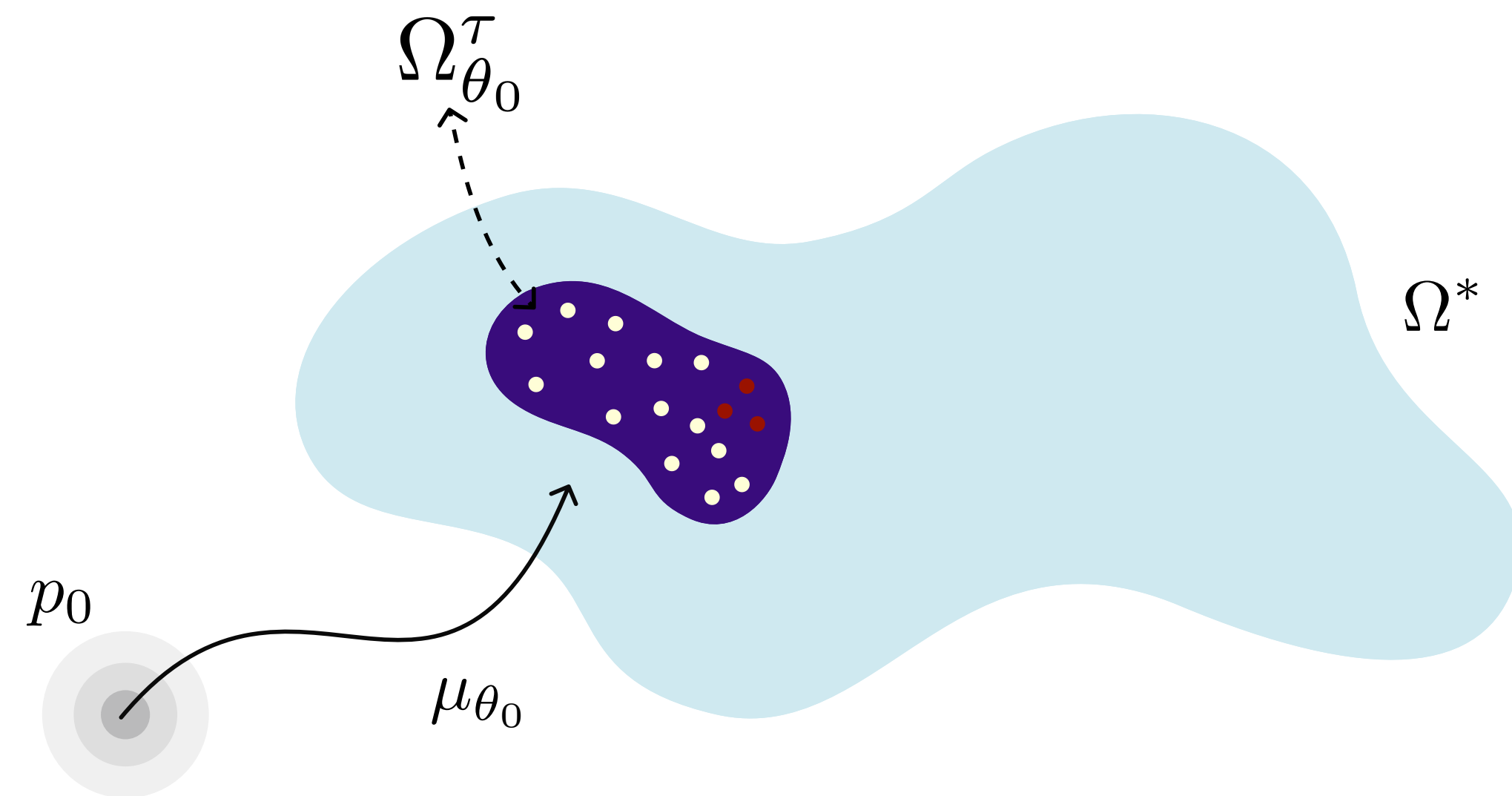
Beyond Distribution Matching



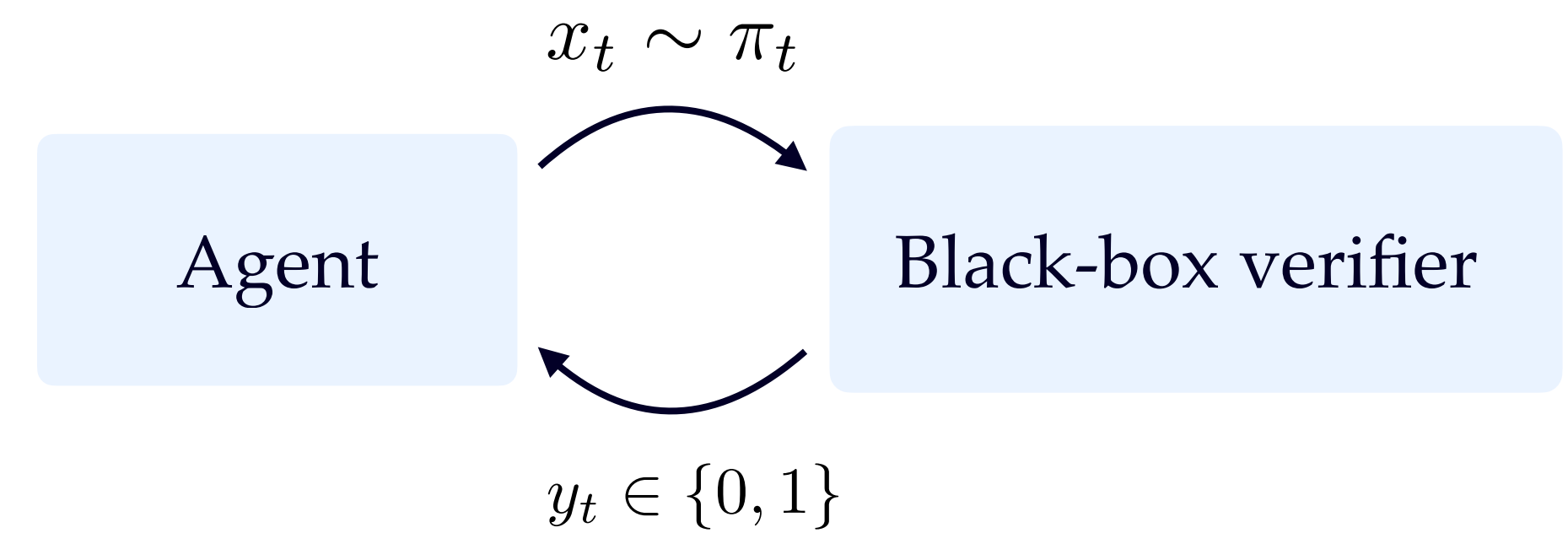
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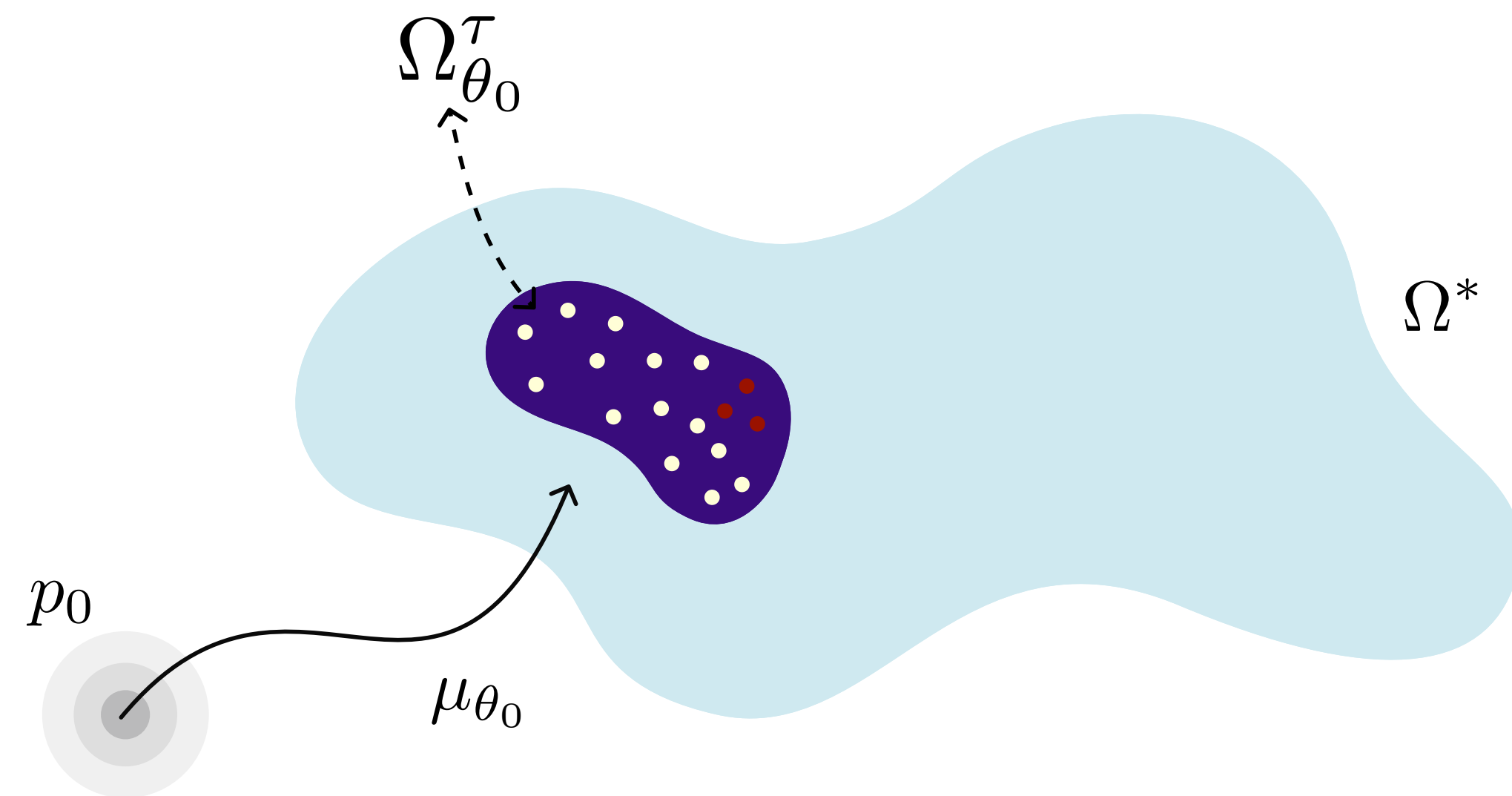
Generable Set Expansion for OOD Flow Modeling



Black-box noisy binary verifier feedback



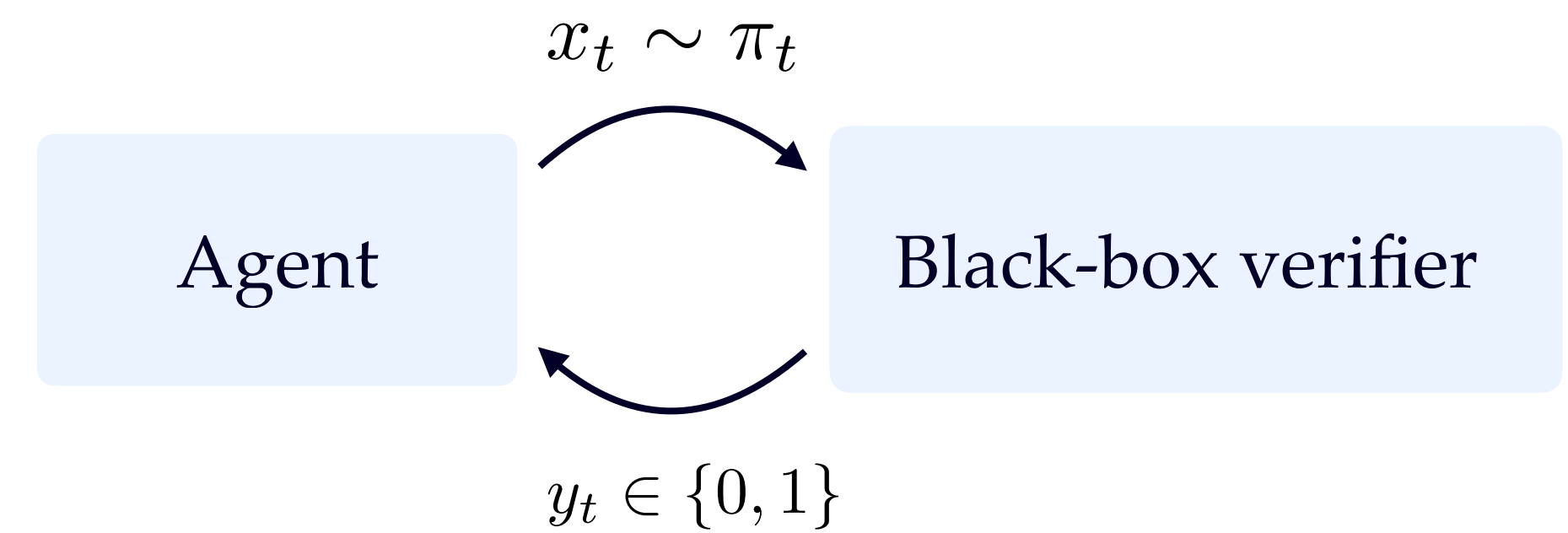
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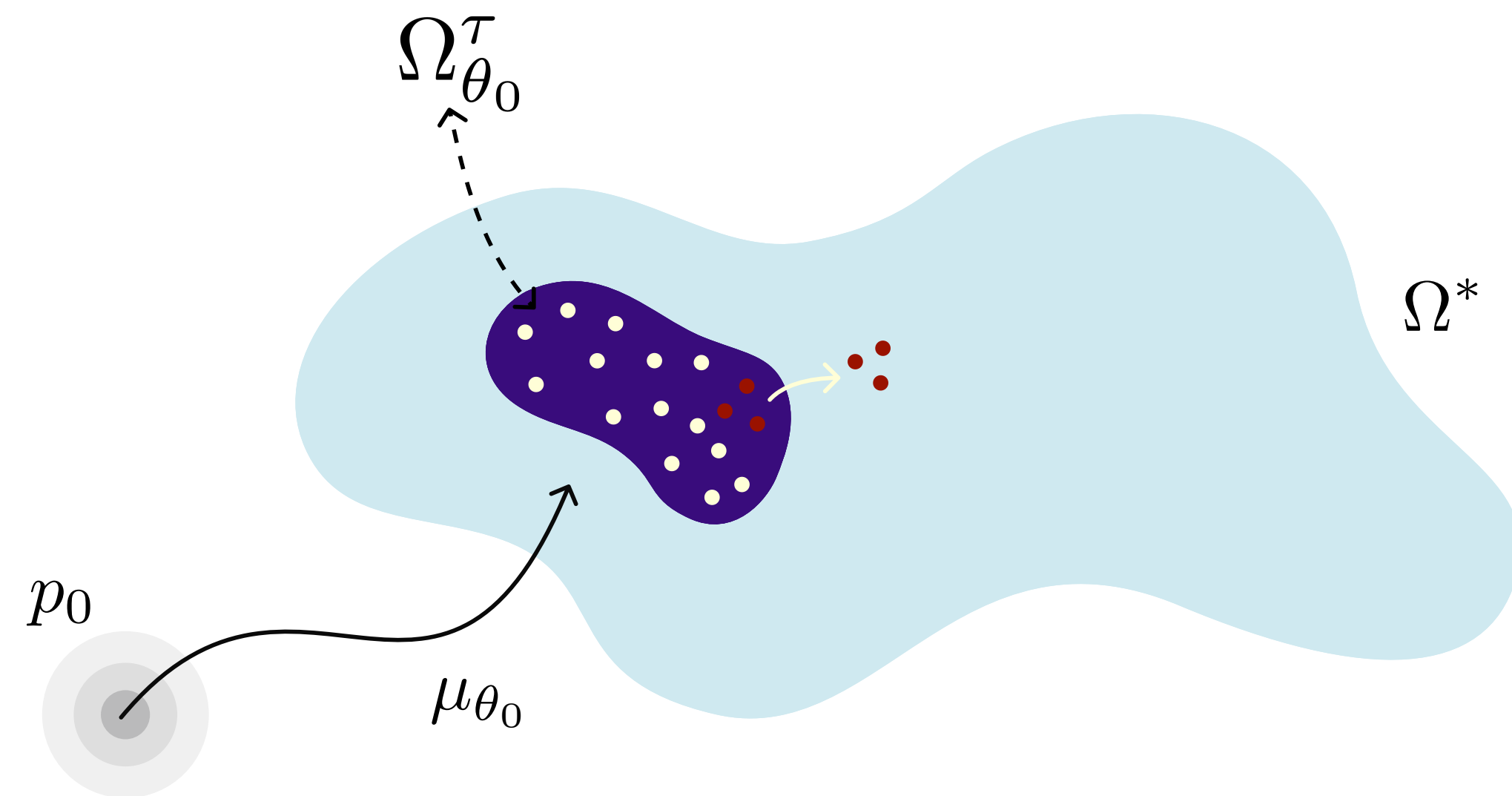
$$\theta^{\text{pre}} = \theta_0$$

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

Black-box noisy binary verifier feedback



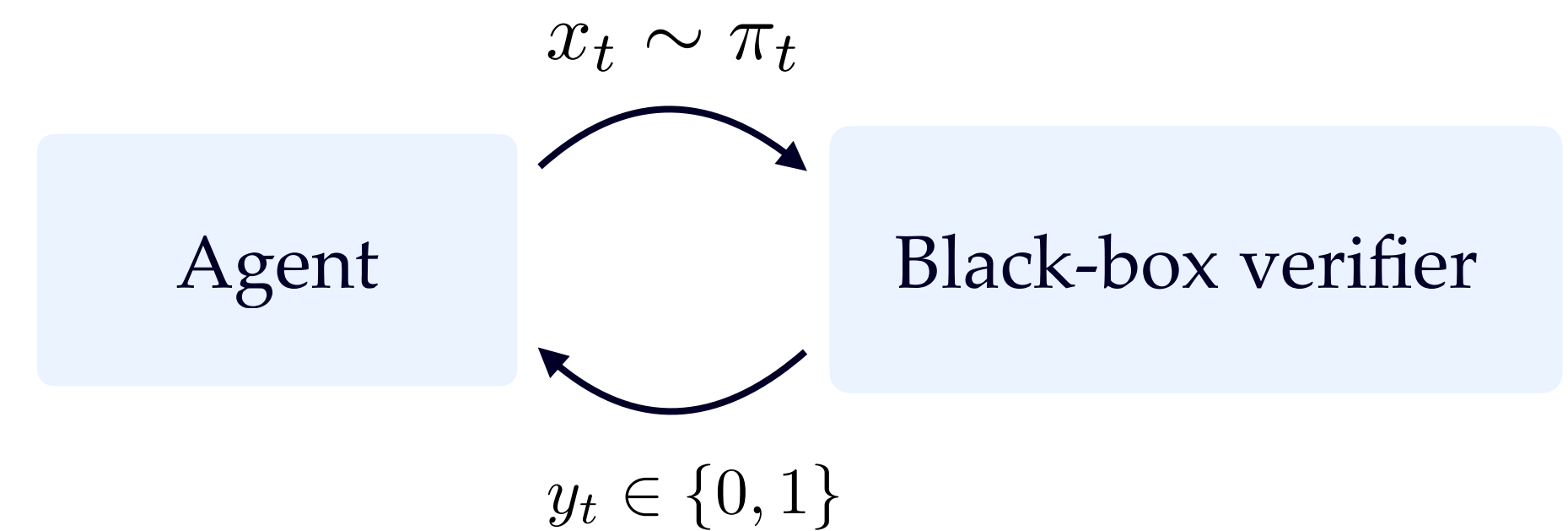
Generable Set Expansion for OOD Flow Modeling



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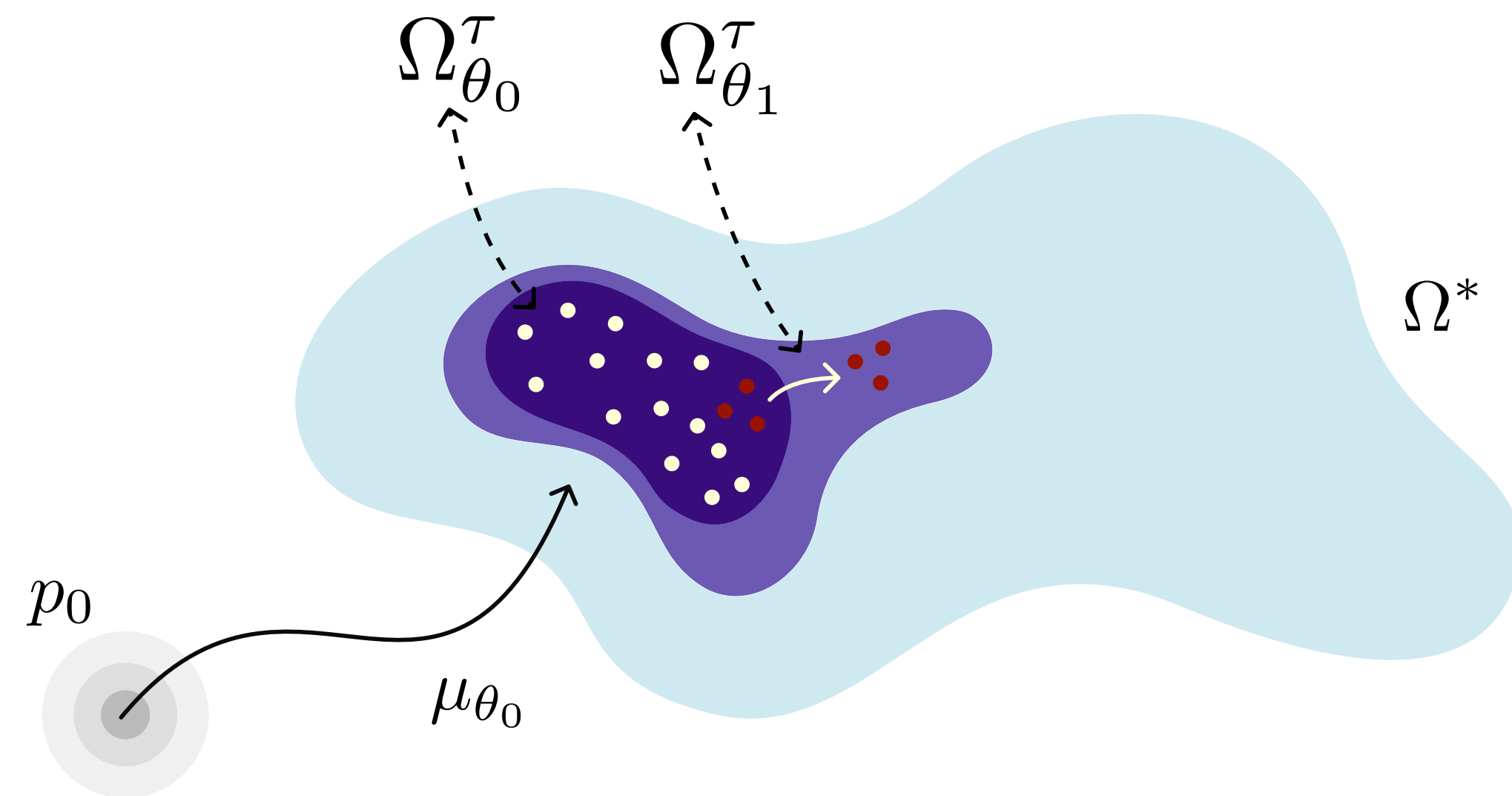
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Black-box noisy binary verifier feedback

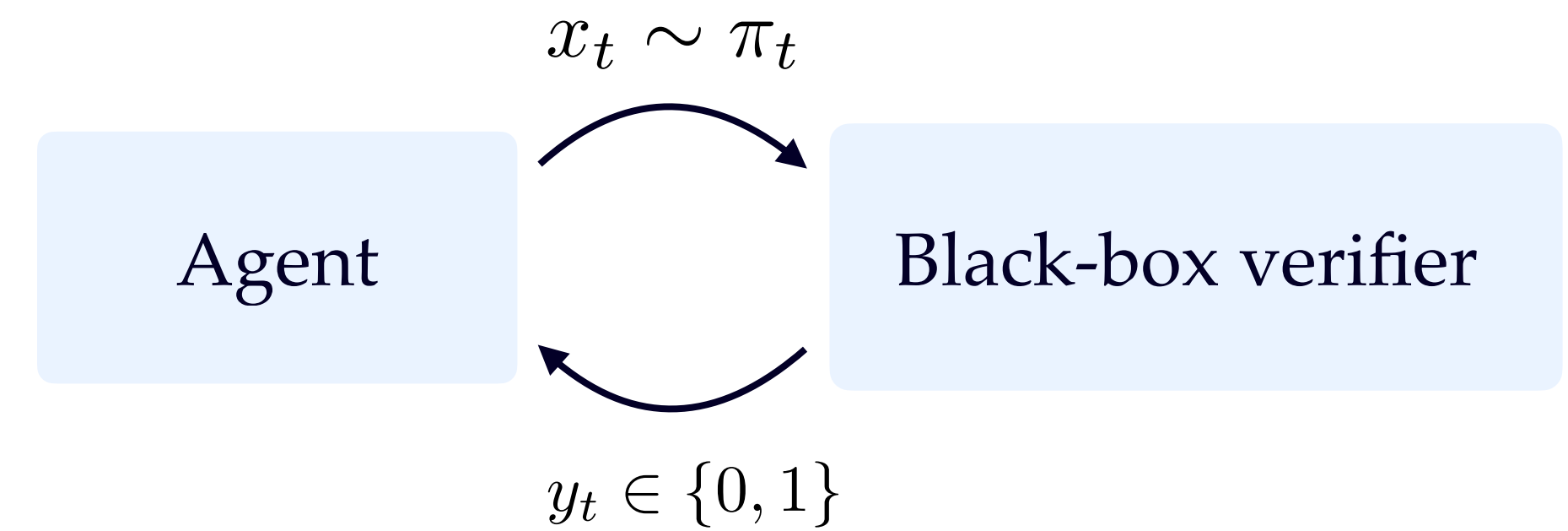


Continual expansion via adaptation on valid **frontier samples**

Generable Set Expansion for OOD Flow Modeling



Black-box noisy binary verifier feedback

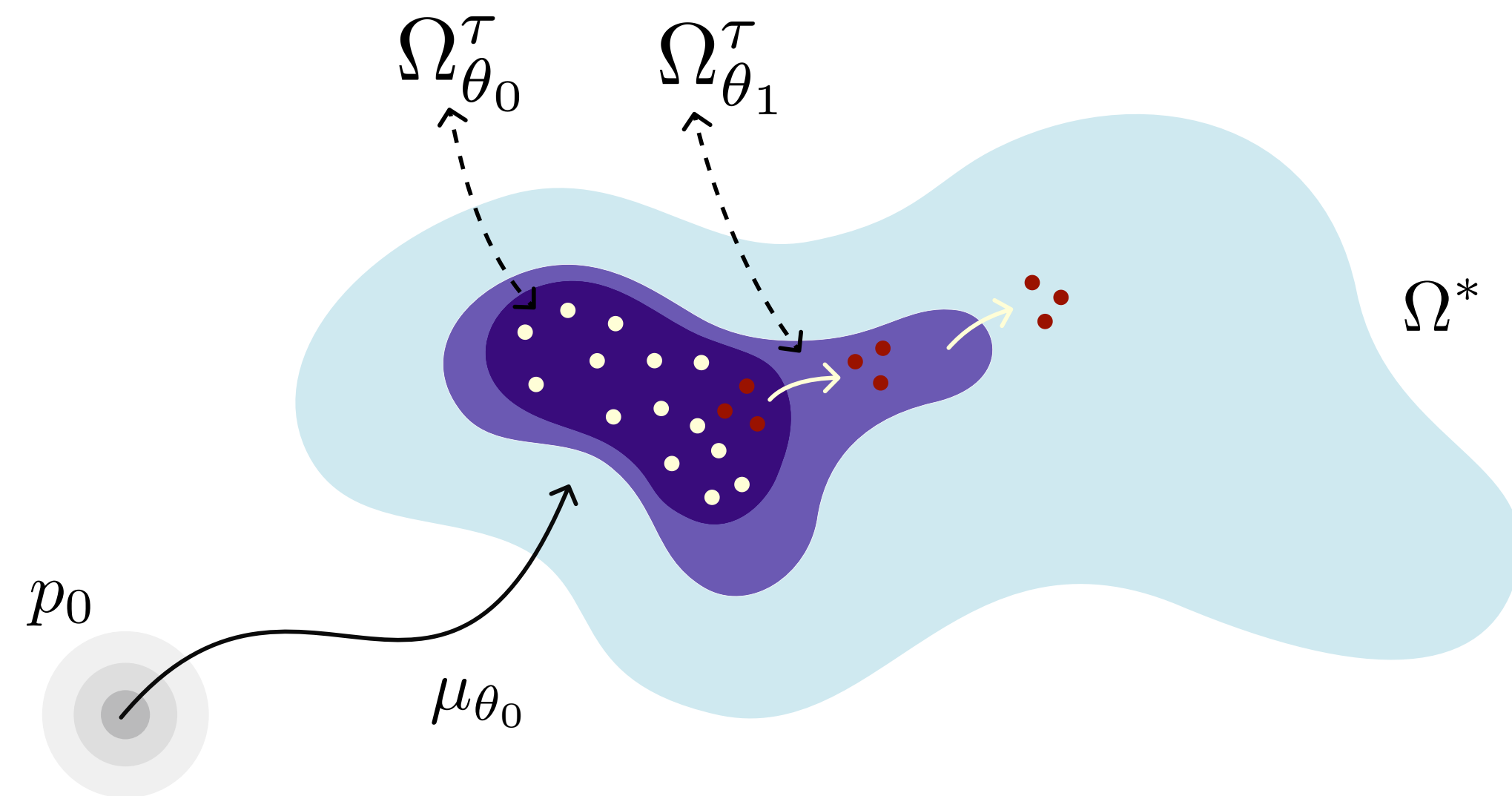


$$\theta^{\text{pre}} = \theta_0 \rightarrow \theta_1$$

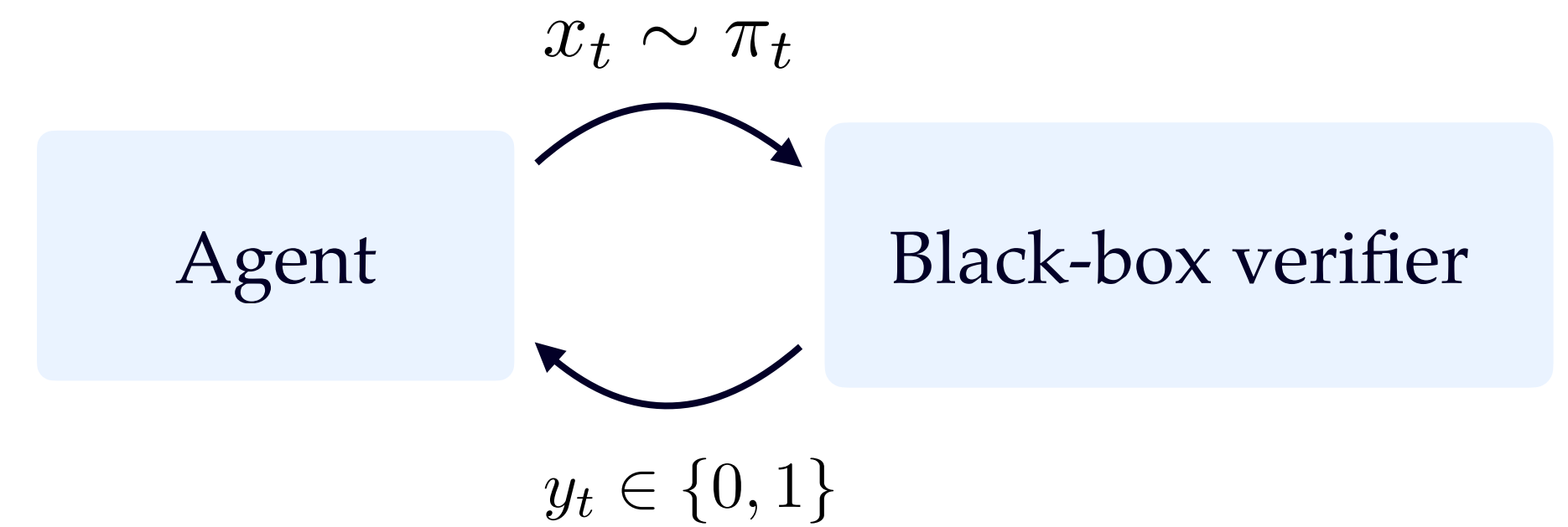
$$\Omega_{\theta_0}^{\tau} \subseteq \Omega_{\theta_1}^{\tau}$$

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Generable Set Expansion for OOD Flow Modeling



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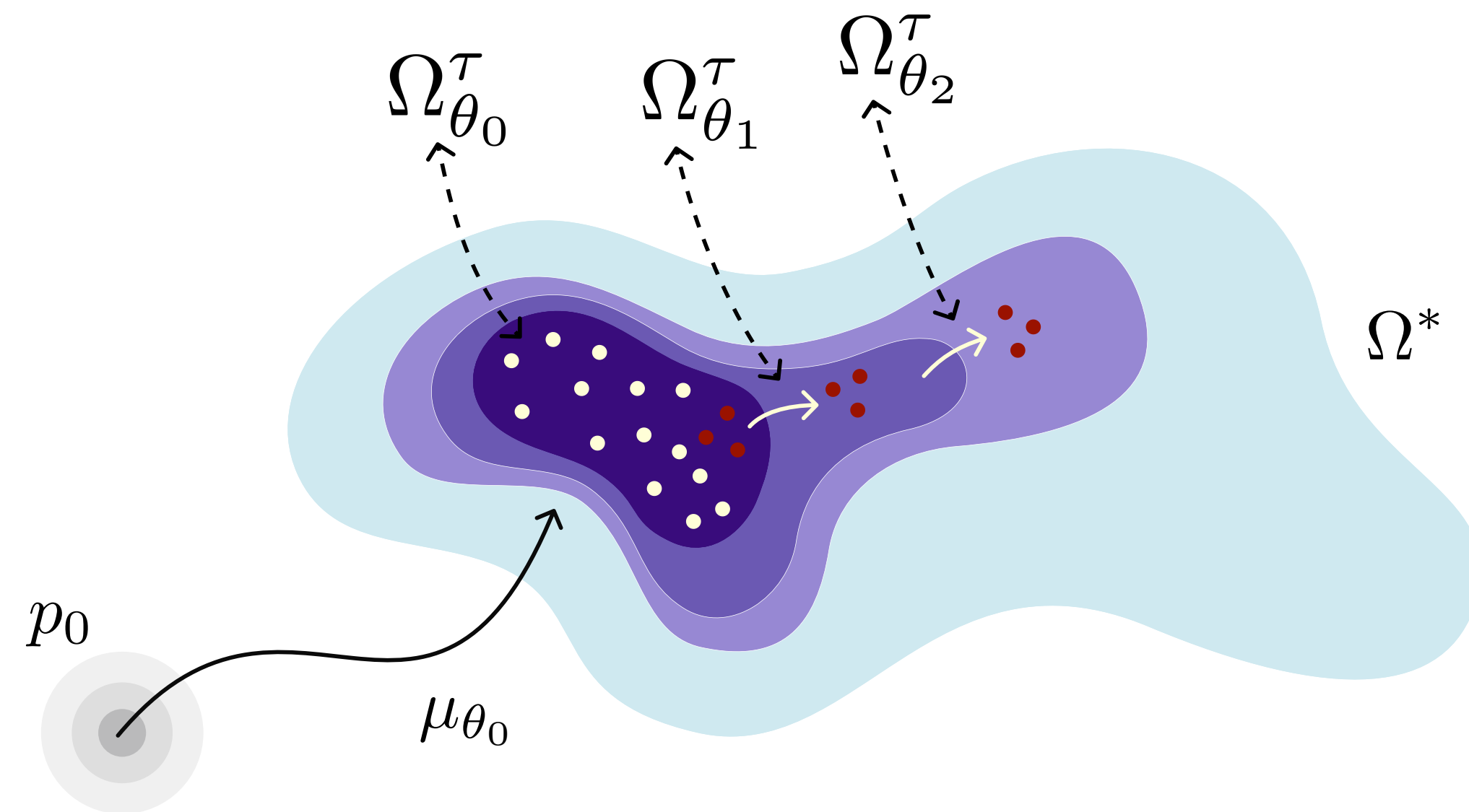


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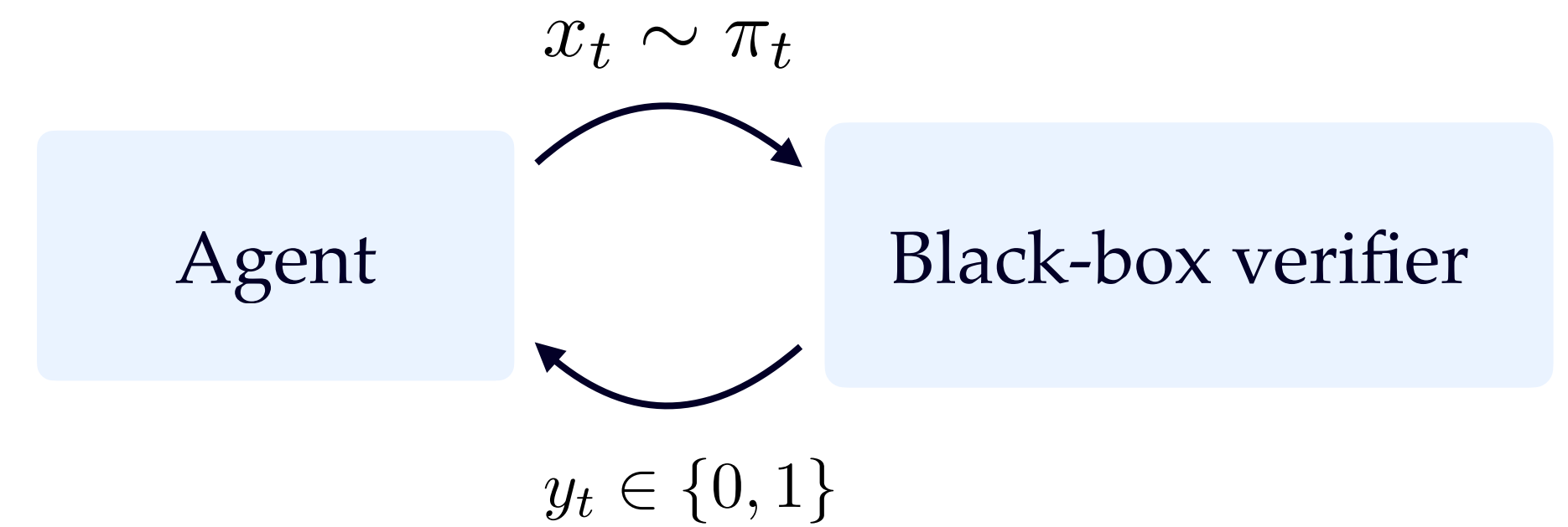
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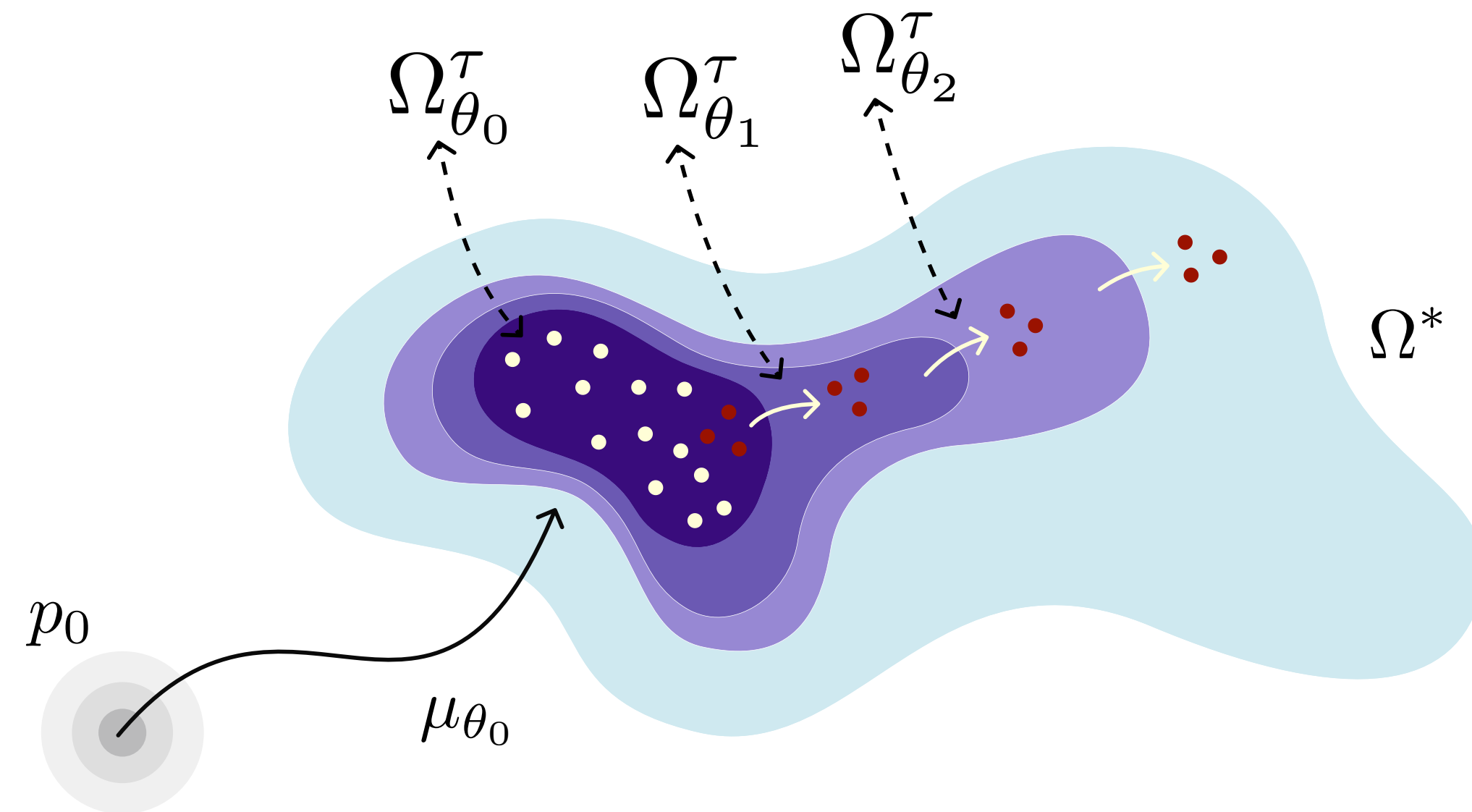


$$\theta^{\text{pre}} = \theta_0 \rightarrow \theta_1 \rightarrow \dots$$

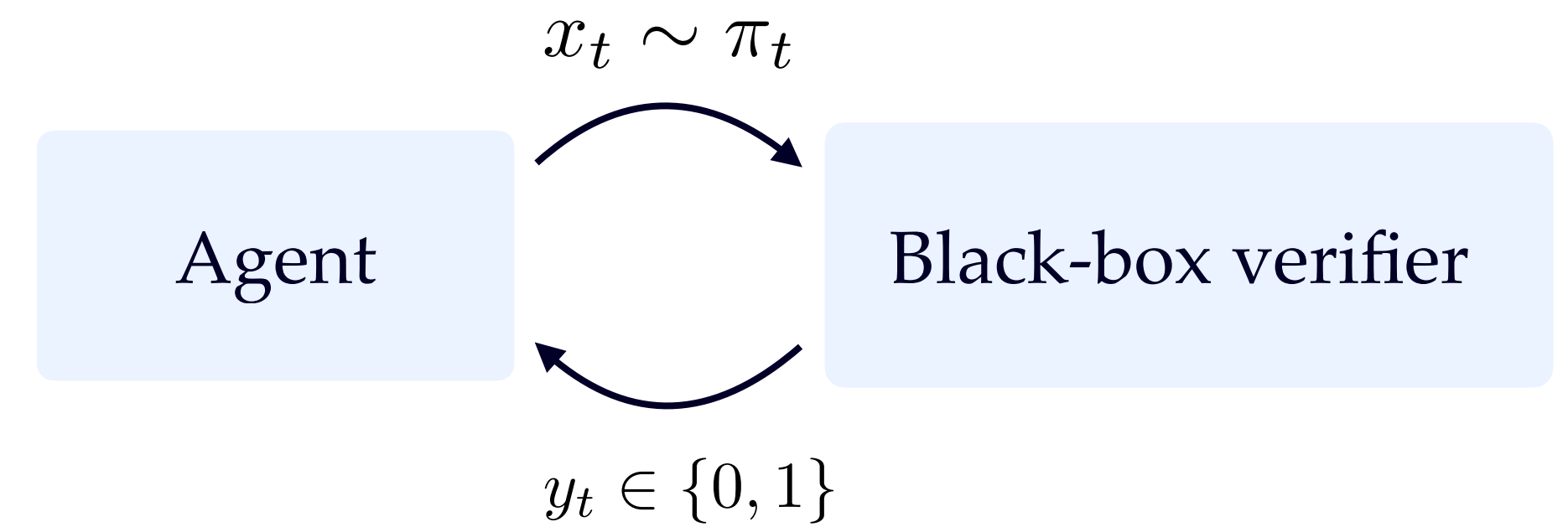
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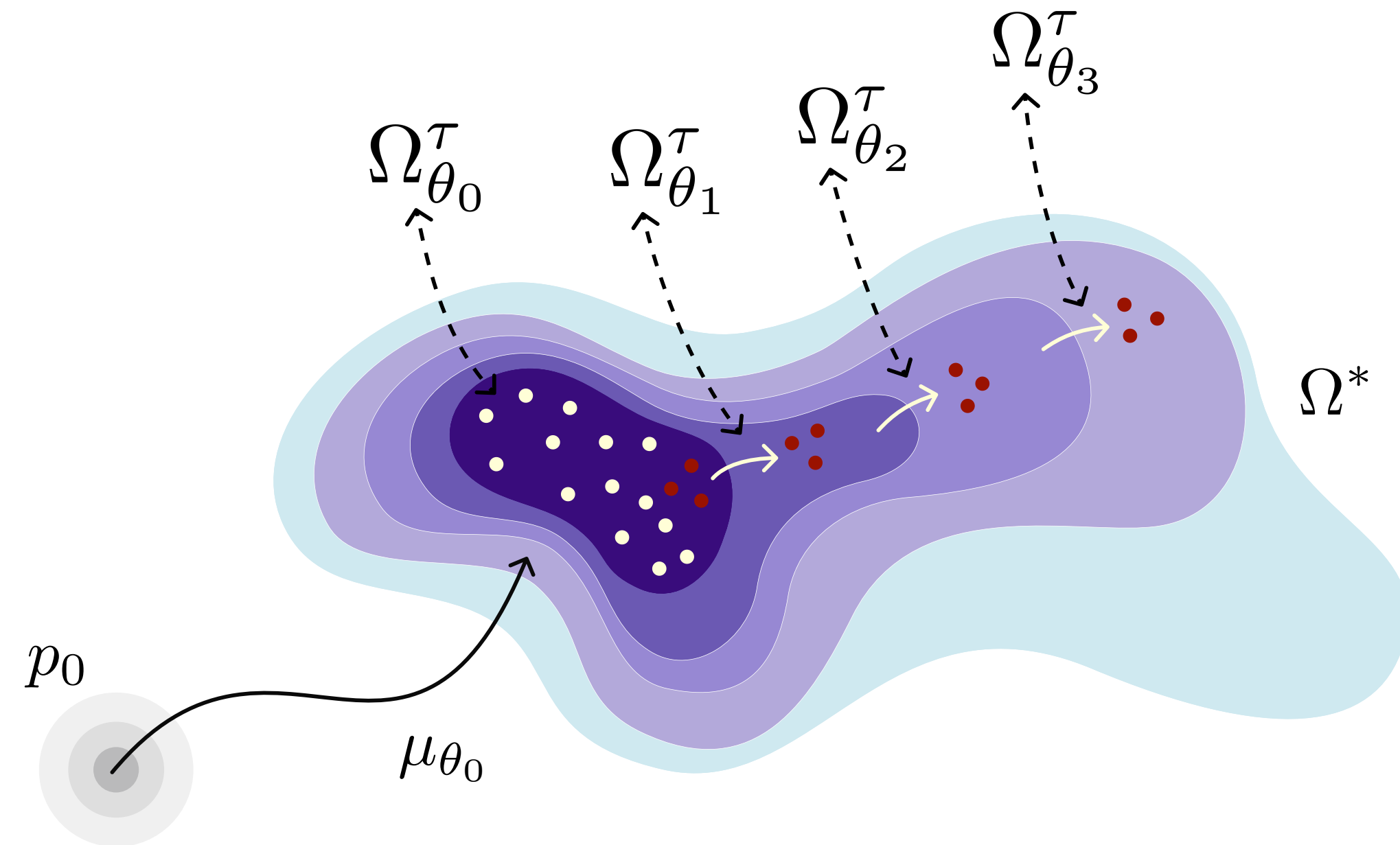


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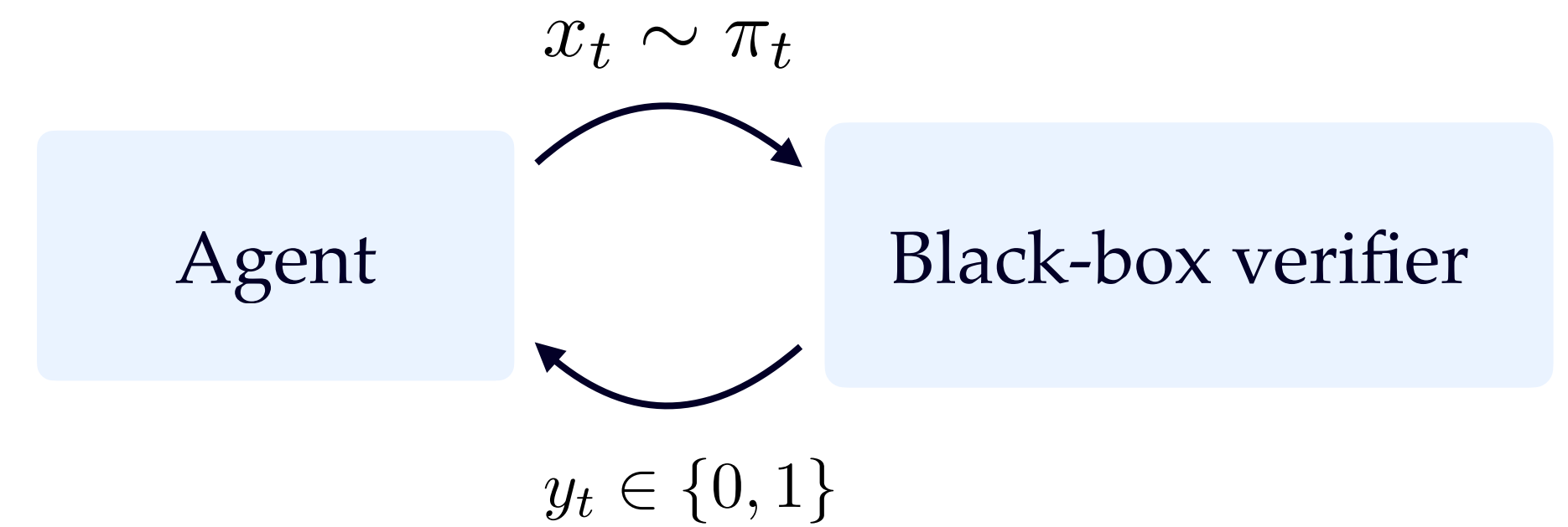
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Black-box noisy binary verifier feedback

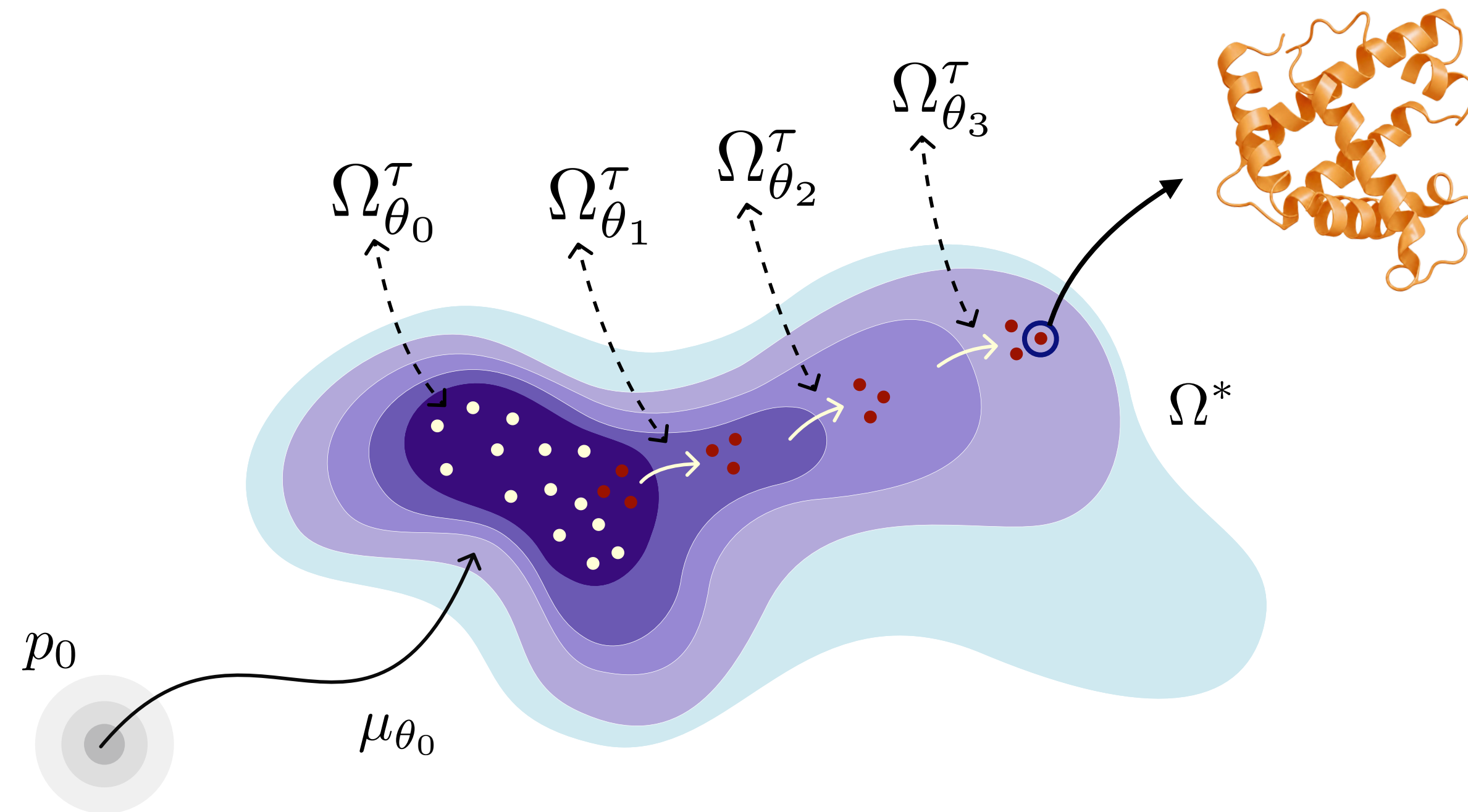


$$\theta^{\text{pre}} = \theta_0 \rightarrow \theta_1 \rightarrow \dots \rightarrow \theta_T$$

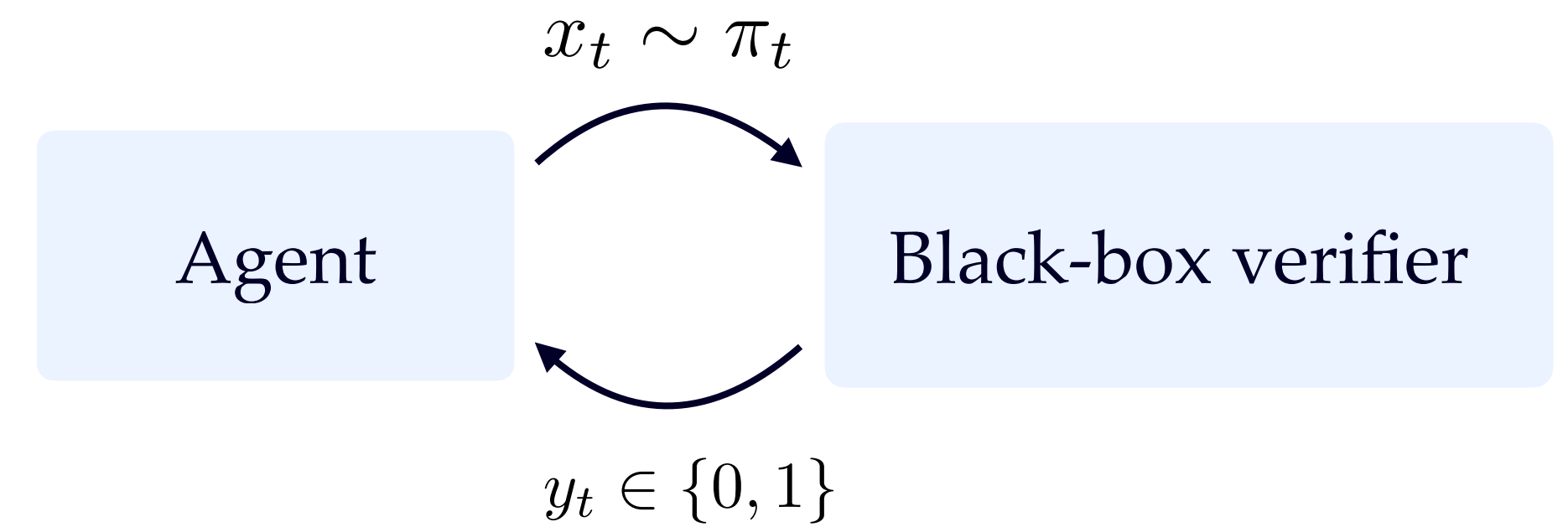
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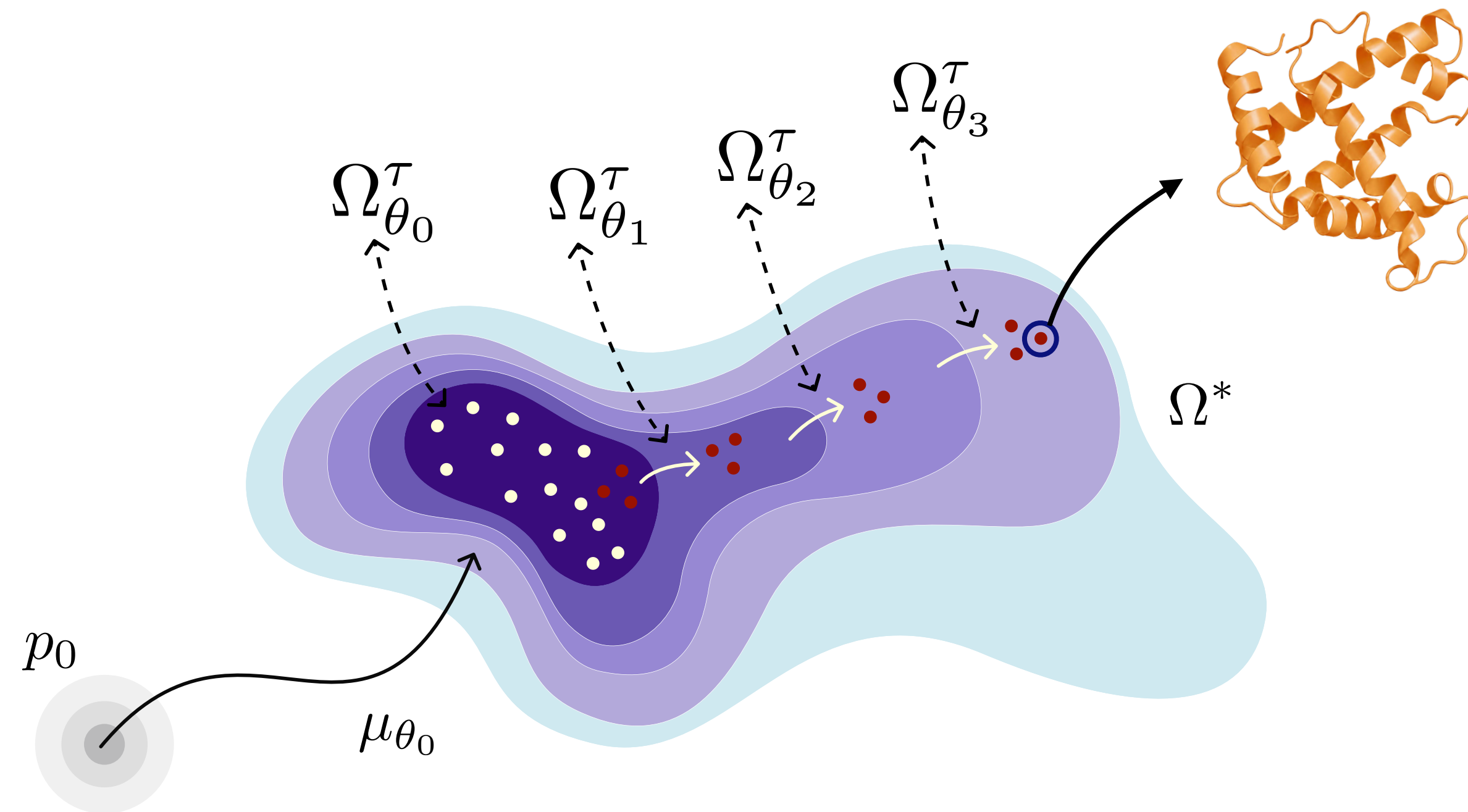
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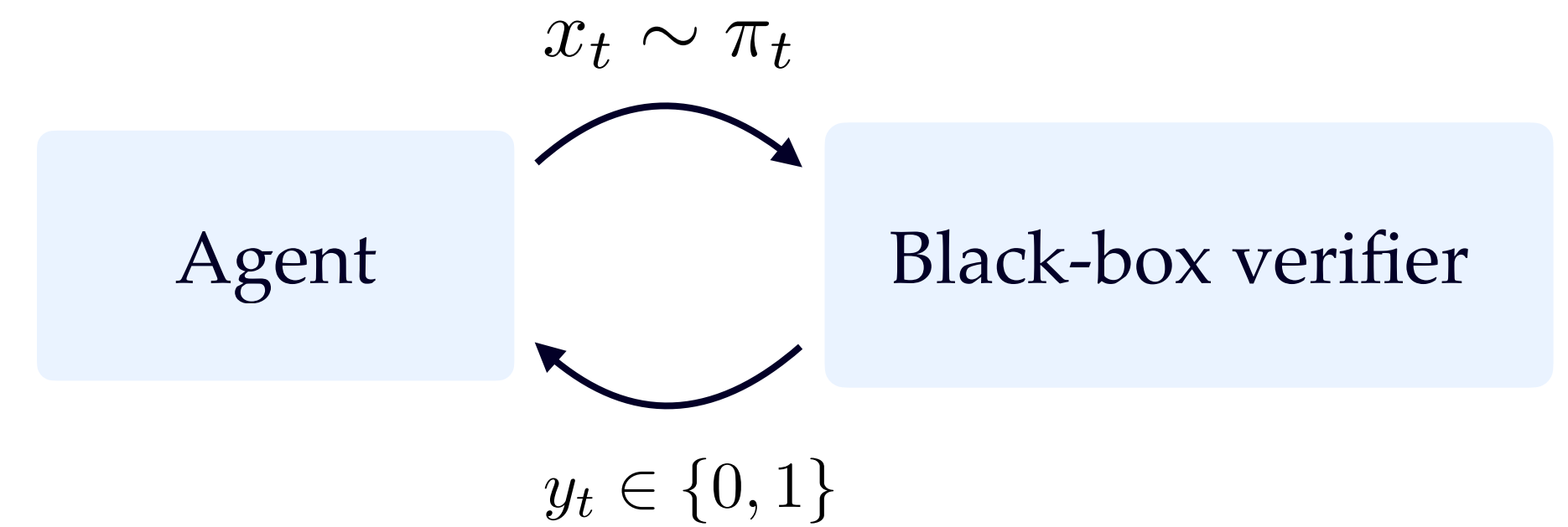
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Generable Set Expansion for OOD Flow Modeling



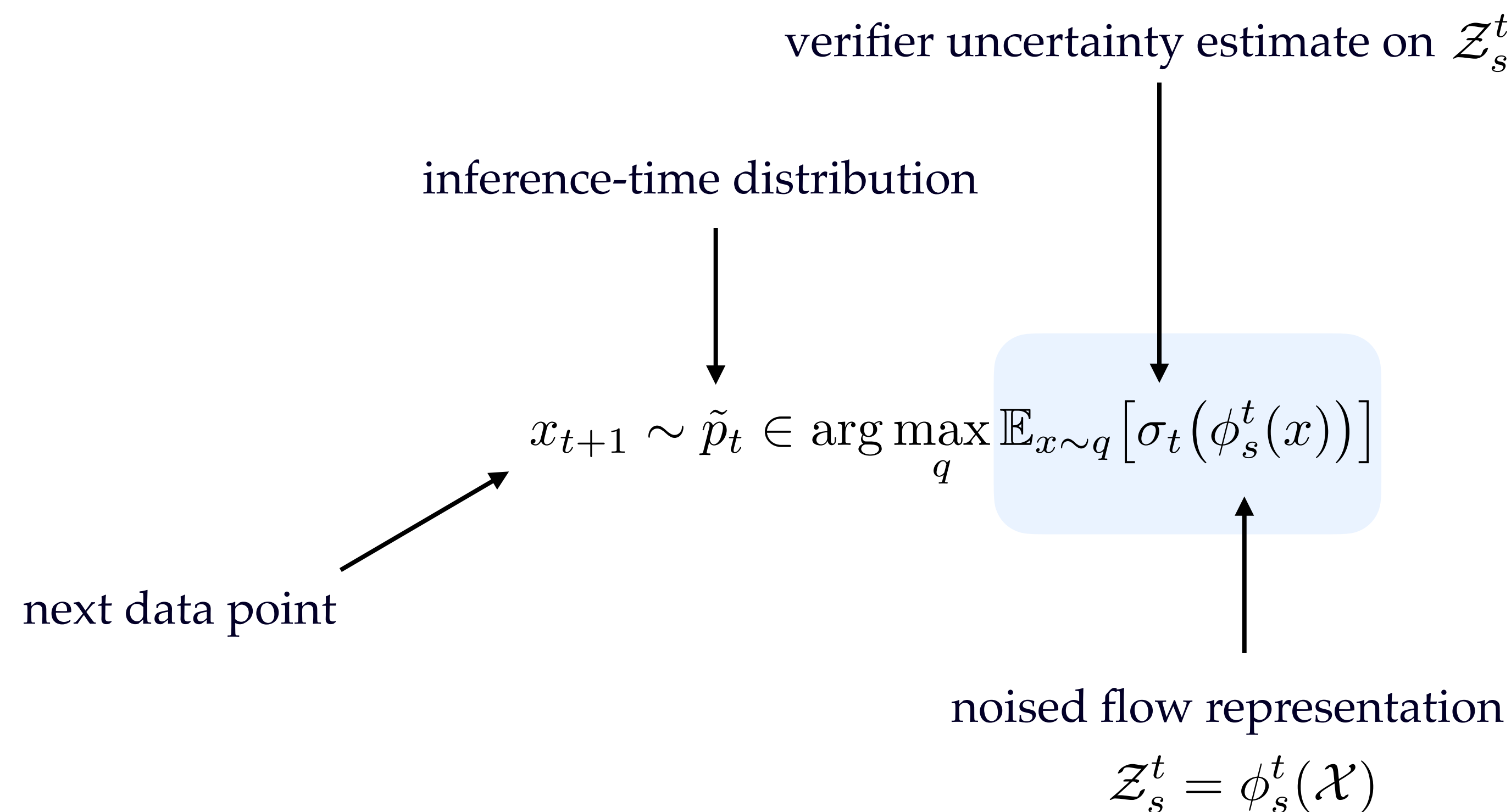
Black-box noisy binary verifier feedback



$$\theta^{\text{pre}} = \theta_0 \rightarrow \theta_1 \rightarrow \cdots \rightarrow \theta_T, \quad \Omega_{\theta_0}^\tau \subseteq \Omega_{\theta_1}^\tau \subseteq \cdots \subseteq \Omega_{\theta_T}^\tau \stackrel{?}{\approx} \Omega^*$$

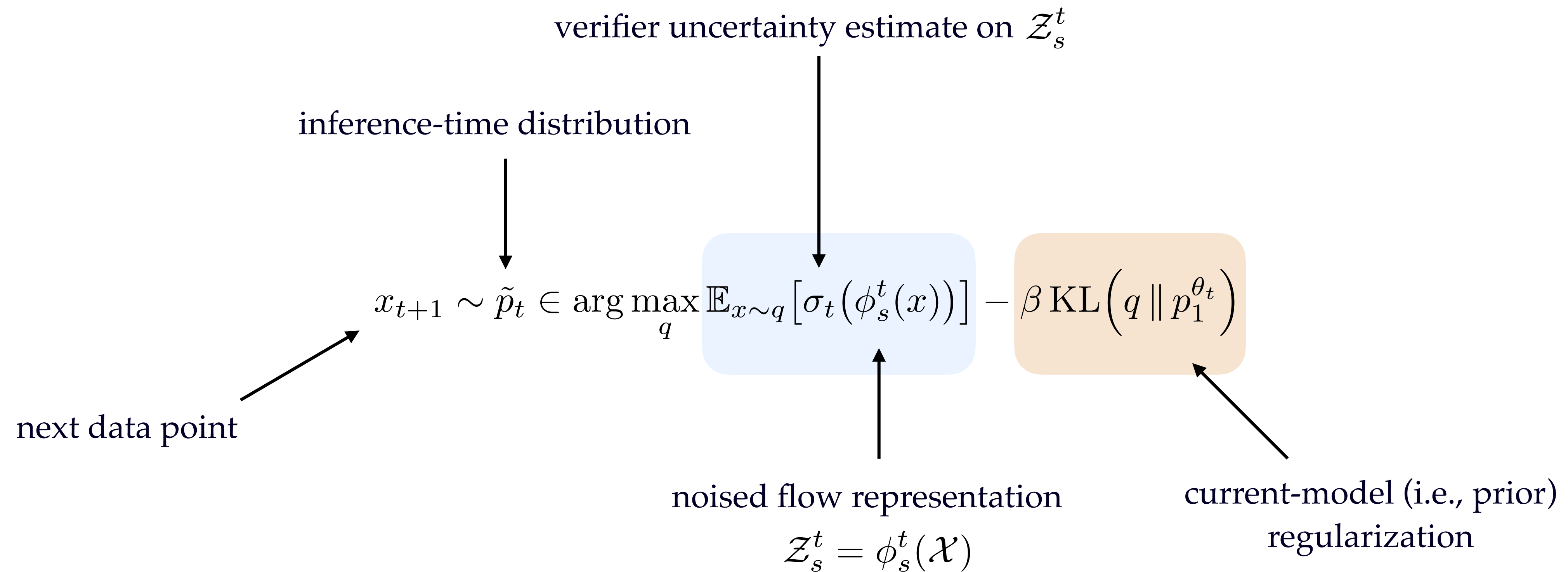
Continual expansion via adaptation on valid frontier samples

How to self-generate **frontier samples** and **avoid model collapse**?



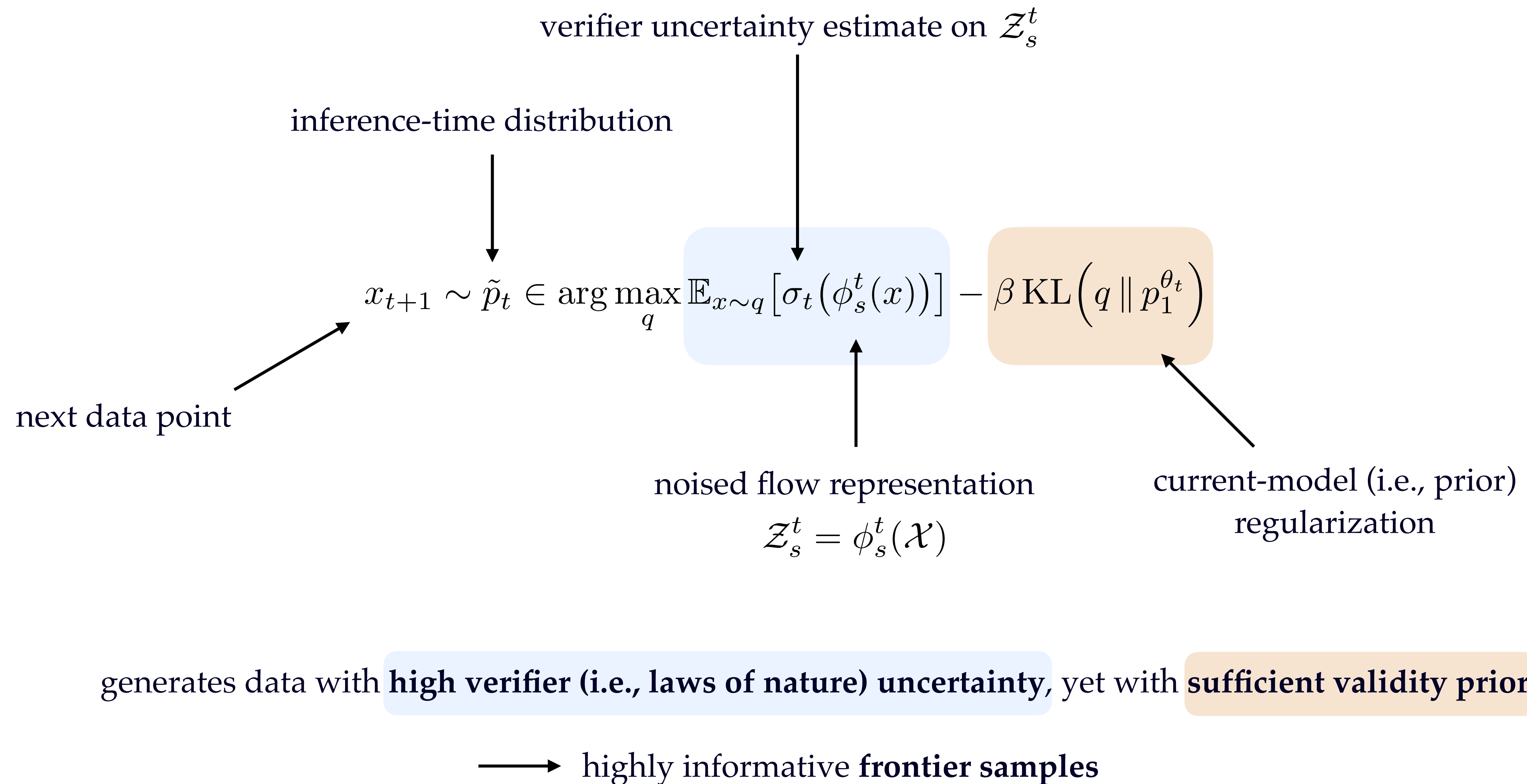
generates data with **high verifier (i.e., laws of nature) uncertainty**

How to self-generate **frontier samples** and **avoid model collapse**?



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

How to self-generate **frontier samples** and **avoid model collapse**?



ActFlow: Active Flow Expansion

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

ActFlow: Active Flow Expansion

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

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

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

Self-generate:

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

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

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

Return μ_{θ_T}

Theoretical Guarantees for Out-of-Distribution Flow Modeling

Distribution matching

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

(Our work)



Design space coverage

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

Discovery requires **coverage guarantees**, not only distributional fit.

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

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

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

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

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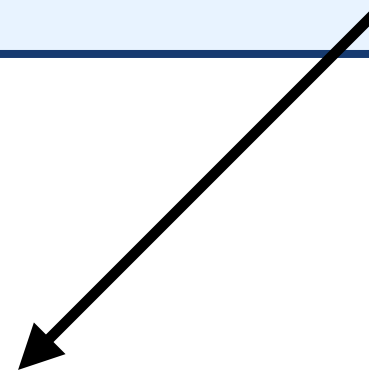
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H-step reachable set given recursive application of **one-step reachability operator** over flow representation:

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γ maximum information gain

More **complex validity laws** (of nature)
require more verifier queries.

generable representation set

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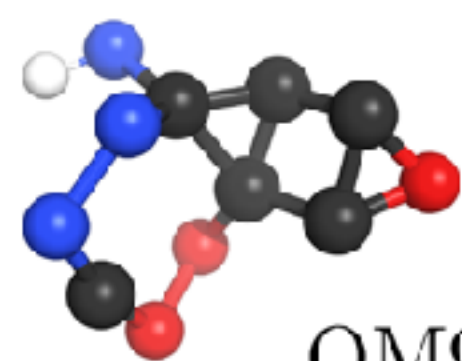
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Takeaway

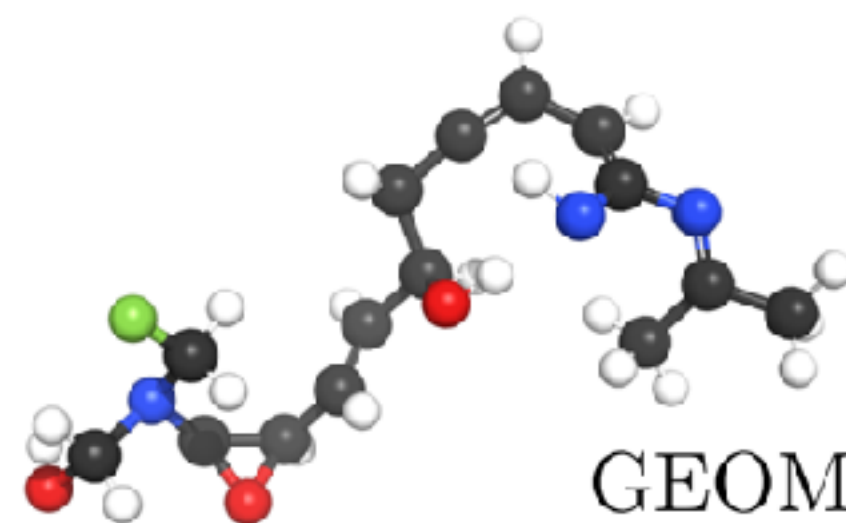
ActFlow provides first-of-their-kind finite-sample **coverage guarantees for out-of-distribution generative modeling**, under reachability assumptions.

Reachability + Sufficient Verifier Queries $\longrightarrow$ Design space coverage
 $\Omega_\theta^\tau \approx \Omega^*$

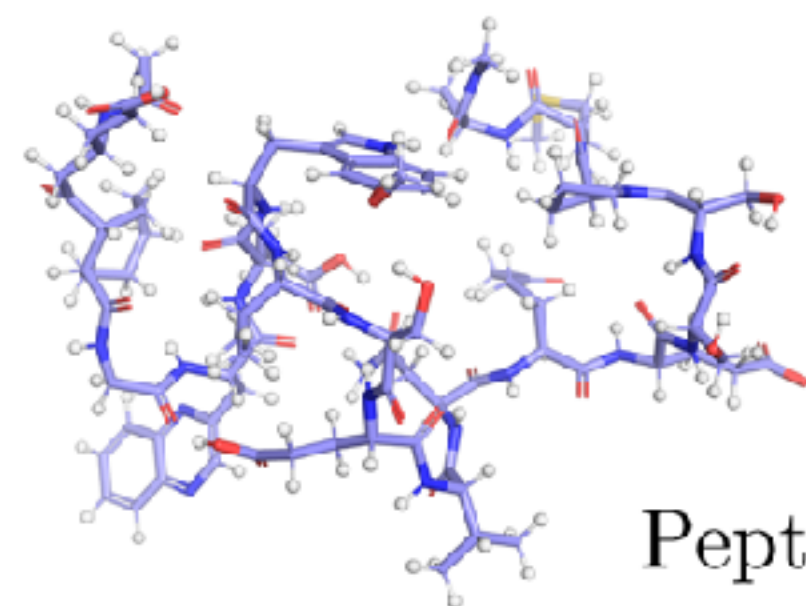
ActFlow with Chemical and Biological Data



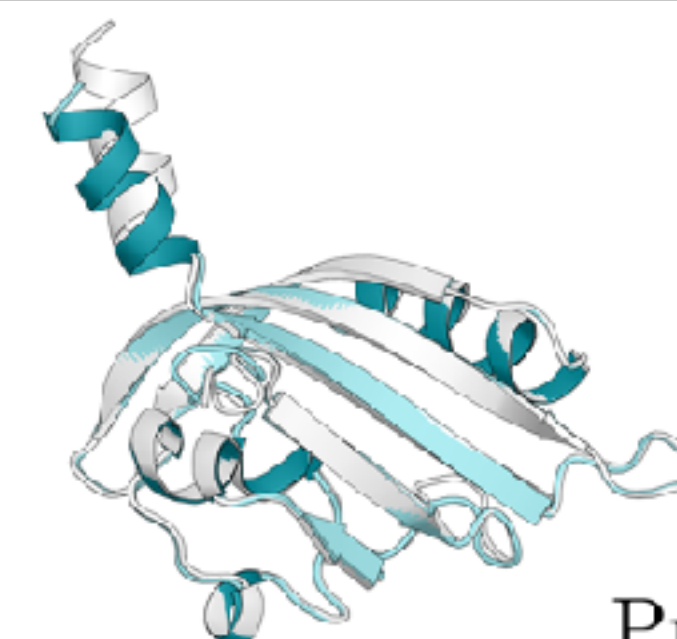
QM9 small
organic molecule



GEOM-Drugs
drug-like molecule

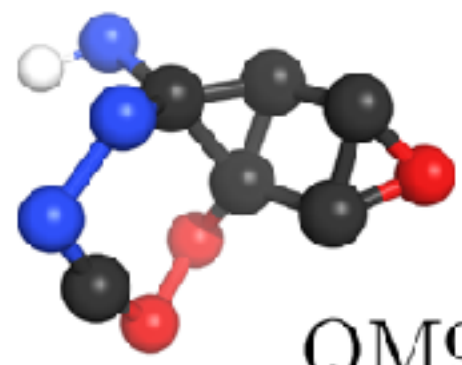


Peptide

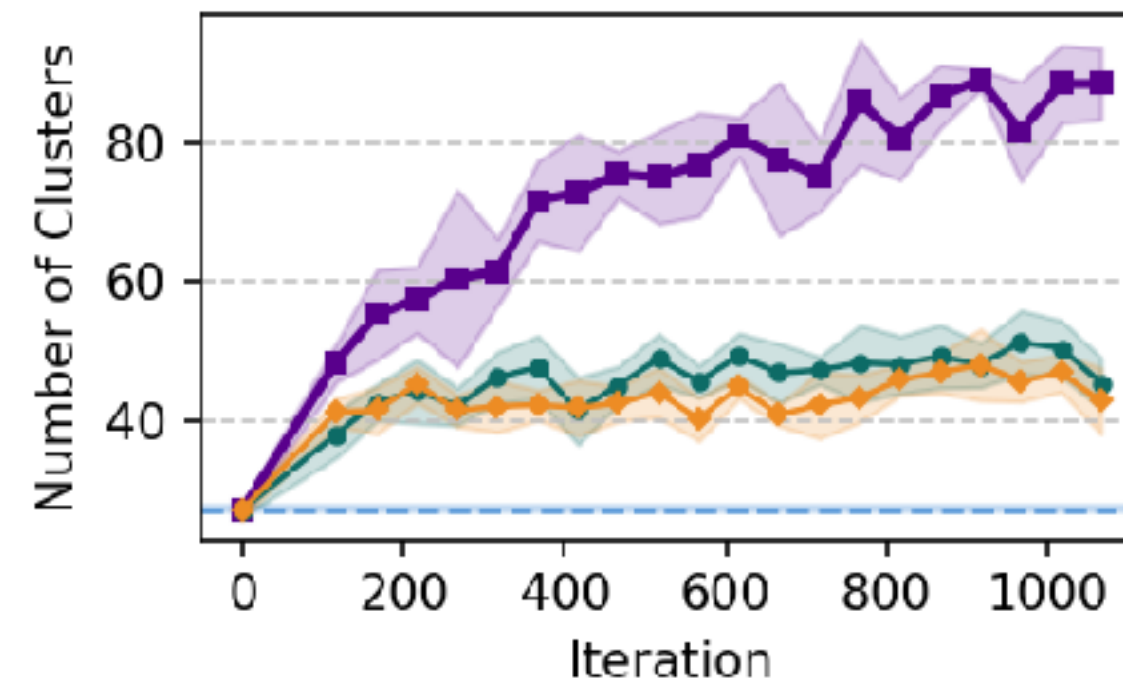
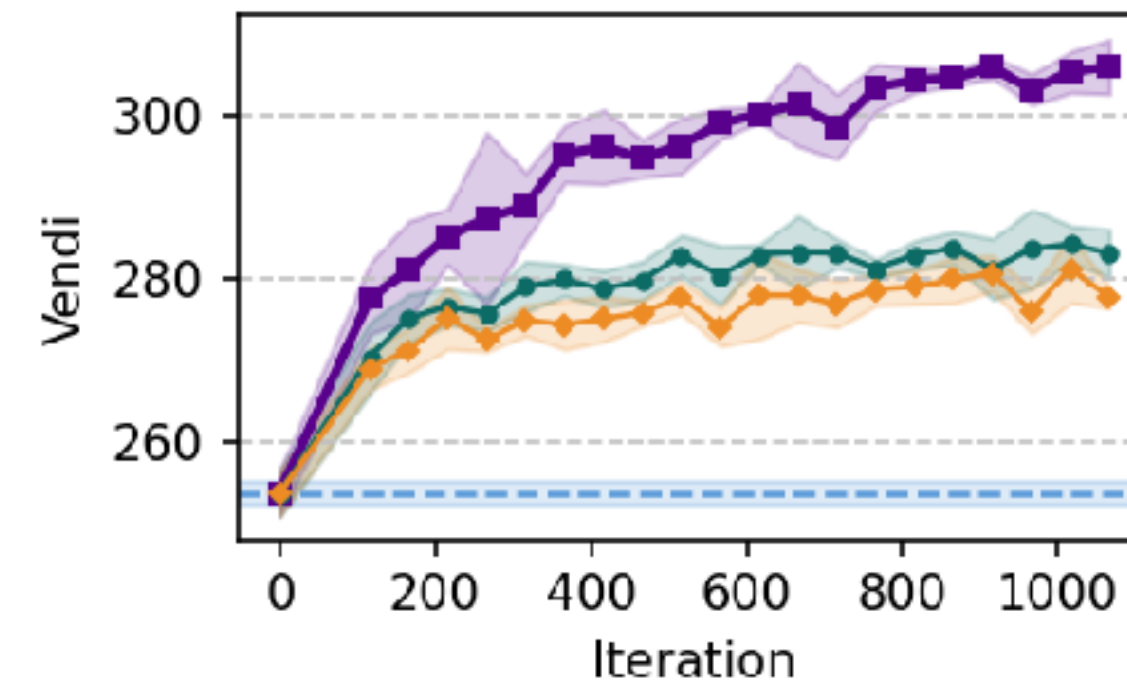
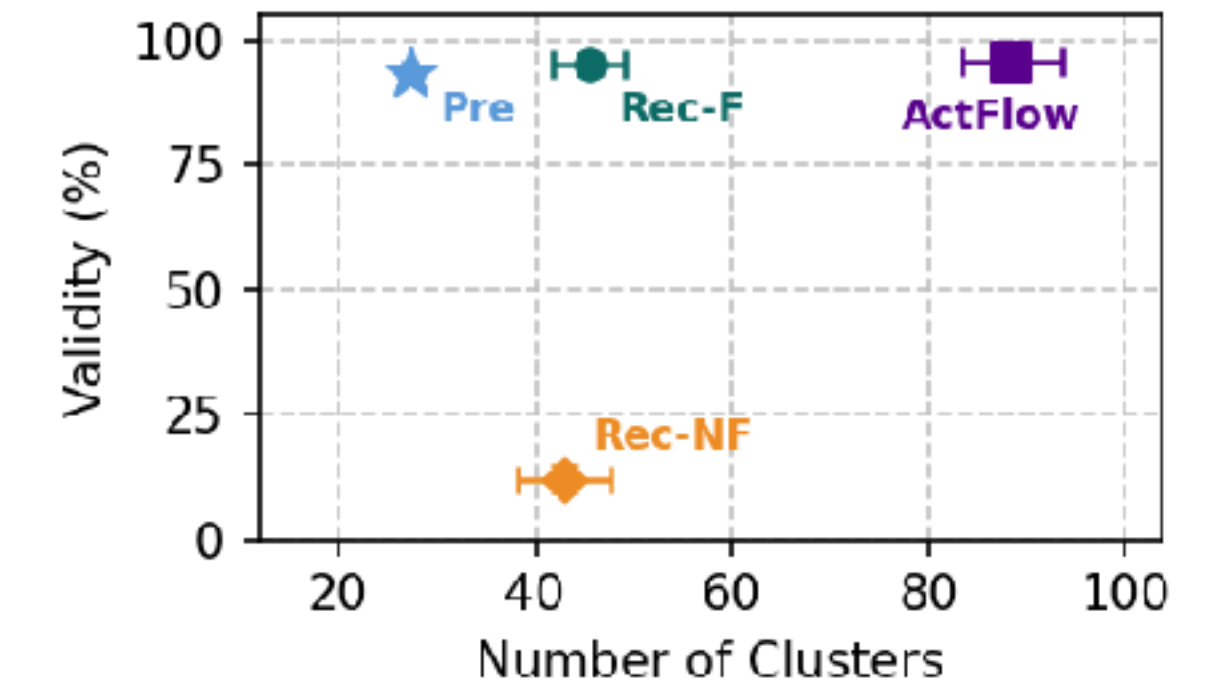
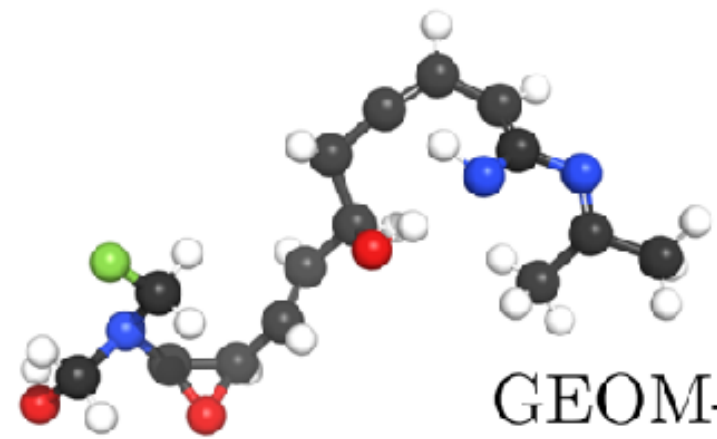


Protein

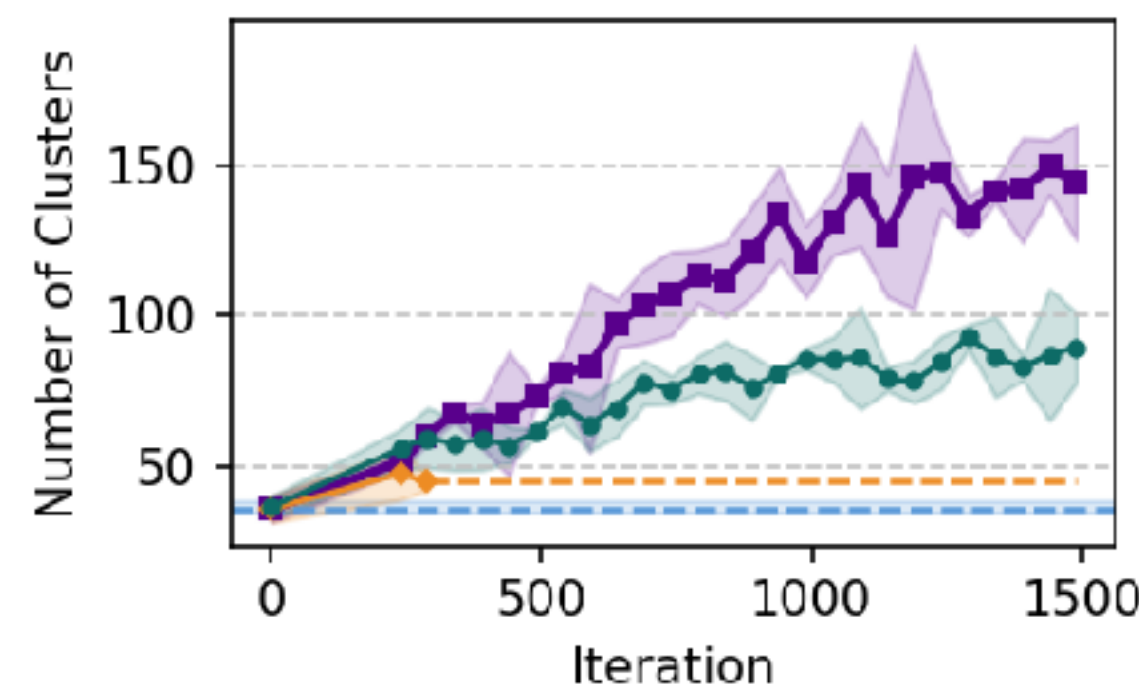
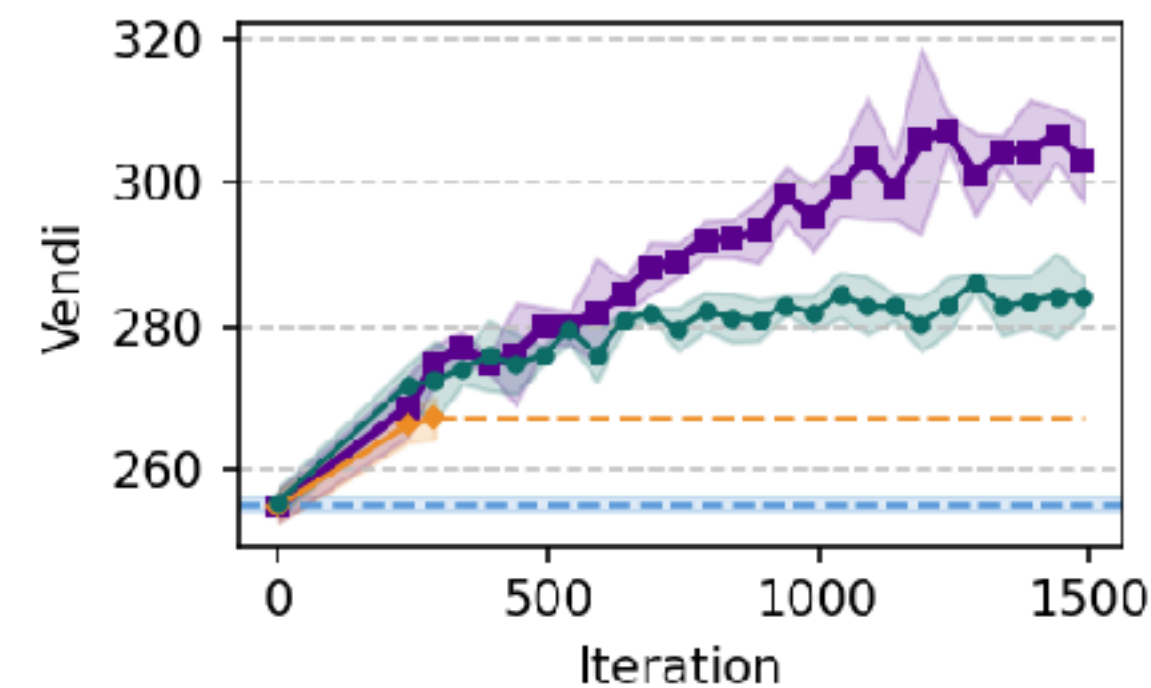
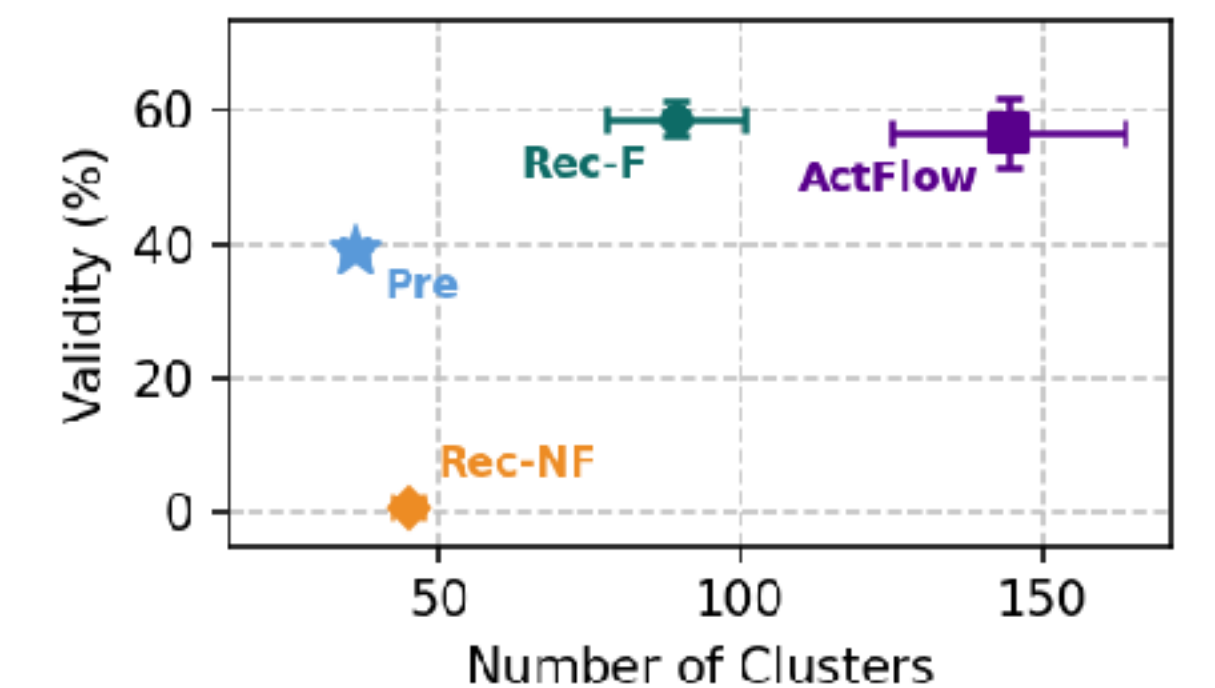
ActFlow for Small Organic and Drug-like Molecules



QM9 small organic molecule

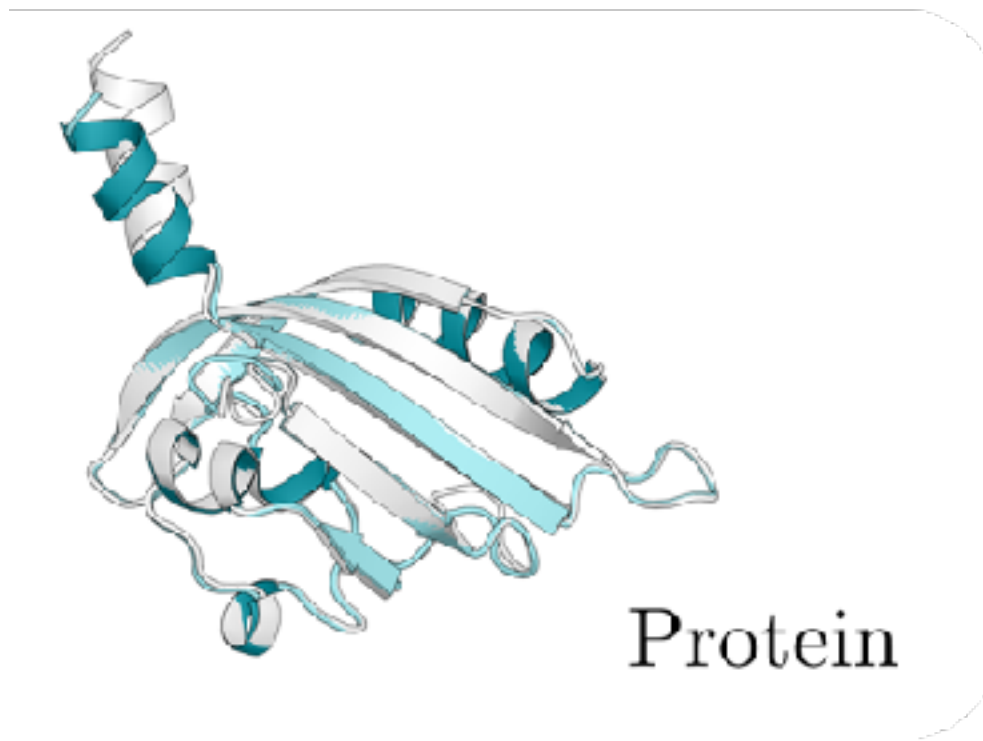
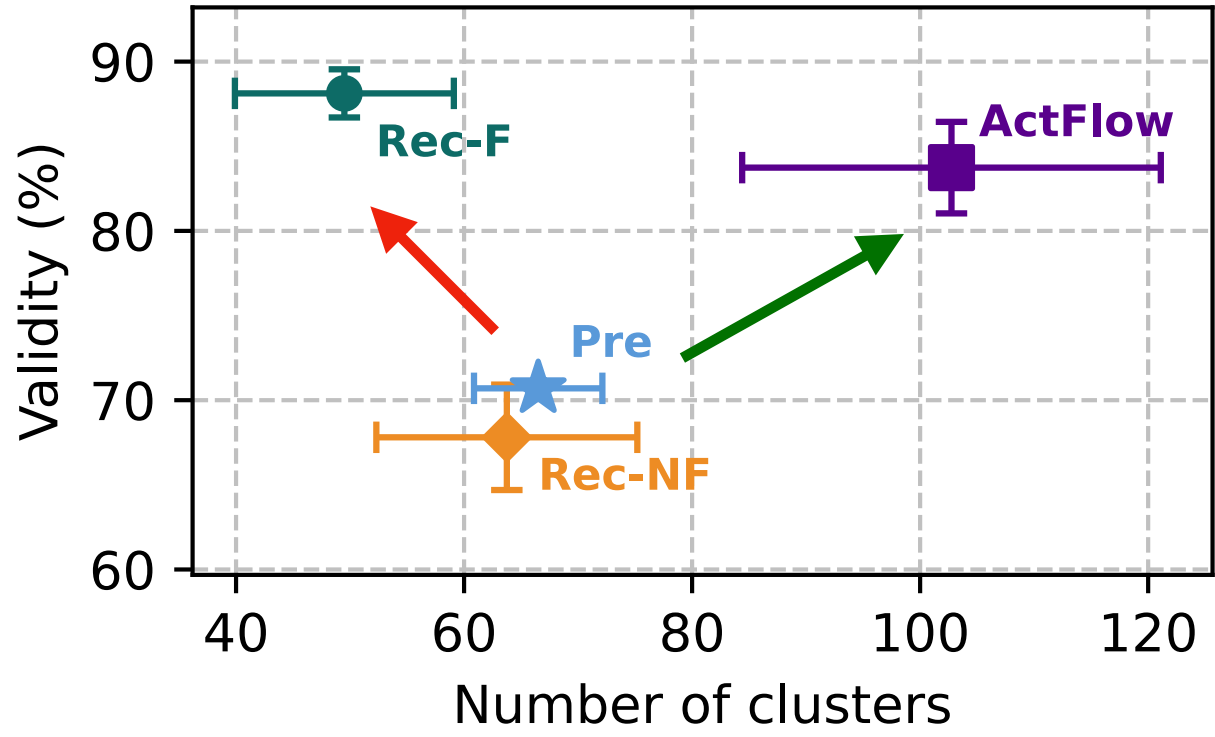


GEOM-Drugs drug-like molecule



ActFlow for Therapeutic Peptides and Protein Design

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



Takeaway

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

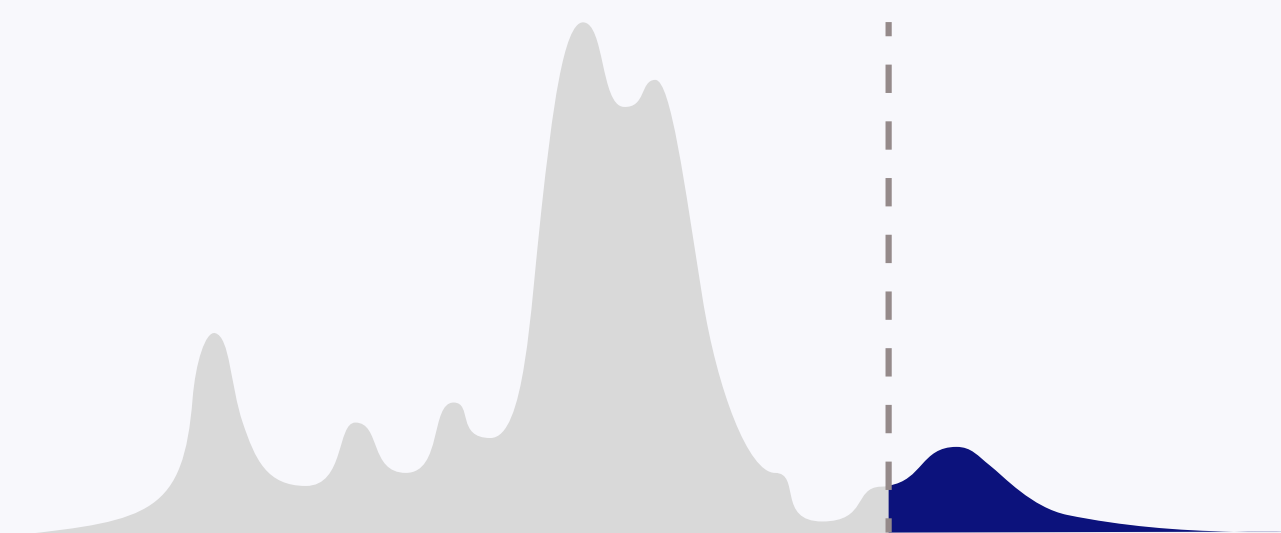
This talk:

Generative Discovery Beyond the Data

Part I

Rare and Diverse
Generation

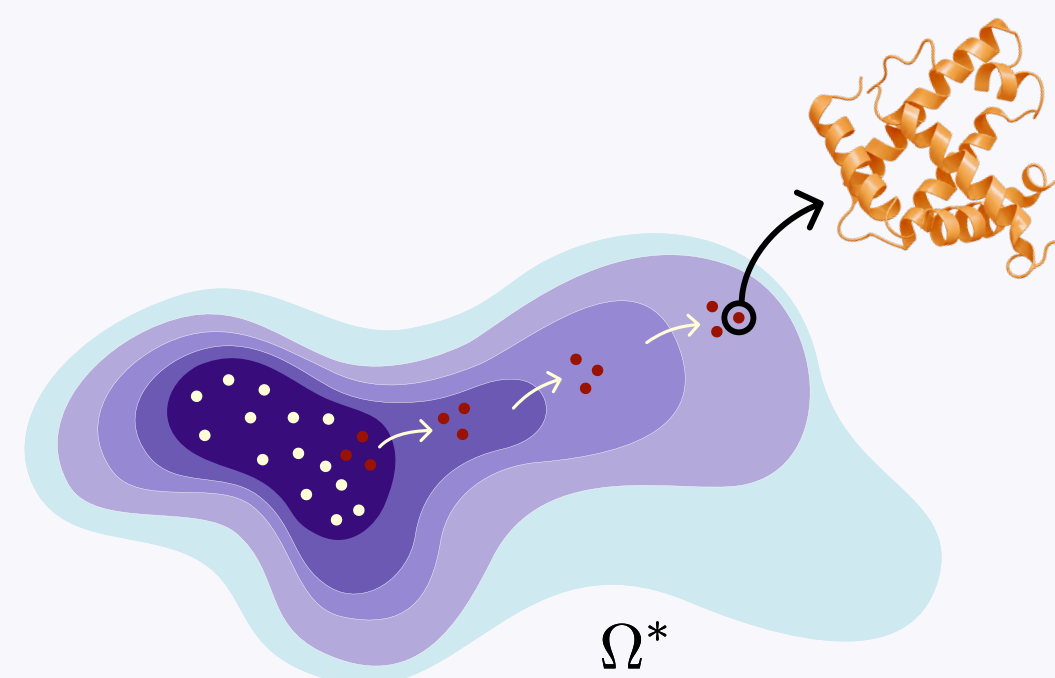
Which candidates matter?



Part II

Out-of-Distribution Flow
Modeling

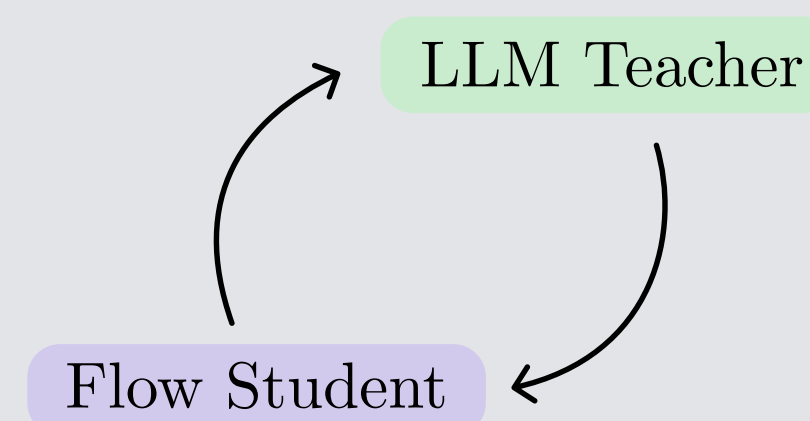
Which regions can we reach?



Part III

Sample-Efficient Discovery
via LLM Feedback

What feedback guides us there?



Expansion for Discovery?

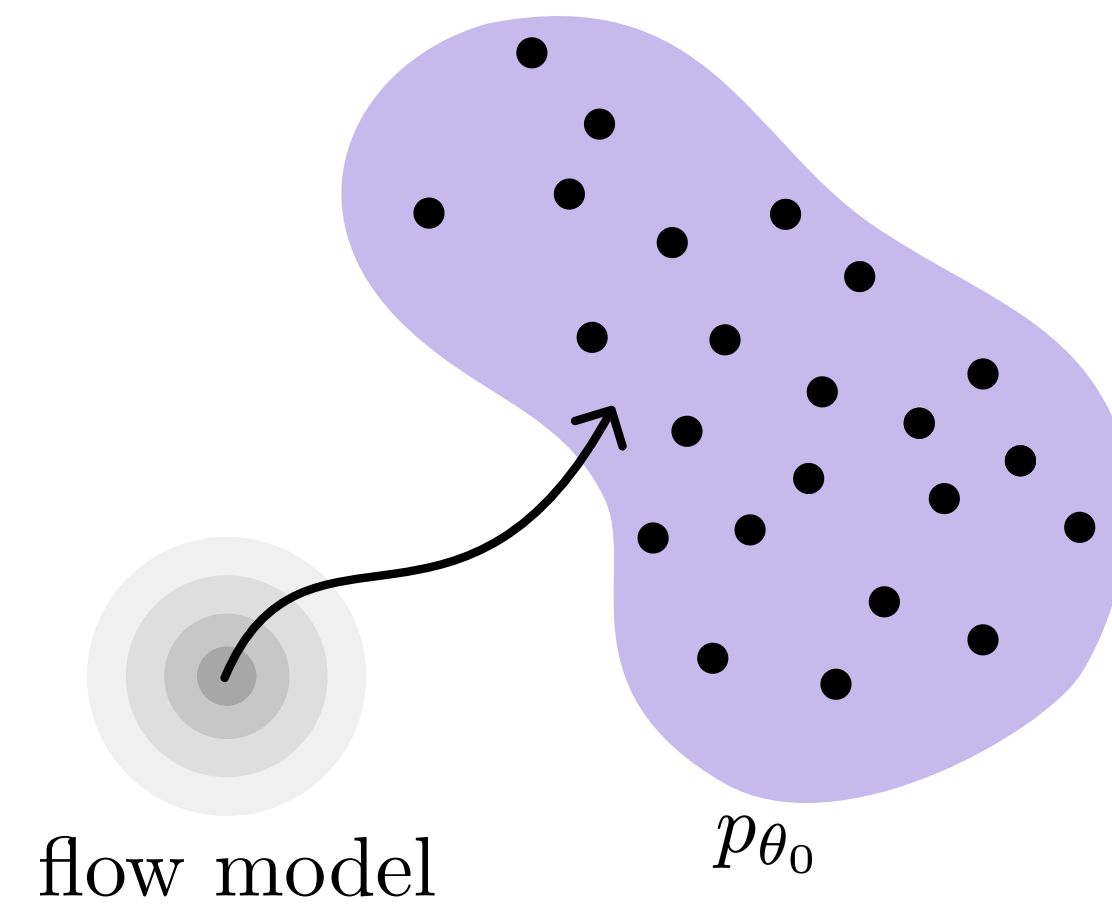
High-level discovery goal

'generate peptides with promising anticancer activity'

Expansion for Discovery?

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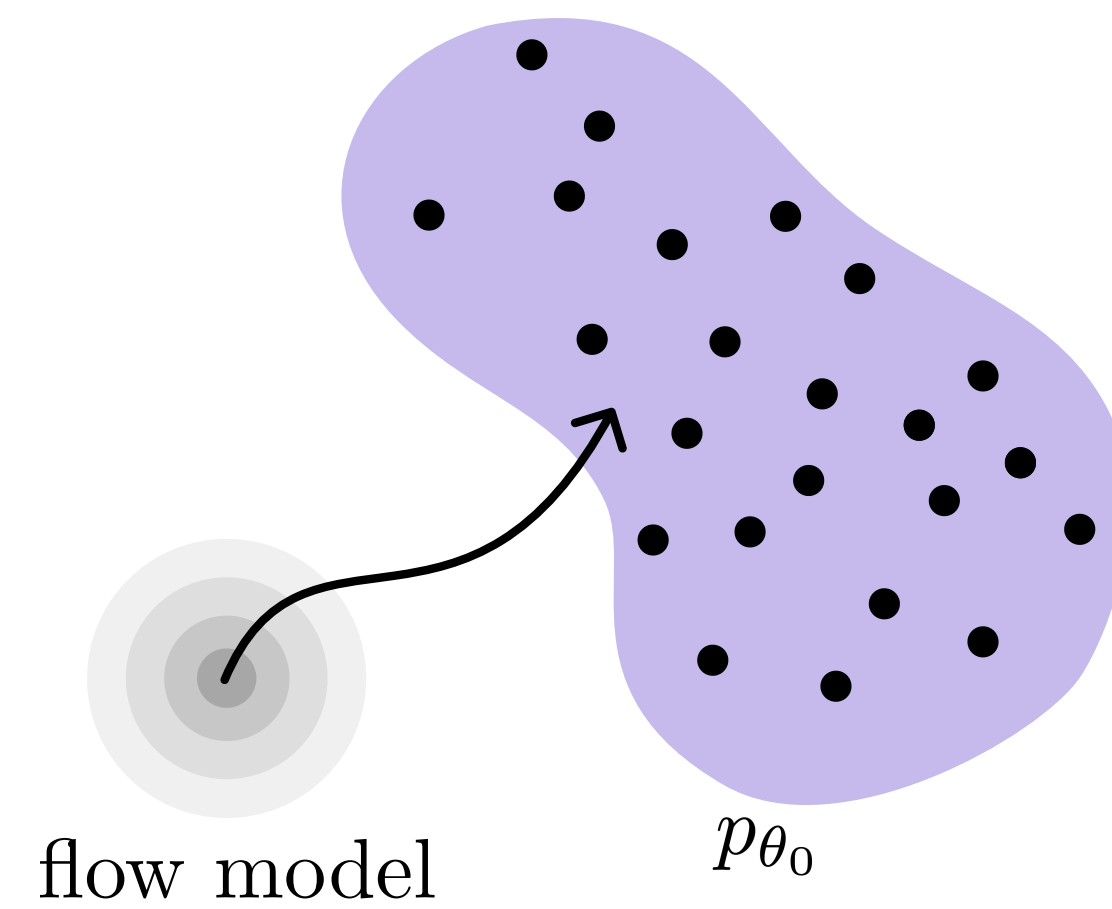
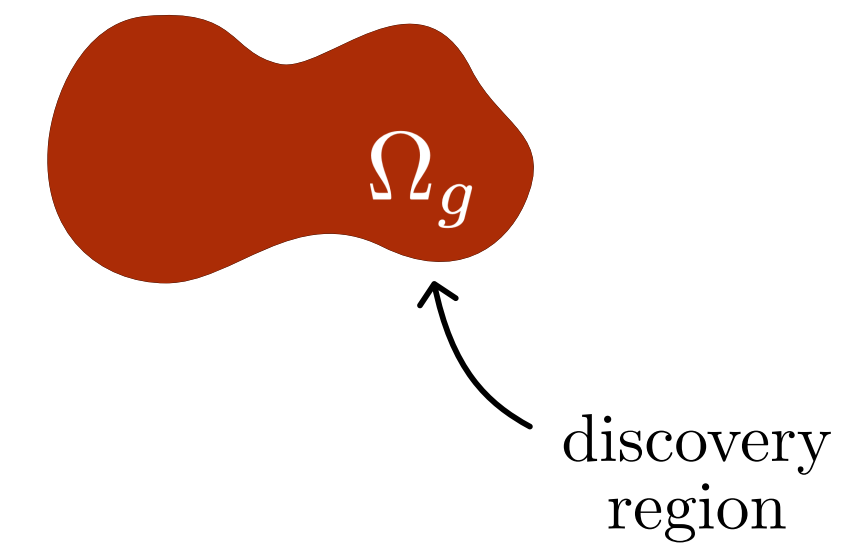
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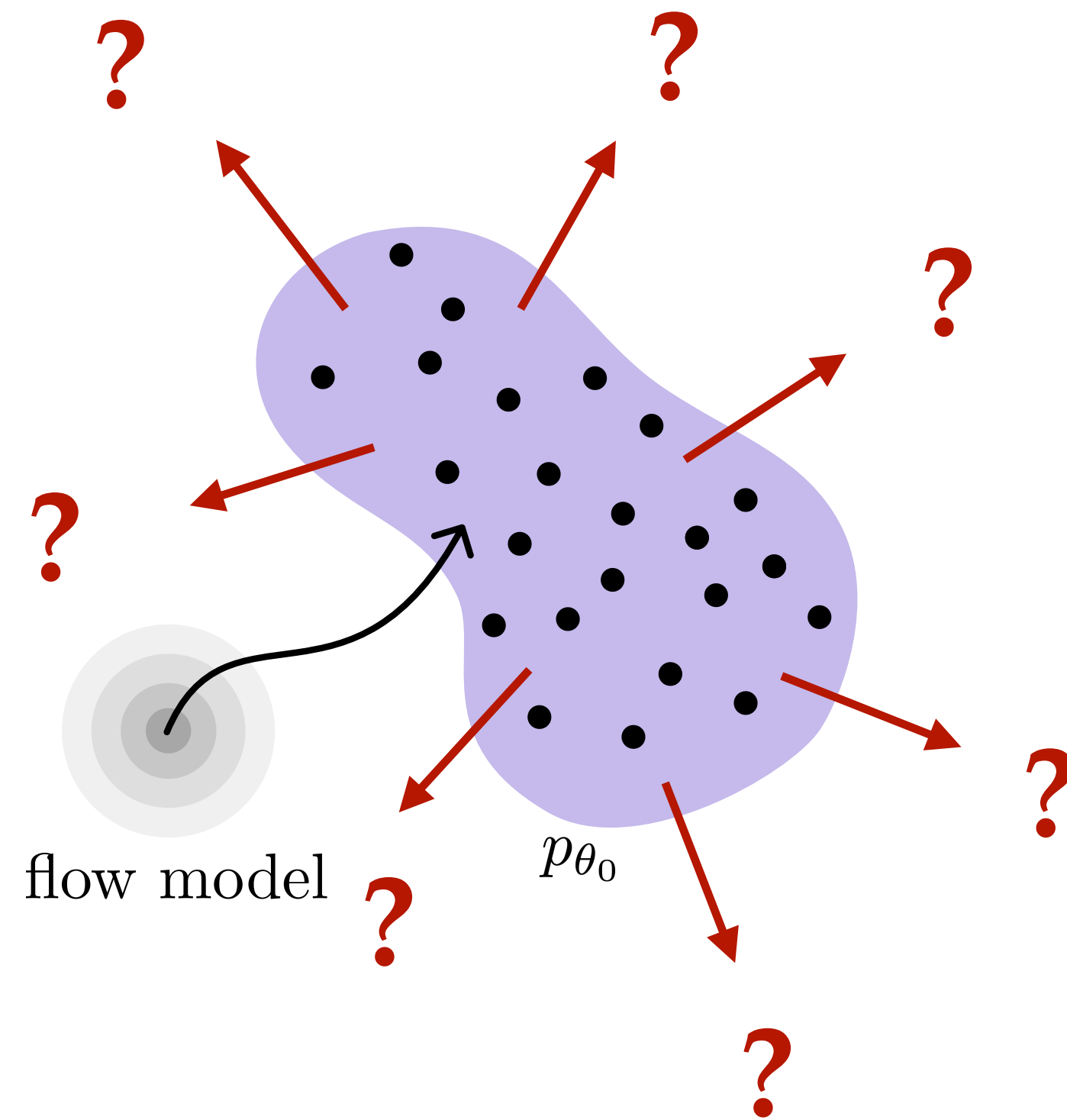
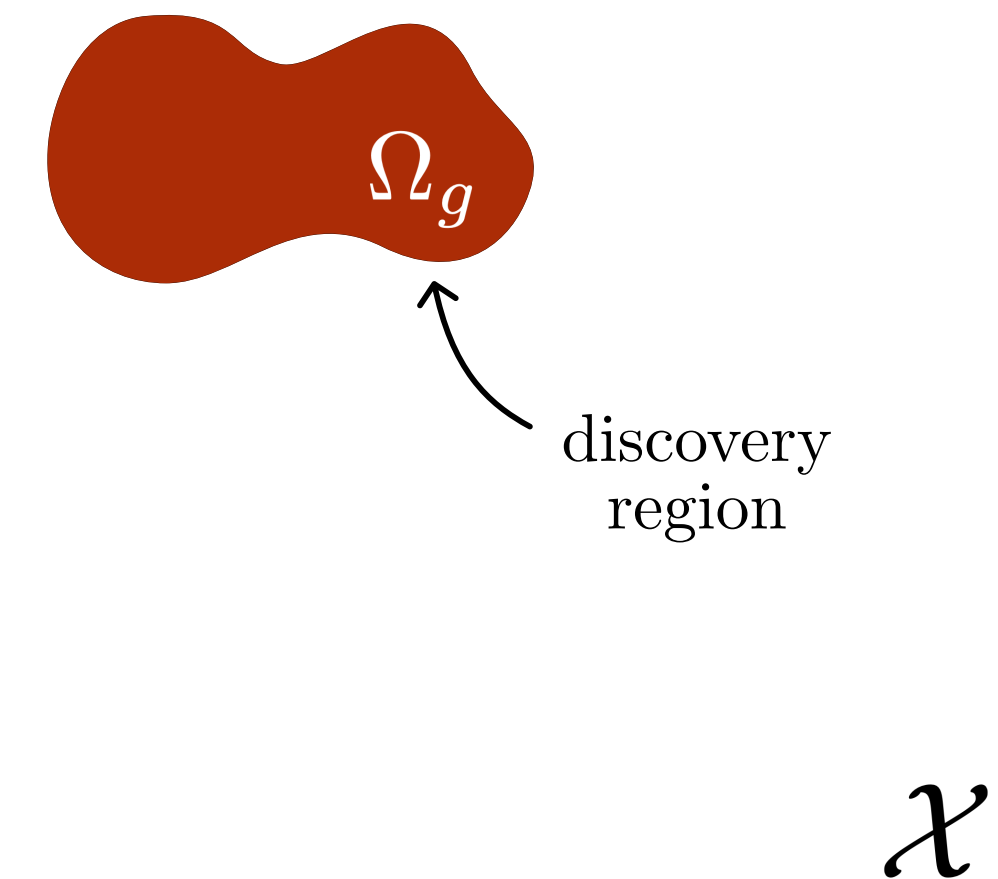


$\mathcal{X}$

Goal-Directed Expansion for Discovery?

High-level discovery goal

'generate peptides with promising anticancer activity'

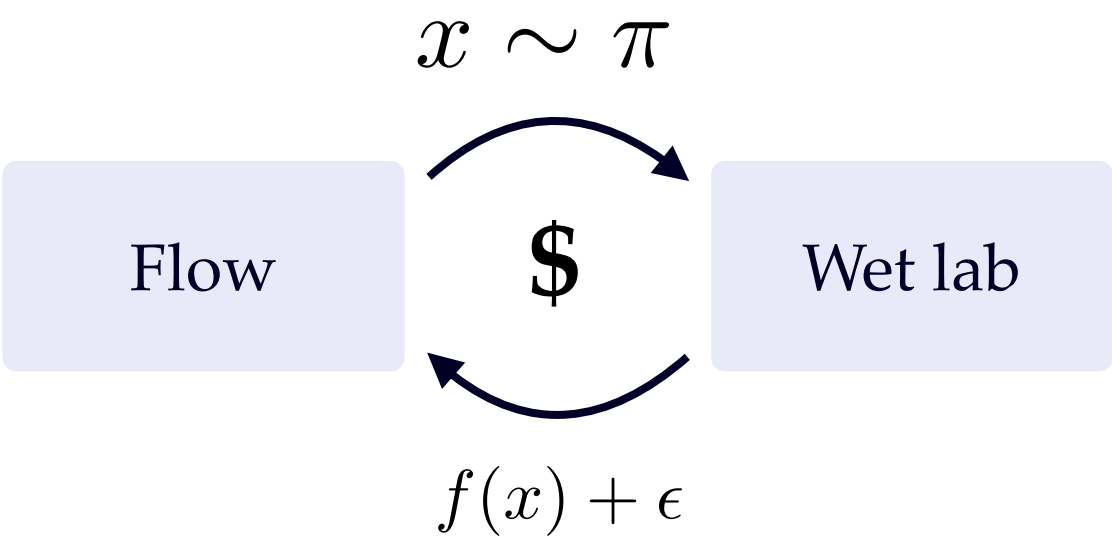
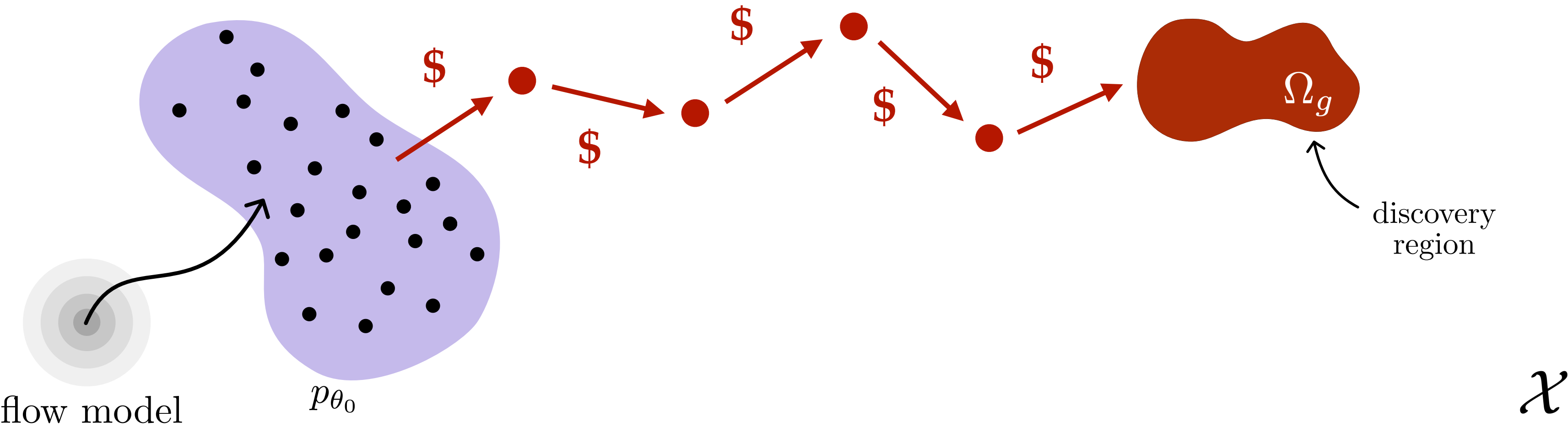


Very hard problem in high-dimensions!

Sample-Efficient and Goal-Directed Expansion for Discovery?

High-level discovery goal

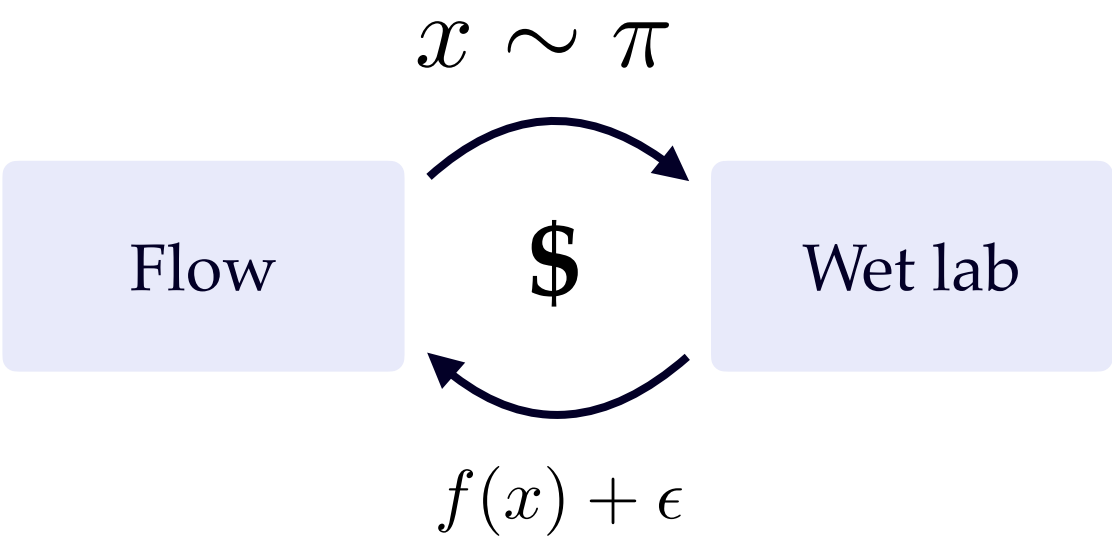
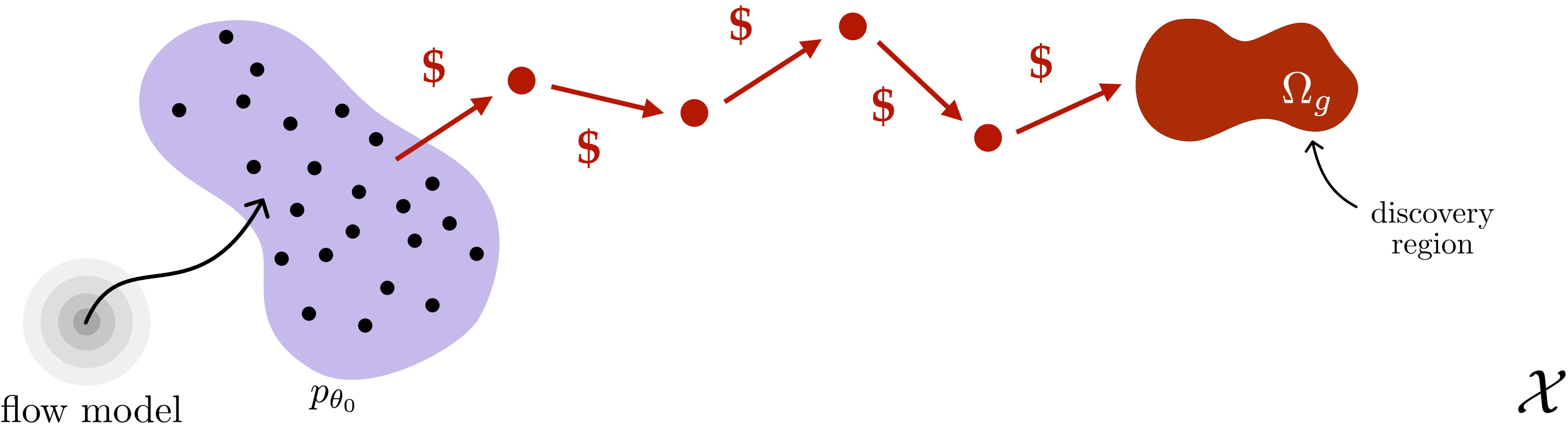
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Sample-Efficient and Goal-Directed Expansion for Discovery?

High-level discovery goal

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Can we exploit existing scientific knowledge in frontier LLMs for efficient discovery?

LLM-to-Flow Distillation: Teaching Natural Language Goals to Scientific Generators

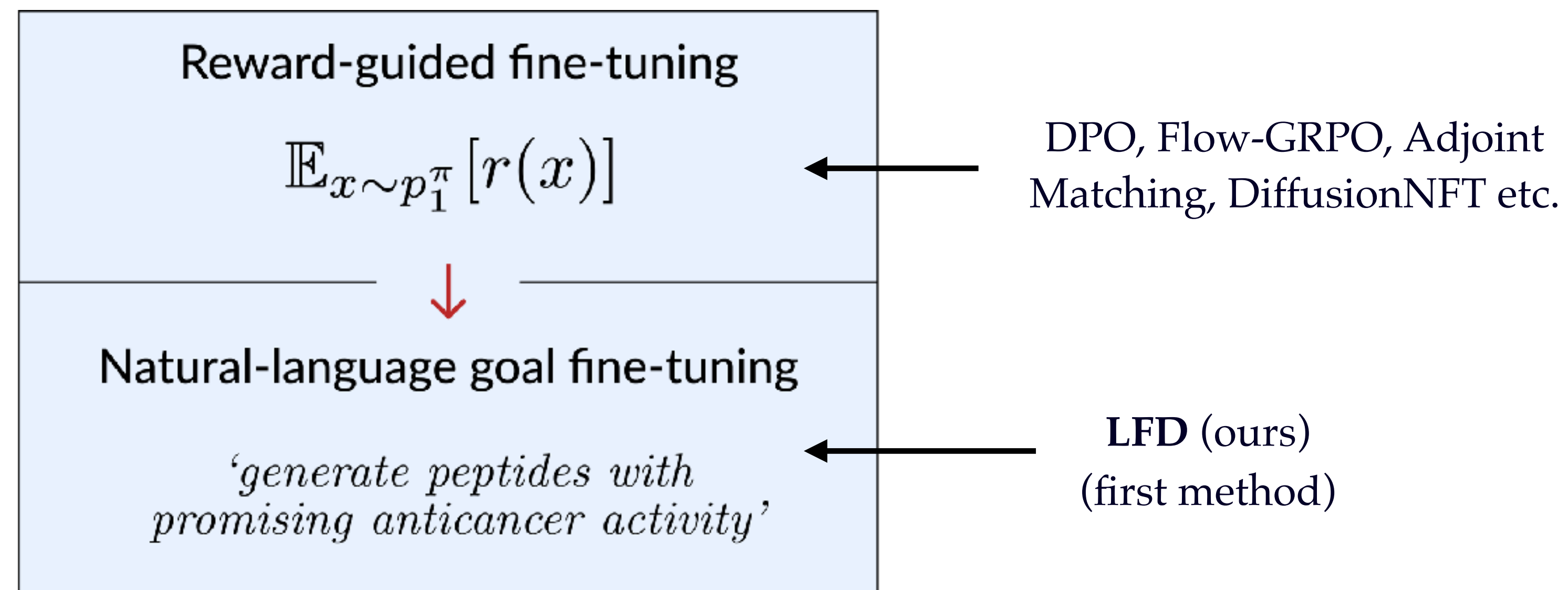
[Riccardo De Santi*, Federico Di Gennaro*, Angelo Gnazzo*, Sophia Tang, Pranam Chatterjee, Fanny Yang, İsmail İlkan Ceylan, Michael M. Bronstein, Andreas Krause]

ArXiv Preprint

From Rewards to Natural-Language Goals

High-level discovery goal

'generate peptides with promising anticancer activity'



LFD is (to our knowledge) the **first method** to **adapt any scientific generator to natural-language goals**

Natural-language discovery goal

Discovery region

$$g = \text{'generate peptides with promising anticancer activity'} \longrightarrow \Omega_g := \{x \in \mathcal{X} : f_g(x) = 1\}$$

Natural-language discovery goal

$g = \text{'generate peptides with promising anticancer activity'}$



Discovery region

$$\Omega_g := \{x \in \mathcal{X} : f_g(x) = 1\}$$

Natural-language goal adaptation:

update $\theta_0 \rightarrow \theta$ such that $p_\theta(\Omega_g) \gg p_{\theta_0}(\Omega_g)$

Natural-language discovery goal

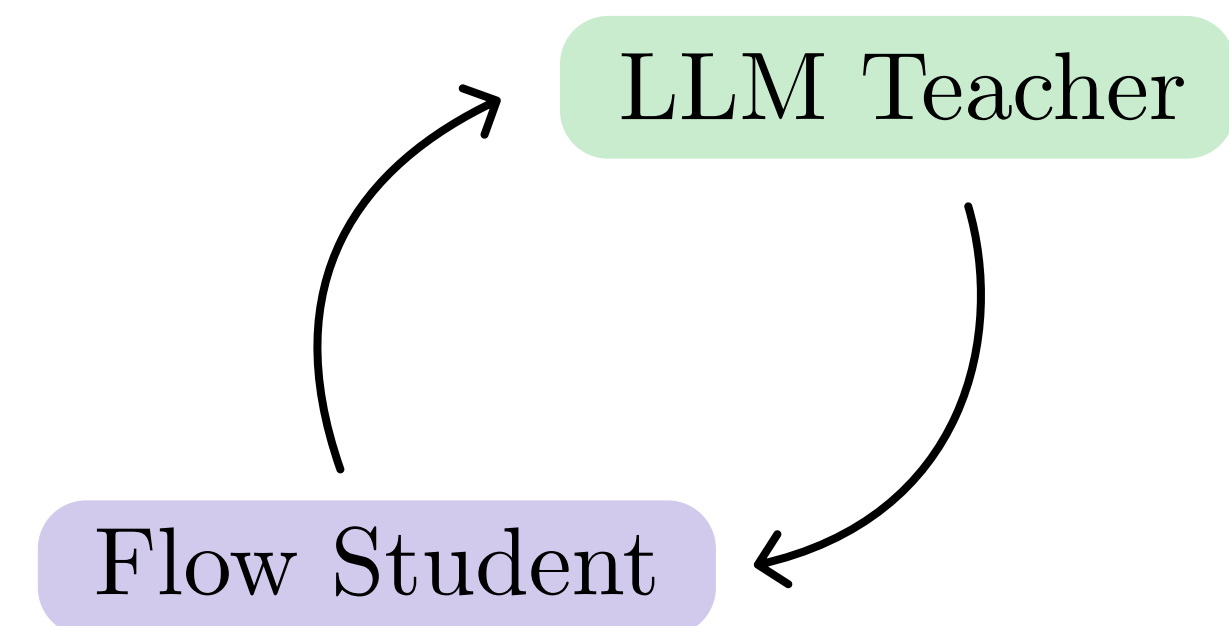
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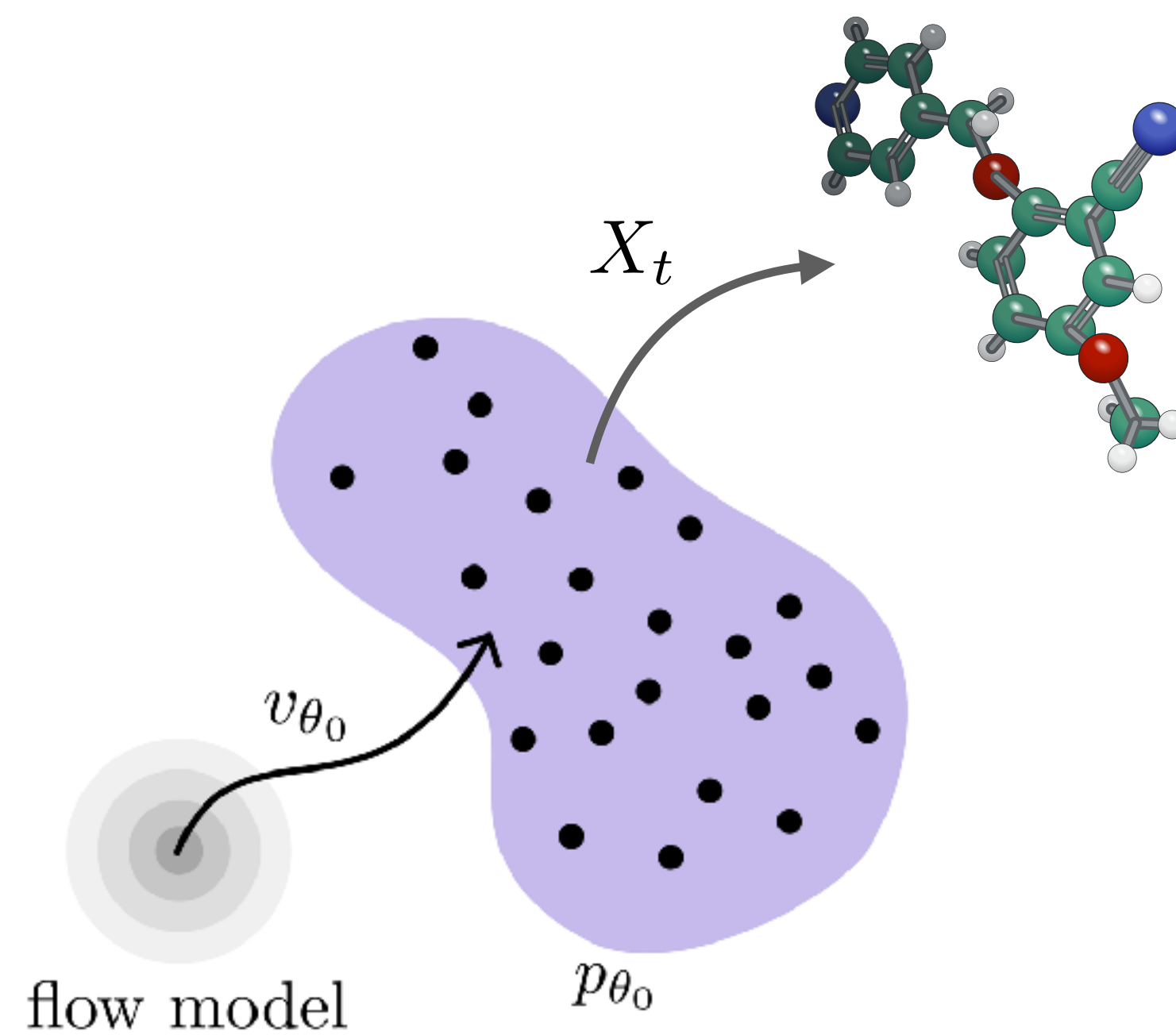
LLM-to-Flow Distillation: distill goal-related LLM scientific knowledge into a domain-specific generator.

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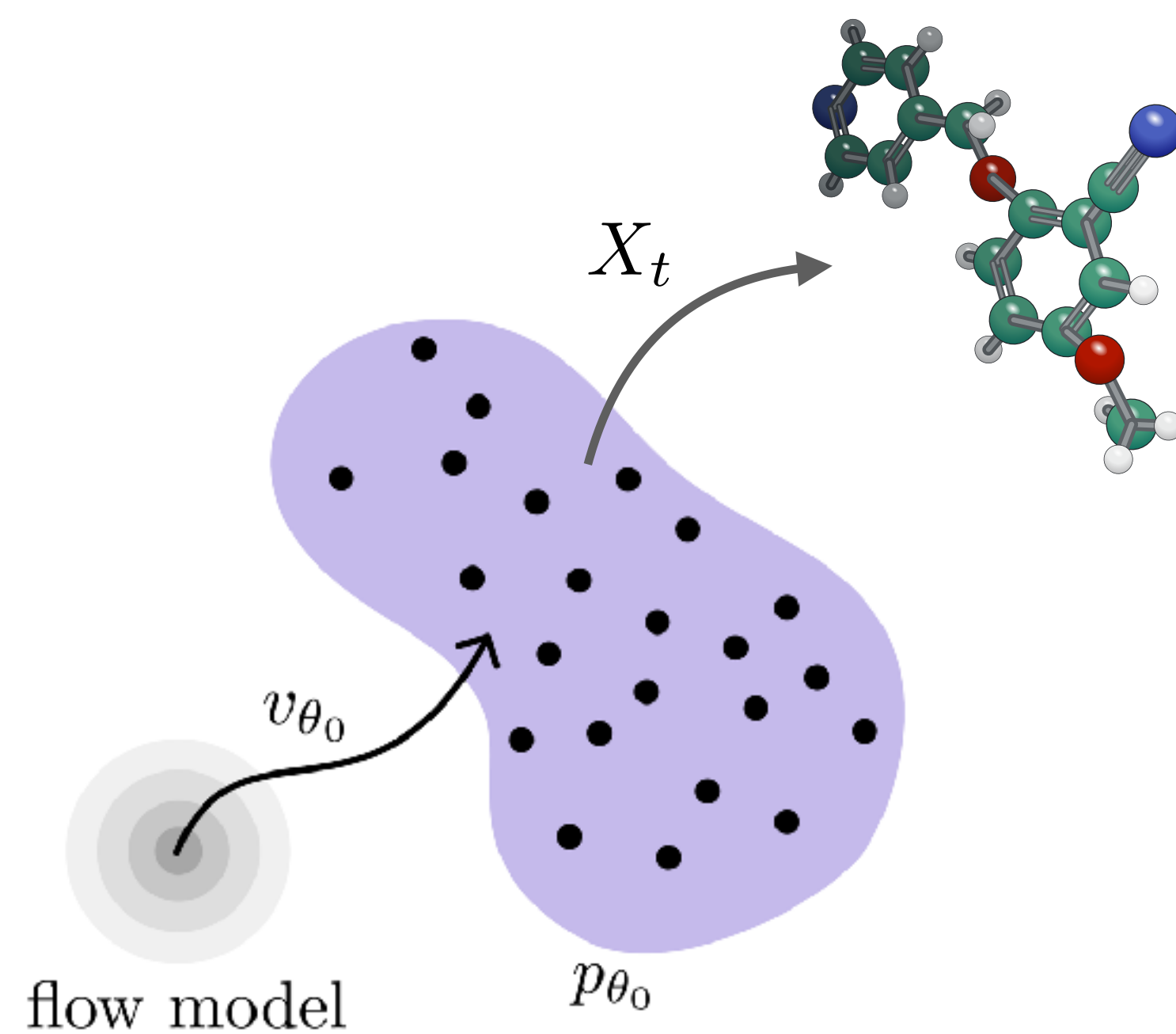
LLM as JUDGE?

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Observables

- SMILES (string)
- Ring counts
- Bond angles
- Atom types
-

LLM as JUDGE?

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LLM as JUDGE?

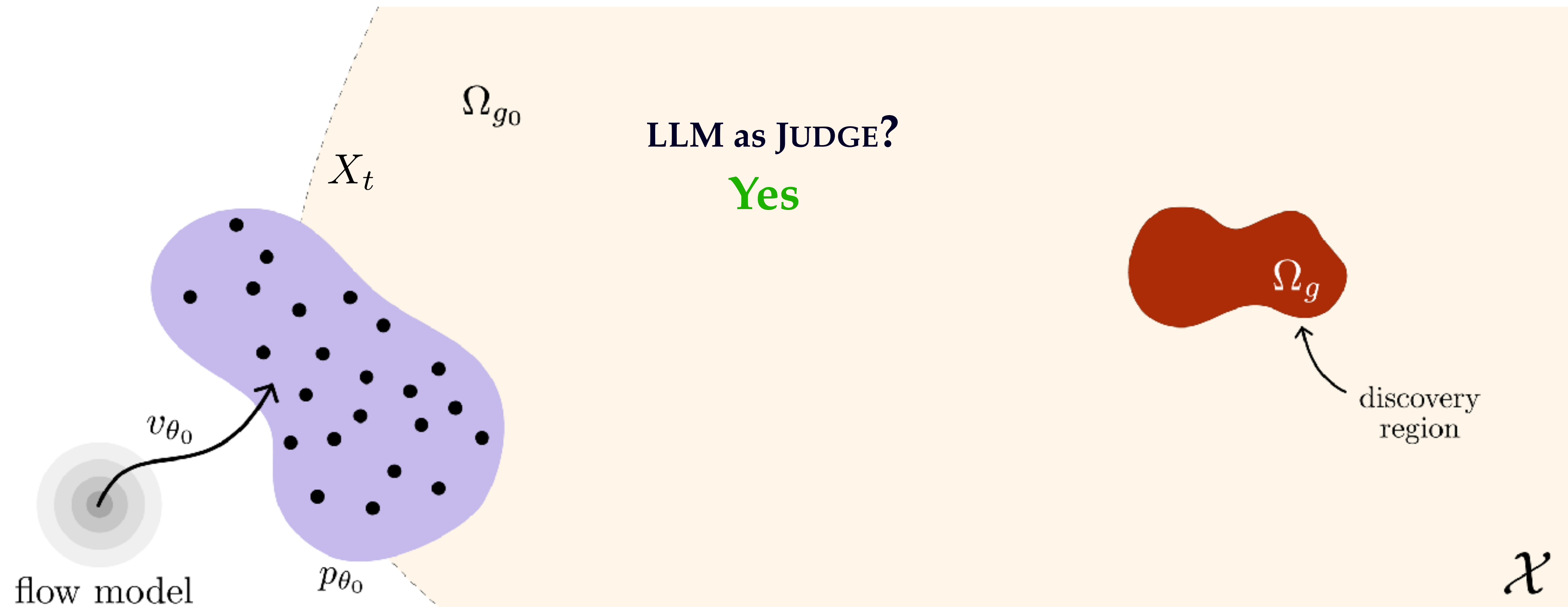


All samples X_t might be all excessively far from Ω_g

Natural-language discovery goal

Discovery region

$$g = \text{'generate peptides with promising anticancer activity'} \longrightarrow \Omega_g := \{x \in \mathcal{X} : f_g(x) = 1\}$$



$$g_0 = \text{'prefer peptides that possess a net positive charge'}$$

LLM-to-Flow Distillation (LFD)

Require: μ_{θ_0} , goal g , observables $\mathcal{O}$

$g_{-1} \leftarrow g$

For $t = 0, \dots, T - 1$

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Proposition: each LFD round is a KL-regularized step toward an **implicit reward**.

$$p_t^* \propto p_{\theta_t} e^{f_{g_t}/\beta} \iff p_t^* = \arg \max_q \{ \mathbb{E}_q[f_{g_t}] - \beta \mathcal{D}_{\text{KL}}(q \parallel p_{\theta_t}) \}$$

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LFD $\approx$ Iterative DPO on implicit LLM rewards

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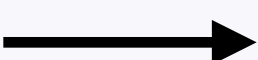
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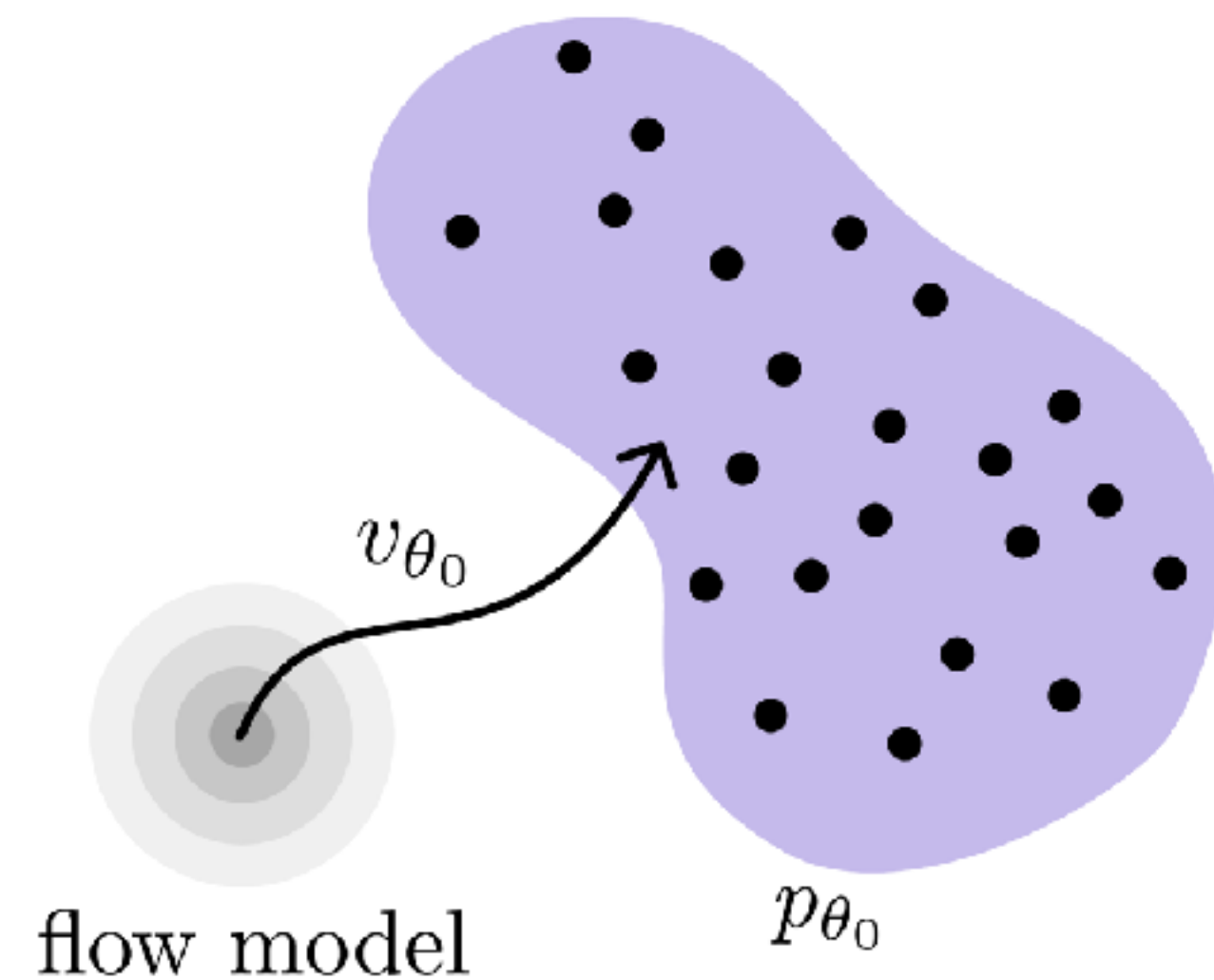
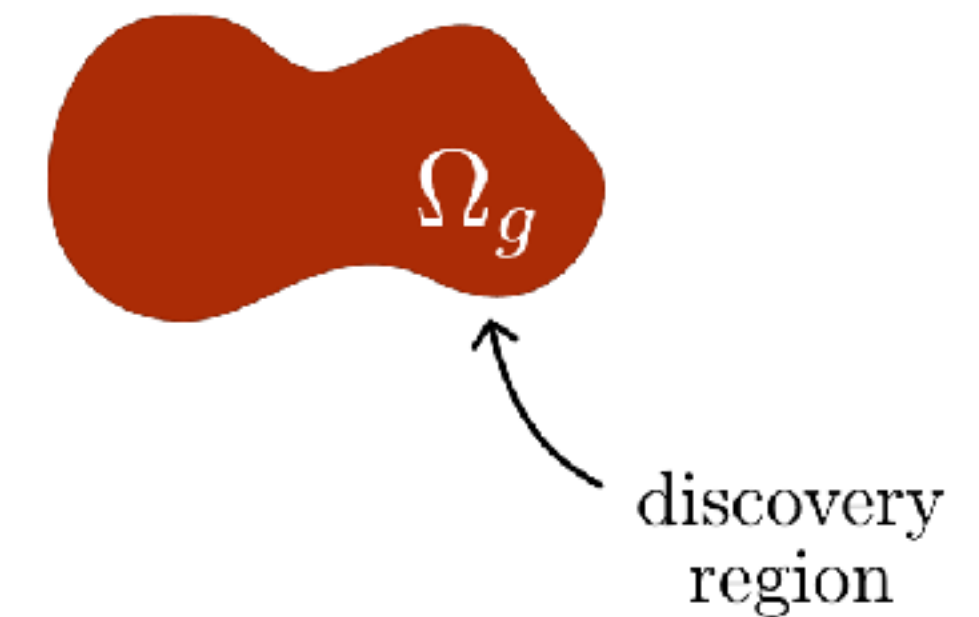
LFD requires only LLM API-access  **Can use any closed frontier model**

From Rewards to Natural-Language Goals

Natural-language discovery goal

Discovery region

$$g = \text{'generate peptides with promising anticancer activity'} \longrightarrow \Omega_g := \{x \in \mathcal{X} : f_g(x) = 1\}$$



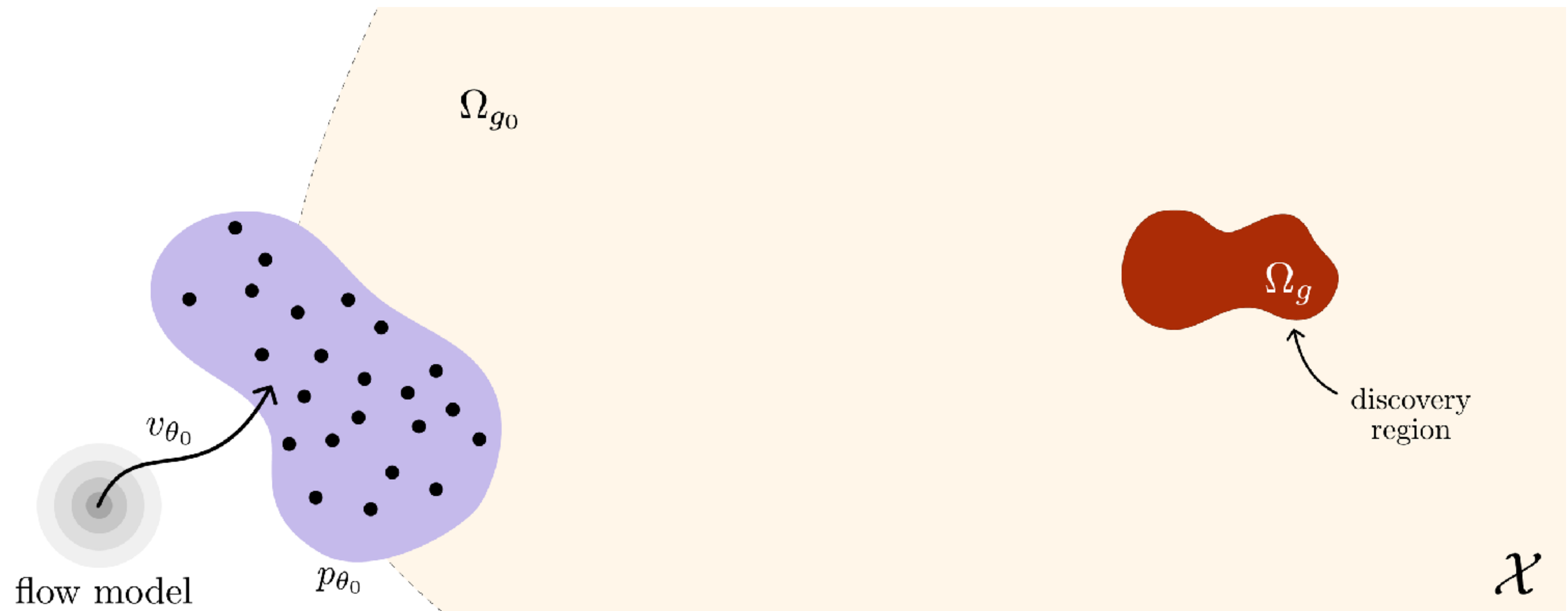
$\mathcal{X}$

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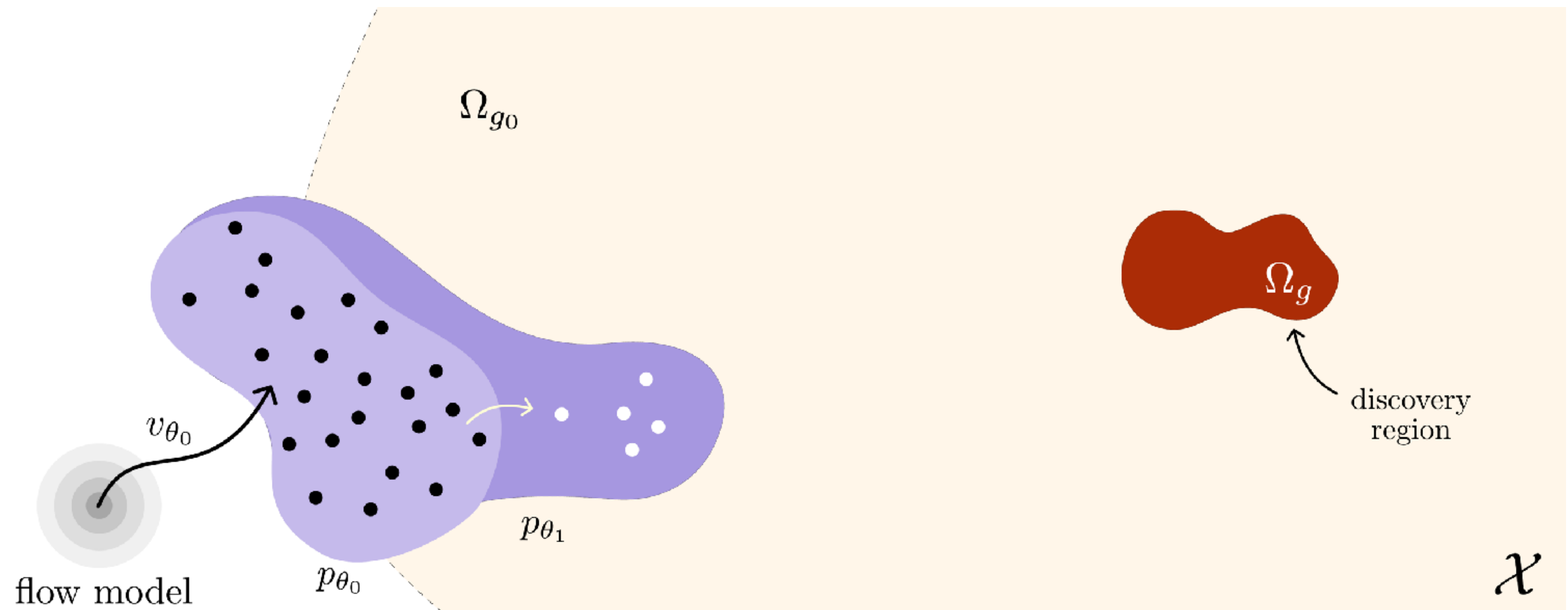


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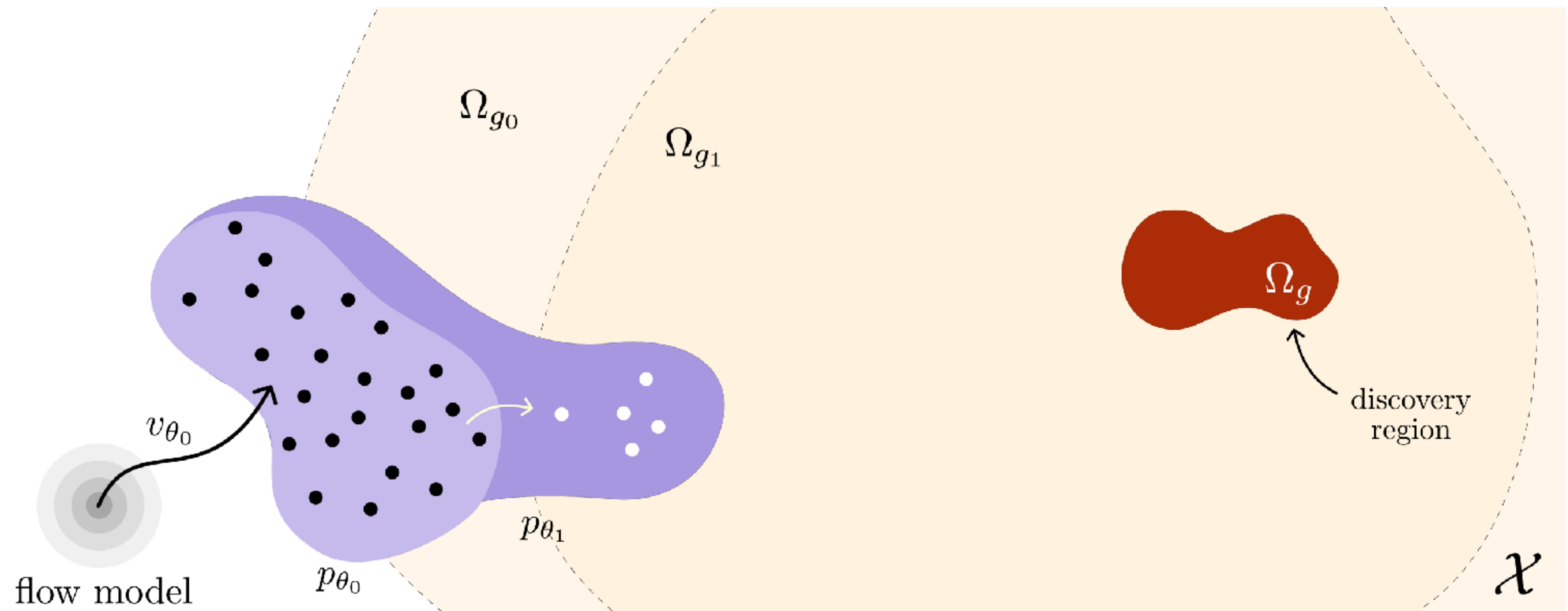


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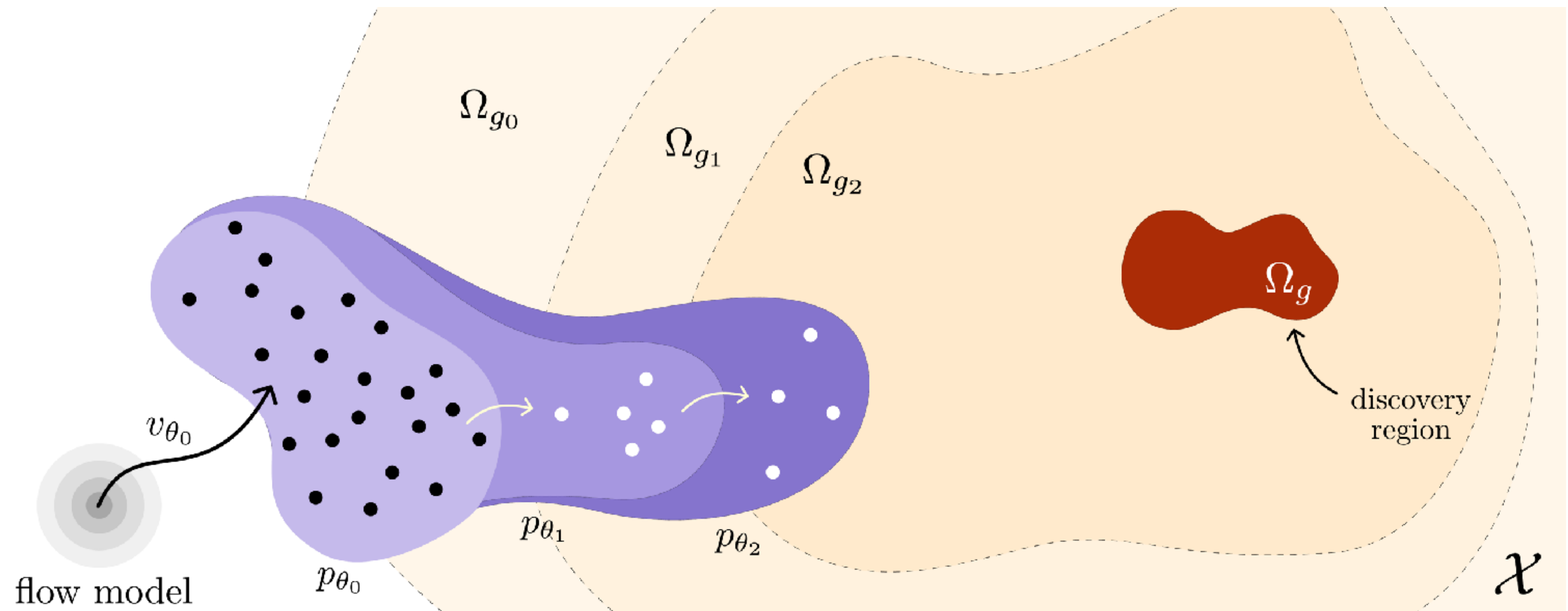


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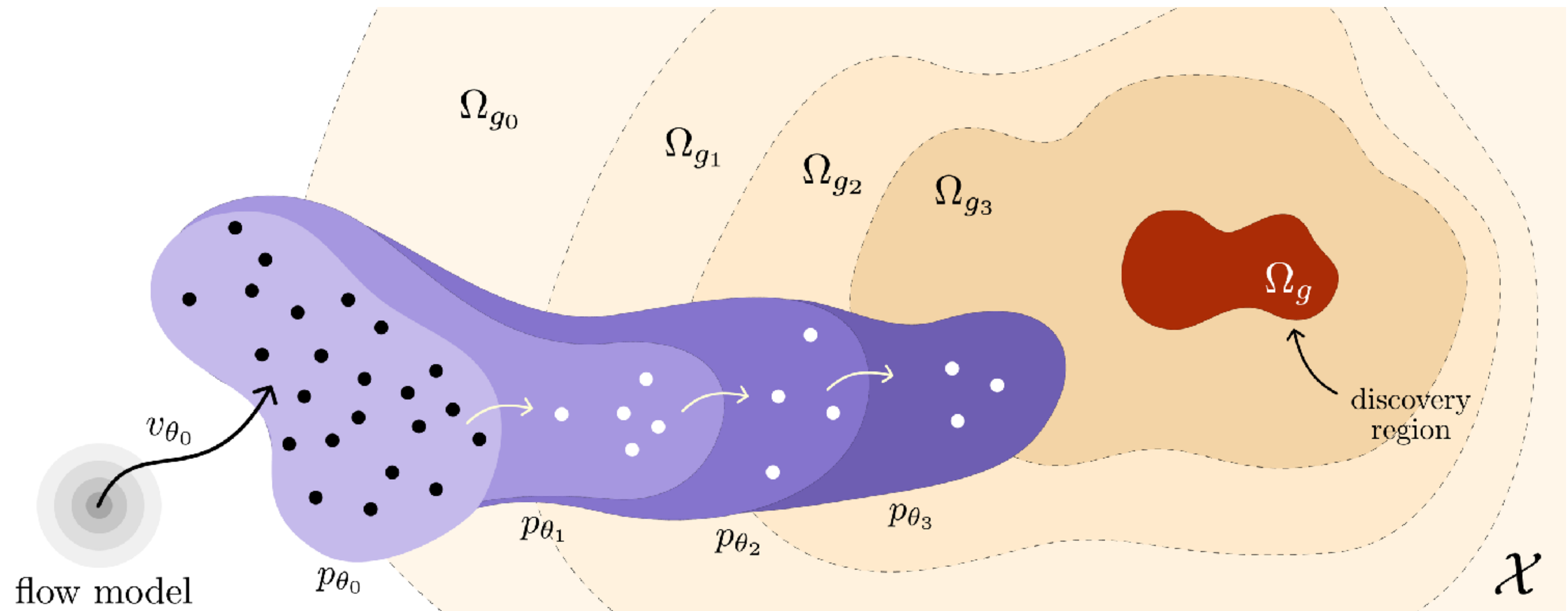


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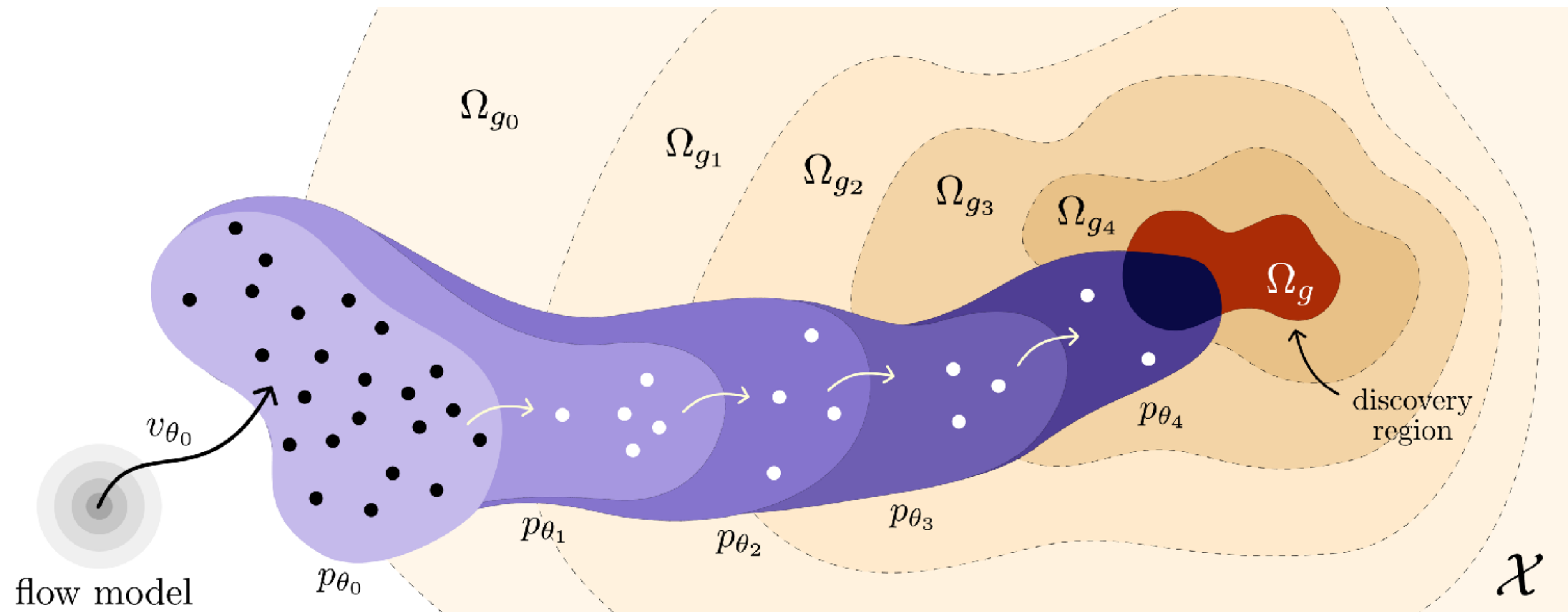


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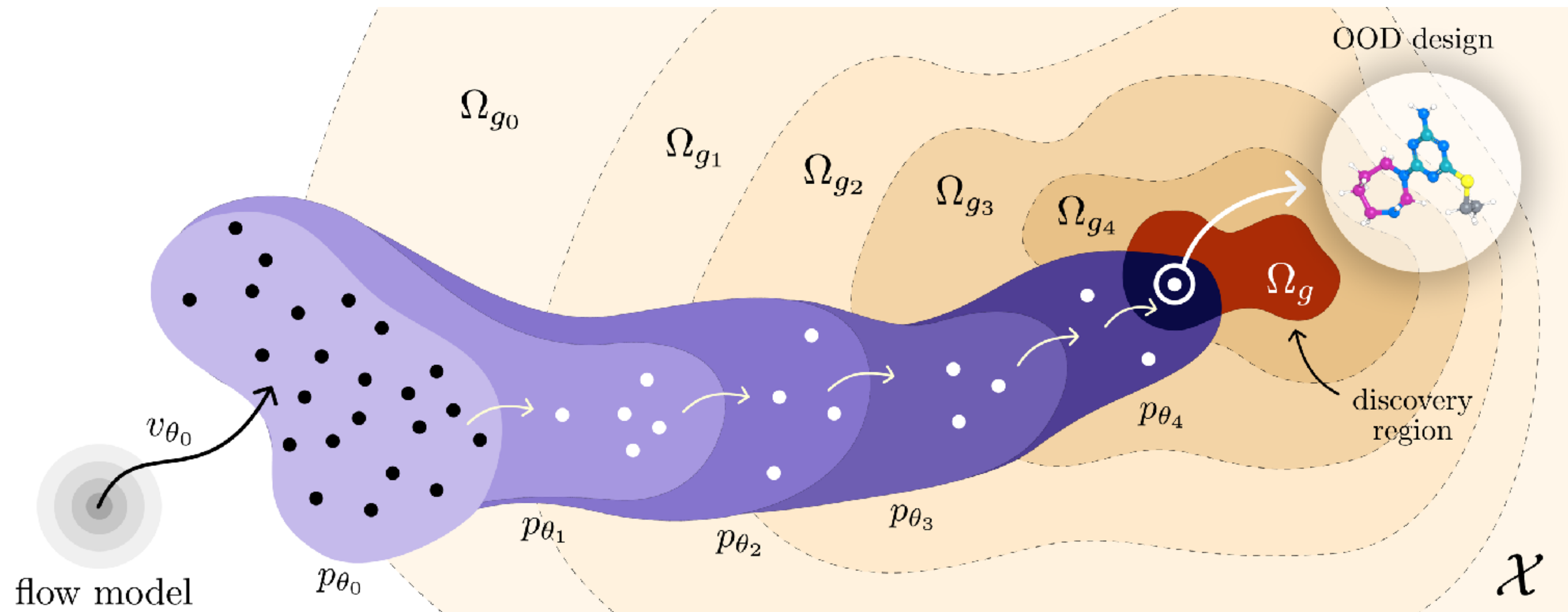


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LFD for Peptide Design

GOAL 1: Generate peptides with promising **anticancer activity** while maintaining **low toxicity** toward healthy cells.

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Method	Therapeutic Peptides (CPP)			Therapeutic Peptides (Anti-Cancer)		
	pLM4CPPs (%) ↑	HemoPI2 (%) ↓	Distance from prior ↑	AntiCP2-alt. (%) ↑	HemoPI2 (%) ↓	Distance from prior ↑
Pre-trained	8.81 ± 3.20	40.84 ± 1.96	0.06 ± 0.04	26.43 ± 2.91	40.85 ± 1.89	0.00 ± 0.00
DPO	10.39 ± 3.19	40.49 ± 1.92	0.07 ± 0.04	25.29 ± 3.19	42.77 ± 1.81	0.08 ± 0.04
DIFFUSIONNFT	57.04 ± 6.22	38.87 ± 1.62	0.29 ± 0.03	33.26 ± 2.76	45.61 ± 2.39	0.16 ± 0.03
GUIDANCE	8.49 ± 3.30	43.45 ± 1.85	0.06 ± 0.04	35.94 ± 2.33	47.25 ± 1.81	0.29 ± 0.03
LFD	69.06 ± 6.36	37.02 ± 1.69	0.34 ± 0.03	53.54 ± 3.32	42.48 ± 2.04	0.31 ± 0.03

LFD surpasses state-of-the-art reward-guided methods on held-out evaluation.

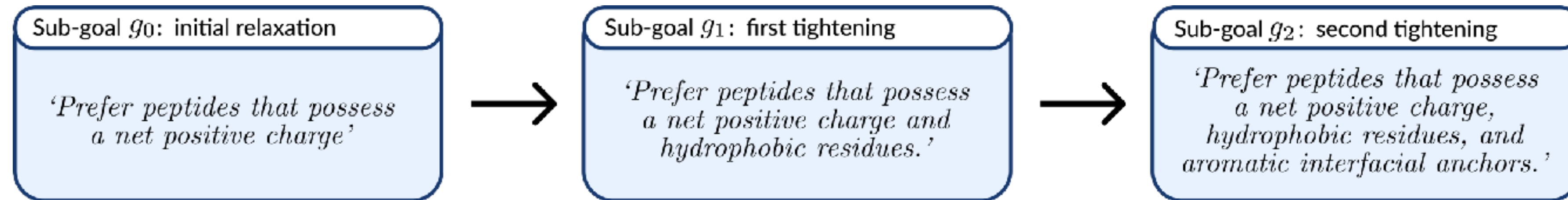
INSIGHT: LFD can align domain-specific scientific generators to high-level, natural-language discovery goals, **without utilizing any proxy reward**.

LFD for Peptide Design: Interpretability

GOAL 1: Generate peptides with promising **anticancer activity** while maintaining **low toxicity** toward healthy cells.

LFD for Peptide Design: Interpretability

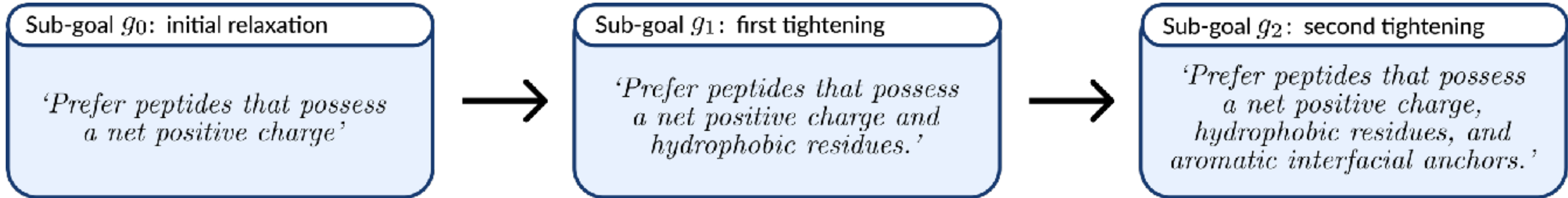
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LFD generates sub-goals interpretable by scientists.

LFD for Peptide Design: Interpretability

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LFD generates sub-goals interpretable by scientists.

LLM interpretable traces

Peptide (-/-):
MLKGRWPDEQKKNHLMNYNFMFLIVFVLTFNISFQSSNI
Charge index = +2.1; hydrophobicity = 47.4%;
lower-third non-hemolysis band.

LLM rationale: *Violates the operative goal (g3) by possessing a prolonged, contiguous hydrophobic tract (MLIVFVL) [...]*

LLM uncertainty: *In vitro hemolytic threshold and aggregation state in physiological buffer.*

INSIGHT: LFD generates scientist-interpretable sub-goals and decision-making traces, allowing human scientists to understand and steer the discovery process.

LFD Surpasses Reward-Adaptation in Molecular Design Tasks

GOAL 3: Generate promising drug-like small molecules for **binding the dopamine D2 receptor**, balancing plausible receptor recognition with moderate lipophilicity and **chemically viable structures**.

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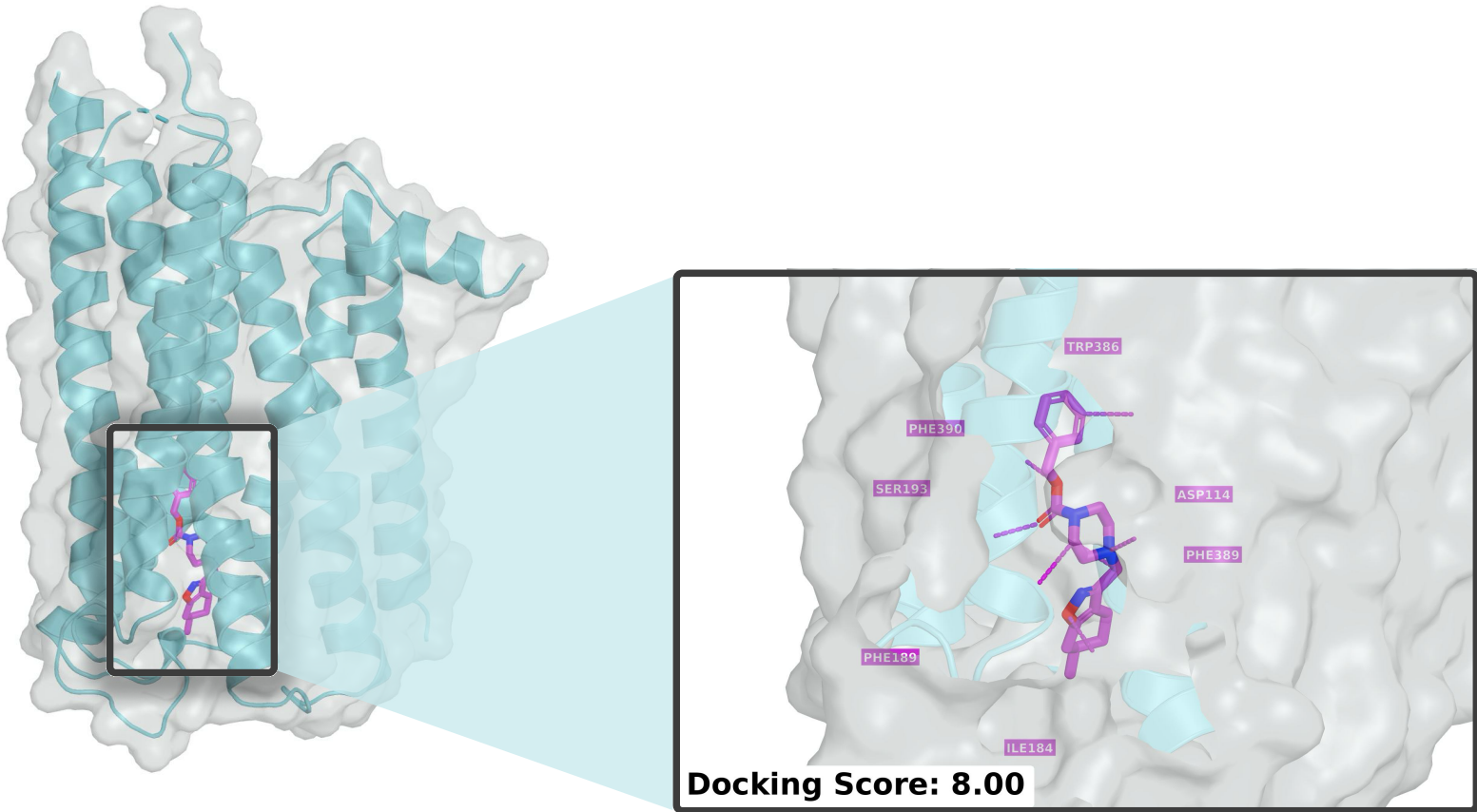
LFD does not observe any docking proxy!

LFD Surpasses Reward-Adaptation in Molecular Design Tasks

GOAL 3: Generate promising drug-like small molecules for **binding the dopamine D2 receptor**, balancing plausible receptor recognition with moderate lipophilicity and **chemically viable structures**.

Method	Small Molecules (D2 Receptor)		
	GNINA $\uparrow$	Vina $\downarrow$	rDock $\downarrow$
Pre-trained	6.11 ± 0.33	-7.52 ± 0.39	-7.64 ± 1.33
DPO	5.60 ± 0.05	-6.81 ± 0.08	-8.11 ± 0.36
FLOW-GRPO	6.32 ± 0.06	-7.83 ± 0.09	-8.15 ± 0.27
DIFFUSIONNFT	6.23 ± 0.07	-7.90 ± 0.23	-9.39 ± 0.26
GUIDANCE	6.29 ± 0.07	-7.65 ± 0.21	-7.92 ± 0.25
LFD	6.54 ± 0.09	-8.48 ± 0.16	-9.89 ± 0.38

LFD outperforms reward-guided baselines on diverse held-out docking scores.



LFD-generated molecule docks to D2 dopamine receptor

98% Validity

89.5% Conformer Quality

LFD for Molecular Design: Complex Constraints + OOD Generation

GOAL 5: Generate **neutral**, connected small molecules for a kinase-focused discovery campaign that contain a **six-membered aza-aromatic ring** bearing a **free primary amino group** on a **ring carbon adjacent to a pyridine-like ring nitrogen**, and a distinct **fully saturated ring** containing a **free secondary amine**.

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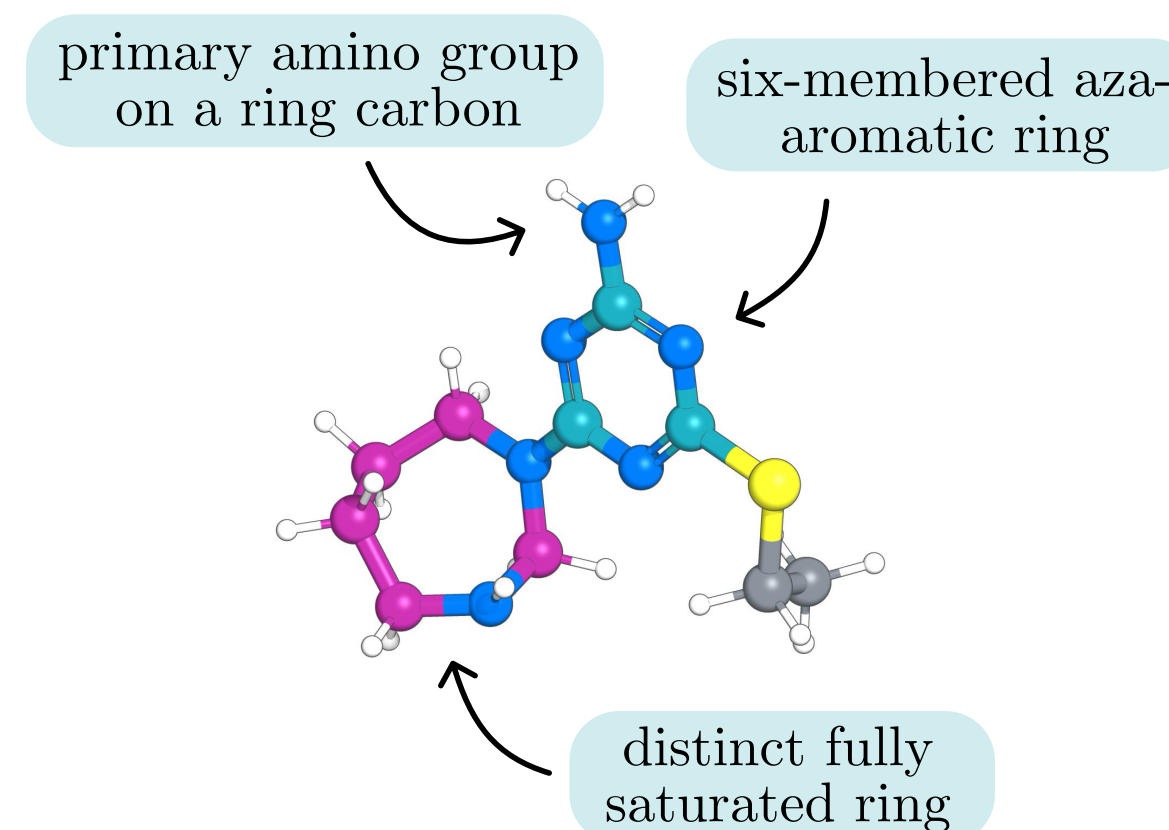
Desired structure is **out of prior model's generable set**

LFD for Molecular Design: Complex Constraints + OOD Generation

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→ **LFD finds a hit** in a 512-sample batch at round 6.



INSIGHT: Through its adaptive LLM-generated sub-goal curriculum, LFD can adapt flow models to OOD discovery goals where state-of-the-art reward-guided methods might fail.

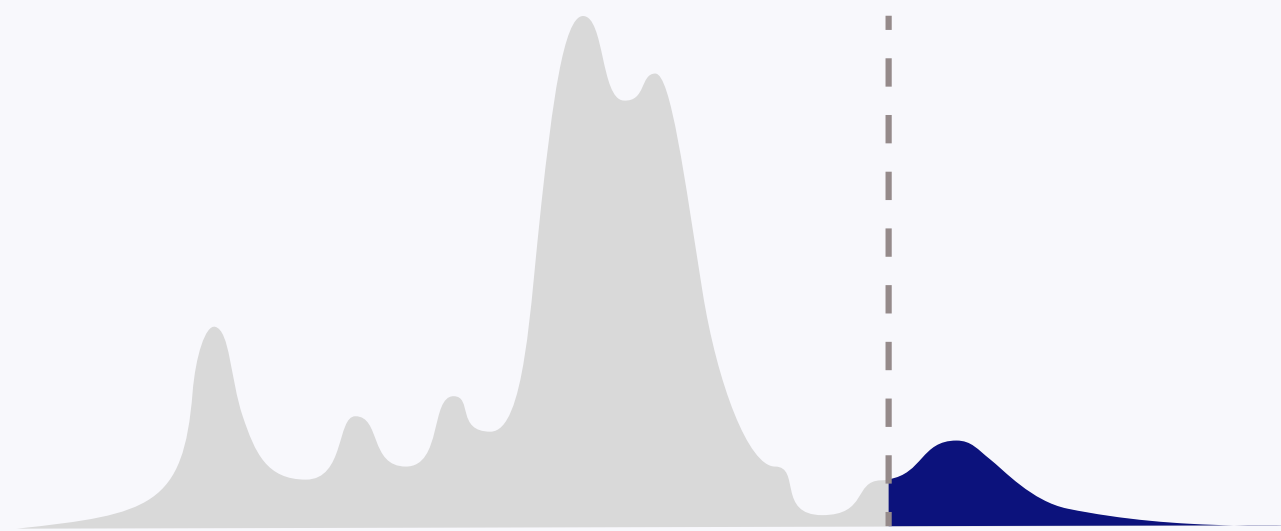
Generative Discovery

Generation of **rare and diverse structures**, potentially **far beyond available data** and **sample-efficiently**

Part I

Rare and Diverse
Generation

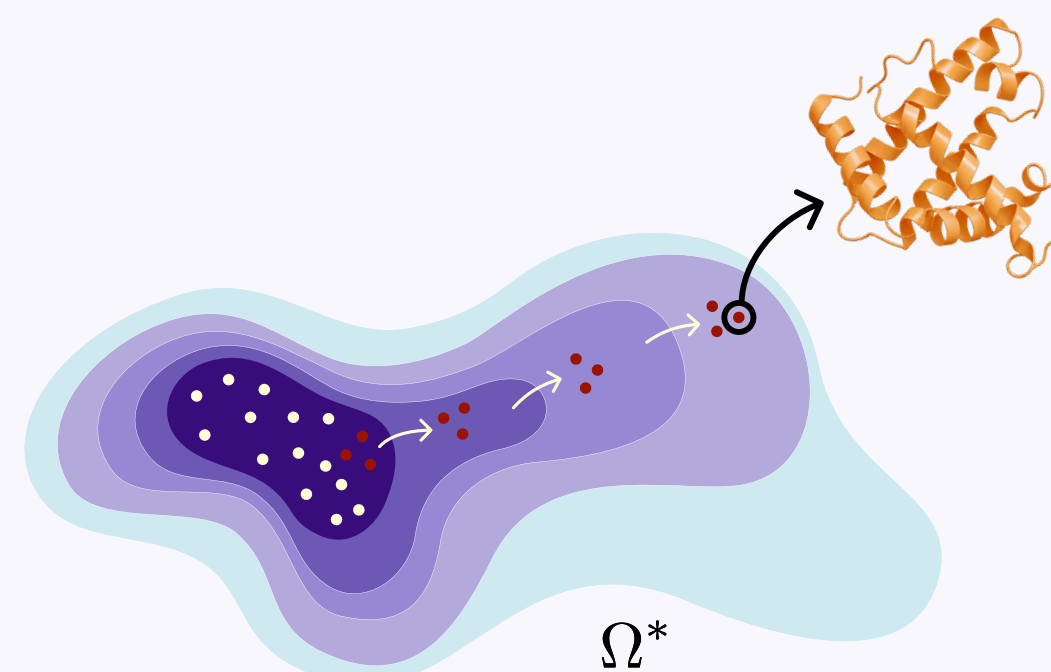
Which candidates matter?



Part II

Out-of-Distribution Flow
Modeling

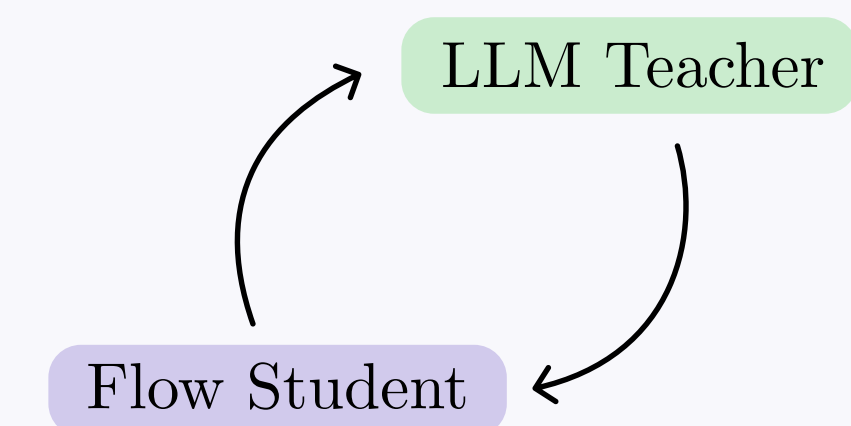
Which regions can we reach?



Part III

Sample-Efficient Discovery
via LLM Feedback

What feedback guides us there?



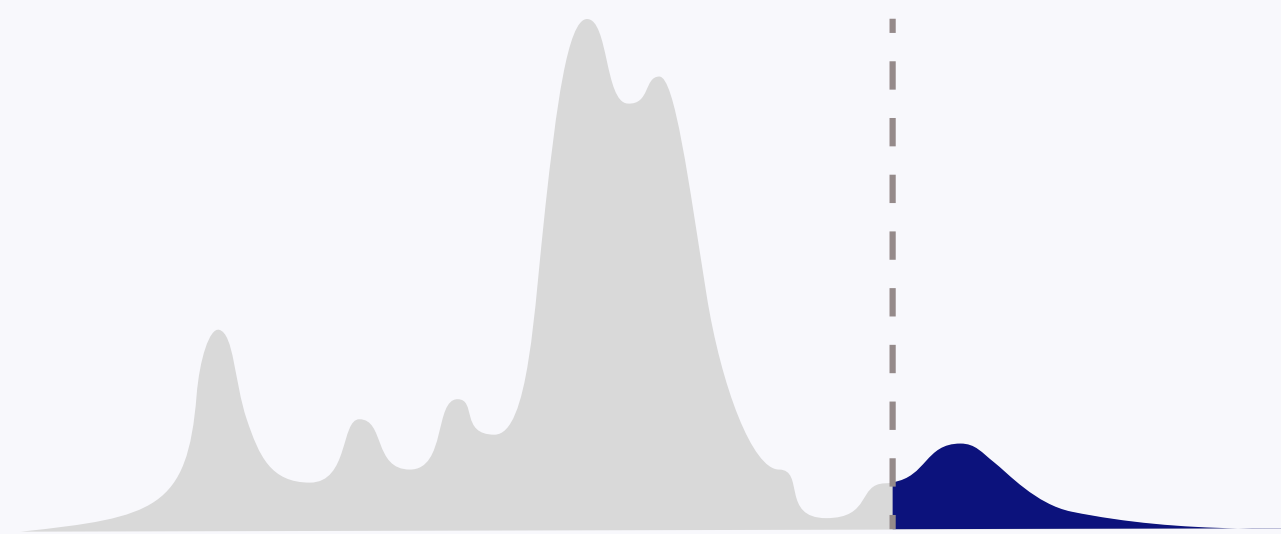
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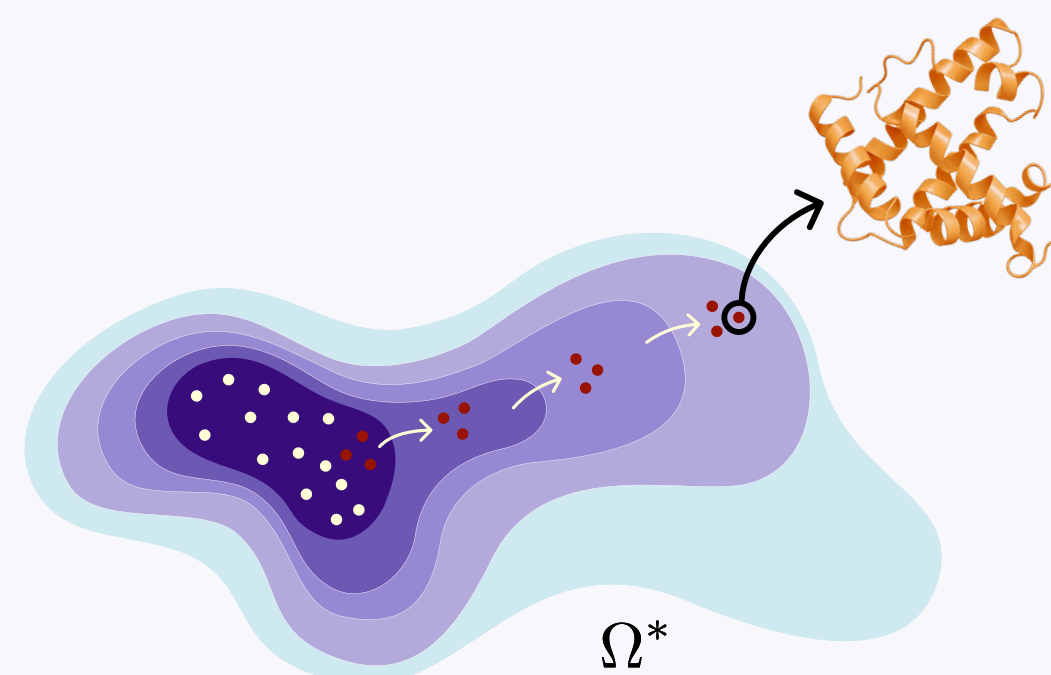


→ FDC

Part II

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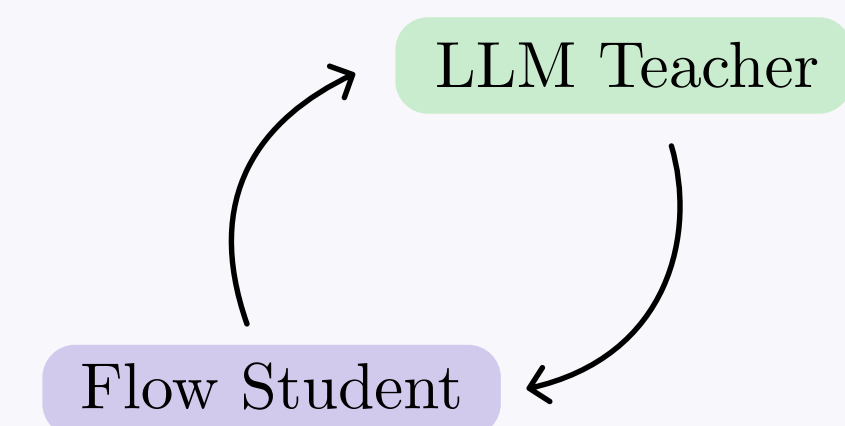


→ ActFlow

Part III

Sample-Efficient Discovery
via LLM Feedback

What feedback guides us there?



→ LFD

Thanks!

Collaborators

Kimion Protopapas, Ya-Ping Hsieh, Sven Gutjahr, Luca Schaufelberger, Zifan Wang, Xiaoyu Mo, Malte Franke, Cristian Perez Jensen, Andrey Kharitenko, Zebang Shen, Marin Vlastelica, Guy Schacht, Mojmir Mutny, Ziyad Sheebaelhamd, Bruce Lee, Sophia Tang, Cheng-Hao Liu, Federico Di Gennaro, Angelo Gnazzo, Michael M. Zavlanos, Harini Vijayshankar, Dylan Abramson, Basile Wicky, Karl H. Johansson, Fanny Yang, İsmail İlkan Ceylan, Kjell Jorner, Florian Dörfler, Frances H. Arnold, Pranam Chatterjee, Michael M. Bronstein, Yisong Yue, Niao He, Andreas Krause.



Thanks!

Papers + Code →

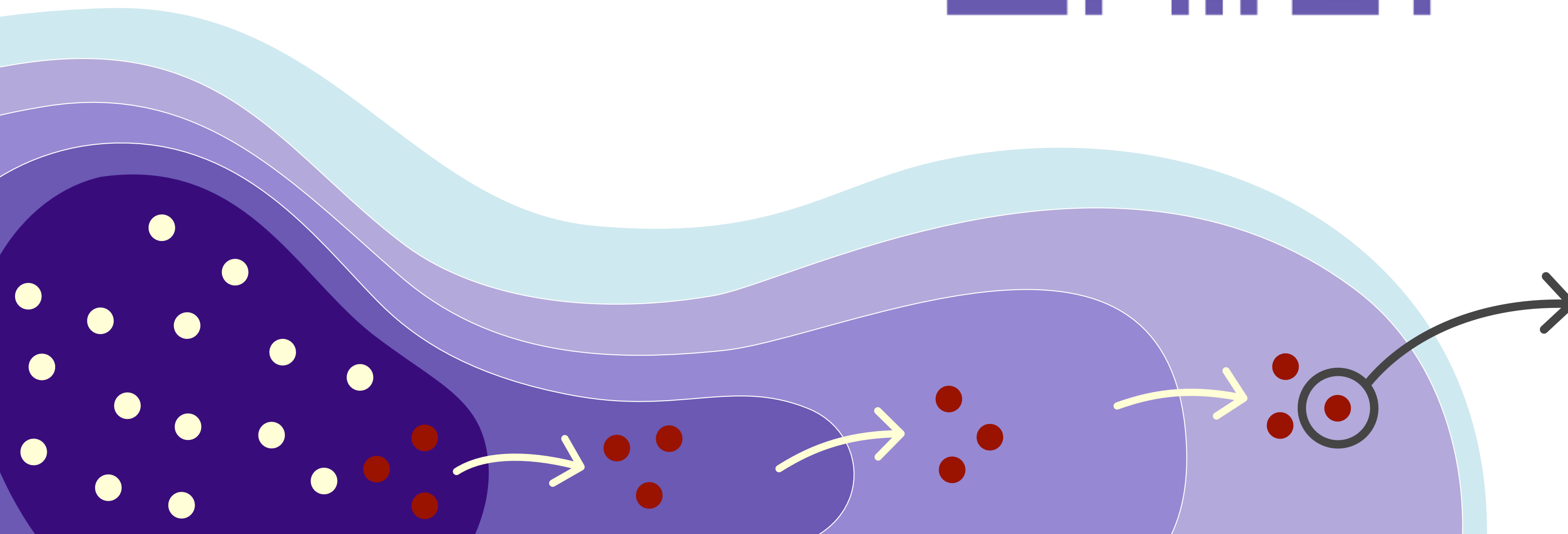
riccardodesanti.com/research



Connect:

X: @r_de_santi

email: rdesanti@ethz.ch



Riccardo De Santi