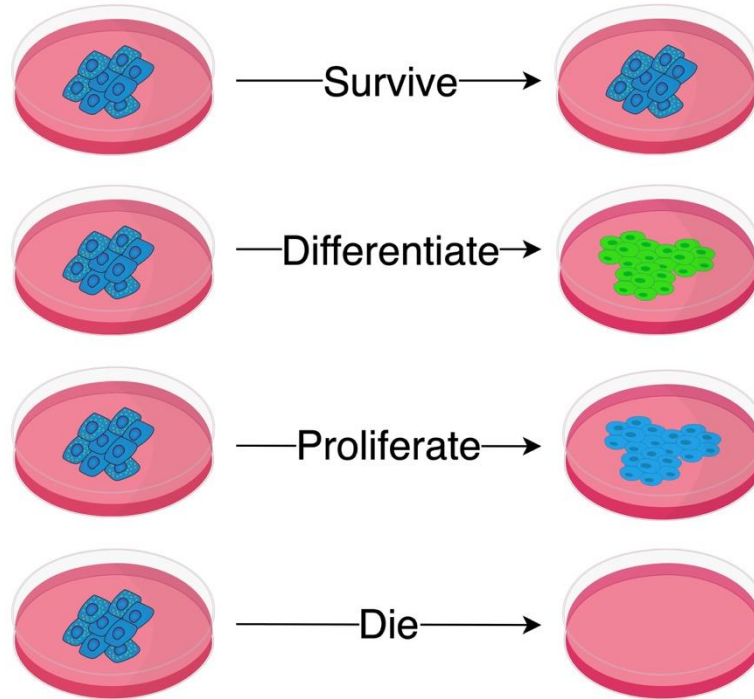# MorphoDiff: Cellular Morphology Painting With Diffusion Models

Zeinab Navidi, Jun Ma, Esteban Miglietta, Le Liu, Anne E Carpenter, Beth A Cimini, Benjamin Haibe-Kains, Bo Wang
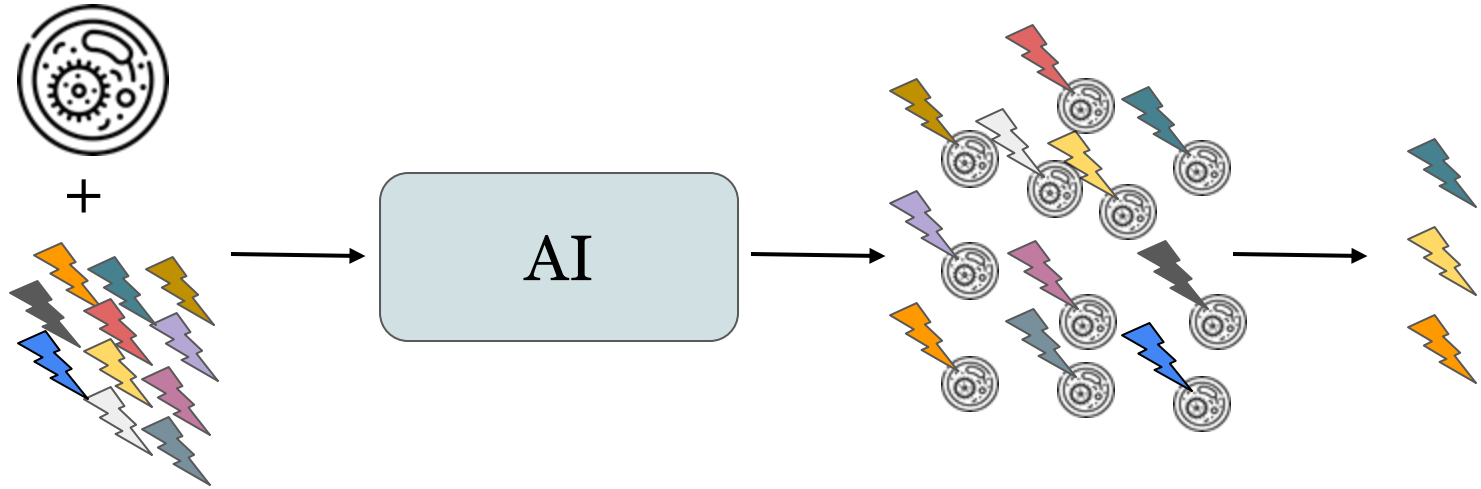
UNIVERSITY OF TORONTO

VECTOR INSTITUTE

UHN
Toronto Gene
Toronto Weste
Princess Marg
Toronto Rehal
Michener Inst

BROAD INSTITUTE

SGC

Understanding Cellular Responses

Inform the design of more effective therapies

AI For Cellular Responses Prediction

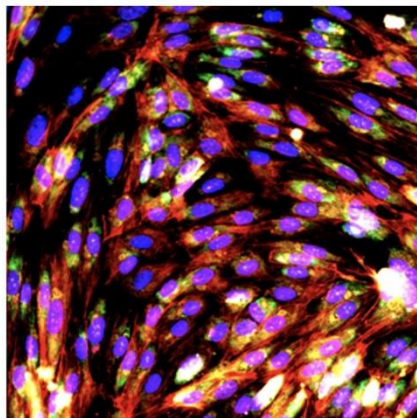Find most effective interventions towards target cell state

Understanding Cellular Morphology

Features that define cellular appearance and how these features change in response to genetic or chemical interventions
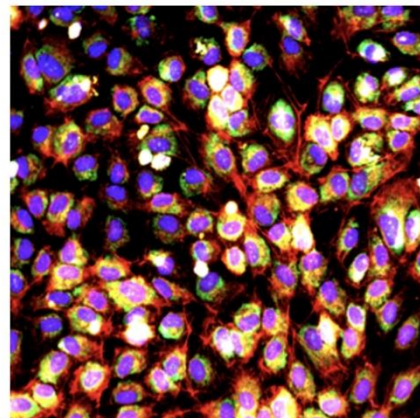
Cell Painting allows to study:

- Dynamic organization of proteins

- Cell viability

- Cell proliferation and toxicity

- DNA damage
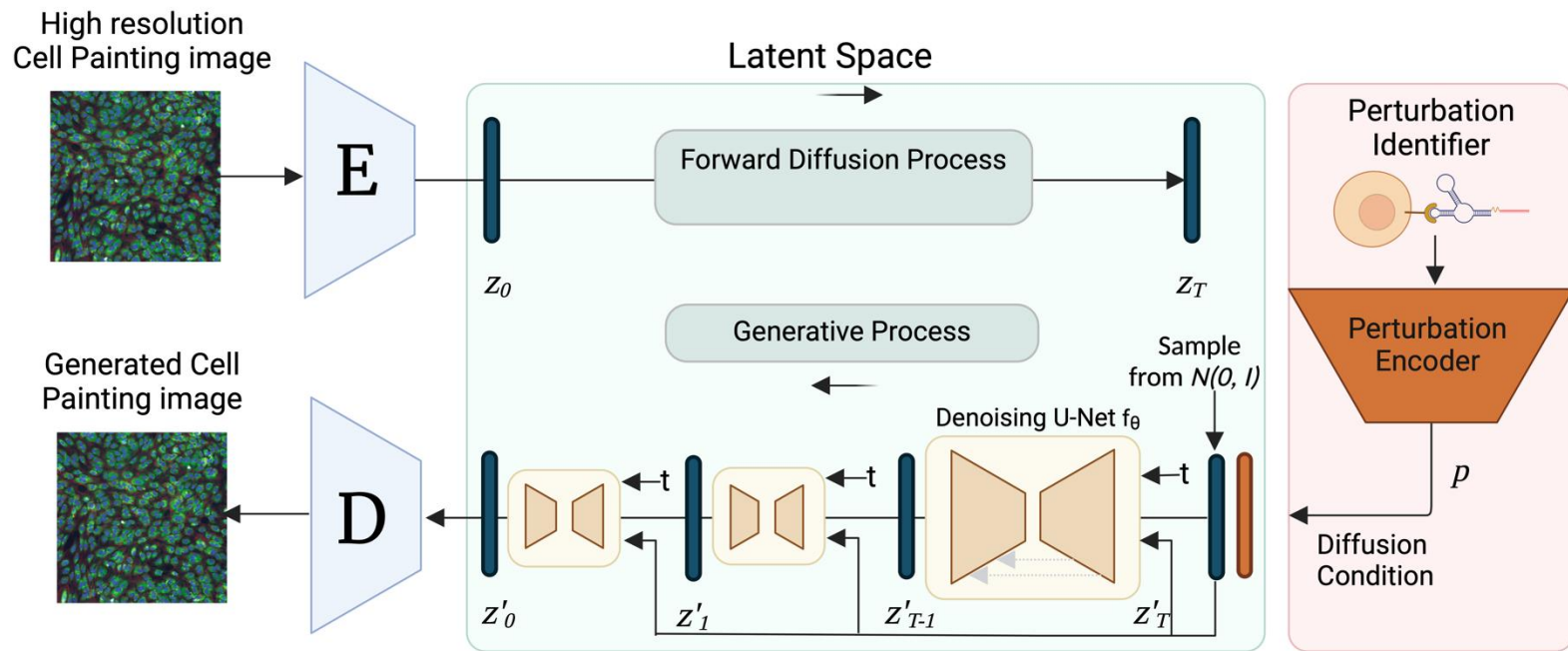

Disease Model X   vs   Healthy control

[https://www.recursion.com/news/nothing-short-of-phenomenal-new-deep-learning-model-available-on-nvidias-bionemo-platform]

4

MorphoDiff

MorphoDiff

Generative module
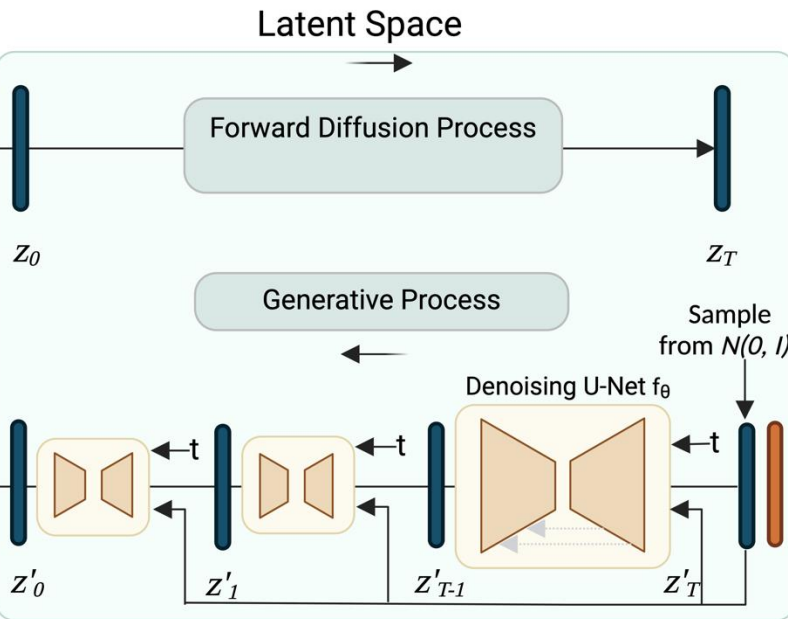Denoising Diffusion Probabilistic Model
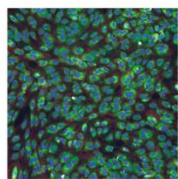   Forward diffusion process
    Generative process
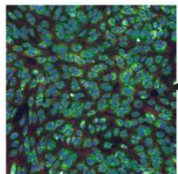Based on conditional latent diffusion models
Fine-tuned on Cell Painting images
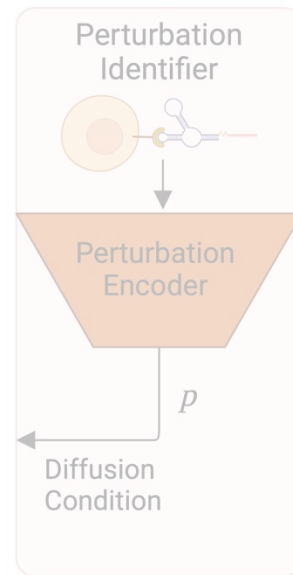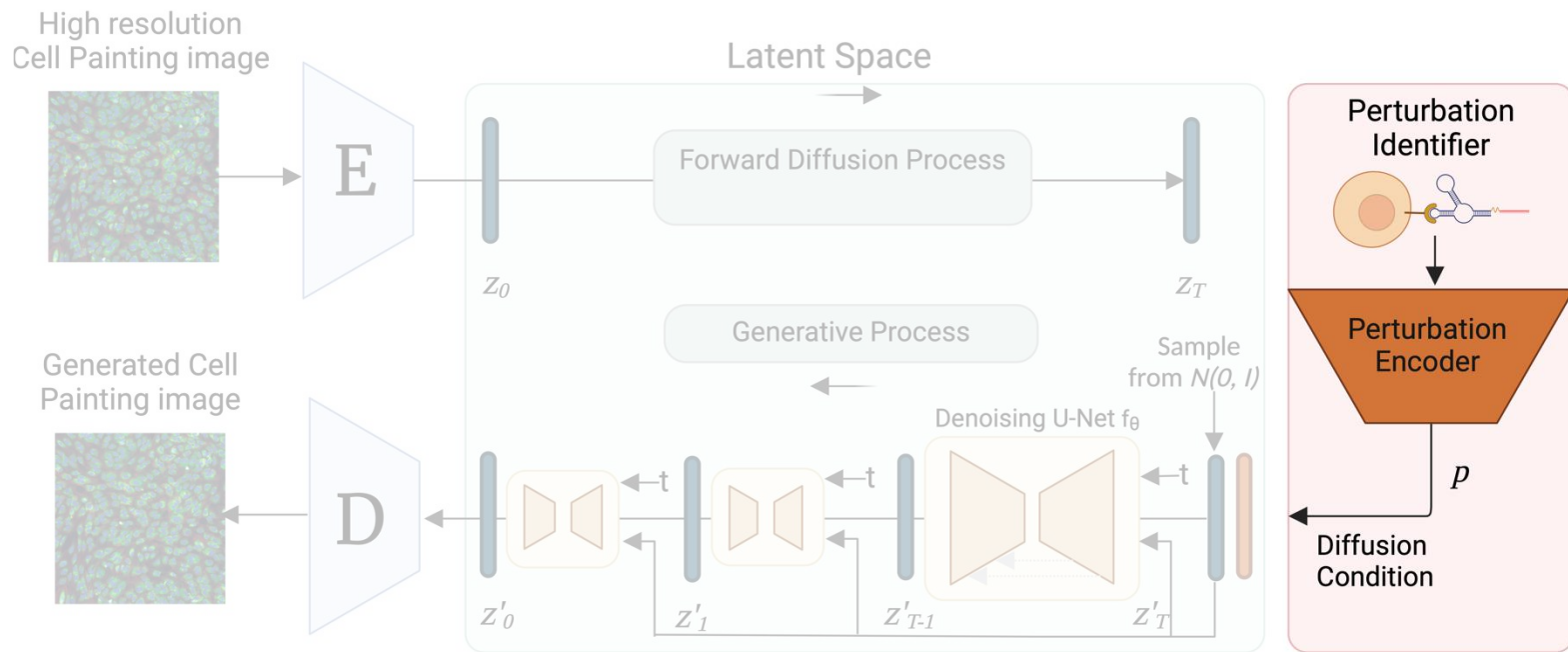
MorphoDiff

Perturbation conditioning module
Genetic perturbations
   scGPT single-cell foundation model
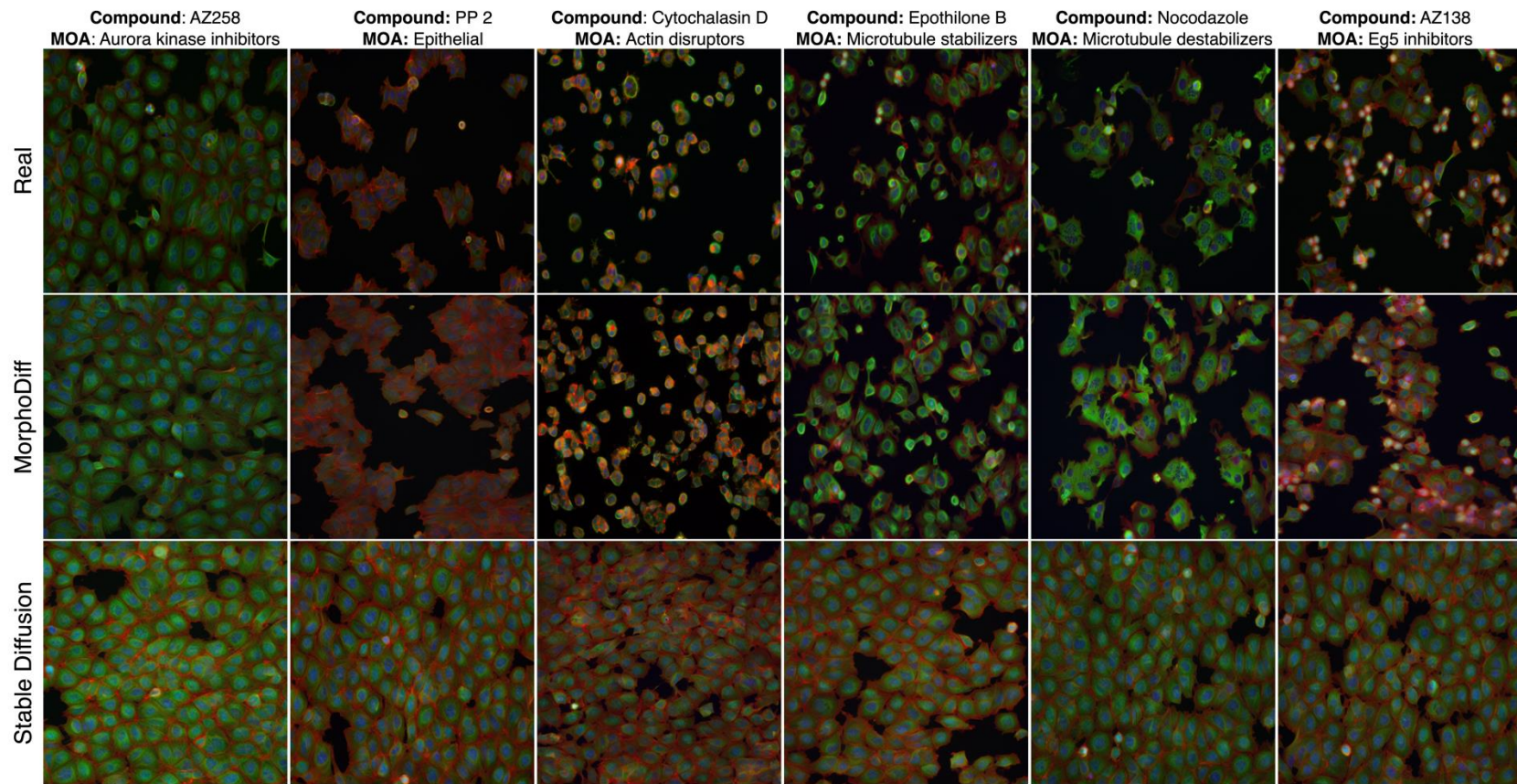
Chemical compounds
   RDKit

Validation

1. Image fidelity
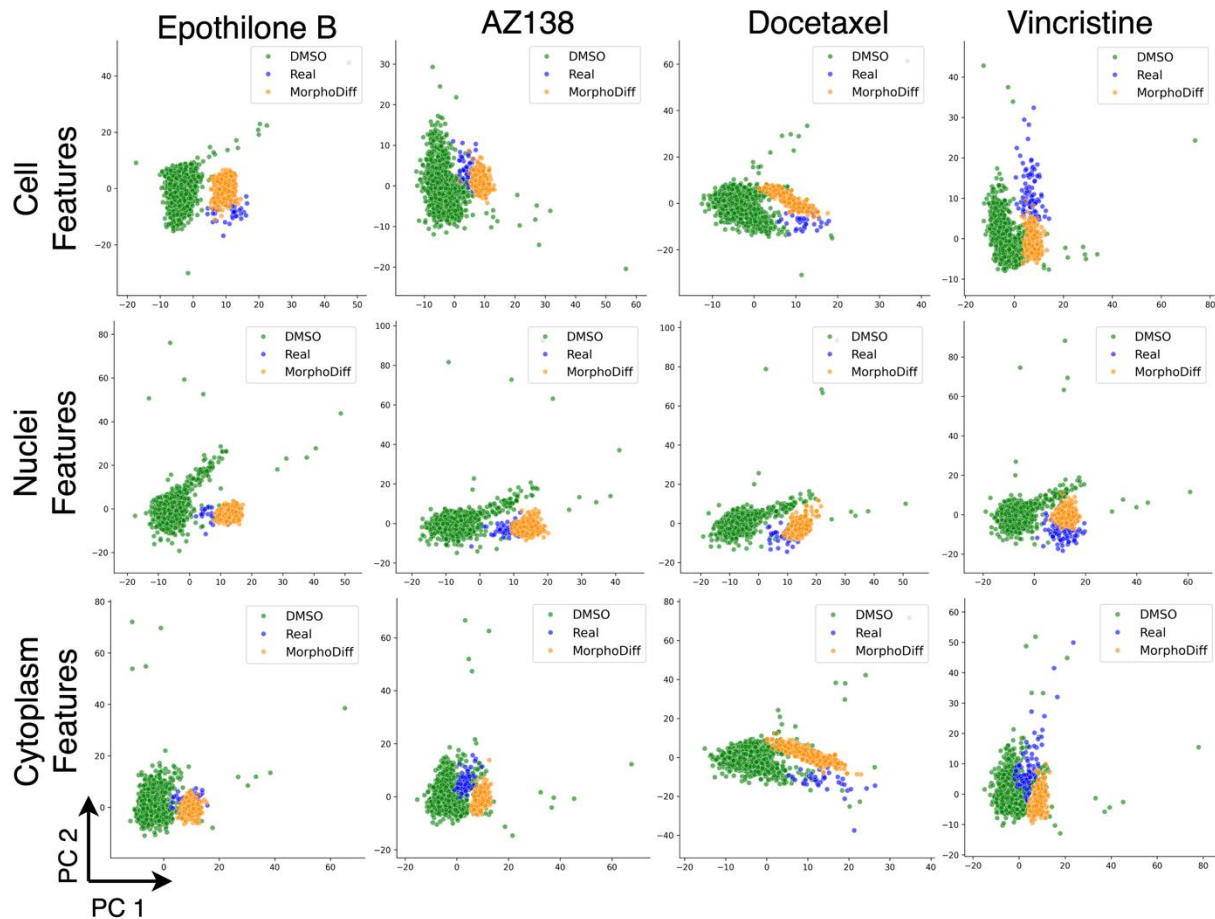
2. Visual assessment

3. Biological interpretability

Validation: Image Fidelity

Dataset	Experiment	Method	FID↓	KID↓
RxRx1	All Batches	MorphoDiff	**0.78****	**0.05****
RxRx1	All Batches	Stable Diffusion	1.15	0.11
RxRx1	Single Batch	MorphoDiff	**1.14****	**0.12***
RxRx1	Single Batch	Stable Diffusion	1.45	0.16
BBBC021	All Compounds	MorphoDiff	**1.99****	**0.21****
BBBC021	All Compounds	Stable Diffusion	3.84	0.47
BBBC021	14 Compounds	MorphoDiff	**2.26***	**0.30**
BBBC021	14 Compounds	Stable Diffusion	3.22	0.42
Rohban et al.	5 Genes	MorphoDiff	**2.51***	**0.33***
Rohban et al.	5 Genes	Stable Diffusion	3.26	0.45
Rohban et al.	12 Genes	MorphoDiff	**2.77***	**0.38****
Rohban et al.	12 Genes	Stable Diffusion	3.17	0.45

Validation: Visual Assessment

| | Compound: AZ258
MOA: Aurora kinase inhibitors | Compound: PP 2
MOA: Epithelial | Compound: Cytochalasin D
MOA: Actin disruptors | Compound: Epothilone B
MOA: Microtubule stabilizers | Compound: Nocodazole
MOA: Microtubule destabilizers | Compound: AZ138
MOA: Eg5 inhibitors |

Real

MorphoDiff

Stable Diffusion

Validation: Biological Interpretability

Discussion

MorphoDiff, a diffusion based generative pipeline

- ✓ enables high-resolution cellular phenotype prediction guided by perturbation signals
- ✓ incorporate diverse perturbation embedding modules
- ✓ generalizable to unseen perturbations
- ✓ SOTA performance based on comprehensive validation:
    - ✓ Image fidelity
    - ✓ Biological interpretability
    - ✓ Visual assessment

Paper