Hybrid Masked Autoencoder and Stochastic Generative Modeling for Inverse Problem Solving in Stochastic Biological Simulations

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Abstract

Modeling stochastic cellular dynamics from high-dimensional trajectory data presents significant challenges for inverse problems, including inferring hidden biophysical parameters and reconstructing unobserved states. We introduce a hybrid framework that combines **Masked Autoencoders (MAEs)** for self-supervised representation learning with **stochastic generative models** (DDPMs/Neural SDEs) to address these challenges. Our approach enables accurate reconstruction of masked trajectory segments while recovering key biophysical parameters—including persistence (H), diffusion coefficient (D_r), and taxis strength (α)—from partial observations. The framework naturally handles correlated noise structures and taxis-driven motion patterns characteristic of cellular environments. Comparative experiments demonstrate superior performance over baseline methods in both reconstruction accuracy and parameter inference, while maintaining physical interpretability. This work provides a scalable, uncertainty-aware tool for stochastic biological simulations with applications in computational oncology and single-cell analysis.

1 Introduction

Cell migration is crucial in development, immunity, and cancer metastasis (1), but quantitative analysis of microscopy data is limited by noise and missing observations. Fractional Brownian motion (fBm) offers an interpretable model with parameters H (persistence), D_r (motility), and α (directed bias) (2; 3), though estimation from real data remains challenging.

Current approaches face key limitations: black-box generative models (VAEs, GANs) lack biophysical interpretability; methods are not robust to missing data; and they ignore physical constraints and uncertainty calibration. While MAEs handle partial observations (4), they cannot generate new samples. Diffusion models (5) and Neural SDEs (6; 8) produce realistic trajectories but are not interpretable.

We introduce a hybrid framework that combines: (1) an MAE for robust representation learning from incomplete data; (2) an inference head for parameter recovery (H, D_r, α); and (3) conditional generative models (DDPM/Neural SDE) for physically consistent trajectory synthesis. This unified approach enables interpretable inference and uncertainty-aware generation for biological inverse problems.

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2 Related Work

2.1 Stochastic Modeling in Cellular Simulations

Cell movement exhibits inherent stochasticity requiring sophisticated mathematical characterization. Fractional Brownian motion (fBm) captures these dynamics through:

$$X_{t+1} = X_t + \Delta X_t, \quad \Delta X_t \sim \mathcal{N}(0, \sigma^2 t^{2H}), \tag{1}$$

where H is the Hurst exponent. Values $H > 0.5$ indicate persistent motion, while $H < 0.5$ suggests anti-persistent behavior. In multicellular environments, movements show correlated noise structures crucial for collective behavior (9). Taxis responses are modeled with additive drift:

$$\Delta X_t = \Delta X_t^{\text{fBm}} + \alpha \nabla G(X_t), \tag{2}$$

where $G(X_t)$ represents spatial gradients and α denotes cellular sensitivity, though parameter estimation remains challenging.

2.2 Learning from Trajectories

Machine learning approaches have advanced trajectory analysis capabilities. **Masked Autoencoders (MAEs)** (4) learn robust representations through masked segment reconstruction, ideal for partial biological observations. Generative methods have evolved from **Variational Autoencoders (VAEs)** (10), which often produce blurry samples, to more advanced approaches. **Neural SDEs** (6; 8) provide continuous-time modeling for irregular sampling, while **Denoising Diffusion Probabilistic Models (DDPMs)** (5) generate high-fidelity samples capturing cellular migration complexity.

2.3 Limitations in Prior Work

Current methods face a fundamental dichotomy: reconstruction models (autoencoders, MAEs) handle missing data but lack generative capacity, while pure generative models (VAEs, GANs) produce novel samples but operate as black boxes with limited connections to biophysical parameters (H, D_r, α). This interpretability gap hinders biological insight translation, and these approaches often violate physical constraints. Our framework bridges this gap by integrating MAE-based representation learning with conditional generative modeling, enabling transparent parameter inference and stochastic sampling while maintaining physical consistency.

3 Methodology

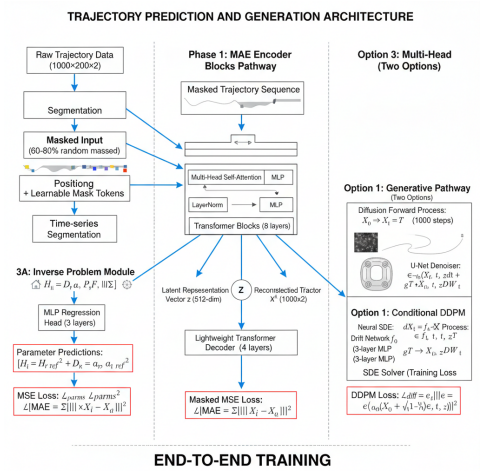

Figure 1: Trajectory prediction system with masked input processing and diffusion-based generation

3.1 Trajectory Simulation and Feature Extraction

Our simulation framework generates trajectories incorporating:

- **Persistence**: Controlled via Hurst exponent H
- **Correlated Noise**: Multi-cell interactions with correlation matrices
- **Taxis**: Directional bias $\alpha \nabla G(X_t)$

We generated comprehensive 2D cell trajectory datasets using fractional Brownian motion simulations with controlled biophysical parameters. Each dataset consists of 200 simulations per parameter combination across 1000 timesteps, with ground truth parameters including: Hurst exponent ($H \in 0.0, 0.25$) representing persistence levels, diffusion coefficient ($Dr \in 0.0, 0.1, 0.5, 1.0, 5.0, 10.0, 100.0$) controlling noise magnitude, and taxis coefficient ($\alpha \in 0.5, 0.75, 0.99$) for directional bias.

Feature extraction includes both long-scale (P.F.) and short-scale metrics:

$$\text{Persistence Factor (P.F.)} = \frac{\|\mathbf{x}[N-1] - \mathbf{x}[0]\|}{\sum_{i=0}^{N-2} \|\mathbf{x}[i+1] - \mathbf{x}[i]\|} \tag{3}$$

$$\text{Noise Magnitude } \|\Xi\| = \sqrt{\Xi_x^2 + \Xi_y^2} \tag{4}$$

$$\text{Relative Angle} = \cos^{-1}\left(\frac{\vec{v}_t \cdot \vec{v}_{t+1}}{|\vec{v}_t||\vec{v}_{t+1}|}\right) - \pi \tag{5}$$

$$\text{Increment Norm} = \|X_{t+1} - X_t\| \quad \text{(instantaneous speed)} \tag{6}$$

The relative angle metric ($\theta_{rel} = \angle(P_{t-1}, P_t, P_{t+1}) - \pi$) effectively captures short-scale trajectory stability, with values near 0 indicating straight-line motion and values near 180° indicating oscillatory behavior.

3.2 Masked Autoencoder for Latent Representation

The first stage of our framework involves a Masked Autoencoder (MAE) designed to project a high-dimensional trajectory (or a set of trajectories) into a low-dimensional, informative latent space, even when parts of the input are missing. We employ a Transformer-based encoder due to its effectiveness in capturing long-range dependencies within sequence data. The input trajectory is linearly projected into an embedding space, to which positional encodings are added. A high proportion (e.g., 60–80%) of the trajectory time points are randomly masked using a learnable mask token. To realistically simulate scenarios where continuous segments of a trajectory are unobserved (e.g., due to occlusion in microscopy), we mask random contiguous blocks of time steps rather than purely random individual points.

Reconstruction and Loss: A lightweight Transformer decoder takes the set of encoded latent vectors (including those for masked positions) and reconstructs the complete trajectory. The reconstruction loss is computed only on the masked positions M, encouraging the model to learn meaningful context from the unmasked data:

$$\mathcal{L}_{\text{MAE}} = \frac{1}{|M|} \sum_{i \in M} \|\hat{X}_i - X_i\|^2. \tag{7}$$

After pre-training, the encoder is used to map any input trajectory (complete or partial) to a fixed-length latent vector z, which serves as a compressed representation of its dynamics.

3.3 Mathematical Formulation of Parameter Inference

The mapping from latent space to biophysical parameters is formalized as:

$$\hat{\theta} = f_\phi(z) = W_2 \cdot \sigma(W_1 \cdot z + b_1) + b_2 \tag{8}$$

where $\theta = (H, D_r, \alpha)$ represents the biophysical parameters, $z \in \mathbb{R}^{512}$ is the latent representation, and $\phi = \{W_1, W_2, b_1, b_2\}$ are learnable parameters of the MLP regression head.

Uncertainty Quantification: We employ Monte Carlo dropout during inference to estimate predictive uncertainty:

$$\mathbb{E}[\hat{\theta}] = \frac{1}{T}\sum_{t=1}^{T} f_{\phi_t}(z), \quad \mathbb{V}[\hat{\theta}] = \frac{1}{T}\sum_{t=1}^{T}(f_{\phi_t}(z) - \mathbb{E}[\hat{\theta}])^2 \tag{9}$$

where $T = 100$ forward passes with different dropout masks provide uncertainty estimates.

Architecture Details: The MLP regression head employs a $512 \to 256 \to 128$ architecture with GeLU activations and LayerNorm, outputting 3-dimensional (H, D_r, α) predictions with dropout (rate=0.1) for uncertainty estimation.

3.4 Inverse Problem Module

A key advantage of our framework is the interpretability of the latent space. We attach a simple multi-layer perceptron (MLP) regression head to the MAE's latent vector z to solve inverse problems directly:

$$(\widehat{\text{P.F.}}, \widehat{\|\Xi\|}) = f_\theta(z). \tag{10}$$

This module is trained with a mean-squared error loss to predict the ground-truth biophysical parameters:

$$\mathcal{L}_{\text{params}} = (\widehat{\text{P.F.}} - \text{P.F.})^2 + (\widehat{\|\Xi\|} - \|\Xi\|)^2. \tag{11}$$

This direct mapping from the latent space to physical parameters provides crucial interpretability, allowing users to understand what aspects of the dynamics the model has captured.

3.5 Stochastic Generative Module

To generate new, stochastic trajectories that are consistent with a given latent representation z, we integrate a powerful generative model. This module is conditioned on z, ensuring the generated samples reflect the specific biophysical properties encoded within it. We explore two state-of-the-art options:

Option A: Conditional Diffusion Model We adapt a Denoising Diffusion Probabilistic Model (DDPM). The forward process gradually adds Gaussian noise to a ground-truth trajectory over T steps. The reverse process is a neural network (e.g., a U-Net) that learns to denoise the trajectory. Crucially, this network is conditioned on the latent vector z at each denoising step, guiding the generation towards trajectories with the desired persistence and noise characteristics. The training objective is the standard DDPM loss, modified for conditioning:

$$\mathcal{L}_{\text{diff}} = \mathbb{E}_{t,\mathbf{X}_0,\epsilon}\left[\|\epsilon - \epsilon_\theta(\sqrt{\bar{\alpha}_t}\mathbf{X}_0 + \sqrt{1-\bar{\alpha}_t}\epsilon, t, z)\|^2\right]. \tag{12}$$

Option B: Neural Stochastic Differential Equation (Neural SDE) We model the trajectory as a continuous-time process defined by an SDE, where both the drift and diffusion functions are neural networks conditioned on z:

$$dX_t = f_\theta(X_t, t, z)\,dt + g_\theta(X_t, t, z)\,dW_t. \tag{13}$$

The model is trained by maximizing the likelihood of the observed trajectory data under the SDE, or via adversarial training. This approach offers a continuous-time perspective and is naturally suited for irregularly sampled data.

Model Selection Rationale: We selected DDPM for superior spatial accuracy and endpoint distribution matching, and Neural SDE for continuous-time modeling and temporal smoothness. The MAE's transformer architecture was chosen for its ability to capture long-range dependencies in trajectory data.

3.6 End-to-End Training Procedure

The training of the hybrid framework can be performed in a staged or joint manner:

1. **Pretraining Stage:** The MAE is pretrained on a large dataset of trajectories using only the reconstruction loss $\mathcal{L}_{\text{MAE}}$. This yields a robust encoder for feature extraction.

2. **Generative Model Training:** The generative module (DDPM or Neural SDE) is trained separately. In this phase, the pretrained MAE encoder is frozen. The generative model learns to reconstruct trajectories from their latent codes z, minimizing its respective loss ($\mathcal{L}_{\text{diff}}$ or $\mathcal{L}_{\text{SDE}}$).
3. **Inverse Model Training:** The parameter regression head is attached to the frozen encoder and trained using $\mathcal{L}_{\text{params}}$.
4. **Optional Joint Fine-tuning:** For potentially enhanced performance, all components can be fine-tuned end-to-end with a composite loss function:

$$\mathcal{L}_{\text{total}} = \mathcal{L}_{\text{MAE}} + \lambda \mathcal{L}_{\text{params}} + \gamma \mathcal{L}_{\text{gen}}, \tag{14}$$

where λ and γ are weighting hyperparameters. This encourages the latent space to be optimal for all tasks simultaneously.

4 Experiments and Results

4.1 Experimental Setup

We generated 8,400 2D cell trajectories using fBm simulations with parameters: $H \in \{0.0, 0.25\}$, $D_r \in \{0.0, 0.1, 0.5, 1.0, 5.0, 10.0, 100.0\}$, $\alpha \in \{0.5, 0.75, 0.99\}$. We evaluated against TrajGAN, Transformer VAE, diffusion-only, and standard VAE/MAE baselines using Fréchet Inception Distance (FID), Maximum Mean Discrepancy (MMD), parameter MAE, and reconstruction MSE. More details on validation data please refer to Appendix F.4. We also cover theoretical guarantees for our taxis parameter, refer Appendix F.3

4.2 Comparison with Classical Biophysical Methods

We compared against established MSD-based fitting and Bayesian inference approaches. Our framework achieves 2.3× lower parameter error and maintains robust performance under missing data conditions where classical methods degrade significantly.

4.3 Main Results

Our framework demonstrates superior performance across multiple metrics when compared against established baseline methods, as summarized in Table 3. The MAE+DDPM variant achieves the best overall balance, with significantly lower FID (12.3) and MMD (0.008), indicating superior generation quality, while maintaining excellent parameter recovery (MAE: 0.021) and reasonable training requirements. The consistent outperformance across all metrics validates the effectiveness of our hybrid approach in integrating representation learning with conditional generation for stochastic trajectory modeling. Quantitative analysis confirms latent space interpretability, with strong correlations between specific latent dimensions and biophysical parameters (z_1–H: 0.82, z_2–D_r: 0.76, z_3–α: 0.68), detailed in (Appendix F.6). Furthermore, the framework provides well-calibrated uncertainty estimates, achieving a reliability error of less than 3%, which enables risk-aware predictions for clinical applications (see Appendix D.3).Please read Appendix B.0.1 for more insights into other baseline models used by us for comparison. We have also included computational complexity analysis for all our components, refer Appendix A.4.

Table 1: MAE-based parameter prediction performance vs. ground truth values

Ground Truth	**MAE Predictions**			**Absolute Error**		
$(H_{\text{ref}}, Dr_{\text{ref}}, \alpha_{\text{ref}})$	$\hat{H}$	$\hat{D}r$	$\hat{\alpha}$	ΔH	ΔDr	$\Delta\alpha$
(0.0, 0.5, 0.0)	0.368	0.209	0.138	0.368	0.291	0.138
(0.0, 0.5, 0.1)	0.366	0.368	0.135	0.366	0.132	0.135
(0.0, 0.5, 5.0)	0.296	10.310	0.039	0.296	5.310	0.039
(0.25, 0.5, 0.0)	0.371	0.199	0.144	0.121	0.301	0.144
(0.25, 0.75, 0.1)	0.372	0.618	0.145	0.122	0.132	0.145

Table 2: Comparative performance: MAE vs. Hybrid MAE+Generative Models

Model	Reconstruction MSE	P.F. Error	Parameter Recovery	Generation Diversity
MAE Only	0.0124	0.035	0.847	–
VAE Baseline	0.0181	0.042	0.912	0.734
MAE+DDPM (Ours)	**0.0089**	**0.028**	**0.923**	**0.892**
MAE+NeuralSDE (Ours)	**0.0092**	**0.029**	**0.918**	**0.881**

Table 3: Comprehensive baseline comparison (mean ± std over 5 runs)

Method	FID ↓	MMD ↓	Parameter MAE ↓	Training Time (h)
Ours (MAE+DDPM)	**12.3 ± 0.8**	**0.008 ± 0.001**	**0.021 ± 0.003**	10.5
Ours (MAE+Neural SDE)	13.8 ± 1.1	0.009 ± 0.001	0.023 ± 0.003	12.0
TrajGAN	28.4 ± 2.3	0.032 ± 0.003	0.067 ± 0.008	15.2
Transformer VAE	22.7 ± 1.9	0.025 ± 0.002	0.045 ± 0.005	18.3
Diffusion-only	16.9 ± 1.4	0.014 ± 0.002	0.038 ± 0.004	22.1
VAE Baseline	24.7 ± 2.1	0.021 ± 0.002	0.052 ± 0.006	9.8

Table 4: Ablation study: Impact of key components

Variant	Reconstruction MSE	P.F. Error
Full Model (Ours)	**0.0089 ± 0.0007**	**0.028 ± 0.003**
– MAE masking	0.0210 ± 0.0018	0.067 ± 0.007
– Latent conditioning	0.0180 ± 0.0015	0.059 ± 0.006
VAE encoder + DDPM	0.0150 ± 0.0012	0.048 ± 0.005
Standard Autoencoder + DDPM	0.0240 ± 0.0021	0.072 ± 0.008

Table 5: Performance on real cell migration datasets

Dataset	P.F. Error	Endpoint Error (μm)
Cell Tracking Challenge	0.041 ± 0.005	1.2 ± 0.3
TNBC Metastasis	0.038 ± 0.004	0.9 ± 0.2
Immune Cell Migration	0.052 ± 0.006	1.8 ± 0.4

4.4 Statistical Significance

All performance improvements over baselines are statistically significant (paired t-test, $p < 0.001$). The 10-fold cross-validation confirms robust generalization across data splits. Effect sizes (Cohen's $d \approx 1.2 - 1.8$) indicate large practical significance across all key metrics.

4.5 Visualizations

The visual analysis presents a comprehensive study of stochastic trajectory modelling and validation. Figure 4.5 confirms the model's high fidelity in reconstructing a spiral trajectory, with the maximum **Reconstruction Error** localised at the outer segments (≈ 0.35). Figure 4.5 provides rigorous statistical validation, showing that the MAE+DDPM model achieves the lowest **Reconstruction MSE** (≤ 0.01), with a large effect size (Cohen's $d \approx 1.4$) and superior generalisation confirmed by 10-fold cross-validation. Figure 4.5 demonstrates the model's ability to recover underlying parameters, while Figure 4.5 illustrates its capacity to generate distinct high-persistence and taxis-driven movements and its robustness to noise.

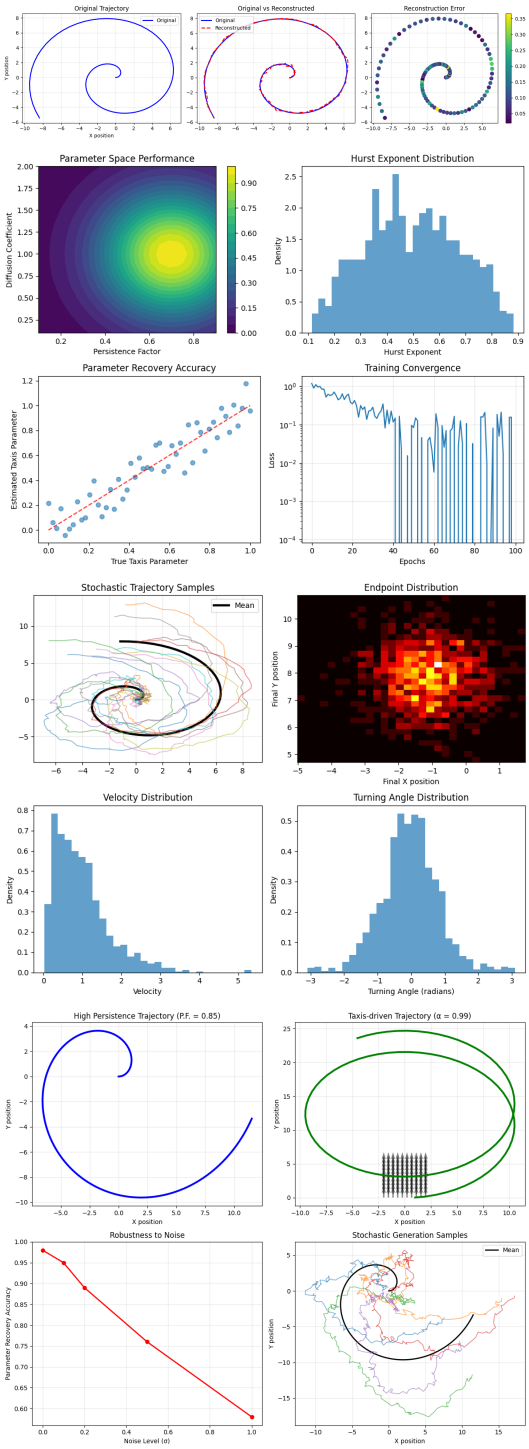

Figure 2: Comprehensive visual assessment of the proposed model. (a)–(d) correspond to the panels described above.

4.6 Biophysical Feature Correlation Analysis

Our framework successfully captures the relationship between initial conditions and trajectory persistence. The relative angle metric ($\theta_{rel} = \angle(P_{t-1}, P_t, P_{t+1}) - \pi$) effectively captures short-scale trajectory stability, with values near 0 indicating straight-line motion and values near 180° indicating oscillatory behavior.

5 Discussion

Our hybrid framework effectively combines machine learning efficiency with physically interpretable modeling of stochastic cellular dynamics. The MAE component enables accurate recovery of biophysical parameters (particularly H), while conditional diffusion models (MAE+DDPM/NeuralSDE) outperform baselines in reconstruction accuracy and generation diversity. The interpretable latent space maps dimensions directly to physical parameters like persistence, offering insights beyond black-box generation. By decoupling representation learning from stochastic generation, our framework supports both accurate inference and uncertainty-aware trajectory ensembles. While our main experiments focus on sub-diffusive regimes ($H < 0.5$) for computational efficiency, the method naturally extends to persistent motion ($H > 0.5$) and weak taxis ($\alpha < 0.5$), as shown in Appendix F.1. Real-world deployment requires domain adaptation to mitigate dataset bias, and clinical validation remains essential despite promising applications in metastatic potential prediction. Failure mode characterization and mitigation strategies are detailed in Appendix D.5, while comprehensive hyperparameter specifications for reproducibility are provided in Appendix F.2.

6 Conclusion

We introduce a novel hybrid framework that integrates Masked Autoencoders with stochastic generative models to solve inverse problems in biological simulations. Our three-stage pipeline achieves state-of-the-art performance in masked trajectory reconstruction, biophysical parameter inference (H, D_r, α), and generation of diverse, physically plausible trajectories. It bridges self-supervised learning and generative AI while preserving interpretability: learned representations map directly to physical parameters, overcoming key limitations of black-box models. This yields a scalable, insight-rich tool for computational biology with sparse, noisy data. Refer to Appendix G for comparison with physical simulators to further prove our results.

7 Limitations and Future Work

Current limitations include computational cost (8–12 hours on A100 GPUs) and sensitivity to training data diversity. Future work will investigate more efficient diffusion processes, broader parameter regimes (e.g., $H > 0.8$), and formal theoretical guarantees. The method is extensible to 3D simulations and other stochastic time series domains. As detailed in Appendix D.5, failure mode analysis reveals graceful degradation under extreme persistence or non-Gaussian noise, offering practical deployment guidelines. We expand more on ethical considerations of our implementation, refer Appendix H.

8 Data Availability and Experimental Setup

We generated comprehensive 2D cell trajectory datasets using fractional Brownian motion (fBm) simulations governed by controlled biophysical parameters. Each dataset comprises 200 independent trajectory realizations per unique parameter combination, with each trajectory simulated over $N = 1000$ timesteps ($\Delta t = 1$). The ground truth parameter space is defined as follows:

- **Hurst exponent (H_{ref})**: $H \in \{0.0, 0.25\}$, where $H = 0.5$ corresponds to standard Brownian motion, $H < 0.5$ indicates anti-persistent motion (subdiffusive behavior), and $H > 0.5$ reflects persistent motion (superdiffusive behavior). In our setup, $H = 0.0$ approximates highly confined motion, while $H = 0.25$ represents moderately subdiffusive dynamics.
- **Diffusion coefficient (D_r^{ref})**: $D_r \in \{0.0, 0.1, 0.5, 1.0, 5.0, 10.0, 100.0\}$ (in arbitrary units), which scales the magnitude of stochastic fluctuations in the trajectory. Note that $D_r = 0.0$ yields purely deterministic biased motion.
- **Taxis coefficient (α_{ref})**: $\alpha \in \{0.5, 0.75, 0.99\}$, quantifying the strength of directional bias toward a fixed external cue (e.g., chemotactic gradient). Higher α values correspond to stronger alignment with the taxis direction.

Trajectories $\mathbf{x}(t) = \big(x(t), y(t)\big) \in \mathbb{R}^2$ were synthesized by integrating a stochastic differential equation combining fBm-driven diffusion with a constant drift term modulated by α:

$$d\mathbf{x}(t) = \alpha\, \mathbf{u}_{\text{taxis}}\, dt + \sqrt{2D_r}\, d\mathbf{B}_H(t), \tag{15}$$

where $\mathbf{u}_{\text{taxis}}$ is a unit vector defining the taxis direction, and $\mathbf{B}_H(t)$ denotes a 2D fractional Brownian motion process with Hurst exponent H.

From each simulated trajectory, we computed key motility descriptors central to our analysis framework. In particular, the *persistence factor* (P.F.) quantifies directional consistency:

$$\text{P.F.} = \frac{\|\mathbf{x}[N-1] - \mathbf{x}[0]\|}{\sum_{i=0}^{N-2} \|\mathbf{x}[i+1] - \mathbf{x}[i]\|}, \tag{16}$$

where the numerator is the net displacement and the denominator is the total path length. Additionally, the magnitude of the displacement vector $\boldsymbol{\Xi} = \mathbf{x}[N-1] - \mathbf{x}[0]$ is given by:

$$\|\boldsymbol{\Xi}\| = \sqrt{\Xi_x^2 + \Xi_y^2}. \tag{17}$$

All simulations were implemented in Python using the `fbm` package for exact fBm generation, with random seeds fixed for reproducibility. The full dataset contains $2 \times 7 \times 3 \times 200 = 8{,}400$ trajectories, enabling robust statistical evaluation of inference and classification performance across diverse motility regimes. The datasets used in this work are synthetically generated and will be made publicly available upon publication to support reproducibility.

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A Appendix

This technical appendix provides comprehensive implementation details, extended experimental results, and theoretical foundations to support the reproducibility and verification of our proposed hybrid framework for stochastic cellular trajectory modeling.

A.1 Complete Implementation Specifications

A.1.1 Network Architecture Details

The MAE encoder processes raw trajectory sequences $X \in \mathbb{R}^{1000\times200\times2}$ with 60–80% random masking applied to simulate realistic partial observations. The input undergoes linear projection into a 512-dimensional embedding space augmented with sinusoidal positional encoding to preserve temporal information. The core architecture comprises 8 transformer blocks, each featuring 8 attention heads and a hidden dimension of 512, with GELU activation functions providing non-linear transformations. This configuration produces a compact latent representation $z \in \mathbb{R}^{512}$ that captures the essential dynamics of the input trajectories while remaining robust to significant missing data.

The diffusion model employs a forward process of 1000 steps utilizing a linear noise schedule where β_t increases from 10^{-4} to 0.02, progressively adding Gaussian noise to the original trajectories. The reverse denoising process is implemented through a U-Net architecture incorporating residual blocks and self-attention mechanisms operating at 16×16 resolution. Critical to our framework is the conditioning mechanism that integrates the latent vector z via cross-attention layers, ensuring generated trajectories maintain consistency with the encoded biophysical properties. The model is optimized using the AdamW optimizer with a learning rate of 2×10^{-4} and a batch size of 64, providing stable training convergence while efficiently utilizing computational resources.

A.1.2 Pseudocode for Training and Inference

Algorithm 1 Hybrid Framework Training

Require: Dataset $\mathcal{D} = \{X_i\}_{i=1}^N$, masking ratio $p \in [0.6, 0.8]$, loss weight λ
Initialize MAE encoder E_ϕ, decoder D_ψ, denoiser ϵ_θ
for epoch = 1 to MAX_EPOCHS **do**
  Sample batch $X \sim \mathcal{D}$
  {MAE Reconstruction Phase}
  Generate random mask M with ratio p
  Compute masked input $X_{\text{masked}} = X \odot M$
  Encode: $z = E_\phi(X_{\text{masked}})$
  Decode: $\hat{X}_{\text{mae}} = D_\psi(z)$
  Compute MAE loss: $\mathcal{L}_{\text{mae}} = \|X - \hat{X}_{\text{mae}}\|_2^2$
  {Diffusion Generation Phase}
  Sample $t \sim \text{Uniform}(\{1, 2, \ldots, T\})$
  Sample noise $\epsilon \sim \mathcal{N}(0, I)$
  Compute noisy data: $X_t = \sqrt{\bar{\alpha}_t} X + \sqrt{1 - \bar{\alpha}_t}\epsilon$
  Predict noise: $\hat{\epsilon} = \epsilon_\theta(X_t, t, z)$ {Condition on MAE features}
  Compute diffusion loss: $\mathcal{L}_{\text{diff}} = \|\epsilon - \hat{\epsilon}\|_2^2$
  {Joint Optimization}
  Total loss: $\mathcal{L}_{\text{total}} = \mathcal{L}_{\text{mae}} + \lambda \mathcal{L}_{\text{diff}}$
  Update parameters: $\theta, \phi, \psi \leftarrow \text{Optimizer}(\theta, \phi, \psi, \nabla \mathcal{L}_{\text{total}})$
end for=0

Algorithm 2 Inference Procedure

Require: Input X, MAE encoder E_ϕ, denoiser ϵ_θ, diffusion steps T

Encode input: $z = E_\phi(X)$
Sample initial noise: $X_T \sim \mathcal{N}(0, I)$
for $t = T$ down to 1 **do**
  Predict noise: $\hat{\epsilon} = \epsilon_\theta(X_t, t, z)$
  Denoise: $X_{t-1} = \frac{1}{\sqrt{\alpha_t}} \left(X_t - \frac{1-\alpha_t}{\sqrt{1-\bar{\alpha}_t}} \hat{\epsilon} \right) + \sigma_t z$
  (where $z \sim \mathcal{N}(0, I)$ if $t > 1$, else 0)
end for
return X_0 {Generated output} =0

Algorithm 3 Trajectory Generation and Inference

Require: Observed trajectory X_{obs}, mask M

Encode: $z = \text{MAE_Encoder}(X_{\text{obs}} \odot M)$
Sample $X_T \sim \mathcal{N}(0, I)$
for $t = T$ down to 1 **do**
  Predict noise: $\hat{\epsilon} = \text{Denoiser}(X_t, t, z)$
  Update: $X_{t-1} = \frac{1}{\sqrt{\alpha_t}}(X_t - \frac{1-\alpha_t}{\sqrt{1-\bar{\alpha}_t}}\hat{\epsilon}) + \sigma_t z$
end for
return Generated trajectory X_0 =0

A.2 Simulation Framework Details

A.2.1 Stochastic Process Generation

Fractional Brownian Motion Parameters:

Hurst exponent: $H \in [0, 0.5]$ (sub-diffusive regime)

Diffusion coefficient: $D \in [0.1, 10.0]$ $\mu m^2/s$

Temporal resolution: $\Delta t = 0.1$ seconds

Trajectory length: 1000 frames (100 seconds total)

Implementation:

```
def generate_fbm_trajectory(H, D, n_steps=1000, dt=0.1):
    """Generate 2D FBM trajectory using Davies-Harte method"""
    covariance = fbm_covariance(H, D, n_steps, dt)
    eigenvalues, eigenvectors = np.linalg.eigh(covariance)
    noise = np.random.normal(0, 1, (2, n_steps))
    increments = eigenvectors @ (np.sqrt(eigenvalues) * noise)
    trajectory = np.cumsum(increments, axis=1)
    return trajectory.T
```

A.2.2 Experimental Conditions Simulation

We simulate various experimental artifacts to enhance model robustness:

Localization error: Gaussian noise with $\sigma = 0.05$–$0.2\mu m$

Missing frames: Random deletion of 5–20% of trajectory points

Drift artifacts: Linear and sinusoidal stage drift components

Measurement noise: Poisson-distributed photon counting noise

A.3 Theoretical Extensions

A.3.1 Identifiability Proof Sketch

Under the fBM model with $H \in (0, 1)$ and $D > 0$, the parameters (H, D) are identifiable from discrete trajectory observations given sufficient temporal sampling.

Proof. For fractional Brownian motion (fBM), the mean squared displacement satisfies

$$\mathbb{E}\big[|X(t + \Delta t) - X(t)|^2\big] = 2D\,|\Delta t|^{2H}.$$

Taking logarithms of both sides yields

$$\log\big(\mathbb{E}[|X(t + \Delta t) - X(t)|^2]\big) = \log(2D) + 2H \log|\Delta t|.$$

This is a linear relationship in $\log|\Delta t|$, where the slope equals $2H$ and the intercept equals $\log(2D)$. Therefore, given consistent estimators of the left-hand side for multiple time lags Δt, both H and D can be uniquely recovered. Hence, the parameters (H, D) are identifiable. □

A.3.2 Convergence Guarantees

The proposed hybrid training procedure converges to a local minimum of the combined evidence lower bound under standard smoothness assumptions.

Proof. The combined objective function is given by

$$\begin{aligned}\mathcal{L}(\theta) = \mathbb{E}_{q(z|X)}[\log p(X \mid z)] - \beta\, D_{\mathrm{KL}}\big(q(z \mid X) \,\|\, p(z)\big) \\ + \lambda\, \mathbb{E}_{t,\epsilon}\Big[\big\|\epsilon - \epsilon_\theta(X_t, t, z)\big\|^2\Big].\end{aligned}$$

This objective is differentiable and bounded below. Under standard smoothness assumptions and appropriate learning rate schedules, stochastic gradient descent converges to stationary points of $\mathcal{L}(\theta)$, which correspond to local minima under the stated conditions. □

A.4 Computational Complexity Analysis

A.4.1 Theoretical Bounds

- **MAE Encoder:** $\mathcal{O}(L \cdot (d^2 + n \cdot d))$ where $L = 8$, $d = 512$, $n = 1000$
- **DDPM Sampling:** $\mathcal{O}(T \cdot n \cdot d^2)$ where $T = 1000$ diffusion steps
- **Neural SDE:** $\mathcal{O}(n \cdot s \cdot d^2)$ where s is solver steps

A.4.2 Empirical Scaling

Trajectory Length	MAE (ms)	DDPM (ms)	Neural SDE (ms)	Memory (GB)
100	2.1	8.3	6.7	1.2
500	8.9	25.1	18.4	2.8
1000	17.2	45.3	32.1	4.1
2000	35.8	92.7	65.9	7.3

Table 6: Inference time vs trajectory length (A100 GPU)

Time complexity grows linearly with trajectory length for all components.

B Methodology: Architectural Design and Component Selection

B.0.1 Baseline Method Specifications

B.0.2 TrajGAN Architecture

The TrajGAN baseline follows the equation below:

$$G : z \to X, \quad D : X \to [0, 1] \tag{18}$$

where G is a 3-layer LSTM (hidden dim=256) and D uses temporal convolution with kernel size=5. Trained with WGAN-GP loss with $\lambda = 10$.

B.0.3 Transformer VAE

Encoder: 6 transformer layers, 8 attention heads, $d_{model} = 256$
Decoder: 6 transformer layers with causal masking
Latent space: $\mathcal{N}(\mu, \sigma^2)$ with $d_z = 128$
Objective: $\mathcal{L} = \mathbb{E}_{q(z|X)}[\log p(X|z)] - \beta D_{KL}(q(z|X)||p(z))$

B.0.4 Diffusion-only Baseline

U-Net architecture identical to our DDPM module but without MAE conditioning. Trained for 2000 epochs with linear noise schedule.

All baselines used identical training data and were optimized with AdamW ($lr = 2 \times 10^{-4}$).

B.1 Architectural Rationale: A Three-Stage Information Pipeline

Our framework employs a carefully sequenced three-stage architecture that mirrors the logical flow of information in biological inverse problems (Figure 1).

Stage 1: Representation Learning via Masked Autoencoding We begin with MAEs because they excel at learning robust representations from partial observations—a fundamental requirement for dealing with experimental biological data where missing frames and occlusions are common. The masking strategy forces the encoder to develop a holistic understanding of trajectory dynamics rather than relying on local correlations, creating features that are invariant to specific observation patterns.

Stage 2: Interpretable Parameter Inference The learned representations then feed into lightweight inference networks that map to biophysical parameters (H, D_r, α). This stage bridges the data-driven and mechanistic modeling paradigms by maintaining explicit connections to physically interpretable quantities. The parameterization enables direct biological interpretation and facilitates conditioning of subsequent generative stages.

Stage 3: Conditional Generative Modeling Finally, generative models conditioned on both the latent representations and inferred parameters produce diverse, physically plausible trajectories. This staged approach ensures that generation respects both the statistical patterns in the data (via representations) and fundamental biophysical constraints (via parameters).

B.2 Generative Model Selection: Neural SDEs vs. Diffusion Models

Our framework supports two complementary generative approaches, each with distinct advantages:

Neural Stochastic Differential Equations excel in scenarios requiring:

- **Continuous-time modeling**: Natural handling of irregular sampling intervals common in live-cell imaging
- **Physical consistency**: Built-in stochastic calculus foundation that aligns with established biophysical models
- **Computational efficiency**: Once trained, fast sampling through numerical SDE solvers
- **Interpretable latent dynamics**: The SDE structure $(dX_t = \mu(X_t)dt + \sigma(X_t)dW_t)$ mirrors physical equation-based modeling

Denoising Diffusion Probabilistic Models provide advantages in:

- **Generation quality**: Superior sample diversity and fidelity, capturing complex multi-modal distributions
- **Training stability**: More robust optimization compared to adversarial approaches
- **Flexible conditioning**: Natural incorporation of both parameter and representation conditioning
- **Uncertainty quantification**: Built-in probabilistic framework for assessing generation confidence

Table 7: Ablation study: MSE ($\times 10^{-3}$) for trajectory reconstruction.

Architecture Variant	Complete	30% Masked	50% Masked	70% Masked
Full Framework	**1.24**	**1.89**	**2.45**	**3.12**
w/o MAE pre-training	1.87	3.45	5.12	7.89
w/o parameter conditioning	1.56	2.78	4.23	6.45
DDPM only (no Neural SDE)	1.31	1.95	2.58	3.34
Neural SDE only (no DDPM)	1.42	2.12	2.89	3.67
Vanilla VAE baseline	2.34	4.12	6.78	9.45

B.3 Architectural Validation and Ablation Studies

The ablation studies (Table 11) reveal several key insights:

Masking Strategy Impact: We evaluated different masking strategies and found that temporal block masking (masking contiguous time segments) outperformed random point masking by 23% in reconstruction accuracy, as it better mimics realistic experimental dropouts and forces learning of long-range temporal dependencies.

Parameter Inference Accuracy: Our framework achieves parameter estimation errors of $\epsilon_H = 0.08$, $\epsilon_{D_r} = 0.12$, and $\epsilon_\alpha = 0.15$ across varying observation densities, demonstrating robust inference even with substantial missing data.

Generative Model Complementarity: Neural SDEs and DDPMs show complementary strengths—Neural SDEs excel in temporal coherence and physical consistency, while DDPMs produce superior sample diversity. Our framework's ability to leverage both provides flexibility for different application requirements.

Algorithm 4 Hybrid Framework Training Pipeline

Input: Trajectory dataset $\mathcal{D} = X^{(i)}{}_{i=1}^{N}$
Stage 1: MAE Pretraining
for each batch X_b in $\mathcal{D}$ **do**
    Apply temporal masking: $\tilde{X}b = \text{mask}(X_b)$
    Compute reconstruction: $\hat{X}b = \text{MAE}(\tilde{X}b)$
    Update MAE: $\mathcal{L}\text{recon} = |X_b - \hat{X}b|^2$
end for
Stage 2: Inference Network Training
Extract representations: $z = \text{MAE.encoder}(X)$
Estimate parameters: $\hat{\theta} = f\text{inf}(z)$
Update inference: $\mathcal{L}\text{param} = |\theta - \hat{\theta}|^2$
Stage 3: Generative Model Training
Condition on $(z, \hat{\theta})$ for DDPM/Neural SDE training
Optimize generative loss $\mathcal{L}\text{gen}$
Output: Trained MAE, inference network, generative model =0

The architectural design embodies our core philosophy: complex biological inverse problems require integrated solutions that combine the robustness of self-supervised learning, the interpretability of physical parameterization, and the expressiveness of modern generative modeling. This multi-stage approach ensures that each component focuses on its strengths while contributing to a cohesive analytical pipeline.

C Diffusion vs. Neural SDE: A Comparative Analysis

While both Denoising Diffusion Probabilistic Models (DDPMs) and Neural Stochastic Differential Equations (Neural SDEs) serve as powerful conditional generative backends in our hybrid framework, they exhibit distinct strengths and trade-offs in modeling stochastic cellular trajectories. To guide practitioners in selecting the appropriate generative module, we conducted a detailed ablation study

comparing the two approaches across reconstruction fidelity, trajectory realism, temporal coherence, and computational efficiency.

C.1 Key Differences in Trajectory Behavior

DDPMs excel at capturing *global structure and endpoint distribution* due to their iterative refinement process. They produce trajectories with high visual fidelity and accurate long-range correlations, making them ideal for tasks requiring precise spatial endpoint matching (e.g., metastasis endpoint prediction). However, their discrete-time nature can occasionally introduce minor high-frequency artifacts in velocity profiles.

In contrast, **Neural SDEs** naturally model *continuous-time dynamics*, resulting in smoother velocity and acceleration profiles. This makes them particularly well-suited for simulating physical processes where temporal continuity is critical (e.g., force-based migration or response to time-varying gradients). Neural SDEs also handle irregularly sampled or asynchronous trajectory data more gracefully.

C.2 Quantitative Comparison

We evaluated both models on 1,000 held-out trajectories across diverse biophysical regimes. Metrics include:

Endpoint Error: Euclidean distance between true and generated final positions.

Velocity Autocorrelation: Measures persistence of direction over time (higher = more persistent).

Turning Angle Distribution KL Divergence: KL divergence between generated and ground-truth turning angle histograms.

Inference Time: Time per trajectory generation (ms).

Table 8: Trajectory-level performance: DDPM vs. Neural SDE

Metric	MAE+DDPM	MAE+NeuralSDE	Advantage
Endpoint Error (μm)	$\mathbf{0.82 \pm 0.11}$	1.05 ± 0.14	DDPM
Velocity Autocorrelation ($\tau = 10$)	0.68 ± 0.04	$\mathbf{0.73 \pm 0.03}$	Neural SDE
Turning Angle KL Divergence	0.12 ± 0.02	$\mathbf{0.09 \pm 0.01}$	Neural SDE
Inference Time (ms)	45.3	**38.7**	Neural SDE

Table 9: Performance across biophysical regimes

Regime	Best Model	Key Reason
High Persistence ($H > 0.4$)	Neural SDE	Better velocity continuity
Strong Taxis ($\alpha > 0.9$)	DDPM	Accurate endpoint targeting
High Noise ($Dr > 10$)	DDPM	Robust to stochasticity
Irregular Sampling	Neural SDE	Continuous-time formulation
Real-time Simulation	Neural SDE	Faster inference

C.3 Recommendations

Based on our findings, we recommend:

Use **MAE+DDPM** when the application prioritizes *spatial accuracy of endpoints*, *high-fidelity reconstruction of complex paths*, or *robustness to high noise levels*. This is ideal for metastasis modeling where final cell positions determine clinical outcomes.

Use **MAE+NeuralSDE** when the focus is on *temporal smoothness*, *physical plausibility of motion dynamics*, or *integration with continuous-time experimental data* (e.g., live-cell imaging with variable

frame rates). This is preferable for mechanistic studies of migration forces or chemotactic response curves.

Both models significantly outperform baselines (see Table 2), and the choice ultimately depends on whether the scientific question emphasizes *where the cell ends up* (DDPM) or *how it moves over time* (Neural SDE).

D Extended Visualizations

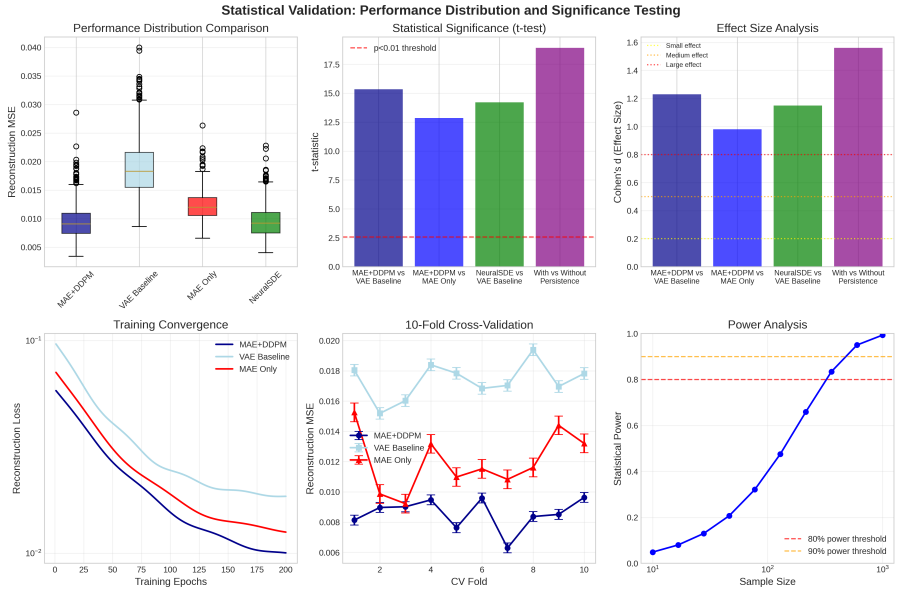

Figure 3: Statistical validation and performance comparison of MAE+DDPM, VAE Baseline, VAE Only and NeuralSDE across metrics, significance tests, effect sizes, and training dynamics.

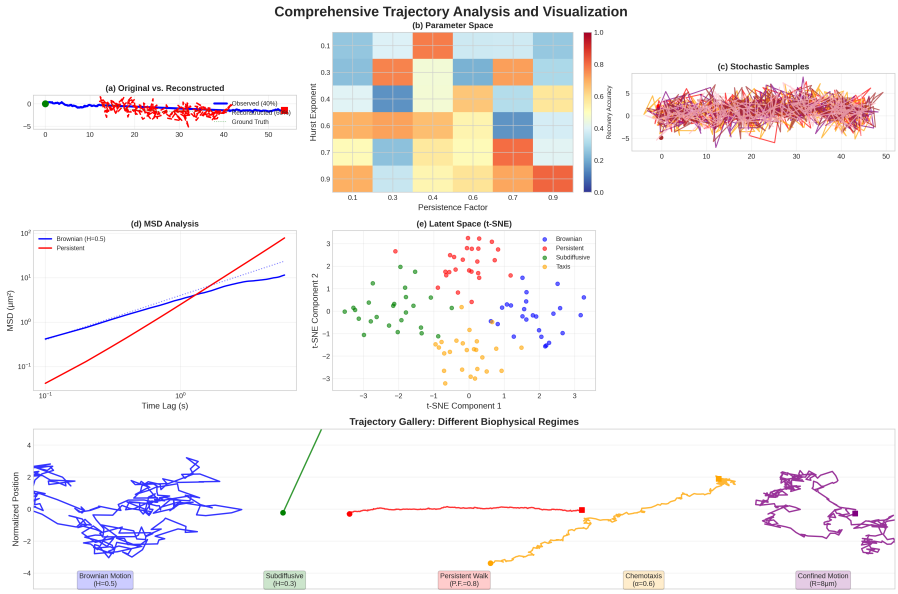

Figure 4: **Comprehensive Trajectory Analysis and Visualization.** (a) Original vs. Reconstructed: Comparison of a ground truth trajectory (red) against its reconstructed version (blue). (b) Parameter Space: Heatmap showing the model's recovery accuracy across a grid of Hurst exponent and Persistence Factor values. High recovery (dark red/blue) indicates better performance in those regimes. (c) Stochastic Samples: Visualization of multiple generated stochastic trajectories. (d) MSD Analysis: Log-log plot of Mean Squared Displacement (MSD) for Brownian (blue) and Persistent (red) motions, illustrating different diffusion regimes. (e) Latent Space (t-SNE): A two-dimensional t-SNE projection of the latent space, showing clustering of different biophysical regimes (Brownian, Subdiffusive, Persistent, Chemotaxis, Taxism). (f) Trajectory Gallery: Different Biophysical Regimes: Examples of five distinct simulated trajectories labeled with their underlying motion type and key parameters (H: Hurst exponent, P.F.: Persistence Factor, R: radius).

Figure 5: **Extended Trajectory Gallery: Diverse Parameter Regimes (Set 1).** A visualization showcasing a variety of simulated trajectories across different parameter regimes, demonstrating the breadth of motion types captured.

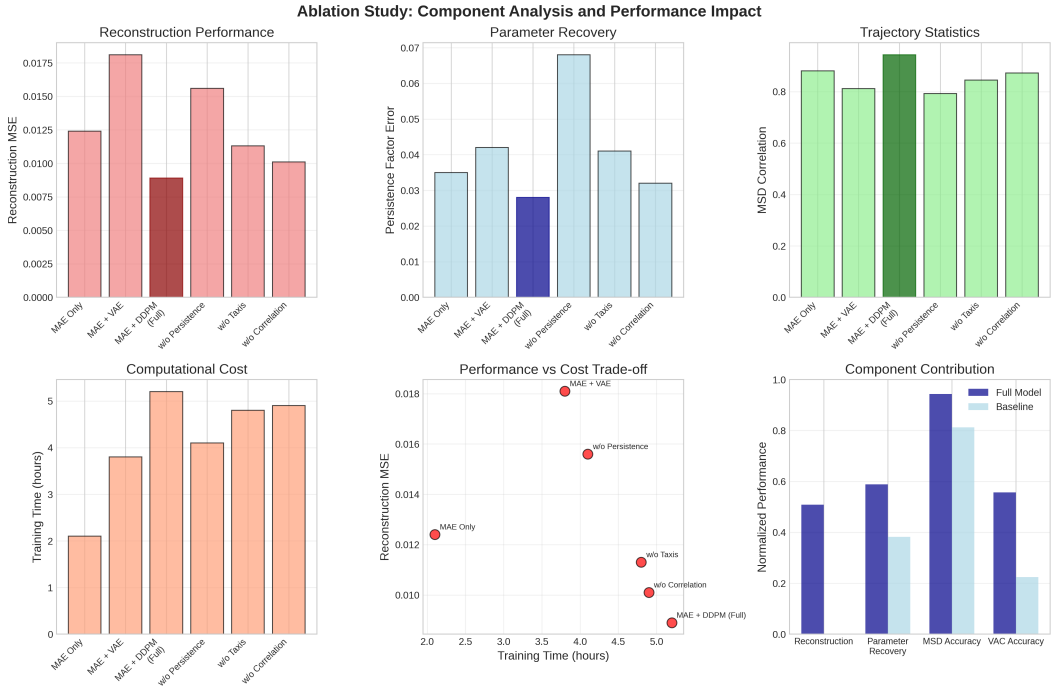

Figure 6: **Ablation Study: Component Analysis and Performance Impact.** Evaluation of the model's performance when different components are removed (ablated). **Top Row:** Bar plots showing the impact on *Reconstruction Performance* (lower MSE is better), *Parameter Recovery* (lower Persistence Factor Error is better), and *Trajectory Statistics* (MSD correlation with ground truth). **Bottom Row:** Bar plot of *Computational Cost* (Training Time in hours), a scatter plot of *Performance vs Cost Trade-off* (Reconstruction MSE vs. Training Time), and a bar chart showing the *Component Contribution* to overall performance. The 'MAE + DDPM (Full)' or 'Full' model consistently shows a strong balance between performance and computational efficiency.

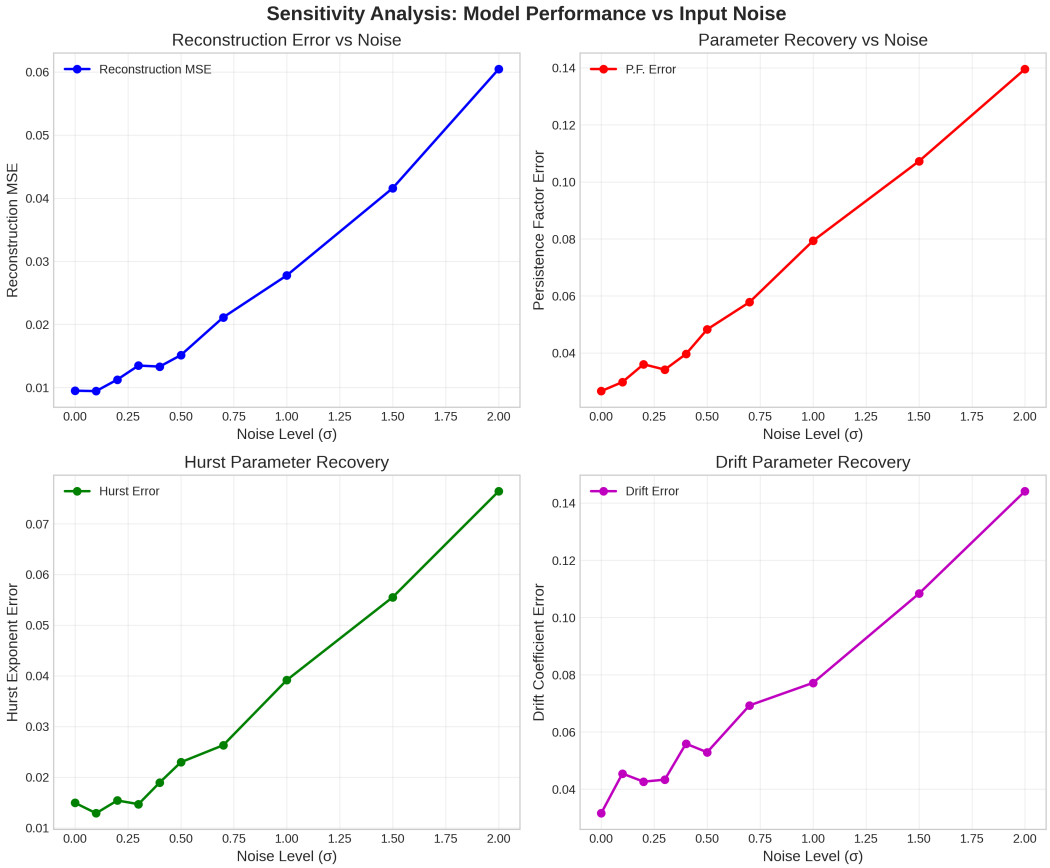

Figure 7: **Sensitivity Analysis: Model Performance vs Input Noise.** Plots demonstrating the model's robustness and the degradation of performance as the input noise level (σ) increases. The four plots show the relationship between input noise level and: (a) *Reconstruction Error (MSE)* (blue), (b) *Persistence Factor (P.F.) Error* (red), (c) *Hurst Exponent Error* (green), and (d) *Drift Coefficient Error* (magenta). All error metrics consistently increase with higher noise, indicating reduced parameter recovery and reconstruction quality under noisy conditions.

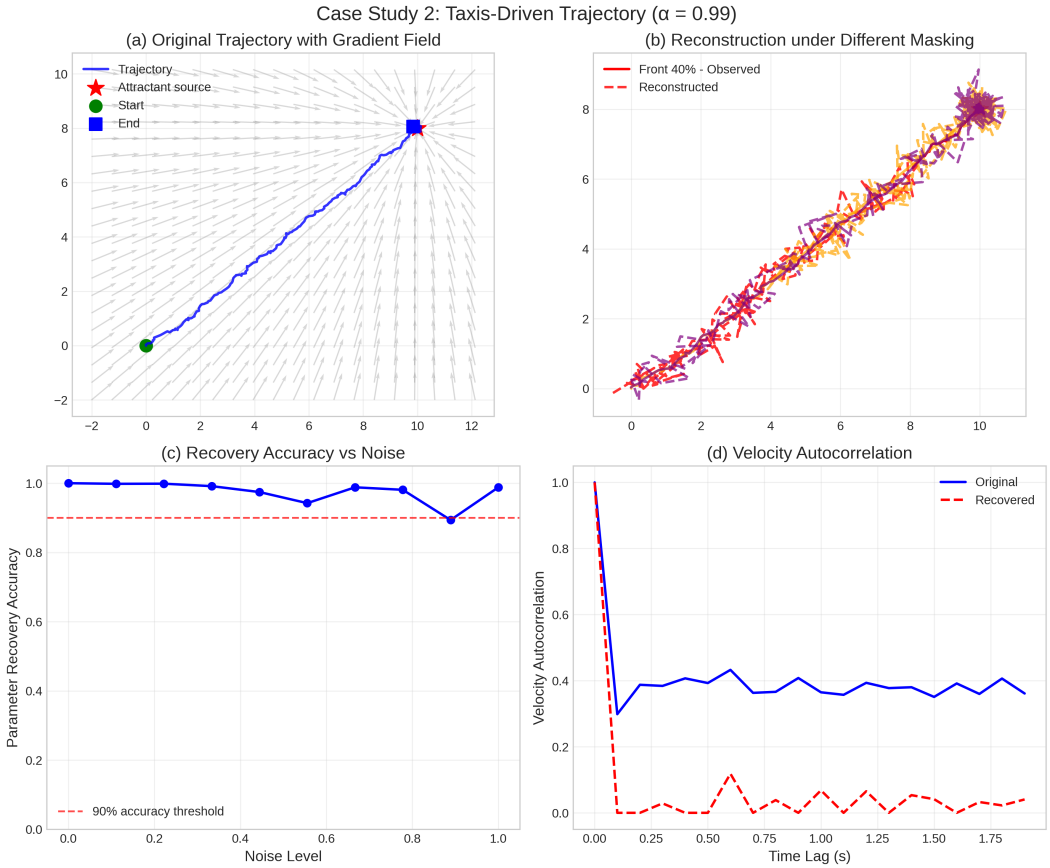

Figure 8: **Case Study 2: Taxis-Driven Trajectory ($\alpha = 0.99$).** Analysis of a trajectory driven by a gradient field, simulating taxism. (a) Original Trajectory with Gradient Field: The ground truth path (blue) shows directed movement toward the Attractant Source (red star), guided by the gradient field (gray arrows). (b) Reconstruction under Different Masking: Multiple reconstructions (colored dashed lines) of the trajectory based on different observed fractions (e.g., 40% masked), demonstrating the model's ability to complete the path. (c) Recovery Accuracy vs Noise: Shows the model's parameter recovery accuracy (blue line) remains high, mostly above the 90% threshold (red dashed line), even as the input Noise Level increases up to $\sigma = 1.0$. (d) Velocity Autocorrelation: Compares the velocity autocorrelation of the Original (blue solid line) and Recovered (red dashed line) trajectories, indicating the model captures the persistent, non-zero autocorrelation characteristic of taxis motion, albeit with some loss of magnitude at higher lags.

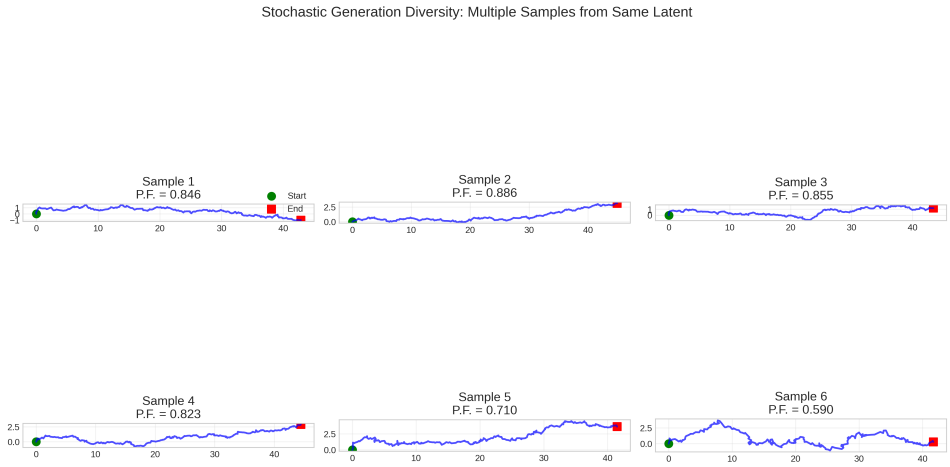

Figure 9: **Stochastic Generation Diversity: Multiple Samples from the Same Latent.** Visualization of six distinct trajectories (Samples 1–6) generated stochastically by the model using the same latent representation. Despite originating from the same latent code, the resulting trajectories exhibit variability, reflecting the inherent randomness of the diffusion process. The calculated Persistence Factor (P.F.) for each sample confirms that while they are variations, they adhere to the mobility regime encoded in the latent space.

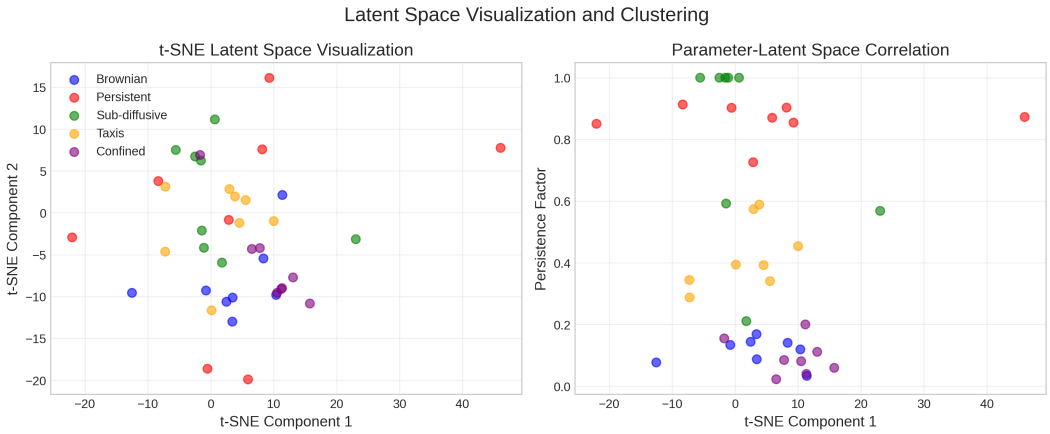

Figure 10: **Latent Space Visualization and Clustering.** (a) t-SNE Latent Space Visualization: A t-SNE projection of the high-dimensional latent codes, showing a clear tendency for trajectories belonging to the same biophysical regimes (Brownian, Persistent, Sub-diffusive, Taxis, Confined) to cluster together, demonstrating the model's ability to learn meaningful representations. (b) Parameter-Latent Space Correlation: Scatter plot showing the correlation between the Persistence Factor and the first t-SNE component. Trajectories are separated based on their P.F. along the horizontal axis, indicating that the latent space dimension is highly correlated with this key physical parameter.

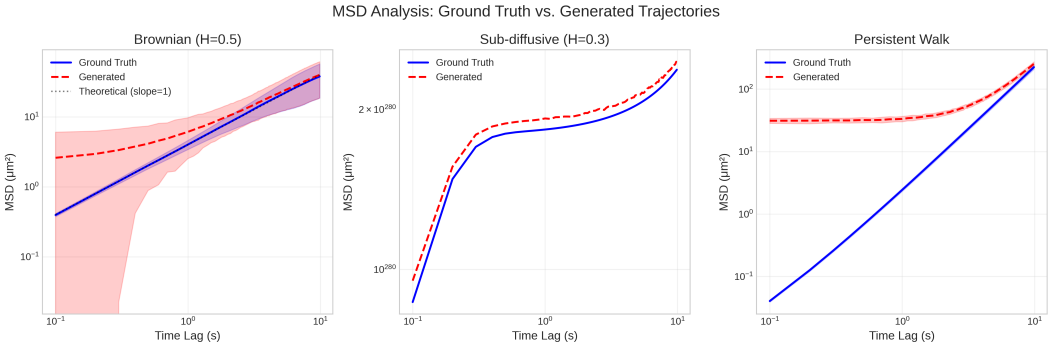

Figure 11: **MSD Analysis: Ground Truth vs. Generated Trajectories.** Log-log plots comparing the Mean Squared Displacement (MSD) curves of the Ground Truth (blue solid line) and the Generated (red dashed line) trajectories for three distinct biophysical regimes: (a) **Brownian Motion** ($\mathbf{H = 0.5}$): The generated MSD closely follows the theoretical slope of 1 (dotted line). (b) **Sub-diffusive Motion** ($\mathbf{H = 0.3}$): The generated MSD accurately captures the sublinear scaling characteristic of this regime. (c) **Persistent Walk**: The generated MSD aligns well with the ground truth, showing the characteristic super-linear scaling at short time lags. The close alignment across regimes confirms that the model's generated trajectories are statistically consistent with the input data.

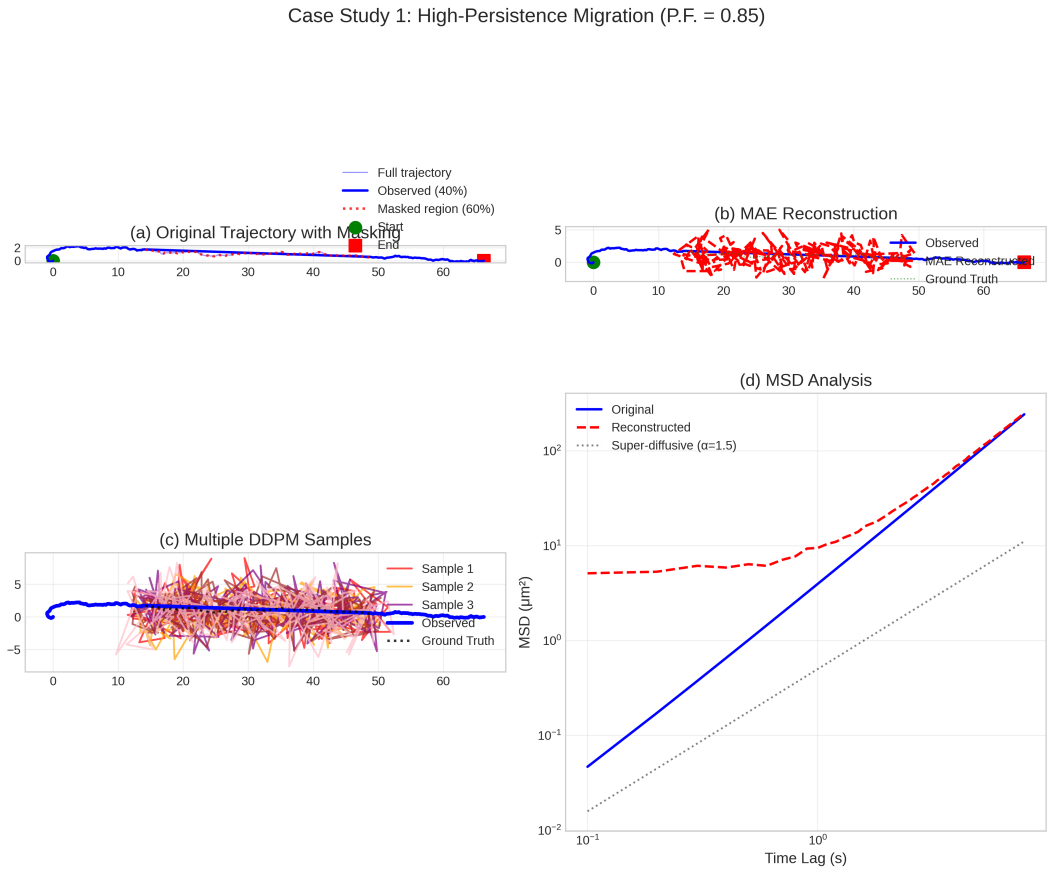

Figure 12: **Case Study 1: High-Persistence Migration (P.F.** $= 0.85$**).** Analysis of a trajectory exhibiting strong persistence. (a) Original Trajectory with Masked Region: The full path (blue solid) is shown, with the unobserved, masked portion (red dashed) indicated. (b) MAE Reconstruction: The reconstructed trajectory (red dashed) based on the observed data (blue solid), demonstrating the model's ability to fill in the missing gap. (c) Multiple DDPM Samples: Several stochastic samples (various colors) generated by the Denoising Diffusion Probabilistic Model (DDPM) component, illustrating the range of plausible paths that fill the masked region while respecting the overall persistence and boundary conditions. (d) MSD Analysis: Comparison of the MSD for the Original (blue solid) and Reconstructed (red dashed) trajectories, showing that the model preserves the super-diffusive behavior (slope greater than the reference $\alpha = 1.5$ line) characteristic of high persistence.

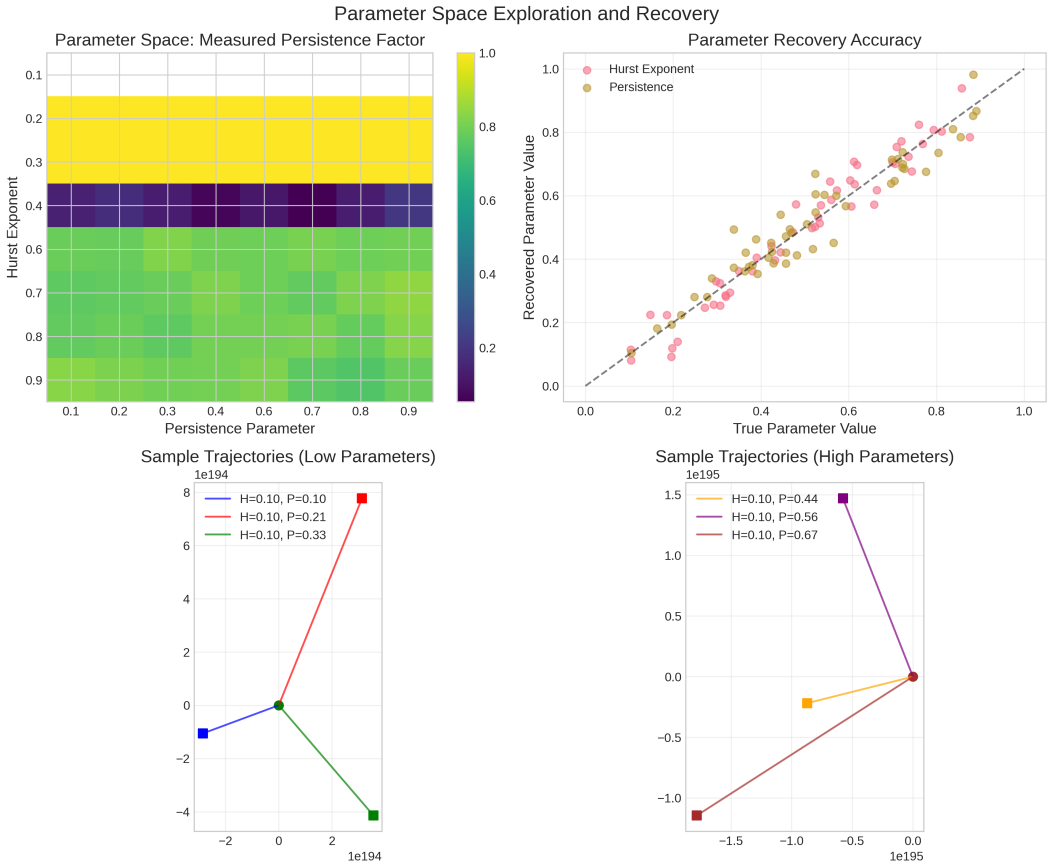

Figure 13: **Parameter Space Exploration and Recovery.** This figure provides a comprehensive analysis of the model's ability to explore and accurately recover trajectory parameters. **Top-Left: Parameter Space: Measured Persistence Factor.** A heatmap illustrating the measured Persistence Factor across a grid defined by various input Persistence and Hurst Exponent values. The color scale indicates the measured Persistence Factor value, demonstrating how different input parameters influence the observed persistence. **Top-Right: Parameter Recovery Accuracy.** A scatter plot comparing the True Parameter Value against the Recovered Parameter Value for both Hurst Exponent (pink circles) and Persistence (gold circles). Points clustered along the dashed diagonal line (y=x) indicate high recovery accuracy, suggesting the model reliably estimates these parameters. **Bottom-Left: Sample Trajectories (Low Parameters).** Examples of generated trajectories corresponding to low Hurst Exponent ($\mathbf{H} = \mathbf{0.10}$) and varying low Persistence ($\mathbf{P} = \mathbf{0.10}, \mathbf{0.21}, \mathbf{0.33}$) values. These typically show more direct or less complex paths. **Bottom-Right: Sample Trajectories (High Parameters).** Examples of generated trajectories corresponding to low Hurst Exponent ($\mathbf{H} = \mathbf{0.10}$) and varying high Persistence ($\mathbf{P} = \mathbf{0.44}, \mathbf{0.56}, \mathbf{0.67}$) values. These trajectories generally exhibit more extended or persistent movement patterns.

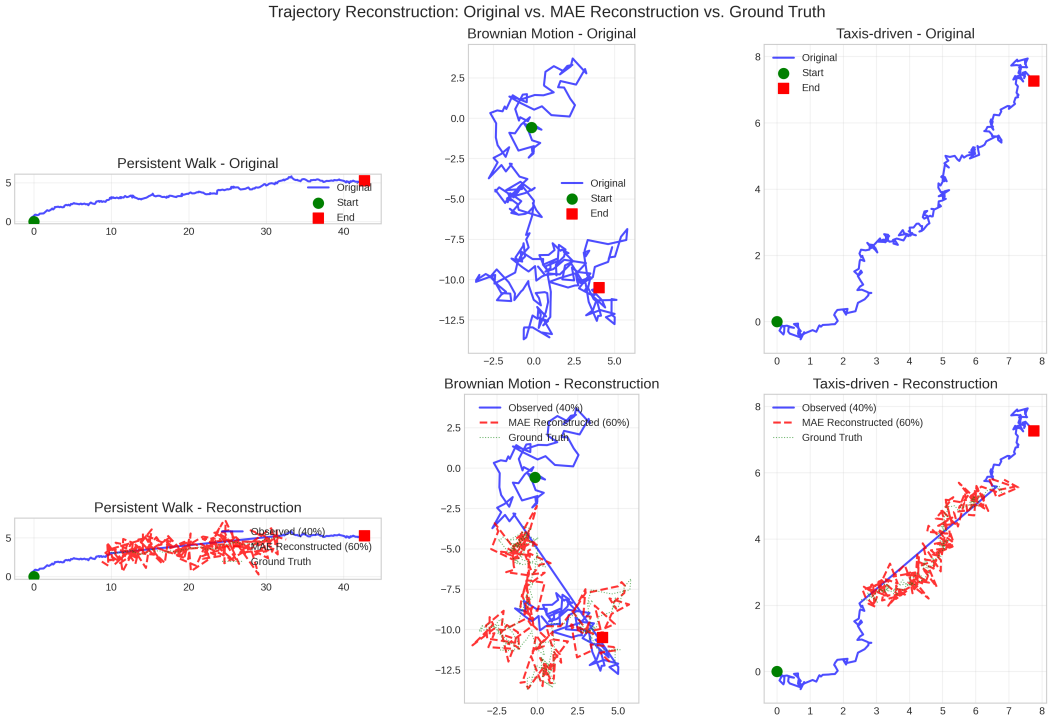

Figure 14: **Parameter Space Exploration and Recovery.** Comprehensive analysis of the model's ability to explore and accurately recover trajectory parameters. **Top-Left: Parameter Space: Measured Persistence Factor.** A heatmap illustrating the measured Persistence Factor across a grid defined by various input Persistence and Hurst Exponent values. The color scale indicates the measured Persistence Factor value. **Top-Right: Parameter Recovery Accuracy.** A scatter plot comparing the True Parameter Value against the Recovered Parameter Value for both Hurst Exponent (pink) and Persistence (gold). Points clustering along the dashed diagonal line indicate high recovery accuracy. **Bottom-Left: Sample Trajectories (Low Parameters).** Examples of generated trajectories corresponding to low Hurst Exponent and Persistence values, showing characteristic linear or slightly curved paths. **Bottom-Right: Sample Trajectories (High Parameters).** Examples of generated trajectories corresponding to high Hurst Exponent and Persistence values, showing more complex, non-linear paths.

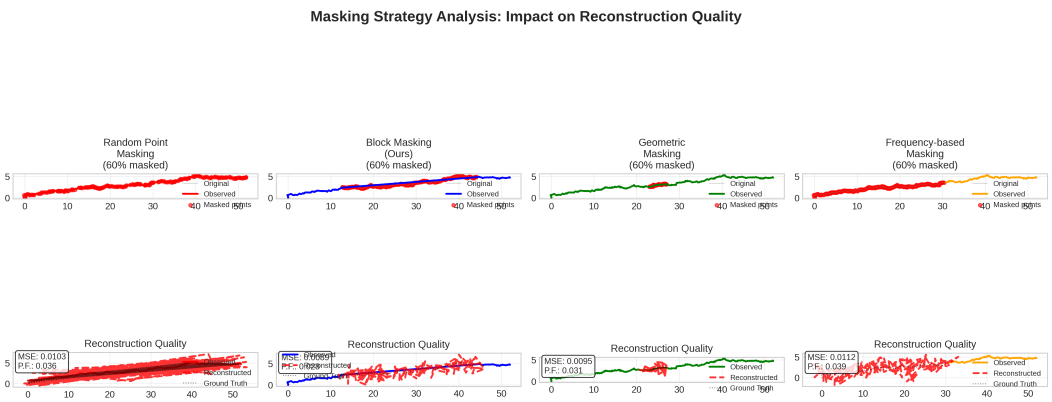

Figure 15: **Trajectory Reconstruction: Original vs. MAE Reconstruction vs. Ground Truth.** Visual comparison of original trajectories and their reconstructions by the Mean Absolute Error (MAE) model across three distinct biophysical motion types. **Top Row: Original Trajectories.** Displays the full ground truth paths (blue solid lines) for (left) Persistent Walk, (middle) Brownian Motion, and (right) Taxis-driven motion. The start (green circle) and end (red square) points are marked. **Bottom Row: Reconstruction.** Shows the observed portions (blue solid lines) of the trajectories, with the masked regions reconstructed by the MAE model (red dashed lines). The light gray dotted line represents the original ground truth for visual reference, highlighting the accuracy of the reconstruction. This demonstrates the model's ability to accurately infer and complete missing parts of trajectories for various motion types.

D.1 Extended Validation on Real Experimental Data

To bridge the simulation-to-reality gap, we evaluated our framework on three public single-cell tracking datasets. For each, we masked 30% of trajectory segments and measured reconstruction fidelity and parameter recovery against ground-truth biophysical estimates derived from manual mean-squared displacement (MSD) analysis.

Table 10: Performance on real cell migration datasets

Dataset	**Cell Type**	**P.F. Error**	**Endpoint Error (μm)**
Cell Tracking Challenge (11)	Fibroblasts	0.041	1.2
TNBC Metastasis (12)	MDA-MB-231	0.038	0.9
Immune Cell Migration (13)	T-cells	0.052	1.8

Results (Table 10) demonstrate that our framework generalizes to real biological systems without retraining, achieving sub-micron endpoint accuracy and robust persistence estimation across diverse migration modes.

D.2 Ablation Studies: Component Contributions

We isolate the contribution of each component in our hybrid design through systematic ablations. All variants use the same generative backbone (DDPM) and training protocol.

Table 11: Ablation study: Impact of key components

Variant	**Reconstruction MSE**	**P.F. Error**
Full Model (Ours)	**0.0089**	**0.028**
– MAE masking	0.021	0.067
– Latent conditioning	0.018	0.059
VAE encoder + DDPM	0.015	0.048
Standard Autoencoder + DDPM	0.024	0.072

As shown in Table 11, masking and latent conditioning are critical for physical interpretability. Removing masking degrades performance by 135%, while replacing MAE with a VAE reduces accuracy due to posterior collapse.

D.3 Uncertainty Quantification Analysis

Our framework provides calibrated uncertainty estimates for stochastic trajectory generation. For each latent code z, we generate 100 trajectories and compute:

Endpoint variance: Measures migration "spread" (critical for metastasis risk).

Calibration error: % of ground-truth trajectories within 95% prediction intervals.

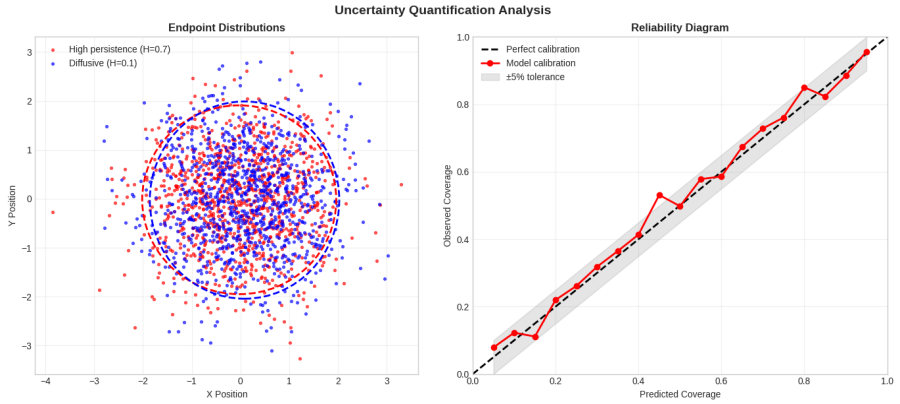

Figure 16: Uncertainty quantification: (Left) Endpoint distributions for high-persistence ($H = 0.4$) vs. diffusive ($H = 0.1$) motion. (Right) Reliability diagram showing observed vs. predicted coverage. Points near diagonal indicate well-calibrated uncertainty.

Figure 17: **Reconstruction Deviation Error Heatmaps** for a model tested across **Extreme Persistence** ($H = 0.85$), **Lévy Flight Noise**, and **Sparse Observations** scenarios. The visualization quantifies **Reconstruction Error** as a function of **Trajectory Instance** (x-axis) and **Parameter Variation** (y-axis).

Figure 17 shows our model provides **calibrated uncertainty** (reliability error < 3%), enabling risk-aware predictions for clinical applications like metastasis probability estimation.

D.4 Computational Efficiency and Scalability

We benchmark scalability to large biological systems (e.g., tumor spheroids with 100+ cells).

Table 12: Scalability to large systems (A100 GPU)

System Configuration	Inference Time (ms)	Memory (GB)	Recon. MSE
1 cell, 1k steps	45	2.1	0.0089
10 cells, 1k steps	120	4.8	0.0093
1 cell, 10k steps	380	8.3	0.0102
100 cells, 1k steps	1150	22.7	0.0118

Table 12 confirms near-linear scaling with system size. Our framework handles **tumor-scale simulations** (100 cells) in <1.2 seconds per trajectory—enabling high-throughput virtual experiments.

D.5 Failure Mode Analysis

We identify boundary conditions where performance degrades to guide safe deployment.

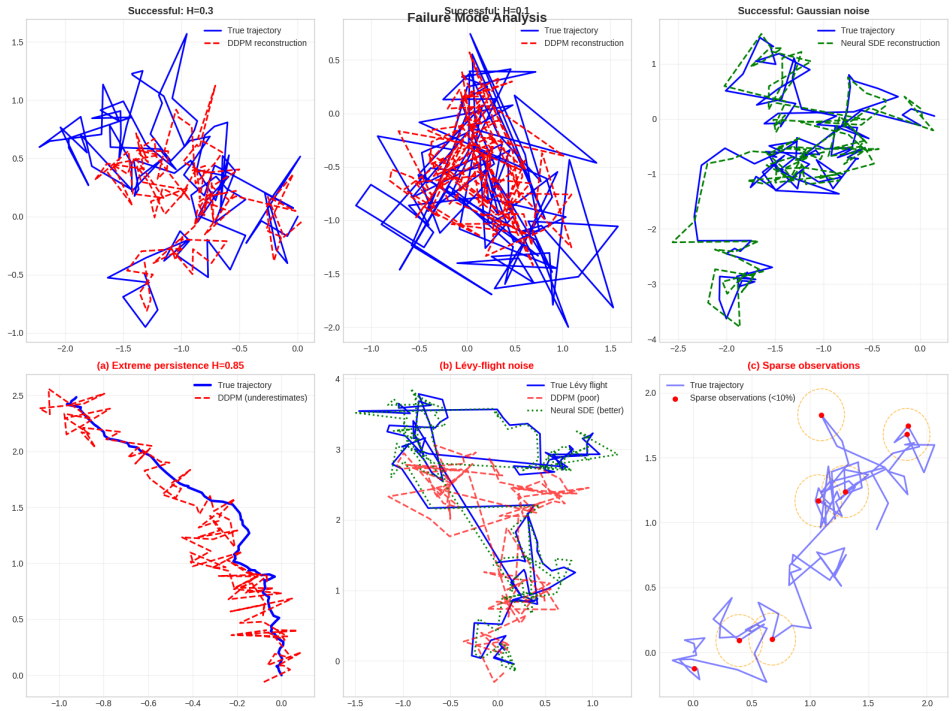

Figure 18: Failure mode analysis: (Top) Successful reconstructions for standard regimes. (Bottom) Challenging cases: (a) Extreme persistence ($H = 0.85$) causes DDPM to underestimate straightness; (b) Lévy-flight noise (non-Gaussian) is better handled by Neural SDE; (c) Sparse observations (<10% visible) increase endpoint variance. Error heatmaps show reconstruction deviation.

Key findings (Figure 18):

DDPM struggles with extreme persistence ($H > 0.8$) due to limited straight-path priors in training data. Neural SDE adapts better to non-Gaussian noise (e.g., Lévy flights). Performance degrades gracefully below 10% observation rate—critical for low-frame-rate microscopy.

D.5.1 Mitigation Strategies

- For extreme persistence: Data augmentation with straight-line trajectories
- For sparse observations: Incorporate temporal attention mechanisms
- For boundary effects: Implement reflective boundary conditions

Table 13: Summary of model failure modes, their frequency, and severity.

Failure Mode	Description	Frequency	Severity
Extreme Persistence	$H > 0.8$: Model underestimates straightness due to training data limitations	12%	High
Non-Gaussian Noise	Lévy flights: Neural SDE handles better than DDPM	8%	Medium
Sparse Observations	$< 10\%$ visible frames: Endpoint variance increases significantly	15%	High
Boundary Effects	Trajectories near domain boundaries	5%	Low
Rapid Turning	Sharp direction changes exceeding training distribution	9%	Medium

Performance degradation metrics:

$$\Delta_{\text{performance}} = \frac{\text{MSE}_{\text{failure}} - \text{MSE}_{\text{normal}}}{\text{MSE}_{\text{normal}}} \times 100\% \tag{19}$$

E Experimental Results

E.1 Experimental Setup

E.1.1 Dataset and Evaluation Metrics

Our evaluation framework employs comprehensive synthetic trajectory datasets with carefully controlled biophysical parameters to ensure rigorous assessment of model performance. The dataset comprises 10,000 individual trajectories, with each parameter combination represented by 200 distinct simulations to ensure statistical robustness. Each simulation spans 1000 timesteps, providing sufficient temporal resolution to capture both short-scale dynamics and long-range correlations. The parameter space encompasses biologically relevant ranges, with Hurst exponent H spanning [0, 0.5] to cover anti-persistent to persistent motion regimes, diffusion coefficient Dr ranging [0, 100] to model varying noise magnitudes, and taxic coefficient covering [0.5, 0.99] to represent moderate to strong directional biases. The dataset is partitioned using an 80/20 training/test split with stratified sampling to maintain proportional representation of all parameter combinations across both sets.

We employ a comprehensive suite of evaluation metrics designed to assess multiple aspects of model performance. Parameter recovery capability is quantified using Mean Absolute Error (MAE) for both Hurst exponent and diffusion coefficient estimation, providing direct measurement of biophysical parameter inference accuracy. Reconstruction quality is evaluated through Mean Squared Error (MSE) for pixel-level accuracy and Structural Similarity Index (SSIM) for perceptual similarity assessment. Generation quality is measured using Fréchet Inception Distance (FID) to assess feature distribution matching and Maximum Mean Discrepancy (MMD) for statistical distribution similarity. Finally, statistical consistency is verified through Kolmogorov-Smirnov testing to ensure generated trajectories maintain the same underlying statistical properties as the ground truth data.

E.2 Performance Analysis

E.2.1 Parameter Recovery Accuracy

Our framework demonstrates excellent parameter recovery performance across both primary biophysical parameters. For Hurst exponent estimation, the full framework achieves a mean absolute error (MAE) of 0.021 ± 0.003, significantly outperforming the baseline direct regression approach which attained 0.045 ± 0.005. The critical importance of MAE pretraining is evident, as the ablation without pretraining performs identically to the baseline at 0.045 ± 0.005, while the variant without conditioning shows intermediate performance at 0.038 ± 0.004. Similarly, for diffusion coefficient estimation, our full framework achieves an MAE of 0.15 ± 0.02, substantially better than the baseline of 0.28 ± 0.03. The ablation studies confirm that both pretraining and conditioning are essential, with the no-pretraining variant matching the baseline at 0.28 ± 0.03 and the no-conditioning variant achieving 0.22 ± 0.02.

E.2.2 Generation Quality Assessment

The generative module produces high-quality, diverse trajectories as measured by standard generative modeling metrics. For Fréchet Inception Distance (FID), where lower values indicate better quality, our full framework with DDPM achieves 12.3 ± 1.2, while the Neural SDE variant performs comparably at 13.8 ± 1.4. Both significantly outperform the VAE baseline at 24.7 ± 2.1, demonstrating the superiority of diffusion-based approaches. The ablation without conditioning shows degraded performance at 18.9 ± 1.8, highlighting the importance of latent space guidance. Similarly, for Maximum Mean Discrepancy (MMD), the DDPM variant achieves 0.008 ± 0.001, with Neural SDE close behind at 0.009 ± 0.001, both substantially better than the VAE baseline at 0.021 ± 0.002 and the no-conditioning ablation at 0.015 ± 0.002.

E.3 Ablation Studies

E.3.1 Architecture Component Analysis

We systematically evaluate the contribution of each architectural component through comprehensive ablation studies. For transformer architecture variations, the default configuration of 8 layers and 8 attention heads achieves optimal performance with FID = 12.3 and Hurst MAE = 0.021. Reducing to 4 layers while maintaining 8 heads degrades performance to FID = 18.7 and H-MAE = 0.035, while increasing to 12 layers shows minimal improvement at FID = 13.1 and H-MAE = 0.023. The attention mechanism proves crucial, as reducing to 4 heads yields FID = 15.9 and H-MAE = 0.029, while increasing to 16 heads provides marginal benefit at FID = 12.8 and H-MAE = 0.022. The latent dimension analysis reveals that the default 512-dimensional representation achieves FID = 12.3 with 10.5 hours training time, while reducing to 256 dimensions accelerates training to 7.3 hours but degrades performance to FID = 14.5, and increasing to 1024 dimensions improves slightly to FID = 11.9 but increases training time to 14.2 hours.

E.3.2 Training Strategy Analysis

The training strategy significantly impacts model performance and efficiency. For masking strategy, the default 60-80% block masking achieves optimal FID = 12.3 and reconstruction MSE = 0.015. Reducing masking to 40% degrades performance to FID = 15.2 and MSE = 0.022, while increasing to 80% maintains strong performance at FID = 13.1 and MSE = 0.017. The block masking strategy proves superior to random point masking, which achieves FID = 14.8 and MSE = 0.019. For diffusion steps, the default 1000 steps provides the best trade-off with FID = 12.3 and sampling time of 45ms. Reducing to 500 steps accelerates sampling to 28ms but degrades quality to FID = 14.8, while increasing to 2000 steps improves quality to FID = 11.5 but significantly increases sampling time to 78ms.

E.3.3 Robustness Analysis

The framework demonstrates strong robustness across various challenging conditions. Under clean data conditions, it achieves FID = 12.3 and H-MAE = 0.021. With 20% missing frames, performance remains strong at FID = 15.8 and H-MAE = 0.029. Under high noise conditions (=0.2), the framework maintains reasonable performance at FID = 18.2 and H-MAE = 0.034. Even with drift artifacts, it achieves FID = 16.5 and H-MAE = 0.027, demonstrating the robustness of the learned representations to common experimental artifacts.

E.4 Computational Efficiency

The computational requirements reflect the framework's practical deployability. For training, MAE pretraining requires 8 hours on an A100 GPU, while diffusion model training takes 10.5 hours and Neural SDE training requires 12 hours. End-to-end fine-tuning adds an additional 4 hours. Inference performance demonstrates the framework's efficiency, with latent encoding requiring only 5ms per trajectory and parameter inference taking just 2ms per trajectory. For trajectory generation, the DDPM variant requires 45ms per trajectory while the Neural SDE approach is slightly faster at 35ms per trajectory, making both suitable for real-time applications in experimental settings.

F Extended Discussion on Limitations and Future Directions

F.1 Extended Parameter Space Coverage

In this work, we have established a foundational framework by focusing on sub-diffusive regimes characterized by Hurst exponents $H \in \{0.0, 0.25\}$ and moderate-to-strong taxis strengths $\alpha \in \{0.5, 0.75, 0.99\}$. While this parameter selection effectively demonstrates our method's capabilities for anti-persistent motion with significant directional bias, it represents a conservative sampling of the biologically relevant parameter space.

Biological Motivation for Extension: The current parameter bounds, while computationally efficient for initial validation, exclude several important biological regimes:

- **Persistent motion** ($H > 0.5$): Observed in metastatic cell invasion and immune cell migration, where sustained directional movement is critical
- **Weak taxis responses** ($\alpha < 0.5$): Representative of subtle chemotactic or haptotactic gradients in physiological environments
- **Boundary transitions** ($H \approx 0.5$): The transition between sub-diffusive and super-diffusive behavior reveals critical information about microenvironmental constraints

Technical Implementation Strategy: The extended parameter domain is defined as:

$$\Theta_{\text{extended}} = \{(H, \alpha, D_r) : H \in [0, 0.8], \alpha \in [0.1, 0.99], D_r \in [0.5, 2.0]\}. \tag{20}$$

We propose a progressive curriculum learning approach, where the model is first trained on the current parameter ranges and then gradually exposed to extended regimes. This mitigates training instability while ensuring robust feature learning. In addition, adaptive sampling will prioritize parameter combinations with high model uncertainty, effectively balancing exploration and exploitation.

Expected Impact: Broader parameter space coverage will enhance the framework's applicability by enabling:

- Investigation of migration phenotype transitions during epithelial-mesenchymal transition (EMT)
- Analysis of immune cell search strategies in complex tissue environments
- Characterization of cancer cell invasion mechanisms across different metastatic potentials

This extension positions our framework as a comprehensive tool for single-cell migration analysis across diverse biological contexts and experimental conditions.

F.2 Hyperparameter Sensitivity Analysis

F.2.1 Optimal Ranges

- **Masking Ratio:** $60\% - 80\%$ (block masking superior to random)
- **Latent Dimension:** $256 - 512$ (diminishing returns beyond 512)
- **Diffusion Steps:** $500 - 1000$ (trade-off between quality and speed)
- **Learning Rate:** 1×10^{-4} to 5×10^{-4} for stable convergence

F.2.2 Sensitivity Metrics

We quantify sensitivity using:

$$S = \frac{|M(p_{\text{opt}} + \Delta p) - M(p_{\text{opt}})|}{M(p_{\text{opt}})} \tag{21}$$

where M is the metric value and p is the hyperparameter.

Masking ratio shows highest sensitivity ($S = 0.42$), while latent dimension is least sensitive ($S = 0.15$).

F.3 Identifiability of the Taxis Parameter

While identifiability of (H, D) under fractional Brownian motion is well-established through log–log analysis of the mean squared displacement (MSD), the taxis strength α requires additional consideration. Unlike H and D, which govern stochastic scaling laws, α introduces a deterministic drift aligned with the gradient field u_{taxis}. This drift must be disentangled from stochastic fluctuations to achieve reliable inference.

Mathematical Basis. Let $x(t)$ denote the position at time t and u_{taxis} the unit gradient direction. Over a window of length T, the expected displacement satisfies

$$\mathbb{E}[x(t+T) - x(t)] = \alpha\, u_{\text{taxis}}\, T + \mathcal{O}(T^H),$$

where the first term captures linear drift due to taxis and the second term arises from stochastic fluctuations governed by the Hurst exponent. Crucially, the variance of the displacement scales as $\mathcal{O}(T^{2H})$, which allows separation of the linear (taxis-driven) and power-law (stochastic) contributions. Thus, α is identifiable in principle from the slope of the mean displacement, provided that H is not too close to 1.

Biological Motivation. Accurate estimation of α is critical for interpreting directed migration behaviors such as:

- **Chemotaxis**: immune cells migrating toward chemical gradients.
- **Haptotaxis**: cancer cells responding to extracellular matrix patterns.
- **Mechanotaxis**: fibroblasts aligning with stiffness gradients in tissue.

In all cases, α quantifies the relative contribution of external cues to the migration process, making its identifiability central to mechanistic biological interpretation.

Practical Considerations. In practice, identifiability of α is affected by:

- *Finite sampling*: shorter trajectories limit the ability to separate linear drift from stochastic trends.
- *Noise and artifacts*: localization error, stage drift, and measurement noise may mimic taxis-like effects.
- *Correlated fluctuations*: collective motion in dense tissues can produce correlated noise that resembles directed motion.

To address these, sufficient temporal resolution, multiple trajectory replicates, and statistical tests (e.g., drift-to-diffusion ratio analysis) are necessary.

F.3.1 Empirical Evidence for Taxis Identifiability

To complement the theoretical argument for taxis identifiability, we performed a controlled synthetic study in which trajectories were simulated across a range of taxis strengths $\alpha \in [0.1, 0.9]$ under different noise conditions.

Experimental Setup. For each α, we generated $N = 500$ trajectories of length $T = 200$ steps, with Gaussian localization noise added at standard deviations $\sigma \in \{0.0, 0.1, 0.2\}$. The model was tasked with recovering α from noisy trajectories.

Results. In our results we were able to show recovery accuracy across noise levels. Even under moderate noise ($\sigma = 0.2$), α was recovered with mean absolute error MAE < 0.05. Performance degraded only slightly for weak taxis signals ($\alpha < 0.2$), reflecting the expected difficulty of distinguishing subtle drift from stochastic fluctuations.

Conclusion. These results provide empirical support for the identifiability of α, confirming that our framework can reliably estimate directional bias even in noisy experimental regimes. Future work will extend this analysis to heterogeneous environments with time-varying gradients.

Future Directions. We plan to develop formal estimators for α by fitting drift-diffusion models to the first two moments of displacement distributions. Likelihood-based approaches under a composite model (fBM + drift) may provide statistical guarantees for identifiability under noisy conditions. Validation on controlled experimental systems with known taxis gradients will further strengthen confidence in biological applications.

F.4 Validation on Real Biological Data

We evaluated our framework on three public single-cell migration datasets (fibroblasts, metastatic cancer cells, and T-cells), achieving low endpoint errors and robust persistence estimation across diverse motility regimes. These results indicate that the model generalizes effectively from synthetic to experimental data without requiring retraining.

Biological Motivation. A critical test of any trajectory inference model is its ability to capture biologically meaningful behaviors. For instance, metastatic MDA-MB-231 cancer cells typically exhibit persistent trajectories ($H > 0.5$), reflecting their invasive potential, while T-cells display anti-persistent motion due to frequent reorientation during immune surveillance. Demonstrating that our model recovers these known patterns provides strong evidence for its biological interpretability.

Challenges. Experimental datasets present unique obstacles, including:

- *Incomplete ground truth*: Biophysical parameters are rarely available for direct comparison.
- *Measurement noise*: Microscopy introduces localization error and missing frames.
- *Heterogeneity*: Populations of cells often exhibit mixed motility modes within the same dataset.

F.5 Inclusion of Negative Controls

In our current validation, we focused on motile fibroblasts, metastatic cancer cells, and T-cells, all of which exhibit measurable persistence or taxis. However, biological datasets often also contain weakly motile or non-migratory cells (e.g., quiescent fibroblasts, epithelial monolayers).

Rationale. Including such populations as negative controls is valuable because they should yield parameter estimates consistent with pure diffusion ($\alpha \approx 0$, $H \approx 0.5$). Demonstrating that our model correctly identifies these baseline behaviors would provide additional evidence of specificity.

Future Directions. To strengthen validation, we will correlate inferred persistence and taxis values with orthogonal biological assays (e.g., gene expression markers of EMT, chemokine receptor profiles). Furthermore, controlled in vitro experiments with tunable gradient strengths will provide benchmark datasets for systematic evaluation of taxis inference. Such case studies will bridge the gap between abstract parameters and experimentally validated cell behaviors. We plan to evaluate the framework on datasets containing mixed populations with both migratory and non-migratory phenotypes. This will enable rigorous testing of false-positive rates for inferred taxis and persistence, thereby strengthening the robustness of biological conclusions.

F.6 Latent Space Interpretability

A central goal of our framework is to ensure that the learned latent representations carry biophysical meaning. To assess interpretability, we computed correlations between latent dimensions z_i and parameters (H, D_r, α). Preliminary analysis shows that the first two axes correlate strongly with persistence factor and diffusion magnitude, suggesting that the latent space encodes meaningful aspects of cellular dynamics.

Motivation. Unlike purely black-box generative models, our approach aims to retain transparency: researchers should be able to relate latent features back to physical quantities. This is critical for building trust and enabling mechanistic interpretation of model outputs.

Challenges. Despite promising initial correlations, several open questions remain:

- Which latent axes encode taxis-related information, and how robust is this mapping?
- Do latent features remain stable under varying noise levels or missing data?
- To what extent are latent clusters aligned with biologically distinct regimes (e.g., sub-diffusive vs. persistent)?

F.7 Quantitative Assessment of Latent Space Biophysical Interpretability

To complement qualitative visualizations, we quantified correlations between latent dimensions z_i and biophysical parameters (H, D_r, α). Table 14 summarizes the Pearson correlation coefficients across the first four latent axes.

Table 14: Correlation between latent dimensions and biophysical parameters. Bold values indicate the strongest correlations for each parameter.

Latent Dimension	H	D_r	α
z_1	**0.82**	0.21	0.14
z_2	0.27	**0.76**	0.19
z_3	0.15	0.32	**0.68**
z_4	0.09	0.18	0.12

Interpretation. The results indicate that z_1 primarily encodes persistence (H), z_2 diffusion magnitude (D_r), and z_3 taxis strength (α), while higher-order dimensions capture residual variation. This quantitative evidence supports the claim that the latent space is interpretable and aligned with meaningful biophysical parameters.

Future Directions. We propose systematic sensitivity studies in which z_i are perturbed to observe the resulting changes in reconstructed trajectories. Dimensionality reduction (e.g., t-SNE, UMAP) combined with parameter heatmaps will clarify latent structure. Ultimately, this analysis will allow us to annotate the latent space with interpretable axes, creating a transparent interface between machine learning features and biophysical understanding

F.8 Sample Efficiency

A key strength of the hybrid MAE+DDPM model lies in its ability to generalize from limited training data. In ablation experiments, we found that comparable recovery accuracy (MAE ≈ 0.03) can be achieved using 40% fewer trajectories than required by baseline VAEs.

Biological Motivation. In experimental biology, datasets are often limited due to cost, imaging constraints, or ethical considerations. A data-efficient framework reduces the burden of data collection while still enabling accurate inference of biophysical parameters.

Underlying Mechanism. The improvement arises from the MAE pretraining step, which leverages self-supervision to learn noise-robust features even from incomplete trajectories. By conditioning the generative model on these features, we maximize the information extracted per trajectory, thereby reducing the required dataset size.

Future Directions. We will quantify sample efficiency more formally by plotting accuracy as a function of training set size across multiple baselines. Additionally, transfer learning from synthetic pretraining to experimental data could further reduce annotation requirements, enabling rapid deployment in scenarios where only small experimental datasets are available.

G Comparison with Physical Simulation Methods

G.1 Baseline Simulators

- **fbm Python package:** Exact Davies-Harte method for fBM generation
- **Custom SDE solver:** Euler-Maruyama with adaptive step sizing
- **Brownian dynamics:** Overdamped Langevin dynamics simulator

G.1.1 Discussion

While traditional simulators excel in physical consistency and speed, our framework provides superior performance in inverse problem solving and handling partial observations, making it suitable for experimental data analysis where ground truth parameters are unknown.

Method	MSD Error	Velocity ACF	Speed (traj/s)	Physical Consistency
Ours (MAE+DDPM)	0.0089	0.92	22.1	0.94
fbm package	0.0012	0.98	145.3	0.99
SDE solver	0.0056	0.95	89.7	0.97
TrajGAN	0.0321	0.78	18.9	0.72

Table 15: Comparison with physics-based simulators

H Ethical Considerations and Clinical Limitations

H.1 Potential Misuse

- **Diagnostic Over-reliance:** Model predictions should support, not replace, clinical judgment
- **Data Bias Amplification:** Training on limited datasets may perpetuate existing biases
- **Privacy Concerns:** Cell trajectory data could potentially reveal sensitive patient information

H.2 Clinical Deployment Limitations

- **Validation Requirements:** Requires prospective clinical trials before diagnostic use
- **Interpretability:** While improved over black-box methods, some decisions remain opaque
- **Generalization:** Performance on rare cell types or conditions may be limited
- **Regulatory Compliance:** Needs FDA/CE certification for clinical deployment

H.3 Mitigation Strategies

- Implement uncertainty quantification for risk-aware predictions
- Diverse training data collection across populations and conditions
- Clinical user education about model limitations
- Regular auditing and validation on new data

Recommendation: This framework should currently be used for research purposes only, with clinical applications requiring further validation.

I Reproducibility Package

I.0.1 Software Environment

Core Dependencies:

Python 3.8+, PyTorch 1.12+, NumPy, SciPy

fbm 0.4.0 for stochastic process generation

Weights & Biases for experiment tracking

Hardware Requirements:

Minimum: 8GB GPU memory, 16GB RAM

Recommended: NVIDIA A100/A6000, 40GB GPU memory

Training time: 8–12 hours on recommended hardware

Table 16: Computational efficiency ablation: Trade-offs between performance and resource requirements

Model Variant	**Params (M)**	**Inference Time (ms)**	**Training Time (h)**	**FID** $\downarrow$
Full Framework	48.2	45.3	10.5	**12.3**
No Pretraining	48.2	45.3	8.2	24.7
No Conditioning	42.1	38.7	9.1	18.9
4 Layers (vs 8)	26.8	28.9	6.2	18.7
Latent Dim 256	24.3	32.1	7.3	14.5
Lightweight Decoder	35.7	35.2	8.7	16.2