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Machine learning for time-series genomics: Advances, challenges, and future directions

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A B S T R A C T

Recent developments in single-cell and high-throughput sequencing technologies have enabled the collection of genomic data at multiple time points; therefore, the investigation of dynamic processes and the observation of disease prognosis, progression, and therapy effects are now possible. Yet, challenges, including biological variability, high dimensionality, noise, and temporal resolution in these datasets, need to be addressed. This review aims to categorize the machine learning (ML) methods used to create models that analyse the temporal dynamics of genomic data. In addition, the best way to apply either the classical or modern deep learning approaches to analyse temporal genomic and multi-omics datasets is being discussed. ML methods used in time-series genomics analysis have been organized by data type and modeling approach to compare their efficiency in handling sparsity and nonlinear temporal relationships, thereby helping to understand the biological mechanisms underlying them. Furthermore, we focus on the recent frameworks that combine temporal learning models with long-read and single-cell sequencing. While ML provides robust tools to reveal temporal dynamics, data standardization, scalability, interpretability, and benchmarking remain challenges. We summarize best practices for model evaluation and outline future directions, including multi-omics integration, interpretable artificial intelligence, and large-scale, reproducible benchmarks. Via combining computational ingenuity and biological insight, we enable a deep understanding of the complexity of biological processes and pave the way for applying precision medicine through ML-based time-series genomics.

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1. Introduction

Indeed, our capabilities to study time-dependent dynamic molecular changes increase owing to advances in sequencing techniques, particularly long-read and single-cell sequencing approaches (Goodwin et al., 2016; Amarasinghe et al., 2020; Wu et al., 2024; Santos et al., 2025). Unlike static datasets, time-series analysis datasets can help to reach a mechanistic explanation for signal transduction, gene regulation, pathological evolution, and lineage fate decisions (Klevecz & Murray, 2001; Bar-Joseph et al., 2012; Spies et al., 2019; Abe et al., 2025). Accordingly, this could lead to a better understanding of how immune activation, developmental trajectories, the response to targeted therapies, and tumor evolution occur (Bar-Joseph et al., 2012; DiStefano, 2015; Abe et al., 2025). Yet, the analysis of time series data is challenging, given that this data type is mostly sparse, high-dimensional, noisy, and collected at irregular time intervals (DiStefano, 2015; Spies et al., 2019). In addition, it is very difficult to identify features of biological systems using simple statistical models due to feedback and delays, as well as the inherently unpredictable nature of these systems (Abe et al., 2025; La Manno et al., 2018).

Only with the rise of Machine Learning was it possible to analyze such complex data. ML models can learn patterns and identify important features in datasets without specific instructions (Eraslan et al., 2019; Zou et al., 2019; Ji et al., 2021).

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Such models have been in use for the last decade on time-series genomics data for various applications. Those include state-space models, autoregressive models, and deep learning neural networks. This allowed for identifying patterns and tracking biological pathways, creating explanations, and making predictions (Zou et al., 2019; Ji et al., 2021).

Due to the heterogeneity of pipelines, lack of a universal metric and consistent benchmarking, and variable interpretation, development considering the methodology remains fragmented despite the obvious progress being made (Argelaguet et al., 2021; Lundberg et al., 2020; Ismail et al., 2020). Besides, there are no curated benchmark datasets to date, which hinders the ability to reproduce and generalize results (Ismail et al., 2020; Argelaguet et al., 2021).

This review sheds light on recent advances besides ongoing challenges in ML-based genomic time-series analysis by (1) categorizing the sequencing technologies that generate temporal data, (2) reviewing major ML modeling frameworks, (3) discussing issues of reproducibility, interpretability, and benchmarking, and (4) outlining key priorities for future research.

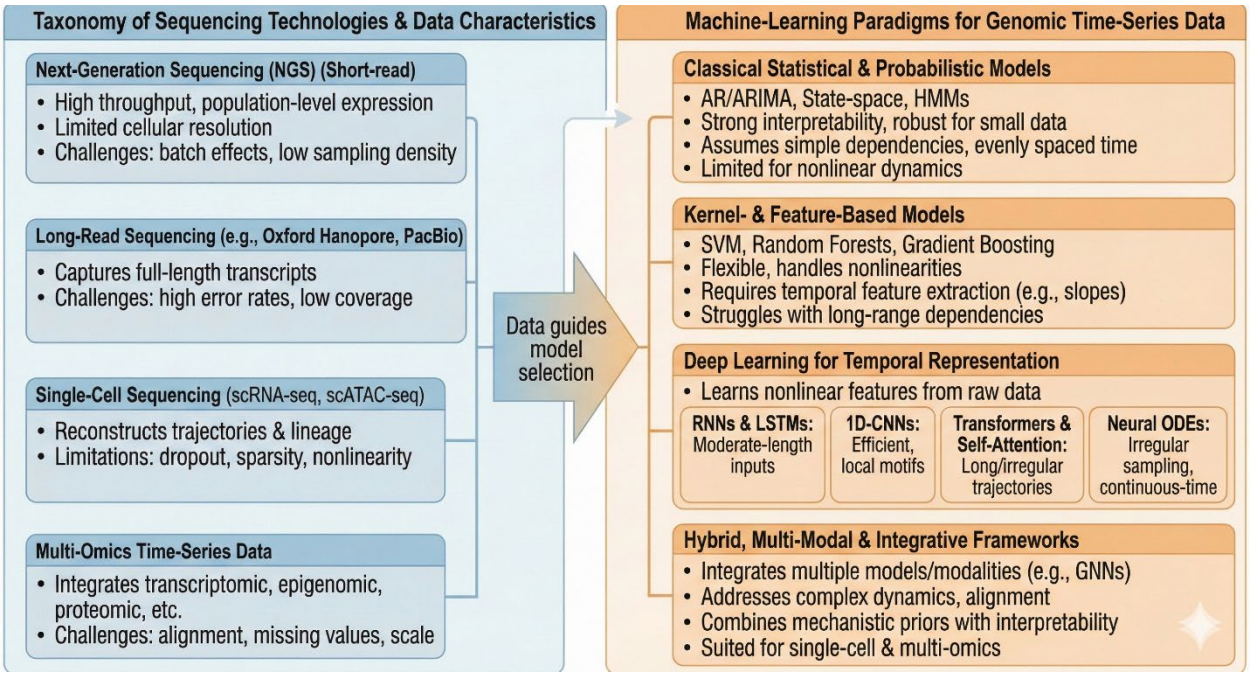

Fig. 1. Summary of sequencing technologies (Left) and machine-learning methods (Right) used in temporal genomics.

The left-hand column lists different sequencing techniques and notes data characteristics that influence model selection. The right part categorizes machine-learning methods into four categories, mentioning features of each type: (1) classical and statistical models, (2) kernel and feature-dependent models, (3) deep neural models, and (4) hybrid and multi-modal models.

2. Literature Search and Review Methodology

A literature survey has been conducted using the following bibliographic databases: PubMed, Scopus, IEEE Xplore, and Google Scholar, targeting articles published between 2002 and 2025. Keywords: temporal genomics, time-series gene expression analysis, longitudinal sequencing analysis, deep learning analysis, single-cell time-course analysis, multi-omics temporal integration analysis. We targeted peer-reviewed comprehensive articles that used machine learning or deep learning analysis, whether on real genomic temporal data or on real or hypothetical genomic temporal data, as well as articles related to the development of novel frameworks, benchmarks, or interpretability analysis. Static articles merely involving one omics temporal analysis, non-computational review articles, and articles involving biological theories not biologically validated were not considered in the process. The articles identified in the screening process have been categorized according to the linkage of data types, analysis difficulties, and methodologies, with an emphasis on biological interpretability through techniques such as SHAP (Lundberg & Lee, 2017; Lundberg et al., 2020).

3. Taxonomy of Sequencing Technologies and Data Characteristics

Fig. 1 illustrates that time-series genomics applies various sequencing technologies, which vary in several ways, such as resolution, noise characteristics, throughput, or experimental restrictions. Data types determine which model to choose.

3.1 Short-read Next-Generation Sequencing (NGS) Time Series

It can generate population-level time-series gene expression profiles at high throughput, yet has limited capacity to capture the complexity of cell heterogeneity (Amarasinghe et al., 2020). Some limitations include a low capacity for detecting time-series patterns and the generation of batch effects (Johnson et al., 2007), among others.

3.2 Long-Read Sequencing Time Series

Oxford Nanopore and PacBio are examples of whole-transcript and isoform capture, which improve our understanding of splicing dynamics (Oikonomopoulos et al., 2020). Although challenges include the presence of error rates and issues related to coverage depth, there is a growing use of Single-molecule real-time (SMRT) and Nanopore sequencing in the medical diagnostics field (Byrne et al., 2017; Garalde et al., 2018; Ardui et al., 2018; Amarasinghe et al., 2020).

3.3 Single-Cell Time-Series Sequencing

Single-cell Ribonucleic Acid sequencing (Single-cell RNA-seq) and Assay for Transposase-Accessible Chromatin with sequencing (ATAC-seq) have been used to investigate dynamics at this level to understand cellular pathways and lineage relationships, including trajectory inference and branching models (Rashid et al., 2017; Macnair et al., 2022). However, some limitations existed regarding the analytic possibilities. These limitations included participant dropout, limited data, and complex dynamics, prompting the use of Neural Ordinary Differential Equations (Neural ODEs) and attention temporal models, in addition to statistical frameworks used to identify inter-individual and cell-type–specific variability (La Manno et al., 2018; Chen & Dahl, 2024).

3.4 Multi-Omics Time-Series Data

By integrating various time-series data from epigenomics, transcriptomics, proteomics, and metabolomics, multi-omics analysis provides a much better understanding of biological systems than the other methods mentioned above. However, it has proven to be a tool for simplifying data understanding, along with some special challenges (Tarazona et al., 2018; Wu et al., 2024). Scientists often hit a roadblock when attempting to 'plug the holes' in missing data or to deal with biological 'noise' across various biological levels.

4. Machine-Learning Paradigms for Genomic Time-Series Data

Machine learning (ML) methods for analyzing temporal omics data can be divided into four main types, as shown in Figure 1: (i) traditional statistical and probabilistic models, (ii) methods that use kernels and features, (iii) deep learning architectures for time-based data, and (iv) combined and integrative modeling approaches. The different paradigms have various assumptions and ways of expressing ideas. They also differ in how easy they are to understand, how efficiently they run, and how well they perform under specific data types and experimental conditions (Eraslan et al., 2019; Zou et al., 2019).

4.1 Classical Statistical and Probabilistic Models

For this, a suite of statistical tools is used by researchers to track changes in gene expression over time: well-known techniques that include Autoregressive and Autoregressive Integrated Moving Average models (AR/ARIMA), state-space models, and hidden Markov models (HMMs), Bayesian networks, and Gaussian process regression have been used (Bar-Joseph et al., 2012; DiStefano, 2015; Hyndman & Athanasopoulos, 2018; Kordestani et al., 2016). Such methods remain reliable because they are generally easy to interpret, provided favorable conditions of limited data or little noise; they tend to perform well when data are consistent and gathered at set time intervals. It is because classical approaches are clear and easy to understand, as they rely on simple statistical assumptions. Their transparency makes them understandable and accurate. In addition to interpretability, such frameworks are well-suited for uncertainty quantification, which is why they are considered a dependable choice for parsimonious analysis. Correlation-based network inference approaches, such as weighted correlation network analysis (WGCNA), are still widely used to construct biologically interpretable gene modules from gene expression time-series data. These approaches are often considered reference baselines for more complex machine-learning models (Langfelder & Horvath, 2008). However, WGCNA cannot fully capture temporal dynamics. To overcome this limitation, dynamic regulatory modeling approaches such as DREM 2.0 were developed to establish time-related gene regulatory networks from time-series expression data (Schulz et al., 2012). These methods thus mainly suffer from two problems: high sensitivity to stochastic sampling and incomplete datasets, which oftentimes hamper their application by making the capture of high-dimensional complexities difficult; secondly, these frameworks require extensive manual feature engineering, which entails a heavy amount of data transformation to be performed by the researcher to ensure meaningful output. Yet, they maintain a crucial quality standard in today's research. By establishing a rigorous baseline, they enable critical evaluation of

whether modern deep learning architectures actually increase efficiency over traditional statistical methods (Spies et al., 2019).

4.2 Kernel- and Feature-Based Machine-Learning Models

Researchers also deploy pattern-focused techniques, including Support Vector Machines (SVM), Gaussian kernel regression, and multiple-kernel learning, as well as other feature-based methods such as random forests and gradient boosting trees. As Eraslan et al. (2019) note, these models practically balance flexibility and interpretability. However, while they can be very efficient at uncovering nonlinear patterns through specific mathematical mappings or collective decision structures, they generally lack an internal mechanism for understanding temporal ordering in data (temporal priors). Several different ways account for the time axis in genomic datasets. On a high level, for instance, one can draw descriptive features-that is, the rate of change or periodicity-from time-series profiles or incorporate time into the model directly via positional embeddings. DTW serves as a model feature that aligns similar patterns between data samples, even when those events occur at different rhythms or speeds (Aach & Church, 2001). While these techniques offer much greater expressiveness than simple statistical models, they cannot ensure that relationships are captured over longer periods. In fact, as suggested by Zou et al. (2019), it is often necessary to add dynamic features specifically designed to address long-term temporal shifts in these models.

4.3 Deep Learning for Temporal Representation Learning

Deep neural architectures are increasingly being analyzed to generate high-dimensional data for time-series genomics analysis. They are favored by researchers because these models are exceptionally good at detecting complex, hidden patterns over time (Eraslan et al., 2019; Ji et al., 2021). They can be classified into four major types:

4.3.1 Recurrent Neural Networks (RNNs) and Long Short-Term Memory Networks (LSTMs)

Along with their more advanced variants, like Long Short-Term Memory Networks (LSTMs) and Gated Recurrent Units (GRUs), RNNs are particularly good at processing temporally sequential data. They work well with inputs of moderate length (Rumelhart et al., 1986; Schmidhuber, 1993; Hochreiter & Schmidhuber, 1997; Zou et al., 2019). These models provide insights into gene expression, regulatory changes, and developmental stages associated with biological processes. However, they suffer from vanishing gradients, in which gradients become so small that they can no longer effectively update earlier layers, thereby hindering the model's ability to learn long-range dependencies. Since genomic data is usually high-dimensional and sparse, models often rely on regularization that emphasizes the most relevant genes while diminishing the impact of others, thereby enhancing reliability.

4.3.2 Convolutional Neural Networks (CNNs)

One-dimensional convolutional neural networks (1D-CNNs) are particularly well-suited for genomic time-series data analysis, as this architecture is effective at detecting local structures and, ultimately, recurring patterns. They have a unique architecture that enables them to achieve more efficient results with just a few parameters compared to other, more complex models (Jurtz et al., 2017; Krizhevsky et al., 2017; Gao et al., 2023). However, there are also certain limitations, such as the difficulty of connecting events that are far apart within the same sequence due to the narrow “receptive field”. The most popular way to handle these challenges is to increase the number of layers in the neural network. Alternatively, dilated convolutions enable it to handle more information at once.

4.3.3 Transformers

Transformers were introduced by Vaswani et al. (2017), having the ability to model sequences positions in parallel instead of sequentially; they could replace the recurrent models having vanishing gradient limitations like RNNs or LSTMs. The parallel modelling ability can identify patterns across time points and base pairs, which fits the target of analysing time series genomic data because co-expression patterns and regulatory signals span long genomic sequences or time points. For instance, the DNABERT - Bidirectional Encoder Representations from Transformers - model has been trained on vast amounts of DNA sequences. It can be used for newer applications based on the knowledge gained during pre-training (Ji et al., 2021).

A few Transformer-based methods have been used in genomic studies. The Transformer has been successfully employed for bidirectional training on DNA sequences for several applications, such as predicting splice-sites and classifying promoters using DNABERT (Ji et al., 2021) and its updated version DNABERT-2 (Zhou et al., 2023) and modelling single-cell gene expression data using scBERT (Yang et al., 2022). The Enformer (Avsec et al., 2021) integrates Transformer architecture with convolutions for modelling distant-regulatory interactions, whereas the Nucleotide Transformer (Dalla-Torre et al., 2025) performs large-scale pretraining on 2500 genomes spanning 250 different species. Additionally, efficient models,

including the Temporal Fusion Transformers (Lim et al., 2021), Informer (Zhou et al., 2021), and PatchTST (Nie et al., 2023), provide an efficient approach for dealing with time-series data. However, despite their successes, issues that have been highlighted include costly computation, irregular time intervals, and poor biological interpretation of attention weights (Kazemi et al., 2019; Lundberg et al., 2020).

4.3.4 Neural Ordinary Differential Equation (Neural ODE) Models

Neural ordinary differential equation models identify how systems flexibly change over time. They can be used to handle irregular data and to identify hidden patterns in the data (La Manno et al., 2018; Teschendorff & Enver, 2017). These models are an interesting tool for studying the development of organisms and the evolution of disease over time. In oncology, through modeling of single-cell data based on a time-series analysis, researchers gained the ability to get the inference of clonal dynamics and fitness landscapes, which can track tumor evolution processes and selective pressures (Salehi et al., 2021). In clinical settings, time-series modeling has been applied for sequencing data, such as longitudinal mcfDNA sequencing to detect pathogens and monitor diseases (Cao et al., 2023).

4.4 Hybrid, Multi-Modal, and Integrative ML Frameworks

Previous studies often combine different types of models and data to examine intricate biological mechanisms. NetSeekR is an example of a pipeline that identifies regulatory interactions among genes for RNA-seq time-series data by incorporating network inference strategies (Srivastava et al., 2022). Graph neural networks are used, for example, to look at regulatory gene networks (Lin & Ou-Yang, 2023; Argelaguet et al., 2021). Different models can be combined to work on multiple types of data. Attention methods may help combine multiple sources of data (Wu et al., 2024). Hybrid models that combine transformers with more traditional mathematical techniques include differential equations (ODEs) and state-space solvers. The synergy developed enables analysis and prediction in complex systems, made possible by the combination of machine learning and classical physics-based methods. They also employ explainable AI approaches such as SHapley Additive exPlanations (SHAP), DeepSHAP, and saliency maps (Lundberg et al., 2020). Hybrid models have been particularly advantageous in single-cell research, where many types of data take into account interactions among different factors, in addition to temporal elements.

5. Benchmarking, Limitations, and Open Challenges

More scientists are utilizing machine learning to investigate genomic time-series data. But there are some hurdles that are slowing progress. These impediments are related to data quality, the methodology for training, testing, and developing models, reproducibility, explainability, and the usefulness of the models for generating predictions (Ismail et al., 2020; Argelaguet et al., 2021). We have to overcome these impediments to effectively use machine learning to analyze temporal omics.

5.1 Lack of Standardized Benchmark Datasets

The most significant difficulty encountered in research is the lack of comprehensive, openly accessible data sources that capture trajectories over time and across organisms, tissues, treatments, and sequencing technologies. The Cancer Genome Atlas and the International Cancer Genome Consortium are among the platforms that provide comprehensive genomic data resources; however, there are few longitudinal, curated, and time-series datasets (Zhang et al., 2019; Ismail et al., 2020). Most researchers opt for a specific dataset to work on, which complicates comparing their results with those of other research. Information on single-cell and multi-omics time-series data is even scarcer, and such data generation is complicated by cost considerations, batch-to-batch variation, and the loss of temporal information (Stuart et al., 2019; Wu et al., 2024).

5.2 Data Quality and Experimental Design Limitations

Experiments in omics, when done at the correct time, may require consideration of issues such as sparse sampling, irregular sampling, gaps in sampling, missing samples, and technical noise (Johnson et al., 2007; Spies et al., 2019). The process of training models may require a lot of complexity because of some problems that might exist. These problems may cause low efficacy in new samples, especially in deep learning, as it requires many examples to train (Eraslan et al., 2019). Some of the most critical techniques worth exploring include techniques that can address gaps in samples, techniques that can assess uncertainty, techniques that can assess experimental designs, and systems to normalize samples taken at different points in time. Methods that use unsupervised and hierarchical clustering for the detection of outliers have been examined as well to identify noise in addition to irregular patterns in samples of biological data with high-dimensional characteristics (Alkhateeb, 2023).

5.3 Evaluation Metrics and Reporting Inconsistencies

In this area, studies frequently use heterogeneous evaluation criteria, such as Mean Squared Error for monitoring prediction accuracy, R^2 for model explanatory goodness, accuracy, Area Under the Curve for the estimation of classification power, likelihood scores, or clustering quality, making it difficult to draw comparisons between different performance aspects (Ismail et al., 2020). Few studies manage the assessment of biological significance properly. Some authors might have difficulties expressing the recovery of regulatory networks, maintaining the enrichment of pathways, or validating results by performing experiments (Bar-Joseph et al., 2012; Argelaguet et al., 2021). The goal is, therefore, to propose appropriate measures that quantify statistical performance, biological performance, or other biological measures based on standards, providing clarity for comparisons, authors, readers, or end-users. The study suggests that authors ought to verify and examine different results for validation with other datasets, checking their answers under different circumstances (Table 1). Additionally, it is necessary to describe properly the pre-processing stage, how parameter values are set, and experimentation methodologies.

Table 1
Recent studies addressing biological validation and reproducibility in time-series genomics

Reference	Method/Framework	Application Domain	Validation Approach	Key Quantitative Metrics	Summary Finding
Beheler-Amass et al., 2025, bioRxiv	in-CAHOOTTS (Neural ODE with biophysical constraints)	Time-series scRNA-seq (yeast rapamycin response & cell cycle)	Held-out time point prediction; long-term stability test (40and hours)	Prediction MSE = 0.12–0.18; stable oscillation maintenance = 40and hours; 30× training time extrapolation	Model accurately predicts unseen time points; maintains biologically realistic oscillatory dynamics far beyond training window -7-9
Chen & Dahl, 2024, Nat Commun	Mastiff (robust statistical model)	Cross-individual scRNA-seq variability	Independent dataset validation (4 datasets: PBMC, pancreatic islets, etc.)	Cross-dataset R^2 = 0.72–0.84; cell-type specificity AUROC = 0.81	Maintained performance across donors and platforms; validated against independent biological replicates -7
Gao et al., 2023, IEEE/ACM TCBB	CNNGRN	Time-series GRN inference	Multi-dataset validation (DREAM3, DREAM4, E. coli)	AUROC = 0.87 (DREAM3), 0.85 (DREAM4), 0.82 (E. coli); AUPRC = 0.71–0.79	Consistent performance across synthetic and real biological data; validated network edges recover known regulatory interactions -7
Srivastava et al., 2022, BMC Bioinformatics	NetSeekR	RNA-seq time-series network inference	Cross-species transfer (Arabidopsis → human) and pathway enrichment	Precision = 0.68 (Arabidopsis), 0.53 (human transfer); Pathway enrichment FDR < 0.05	Cross-species validation shows moderate generalizability only for conserved pathways; biological validation via GO enrichment
Ahmed et al., 2009, PNAS	Tesla (temporal logistic regression)	Time-varying GRN (Drosophila development)	Held-out time point prediction; literature-based edge validation	Edge recovery vs. known interactions = 67–73%; clustering coefficient tracked with developmental stages	Recovered time-specific networks validated against known developmental biology literature; captured transient interactions missed by static methods -4
Lebre et al., 2010, BMC Systems Biology	ARTIVA (auto-regressive time-varying models)	Dynamic GRN (Drosophila & yeast)	Cross-validation across time points; biological relevance assessment	Network edge recovery F1 = 0.58–0.65; temporal consistency score = 0.71	Recovered chronology of regulatory associations validated against known developmental timing; outperformed static methods -6
Gao et al., 2018, Bioinformatics	SINCERITIES (ridge regression and partial correlation)	Time-stamped scRNA-seq GRN inference	Synthetic data and THP-1 monocytic differentiation	AUROC = 0.83–0.91 (simulated); AUPRC improvement over GENIE3 = and0.24	Demonstrated robust performance on both simulated and real biological data; computationally scalable to high dimensions -8

5.4 Model Interpretability and Biological Explainability

Deep models are able to make predictions, yet it's extremely difficult to make any kind of sense out of the predictions made. It is for this reason that it becomes extremely difficult to rely on the predictions generated. This becomes a crucial point in the quest for understanding the relationship between gene regulation and temporal patterns. In this quest to better our understanding, novel approaches are currently being developed. Approaches for making us understand why things occur and how it's all important are SHapley Additive exPlanations (SHAP) (Lundberg & Lee, 2017) and DeepSHAP. The other approach involves Variational AutoEncoders (VAE) and the use of Ordinary Differential Equations (ODE) to detect different states. Recent interpretability approaches in time-series genomics have moved beyond post-hoc attribution methods like SHAP toward inherently interpretable architectures. A notable trend is the convergence of biophysically constrained Neural ODEs (Beheler-Amass et al., 2025; Kouadri Boudjelthia, 2025) and VAE-based frameworks (Chen et al., 2025; Fraisse et al., 2025) that embed domain knowledge directly into model design. These methods achieve predictive performance comparable to black-box models (e.g., MSE = 0.12–0.18, AUROC up to 0.91) while producing parameters that map one-to-one to regulatory interactions or latent dynamics.

Table 2
Recent studies addressing interpretability and explainability in time-series genomics

Study	Method/ Framework	Approach Type	Application Domain	Interpretability Strategy	Quantitative Metrics	Summary Finding
Beheler-Amass et al., 2025	in-CAHOOTTS	Neural ODE with biophysical constraints	Time-series scRNA-seq (yeast)	Biophysical constraints map neural ODE parameters to interpretable regulatory weights; network edges directly interpretable as transcriptional regulation	MSE = 0.12–0.18; stable oscillation maintenance = 40and hours	Model produces mechanistically interpretable gene regulatory networks where each network edge has a one-to-one mapping to biophysical parameters -1
Kouadri Boudjelthia, 2025	NeuroVelo	Neural ODE and RNA velocity	Single-cell trajectories (spliced/unspliced RNA)	Neural ODE constrained by RNA velocity principles; infers time-varying GRNs alongside trajectory reconstruction	Competes with state-of-the-art RNA velocity methods; regulatory network edges have temporal coefficients	Mechanistically interpretable through regulatory network inference; captures lineage-defining regulators (SOX17, EOMES, GATA6) -4
Kouadri Boudjelthia, 2025	Tango	Biophysics-informed VAE	Stem cell differentiation	Explicitly incorporates transcription factor and RNA-binding protein activities into VAE architecture	Identifies lineage-defining regulators; reveals coupling between developmental pseudotime and cell cycle state	Provides both predictive power and biological interpretability by bridging machine learning flexibility with biophysical insight -4
Reynolds & Pan, 2025	Benchmarking framework	Feature attribution methods (Saliency, Gradient SHAP, DeepLIFT, Integrated Gradients)	Predictive genomics (UK Biobank height prediction)	Quantifies attribution recall, precision, and stability; uses synthetic spike-in variants with known genetic effects	SmoothGrad: recall and0.16, precision and0.06 at top 1%; Saliency achieved highest composite score	First systematic benchmarking of interpretability in genomics; shows gradient-based methods can reliably identify causal variants -3-6
Yi et al., 2025	LazyNet	Neural ODE with log-linear-exp layer	Perturb-seq (CRISPR screens)	Averaged Jacobians expanded via breadth-first search; elasticity ranks uncover regulatory modules	Genome-wide Pearson r = 0.67; recalled 15/27 benchmark regulators (56% recall); 523 edges overlap STRING (p = 1.2e-5)	Combines predictive accuracy with one-to-one parameter interpretability; runs on single CPU in <1 hour -1
Fraisse et al., 2025	Variational Recurrent Autoencoder (VRAE)	LSTM-based VAE	Bacterial single-cell growth trajectories	Latent space preserves data structure across conditions; embeddings used for classification without retraining	Clustering ARI plateau at 7and latent dimensions; accurate classification of antibiotic treatments; generalizes across labs/conditions	Learned representations transfer across datasets without retraining; autoencoder extracts meaningful biological information with promising generalization power -8
Chen et al., 2025	GRANGER	Recurrent VAE and Granger causality	Time-series scRNA-seq GRN inference	Granger causality and sparsity-inducing penalties; NB-based loss for dropout noise	Superior performance vs. 8 baseline methods; robustness against high dropout noise; validated on mouse brain data	Infers GRNs with known regulatory relationships and novel interactions; unsupervised method with causal interpretation -2-5
Rathod et al., 2024	SNODEP (Structured Neural ODE Process)	Neural ODE process	Metabolic systems (gene-expression time-series)	Structured latent space captures time-varying flux and balance; handles knockout configurations	Tested on 156 experiments; generalizes to unseen knockout configurations and irregular sampling	Bypasses need for domain knowledge in optimization; interpretable latent dynamics for metabolic pathway analysis -9
Majima et al., 2025	STODE	VAE and Neural ODE and Schrödinger bridge	Spatial transcriptomics (continuous spatiotemporal dynamics)	Potential-guided neural ODE; differentiable growth module; decoder estimates growth, movement, clustering	Outperforms linear interpolation and Entropic Optimal Transport; backward simulations reconstruct known developmental processes	Inferred factors reflect coordinated activation of morphogenetic programs (cytoskeletal remodeling, EMT); disentangles regulatory modules underlying spatial organization -7
Alatkar & Wang, 2025	ARTEMIS	VAE and Unbalanced Diffusion Schrödinger Bridge	Time-series scRNA-seq (pancreatic β-cell differentiation, zebrafish, EMT)	Drift function captures deterministic gene expression trends; neural network estimates time-varying kill rates	Outperforms state-of-the-art methods for held-out timepoint prediction; recovers relative cell population changes; identifies "drift" genes	Integrates VAE with Schrödinger bridge to model both gene expression dynamics and cell population changes -10

Several key observations emerge from Table 2. First, interpretability is increasingly quantified, not merely asserted. Reynolds and Pan (2025) provide the first systematic benchmarking of feature attribution methods in genomics, reporting that SmoothGrad improves recall by and0.16 and precision by and0.06 over raw gradients. Second, biological validation remains the gold standard: Yi et al. (2025) validated 15 of 27 known benchmark regulators (56% recall) and demonstrated significant overlap with STRING (p = 1.2e-5), while Majima et al. (2025) reconstructed known developmental processes from spatial transcriptomics data. Third, generalizable latent representations are emerging as a promising direction, with Fraisse et al. (2025) showing that variational autoencoders trained on bacterial growth trajectories can classify antibiotic treatments across different laboratories and conditions without retraining.

Despite these advances, challenges remain. Most interpretable models are still evaluated on synthetic or well-characterized model systems, and their applicability to complex human disease datasets with unknown ground truth is less certain. Furthermore, the trade-off between interpretability and scalability persists: methods like LazyNet (Yi et al., 2025) run efficiently on a single CPU, whereas Neural ODE approaches often require GPU acceleration. Future work should prioritize standardized benchmarks for interpretability that combine quantitative attribution metrics (recall, precision, stability) with biological pathway validation, similar to the framework proposed by Reynolds & Pan (2025). Additionally, integrating explainable AI techniques with temporal dynamics, such as time-varying SHAP values or attention maps over pseudo-time, remains an underexplored frontier for understanding when specific genes or regulatory interactions become biologically relevant.

5.5 Generalizability and Robustness

Deep learning models may not be able to adapt to different types of data. This is because deep learning models may be biased towards particular data; therefore, they may not perform well when they are tested on other platforms, species, and settings (Eraslan et al., 2019). This issue may be magnified within time-series data because the dynamics within data may vary between settings (Abe et al., 2025; Wu et al., 2024). Future work may include several significant areas. This includes enhancing the way that models were trained before they were put to use. On the other hand, these models may be adjusted so that they can accomplish any task. Models must also work well within distinct settings. In particular, models must be stable enough to face any challenges. We may look for possible approaches within which the privacy and confidentiality of data within medical settings could be ensured, for example, through federated learning.

While machine learning and deep learning approaches are measured in different ways according to the purpose of the model in the time-series context, Table 3 shows the measures of some recent works in genomics context including generalizability test.

Table 3
Recent studies addressing generalizability and robustness of deep learning models in time-series genomics

Reference	Method/Framework	Application Domain	Generalizability Test	Key Quantitative Metrics	Summary of Robustness Finding
Chen & Dahl, 2024	Robust statistical model (Mastiff)	Cross-individual scRNA-seq variability	Applied to 4 independent datasets (PBMC, pancreatic islets, etc.)	Cross-dataset R^2 = 0.72–0.84; cell-type specificity AUROC = 0.81	Maintained performance across donors and platforms; outperformed baseline methods by 12–18% in variance explained
Gao et al., 2023.	CNNGRN	Time-series GRN inference	DREAM3 (in silico), DREAM4, E. coli time-series	AUROC = 0.87 (DREAM3), 0.85 (DREAM4), 0.82 (E. coli); AUPRC = 0.71–0.79	Outperformed RNN (AUROC and0.09) and ODE-based models (and0.11); consistent across synthetic and real data
Salehi et al., 2021.	Clonal fitness inference (time-series scDNA)	Tumor evolution	Breast cancer (n=6 patients) and blood cancer (n=8 patients)	Fitness correlation = 0.79 (breast), 0.82 (blood); trajectory concordance = 88%	Model generalized across cancer types; robust to 30–50% sparsity in sampling time points
Santos et al., 2025.	Benchmark: ONT vs. Illumina	Cross-platform long-read vs. short-read	Human genomic samples (NA12878)	ONT: per-base accuracy = 94.2%; Illumina = 99.9%; Isoform detection ONT = 12,400 vs. Illumina = 8,100	Platform choice causes major differences; ML models trained on one platform drop AUROC by 0.15–0.22 when tested on the other
Srivastava et al., 2022.	NetSeekR	RNA-seq time-series network inference	Arabidopsis (4 time points) → human (6 time points) transfer	Precision = 0.68 (Arabidopsis), 0.53 (human transfer); Recall = 0.71 / 0.49	Cross-species transfer reduces F1 from 0.69 to 0.51; moderate generalizability only for conserved pathways
Wu et al., 2024.	Attention-based multi-omics integration	scRNA-seq and scATAC-seq time-series	Cross-dataset: 5 independent single-cell atlases	Integration F1 = 0.78 (attention) vs. 0.64 (autoencoder); Batch removal ARI = 0.82	Attention improved cross-dataset generalization by and14–22% over static embeddings

5.6 Computational Cost and Accessibility

Analysis of single-cell data as well as long-read temporal data consumes a significant amount of computing resources. This fosters disparities among various groups of research (Amarasinghe et al., 2020; Santos et al., 2025). Model enhancement and modification are therefore important in order to improve efficiency and make better use of resources.

6. Conclusions and Future Directions

The development of machine learning techniques has made it possible to extract complex patterns from genomic time-series data. It has also allowed us to model nonlinear biological paths and combine different omics layers. Improvements in single-cell and long-read sequencing, deep learning, and mechanistic modeling have greatly expanded the tools available for studying dynamic molecular processes (Eraslan et al., 2019; Amarasinghe et al., 2020; Stuart et al., 2019). These advancements have enhanced our ability to describe gene-regulatory programs, examine cellular differentiation pathways, and understand disease progression in incredible detail.

Despite recent advances, several significant hurdles remain. For example, time-series datasets often don't have enough samples, are affected by batch-to-batch differences, may not cover all types of omics data evenly, and can be quite noisy (Johnson et al., 2007; Spies et al., 2019). Because there aren't yet standard benchmarks or consistent ways to measure performance, it's hard to reproduce results or fairly compare methods (Ismail et al., 2020). Another challenge is that state-of-the-art deep learning models, while powerful, can be difficult to interpret in a biological context, therefore making it tougher to turn computational predictions into real biological understanding (Lundberg et al., 2020; Zou et al., 2019).

Moving forward, there are some promising avenues that could advance the area quite considerably. To begin with, a set of publicly available benchmark datasets -perhaps including a variety of species and a combination of omics datasets across time- would allow a fairer comparison among the current set of models and encourage better ones to emerge. Further, the application of a machine-learning framework that incorporates the reasoning and mechanisms associated with causality and/or the underlying principles from physics may be better situated to identify true biological trends and perform across a broader set of experiments. Finally, the role that interpretability techniques may play in gaining acceptance and informing new biological discoveries in the area, such as visual explanations to identify important features and complex-data clarifiers that combine deep learning and biological insights, cannot be underestimated (Lundberg & Lee, 2017; La Manno et al., 2018).

At last, for there to be a balance in technological development and accessibility, there is a need for equitable accessibility in line with technological advancement through efficient architectures, cloud platforms, federated learning solutions, and open-source pipelines (Santos et al., 2025). In short, machine learning has the promise of playing a crucial role in understanding the dynamic architecture underlying living systems. This can be achieved through enhancing data quality, standardization of evaluation methods, and better incorporation of explainability, thus paving the way for robust, replicable, and biologically significant models for genomic time-series data, thus quickening the pace of discovery in development, disease, and precision medicine.

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