



Background

- A **pre-trained conditional diffusion** model excels at modeling $p(x|c)$.
 - For example, in Stable Diffusion, $c \in C$ is a prompt, and $x \in X$ is the image generated according to this prompt.
 - Many tailored DMs are able to generate biological sequences (e.g., DDSM).
- In practice, **we often want to add additional controls into pre-trained diffusion models**, e.g.
 - Stable Diffusion.**
 - existing condition: prompts
 - new condition: certain layouts or backgrounds.
 - DDSM tailored for generating DNA enhancers.**
 - existing condition: activity level in HepG2
 - new condition: activity level in other cell lines such as K562.

Settings

- Given the pre-trained model, which enables us to sample from $p^{pre}(x|c): C \mapsto \Delta(X)$.
- Goal:** add new conditional controls $y \in Y$ such that we can sample from $p(x|c,y)$.
- Assume we can access to offline data:

$$D = \{(c^{(i)}, x^{(i)}, y^{(i)})\}_{i=1}^n$$

where conditional distribution is denoted by $p^\gamma(y|x,c)$.

Target Distribution

our goal is to obtain a diffusion model such that we can sample from

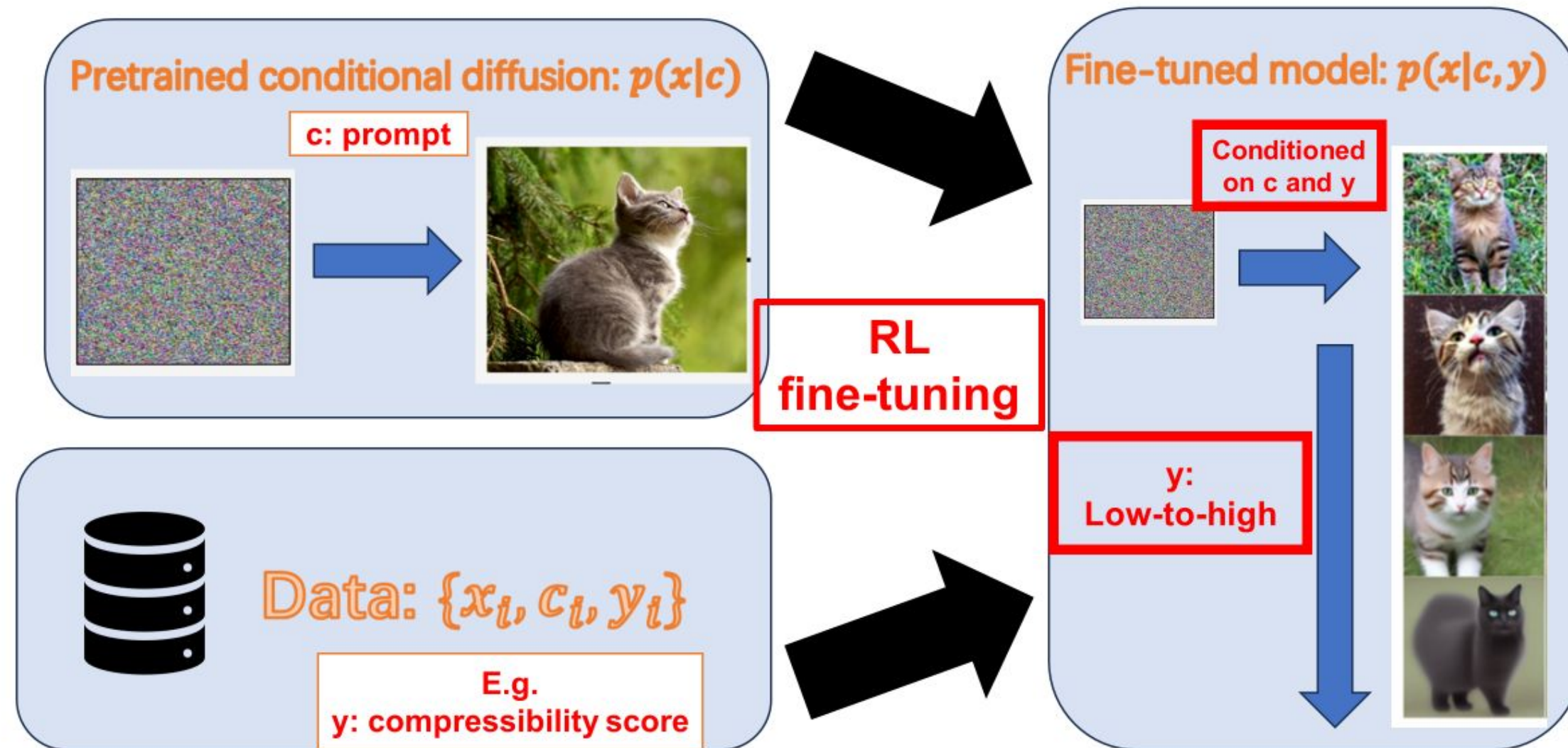
$$p_\gamma(\cdot|c,y) \propto (p^\gamma(y|\cdot,c))^\gamma p^{pre}(\cdot|c)$$

where γ represents the strength of the additional guidance.

Methodology & Results

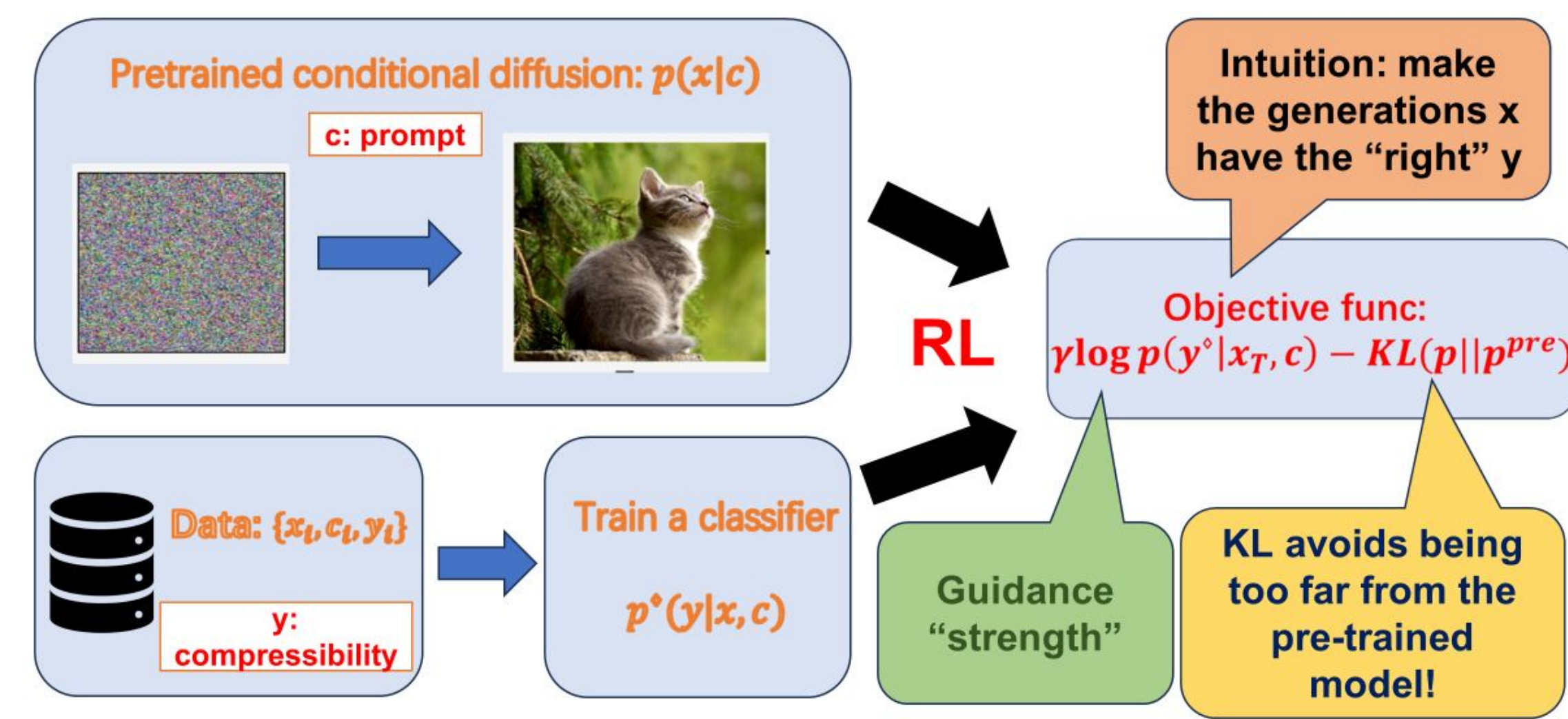
Roadmap

Our goal: adding control via fine-tuning



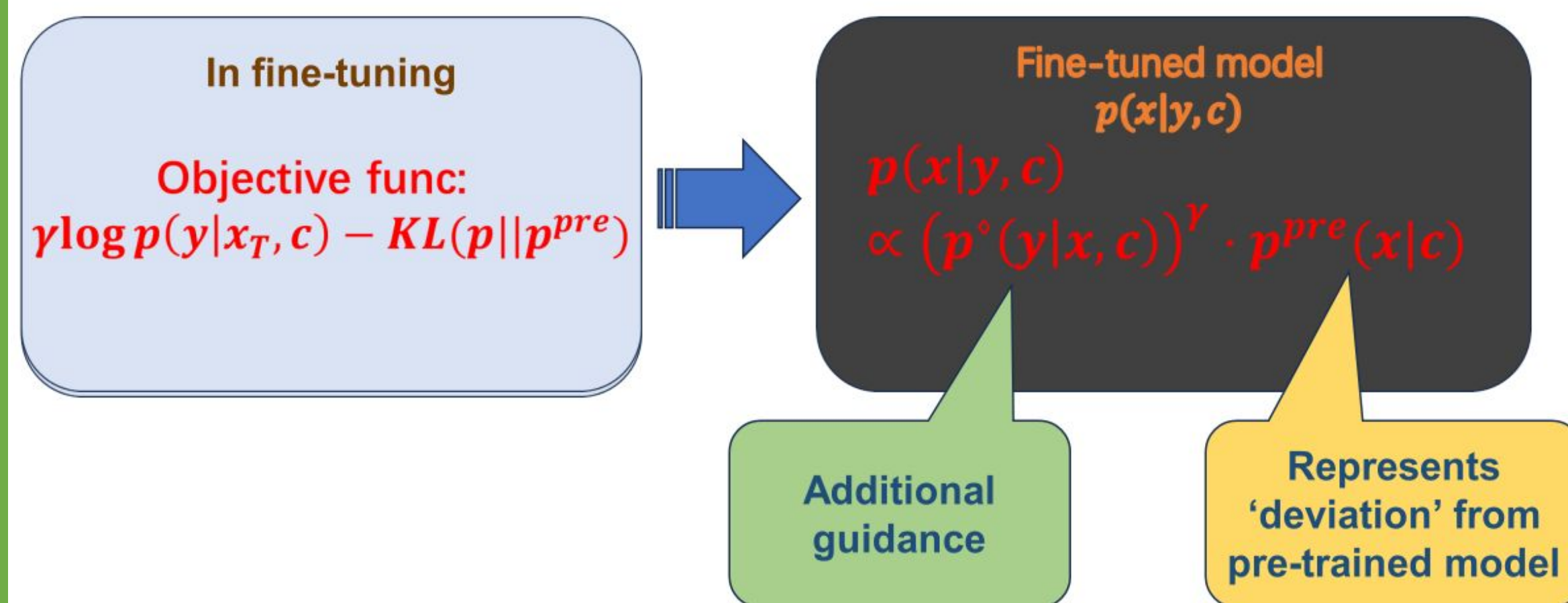
RL-based Fine-tuning

Methodology



Advantages of Our Approach

Theoretical justification (incomplete)



★ Compared to classifier-free guidance

Our method demonstrates superiority by **leveraging the conditional independence**.

- Example 1: $Y \perp C | X$.** Then

$$p^\gamma(y|x,c) = p^\gamma(y|x)$$

- This means we only need (x,y) sample pairs to train the classifier, rather than triplets (c,x,y) .

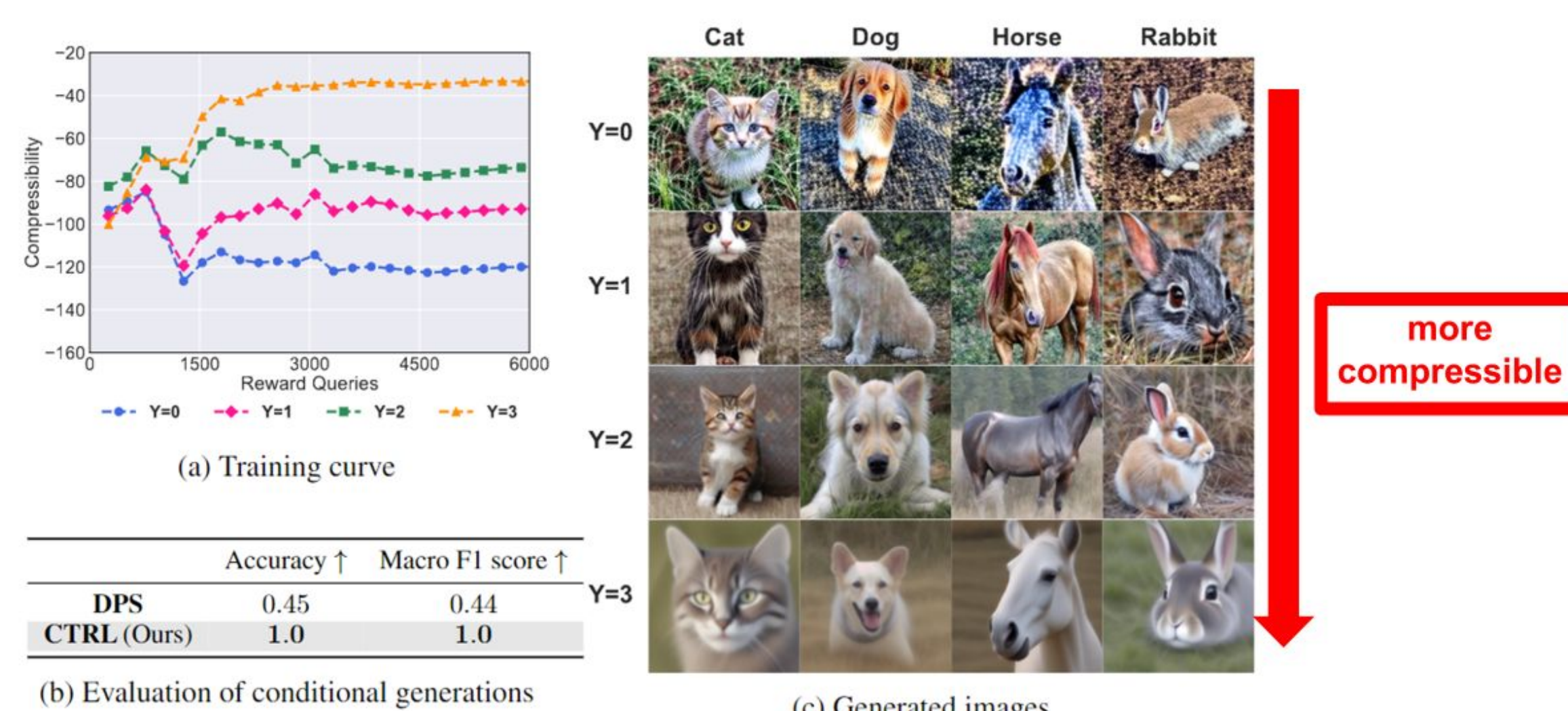
- Example 2 (multi-task): $Y_1 \perp Y_2 | C, X, Y_1 \perp C | X$ and $Y_2 \perp C | X$.** Then

$$\log p^\gamma(y_1, y_2 | x, c) = \log p^\gamma(y_1 | x) + \log p^\gamma(y_2 | x)$$

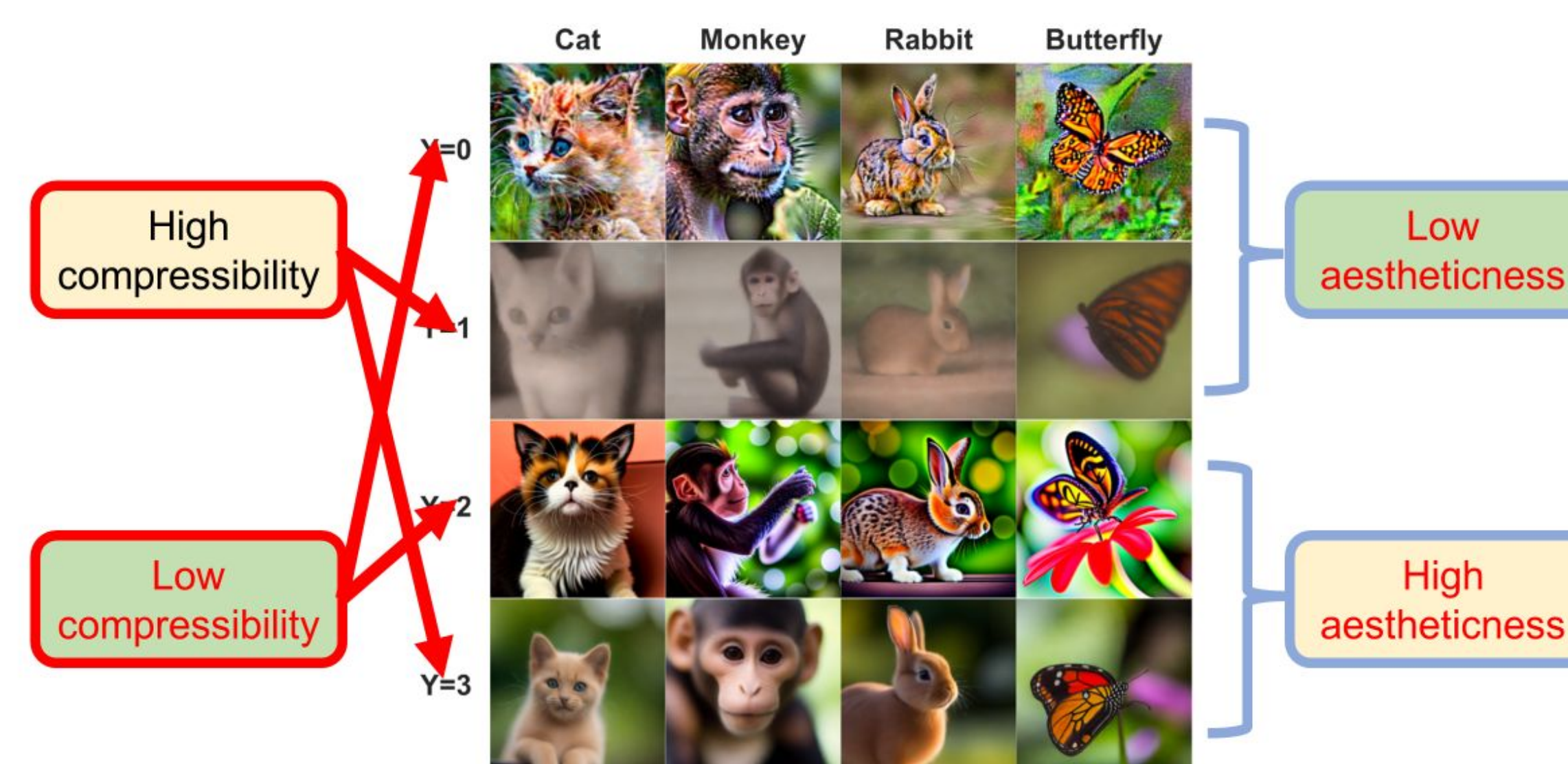
- This means we only need (x, y_1) and (x, y_2) pairs.
- Significantly simplifying dataset construction: classifier free guidance must require quadruples (c, x, y_1, y_2) !

Results

Example 1: Compressibility



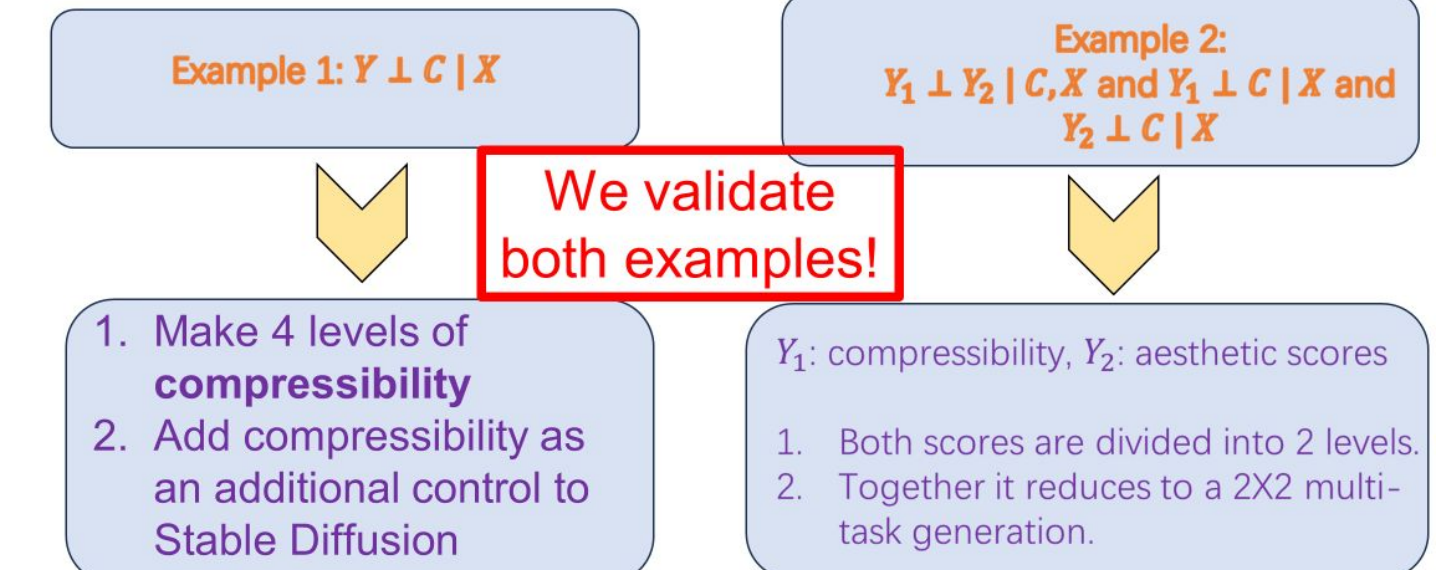
Example 2: Compressibility & Aestheticness



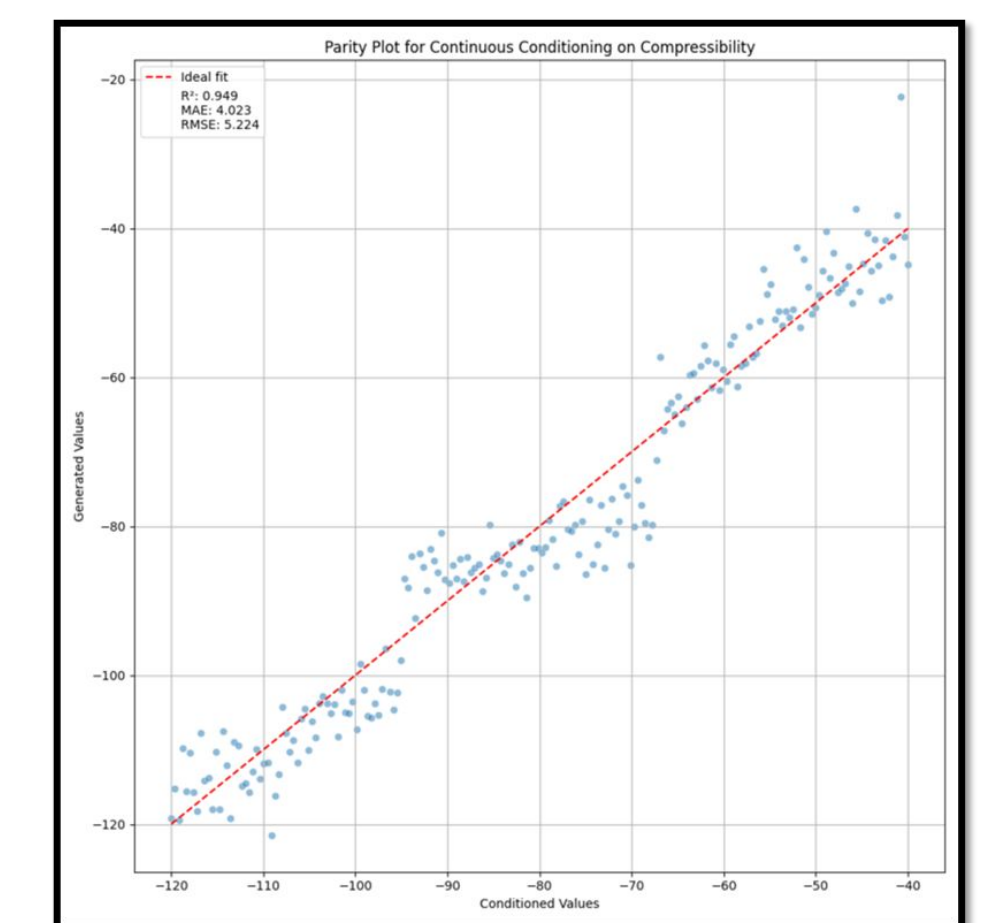
Experimental Details

Settings

Experiments



Extension: conditioned on continuous y



- We can use the **model fine-tuned on discretized y** and **interpolate** discrete class embeddings for **continuous y**.
- This naive approach can achieve **$R^2=0.95$** .

Conclusions

- We introduce an **RL-based fine-tuning** approach for conditioning pre-trained diffusion models on new additional labels.
- Compared to **classifier-free guidance**, our proposed method allows for **leveraging the conditional independence**, thereby greatly simplifying the construction of the offline dataset.
- We also **theoretically justify** our approach and build the connection with **classifier-based guidance**.
- Future work includes applying this method to design **DNA enhancers** and **5'UTR**.
- The goal is achieve **cell-specific promoters design!**

