



Generative models of cell dynamics: from Neural ODEs to flow matching



Till Richter^{1,2}, Weixu Wang^{1,2}, Alessandro Palma^{1,2} & Fabian J. Theis^{1,2} ✉

Neural Ordinary Differential Equations (Neural ODEs) have emerged as a prominent framework for modeling complex dynamical systems. Their ability to describe a system's underlying dynamical law has attracted attention to applications in life sciences. Single-cell data presents challenges due to noise, sparsity, and the inability to explicitly profile single cells across time. However, pioneering works have demonstrated how Neural ODE-based models can overcome these hurdles, aid mechanistic modeling of cellular development, and approximate population dynamics through the lens of Flow Matching. This article studies why Neural ODEs are suited for modeling the dynamic processes in single-cell data and broader computational health fields, from standard time-series parameterizations to generative models based on optimal transport. We first explore the mathematical properties of Neural ODEs and their application to modeling cellular dynamics. Successively, we zoom into how recent innovations in generative modeling enable efficient and expressive cell state transition modeling through the simulation-free Flow Matching approach. Finally, we present challenges in modeling single-cell dynamics that drive ongoing research in single-cell biology. This work shows that Neural ODEs, as a machine learning framework, are appropriate for modeling dynamic processes in cellular data and promises to advance our understanding of the dynamics in cellular systems.

Dynamical perspectives in single-cell biology

Single-cell differentiation - the transformation of a progenitor cell into a specialized entity - plays a pivotal role in the development of complex organisms and in maintaining tissue homeostasis¹. Central to fields like developmental biology, regenerative medicine, and cancer research, a comprehensive understanding of single-cell differentiation opens avenues for disease treatments, tissue regeneration, and therapeutic cell manipulation^{2,3}. Differentiation is driven by gene regulatory networks (GRNs), systems of genes and their regulatory elements that govern cellular functions and response to perturbations. Specifically, during differentiation, GRNs control the activation and suppression of genes, directing the cell's transition from an undifferentiated to a specialized state. This process is often depicted by Waddington's landscape⁴, a classical metaphor for cell-fate dynamics.

To capture these GRNs, systems biology has often employed dynamical systems theory, typically constrained to low-dimensional models⁵. These models often rely on coarse-graining, representing the system through a few key variables to make the problem tractable. Yet, the inherent complexity and dynamism of GRNs, marked by multilayered regulation, often exhibit non-linear behaviors beyond the scope of low-dimensional networks. More complex models are essential to unravel these dynamical systems⁶.

Advancements in computational tools and single-cell sequencing have enhanced our understanding of cell differentiation regulation through more complex, high-dimensional GRNs in extensive datasets, including diverse molecular modalities⁷. These vast and intricate datasets offer new insights but present modeling challenges: the data is noisy, sparse, and typically captures only a snapshot of the cellular state. Data-driven methods are emerging that often combine traditional differential equations to capture system dynamics^{2,8}. Moreover, ordinary differential equation (ODE)-based generative models offer an expressive framework for learning how distributions of cells evolve.

Temporal versus observational data

Modern single-cell analysis encompasses temporal, spatial, and spatial-temporal perspectives. Ideally, one would track the temporal evolution of individual cells over time. However, the destructive nature of standard RNA sequencing technologies prevents direct time-course measurements for the same cell across multiple time points. Instead, experiments capture snapshots of cell states as n -dimensional data points, resulting in disjoint cellular samples. To model dynamics from such data, one approach is to infer the evolving composition of the cell population over experimental time. Alternatively, single-cell dynamics can be reconstructed by assigning discrete time points $t \in \{t_0, t_1, \dots, t_T\}$ to individual cells. This can be done using

¹Helmholtz Munich, Munich, Germany. ²Technical University of Munich, Munich, Germany. ✉e-mail: fabian.theis@helmholtz-munich.de

pseudotime, which infers a temporal ordering based on gene expression similarities, or RNA velocity, which estimates directional transcriptome changes to predict future cell states^{9,10}. It is important to distinguish between true experimental time (when snapshots are taken at known intervals) and pseudotime (inferred ordering for unsynchronized populations).

Originally centered on inferring cellular trajectories through latent differentiation manifolds¹¹, single-cell dynamics research has expanded to include modeling gene regulation^{12,13}, estimating cellular velocity^{2,14}, and mapping differentiation vector fields^{8,15}. These approaches are particularly valuable for non-synchronized populations or steady-state systems where explicit time snapshots are unavailable or lack biological meaning. These advancements have significantly improved our ability to predict the cellular fate and gene regulation^{8,16,17}. ODEs have become a popular method for capturing cellular dynamics (Table 1).

When analyzing time-resolved single-cell trajectories from disjoint populations, optimal-transport-based methods have been crucial for learning cellular state transitions across experimental time¹⁸. Recent technical breakthroughs have further leveraged the connection between the continuous formulation of optimal transport and ODE-based generative models like Flow Matching^{19,20}, leading to powerful new approaches for modeling the evolution of cellular distributions over time. This review highlights the emerging role of Neural ODEs in computational cellular biology, showcasing their potential as versatile tools for both mechanistic and generative modeling. Hence, pseudotime is best suited for unsynchronized data, while real-time methods require explicit time labels.

Configuration space and challenges of pseudotime

The configuration space¹⁰ is inspired by classical mechanics and often works in an embedded space via methods like PCA. The trajectory of cell

differentiation are captured by uniquely specifying cellular states in the latent space (Fig. 1).

Early research used the configuration space to extract key cellular attributes, such as differentiation stage and pseudotime. Techniques like Monocle^{21,22}, Slingshot²³, TSCAN²⁴, Palantir²⁵, and Diffusion pseudotime^{26,27} utilize a variety of methods, including ICA, PCA, DDRtree embedding²⁸, and diffusion components to predict cellular trajectories. Comprehensive benchmarks comparing these trajectory inference methods on configuration space, such as those conducted in Saelens et al.²⁹, provide insights into their relative strengths and limitations across different datasets and biological contexts.

However, pseudotime-based models introduce conflicts when multiple branches exist within the differentiation manifold. If two cells originate from different lineages or branches but are close in pseudotime, the evolutionary process between them is challenging to formulate. With its cell-state-dependent representation, LatentVelo³⁰ effectively disentangles the dynamics by conditioning them on this representation. Additionally, some approaches model intrinsic cellular time along processes such as the cell cycle or differentiation by combining pseudotime ordering with dynamic gene regulatory models³¹, though challenges remain in accurately capturing true temporal dynamics from snapshot data.

Phase space and mechanistic modeling

The study of single-cell dynamics has evolved from the configuration space to include concepts from a phase space that involves a generalized position and momentum (Fig. 1). This space offers a cellular state and transition rates in a unified trajectory. Population Balance Analysis (PBA)⁶ refine the dynamics by modeling potential functions and momenta using a balance equation. RNA velocity^{2,32} determines cell velocity using splicing rate functions to describe mRNA life cycles, while scVelo² uses transient transcription states to describe the entire splicing process. Recent studies such as veloVI¹⁴ and VeloVAE³³ focus on kinetic parameter modeling with deep generative models in the RNA velocity framework. However, these methods cannot predict continuous cell-state transitions, marking a gap that newer approaches aim to bridge.

Another approach creates a continuous vector field, mapping position coordinates (e.g., gene expression, principal components) to momentum coordinates. This approach enables differential geometry analysis to measure geometric characteristics like Jacobian, curl, and curvature. Dynamo³ utilizes vector-valued support-vector machines for this, revealing gene regulations governing cell fate decisions. DeepVelo¹⁵ employs a variational autoencoder (VAE) to assess uncertainty in the latent space, quantifying cell instability potentially linked to differentiation priming stages. However, these methods, relying on RNA velocity, are limited by assuming gene independence in velocity estimation, hence not accounting for regulatory effects between genes. In contrast, incorporating Neural-ODEs allows for coupling genes' dynamics and joint learning of the mapping function and velocity, providing a more accurate representation of cellular dynamics³⁴.

Numerous cellular functions, ranging from determining cell fate to responding to perturbations, follow causal systems, such as the GRN. Guided by the principles of Granger causality³⁵, stating that causality cannot

Table 1 | Classical ODE approaches in computational biology

Method	Application Area	Key Contribution
Kinetic Modeling		
Dynamo ⁸	Cell-state transitions	Vector field reconstruction
RNA-ODE ⁷¹	Trajectory inference	Gene expression dynamics
scVelo ²	RNA velocity inference	Likelihood-based splicing kinetics
NN-based Dynamic Inference		
PRESCIENT ⁷²	Cell fate prediction	Intervention simulation
veloVI ⁷³	RNA velocity	Uncertainty modeling
Regulatory Inference		
CausalKinetiX ⁷⁴	Metabolic networks	Causal structure learning
Cellbox ⁷⁵	GRN inference	Mechanistic cell responses
D-CODE ⁷⁶	Model discovery	Symbolic regression
FLeCS ⁷⁶	GRN inference and use	GRN-based transcription dynamics
RegVelo ³⁴	Velocity and GRN	Unified dynamics framework

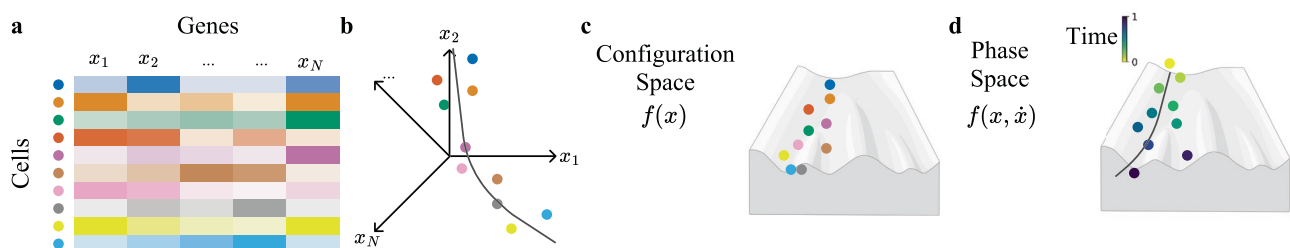
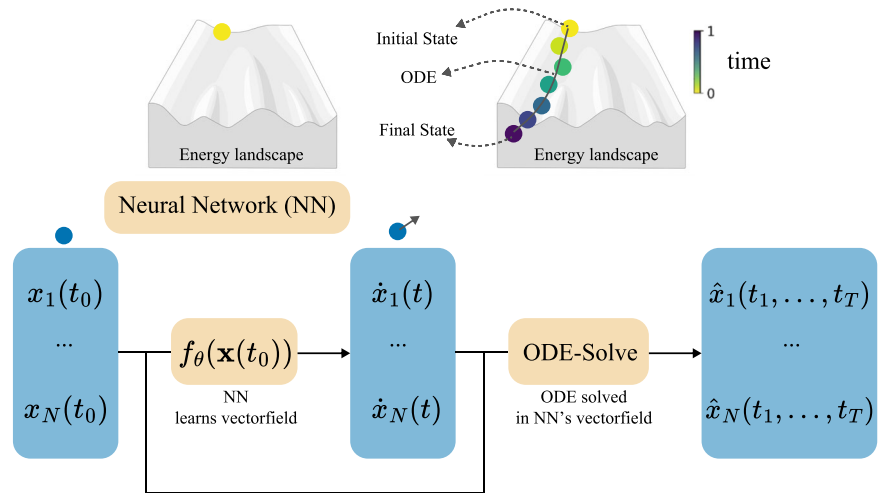


Fig. 1 | Illustration of Configuration and Phase Space. **a** Cell-by-gene matrix illustrating RNA-sequencing data. **b** High-dimensional data representation. **c** Configuration space in Waddington's landscape⁴, a metaphor illustrating cell

differentiation as a journey from a hilltop to valleys, representing distinct cellular stages. **d** Phase space, extending the landscape to include cellular momentum.

Fig. 2 | Concept of the Neural ODE framework for single-cell transcriptomics. The Neural ODE takes a cell’s gene expression vector $\mathbf{x}(t_0)$, $\mathbf{x} \in \mathbb{R}^N$ at time point t_0 as input. A neural network f_θ , parameterized by θ , estimates the momentum $\dot{\mathbf{x}}$, that is together with the initial position the input of an ODE-Solver *ODE-Solve* (in the case of a first-order ODE). Implicitly, the neural network parameterizes the vector field in which the ODE is solved, and the ODE-Solver predicts the expression values at future time points t_1 to T .



work against time, dynamical systems allow causal discovery among variables such as genes. Knowing these relationships is crucial for biological systems, as it holds the key to interpreting critical behaviors such as bifurcation, cycling, and other topological phenomena within the differentiation manifold. Distinguishing mere correlations from authentic regulatory interactions within Neural ODEs remains non-trivial. Prior work has employed sparsity assumptions^{13,36,37}, *i.e.*, that the simplest law is favorable among possible governing laws, but challenges in spurious correlations and unobserved confounders persist. Using interventional data or domain-specific priors could guide the model toward identifying the underlying causal structure³⁸, which is crucial to unlocking the true potential of Neural ODEs.

Theoretical foundations of NeuralODEs and their applications

Motivated by the emergence of data-driven dynamics modeling, this review investigates Neural ODEs—ODEs solved in vector fields that are parameterized by a neural network—as one promising approach. As a potent computational framework, Neural ODEs can naturally model the continuous-time dynamics of cellular states, offering both robustness and explainability.

Mathematical foundations of Neural ODEs

The rapid rise of neural network (NN)-based methods has transformed how latent spaces are learned from single-cell data. Particularly autoencoders³⁹ and VAEs⁴⁰ have been widely adopted to capture meaningful low-dimensional structures, improving batch correction, denoising, and trajectory inference.

Neural Ordinary Differential Equations (Neural ODEs) have emerged as a promising approach for modeling complex system dynamics. Unlike discrete-time Recurrent Neural Networks (RNNs), Neural ODEs excel at capturing the underlying continuous dynamics of noisy and irregularly sampled data⁴¹. Their causal interpretation allows connections to Structural Causal Models (SCMs) in equilibrium states^{35,42}, demonstrated by translating deterministic behavior in ODE systems into a causal framework. With their efficacy in handling noisy data and offering causal insights, Neural ODEs are well-suited for studying biological systems, including single-cell data.

Neural ODEs require the assumption that the data evolves continuously, a process that can be described by a differential equation. We consider a continuous time variable t observed at a finite set of discrete time points $t \in [0, T]$. Specifically, we capture snapshots (e.g., of a cell population \mathcal{X}) ranging from $\mathbf{x}(t_0) \sim \mathbb{P}(\mathcal{X})_{t=0}$ to $\mathbf{x}(t_T) \sim \mathbb{P}(\mathcal{X})_{t=T}$. In single-cell RNA-sequencing, \mathbf{x} represents a transcriptome vector with RNA-sequencing counts x_i for each gene i .

Neural ODEs model such a dynamical system by learning a NN $f_\theta \approx f$ parameterized by θ of the true (e.g., first order) ODE

$$\dot{\mathbf{x}}(t) = f(\mathbf{x}(t)). \tag{1}$$

By learning the function f_θ , a Neural ODE parameterizes a vector field in which the ODE is solved.

Figure 2 illustrates the Neural ODE framework. The ODE solver *ODE-Solve*, often sourced from libraries like `torchdiffeq`⁴³, numerically integrates a learned function f_θ to compute a trajectory. Starting from an initial position (*i.e.*, timepoint) $\mathbf{x}(t_0)$, the solver uses f_θ to predict the momentum $\dot{\mathbf{x}}$ at that position. It then computes the next position in the trajectory based on this momentum. The solver repeats this process iteratively to generate the entire trajectory $\mathbf{x}(t)$ for $t \in (t_0, t_T]$:

$$\widehat{\mathbf{x}}(t_1), \dots, \widehat{\mathbf{x}}(t_T) = \text{ODE-Solve}(f_\theta, \mathbf{x}(t_0), t_1, \dots, t_T). \tag{2}$$

The parameters θ of the learned function f_θ are updated with a loss function, such as the mean-squared-error (MSE), that evaluates how well the inferred data points $\widehat{\mathbf{x}}(t)$ match the original data points $\mathbf{x}(t)$ for all t .

$$\begin{aligned} L(\widehat{\mathbf{x}}(t), \mathbf{x}(t)) &= \mathcal{L} \left(\mathbf{x}(t_0) + \int_{t_0}^t f_\theta(\mathbf{x}(\tau), \tau) d\tau, \mathbf{x}(t) \right) \\ &= \mathcal{L}(\text{ODE-Solve}(f_\theta, \mathbf{x}(t_0), t_0, t), \mathbf{x}(t)) \end{aligned} \tag{3}$$

To satisfy applications involving causal systems such as GRNs, we extend the above Neural ODE notation with a notion of causality. We denote the set of causal parents of variable x_i as $\text{pa}(i)$:

$$\dot{x}_i(t) = f_i(x_{\text{pa}(i)}(t)), \tag{4}$$

where a causal parent enters into sufficiently smooth function $f_i : \mathcal{R}_{\text{pa}(i)} \rightarrow \mathcal{R}_i$. The causal interpretation of ODEs is essential for inferring the SCM

$$x_i = f_i(\mathbf{x}_{\text{pa}(i)}), \quad i \in \mathcal{I} \tag{5}$$

$$\mathcal{I} := \{1, \dots, N\}, \tag{6}$$

where \mathcal{M} is the SCM on the N variables $\{x_i\}_{i \in \mathcal{I}}$. The set of causal parents of x_i is given by $\text{pa}_{\mathcal{M}}(i) \subseteq \mathcal{I} \setminus \{i\}$. The SCM is constructed by assigning one node per ODE variable and a directed edge from x_j to x_i if \dot{x}_i depends on x_j .

Fig. 3 | Exemplary applications of Neural ODEs in single-cell genomics. The methods (blue) have included the respective applications but are not restricted to them.

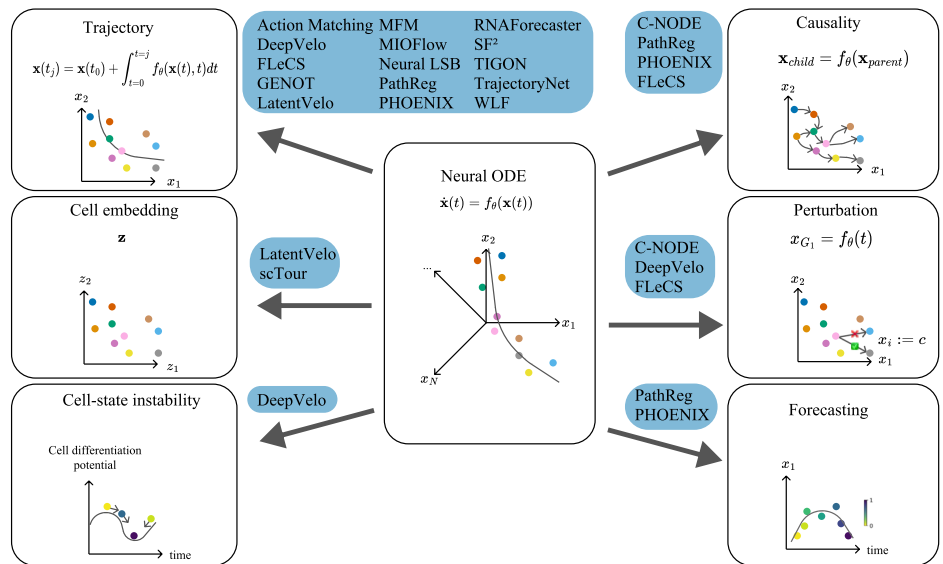


Table 2 | Methodological overview of Neural ODE approaches in single-cell genomics

Method	Primary Focus	Technical Innovation
Optimal Transport and Flow Methods		
Action Matching ⁵³	Irregular sampling	Action-based marginal matching
CFM ²⁰	Continuous trajectories	Flow-based transitions
MFM ⁶²	Complex paths	Metric-based flow matching
MIOFlow ⁵⁴	Manifold data	Geodesic transport
Neural LSB ⁵⁵	Stochastic dynamics	Neural SDE framework
[SF] ² M ⁵⁹	Bidirectional analysis	Score-flow matching
TrajectoryNet ⁴⁴	Population dynamics	CNF with optimal transport
WLF ⁶¹	Transport phenomena	Wasserstein optimization
Network Inference		
C-NODE ³⁷	Sparse networks	L1 regularization
PathReg ¹³	Mechanistic analysis	L0-L1 regularization
PHOENIX ⁴⁵	Large networks	Hill-Langmuir kinetics
TIGON ⁵⁷	Population dynamics	Unbalanced transport
Representation Learning		
DeepVelo ¹⁵	Noisy data	VAE uncertainty modeling
GENOT ⁶⁰	Multi-modal data	Flexible transport
LatentVelo ³⁰	High dimensions	Latent dynamics
scTour ⁴⁷	Multi-task learning	Joint embedding

The Neural ODE framework offers two key advantages. First, the universal approximation theorem ensures that f_θ can model any continuous vector field without prior assumptions about its form. However, in practice, high-dimensional dynamics pose challenges due to limited data and computational constraints. Second, its simple NN foundation enables flexible modifications to address diverse biological questions.

Applications in single-cell dynamics

Neural ODEs are particularly valuable in single-cell genomics due to their versatility. As illustrated in Fig. 3 and detailed in Table 2, researchers have adapted the framework for tasks ranging from trajectory inference to the reconstruction of the GRN.

Trajectory Inference. The concept of trajectory inference is one of the earliest applications of Neural ODEs in single-cell genomics^{15,30,44}. Rather than inferring static gene expressions, Neural ODEs predict them as a function of time, thereby providing a trajectory along the phenotypic manifold that contains the cellular differentiation process. Trajectory inference complements pseudotime-based analyses and offers a dynamic view of cellular state transitions.

Cell differentiation and mechanistic modeling. The evolution of individual genes along a trajectory, as described by the learned differential equation, promises insights into cell differentiation, e.g., at branching events^{13,37,45}, or the concluding cell-state instability¹⁵. The work in Aliee et al.³⁷ highlights the potential of Neural ODEs combined with regularization to uncover system dynamics and causal structures. In Aliee et al.¹³, the focus shifts to the importance of feature sparsity in Neural ODEs for accurately identifying dynamical laws. The study in Hossain et al.⁴⁵ introduces PHOENIX, a framework enhancing the interpretability of ODE representations in gene expression prediction. Finally, DeepVelo¹⁵ models transcriptome dynamics, emphasizing cell-state instability and developmental driver gene identification.

A further notable innovation stems from the problem of non-identifiability of the governing dynamical system from observational data, shown in Aliee et al.³⁷. The assumption of sparse causal connections³⁶ inspires the regularization of the input-output connections of the function f_θ to prefer simplicity in the governing system. Such regularization promises sparse relationships in the GRN^{13,37}. Building upon these principles, RegVelo³⁴ combines RNA velocity and GRN inference into a unified framework, enabling dynamic and interpretable modeling of gene regulation. It achieves superior predictive power for both regulatory interactions and perturbation simulations.

GRN inference and causality. Furthermore, GRNs model the (causal) relationship between genes that govern the activation and suppression of genes. The function f_θ gives rise to such a variable interplay that^{13,37,45} investigate for GRN inference. Methods such as RegVelo³⁴ can incorporate such a GRN as prior regulation knowledge. Perturbation experiments (gene knockouts, drug treatments) provide crucial causal evidence by revealing which regulatory links change under controlled interventions, helping distinguish causal interactions from correlations. FLeCS⁴⁶ exemplifies this approach by inferring kinetic parameters (regulatory interaction strengths and mRNA half-lives) through coupled ODEs, enabling causal network inference at scale.

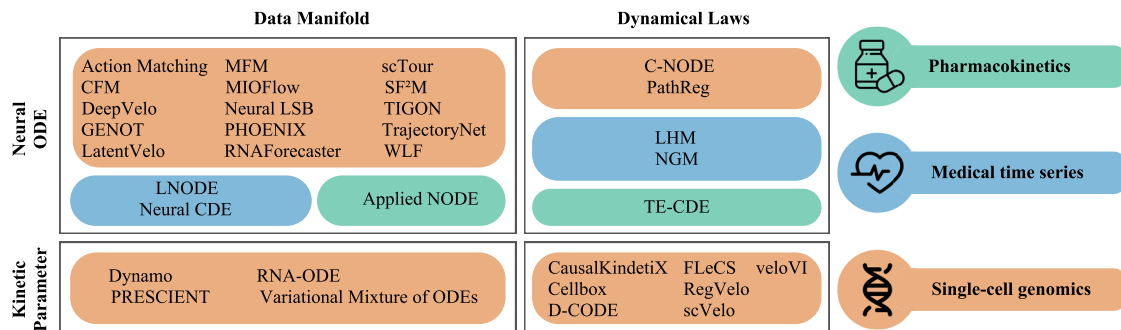


Fig. 4 | Overview of dynamical models with Neural ODEs (up) and ODEs (down), modeling a data manifold (left) or the governing dynamical laws (right). Applications stem from single-cell genomics and exemplary applications in pharmacokinetics and medical time-series.

Representation learning and dimensionality reduction. The embedding analysis is a separate but essential line of investigation in single-cell genomics. Neural ODEs can also operate on data representations transformed by an encoder NN, the weights of which are learned during the process. These embeddings offer valuable perspectives on single-cell data^{30,47}.

Dynamic modeling from time-resolved datasets

Driven by the challenges in learning the single-cell dynamics beyond parametric models and RNA velocity, diverse technical approaches based on cellular manifold estimation and optimal transport emerged, encompassing graph-based single-cell data representations as well as powerful generative approaches (Fig. 4).

Optimal transport approaches

The scRNA-seq technique destroys a cell during sequencing. Consequently, it is not possible to track the evolving state of an individual cell across experimental time. Instead, time-resolved scRNA-seq involves collecting disjoint snapshots of single cells at successive time points. Cellular evolution can, therefore, be modeled in terms of population dynamics. Specifically, it can be described by a parameterized map that transports distributions of cells forward in time to match future population snapshots. The meaningfulness of the temporal dimension depends on the experimental design: when snapshots are taken at known intervals, the time labels carry real physical meaning as biological time; when they represent an inferred ordering, the temporal axis serves as a modeling construct for population dynamics²⁶. Therefore, optimal transport (OT) methods are well suited when discrete time-point data are available as snapshots of cell populations. In pursuing real-time dynamics inference, utilizing discrete OT to deduce the cell state transitions across distinct time points is a promising approach^{18,48–50}. In this scenario, Waddington-OT⁴⁸ infers ancestor-descendant fates and modeling regulatory programs, revealing a diverse range of developmental programs from single-cell RNA sequencing profiles. Moslin⁴⁹ couples matching cellular profiles across time points by leveraging both lineage relations and gene expression similarity, Moscot¹⁸ is a scalable framework for optimal transport in single-cell genomics, enabling efficient reconstruction of developmental trajectories and identification of driver genes across temporal and spatial datasets. JKONet⁵¹ learns optimal transport via Input Convex Neural Networks by minimizing a parameterized energy function. However, these methods do not yield a continuous vector field but only infer the transport plan across time points⁴⁸, also necessitating an assumption of linearity in velocity between different time points^{18,48}. By incorporating a Neural ODE solver and leveraging prior biological knowledge, inferring continuous dynamics guided by vector fields grounded in robust biological hypotheses becomes conceivable⁴⁵.

Continuous normalizing flows and ODE-based generative models

Inspired by the success of OT in dynamical modeling, several works have explored OT-based regularization techniques for Neural ODEs. These

regularizers are incorporated within the continuous normalizing flow (CNF) framework⁴¹, which models data distributions with a flow of infinitesimal transformations (change of variables formula) from noise to data, using an ODE solver to learn the transformation over time. Infusing OT into CNFs enables training a Neural ODE that matches distributions of samples across time, improving dynamics fitting by minimizing displacement costs while forcing trajectory to reconstruct marginal time points. For example, TrajectoryNet⁴⁴ uses the Kullback-Leibler divergence between real samples and observations integrated over time with a Neural ODE as part of an energy loss to approximate the L^2 Wasserstein distance between single-cell snapshots⁵². Meanwhile,⁵³ formulates the optimal vector field matching temporal marginals as the gradient of a function called action, deriving a tractable objective based on kinetic energy minimization. Other methods include the 2-Wasserstein distance regularization of trajectories learned in the latent space of an approximately Euclidean geodesic autoencoders⁵⁴ or extending learning population dynamics to a stochastic setting, representing paths between temporal snapshots as the solutions of Neural SDEs approximating the Schrödinger bridge problem^{55,56}. The Schrödinger Bridge problem finds the most likely stochastic process (diffusion) connecting two observed distributions while minimizing entropy relative to a reference process. Finally, OT has been successfully shown to approximate population growth and gene regulatory interactions across the dynamics⁵⁷.

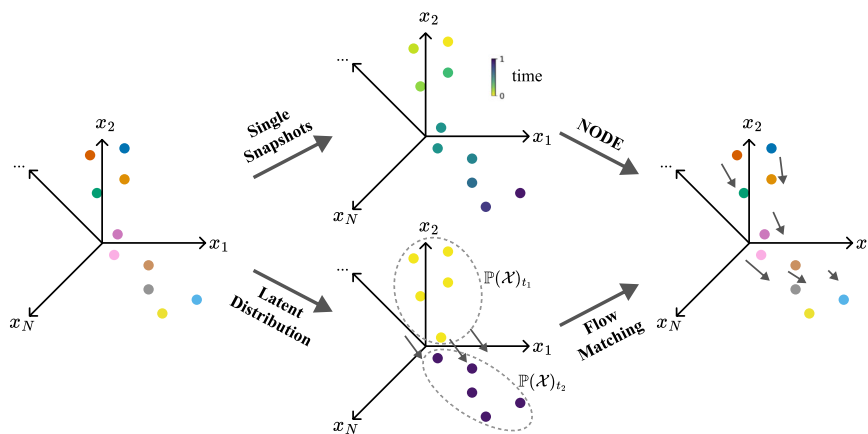
Flow matching and simulation-free approaches

Flow matching. Flow matching¹⁹ simplifies the learning of data transformations by directly minimizing the difference between the learned vector field and the optimal transport vector field, approximated along a straight line connecting samples from consecutive timepoints matched with minibatch OT (see Fig. 5). Like OT, flow matching is well suited for datasets comprising discrete snapshots of cell populations at successive time points, inferring dynamics without requiring continuous single-cell tracking. This approach avoids expensive ODE integration during training. Besides its generative capabilities⁵⁸, flow matching has also inspired extensions to model single-cell dynamics, such as OT-based regularization to stabilize training and inference for single-cell modeling²⁰. Simulation-free score and flow matching ([SF]²M)⁵⁹ solves the Schrödinger bridge problem, efficiently modeling high-dimensional cell dynamics without requiring full trajectory simulation. Similarly, generative entropic neural OT (GENOT)⁶⁰ applies flow matching to unbalanced Gromov-Wasserstein problems, extending the framework to handle multimodal single-cell data and developmental trajectories. Wasserstein Lagrangian Flows (WLF)⁶¹ improve computational efficiency in large-scale cell trajectory modeling by solving transport problems with entropic regularization. Finally, Metric Flow Matching (MFM)⁶² introduces a metric-based flow matching variant, which offers improved geometric fidelity for learning dynamic processes.

Stochasticity and noise in single-cell dynamics

Single-cell processes exhibit inherent stochasticity due to noisy expression patterns and experimental artefacts. While Neural ODEs model average

Fig. 5 | Inferring cellular dynamics through neural ODEs and Flow Matching. Neural ODEs consider snapshots of cell states at discrete (pseudo-) time points $t \in t_0, t_1, \dots, t_T$. Flow matching considers latent distributions of cells $\mathbb{P}(\mathcal{X})$. Both approaches result in a vector field describing cellular dynamics.



trajectories, they can be extended to Neural SDEs (Stochastic Differential Equations) to account for random fluctuations and incorporate knowledge on biological stochasticity⁶³. Learning stochastic dynamics has been explored in the context of optimal transport through the Schrödinger Bridge problem, which finds the most likely stochastic process connecting two observed cell state distributions, balancing fit and randomness. Established approaches^{57,64} learn to fit stochastic dynamics with neural networks, accounting for cell growth and death in developmental processes. Schrödinger Bridges have been combined with flow models as well in methods like Neural LSB⁵⁵ and [SF]²M⁵⁹, capturing stochastic differentiation patterns driven by optimal transport.

Challenges

Neural ODEs have emerged as a compelling framework for modeling dynamics in single-cell genomics and related computational health disciplines. However, fully addressing the diverse characteristics of biological data faces three predominant challenges from the technical standpoint.

First, understanding the causal relationships and underlying regulatory mechanisms presents a challenge. Guided by the principles of Granger causality³⁵, stating that causality cannot work against time, dynamical systems allow causal discovery among variables such as genes. Knowing these relationships is crucial for biological systems, as it holds the key to interpreting critical behaviors such as bifurcation, cycling, and other topological phenomena within the differentiation manifold. Distinguishing mere correlations from authentic regulatory interactions within Neural ODEs remains non-trivial. This challenge is compounded by the difficulty of distinguishing direct regulatory effects from indirect effects mediated by intermediate genes, as well as the presence of feedback loops in GRNs that can confound causal interpretation. Prior work has employed sparsity assumptions^{13,36,37}, *i.e.*, that the simplest law is favorable among possible governing laws, but challenges in spurious correlations and unobserved confounders persist. Using interventional data or domain-specific priors could guide the model toward identifying the underlying causal structure, which is crucial to unlocking the true potential of Neural ODEs.

Second, the necessity for generalizing beyond interpolation is critical¹³. Models should not overfit the training data but learn the governing laws behind biological dynamics instead. Applications from single-cell genomics, such as driver gene perturbation⁶⁵ and predicting future cell states¹⁵, require learning the underlying dynamics that govern the evolution of biological systems. Evaluation metrics must extend beyond interpolation, focusing on a model's ability to robustly capture underlying dynamical laws. This objective is challenging due to, *e.g.*, lacking ground truth and numerous out-of-distribution definitions. Rigorous out-of-distribution testing constitutes a promising research direction.

Third, effectively incorporating real-world data entails accounting for confounding variables ranging from stochasticity to latent influences⁶. To

Table 3 | Neural ODE applications in medicine and pharmacology

Method	Application Area	Key Contribution
Disease Monitoring		
Neural CDE ⁷⁷	Disease detection	Continuous monitoring
LHM ⁷⁸	Health trajectories	Expert knowledge integration
LNODE ⁷⁹	Cardiac dynamics	Heart failure progression
Biological Systems		
NGM ⁸⁰	Biological oscillations	Chaotic dynamics
Neural ODE-PK ⁸¹	Drug response	Pharmacokinetics modeling
TE-CDE ⁸²	Treatment planning	Counterfactual analysis

achieve robustness, strategies such as regularization and including biological priors have been proposed^{13,45}.

Beyond single-cell genomics, Neural ODEs have demonstrated broad applicability in computational health. As summarized in Table 3, these models support disease monitoring, pharmacology, and biological systems by integrating expert knowledge, capturing stochastic processes, and enabling counterfactual analysis. In genomics, multi-omics techniques provide complementary information across molecular layers⁶⁶, yet integrating these modalities remains challenging⁶⁷. Extending Neural ODEs to further real-world applications thus requires robust strategies for handling heterogeneous data while preserving mechanistic interpretability.

Conclusion and outlook

This article has studied the ODEs framework and its diverse applications in single-cell genomics. We have portrayed single-cell dynamics through the lens of the Waddington landscape, derived the Neural ODE framework in the context of biological application, and reviewed recent literature concerning their technical and practical innovations.

Exploring biological dynamics through computational models holds the potential for illuminating their underlying mechanisms. Despite growing interest in modeling techniques, such as Neural ODEs, the fundamental technical challenges of explainability, generalizability, and robustness persist. Synergistic approaches to improve Neural ODE optimization, such as optimal transport-based regularization, have shown promising results. We anticipate continued innovation by integrating the strengths of diverse modeling paradigms such as optimal transport, classical dynamics modeling, or incorporating regulatory elements from computational biology.

Other advancements in applying Neural ODEs to single-cell data aim to achieve robust learning and causal modeling of the governing dynamical laws. By delving deeper into this domain, we envision revealing the causal mechanisms governing cellular dynamics. Such insights into the underlying

dynamical law enable in-silico simulations and predictions, allowing us to anticipate the impact of various factors on biological readouts like single-cell gene expression.

From an application standpoint, Neural ODE methods promise generalizable insights into single-cell dynamics. Their technical versatility allows deployment in numerous downstream applications within and beyond single-cell genomics, including medical time series and pharmacokinetics, highlighting the broad applicability of dynamical systems modeling.

In the broader machine learning landscape, foundation models such as SORA^{68,69} are beginning to capture the dynamic world. While single-cell foundation models largely focus on static settings⁷⁰, the development of such dynamic models offers an intriguing future direction. By advancing Neural ODEs and similar approaches, we come closer to achieving a large-scale model of the dynamic world of cellular processes.

In conclusion, Neural ODEs are an empowering and innovative framework for modeling underlying dynamics in single cells and the broader realm of computational health. The technical innovations of Neural ODEs and their future prospects foreshadow a more holistic understanding of the governing dynamical laws that steer cell differentiation. The presented applications and challenges collectively contribute to a captivating and promising journey, inspiring further advancements in this transformative field.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Received: 30 April 2025; Accepted: 16 February 2026;

Published online: 27 February 2026

References

- Newman, S. A. Cell differentiation: what have we learned in 50 years? *J. Theor. Biol.* **485**, 110031 (2020).
- Bergen, V., Lange, M., Peidli, S., Wolf, F. A. & Theis, F. J. Generalizing rna velocity to transient cell states through dynamical modeling. *Nat. Biotechnol.* **38**, 1408–1414 (2020).
- Shi, J., Aihara, K., Li, T. & Chen, L. Energy landscape decomposition for cell differentiation with proliferation effect. *Natl. Sci. Rev.* **9**, nwac116 (2022).
- Waddington, C. H. *The Strategy of the Genes*, 1st edn. <https://doi.org/10.4324/9781315765471>. Reprinted as eBook in 2014. (Routledge, London, 1957).
- Qiu, X., Ding, S. & Shi, T. From understanding the development landscape of the canonical fate-switch pair to constructing a dynamic landscape for two-step neural differentiation. *PLoS ONE* **7**, e49271 (2012).
- Weinreb, C., Wolock, S., Tusi, B. K., Socolovsky, M. & Klein, A. M. Fundamental limits on dynamic inference from single-cell snapshots. *Proc. Natl. Acad. Sci.* **115**, E2467–E2476 (2018).
- Angerer, P. et al. Single cells make big data: new challenges and opportunities in transcriptomics. *Curr. Opin. Syst. Biol.* **4**, 85–91 (2017).
- Qiu, X. et al. Mapping transcriptomic vector fields of single cells. *Cell* **185**, 690–711 (2022).
- Teschendorff, A. E. & Feinberg, A. P. Statistical mechanics meets single-cell biology. *Nat. Rev. Genet.* **22**, 459–476 (2021).
- Deconinck, L., Cannoodt, R., Saelens, W., Deplancke, B. & Saeys, Y. Recent advances in trajectory inference from single-cell omics data. *Curr. Opin. Syst. Biol.* **27**, 100344 (2021).
- Trapnell, C. et al. The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells. *Nat. Biotechnol.* **32**, 381–386 (2014).
- Qiu, X. et al. Inferring causal gene regulatory networks from coupled single-cell expression dynamics using scribe. *Cell Syst.* **10**, 265–274 (2020).
- Aliee, H. et al. Sparsity in continuous-depth neural networks. *Adv. Neural Inf. Process. Syst.* **35**, 901–914 (2022). Systematically explores the impact of weight and feature sparsity on the generalization and dynamical law identification capabilities of Neural Ordinary Differential Equations (NODEs), introducing a novel regularization method, PathReg, to enhance input-output relation sparsity, and evaluate it across real-world datasets to assess out-of-distribution generalization in dynamical systems.
- Gayoso, A. et al. Deep generative modeling of transcriptional dynamics for RNA velocity analysis in single cells. *Nat. Methods* **21**, 50–59 (2024).
- Chen, Z., King, W. C., Hwang, A., Gerstein, M. & Zhang, J. Deepvelo: single-cell transcriptomic deep velocity field learning with neural ordinary differential equations. *Sci. Adv.* **8**, eabq3745 (2022).
- Lange, M. et al. Cellrank for directed single-cell fate mapping. *Nat. methods* **19**, 159–170 (2022).
- Weiler, P., Lange, M., Klein, M., Pe'er, D. & Theis, F. Unified fate mapping in multiview single-cell data. *Nat. Methods* **21**, 1196–1205 (2024).
- Klein, D. et al. Mapping cells through time and space with moscot. *Nature* **638**, 1065–1075 (2025).
- Lipman, Y., Chen, R. T. Q., Ben-Hamu, H., Nickel, M. & Le, M. Flow matching for generative modeling. In *The Eleventh International Conference on Learning Representations*. <https://openreview.net/forum?id=PqvMRDCJT9t> (2023).
- Tong, A. et al. Improving and generalizing flow-based generative models with minibatch optimal transport. *Trans. Mach. Learn. Res.* <https://openreview.net/forum?id=CD9Snc73AW>. Expert Certification (2024).
- Trapnell, C., Cacchiarelli, D. & Qiu, X. Monocle: Cell counting, differential expression, and trajectory analysis for single-cell RNA-seq experiments. *Bioconductor* <https://www.bioconductor.org/packages/release/bioc/html/monocle.html> (2017).
- Saunders, L. M. et al. Embryo-scale reverse genetics at single-cell resolution. *Nature* **623**, 782–791 (2023).
- Street, K. et al. Slingshot: cell lineage and pseudotime inference for single-cell transcriptomics. *BMC Genom.* **19**, 1–16 (2018).
- Ji, Z. & Ji, H. Tscan: Pseudo-time reconstruction and evaluation in single-cell RNA-seq analysis. *Nucleic Acids Res.* **44**, e117–e117 (2016).
- Setty, M. et al. Characterization of cell fate probabilities in single-cell data with Palantir. *Nat. Biotechnol.* **37**, 451–460 (2019).
- Haghverdi, L., Büttner, M., Wolf, F. A., Büttner, F. & Theis, F. J. Diffusion pseudotime robustly reconstructs lineage branching. *Nat. methods* **13**, 845–848 (2016).
- Wei, J., Zhou, T., Zhang, X. & Tian, T. Dtflo: inference and visualization of single-cell pseudotime trajectory using diffusion propagation. *Genom. Proteom. Bioinform.* **19**, 306–318 (2021).
- Mao, Q., Wang, L., Goodison, S. & Sun, Y. Dimensionality reduction via graph structure learning. In *Proc. 21th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. 765–774 (Association for Computing Machinery, New York, NY, 2015).
- Saelens, W., Cannoodt, R., Todorov, H. & Saeys, Y. A comparison of single-cell trajectory inference methods. *Nat. Biotechnol.* **37**, 547–554 (2019).
- Farrell, S., Mani, M. & Goyal, S. Inferring single-cell transcriptomic dynamics with structured latent gene expression dynamics. *Cell Rep. Methods* **3**, 100581 (2023). Available at SSRN 4330809 LatentVelo leverages deep learning to compute low-dimensional gene dynamics, embedding cells in a dynamics-based latent space via a variational autoencoder and modeling differentiation with neural ordinary

- differential equations, enabling accurate prediction of cell trajectories and superior batch correction by focusing on gene expression dynamics.
31. Ocone, A., Haghverdi, L., Mueller, N. S. & Theis, F. J. Reconstructing gene regulatory dynamics from high-dimensional single-cell snapshot data. *Bioinformatics* **31**, i89–i96 (2015).
 32. La Manno, G. et al. RNA velocity of single cells. *Nature* **560**, 494–498 (2018).
 33. Gu, Y., Blaauw, D. & Welch, J. D. Bayesian inference of RNA velocity from multi-lineage single-cell data. *bioRxiv* <https://doi.org/10.1101/2022.07.08.499381> (2022).
 34. Wang, W. et al. Regvelo: gene-regulatory-informed dynamics of single cells. *bioRxiv* <https://doi.org/10.1101/2024.12.11.627935> (2024).
 35. Granger, C. W. Some recent development in a concept of causality. *J. Econ.* **39**, 199–211 (1988).
 36. Schölkopf, B. et al. Toward causal representation learning. *Proc. IEEE* **109**, 612–634 (2021).
 37. Aliee, H., Theis, F. J. & Kilbertus, N. Beyond predictions in neural odes: identification and interventions. *arXiv preprint* <https://doi.org/10.48550/arXiv.2106.12430> (2021).
 38. Tejada-Lapuerta, A. et al. Causal machine learning for single-cell genomics. *Nat. Genet.* **57**, 797–808 (2025).
 39. Eraslan, G., Simon, L. M., Mircea, M., Mueller, N. S. & Theis, F. J. Single-cell RNA-seq denoising using a deep count autoencoder. *Nat. Commun.* **10**, 390 (2019).
 40. Lopez, R., Regier, J., Cole, M. B., Jordan, M. I. & Yosef, N. Deep generative modeling for single-cell transcriptomics. *Nat. methods* **15**, 1053–1058 (2018).
 41. Chen, R. T. Q., Rubanova, Y., Bettencourt, J. & Duvenaud, D. K. Neural Ordinary Differential Equations. In *Advances in Neural Information Processing Systems* Vol. 31 (Curran Associates, Inc., 2018).
 42. Mooij, J. M., Janzing, D. & Schölkopf, B. From ordinary differential equations to structural causal models: the deterministic case. In *Proceedings of the Twenty-Ninth Conference on Uncertainty in Artificial Intelligence*. UAE'13, pp.440–448. <https://doi.org/10.48550/arXiv.1304.7920> (AUAI Press, Bellevue, WA, 2013).
 43. Chen, R. T. Q. torchdiffeq. <https://github.com/rtqichen/torchdiffeq> (2018).
 44. Tong, A., Huang, J., Wolf, G., Van Dijk, D. & Krishnaswamy, S. Trajectorynet: A dynamic optimal transport network for modeling cellular dynamics. In *International conference on machine learning*, 9526–9536 (PMLR, 2020). TrajectoryNet leverages the integration of continuous normalizing flows with dynamic optimal transport to model continuous, non-linear paths in dynamic systems, overcoming the limitations of static optimal transport models by constraining the flow of entities between distributions, showcasing enhanced modeling of cellular dynamics in scRNA-seq data.
 45. Hossain, I., Fanfani, V., Fischer, J., Quackenbush, J. & Burkholz, R. Biologically informed neuralodes for genome-wide regulatory dynamics. *Genome Biol.* **25**, 127 (2024). PHOENIX advances ODE-based modeling of gene expression dynamics by integrating neural ODEs with Hill-Langmuir kinetics, offering a scalable framework that enhances biological interpretability through sparse representations and prior knowledge incorporation, demonstrated across in silico experiments, yeast cell oscillations, and genome-scale breast cancer studies.
 46. Bertin, P. et al. A scalable gene network model of regulatory dynamics in single cells. *arXiv preprint arXiv* <https://doi.org/10.48550/arXiv.2503.20027> (2025).
 47. Li, Q. sctour: a deep learning architecture for robust inference and accurate prediction of cellular dynamics. *Genome Biol.* **24**, 149 (2023).
 48. Schiebinger, G. et al. Optimal-transport analysis of single-cell gene expression identifies developmental trajectories in reprogramming. *Cell* **176**, 928–943 (2019).
 49. Lange, M. et al. Mapping lineage-traced cells across time points with Moslin. *Genome Biol.* **25**, 277 (2024).
 50. Eyring, L. et al. Unbalancedness in neural monge maps improves unpaired domain translation. *The Twelfth International Conference on Learning Representations*. <https://openreview.net/forum?id=2UnCj3jeao> (2024).
 51. Bunne, C., Papaxanthos, L., Krause, A. & Cuturi, M. Proximal optimal transport modeling of population dynamics. In *International Conference on Artificial Intelligence and Statistics*, 6511–6528 (PMLR, 2022).
 52. Benamou, J.-D. & Brenier, Y. A computational fluid mechanics solution to the monge-kantorovich mass transfer problem. *Numer. Math.* **84**, 375–393 (2000).
 53. Neklyudov, K., Brekelmans, R., Severo, D. & Makhzani, A. Action matching: learning stochastic dynamics from samples. In *International conference on machine learning*, 25858–25889 (PMLR, 2023).
 54. Huguet, G. et al. Manifold interpolating optimal-transport flows for trajectory inference. In *Advances in Neural Information Processing Systems*. Vol. 35, (eds Koyejo, S. et al.) 29705–29718 (Curran Associates, Inc., 2022). MIOFlow introduces a novel integration of dynamic models, manifold learning, and optimal transport through Neural ODEs and a geodesic autoencoder, offering superior interpolation between static population snapshots by embedding data in a geometry-aware latent space, outperforming existing generative models in capturing continuous population dynamics.
 55. Koshizuka, T. & Sato, I. Neural lagrangian schrödinger bridge: Diffusion modeling for population dynamics. In *The Eleventh International Conference on Learning Representations* (2023). Addresses the challenge of modeling biological population dynamics with coarse temporal data by introducing a method that combines the Lagrangian Schrödinger bridge problem with neural stochastic differential equations, enabling the approximation of both deterministic and stochastic sample trajectories in line with the principle of least action, and demonstrating efficient high-dimensional dynamics estimation.
 56. Bunne, C., Hsieh, Y.-P., Cuturi, M. & Krause, A. The schrödinger bridge between Gaussian measures has a closed form. In *International Conference on Artificial Intelligence and Statistics*, 5802–5833 (PMLR, 2023).
 57. Sha, Y., Qiu, Y., Zhou, P. & Nie, Q. Reconstructing growth and dynamic trajectories from single-cell transcriptomics data. *Nat. Mach. Intell.* **6**, 25–39 (2024).
 58. Palma, A. et al. Generating multi-modal and multi-attribute single-cell counts with CFGen. In *The Thirteenth International Conference on Learning Representations*. <https://openreview.net/forum?id=3MnMGLctKb> (2025).
 59. Tong, A. et al. Simulation-free schrödinger bridges via score and flow matching. In *Proceedings of The 27th International Conference on Artificial Intelligence and Statistics*. <https://proceedings.mlr.press/v238/tong24a.html> (2023).
 60. Klein, D., Uscidda, T., Theis, F. & Cuturi, M. Generative entropic neural optimal transport to map within and across spaces. *Advances in Neural Information Processing Systems*. Vol. 37, 103897–103944 https://proceedings.neurips.cc/paper_files/paper/2024/file/bc46e29f91e676747c584ca181cb0ea1-Paper-Conference.pdf (2024).
 61. Neklyudov, K. et al. A computational framework for solving Wasserstein Lagrangian flows. In *Proceedings of the 41st International Conference on Machine Learning*. <https://doi.org/10.48550/arXiv.2310.10649> (2023).

62. Kapusniak, K. et al. Metric flow matching for smooth interpolations on the data manifold. In *The Thirty-eighth Annual Conference on Neural Information Processing Systems*. <https://doi.org/10.48550/arXiv.2405.14780> (2024).
63. Maizels, R. J., Snell, D. M. & Briscoe, J. Reconstructing developmental trajectories using latent dynamical systems and time-resolved transcriptomics. *Cell Syst.* **15**, 411–424 (2024).
64. Zhang, Z., Wang, Z., Sun, Y., Li, T. & Zhou, P. Modeling cell dynamics and interactions with unbalanced mean field Schrödinger bridge. In *The Thirty-ninth Annual Conference on Neural Information Processing Systems*. <https://doi.org/10.48550/arXiv.2505.11197> (2025).
65. Krumsiek, J., Marr, C., Schroeder, T. & Theis, F. J. Hierarchical differentiation of myeloid progenitors is encoded in the transcription factor network. *PLoS one* **6**, e22649 (2011).
66. Trimbour, R., Deutschmann, I. M. & Cantini, L. Molecular mechanisms reconstruction from single-cell multi-omics data with hummus. *Bioinformatics* **40**, btae143 (2024).
67. Bergen, V., Soldatov, R. A., Kharchenko, P. V. & Theis, F. J. RNA velocity-current challenges and future perspectives. *Mol. Syst. Biol.* **17**, e10282 (2021).
68. Brooks, T. et al. Video generation models as world simulators. 2024. <https://openai.com/research/video-generation-models-as-world-simulators> **3** (2024).
69. Zhu, Z. et al. Is Sora a world simulator? A comprehensive survey on general world models and beyond. *arXiv preprint* <https://doi.org/10.48550/arXiv.2405.03520> (2024).
70. Szalata, A. et al. Transformers in single-cell omics: a review and new perspectives. *Nat. Methods* **21**, 1430–1443 (2024).
71. Liu, R., Pisco, A. O., Braun, E., Linnarsson, S. & Zou, J. Dynamical systems model of RNA velocity improves inference of single-cell trajectory, pseudo-time and gene regulation. *J. Mol. Biol.* **434**, 167606 (2022).
72. Yeo, G. H. T., Saksena, S. D. & Gifford, D. K. Generative modeling of single-cell time series with prescient enables prediction of cell trajectories with interventions. *Nat. Commun.* **12**, 3222 (2021).
73. Gayoso, A. et al. Deep generative modeling of transcriptional dynamics for RNA velocity analysis in single cells. *Nat. Methods* **21**, 50–59 (2022).
74. Pfister, N., Bauer, S. & Peters, J. Learning stable and predictive structures in kinetic systems. *Proc. Natl. Acad. Sci.* **116**, 25405–25411 (2019).
75. Yuan, B. et al. Cellbox: interpretable machine learning for perturbation biology with application to the design of cancer combination therapy. *Cell Syst.* **12**, 128–140 (2021).
76. Qian, Z., Kacprzyk, K. & van der Schaar, M. D-code: Discovering closed-form odes from observed trajectories. In *International Conference on Learning Representations (ICLR, 2022)*.
77. Kidger, P., Morrill, J., Foster, J. & Lyons, T. Neural controlled differential equations for irregular time series. In *Advances in Neural Information Processing Systems*. Vol. 33 (eds Larochelle, H., Ranzato, M., Hadsell, R., Balcan, M. & Lin, H.) 6696–6707 (Neural Information Processing Systems Foundation, Inc. NeurIPS, 2020).
78. Qian, Z., Zame, W., Fleuren, L., Elbers, P. & van der Schaar, M. Integrating expert odes into neural odes: pharmacology and disease progression. *Adv. Neural Inf. Process. Syst.* **34**, 11364–11383 (2021).
79. Salvador, M. et al. Real-time whole-heart electromechanical simulations using latent neural ordinary differential equations. *npj Digit. Med.* **7**, 90 (2024).
80. Bellot, A., Branson, K. & van der Schaar, M. Neural graphical modelling in continuous-time: consistency guarantees and algorithms. In *International Conference on Learning Representations (ICLR, 2022)*.
81. Lu, J., Deng, K., Zhang, X., Liu, G. & Guan, Y. Neural-ode for pharmacokinetics modeling and its advantage to alternative machine learning models in predicting new dosing regimens. *iScience* **24**, 102804 (2021).
82. Seedat, N., Imrie, F., Bellot, A., Qian, Z. & van der Schaar, M. Continuous-time modeling of counterfactual outcomes using neural controlled differential equations. In *Proc. 39th International Conference on Machine Learning*. Vol. 162, 19497–19521 (PMLR, 2022).

Acknowledgements

We thank Philipp Weiler for his valuable feedback and rigorous review, which significantly contributed to the quality of this paper. ChatGPT by OpenAI and Grammarly by Grammarly Inc. were used to reformulate parts of the text. BioRender.com was used to create parts of the figures. T.R. and A.P. are supported by the Helmholtz Association through the Munich School for Data Science. T.R. also receives funding from the Munich Center for Machine Learning (MCML; BMBF; grant #01IS18053A). T.R., A.P., and F.J.T. acknowledge support from the Helmholtz Association's Initiative and Networking Fund via CausalCellDynamics (grant #Interlabs-0029). WW is funded by Neurocov under the EU Horizon 2022 programme (grant #101057775). A.P. is further supported by HOPARL (BMBF; grant #031L0289A). F.J.T. acknowledges support from the European Union (ERC, DeepCell—#101054957). The views expressed are those of the authors and not necessarily of the EU or ERC; neither can be held responsible for them.

Author contributions

T.R. and F.J.T. conceptualized the review. T.R. and W.W. led the literature synthesis and developed the overall storyline. T.R., W.W., and A.P. contributed to writing and figure creation. All authors discussed the manuscript and provided feedback.

Funding

Open Access funding enabled and organized by Projekt DEAL.

Competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: F.J.T. consults for Immunai, CytoReason, BioTuring, Genbio and Valinor Industries, and has ownership interest in RN.AI Therapeutics, Dermagnostix, and Cellarity. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s42003-026-09758-w>.

Correspondence and requests for materials should be addressed to Fabian J. Theis.

Peer review information *Communications Biology* thanks Elias Ventre and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editors: Aylin Bircan and Christina Karlsson Rosenthal.

Reprints and permissions information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2026