# How to go with the flow: flow matching in bioinformatics and computational biology

Alex Morehead[1*†], Lazar Atanackovic[2†], Akshata Hegde[3†], Yanli Wang[3†], Frimpong Boadu[3†], Joel Selvaraj[3†], Alexander Tong[4], Aditi Krishnapriyan[5,1], Jianlin Cheng[3*]

[1*]Lawrence Berkeley National Laboratory, Berkeley, California, USA.
[2]Electrical & Computer Engineering, Vector Institute, University of Toronto, Toronto, Canada.
[3*]Electrical Engineering & Computer Science, NextGen Precision Health, University of Missouri, Columbia, Missouri, USA.
[4]Mila - Quebec AI Institute, Université de Montréal, Montréal, Canada.
[5]Computer Science & Chemical Engineering, University of California-Berkeley, Berkeley, California, USA.

*Corresponding author(s). E-mail(s): acmwhb@lbl.gov; chengji@missouri.com;
Contributing authors: l.atanackovic@mail.utoronto.ca; aghktb@missouri.edu; yw7bh@missouri.edu; fbqc9@missouri.edu; jsbrq@missouri.edu; alexander.tong@mila.quebec; aditik1@berkeley.edu;
†These authors contributed equally to this work.

**Abstract**

Numerous problems in bioinformatics and computational biology can be framed as a task of learning a mapping from one state of a biological system to another relevant state or to explore novel data points across biologically-constrained spaces. However, manually deriving such mappings (e.g., to transform cells in a diseased state back into a healthy state) or extrapolating from existing datasets to create new data (e.g., for molecular design) is often nontrivial and can require extraordinary domain expertise and resources. Fortunately, the field of generative artificial intelligence (AI) has introduced a new training paradigm referred to as (conditional) flow matching, which has emerged as a promising solution to this problem, with broad applicability in computer vision, natural language processing, and the physical and life sciences. Flow matching is a powerful and

principled (data-driven) framework for efficiently learning a mapping between arbitrary pairs of high-dimensional data distributions, making it well suited for addressing problems in molecular and cell biology. In this Review, we characterize the theoretical foundations of flow matching and its applications in biomolecular modeling (e.g., for proteins, DNA/RNA, small molecules, and their interactions) and single/multi-cellular modeling (e.g., for cell phenotyping and imaging), each contributing towards the development of an AI-based virtual cell. Lastly, this review highlights open-source flow matching methods and discusses future directions in flow-based generative modeling for bioinformatics and computational biology.

**Keywords:** Flow matching, generative AI, bioinformatics, computational biology

# 1 Introduction

The field of generative AI has developed numerous important applications for biological and biomedical data analysis to date. For instance, Frazer et al. [1] introduced Bayesian variational autoencoders (VAEs) [2] for evolutionary protein sequence modeling, while Cui et al. [3] created a generative pre-trained transformer (GPT)-style [4] foundation model [5] for single-cellular data. As first of their kind results, Anand and Huang [6] generated protein structures *in silico* using a deep generative adversarial network (GAN) and further experimentally validated structures generated using an autoregressive model [7]. Interestingly, applications of generative AI in bioinformatics have also adapted ideas from non-equilibrium statistical physics to develop denoising diffusion models [8] for high-quality molecule [9] and protein [10] generation and even robust translation between biomedical imaging techniques [11].

More recently, generative AI has been experiencing a surge of research interest in developing new deep learning (DL) algorithms [12] for sampling from arbitrary (e.g., biological) data distributions based on principles from optimal transport (OT) theory (Box 1). The most prominent of such new methods are based primarily on a new paradigm of generative modeling called **flow matching (FM)** [13]. At a high level, FM refers to a class of methods designed to learn a transformation that maps samples from a simple, tractable source distribution—such as a standard Gaussian—into samples from a more complex target distribution. The target distribution is typically defined by an empirical dataset and may represent intricate structures or patterns present in real-world data. The overarching goal of FM is to construct a continuous, learnable transport path that progressively aligns the source distribution with the target, facilitating efficient sample generation and enabling applications in generative modeling, density estimation, and probabilistic inference (see Box 2 for more details).

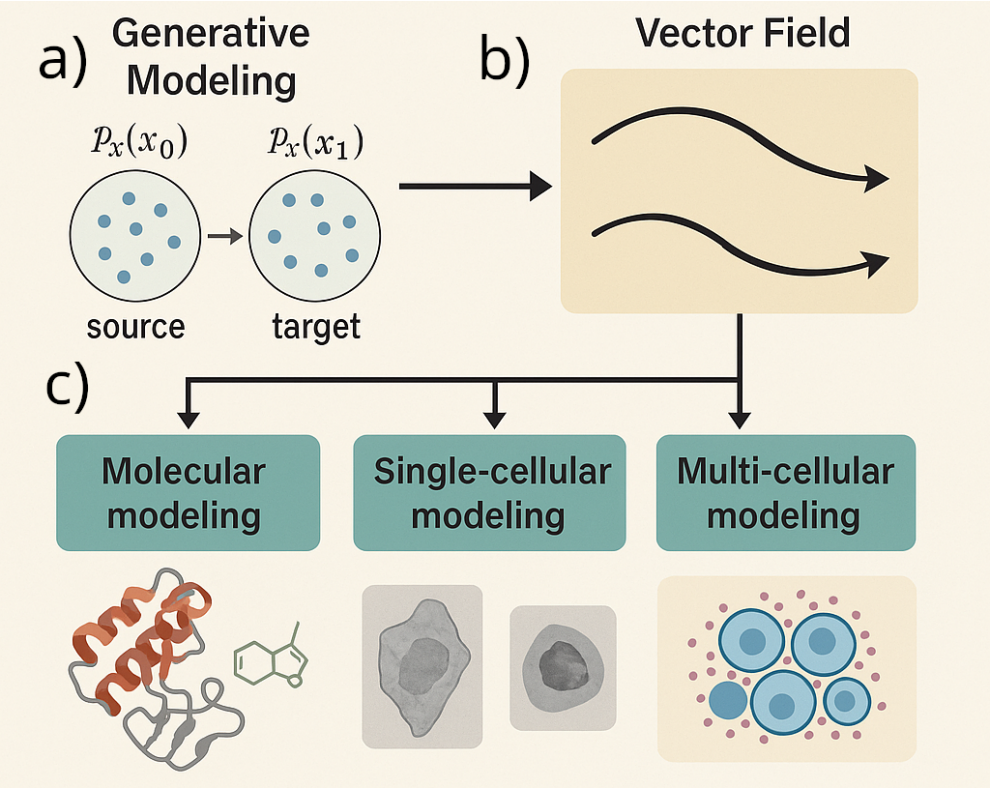


**Fig. 1 An overview of flow matching and its applications in bioinformatics. a**, Generative modeling for optimal transport of samples derived from a source distribution to a target distribution. **b**, An illustration of flow matching's standard vector field parametrization. **c**, Application areas of flow matching in bioinformatics relevant to developing an AI-based virtual cell.

## Box 1

### Deep learning and generative modeling

Deep learning (DL) [12] represents a subset of artificial intelligence and machine learning research focused on developing many-layer (i.e., deep) artificial neural networks. Each neuron in an artificial neural network receives input data features and provides output data representations to a subsequent layer of interconnected neurons. Through their hierarchical structure, deep neural networks can learn increasingly abstract yet informative representations of the network's input data, which can be used for predicting properties of unseen data or generating new data entirely.

In the realm of generative modeling, DL underpins advanced techniques such as diffusion models [14] and flow matching [13]. Diffusion models generate data by simulating a process that gradually transforms simple noise into complex structures, achieving impressive results in image, text, and graph synthesis. Flow matching, a related approach, trains models to learn optimal transport paths between data distributions, offering efficient and scalable solutions for generating high-quality samples. These methods exemplify the versatility of DL in capturing and reproducing the underlying distributions of complex datasets. Some of the most well-known examples of successful generative DL applications include GPT-4o for multi-modal natural language understanding and reasoning [15], Stable Diffusion for image generation [16], and AlphaFold 3 for biomolecule 3D structure prediction [17].

Developing powerful FM generative models could unlock several promising new application areas within bioinformatics and computational biology, including obtaining end-to-end learnable mappings between functional states of 3D (structural) biomolecules and single or multi-cellular systems. With data-driven mappings like these, the development of an AI-based virtual cell (AIVC) [18] may be within the scientific community's grasp in the coming decade, ushering in a new era of rapid biological hypothesis generation and testing via techniques from computational molecular and cell biology. In Section 2 of this Review, we first introduce the theoretical foundations of FM and how its core techniques may be improved in the coming years. We then discuss in Section 3 how FM has already been applied within diverse biological modeling contexts to accelerate scientific discovery. Lastly, in Section 4, we provide readers with an outlook on the future of FM's role in bioinformatics.

## 2 Fundamentals of flow matching

In this section, we will adopt the standardized FM notation of Lipman et al. [19]. At its core, FM theory is centered on learning to transport samples between arbitrary pairs of distributions, one often referenced as a (easy-to-sample) source distribution $p_0 = p$ and the other denoted as a (empirical) target distribution $p_1 = q$, where $p$ and $q$ are distributions defined over $\mathbb{R}^d$. Notably, what sets FM apart from previous popular generative modeling frameworks such as diffusion models [14, 20] is that, with FM, the source distribution $p_0$ is not restricted to be Gaussian in nature and can instead be any distribution of one's choosing [21]. FM can thus be viewed as a generalization of diffusion models. Further, one can subsequently employ optimal transport paths to considerably reduce the time required to sample new data points from the generative model. Excitingly, this opens the possibility to use FM to learn arbitrary mappings between different states of (biological) systems to accelerate data modeling and analysis in numerous scientific domains.

## 2.1 Designing a probability path

Concretely, to learn such generative paths for data sampling, FM builds a **probability path** $(p_t)_{0\leq t\leq 1}$, where each $p_t$ also denotes a distribution over $\mathbb{R}^d$. With this path defined, FM theory turns to training a deep neural network to predict the **vector field** needed to convert samples from the source distribution $p_0$ to the target distribution $p_1$ along the probability path $p_t$. Namely, using a trained vector field network, FM enables one to generate a new data point from the target distribution $X_1 \sim q$ by randomly sampling a point from the source distribution $X_0 \sim p$ and subsequently solving the ordinary differential equation (ODE) the vector field characterizes. Specifically, with neural network parameters $\theta$, this time-dependent vector field $u^\theta : [0,1] \times \mathbb{R}^d \to \mathbb{R}^d$ determines the time-dependent **flow** $\psi : [0,1] \times \mathbb{R}^d \to \mathbb{R}^d$ defined as:

$$\frac{\mathrm{d}}{\mathrm{d}t}\psi_t(x) = u_t^\theta(\psi_t(x)), \text{ with } \psi_t := \psi(t,x) \text{ and } \psi_0(x) = x. \tag{1}$$

With FM, we say that the vector field $u_t^\theta$ *generates* the probability path $p_t$ if, for its corresponding flow $\psi_t$, the following statement is satisfied:

$$X_t := \psi_t(X_0) \sim p_t \text{ for } X_0 \sim p_0. \tag{2}$$

Now, we proceed to design our probability path $p_t$. For the sake of notational simplicity, let our source distribution $p := p_0 = \mathcal{N}(x|0,I)$ denote a standard Gaussian. The probability path $p_t$ is then the aggregation of conditional probability paths $p_{t|1}(x|X_1)$ which are *conditioned* on the training dataset's (ground-truth) data points $X_1$. With $p_{t|1}(x|X_1) = \mathcal{N}(x|tX_1, (1-t)^2 I)$, this means we can express $p_t$ as the *conditional optimal transport path*:

$$p_t(x) = \int p_{t|1}(x|X_1)q(X_1)\mathrm{d}X_1 \tag{3}$$

which allows one to define the random variable $X_t \sim p_t$ simply via the linear combination:

$$X_t = tX_1 + (1-t)X_0. \tag{4}$$

## 2.2 Defining a training objective

After designing the probability path $p_t$, we now turn to defining the training objective of our vector field network $u_t^\theta$. The **standard** FM **loss** is defined as:

$$\mathcal{L}_{\mathrm{FM}}(\theta) = \mathbb{E}_{t,X_t}\|u_t^\theta(X_t) - u_t(X_t)\|^2, \text{ with } t \sim \mathcal{U}[0,1] \text{ and } X_t \sim p_t. \tag{5}$$

## Box 2

### Key concepts related to flow matching models

**Generative models [22]:** Models that learn to generate new data samples from a learned distribution, often by transforming noise into structured outputs such as images, sequences, or graphs. These form the basis of most generative AI applications to date.

**Optimal transport [23]:** The study of transforming probability distributions by minimizing a cost function over mappings, often used to compare or interpolate between distributions.

**Continuous normalizing flows [24] (CNFs):** Generative models that transform a simple base distribution into a target distribution using invertible flows parameterized by neural ordinary differential equations, allowing exact likelihood computation.

**Conditional flow matching [19] (CFM):** A simulation-free method for training continuous normalizing flows by regressing a vector field to known conditional transitions, enabling efficient and scalable generative modeling.

**Rectified flow [25]:** A simplified flow model first popularized in the field of computer vision, where data points follow straight-line paths in latent space, which improves sample efficiency and aligns with optimal transport objectives.

**Vector field parametrization [19]:** A core modeling component in flow matching methods, where a neural network is trained to predict the time-dependent velocity vector that transports data points along learned trajectories from a source to the target distribution.

**Diffusion models [8]:** A class of generative models that learn to reverse a diffusion (noise injection) process, closely related to flow matching (FM) methods but typically trained with score-based objectives over noisy data.

**Transformers [26]:** Neural network architectures based on self-attention mechanisms, widely used in sequence and graph modeling, including in flow-based generative tasks due to their scalability and expressiveness.

**Graph neural networks [27] (GNNs):** Architectures that operate on graph-structured data by iteratively updating node representations via message passing, commonly used when modeling social, physical, or biomolecular structures.

**SE(3)-equivariant networks [28]:** Neural network models that preserve geometric equivariance under the special Euclidean group in $\mathbb{R}^3$ (i.e., the group SE(3)) consisting of 3D rotations and translations, important for learning over molecular or physical systems where symmetry is important.

Unfortunately, calculating the ground-truth vector field $u_t(X_t)$ is computationally intractable, as doing so requires integrating over all possible transformations between

two high-dimensional distributions. Instead, in each training iteration, we can condition the loss on a single random example $X_1$ from the training dataset. To this end, we first reference Equation 4 to define the conditional random variables $X_{t|1}$ as:

$$X_{t|1} = tX_1 + (1-t)X_0, \text{ where } X_0 \sim p_{t|1}(\cdot|X_1) = \mathcal{N}(\cdot|tX_1, (1-t)^2 I). \tag{6}$$

Then, solve for $X_0$ in Equation 6 as $X_0 = \frac{X_{t|1} - tX_1}{1-t}$. We then calculate the (tractable) derivative $u_t(X_{t|1}|X_1) = \frac{\mathrm{d}}{\mathrm{d}t} X_{t|1} = \frac{\mathrm{d}}{\mathrm{d}t}(tX_1 + (1-t)X_0) = X_1 - X_0$ which, after substituting $X_0$ to obtain $u_t(X_{t|1}|X_1) = X_1 - \frac{X_{t|1} - tX_1}{1-t}$, simplifies to the following **conditional vector field**:

$$u_t(X_{t|1}|X_1) = \frac{X_1 - X_{t|1}}{1-t}. \tag{7}$$

Notably, this conditional vector field *generates* the conditional probability path $p_{t|1}(\cdot|X_1)$, which subsequently yields the following **conditional** FM **loss**:

$$\mathcal{L}_{\mathrm{CFM}}(\theta) = \mathbb{E}_{t, X_1, X_{t|1}} \| u_t^\theta(X_{t|1}) - u_t(X_{t|1}|X_1) \|^2, \tag{8}$$

where $X_{t|1} = tX_1 + (1-t)X_0$. From a practical perspective, previous works [13, 21] importantly have demonstrated the equality of the following gradients of Equations 5 and 8:

$$\nabla_\theta \mathcal{L}_{\mathrm{FM}}(\theta) = \nabla_\theta \mathcal{L}_{\mathrm{CFM}}(\theta), \tag{9}$$

which allows one to optimize the vector field network $u_t^\theta$ for both training objectives simultaneously (n.b., the first intractable and the second tractable). Lastly, if we consider the Gaussian flow $\psi_t(x) = \mu_t(X_1) + \sigma_t(X_1)x = tX_1 + (1-t)x$, let $X_{t|1} = X_0$, and solve $u_t(X_{t|1}|X_1) = \frac{\mathrm{d}}{\mathrm{d}t}\psi_t(X_{t|1}) = \frac{\mathrm{d}}{\mathrm{d}t}\psi_t(X_0) = X_1 - X_0$, one can plug $u_t(X_{t|1}|X_1)$ of Equation 7 into Equation 8 to derive the following **Gaussian**-based **optimal transport** FM **loss** [19]:

$$\mathcal{L}_{\mathrm{CFM}}^{\mathrm{OT,\ Gauss}}(\theta) = \mathbb{E}_{t, X_0, X_1} \| u_t^\theta(X_t) - (X_1 - X_0) \|^2, \tag{10}$$

where $X_0 \sim \mathcal{N}(0, I)$.

## 2.3 Sampling with a learned vector field

To sample a new data point $X_1$ from a (random) easy-to-obtain starting point $X_0$, one can use the trained vector field network $u_t^\theta$ to solve the corresponding *push-forward* ODE. Namely, using a simple update rule of the *Euler method*:

$$X_{t+h} = X_t + h u_t^\theta(X_t), \text{ where } h = n^{-1} > 0 \text{ determines the step size,} \tag{11}$$

one can arrive at a novel sample $X_1$ in a fixed number of steps $n \in \mathbb{N}$ iteratively. Note that many other ODE solvers can be substituted for the Euler method [48]. In particular, many prior works on FM adopt the Dormand–Prince (DOPRI5) method as a common ODE solver for generative modeling due to its empirically-improved performance compared to an Euler solver.

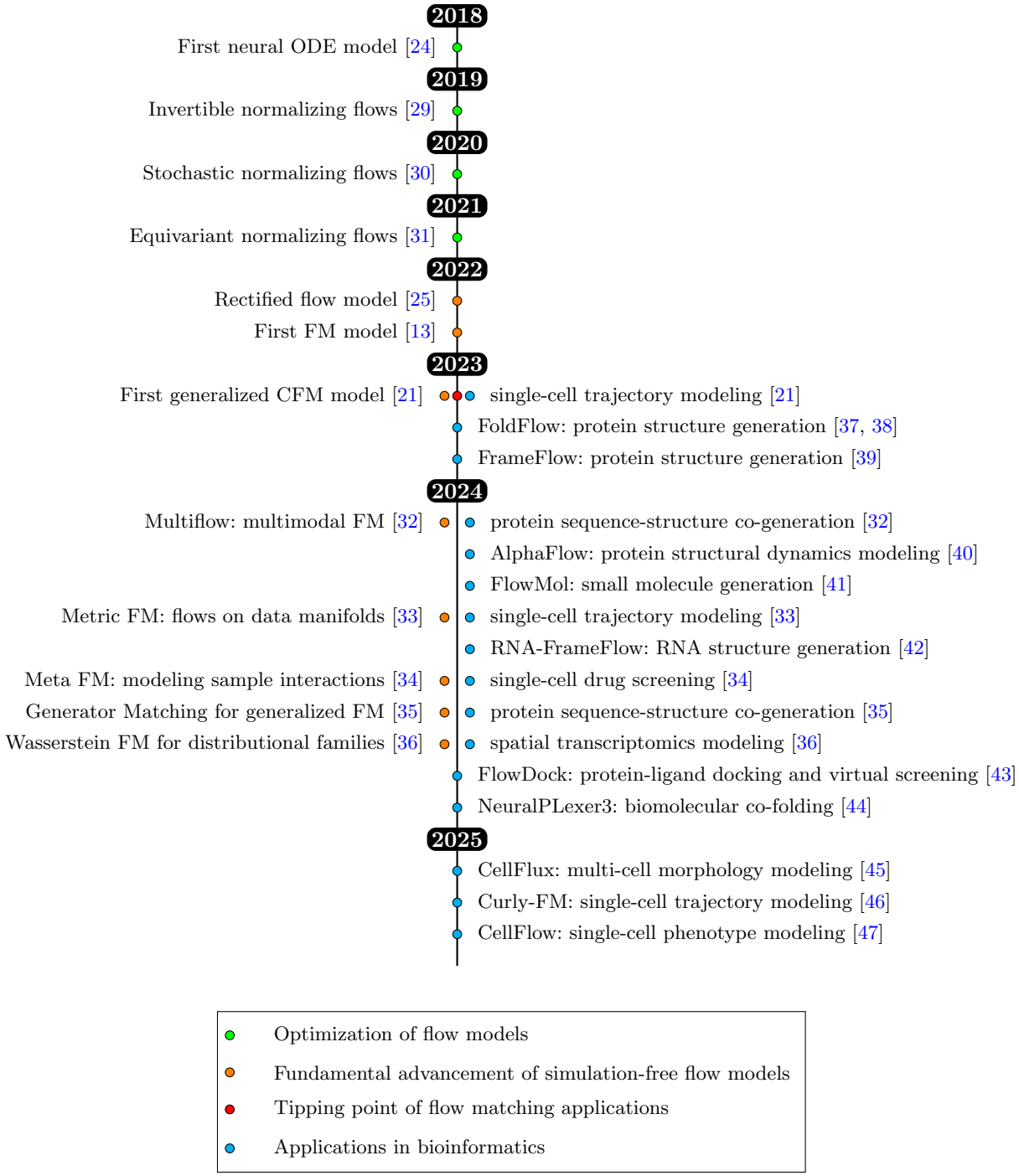


**Fig. 2 Timeline of flow matching model development and applications in bioinformatics.**

### 2.4 Improving flow matching models

While FM models offer an elegant and theoretically grounded framework for generative modeling, several challenges must be addressed to improve their empirical performance, particularly in bioinformatics applications involving high-dimensional, structured, and multimodal data. To this end, recent work has introduced multiple avenues for enhancement. For example, Rectified Flows [25] solve a nonlinear least squares optimization problem to improve the sampling speed of FM, in some cases enabling high-quality sample generation in a single ODE solver step. Moreover, Generator Matching [35] provides a theoretical unification of various diffusion and FM methods, which may yield new multi-modal applications of FM models in future work. See Table 1 for a comprehensive listing of open-source methods for implementing and improving FM models.

## 3 Applications of flow matching in bioinformatics

In this section, we outline several applications of FM in bioinformatics, in particular those that contribute to the development of an AIVC for multi-scale biological simulation and modeling (see Figure 1), which we posit will spark important new research directions in flow-based generative AI for molecular and cellular biology in the coming years. Towards this end, Section 3.1 characterizes FM applications for molecular modeling, while Sections 3.2, 3.3, and 3.4 describe recent applications of FM in single/multi-cellular modeling and bioimaging, respectively. To complement the following sections, Table 2 lists the latest FM methods for bioinformatics. For a historical timeline of the development of FM methods and their applications in bioinformatics, please see Figure 2. Further, for practical advice on how to build and apply FM models in bioinformatics applications, please see Box 3.

## Box 3

### A pragmatic guide for developing and applying flow matching models in bioinformatics

**1. Define the mapping task.** Clearly identify the biological states or data distributions between which you aim to learn a mapping (e.g., perturbed vs. unperturbed cellular states, random vs. ground-truth 3D structures, or latent phenotype trajectories). Flow matching is best suited for problems that can be expressed as transporting samples between two distributions in $\mathbb{R}^d$.

**2. Choose appropriate data representations.** Select feature encodings that capture relevant biological information while being compatible with neural network inputs. For molecules, this may include graph-based representations or 3D atomic coordinates; for cellular data, it may involve gene expression vectors, imaging embeddings, or latent phenotypes.

**3. Select a model class and vector field parameterization.** Use architectures tailored to the domain: SE(3)-equivariant or (rotation-augmented) transformer-based networks for 3D molecular modeling, convolutional or transformer-based encoders for high-dimensional cellular data, and GNNs for biomolecular interaction tasks. Consider ensuring the vector field respects certain (non-trivial) symmetries when necessary.

**4. Define the source distribution $p_0$ and sampling strategy.** While a standard Gaussian is often used for $p_0$, FM permits more biologically meaningful priors (e.g., empirical distributions or structured noise priors) when justified by domain knowledge.

**5. Design the training objective and probability path.** Choose a probability path $p_t$ (e.g., linear interpolation, optimal transport geodesic) and loss formulation (e.g., squared vector field deviation or dual potential-based objectives) appropriate for the application and model capacity.

**6. Validate with domain-relevant metrics.** Evaluate generated samples using biologically meaningful metrics, such as structural accuracy [44] (e.g., RMSD, TM-score), functional annotations, or predictive consistency with downstream tasks.

**7. Integrate constraints when applicable.** For improved biological fidelity, incorporate inductive biases such as geometric constraints, known interaction priors, or energy functions, either directly in the model or during post-processing. However, note that doing so may make model training more complex or challenging [49].

**8. Use and contribute to open-source FM libraries.** Several frameworks support FM training, including Meta AI's beginner-friendly `flow_matching` GitHub repository. Starting with open-source implementations can greatly accelerate model development and reproducibility.

## 3.1 Flow matching for molecular modeling

In this section, we discuss selected FM generative models for 3D biomolecules, as listed in Table 2, encompassing small molecules, peptides, proteins, RNAs and DNAs. Towards this end, we begin by introducing readers to the notion of representing geometric data types with generative models.

### 3.1.1 Introduction to geometric generative modeling

Rigid bodies in three-dimensional space are fully described by their position and orientation, forming a configuration space structured as the Lie group $SE(3)$, which combines translations ($\mathbb{R}^3$) and rotations ($SO(3)$) [19, 37, 38]. This group is a smooth Riemannian manifold, supporting definitions of distances, angles, and geodesics essential for modeling motions and probability distributions. In biological macromolecules such as proteins, each residue can be represented as a rigid body with a specific position and orientation, and the entire backbone as a sequence of frames in $SE(3)^N$ [37, 38, 50, 51]. Chirality is preserved by restricting to rotations and translations, as reflections in certain contexts are considered biologically invalid.

Generative modeling of protein and nucleotide backbones thus often involves learning distributions over $SE(3)^N$, requiring models that respect the manifold's symmetries and geometry [10, 14, 52]. Traditional diffusion models, adapted from Euclidean spaces, often struggle with manifold constraints and require many inference steps. FM [19, 53] overcomes these limitations by learning vector fields that more succinctly transport samples from a prior to the data distribution along continuous paths on the manifold. In particular, FM offers four key advantages simultaneously: it (1) needs fewer inference steps; (2) is simpler to implement; (3) allows explicit control over distribution couplings; and (4) can preserve important geometric properties such as equivariance.

### 3.1.2 Generative modeling of proteins

Designing proteins that satisfy geometric, physicochemical, and functional constraints is a complex challenge due to the vast conformational landscape and intricate sequence–structure dependencies. Traditional diffusion-based models like RFdiffusion are effective but computationally intensive and often treat sequence and structure separately. Recent advances leverage FM to efficiently learn generative models on the product manifold $\mathrm{SE}(3)^N$, capturing both the geometry and symmetries of protein backbones. State-of-the-art methods—including FrameFlow [50], FoldFlow [37], MultiFlow [32], and OriginFlow [54]—employ equivariant architectures, optimal-transport objectives, and discrete-state flows to accelerate protein structure generation and enable holistic sequence–structure co-design. FrameFlow and FoldFlow focus on fast, accurate backbone generation by learning continuous or stochastic flows on $\mathrm{SE}(3)^N$, with FoldFlow introducing optimal transport and stochasticity for improved diversity and robustness. MultiFlow extends this paradigm to joint sequence and structure generation, integrating discrete (sequence) and continuous (structure) flows for efficient, multimodal protein co-design.

| Method name | Year | Brief description | Source Code |
|---|---|---|---|
| Neural Autoregressive Flows [55] | 2018 | Foundational model | GitHub |
| Neural (latent) ODE [24] | 2018 | Foundational model | GitHub |
| GLOW [56] | 2018 | Foundational generative flows | GitHub |
| FFJORD [57] | 2019 | Improves computational efficiency of [24] | GitHub |
| Augmented Neural ODEs [58] | 2019 | Foundational neural ODE | GitHub |
| Residual Flows [29] | 2019 | Invertible generative flows | GitHub |
| Graph Normalizing Flows [59] | 2019 | Generative geometric flows | Github |
| Stochastic Normalizing Flows [30, 60] | 2020 | Generative stochastic flows | GitHub |
| Equivariant Normalizing Flows [31] | 2021 | Generative equivariant flows | GitHub |
| Diffusion Normalizing Flow [61] | 2021 | Generative stochastic flows | GitHub |
| Monte Carlo Flows [62] | 2022 | Flows for MCMC | GitHub |
| Divergence-free Neural Conservation Laws [63] | 2022 | Flows with divergence-free neural networks | GitHub |
| Rectified Flows [25] | 2022 | Straight and fast flow trajectories | GitHub |
| Flow Matching for Generative Modeling [13, 19] | 2022 | Generative flows with Gaussian probability paths | GitHub |
| Stochastic Interpolants (InterFlow) [53, 64, 65] | 2022 | Building flows with stochastic interpolants & diffusion | GitHub |
| RIVER [66] | 2022 | Flow matching for video prediction | GitHub |
| Point Straight Flow [67] | 2022 | Generating point clouds with Straight and fast flows | GitHub |
| Action Matching [68] | 2023 | Generative optimal transport with arbitrary paths | GitHub |
| OT Conditional Flow Matching [21] | 2023 | Generative (conditional) continuous flows | GitHub |
| Fast-ODE [69] | 2023 | Minimizing trajectory curvature of ODE-based generative models | GitHub |
| Latent Flow Matching [70] | 2023 | Flow matching in the latent space | GitHub |
| $[SF]^2M$ [71] | 2023 | Simulation-free stochastic dynamics | GitHub |
| Riemannian Flow Matching [72] | 2023 | Generative geometric flows | GitHub |
| Equivariant Flow Matching [73] | 2023 | Generative equivariant flows | GitHub |
| Wasserstein Lagrangian Flows [74] | 2023 | Unified flows and optimal transport | GitHub |
| FM Boosting [75] | 2023 | Boosting latent diffusion models with flow matching | GitHub |
| Motion Flow Matching [76] | 2023 | Flow matching for human motion synthesis and editing | GitHub |
| InstaFlow [77] | 2023 | Flows for accelerating text-to-image generation | GitHub |
| Multimodal Flow Matching [32] | 2024 | Continuous-discrete data generation | GitHub |
| Functional Flow Matching [78] | 2024 | Flow matching for infinite dimensional spaces | GitHub |
| Dirichlet Flow Matching [79] | 2024 | Discrete data generation | GitHub |
| Discrete Flow Matching [80] | 2024 | Discrete data generation | GitHub |
| Fisher Flow Matching [81] | 2024 | Discrete data generation | GitHub |
| Bellman Optimal Stepsize Straightening [82] | 2024 | Distilling and fine-tuning flow matching generative models | GitHub |
| Consistency Flow Matching [83] | 2024 | Learning strait flows with self-consistency in velocity fields | GitHub |
| Metric Flow Matching [33] | 2024 | Flows on the data manifold | GitHub |
| Depth FM [84] | 2024 | Flow matching for depth estimation | GitHub |
| Probabilistic Forecasting with Interpolants [85] | 2024 | Stochastic interpolants for probabilistic forecasting of dynamical systems | GitHub |
| SemFlow [86] | 2024 | Flows for semantic segmentation & semantic image synthesis | GitHub |
| Preference Flow Matching [87] | 2024 | Flow matching for preference-based reinforcement learning | GitHub |
| COT-FM [88] | 2024 | Conditional optimal transport with simulation-free flows | GitHub |
| FlowSeq [89] | 2024 | Flow matching for conditional text generation | GitHub |
| Statistical Flow Matching [90] | 2024 | Flows on the manifold of parameterized probability measures | GitHub |
| Optimal Flow Matching [91] | 2024 | Shorter flow trajectories | GitHub |
| Discrete Guidance [92] | 2024 | Guidance of discrete state space flow and diffusion models | GitHub |
| Meta Flow Matching [34] | 2024 | Flows across measures and modeling sample interactions | GitHub |
| Trajectory Flow Matching [93] | 2024 | Simulation-free modeling of stochastic time-series | GitHub |
| Generator Matching [35] | 2024 | Generalized multi-modal flow matching | GitHub |
| Wasserstein Flow Matching [36] | 2024 | Flows for families of distributions | GitHub |
| Multi-Marginal Flow Matching [94] | 2025 | Flows with smooth spline-based interpolation | GitHub |
| Contrastive Flow Matching [95] | 2025 | Unique conditional flows | GitHub |
| TFG-Flow [96] | 2025 | Continous-discrete flow guidance | GitHub |
| SDE Matching [97] | 2025 | Simulation-free latent SDEs | GitHub |

**Table 1 Open-source methods for implementing and improving flow matching models.** O(S)DE, ordinary (stochastic) differential equation; MCMC, Markov chain Monte Carlo.

OriginFlow represents a notable advance in de novo protein design by combining FM with expressive neural architectures, such as Invariant Point Attention and graph neural networks, to robustly generate functional protein structures from noise for PD-L1, RBD, and VEGF targets, achieving overall expression, affinity, and solubility rates of 90%. Accordingly, it achieves remarkable experimental success rates, particularly in challenging tasks like binder design, outperforming previous models in both speed and controllability. Collectively, these FM-based approaches deliver significant improvements in designability, diversity, accuracy, and experimental validation, marking a shift from mere structure prediction to practical, AI-driven functional protein design and accelerating the integration of generative AI into real-world biopharma pipelines.

### 3.1.3 Generative modeling of small molecules

Designing 3D small molecules with high chemical fidelity is a core challenge in computational chemistry, where traditional generative models—such as graph-based autoencoders and diffusion models—are often hampered by slow sampling and difficulties in handling the discrete-continuous nature of molecular data. Recent FM approaches provide a promising solution by learning continuous velocity fields that efficiently map noise to valid molecular structures in a handful of steps. State-of-the-art models like SemlaFlow [98] and FlowMol [41] advance this frontier by combining geometric deep learning, equivariant architectures, and optimal transport objectives. SemlaFlow leverages a message-passing neural network with latent attention and E(3)-equivariance to generate high-quality molecules up to 100× faster than diffusion models, while FlowMol bridges continuous and categorical data using chirality-aware Geometric Vector Perceptrons [99] and simplex-based or relaxed categorical modeling, achieving fast, accurate, and chemically valid one-shot molecular generation.

Further pushing the boundaries, ADiT [52] introduces a unified Transformer-based framework for both molecular and crystalline material generation, performing denoising in latent space for efficiency and scalability without relying on graph-specific inductive biases. ET-Flow [100] employs an equivariant transformer architecture and harmonic priors to generate low-energy molecular conformers directly from graphs, with post hoc correction for chirality and a lightweight, scalable design. Collectively, these FM-based models demonstrate that with the right combination of geometric learning, symmetry-aware architectures, and efficient FM, it is possible to achieve fast, faithful, and generalizable 3D molecular generation—opening new possibilities for drug discovery and atomistic material design.

### 3.1.4 Generative modeling of nucleotides

Generative modeling of nucleotide sequences and structures is a central challenge in synthetic biology and RNA therapeutics, given the discrete nature of DNA/RNA alphabets and the complex, high-dimensional biological constraints they encode. FM provides a powerful alternative to traditional autoregressive and diffusion models by enabling efficient, parallelizable, and controllable transformations from noise to structured sequences. Recent advances such as Dirichlet Flow Matching [79] and Fisher FM [81] introduce geometry-aware flows on the probability simplex, improving expressivity, stability, and performance in DNA design tasks. For RNA, frameworks like

RNACG [101] leverage Dirichlet FM and multimodal transformers for high-fidelity, conditional sequence generation, outperforming previous approaches across a range of RNA design benchmarks.

Beyond sequence generation, FM-based models have also advanced RNA structure and sequence-structure co-design. RNAFlow [102] and RiboFlow [103] unify RNA sequence and structure generation by conditioning on protein or ligand geometry, using SE(3)-equivariant architectures and multi-scale representations to capture RNA's conformational flexibility. RNA-EFM [104] further incorporates energy-based priors for protein-conditioned co-design, while RNA-FrameFlow [42] and RNAbpFlow [105] address unconditional and base-pair-constrained 3D RNA structure generation, respectively, achieving state-of-the-art accuracy and scalability. Collectively, these FM-based approaches establish a robust and unified foundation for DNA/RNA sequence and structure design, enabling principled, controllable, and efficient engineering of nucleic acids for diverse biological applications.

### 3.1.5 Generative modeling of biomolecular interactions

Recent advances in generative modeling—especially those leveraging geometric FM and continuous normalizing flows—have enabled direct, scalable prediction of biomolecular interactions and complex structures, bypassing traditional docking and alignment-dependent pipelines. Models like FlowDock [43] use conditional FM to map unbound protein structures to holo complexes, supporting simultaneous multi-ligand docking and accurate affinity prediction, and outperforming AlphaFold 3 and other baselines in certain benchmarking settings. NeuralPLexer3 [44] employs physics-inspired normalizing flows for fast, high-resolution prediction of diverse biomolecular complexes, exceeding the accuracy of diffusion-based and docking methods across a wide range of targets. FlexDock [106] introduces Unbalanced Flow Matching to model flexible protein-ligand docking, relaxing strict mass preservation to better capture conformational changes; this two-stage approach significantly improves docking accuracy and physical plausibility, as measured by PoseBusters and PDBBind benchmarks.

### 3.1.6 Generative modeling of biomolecular dynamics

Biomolecules are inherently dynamic entities, often transitioning between multiple conformations to carry out their biological functions. Capturing this structural heterogeneity is essential for understanding allostery, binding mechanisms, and functional regulation. Fortuitously, generative FM techniques are also transforming the modeling of biomolecular dynamics, enabling the simulation of conformational ensembles and transition pathways beyond static structure prediction. AlphaFlow [40] and related frameworks reinterpret AlphaFold and ESMFold as generative denoisers within FM, producing realistic protein conformational ensembles directly from sequence. FMRC [107] leverages FM to learn optimal reaction coordinates, outperforming traditional kinetic modeling methods and enhancing both Markov state model construction and enhanced sampling. MDGen [108] extends FM to generate full molecular dynamics trajectories, accurately capturing free-energy landscapes and kinetic properties in an SE(3)-invariant manner. Finally, Onsager-Machlup-based action minimization [109] enables efficient, zero-shot transition path sampling by optimizing generative model

trajectories, offering scalable and model-agnostic solutions for simulating biomolecular motions. Collectively, these advances establish FM-based generative modeling as a powerful and unified framework for predicting the dynamics of 3D biomolecules.

## 3.2 Flow matching for single-cellular modeling

Generative modeling with FM has emerged as a powerful approach for simulating and predicting single-cell phenotypes under diverse perturbations, addressing the (perturbation/conditioning-related) combinatorial and high-dimensional challenges inherent in systems biology and precision medicine. By learning continuous-time vector fields that transport distributions of unperturbed cellular states to those under complex perturbations, FM enables efficient and interpretable inference as well as simulation-free training across vast phenotypic landscapes. Leading frameworks such as CellFlow [47] and CFGen [110] integrate optimal transport, multimodal biological embeddings, and permutation-invariant architectures to model realistic single-cell responses. CellFlow excels at virtual phenotyping and systematic perturbation design, while CFGen extends FM to discrete count data and multi-modal settings, enabling compositional and attribute-guided simulation of cellular phenotypes.

Beyond static phenotype modeling, FM-based methods have advanced the reconstruction of cellular dynamics and trajectories from single-cell snapshot data, overcoming the limitations of destructive assays and the simplifying assumptions of traditional approaches. Conditional Flow Matching (CFM) [21] and $[\mathrm{SF}]^2\mathrm{M}$ [71] provide simulation-free objectives for learning deterministic and stochastic flows, respectively, while GENOT [111] generalizes to stochastic, entropic, and unbalanced optimal transport, supporting cross-modal and heterogeneous data. Further innovations like Meta FM [34] and Wasserstein Flow Matching (WFM) [36] extend FM to population-level and distributional settings, enabling personalized trajectory modeling and the synthesis of spatial cellular niches.

Recent work has also focused on incorporating geometric, biological, and dynamical realism into FM-based cellular modeling. Metric FM [33] leverages data-induced Riemannian metrics to ensure learned trajectories remain close to the true data manifold, improving biological plausibility. Unbalanced Mean-Field Schrödinger Bridge and CytoBridge [112] jointly model state transitions, population growth, and cell-cell interactions, while Curly-FM [46] enables the modeling of non-gradient, cyclic dynamics such as the cell cycle by matching both distributional and velocity field constraints. Velocity–Growth Flow Matching (VGFM) [113] further extends FM to jointly infer cellular state transitions and population-level mass changes with regression-based and growth-aware training objectives. Consequently, VGFM ensures scalability and training efficiency, supporting the realistic modeling of development and disease progression.

Finally, Multi-Marginal Flow Matching [94] generalizes FM to handle transitions across multiple time points, enabling globally consistent trajectory inference in complex experimental designs. Collectively, these advances establish FM as a flexible, scalable, and interpretable foundation for single-cell generative modeling—enabling virtual phenotyping, dynamic trajectory reconstruction, and the principled integration of biological knowledge across high-dimensional and heterogeneous datasets.

| Research area | Applications | Method name | Flow conditioning | Network architecture | Source Code |
|---|---|---|---|---|---|
| Molecular modeling | Protein sequence generation | ProtFlow [114] | Conditioned | Transformer | GitHub |
| | Protein structure generation | FrameFlow [39] | Unconditioned | SE(3)-equivariant transformer | GitHub |
| | Protein structure generation | FoldFlow [37, 38] | Unconditioned | SE(3)-equivariant transformer | GitHub |
| | Protein side-chain packing | FlowPacker [51] | Conditioned | SE(3)-equivariant transformer | GitHub |
| | Protein sequence & structure generation | Multiflow [32] | Unconditioned | SE(3)-equivariant transformer | GitHub |
| | Protein sequence & structure generation | CoFlow [115] | Conditioned | Transformer | GitHub |
| | Protein sequence & structure generation | OriginFlow [54] | Unconditioned/Conditioned | Transformer | GitHub |
| | Antibody protein sequence & structure generation | FlowDesign [116] | Conditioned | SE(3)-equivariant transformer | - |
| | Peptide protein sequence & structure generation | D-Flow [117] | Conditioned | Transformer | GitHub |
| | Small molecule generation | MolFM [118] | Unconditioned | Geometric GNN | GitHub |
| | Small molecule generation | SemlaFlow [98] | Unconditioned | Geometric GNN | GitHub |
| | Small molecule generation | FlowMol [41] | Unconditioned | Geometric GNN | GitHub |
| | Small molecule conformer prediction | ET-Flow [100] | Conditioned | Transformer | GitHub |
| | Small molecule & materials generation | ADiT [52] | Unconditioned | All-atom transformer | GitHub |
| | DNA sequence generation | Dirichlet FM [79] | Unconditioned | Transformer with FM on simplex | GitHub |
| | DNA sequence generation | Fisher-Flow [81] | Unconditioned | Hyperspherical (Fisher-Rao) FM | GitHub |
| | RNA sequence generation | RNACG [101] | Conditioned | Multimodal Diffusion Transformer with Dirichlet FM | - |
| | RNA sequence & structure generation | RNAFlow [102] | Conditioned | Geometric GNN | GitHub |
| | Ligand-conditioned RNA sequence & structure generation | RiboFlow [103] | Conditioned | SE(3) flow with torsion angle modeling | - |
| | Protein-conditioned RNA sequence & structure generation | RNA-EFM [104] | Conditioned | Energy-based SE(3) flow with protein contacts | - |
| | RNA structure generation | RNA-FrameFlow [42] | Unconditioned | Torsion-based SE(3)-equivariant transformer | GitHub |
| | RNA structure prediction | RNAbpFlow [44] | Conditioned | Base-pair-augmented SE(3)-equivariant transformer | GitHub |
| | Biomolecular interactions | FlowDock [43] | Conditioned | SE(3)-equivariant transformer | GitHub |
| | Biomolecular interactions | NeuralPLexer3 [44] | Conditioned | All-atom transformer | GitHub |
| | Biomolecular interactions | FlexDock [106] | Conditioned | SE(3)-equivariant GNN | GitHub |
| | Biomolecular dynamics | AlphaFlow [40] | Conditioned | SE(3)-equivariant transformer | GitHub |
| | Biomolecular dynamics | FMRC [107] | Conditioned | Fully-connected neural network | GitHub |
| | Biomolecular dynamics | MDGen [108] | Conditioned | Transformer | GitHub |
| | Biomolecular dynamics | OM-TPS [109] | Conditioned | Diffusion or flow-based neural network | GitHub |
| Single-cellular modeling | Cell phenotype modeling | CellFlow [47] | Conditioned | Residual neural network | GitHub |
| | Phenotype generation | CFGen [110] | Compositional (multi-attribute) | Flow matching with discrete likelihoods | GitHub |
| | Simulation-free flows | CFM [21] | Conditioned | Conditional FM (regression) | GitHub |
| | Stochastic bridges | $[SF]^2M$ [71] | Unconditioned | Score-FM | GitHub |
| | Stochastic flow alignment | GENOT [111] | Unconditioned | Entropic Gromov–Wasserstein flows | GitHub |
| | Population-conditioned flow modeling | Meta FM [34] | Population-conditioned | FM-based GNN | GitHub |
| | Distribution-level modeling | Wasserstein FM [36] | Distributional | Bures–Wasserstein FM | GitHub |
| | Manifold-constrained flows | Metric FM [33] | Metric-conditioned | Geodesic interpolant + flow field | GitHub |
| | Interaction-aware bridges | CytoBridge [112] | Conditioned (mean-field) | Unbalanced mean-field Schrödinger bridge | - |
| | Rotational dynamics | Curly-FM [46] | Velocity-conditioned | Schrödinger bridge with drift | - |
| | Growth-aware flows | VGFM [113] | Conditioned (growth + velocity) | Flow and growth field regression | - |
| | Multi-context flow learning | MMFM [94] | Conditioned (time + condition) | Global vector field + spline guidance | GitHub |
| Multi-cellular modeling | Cell imaging | CellFlux [45] | Conditioned | U-Net | GitHub |
| Bioimaging | Cryo-EM denoising & 3D reconstruction | CryoFM [119] | Conditioned | Transformer | - |
| | Microscopic Image Segmentation | FlowSDF [120] | Conditioned | U-Net | GitHub |
| | Biomedical Image Reconstruction | GTF2M [121] | Unconditioned | U-Net | - |
| | Biomedical Image Reconstruction | MMSflow [122] | Unconditioned | U-Net | - |
| | Biomedical Image Synthesis | MOTFM [123] | Conditioned | U-Net | GitHub |

**Table 2 Flow matching methods for bioinformatics.** SE(3), the special Euclidean group in $\mathbb{R}^3$; GNN, graph neural network; FM, flow matching; U-Net, U-shaped neural network.

## 3.3 Flow matching for multi-cellular modeling

Extending FM to image-based multi-cellular phenotypic modeling enables a new level of insight into cellular morphology and its response to perturbations. High-content imaging assays provide rich spatial information but present challenges for generative modeling due to batch effects, experimental variability, and morphological complexity. Recent advances, such as CellFlux [45], leverage conditional FM to simulate morphological changes at the pixel level, bridging the gap between generative modeling and high-resolution cellular imaging.

CellFlux employs a U-Net-based FM architecture to learn continuous transformations from control to perturbed cell images, incorporating classifier-free guidance and noise augmentation for improved fidelity. Evaluated across diverse datasets—including BBBC021, RxRx1, and JUMP—CellFlux achieves superior Fréchet Inception Distance (FID) and mode-of-action prediction accuracy compared to prior baselines [124, 125], and generalizes well to unseen perturbations. Notably, it corrects for batch effects by conditioning on batch-specific control images, enabling realistic and interpretable interpolation between cellular states. These advances position CellFlux as a promising foundation for "virtual cell" platforms in drug discovery and personalized medicine, with future potential to scale across cell types and perturbation regimes.

### 3.4 Flow matching for bioimaging

FM is transforming bioimaging by enabling scalable, probabilistic models that capture complex spatial structures and provide principled uncertainty quantification. FM frameworks learn continuous-time vector fields to map simple priors to intricate biological images, supporting flexible inference without the need for extensive fine-tuning. Recent advances highlight FM's versatility across modalities, from cryo-electron microscopy (cryo-EM) to medical image segmentation, unifying representation learning and generative modeling in high-dimensional, noisy, and structured imaging data.

CryoFM [119], an unconditional FM model, exemplifies this potential as a foundation model for cryo-EM density maps, learning the distribution of high-quality protein densities and generalizing to tasks such as denoising and 3D reconstruction without task-specific retraining. They achieve this by using a task-specific flow posterior sampling method during inference to convert CryoFM's unconditional vector field into a conditional variant. FlowSDF [120] advances microscopic image segmentation by modeling probability flows over signed-distance functions, yielding smooth, accurate segmentation masks and providing uncertainty estimates. FlowSDF reaches or surpasses state-of-the-art segmentation accuracy in tumor cell nuclei (MoNuSeg) [126] and gland (GlaS) [127] segmentation. In biomedical imaging, FM has shown recent success in MRI image reconstruction [121, 122] and medical image synthesis [123]. Together, these methods demonstrate how FM can bridge generative modeling and classical imaging approaches, offering robust, interpretable, and uncertainty-aware tools for a wide range of bioimaging applications.

## 4 Outlook

The rapid emergence of FM as a unifying paradigm for generative modeling marks a pivotal moment in the computational life sciences. Across molecular, cellular, and imaging domains, FM has already demonstrated significant advantages over previous simulation-based generative models, offering simulation-free training, efficient sampling, principled incorporation of geometry, and interpretable, controllable mappings between biological states. As surveyed in this Review, FM-based models now set the state-of-the-art in a wide array of bioinformatics tasks: from de novo protein and RNA design, to conditional single-cell phenotype prediction, to generative modeling of high-content imaging data. Yet, the field is only beginning to realize the full potential of flow-based generative modeling in biology.

### From foundational advances to biological impact

The past two years have seen foundational advances in FM theory and practice. New formulations—such as optimal transport FM, discrete and manifold-valued flows, and simulation-free Schrödinger bridges—have expanded the scope of generative modeling to settings previously inaccessible to diffusion or normalizing flow methods. These innovations have enabled the modeling of complex, multimodal, and structured biological data, accommodating discrete sequences, geometric manifolds (e.g., SE(3) for

proteins), and high-dimensional empirical distributions (e.g., single-cell omics or cellular images). Crucially, FM models have begun to bridge the gap between generative modeling and biological interpretability. By learning explicit vector fields and probability paths, FM provides a transparent lens on the transformations between biological states—be they conformational transitions in biomolecules, cell-state changes under perturbation, or morphological shifts in response to drugs. This interpretability, coupled with the ability to condition on rich biological context (e.g., protein partners, ligand structures, perturbation embeddings), positions FM as a cornerstone for the next generation of AI-driven virtual biology.

## Unifying and extending the generative toolkit

A striking trend is the unification of previously disparate generative modeling approaches under the FM umbrella. Recent work has shown that FM subsumes diffusion models, continuous normalizing flows, and optimal transport as special cases, while enabling new hybrid and multimodal architectures. This theoretical convergence is mirrored by practical advances: models such as FrameFlow, FoldFlow, FlowDock, MultiFlow, and CellFlow demonstrate how FM can be flexibly adapted to discrete, continuous, or mixed data; to Euclidean, Riemannian, or statistical manifolds; and to both unconditional and richly conditional settings. Looking forward, we anticipate three key directions for extending the FM toolkit:

1. **Generalization to new data modalities and biological scales.** FM has already proven effective for sequences, structures, and images. Extensions to spatial omics, multi-modal single-cell data, multi-scale tissue modeling, and even population-level dynamics are natural next steps. Lifting FM to operate over distributions of distributions, as in WFM, or to model time-evolving population heterogeneity, as in Meta FM and VGFM, will be essential for capturing the complexity of biological systems.
2. **Principled incorporation of biological priors and constraints.** Future FM models will increasingly encode domain knowledge: physical symmetries, energetic constraints, evolutionary couplings, or experimentally derived priors. Advances in geometry-aware and energy-based flows, as well as integration with large pre-trained biological language models, will enable more accurate, controllable, and biologically meaningful generation.
3. **Scalable, interpretable, and uncertainty-aware modeling.** As FM models are deployed in high-stakes applications—such as therapeutic design, synthetic biology, or personalized medicine—scalability and interpretability become paramount. Efficient distillation and one-step generative flows (e.g., via Reflow or distilled FM), uncertainty quantification (as in FlowSDF), and explainable vector field visualization will be critical for building trust and enabling scientific discovery.

## Toward the artificial intelligence-based virtual cell

A central vision emerging from recent FM advances is the realization of an AIVC: a unified, generative framework capable of simulating the molecular, structural, and phenotypic consequences of genetic, chemical, and environmental perturbations. FM

models are uniquely well-suited to this challenge. By enabling efficient, simulation-free mappings across molecular, cellular, and imaging spaces—and by supporting conditional, context-aware generation—FM provides the scaffolding for an end-to-end, multi-scale virtual cell platform. Realizing this vision will require continued progress in several areas. Integrating FM models across biological scales and modalities—e.g., coupling protein–protein interaction flows with single-cell phenotype generators, or linking nucleotide design flows with 3D chromatin structure models—will demand advances in compositional and multi-modal FM architectures. Robust benchmarking, open-source tool development, and community standards for biological generative modeling (see Tables 1 and 2) will be essential to ensure reproducibility, interoperability, and broad adoption.

## Open challenges and future research directions

Despite its promise, FM-based generative modeling faces open challenges. Theoretical questions remain regarding optimality, convergence, and expressivity of learned flows, especially in high-dimensional or data-sparse regimes. Efficient training and inference for very large or multi-modal biological datasets remains an area of active development. Furthermore, the integration of FM with experimental design—enabling closed-loop, AI-driven hypothesis generation and validation—remains largely unexplored. Key future directions include:

- **Learning on limited or noisy data:** Developing robust, data-efficient FM models that can generalize from scarce or noisy biological measurements.
- **Integration with experimental feedback:** Coupling FM-based generators with experimental platforms (e.g., high-throughput screening, CRISPR perturbation) for active learning and closed-loop discovery.
- **Interpretability and validation:** Building tools for visualizing, interpreting, and experimentally validating learned flows, ensuring that generative models yield biologically meaningful and actionable hypotheses.
- **Ethical and societal considerations:** As generative AI becomes increasingly influential in biological design, careful consideration of ethical, safety, and regulatory implications will be critical.

## Conclusion

In summary, flow matching has rapidly matured from a theoretical curiosity to a practical, unifying framework for generative modeling in bioinformatics and computational biology. Its principled foundation, flexibility, and scalability have catalyzed breakthroughs across molecular, cellular, and imaging domains. As the field advances, flow matching is poised to underpin the next wave of AI-driven biological discovery, design, and simulation—bringing the vision of the virtual cell, and ultimately virtual biology, one step closer to reality.

**Acknowledgements.** This research used resources of the National Energy Research Scientific Computing Center (NERSC), a U.S. Department of Energy User Facility, using NERSC award DDR-ERCAP 0034574 awarded to AM. This work was

also financially supported by the U.S. National Science Foundation [grant number DBI2308699, awarded to JC] and the U.S. National Institutes of Health [grant numbers: R01GM146340 and R01GM093123, awarded to JC].

**Author Contributions.**

- **Alex Morehead:** Investigation; writing - original draft; writing - reviewing and editing.
- **Lazar Atanackovic:** Investigation; writing - original draft; writing - reviewing and editing.
- **Akshata Hegde:** Investigation; writing - original draft; writing - reviewing and editing.
- **Yanli Wang:** Investigation; writing - original draft; writing - reviewing and editing.
- **Frimpong Boadu:** Investigation; writing - original draft; writing - reviewing and editing.
- **Joel Selvaraj:** Investigation; writing - original draft; writing - reviewing and editing.
- **Alexander Tong:** Investigation; writing - original draft; writing - reviewing and editing.
- **Aditi Krishnapriyan:** Investigation; writing - original draft; writing - reviewing and editing.
- **Jianlin Cheng:** Conceptualization; investigation; writing - challenges and future perspectives, writing - reviewing and editing.

**Competing interests.** The authors declare no competing interests.

**Key points.**

- Flow matching is a generative artificial intelligence technology that can be applied to numerous problems in computer vision, natural language processing, and bioinformatics.
- Flow matching models can learn to transport samples between any pair of data distributions.
- Flow matching has contributed greatly to computational biomolecule prediction and design, biomolecular dynamics modeling, cellular data modeling, and bioimaging.
- Although flow matching is promising compared to well-known generative modeling methods such as diffusion models and generative adversarial networks, applying it effectively to individual problems often requires considerable domain expertise.

**Related links.**

- Accompanying paper list as a GitHub repository: https://github.com/amorehead/awesome-generative-flows.
- Meta AI's flow matching guide and code [19]: https://ai.meta.com/research/publications/flow-matching-guide-and-code.
- A PyTorch-friendly library [128] for training conditional flow matching models [21]: https://github.com/atong01/conditional-flow-matching.

**Videos.** Illustrations of generative flow matching sampling trajectories driven by the FlowDock model for protein-ligand docking:

- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/6I67.gif
- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/L1003.gif
- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/L3068.gif
- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/L3132.gif
- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/L3158.gif
- https://github.com/BioinfoMachineLearning/FlowDock/blob/7713d103ab40f32299d4c2b91c3cc5d94cfc3aa3/img/T1152.gif

# References


[1] Frazer, J., Notin, P., Dias, M., Gomez, A., Min, J.K., Brock, K., Gal, Y., Marks, D.S.: Disease variant prediction with deep generative models of evolutionary data. Nature **599**(7883), 91–95 (2021)

[2] Kingma, D.P., Welling, M.: Auto-encoding variational bayes. In: International Conference on Learning Representations (2014)

[3] Cui, H., Wang, C., Maan, H., Pang, K., Luo, F., Duan, N., Wang, B.: scgpt: toward building a foundation model for single-cell multi-omics using generative ai. Nature Methods **21**(8), 1470–1480 (2024)

[4] Achiam, J., Adler, S., Agarwal, S., Ahmad, L., Akkaya, I., Aleman, F.L., Almeida, D., Altenschmidt, J., Altman, S., Anadkat, S., et al.: Gpt-4 technical report. arXiv preprint arXiv:2303.08774 (2023)

[5] Bommasani, R., Hudson, D.A., Adeli, E., Altman, R., Arora, S., Arx, S., Bernstein, M.S., Bohg, J., Bosselut, A., Brunskill, E., et al.: On the opportunities and risks of foundation models. arXiv preprint arXiv:2108.07258 (2021)

[6] Anand, N., Huang, P.: Generative modeling for protein structures. Advances in neural information processing systems **31** (2018)

[7] Anand, N., Eguchi, R., Mathews, I.I., Perez, C.P., Derry, A., Altman, R.B., Huang, P.-S.: Protein sequence design with a learned potential. Nature communications **13**(1), 746 (2022)

[8] Ho, J., Jain, A., Abbeel, P.: Denoising diffusion probabilistic models. Advances in neural information processing systems **33**, 6840–6851 (2020)

[9] Hoogeboom, E., Satorras, V.G., Vignac, C., Welling, M.: Equivariant diffusion for molecule generation in 3d. In: International Conference on Machine Learning, pp. 8867–8887 (2022). PMLR

[10] Watson, J.L., Juergens, D., Bennett, N.R., Trippe, B.L., Yim, J., Eisenach, H.E., Ahern, W., Borst, A.J., Ragotte, R.J., Milles, L.F., *et al.*: De novo design of protein structure and function with rfdiffusion. Nature **620**(7976), 1089–1100 (2023)

[11] Shome, D., Sarkar, P., Etemad, A.: Region-disentangled diffusion model for high-fidelity ppg-to-ecg translation. In: Proceedings of the AAAI Conference on Artificial Intelligence, vol. 38, pp. 15009–15019 (2024)

[12] LeCun, Y., Bengio, Y., Hinton, G.: Deep learning. nature **521**(7553), 436–444 (2015). **This article characterizes foundational algorithms and applications of deep learning in artificial intelligence and beyond.**

[13] Lipman, Y., Chen, R.T., Ben-Hamu, H., Nickel, M., Le, M.: Flow matching for generative modeling. In: The Eleventh International Conference on Learning Representations (2023). **This article reports the first modern formulation of flow matching for generative AI.**

[14] Yang, L., Zhang, Z., Song, Y., Hong, S., Xu, R., Zhao, Y., Zhang, W., Cui, B., Yang, M.-H.: Diffusion models: A comprehensive survey of methods and applications. ACM Computing Surveys **56**(4), 1–39 (2023)

[15] Hurst, A., Lerer, A., Goucher, A.P., Perelman, A., Ramesh, A., Clark, A., Ostrow, A., Welihinda, A., Hayes, A., Radford, A., et al.: Gpt-4o system card. arXiv preprint arXiv:2410.21276 (2024)

[16] Esser, P., Kulal, S., Blattmann, A., Entezari, R., Müller, J., Saini, H., Levi, Y., Lorenz, D., Sauer, A., Boesel, F., *et al.*: Scaling rectified flow transformers for high-resolution image synthesis. In: Forty-first International Conference on Machine Learning (2024)

[17] Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., Ronneberger, O., Willmore, L., Ballard, A.J., Bambrick, J., *et al.*: Accurate structure prediction of biomolecular interactions with alphafold 3. Nature **630**(8016), 493–500 (2024)

[18] Bunne, C., Roohani, Y., Rosen, Y., Gupta, A., Zhang, X., Roed, M., Alexandrov, T., AlQuraishi, M., Brennan, P., Burkhardt, D.B., *et al.*: How to build the virtual cell with artificial intelligence: Priorities and opportunities. Cell **187**(25), 7045–7063 (2024). **This article presents the first formulation of virtual cell modeling with artificial intelligence.**

[19] Lipman, Y., Havasi, M., Holderrieth, P., Shaul, N., Le, M., Karrer, B., Chen, R.T., Lopez-Paz, D., Ben-Hamu, H., Gat, I.: Flow matching guide and code. arXiv preprint arXiv:2412.06264 (2024)

[20] Guo, Z., Liu, J., Wang, Y., Chen, M., Wang, D., Xu, D., Cheng, J.: Diffusion models in bioinformatics and computational biology. Nature reviews bioengineering **2**(2), 136–154 (2024)

[21] Tong, A., Fatras, K., Malkin, N., Huguet, G., Zhang, Y., Rector-Brooks, J., Wolf, G., Bengio, Y.: Improving and generalizing flow-based generative models with minibatch optimal transport. Transactions on Machine Learning Research (2024). **This article introduces the first generally tractable training objective for flow matching in generative AI.**

[22] Salakhutdinov, R.: Learning deep generative models. Annual Review of Statistics and Its Application **2**(1), 361–385 (2015)

[23] Peyré, G., Cuturi, M., *et al.*: Computational optimal transport: With applications to data science. Foundations and Trends® in Machine Learning **11**(5-6), 355–607 (2019)

[24] Chen, R.T., Rubanova, Y., Bettencourt, J., Duvenaud, D.K.: Neural ordinary differential equations. Advances in neural information processing systems **31** (2018). **This article introduces the theoretical foundations necessary for generative flow matching of differential systems.**

[25] Liu, X., Gong, C., *et al.*: Flow straight and fast: Learning to generate and transfer data with rectified flow. In: The Eleventh International Conference on Learning Representations (2023). **This article presents the first few-step formulation of generative flow matching.**

[26] Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A.N., Kaiser, Ł., Polosukhin, I.: Attention is all you need. Advances in neural information processing systems **30** (2017)

[27] Corso, G., Stark, H., Jegelka, S., Jaakkola, T., Barzilay, R.: Graph neural networks. Nature Reviews Methods Primers **4**(1), 17 (2024)

[28] Geiger, M., Smidt, T.: e3nn: Euclidean neural networks. arXiv preprint arXiv:2207.09453 (2022)

[29] Chen, R.T., Behrmann, J., Duvenaud, D.K., Jacobsen, J.-H.: Residual flows for invertible generative modeling. Advances in Neural Information Processing Systems **32** (2019)

[30] Wu, H., Köhler, J., Noé, F.: Stochastic normalizing flows. Advances in neural information processing systems **33**, 5933–5944 (2020)

[31] Garcia Satorras, V., Hoogeboom, E., Fuchs, F., Posner, I., Welling, M.: E (n) equivariant normalizing flows. Advances in Neural Information Processing Systems **34**, 4181–4192 (2021)

[32] Campbell, A., Yim, J., Barzilay, R., Rainforth, T., Jaakkola, T.: Generative flows on discrete state-spaces: Enabling multimodal flows with applications to protein co-design. In: International Conference on Machine Learning, pp. 5453–5512 (2024). PMLR. **This article was the first to generalize flow matching to discrete data types.**

[33] Kapusniak, K., Potaptchik, P., Reu, T., Zhang, L., Tong, A., Bronstein, M., Bose, J., Di Giovanni, F.: Metric flow matching for smooth interpolations on the data manifold. Advances in Neural Information Processing Systems **37**, 135011–135042 (2024)

[34] Atanackovic, L., Zhang, X., Amos, B., Blanchette, M., Lee, L.J., Bengio, Y., Tong, A., Neklyudov, K.: Meta flow matching: Integrating vector fields on the wasserstein manifold. arXiv preprint arXiv:2408.14608 (2024)

[35] Holderrieth, P., Havasi, M., Yim, J., Shaul, N., Gat, I., Jaakkola, T., Karrer, B., Chen, R.T.Q., Lipman, Y.: Generator matching: Generative modeling with arbitrary markov processes. In: The Thirteenth International Conference on Learning Representations (2025). **This article comprehensively generalizes flow matching across modalities and data types.** https://openreview.net/forum?id=RuP17cJtZo

[36] Haviv, D., Pooladian, A.-A., Pe'er, D., Amos, B.: Wasserstein flow matching: Generative modeling over families of distributions. arXiv preprint arXiv:2411.00698 (2024)

[37] Bose, J., Akhound-Sadegh, T., Huguet, G., Fatras, K., Rector-Brooks, J., Liu, C.-H., Nica, A.C., Korablyov, M., Bronstein, M.M., Tong, A.: Se(3)-stochastic flow matching for protein backbone generation. In: The Twelfth International Conference on Learning Representations (2024). **This article reports one of the first applications of geometric generative flow matching in bioinformatics.**

[38] Huguet, G., Vuckovic, J., Fatras, K., Thibodeau-Laufer, E., Lemos, P., Islam, R., Liu, C., Rector-Brooks, J., Akhound-Sadegh, T., Bronstein, M., *et al.*: Sequence-augmented se (3)-flow matching for conditional protein generation. Advances in neural information processing systems **37**, 33007–33036 (2024)

[39] Yim, J., Campbell, A., Foong, A.Y., Gastegger, M., Jiménez-Luna, J., Lewis, S., Satorras, V.G., Veeling, B.S., Barzilay, R., Jaakkola, T., et al.: Fast protein backbone generation with se (3) flow matching. arXiv preprint arXiv:2310.05297 (2023)

[40] Jing, B., Berger, B., Jaakkola, T.: Alphafold meets flow matching for generating protein ensembles. In: Forty-first International Conference on Machine Learning (2024)

[41] Dunn, I., Koes, D.R.: Mixed continuous and categorical flow matching for 3d de novo molecule generation. ArXiv, 2404 (2024)

[42] Anand, R., Joshi, C.K., Morehead, A., Jamasb, A.R., Harris, C., Mathis, S.V., Didi, K., Hooi, B., Lio, P.: RNA-frameflow: Flow matching for de novo 3d RNA backbone design. Transactions on Machine Learning Research (2025)

[43] Morehead, A., Cheng, J.: Flowdock: Geometric flow matching for generative protein-ligand docking and affinity prediction. In: Intelligent Systems for Molecular Biology (ISMB) (2025)

[44] Qiao, Z., Ding, F., Dresselhaus, T., Rosenfeld, M.A., Han, X., Howell, O., Iyengar, A., Opalenski, S., Christensen, A.S., Krishna Sirumalla, S., et al.: Neuralplexer3: Physio-realistic biomolecular complex structure prediction with flow models. arXiv e-prints, 2412 (2024)

[45] Zhang, Y., Su, Y., Wang, C., Li, T., Wefers, Z., Nirschl, J., Burgess, J., Ding, D., Lozano, A., Lundberg, E., *et al.*: Cellflux: Simulating cellular morphology changes via flow matching. In: Proceedings of the 42nd International Conference on Machine Learning (2025)

[46] Petrović, K., Atanackovic, L., Kapusniak, K., Bronstein, M.M., Bose, J., Tong, A.: Curly flow matching for learning non-gradient field dynamics. In: ICLR 2025 Workshop on Machine Learning for Genomics Explorations (2025)

[47] Klein, D., Fleck, J.S., Bobrovskiy, D., Zimmermann, L., Becker, S., Palma, A., Dony, L., Tejada-Lapuerta, A., Huguet, G., Lin, H.-C., et al.: Cellflow enables generative single-cell phenotype modeling with flow matching. bioRxiv, 2025–04 (2025)

[48] Iserles, A.: A First Course in the Numerical Analysis of Differential Equations. Cambridge University Press, Cambridge (2009)

[49] Krishnapriyan, A., Gholami, A., Zhe, S., Kirby, R., Mahoney, M.W.: Characterizing possible failure modes in physics-informed neural networks. Advances in neural information processing systems **34**, 26548–26560 (2021)

[50] Yim, J., Trippe, B.L., De Bortoli, V., Mathieu, E., Doucet, A., Barzilay, R., Jaakkola, T.: Se (3) diffusion model with application to protein backbone generation. arXiv preprint arXiv:2302.02277 (2023)

[51] Lee, J.S., Kim, P.M.: Flowpacker: protein side-chain packing with torsional flow matching. Bioinformatics **41**(3), 010 (2025)

[52] Joshi, C.K., Fu, X., Liao, Y.-L., Gharakhanyan, V., Miller, B.K., Sriram, A., Ulissi, Z.W.: All-atom diffusion transformers: Unified generative modelling of molecules and materials. In: International Conference on Machine Learning

(2025). PMLR

[53] Albergo, M.S., Vanden-Eijnden, E.: Building normalizing flows with stochastic interpolants. arXiv preprint arXiv:2209.15571 (2022)

[54] Yan, J., Cui, Z., Yan, W., Chen, Y., Pu, M., Li, S., Ye, S.: Robust and Reliable de novo Protein Design: A Flow-Matching-Based Protein Generative Model Achieves Remarkably High Success Rates. bioRxiv. preprint, 2025-04 (2025)

[55] Huang, C.-W., Krueger, D., Lacoste, A., Courville, A.: Neural autoregressive flows. In: International Conference on Machine Learning, pp. 2078–2087 (2018). PMLR

[56] Kingma, D.P., Dhariwal, P.: Glow: Generative flow with invertible 1x1 convolutions. Advances in neural information processing systems **31** (2018)

[57] Grathwohl, W., Chen, R.T., Bettencourt, J., Sutskever, I., Duvenaud, D.: Ffjord: Free-form continuous dynamics for scalable reversible generative models. In: International Conference on Learning Representations (2019)

[58] Dupont, E., Doucet, A., Teh, Y.W.: Augmented neural odes. Advances in neural information processing systems **32** (2019)

[59] Liu, J., Kumar, A., Ba, J., Kiros, J., Swersky, K.: Graph normalizing flows. Advances in Neural Information Processing Systems **32** (2019)

[60] Hodgkinson, L., Heide, C., Roosta, F., Mahoney, M.W.: Stochastic continuous normalizing flows: training sdes as odes. In: Uncertainty in Artificial Intelligence, pp. 1130–1140 (2021). PMLR

[61] Zhang, Q., Chen, Y.: Diffusion normalizing flow. Advances in neural information processing systems **34**, 16280–16291 (2021)

[62] Gabrié, M., Rotskoff, G.M., Vanden-Eijnden, E.: Adaptive monte carlo augmented with normalizing flows. Proceedings of the National Academy of Sciences **119**(10), 2109420119 (2022)

[63] Richter-Powell, J., Lipman, Y., Chen, R.T.: Neural conservation laws: A divergence-free perspective. Advances in Neural Information Processing Systems **35**, 38075–38088 (2022)

[64] Albergo, M.S., Boffi, N.M., Vanden-Eijnden, E.: Stochastic interpolants: A unifying framework for flows and diffusions. arXiv preprint arXiv:2303.08797 (2023)

[65] Albergo, M.S., Goldstein, M., Boffi, N.M., Ranganath, R., Vanden-Eijnden, E.: Stochastic interpolants with data-dependent couplings. In: International Conference on Machine Learning, pp. 921–937 (2024). PMLR

[66] Davtyan, A., Sameni, S., Favaro, P.: Efficient video prediction via sparsely conditioned flow matching. In: Proceedings of the IEEE/CVF International Conference on Computer Vision, pp. 23263–23274 (2023)

[67] Wu, L., Wang, D., Gong, C., Liu, X., Xiong, Y., Ranjan, R., Krishnamoorthi, R., Chandra, V., Liu, Q.: Fast point cloud generation with straight flows. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition, pp. 9445–9454 (2023)

[68] Neklyudov, K., Brekelmans, R., Severo, D., Makhzani, A.: Action matching: Learning stochastic dynamics from samples. In: International Conference on Machine Learning, pp. 25858–25889 (2023). PMLR

[69] Lee, S., Kim, B., Ye, J.C.: Minimizing trajectory curvature of ode-based generative models. In: International Conference on Machine Learning, pp. 18957–18973 (2023). PMLR

[70] Dao, Q., Phung, H., Nguyen, B., Tran, A.: Flow matching in latent space. arXiv preprint arXiv:2307.08698 (2023)

[71] Tong, A., Malkin, N., Fatras, K., Atanackovic, L., Zhang, Y., Huguet, G., Wolf, G., Bengio, Y.: Simulation-free schrödinger bridges via score and flow matching. In: AISTATS, pp. 1279–1287 (2024). https://proceedings.mlr.press/v238/y-tong24a.html

[72] Chen, R.T.Q., Lipman, Y.: Flow matching on general geometries. In: The Twelfth International Conference on Learning Representations (2024). **This article reports a theoretical framework crucial to developing flow matching models for geometric data.** https://openreview.net/forum?id=g7ohDlTITL

[73] Klein, L., Krämer, A., Noé, F.: Equivariant flow matching. Advances in Neural Information Processing Systems **36**, 59886–59910 (2023)

[74] Neklyudov, K., Brekelmans, R., Tong, A., Atanackovic, L., Liu, Q., Makhzani, A.: A computational framework for solving wasserstein lagrangian flows. arXiv preprint arXiv:2310.10649 (2023)

[75] Fischer, J.S., Gui, M., Ma, P., Stracke, N., Baumann, S.A., Ommer, B.: Boosting latent diffusion with flow matching. arXiv preprint arXiv:2312.07360 (2023)

[76] Hu, V.T., Yin, W., Ma, P., Chen, Y., Fernando, B., Asano, Y.M., Gavves, E., Mettes, P., Ommer, B., Snoek, C.G.: Motion flow matching for human motion synthesis and editing. arXiv preprint arXiv:2312.08895 (2023)

[77] Liu, X., Zhang, X., Ma, J., Peng, J., *et al.*: Instaflow: One step is enough for high-quality diffusion-based text-to-image generation. In: The Twelfth International

Conference on Learning Representations (2023)

[78] Kerrigan, G., Migliorini, G., Smyth, P.: Functional flow matching. In: International Conference on Artificial Intelligence and Statistics, pp. 3934–3942 (2024). PMLR

[79] Stark, H., Jing, B., Wang, C., Corso, G., Berger, B., Barzilay, R., Jaakkola, T.: Dirichlet flow matching with applications to dna sequence design. In: International Conference on Machine Learning, pp. 46495–46513 (2024). PMLR

[80] Gat, I., Remez, T., Shaul, N., Kreuk, F., Chen, R.T., Synnaeve, G., Adi, Y., Lipman, Y.: Discrete flow matching. Advances in Neural Information Processing Systems **37**, 133345–133385 (2024)

[81] Davis, O., Kessler, S., Petrache, M., Ceylan, I., Bronstein, M., Bose, J.: Fisher flow matching for generative modeling over discrete data. Advances in Neural Information Processing Systems **37**, 139054–139084 (2024)

[82] Nguyen, B., Nguyen, B., Nguyen, V.A.: Bellman optimal stepsize straightening of flow-matching models. arXiv preprint arXiv:2312.16414 (2023)

[83] Yang, L., Zhang, Z., Zhang, Z., Liu, X., Xu, M., Zhang, W., Meng, C., Ermon, S., Cui, B.: Consistency flow matching: Defining straight flows with velocity consistency. arXiv preprint arXiv:2407.02398 (2024)

[84] Gui, M., Schusterbauer, J., Prestel, U., Ma, P., Kotovenko, D., Grebenkova, O., Baumann, S.A., Hu, V.T., Ommer, B.: Depthfm: Fast generative monocular depth estimation with flow matching. In: Proceedings of the AAAI Conference on Artificial Intelligence, vol. 39, pp. 3203–3211 (2025)

[85] Chen, Y., Goldstein, M., Hua, M., Albergo, M.S., Boffi, N.M., Vanden-Eijnden, E.: Probabilistic forecasting with stochastic interpolants and föllmer processes. In: Proceedings of the 41st International Conference on Machine Learning, pp. 6728–6756 (2024)

[86] Wang, C., Li, X., Qi, L., Ding, H., Tong, Y., Yang, M.-H.: Semflow: Binding semantic segmentation and image synthesis via rectified flow. Advances in Neural Information Processing Systems **37**, 138981–139001 (2024)

[87] Kim, M., Lee, Y., Kang, S., Oh, J., Chong, S., Yun, S.-Y.: Preference alignment with flow matching. Advances in Neural Information Processing Systems **37**, 35140–35164 (2024)

[88] Kerrigan, G., Migliorini, G., Smyth, P.: Dynamic conditional optimal transport through simulation-free flows. Advances in Neural Information Processing Systems **37**, 93602–93642 (2024)

[89] Hu, V., Wu, D., Asano, Y., Mettes, P., Fernando, B., Ommer, B., Snoek, C.: Flow matching for conditional text generation in a few sampling steps. In: Proceedings of the 18th Conference of the European Chapter of the Association for Computational Linguistics (Volume 2: Short Papers), pp. 380–392 (2024)

[90] Cheng, C., Li, J., Peng, J., Liu, G.: Categorical flow matching on statistical manifolds. Advances in Neural Information Processing Systems **37**, 54787–54819 (2024)

[91] Kornilov, N., Mokrov, P., Gasnikov, A., Korotin, A.: Optimal flow matching: Learning straight trajectories in just one step. Advances in Neural Information Processing Systems **37**, 104180–104204 (2024)

[92] Nisonoff, H., Xiong, J., Allenspach, S., Listgarten, J.: Unlocking guidance for discrete state-space diffusion and flow models. In: The Thirteenth International Conference on Learning Representations

[93] Zhang, X.N., Pu, Y., Kawamura, Y., Loza, A., Bengio, Y., Shung, D., Tong, A.: Trajectory flow matching with applications to clinical time series modelling. Advances in Neural Information Processing Systems **37**, 107198–107224 (2024)

[94] Rohbeck, M., De Brouwer, E., Bunne, C., Huetter, J.-C., Biton, A., Chen, K.Y., Regev, A., Lopez, R.: Modeling complex system dynamics with flow matching across time and conditions. In: The Thirteenth International Conference on Learning Representations (2025)

[95] Stoica, G., Ramanujan, V., Fan, X., Farhadi, A., Krishna, R., Hoffman, J.: Contrastive flow matching. arXiv preprint arXiv:2506.05350 (2025) arXiv:2506.05350 [cs.CV]

[96] Lin, H., Li, S., Ye, H., Yang, Y., Ermon, S., Liang, Y., Ma, J.: Tfg-flow: Training-free guidance in multimodal generative flow. arXiv preprint arXiv:2501.14216 (2025)

[97] Bartosh, G., Vetrov, D., Naesseth, C.A.: Sde matching: Scalable and simulation-free training of latent stochastic differential equations. arXiv preprint arXiv:2502.02472 (2025)

[98] Irwin, R., Tibo, A., Janet, J.P., Olsson, S.: Semlaflow–efficient 3d molecular generation with latent attention and equivariant flow matching. arXiv preprint arXiv:2406.07266 (2024)

[99] Jing, B., Eismann, S., Suriana, P., Townshend, R.J.L., Dror, R.: Learning from protein structure with geometric vector perceptrons. In: International Conference on Learning Representations (2021)

[100] Hassan, M., Shenoy, N., Lee, J., Stärk, H., Thaler, S., Beaini, D.: Et-flow: Equivariant flow-matching for molecular conformer generation. In: Advances in Neural Information Processing Systems, vol. 37, pp. 128798–128824 (2024)

[101] Gao, L., Lu, Z.J.: Rnacg: A universal rna sequence conditional generation model based on flow-matching. arXiv preprint arXiv:2407.19838 (2024)

[102] Nori, D., Jin, W.: RNAFlow: RNA Structure & Sequence Design via Inverse Folding-based Flow Matching. arXiv preprint arXiv:2405.18768 (2024)

[103] Ma, R., Zhang, Z., Wang, Z., Hua, C., Zhou, Z., Cao, F., Rao, J., Zheng, S.: Riboflow: Conditional de novo rna sequence-structure co-design via synergistic flow matching. arXiv preprint arXiv:2503.17007 (2025)

[104] Abir, A.R., Zhang, L.: Rna-efm: Energy based flow matching for protein-conditioned rna sequence-structure co-design. bioRxiv, 2025–02 (2025)

[105] Tarafder, S., Bhattacharya, D.: Rnabpflow: Base pair-augmented se (3)-flow matching for conditional rna 3d structure generation. bioRxiv (2025)

[106] Corso, G., Somnath, V.R., Getz, N., Barzilay, R., Jaakkola, T., Krause, A.: Composing unbalanced flows for flexible docking and relaxation. In: The Thirteenth International Conference on Learning Representations (2025). https://openreview.net/forum?id=gHLWTzKiZV

[107] Zhang, M., Zhang, Z., Wu, H., Wang, Y.: Flow matching for optimal reaction coordinates of biomolecular systems. Journal of Chemical Theory and Computation **21**(1), 399–412 (2024)

[108] Jing, B., Stärk, H., Jaakkola, T., Berger, B.: Generative modeling of molecular dynamics trajectories. Advances in Neural Information Processing Systems **37**, 40534–40564 (2024)

[109] Raja, S., Sipka, M., Psenka, M., Kreiman, T., Pavelka, M., Krishnapriyan, A.S.: Action-minimization meets generative modeling: Efficient transition path sampling with the onsager-machlup functional. In: Forty-second International Conference on Machine Learning (2025)

[110] Palma, A., Richter, T., Zhang, H., Lubetzki, M., Tong, A., Dittadi, A., Theis, F.J.: Multi-modal and multi-attribute generation of single cells with CFGen. In: The Thirteenth International Conference on Learning Representations (2025). https://openreview.net/forum?id=3MnMGLctKb

[111] Klein, D., Uscidda, T., Theis, F., Cuturi, M.: Genot: Entropic (gromov) wasserstein flow matching with applications to single-cell genomics. Advances in Neural Information Processing Systems **37**, 103897–103944 (2024)

[112] Zhang, Z., Wang, Z., Sun, Y., Li, T., Zhou, P.: Modeling cell dynamics and interactions with unbalanced mean field schr\" odinger bridge. arXiv preprint arXiv:2505.11197 (2025)

[113] Wang, D., Jiang, Y., Zhang, Z., Gu, X., Zhou, P., Sun, J.: Joint velocity-growth flow matching for single-cell dynamics modeling. arXiv preprint arXiv:2505.13413 (2025)

[114] Kong, Z., Zhu, Y., Xu, Y., Zhou, H., Yin, M., Wu, J., Xu, H., Hsieh, C.-Y., Hou, T., Wu, J.: ProtFlow: Fast Protein Sequence Design via Flow Matching on Compressed Protein Language Model Embeddings. arXiv preprint arXiv:2504.10983 (2025)

[115] Yang, S., Ju, L., Cheng, P., Zhou, J., Cai, Y., Feng, D.: Co-design protein sequence and structure in discrete space via generative flow. Bioinformatics **41**(5), 248 (2025)

[116] Wu, J., Kong, X., Sun, N., Wei, J., Shan, S., Feng, F., Wu, F., et al.: Flowdesign: Improved design of antibody cdrs through flow matching and better prior distributions. Cell Systems **16**(6) (2025)

[117] Wu, F., Xu, T., Jin, S., Tang, X., Xu, Z., Zou, J., Hie, B.: D-Flow: Multi-modality Flow Matching for D-peptide Design. arXiv preprint arXiv:2411.10618 (2024)

[118] Song, Y., Gong, J., Xu, M., Cao, Z., Lan, Y., Ermon, S., Zhou, H., Ma, W.-Y.: Equivariant flow matching with hybrid probability transport for 3d molecule generation. Advances in Neural Information Processing Systems **36**, 549–568 (2023)

[119] Zhou, Y., Li, Y., Yuan, J., Gu, Q.: CryoFM: A flow-based foundation model for cryo-EM densities. In: The Thirteenth International Conference on Learning Representations (2025). https://openreview.net/forum?id=T4sMzjy7fO

[120] Bogensperger, L., Narnhofer, D., Falk, A., Schindler, K., Pock, T.: Flowsdf: Flow matching for medical image segmentation using distance transforms. International Journal of Computer Vision **133**(7), 4864–4876 (2025) https://doi.org/10.1007/s11263-025-02373-y

[121] Luo, X., Li, Y., Qin, C.: Unsupervised accelerated mri reconstruction via ground-truth-free flow matching. In: 29th International Conference on Information Processing in Medical Imaging (2025)

[122] Zhang, D., Han, Q., Xiong, Y., Du, H.: Mutli-modal straight flow matching for accelerated mr imaging. Computers in Biology and Medicine **178**, 108668 (2024) https://doi.org/10.1016/j.compbiomed.2024.108668

[123] Yazdani, M., Medghalchi, Y., Ashrafian, P., Hacihaliloglu, I., Shahriari, D.: Flow

matching for medical image synthesis: Bridging the gap between speed and quality. arXiv preprint arXiv:2503.00266 (2025)

[124] Bourou, A., Boyer, T., Gheisari, M., Daupin, K., Dubreuil, V., De Thonel, A., Mezger, V., Genovesio, A.: Phendiff: Revealing subtle phenotypes with diffusion models in real images, pp. 358–367. Springer, Berlin, Heidelberg (2024). https://doi.org/10.1007/978-3-031-72384-1_34

[125] Palma, A., Theis, F.J., Lotfollahi, M.: Predicting cell morphological responses to perturbations using generative modeling. Nat. Commun. **16**(1), 505 (2025)

[126] Kumar, N., Verma, R., Sharma, S., Bhargava, S., Vahadane, A., Sethi, A.: A dataset and a technique for generalized nuclear segmentation for computational pathology. IEEE Transactions on Medical Imaging **36**(7), 1550–1560 (2017) https://doi.org/10.1109/TMI.2017.2677499

[127] Sirinukunwattana, K., Pluim, J.P.W., Chen, H., Qi, X., Heng, P.-A., Guo, Y.B., Wang, L.Y., Matuszewski, B.J., Bruni, E., Sanchez, U., Böhm, A., Ronneberger, O., Cheikh, B.B., Racoceanu, D., Kainz, P., Pfeiffer, M., Urschler, M., Snead, D.R.J., Rajpoot, N.M.: Gland segmentation in colon histology images: The glas challenge contest. Medical Image Analysis **35**, 489–502 (2017) https://doi.org/10.1016/j.media.2016.08.008

[128] Paszke, A.: Pytorch: An imperative style, high-performance deep learning library. arXiv preprint arXiv:1912.01703 (2019)