RESEARCH-ARTICLE

Gene Regulatory Network Inference from Pseudotime-Ordered scRNA-seq Data via Time-Lagged Divergence Measures

Published: 19 September 2025

ICBRA 2025: The 12th International Conference on Bioinformatics Research and Applications
September 19 - 21, 2025
Prague, Czech Republic

ICBRA '25: Proceedings of the 12th International Conference on Bioinformatics Research and Applications (September 2025)
https://doi.org/10.1145/3774976.3774995
ISBN: 9798400715808

Gene Regulatory Network Inference from Pseudotime-Ordered scRNA-seq Data via Time-Lagged Divergence Measures

Lingling Zhang*
Department of Mathematics
State University of New York at Brockport
Brockport, NY, USA
lzhang@brockport.edu

Tong Si*
Department of Health and Clinical Outcomes Research
Saint Louis University
St. Louis, MO, USA
tong.si@slu.edu

Lucas Koch
Department of Mathematics and Statistics
Saint Louis University
St. Louis, MO, USA
lucas.koch@slu.edu

Haijun Gong*
Department of Mathematics and Statistics
Saint Louis University
St. Louis, MO, USA
haijun.gong@slu.edu

Abstract

Inferring cell type-specific gene regulatory networks (GRNs) from time-series single-cell RNA sequencing (scRNA-seq) data is challenging due to sparse temporal resolution, high dimensionality, and inherent cellular heterogeneity. We present a novel integrative framework, called PseudoGRN, that unifies multiple pseudotime inference methods, different time-lagged divergence measures, non-redundant penalized network inference, and partial correlation analysis to reconstruct directed GRNs from time-series scRNA-seq data. Applying our method to the real-world scRNA-seq dataset, we demonstrate its superior performance over existing approaches, offering a robust and interpretable tool for uncovering dynamic regulatory mechanisms in single-cell systems.

CCS Concepts

• **Applied Computing** → **Bioinformatics**.

Keywords

Gene Regulatory Network, scRNA-seq Data, f-Divergence, Pseudotime Analysis, Integral Probability Metric, Partial Correlation

ACM Reference Format:
Lingling Zhang, Tong Si, Lucas Koch, and Haijun Gong. 2025. Gene Regulatory Network Inference from Pseudotime-Ordered scRNA-seq Data via Time-Lagged Divergence Measures. In *The 12th International Conference on Bioinformatics Research and Applications (ICBRA 2025), September 19–21, 2025, Prague, Czech Republic.* ACM, New York, NY, USA, 5 pages. https://doi.org/10.1145/3774976.3774995

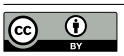
1 Introduction

Single-cell RNA sequencing enables gene expression profiling at single-cell level, allowing researchers to identify distinct cell states, uncover differentiation trajectories, and investigate dynamic cellular processes [9, 13]. Analysis of scRNA-seq data has greatly deepened our understanding of complex biological processes and opened new avenues for the development of personalized medicine [27]. In particular, time-series scRNA-seq data further provides temporal information that can be used to reconstruct cell type-specific gene regulatory networks (GRNs) and investigate dynamic transcriptional regulation [5]. A variety of machine learning methods have been developed for GRN inference from omics data, including scRNA-seq, including Boolean networks [11], differential equation models [14], correlation networks [4], dynamic Bayesian networks [1, 18], regression-based frameworks [16, 28], and deep learning approaches [22, 24]. Most of these methods are based on canonical time, which reflects the actual chronological progression of molecular events. A major challenge in time-series scRNA-seq data analysis is the limited number of discrete time points, which reduces the temporal resolution and complicates the GRNs inference.

To address the challenges of network inference from time-series scRNA-seq data, particularly the sparse temporal sampling, and intrinsic cellular variability, pseudotime analysis [19] has emerged as a critical preprocessing step. Also known as trajectory inference, pseudotime methods estimate the relative progression of individual cells by ordering them along a continuous trajectory based on similarities in their gene expression profiles. This approach provides a high-resolution temporal framework that approximates dynamic biological processes without relying on explicitly measured time points. A variety of pseudotime inference methods have been developed to reconstruct cellular trajectories from single-cell transcriptomic data. These include graph-based approaches such as Monocle [26], Slingshot [23], PHATE [15], diffusion-based methods like Diffusion Pseudotime (DPT) [8] and Diffusion Maps [7], as well as probabilistic and velocity-based models such as scVelo [2].

Recently, Zeng et al.'s work [30] proposed a method called Normi, which integrates the Slingshot pseudotime algorithm with mutual information to infer gene regulatory networks. Normi has demonstrated promising performance, however, it also has several notable limitations. A major issue is the assumption that regulatory effects can have long time delays, suggesting that a gene's expression may be influenced by distant past events, an idea often inconsistent with biological evidence. Most studies support the first-order Markov

*Corresponding authors



ICBRA 2025, Prague, Czech Republic

ACM ISBN 979-8-4007-1580-8/25/09
https://doi.org/10.1145/3774976.3774995

property [6], where the current state depends primarily on the immediate past. Thus, a time lag of one is typically sufficient and biologically more plausible for modeling regulatory dependencies [28]. Moreover, the estimation of the optimal time lag in Normi is computationally intensive, significantly limiting its scalability to larger datasets. Another limitation lies in its reliance on mutual information (MI) to infer regulatory relationships. Since MI is symmetric, it cannot capture directionality and is thus unsuitable for inferring causal interactions. Moreover, methods like Normi cannot distinguish between activation and inhibition, critical features of gene regulation, leading the inferred networks to resemble directed correlation networks rather than true regulatory networks.

To address these limitations, we propose a novel integrative framework, called PseudoGRN, that incorporates multiple pseudotime inference strategies, time-lagged f-divergence and integral probability metrics (IPMs), penalized non-redundant edge selection and partial correlation analysis within a unified platform for reconstructing directed gene regulatory networks from time-series scRNA-seq data. The remainder of this paper is organized as follows. Section 2 introduces the proposed methodology and algorithm. In Section 3, we evaluate the performance of our approach using real-world scRNA-seq datasets. Finally, Section 4 concludes the paper with a discussion of the results and directions for future research.

2 Methods

The time-series single-cell RNA sequencing dataset at any given time point t can be represented by a matrix $\mathbf{X}^{(t)} \in \mathbb{R}^{m\times n}$, where m denotes the number of genes and n denotes the number of cells. Our aim is to reconstruct the regulatory networks from the time-series scRNA-seq data. Since cells captured at the same experimental time point can be at different stages of biological progression, relying solely on discrete time points may obscure the true temporal dynamics. To more accurately estimate cellular progression, we apply different pseudotime inference methods to generate a continuous-valued vector representing the inferred temporal ordering of individual cells.

2.1 Pseudotime Inference

In this work, we implement several pseudotime inference methods, including Slingshot, PHATE, Diffusion Maps, PAGA, and PCA, to estimate cellular trajectories from scRNA-seq data. Below, we briefly describe two widely used approaches, Slingshot and PHATE. For details on Diffusion Maps and PAGA, readers are referred to the original publications [7, 29].

Slingshot [23] first constructs a minimum spanning tree (MST) over cell clusters to infer the global lineage structure, incorporating prior biological knowledge to guide the branching topology. Then, it fits simultaneous principal curves to model smooth, branching trajectories through the expression space. The pseudotime values are assigned to individual cells along each inferred lineage, providing a continuous and biologically meaningful temporal ordering that captures cellular progression.

PHATE [15] first computes local affinities between cells, models transitions using a diffusion process, and transforms the result into a heat potential representation to stabilize structure. Finally, non-metric multidimensional scaling embeds the data into a low-dimensional space, revealing smooth progression paths and branching trajectories. The pseudotime values are estimated by computing the Euclidean distances from each cell to a designated root cell along the PHATE manifold.

Since pseudotime inference can introduce noise and errors due to inaccuracies in temporal ordering, we adopt the approach of Zeng et al. [30], applying a sliding window (width $k = 5$, step size 1) and average smoothing to construct representative, smoothed cell profiles along the pseudotime trajectory.

2.2 Time-lagged Divergence Measures

Previous studies [30, 31] have applied mutual information to infer gene regulatory networks (GRNs). In particular, the Normi method [30] infers regulatory links by computing time-delayed mutual information. However, due to the limitations discussed in the Introduction, we extend this idea and propose a more general framework that employs time-lagged f-divergence and integral probability metrics (IPMs) to quantify the influence of gene X on gene Y.

The time-lagged f-divergence quantifying the directional dependency between gene X at time $t-l$ and gene Y at time t is defined as

$$D_f\left(P_X^{(t-l)} \,\|\, P_Y^{(t)}\right) = \int P_Y^{(t)}(z)\, f\left(\frac{P_X^{(t-l)}(z)}{P_Y^{(t)}(z)}\right) dz,$$

where, $P_X^{(t-l)}$ and $P_Y^{(t)}$ are the probability distribution functions of genes X and Y at time points $t-l$ and t, respectively, with l denoting the time lag. The function $f(u)$ is a proper, lower semi-continuous, and convex function satisfying $f(1) = 0$. This formulation generalizes several well-known divergence measures, including Kullback–Leibler, Jensen-Shannon, and Pearson divergence.

Similar to the time-lagged f-divergence, the time-lagged integral probability metric (IPM) is defined as:

$$D_{IPM}\left(P_X^{(t-l)} || P_Y^{(t)}\right) = \sup_{f\in\mathcal{F}} \left| \mathbb{E}_{x\sim P_X^{(t-l)}}[f(x)] - \mathbb{E}_{y\sim P_Y^{(t)}}[f(y)] \right|,$$

where $\mathcal{F}$ is a class of bounded, measurable functions. The choice of $\mathcal{F}$ determines the specific form of the divergence, such as the Wasserstein, Cramér and Energy distance.

In the previous study [30], the time lag was determined by maximizing the distance correlation between two genes, allowing the lag to be greater than one. This implies that gene expression could be influenced by events in a very distant past. However, biological studies support the Markov property in gene regulatory network modeling [6], which suggests that the current state of a gene is primarily influenced by its immediate past. Therefore, a time lag of one is typically sufficient and more biologically plausible for capturing regulatory dependencies [28]. Moreover, estimating the optimal lag in Normi [30] introduces substantial computational overhead. In our method, we adopt a first-order time lag assumption, $l = 1$, to enhance both biological relevance and computational efficiency. A time-lagged divergence-based score between a transcription factor X and a target gene Z is defined as $D(X||Z) = D(X_t||Z_{t+1})$, where $D(\cdot\,\|\,\cdot)$ denotes either an f-divergence or an integral probability metric (IPM), which quantifies how changes in the expression of X at time t influence the expression of Z at a later time point $t+1$.

2.3 Directed Network Inference Algorithm

Algorithm 1 outlines the pseudocode for the proposed divergence-based method PseudoGRN for inferring directed gene regulatory networks from scRNA-seq data. The procedure consists of four key steps: (1) pseudotime analysis, (2) computation of time-lagged divergence, (3) inference of non-redundant edges, and (4) identification of regulatory relationship.

Algorithm 1 Divergence-Based Directed Network Inference

Require: scRNA-seq data, Pseudotime methods, Divergence measures, Parameter λ.
Ensure: Signed gene regulatory network

Step 1: Pseudotime Analysis
Estimate pseudotime using trajectory inference methods (Slingshot, PHATE...)
Sort the single cells according to pseudotime
Step 2: Computation of Time-lagged Divergence
for all gene pairs (X, Z) **do**
    Compute time-lagged divergence: $D(X||Z) = D(X_t||Z_{t+l})$ using f-divergence or IPM.
end for
Step 3: Inference of Non-redundant Edges
for each target gene Z **do**
    Initialize candidate TF set U (all TFs)
    Initialize selected TF set $S \leftarrow \emptyset$
    Rank all $X \in U$ by descending $D(X, Z)$
    $X^{(1)} \leftarrow \arg\max_{X \in U} D(X, Z)$
    $S \leftarrow S \cup \{X^{(1)}\}$
    while $S \neq U$ **do**
        for all $X \in U \setminus S$ **do**
            Compute $D^*(X||Z) = D(X||Z) - \frac{\lambda}{|S|} \sum_{Y \in S} D(X||Y)$
        end for
        $X^* \leftarrow \arg\max_{X \in U \setminus S} D^*(X||Z)$
        $S \leftarrow S \cup \{X^*\}$
    end while
    for all $X \in S$ **do**
        if $D^*(X||Z) > 0$ **then**
            Add edge $X \rightarrow Z$ to GRN
        end if
    end for
end for
Step 4: Identification of Regulatory Relationship
for all inferred edges $X \rightarrow Z$ **do**
    Compute partial correlation P_{XZ}
    Label activation if $P_{XZ} > 0$, inhibition if $P_{XZ} < 0$
end for

After computing the first-order time-lagged divergence-based scores $D(\cdot \,\|\, \cdot)$ for all gene pairs using either f-divergence or IPM, next, we proposed a penalized variant of the max-relevance and min-redundancy (mRMR) strategy, originally introduced in [17] and later adapted for mutual information-based network inference in [30]. In our framework, we replace mutual information with divergence-based scores and incorporate a tunable penalization term, allowing for more flexible and accurate modeling of regulatory relationships. Step 3 in Algorithm 1 details this inference procedure. To infer regulatory links for a target gene Z, we first construct a candidate set of transcription factors U and initialize an empty selected set S. Genes in U are ranked in descending order based on their time-lagged divergence with Z, and the top-ranked gene is added to S. For each remaining candidate gene $X \in U \setminus S$, we compute an adjusted divergence score which is defined as:

$$D^*(X||Z) = D(X||Z) - \frac{\lambda}{|S|} \sum_{Y \in S} D(X||Y),$$

where the first term captures relevance to the target gene Z , and the second term penalizes redundancy with previously selected regulators, and λ is a turning parameter. This selection process is repeated iteratively to identify the most relevant and least redundant regulators, retaining only those with non-negative divergence scores as edges in the network.

The final step of Algorithm 1 determines the type of regulatory interaction, activation or inhibition. Following our recent work [28], we compute the partial correlation P_{XZ} between each gene pair (X, Z) along the inferred edges from Step 3. A positive P_{XZ} indicates activation, while a negative value suggests inhibition.

3 Results

In this section, we apply Algorithm 1 to reconstruct gene regulatory networks from time-series scRNA-seq data.

3.1 Data and Evaluation Metrics

To evaluate the performance of PseudoGRN, we analyze both simulated and real-world single-cell RNA-seq datasets. Due to space limitations, we present only the results on the real-world THP-1 dataset, which profiles the differentiation of THP-1 human myeloid leukemia cells into macrophages across eight time points, with 120 cells sampled at each time point [10]. The THP-1 dataset has been widely used as a benchmark for network inference [30].

To evaluate the performance of our method, we compute the Area Under the Receiver Operating Characteristic Curve (AUROC) and Area Under the Precision-Recall Curve (AUPRC), two standard metrics commonly used to assess the accuracy of predicted regulatory edges. The tuning parameter λ, which controls redundancy and sparsity of the inferred network in our algorithm, is selected via 5-fold cross-validation using Slingshot pseudotime and the Cramér divergence. The cross-validation results identify $\lambda = 1.5$ as the optimal value, which is used in all subsequent analyses for GRN reconstruction.

3.2 Network Inference Analysis

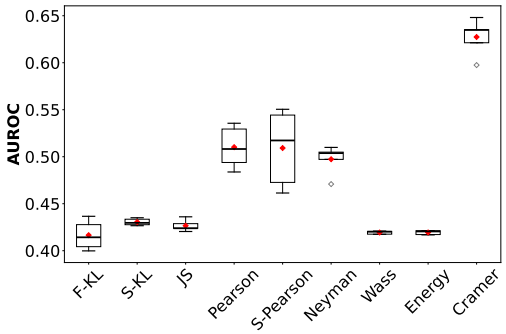
We implement Algorithm 1 using five pseudotime inference methods, including Slingshot, PHATE, Diffusion Maps (DiffMap), PCA, and PAGA, and nine divergence measures: forward KL (F-KL), symmetric KL (S-KL), Jensen-Shannon (JS), Pearson, symmetric Pearson (S-Pearson), Neyman, Wasserstein (Wass), Energy, and Cramér divergence. In all experiments, each trial is repeated five times, and we report the average AUROC and AUPRC scores. Performance is assessed by comparing the inferred network against a known gene regulatory network composed of 20 genes [25].

Table 1 summarizes the mean AUROC and AUPRC scores for gene regulatory networks inferred using nine different divergence measures in combination with five pseudotime inference methods, all evaluated at the optimal regularization parameter $\lambda = 1.5$. Standard errors are not reported, as their magnitudes are on the order of 10^{-3} and thus negligible. Our results indicate that, for a given divergence measure, the overall performance is relatively robust to the choice of pseudotime inference method. However, the performance is substantially affected by the choice of divergence measure, highlighting its critical role in network reconstruction.

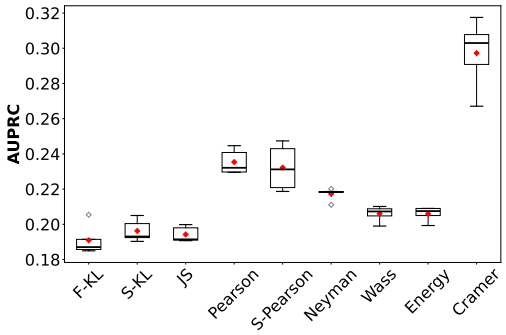
Table 1: Mean AUROC and AUPRC scores using nine different divergence measures and five pseudotime inference methods.

Method	Slingshot	PHATE	DiffMap	PCA	PAGA
		AUROC			
Cramér	0.6481	0.6213	0.6351	0.5975	0.6349
S-Pearson	0.5173	0.4614	0.5443	0.4727	0.5505
Neyman	0.5099	0.4972	0.5049	0.4709	0.5038
Pearson	0.5082	0.4838	0.5294	0.4939	0.5356
F-KL	0.4043	0.4366	0.4143	0.4278	0.3998
S-KL	0.4266	0.4351	0.4335	0.4277	0.4296
JS	0.4288	0.4361	0.4239	0.4204	0.4239
Wass	0.4209	0.4176	0.4205	0.4175	0.4202
Energy	0.4205	0.4168	0.4213	0.4172	0.4213
		AUPRC			
Cramér	0.3175	0.2908	0.3030	0.2671	0.3078
S-Pearson	0.2312	0.2187	0.2430	0.2209	0.2474
Neyman	0.2201	0.2181	0.2186	0.2111	0.2183
Pearson	0.2321	0.2295	0.2408	0.2297	0.2447
F-KL	0.1857	0.2054	0.1871	0.1915	0.1849
S-KL	0.2050	0.2004	0.1931	0.1924	0.1903
JS	0.1980	0.1998	0.1907	0.1914	0.1910
Wass	0.1990	0.2048	0.2101	0.2073	0.2088
Energy	0.1993	0.2075	0.2090	0.2050	0.2090

Among all the divergence measures, Cramér, a special case of the integral probability metric (IPM), consistently achieves the best performance, with a mean AUROC exceeding 0.6 and an AUPRC around 0.3 across nearly all pseudotime inference methods. This significantly outperforms baseline methods reported in [30], including DeepSEM, GRNBOOST2, SCODE, SCRIBE, GRNVBEM, LEAP, and SINCERITIES, whose mean AUROC scores typically hover around 0.5 and AUPRC values remain below 0.2. Under the Slingshot pseudotime, the AUROC of the Cramér-based method reaches approximately 0.65, while the computation time is only one-fifth of that required by Normi, which involves estimating an optimal time lag, a step that may not be biologically meaningful. Additionally, symmetric Pearson, Neyman, and standard Pearson divergences demonstrate competitive performance across various pseudotime strategies, further highlighting the robustness and effectiveness of divergence-based approaches. These results are consistent with Fig. 2, which presents boxplots of AUROC and AUPRC scores for each divergence measure, aggregated across five pseudotime inference methods. The boxplots illustrate the distribution of scores and their associated standard errors, highlighting the relative stability and performance of each measure.



(a) AUROC



(b) AUPRC

Figure 1: Boxplots of AUROC and AUPRC scores for each divergence measure, aggregated over five pseudotime methods.

To illustrate the inferred directed regulatory networks using our PseudoGRN method, Fig. 2 presents representative structures obtained using Slingshot and Cramér divergence under varying regularization parameters λ. The results show that both network structure and sparsity depend on λ; larger values of λ yield sparser networks with higher AUROC scores.

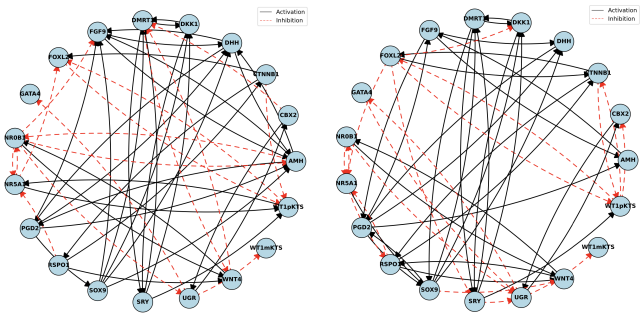


Figure 2: Gene regulatory networks inferred using Slingshot and Cramér with $\lambda = 1$ (left) and $\lambda = 1.5$ (right).

4 Conclusion

In this study, we introduce PseudoGRN, an integrative framework for inferring directed gene regulatory networks from scRNA-seq data. PseudoGRN incorporates several methodological innovations. First, multiple pseudotime inference methods are employed to estimate cellular trajectories. Next, we define a first-order time-lagged divergence-based score to quantify directional dependencies between gene pairs. A penalized, non-redundant edge selection strategy is then used to infer sparse, biologically meaningful network structures. Finally, partial correlation analysis is applied to classify each regulatory interaction as either activation or inhibition.

We evaluate the performance of our framework using real-world scRNA-seq data from THP-1 cells. Our experimental results demonstrate that the proposed approach outperforms all existing methods, including DeepSEM, GRNBOOST2, SCODE, SINCERITIES, and Normi. Notably, our results suggest that the overall performance is not highly sensitive to the choice of pseudotime analysis methods, but is significantly influenced by the choice of divergence function. Among the divergence measures evaluated, the Cramér distance achieved the best performance, substantially higher than those obtained by other divergence measures and all existing baseline methods. Compared to the Normi method, PseudoGRN demonstrates superior biological interpretability and computational efficiency.

Since scRNA-seq data often contain a large proportion of missing values that our current method cannot handle directly, one direction of future work is to incorporate our missing value imputation techniques [3, 12, 20] into this framework to enhance the accuracy of network inference. In addition, gene regulatory networks may exhibit non-stationary structures across different stages of cellular processes. Another future direction is to integrate change-point detection algorithms [21] with pseudotime analysis to infer time-varying gene regulatory networks across different biological stages.

Acknowledgments

This research was partially supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R15GM148915 (HG). The code in this study is available at https://github.com/toutoubest/Pseudo-network.

References

[1] Hamda B. Ajmal and Michael G. Madden. 2022. Dynamic Bayesian Network Learning to Infer Sparse Models From Time Series Gene Expression Data. *IEEE/ACM Transactions on Computational Biology and Bioinformatics* 19, 5 (Sept. 2022), 2794–2805.

[2] Volker Bergen, Marius Lange, Stefan Peidli, F Alexander Wolf, and Fabian J Theis. 2020. Generalizing RNA velocity to transient cell states through dynamical modeling. *Nature biotechnology* 38, 12 (2020), 1408–1414.

[3] Graham Bishop, Tong Si, Isabelle Luebbert, Noor Al-Hammadi, and Haijun Gong. 2025. tBN-CSDI: a time-varying blue noise-based diffusion model for time-series imputation. *Bioinformatics Advances* 5, 1 (2025), vbaf225.

[4] Thalia E Chan, Michael PH Stumpf, and Ann C Babtie. 2017. Gene regulatory network inference from single-cell data using multivariate information measures. *Cell systems* 5, 3 (2017), 251–267.

[5] Jun Ding, Nadav Sharon, and Ziv Bar-Joseph. 2022. Temporal modelling using single-cell transcriptomics. *Nature Reviews Genetics* 23, 6 (2022), 355–368.

[6] Marco Grzegorczyk and Dirk Husmeier. 2009. Non-stationary continuous dynamic Bayesian networks. *Advances in neural information processing systems* 22 (2009).

[7] Laleh Haghverdi, Florian Buettner, and Fabian J Theis. 2015. Diffusion maps for high-dimensional single-cell analysis of differentiation data. *Bioinformatics* 31, 18 (2015), 2989–2998.

[8] Laleh Haghverdi, Maren Büttner, F Alexander Wolf, Florian Buettner, and Fabian J Theis. 2016. Diffusion pseudotime robustly reconstructs lineage branching. *Nature methods* 13, 10 (2016), 845–848.

[9] Dragomirka Jovic, Xue Liang, Hua Zeng, Lin Lin, Fengping Xu, and Yonglun Luo. 2022. Single-cell RNA sequencing technologies and applications: A brief overview. *Clinical and translational medicine* 12, 3 (2022), e694.

[10] Tsukasa Kouno, Michiel de Hoon, Jessica C Mar, Yasuhiro Tomaru, Mitsuoki Kawano, Piero Carninci, Harukazu Suzuki, Yoshihide Hayashizaki, and Jay W Shin. 2013. Temporal dynamics and transcriptional control using single-cell gene expression analysis. *Genome biology* 14 (2013), 1–12.

[11] Chee Yee Lim, Huange Wang, Steven Woodhouse, Nir Piterman, Lorenz Wernisch, Jasmin Fisher, and Berthold Göttgens. 2016. BTR: training asynchronous Boolean models using single-cell expression data. *BMC bioinformatics* 17 (2016), 1–18.

[12] Wen-Shan Liu, Tong Si, Aldas Kriauciunas, Marcus Snell, and Haijun Gong. 2025. Bidirectional f-Divergence-Based Deep Generative Method for Imputing Missing Values in Time-Series Data. *Stats* 8, 1 (2025), 7.

[13] Rory J Maizels. 2024. A dynamical perspective: moving towards mechanism in single-cell transcriptomics. *Philosophical Transactions of the Royal Society B* 379, 1900 (2024), 20230049.

[14] Hirotaka Matsumoto and Hisanori Kiryu. 2016. SCOUP: a probabilistic model based on the Ornstein–Uhlenbeck process to analyze single-cell expression data during differentiation. *BMC bioinformatics* 17 (2016), 1–16.

[15] Kevin R Moon, David Van Dijk, Zheng Wang, Scott Gigante, Daniel B Burkhardt, William S Chen, Kristina Yim, Antonia van den Elzen, Matthew J Hirn, Ronald R Coifman, et al. 2019. Visualizing structure and transitions in high-dimensional biological data. *Nature biotechnology* 37, 12 (2019), 1482–1492.

[16] Nan Papili Gao, SM Minhaz Ud-Dean, Olivier Gandrillon, and Rudiyanto Gunawan. 2018. SINCERITIES: inferring gene regulatory networks from time-stamped single cell transcriptional expression profiles. *Bioinformatics* 34, 2 (2018), 258–266.

[17] Hanchuan Peng, Fuhui Long, and Chris Ding. 2005. Feature selection based on mutual information criteria of max-dependency, max-relevance, and min-redundancy. *IEEE Transactions on pattern analysis and machine intelligence* 27, 8 (2005), 1226–1238.

[18] Helen Richards, Yunge Wang, Tong Si, Hao Zhang, and Haijun Gong. 2021. Intelligent learning and verification of biological Nnetworks. *Advances in artificial intelligence, computation, and data science: For medicine and life science* (2021), 3–28.

[19] Wouter Saelens, Robrecht Cannoodt, Helena Todorov, and Yvan Saeys. 2019. A comparison of single-cell trajectory inference methods. *Nature biotechnology* 37, 5 (2019), 547–554.

[20] Tong Si, Zackary Hopkins, John Yanev, Jie Hou, and Haijun Gong. 2023. A novel f-divergence based generative adversarial imputation method for scRNA-seq data analysis. *Plos one* 18, 11 (2023), e0292792.

[21] Tong Si, Yunge Wang, Lingling Zhang, Evan Richmond, Tae-Hyuk Ahn, and Haijun Gong. 2024. Multivariate Time Series Change-Point Detection with a Novel Pearson-like Scaled Bregman Divergence. *Stats* 7, 2 (2024), 462–480.

[22] Qi Song, Matthew Ruffalo, and Ziv Bar-Joseph. 2023. Using single cell atlas data to reconstruct regulatory networks. *Nucleic Acids Research* 51, 7 (2023), e38–e38.

[23] Kelly Street, Davide Risso, Russell B Fletcher, Diya Das, John Ngai, Nir Yosef, Elizabeth Purdom, and Sandrine Dudoit. 2018. Slingshot: cell lineage and pseudotime inference for single-cell transcriptomics. *BMC genomics* 19, 1 (2018), 477.

[24] Guangxin Su, Hanchen Wang, Ying Zhang, Marc R. Wilkins, Pablo F. Canete, Di Yu, Yang Yang, and Wenjie Zhang. 2025. Inferring gene regulatory networks by hypergraph generative model. *Cell Reports Methods* 5, 4 (2025), 101026.

[25] Yasuhiro Tomaru, Christophe Simon, Alistair RR Forrest, Hisashi Miura, Atsutaka Kubosaki, Yoshihide Hayashizaki, and Masanori Suzuki. 2009. Regulatory interdependence of myeloid transcription factors revealed by Matrix RNAi analysis. *Genome biology* 10 (2009), 1–13.

[26] Cole Trapnell, Davide Cacchiarelli, and et al. 2014. The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells. *Nature biotechnology* 32, 4 (2014), 381–386.

[27] Allon Wagner, Aviv Regev, and Nir Yosef. 2016. Revealing the vectors of cellular identity with single-cell genomics. *Nature biotechnology* 34, 11 (2016), 1145–1160.

[28] Yunge Wang, Lingling Zhang, Tong Si, Sarah Roberts, Yuqi Wang, and Haijun Gong. 2025. Reconstructing Dynamic Gene Regulatory Networks Using f-Divergence from Time-Series scRNA-Seq Data. *Current Issues in Molecular Biology* 47, 6 (2025), 408.

[29] F Alexander Wolf, Fiona K Hamey, Mireya Plass, Jordi Solana, Joakim S Dahlin, Berthold Göttgens, Nikolaus Rajewsky, Lukas Simon, and Fabian J Theis. 2019. PAGA: graph abstraction reconciles clustering with trajectory inference through a topology preserving map of single cells. *Genome biology* 20, 1 (2019), 59.

[30] Yanping Zeng, Yongxin He, Ruiqing Zheng, and Min Li. 2023. Inferring single-cell gene regulatory network by non-redundant mutual information. *Briefings in Bioinformatics* 24, 5 (2023), bbad326.

[31] Juan Zhao, Yiwei Zhou, Xiujun Zhang, and Luonan Chen. 2016. Part mutual information for quantifying direct associations in networks. *Proceedings of the National Academy of Sciences* 113, 18 (2016), 5130–5135.