Combining deep learning and modeling for time-series single-cell RNA-sequencing data

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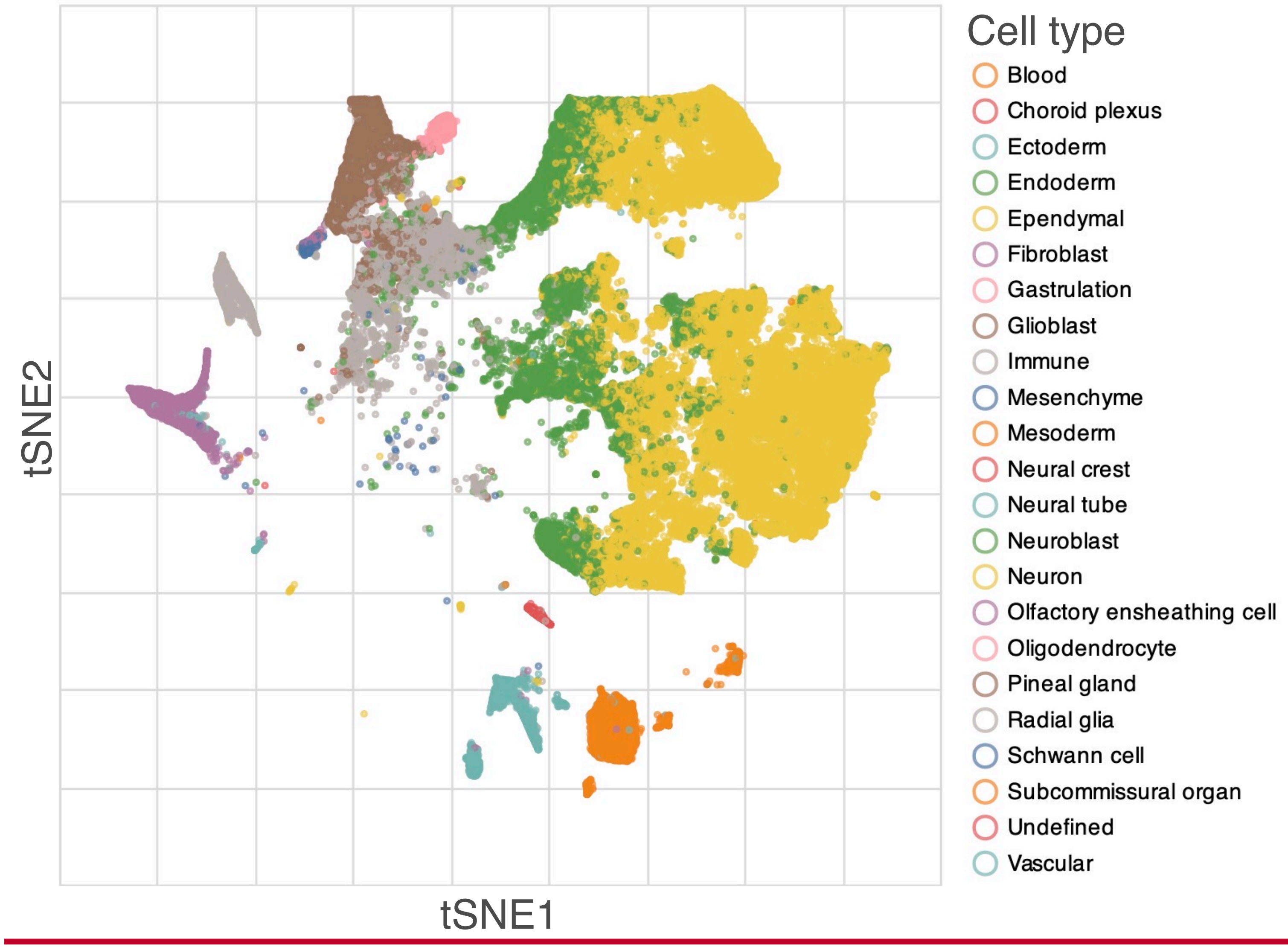
Bioinformatics Club – April 11, 2022

How do you typically look at single-cell RNA-seq data?

t-stochastic neighborhood embedding (tSNE) for dimension reduction



Data from La Manno et al. (2021) Molecular architecture of the developing mouse brain. *Nature* 596, 92-96.

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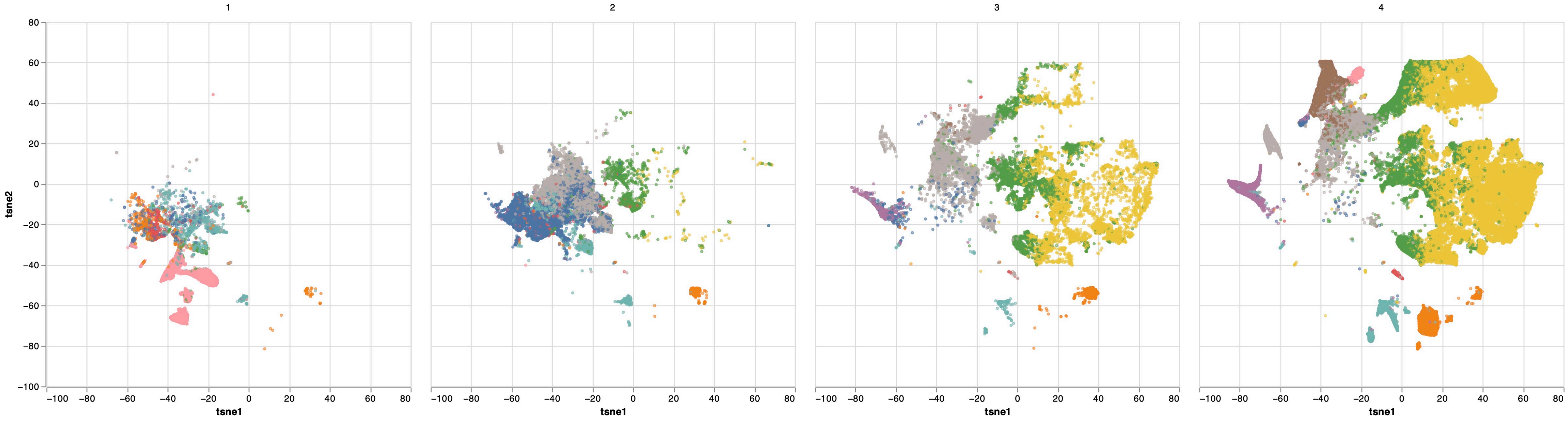
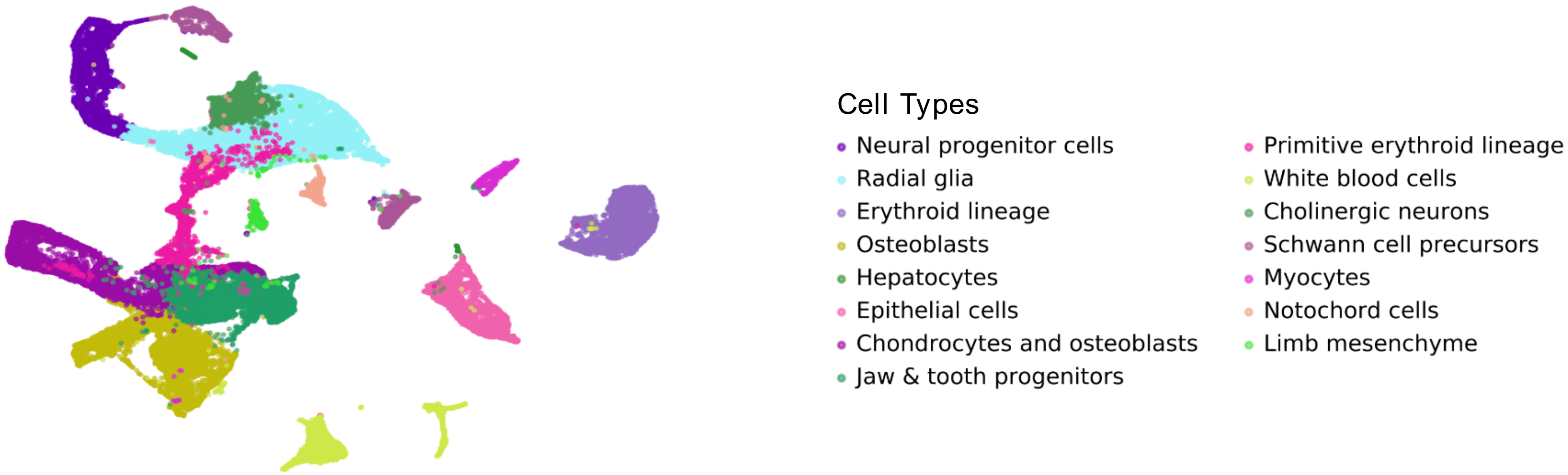
Developmental stage

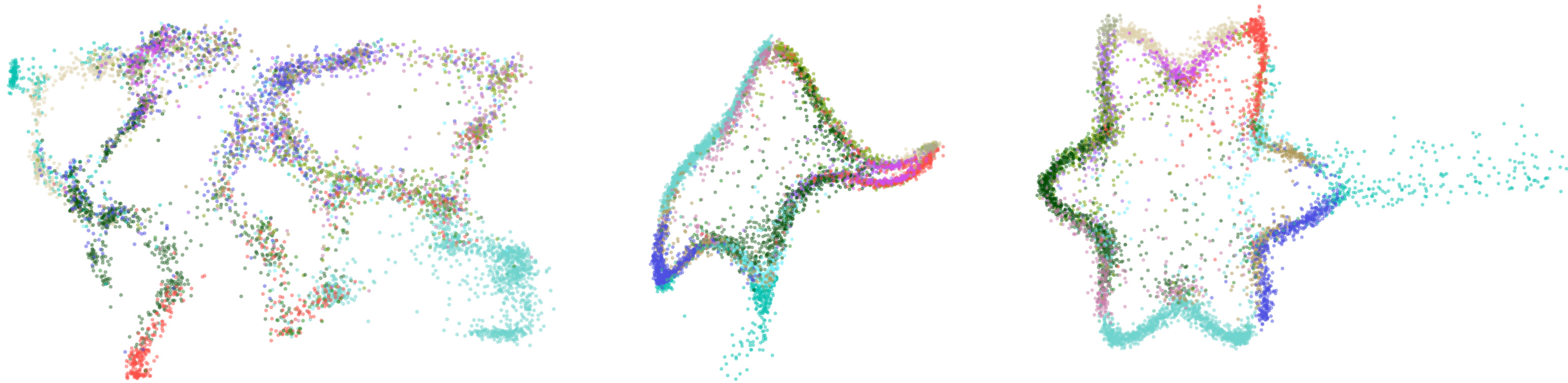


Data from La Manno et al. (2021) Molecular architecture of the developing mouse brain. *Nature* 596, 92-96.

Dimension reduction can be misleading

Data: ex utero mouse embryo E8.5





Figures taken from Chari et al. (2021) The specious art of single-cell genomics. *bioRxiv preprint,* doi*:* 10.1101/2021.08.25.457696.

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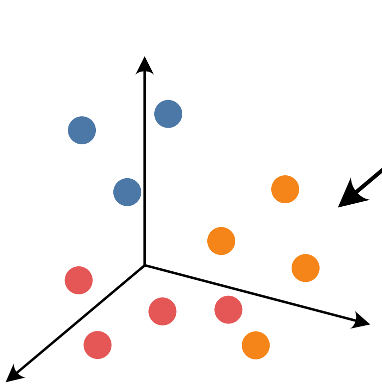
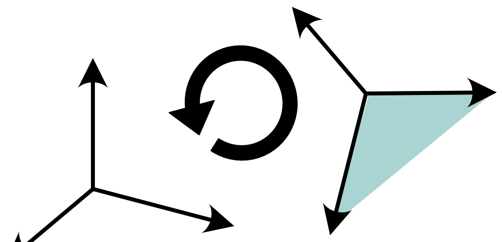
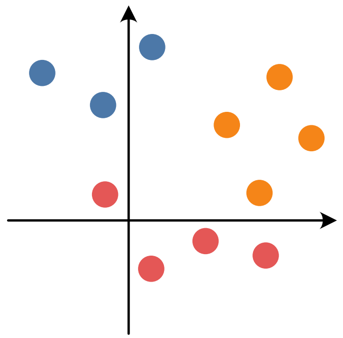
Comparing popular dimension reduction methods

PCA

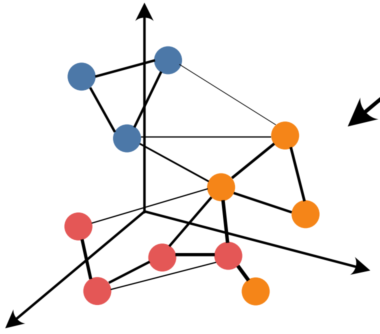


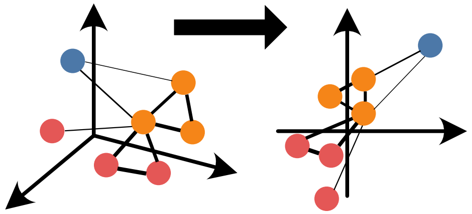


rotate and project to axes of greatest variation

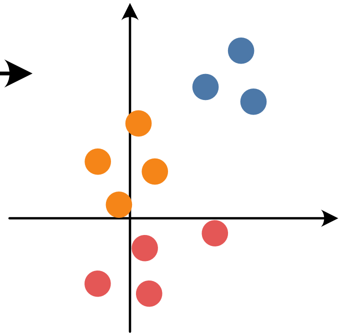


UMAP

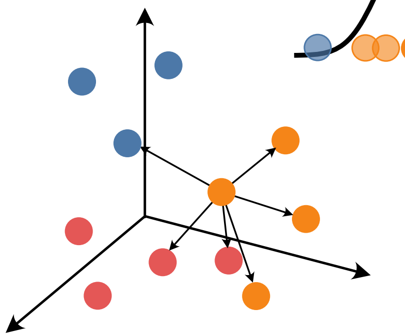


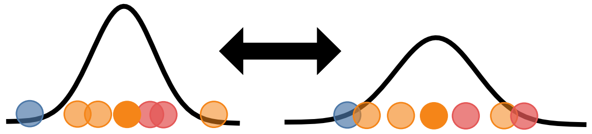


preserve graph structure

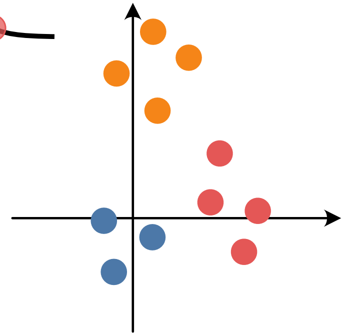


tSNE

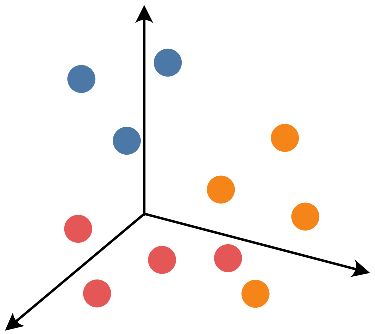


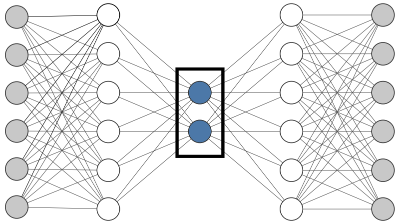


preserve distributions of distances to nearest neighbors

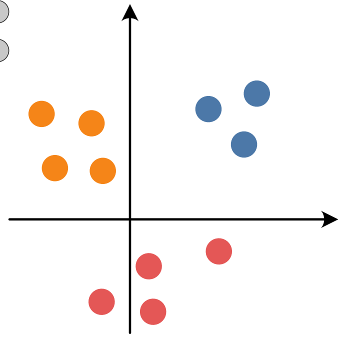


VAE

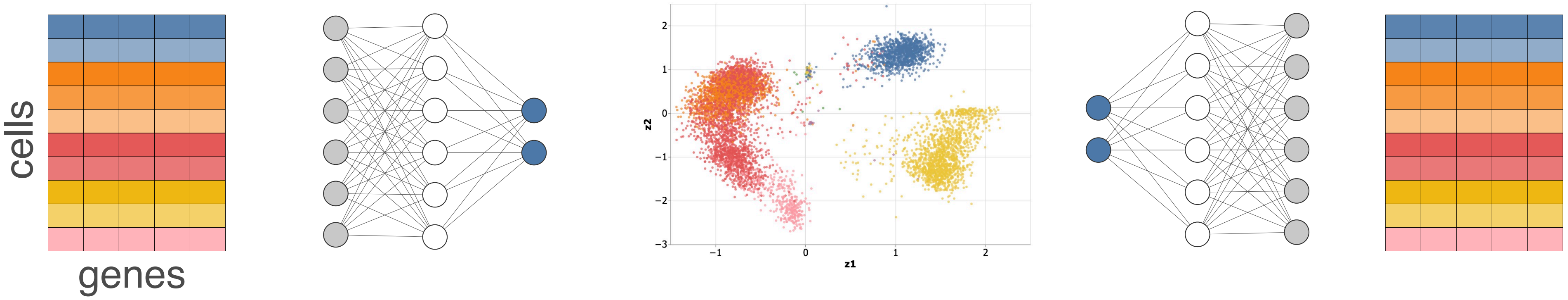




use neural-network based Variational Autoencoder

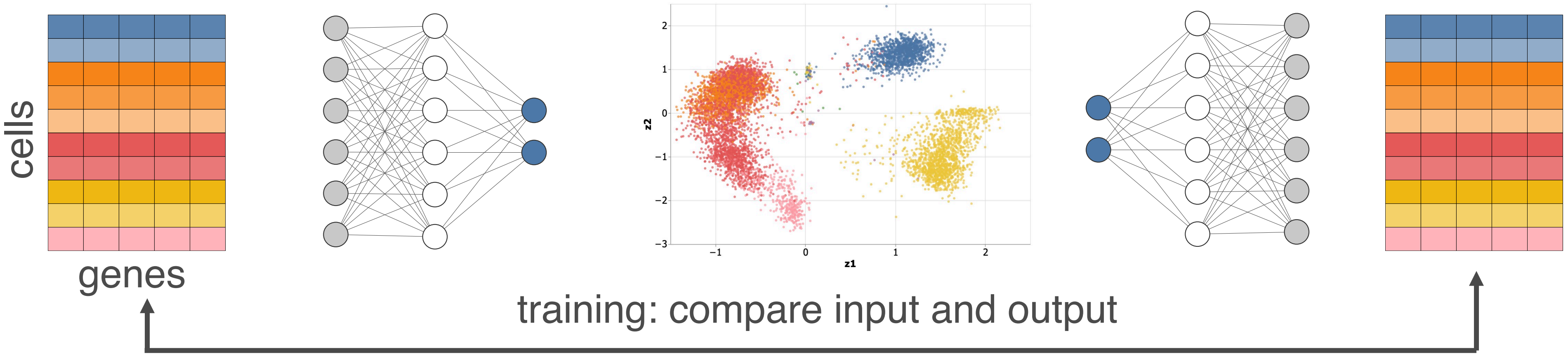


Creating synthetic temporal patterns in scRNA-seq data



1. Use a VAE to learn a low-dimension representation of a snapshot scRNA-seq dataset

Creating synthetic temporal patterns in scRNA-seq data



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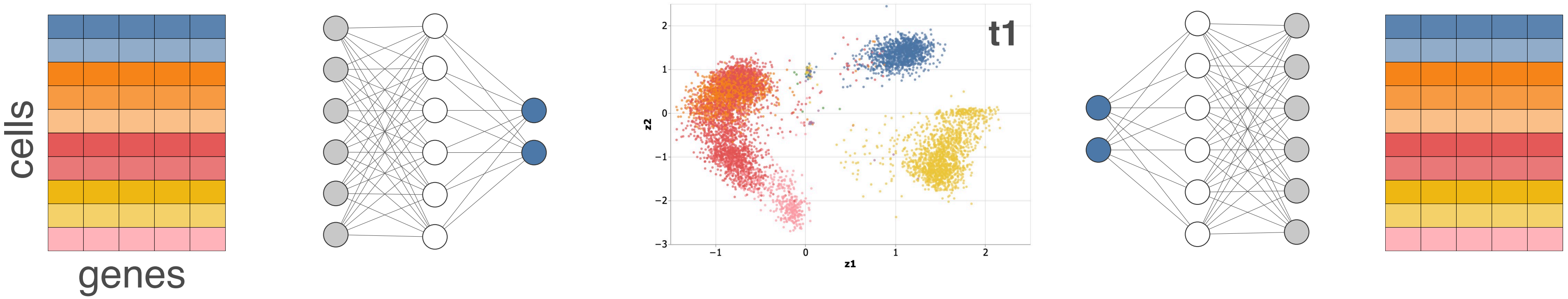

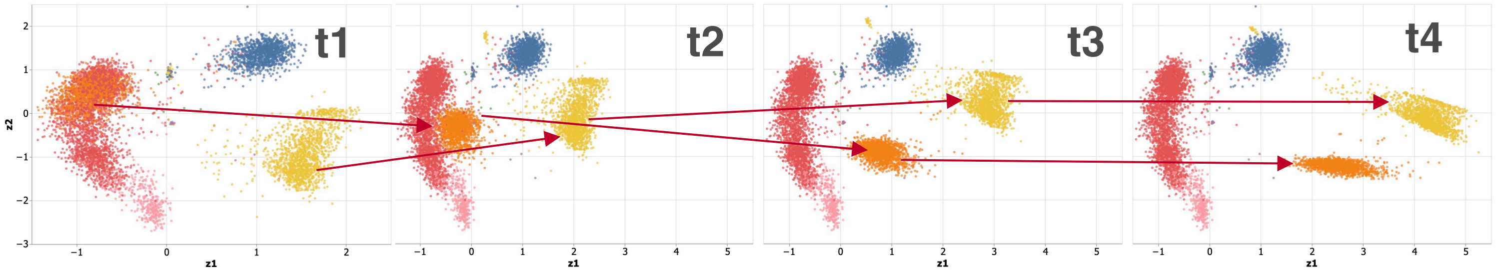

1. Use a VAE to learn a low-dimension representation of a snapshot scRNA-seq dataset
2. In the latent representation, induce a synthetic temporal pattern by vector field transformations

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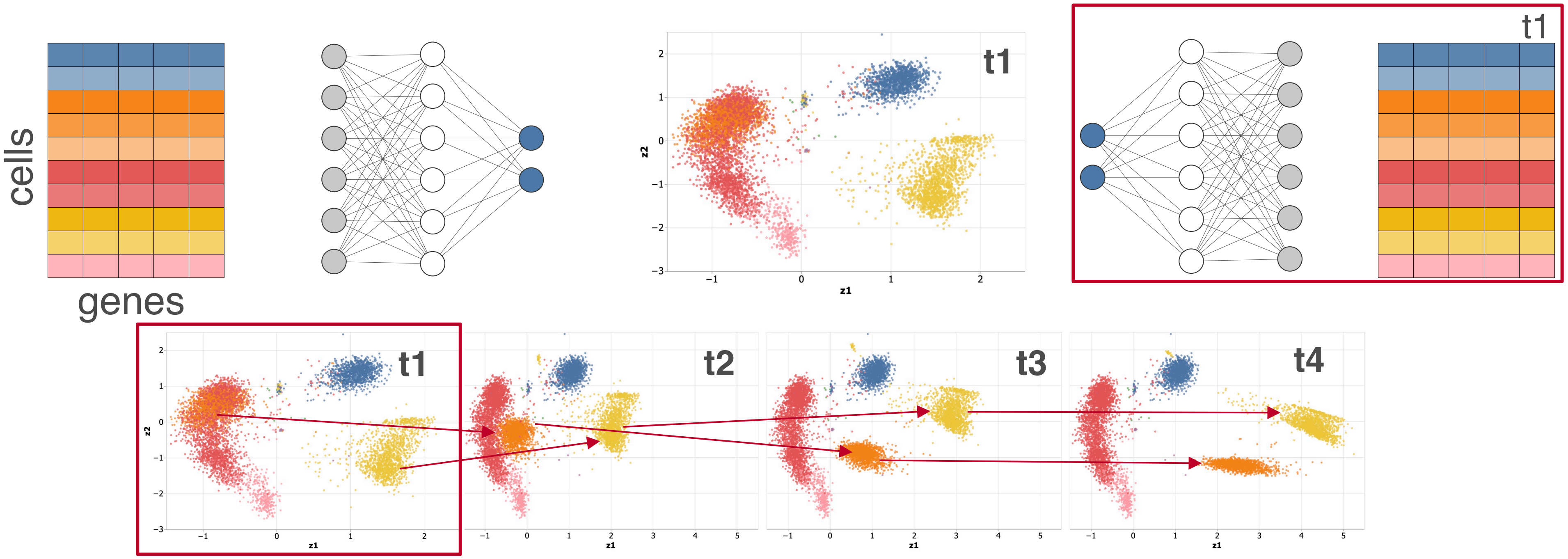

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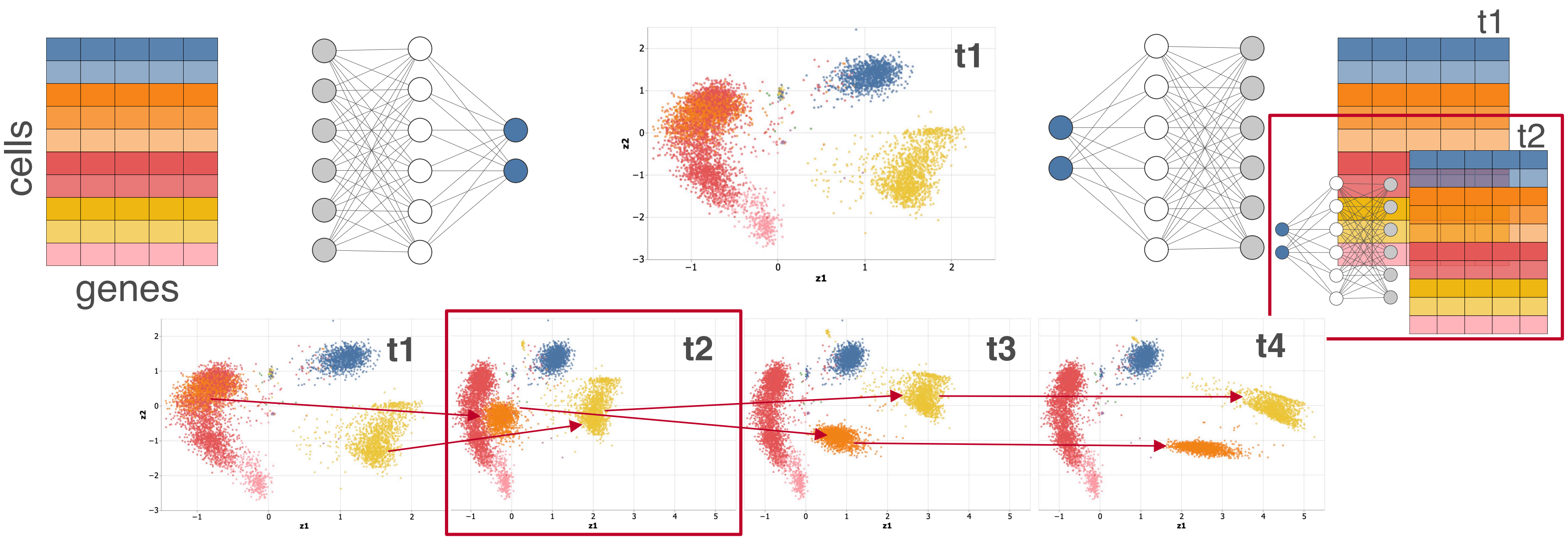

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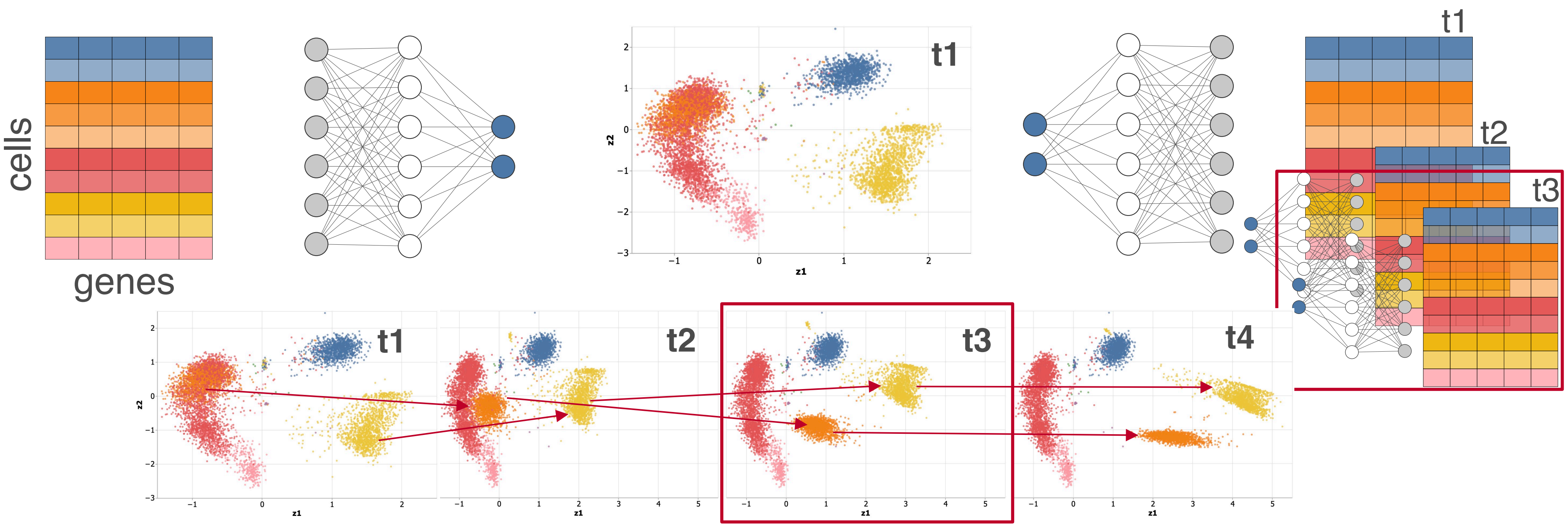

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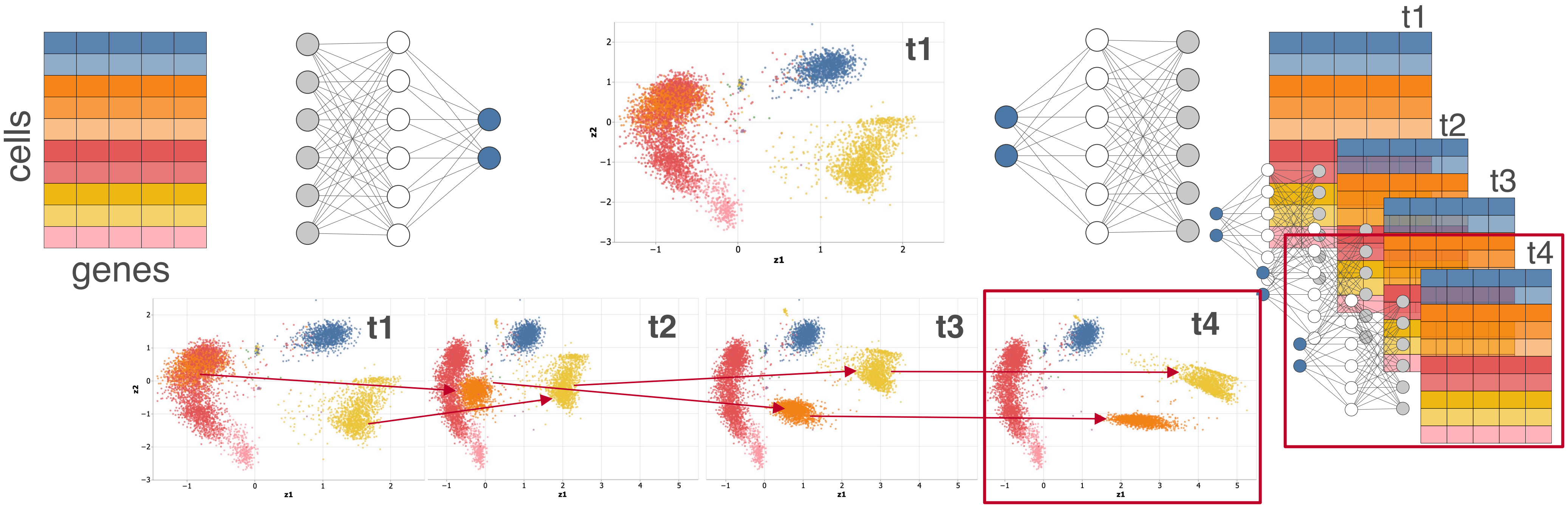

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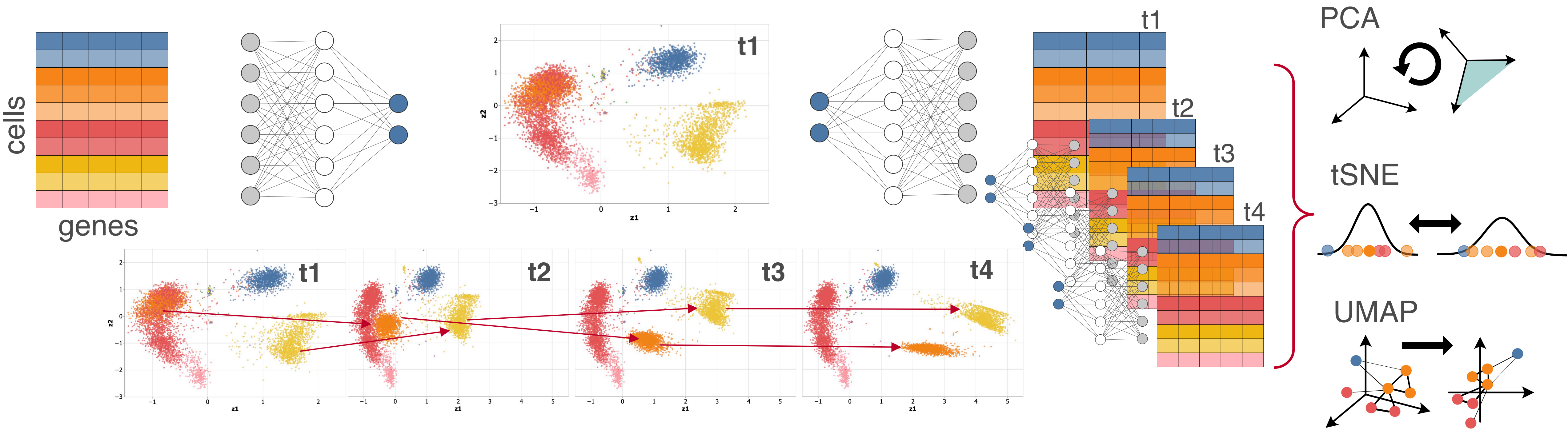

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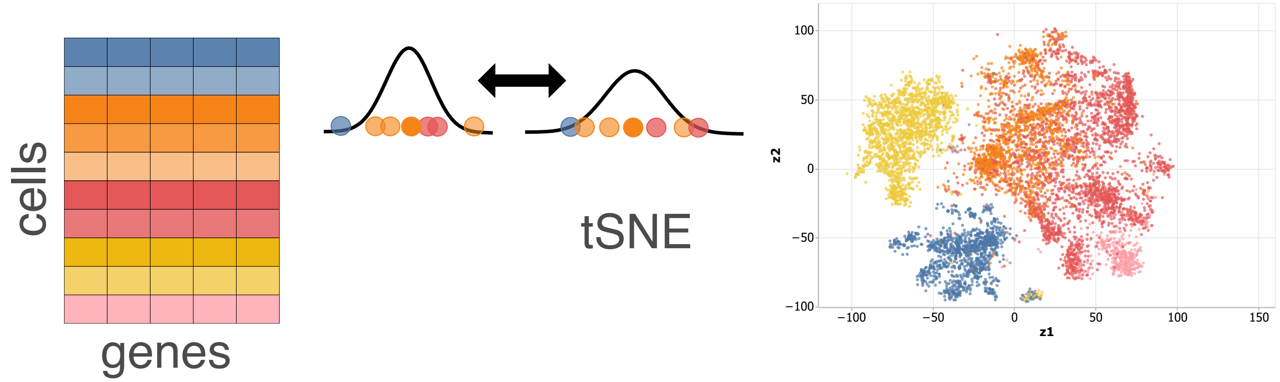
Inducing temporal patterns in tSNE-space

How to generate high-dimensional data from the low-dimensional time series?



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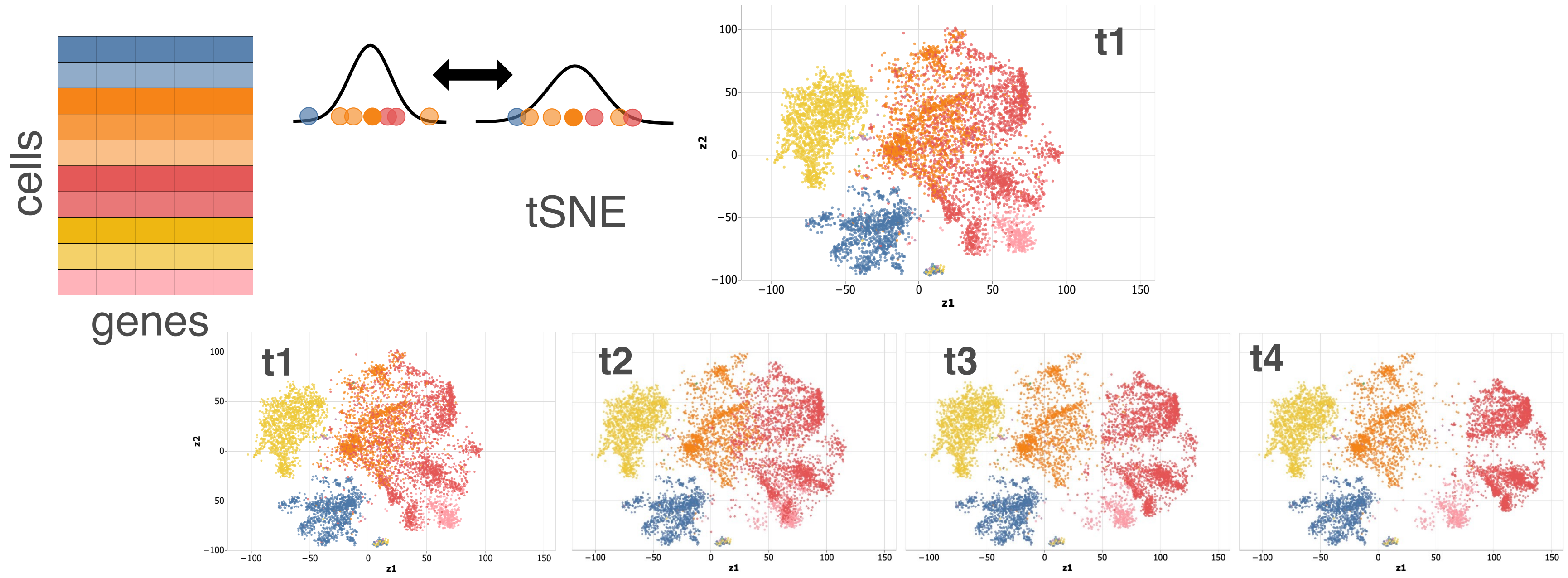

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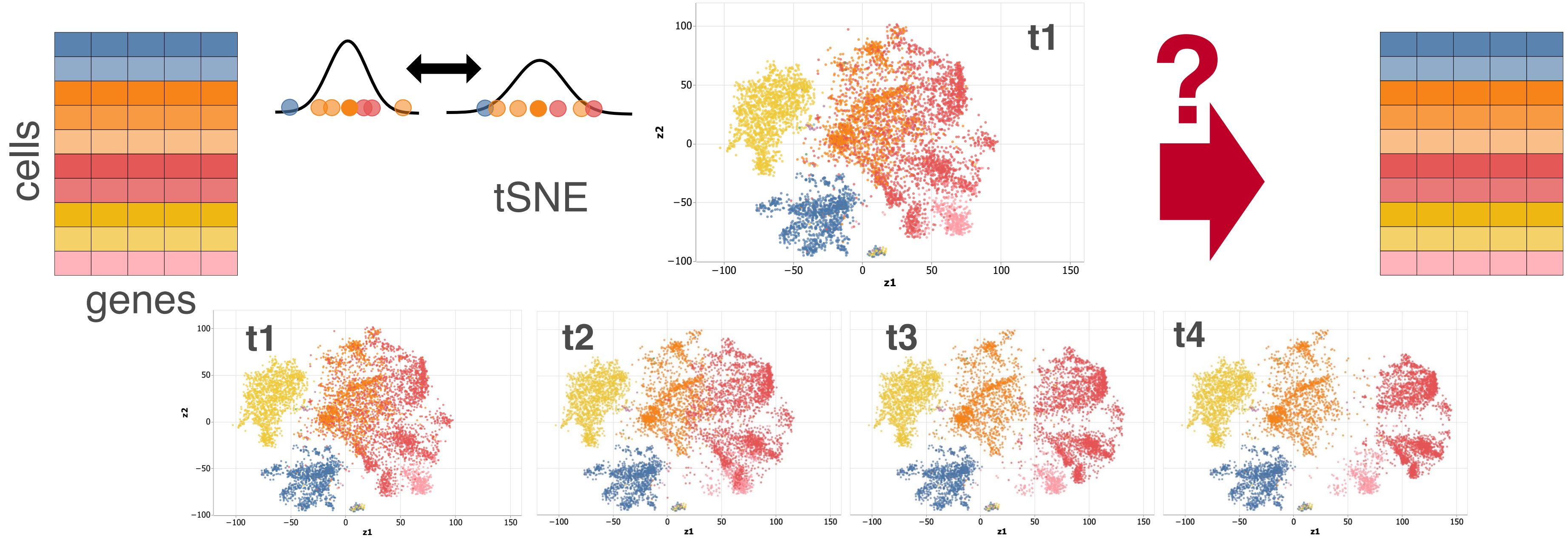

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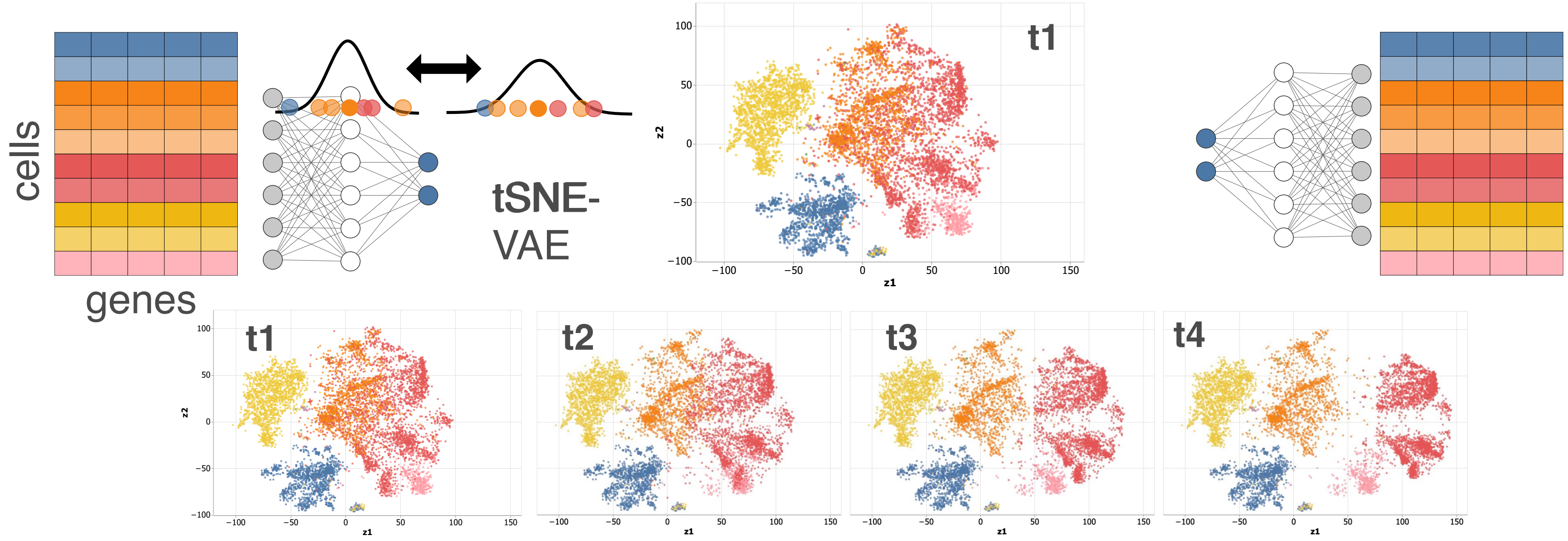

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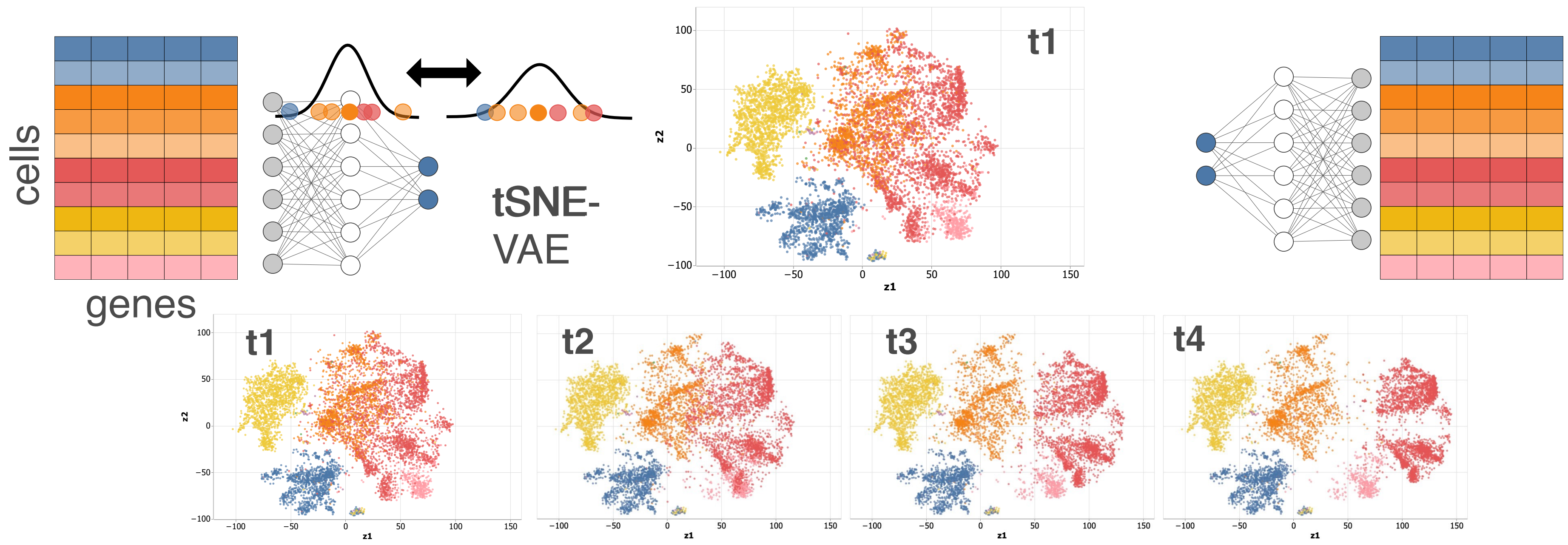

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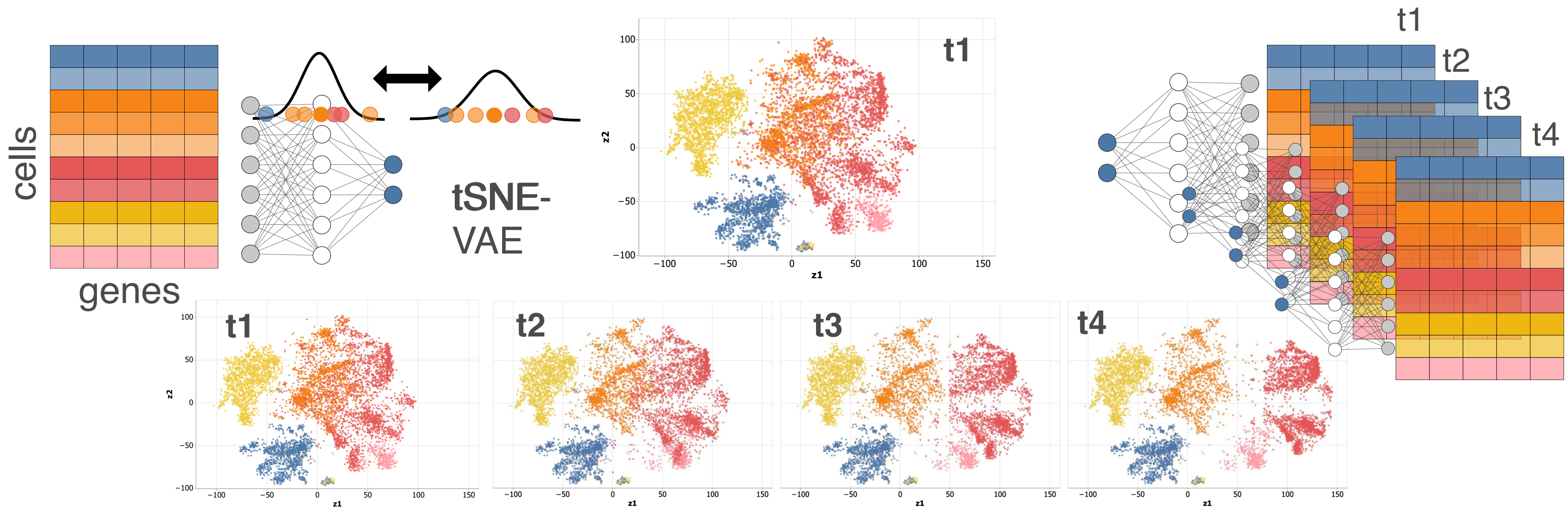

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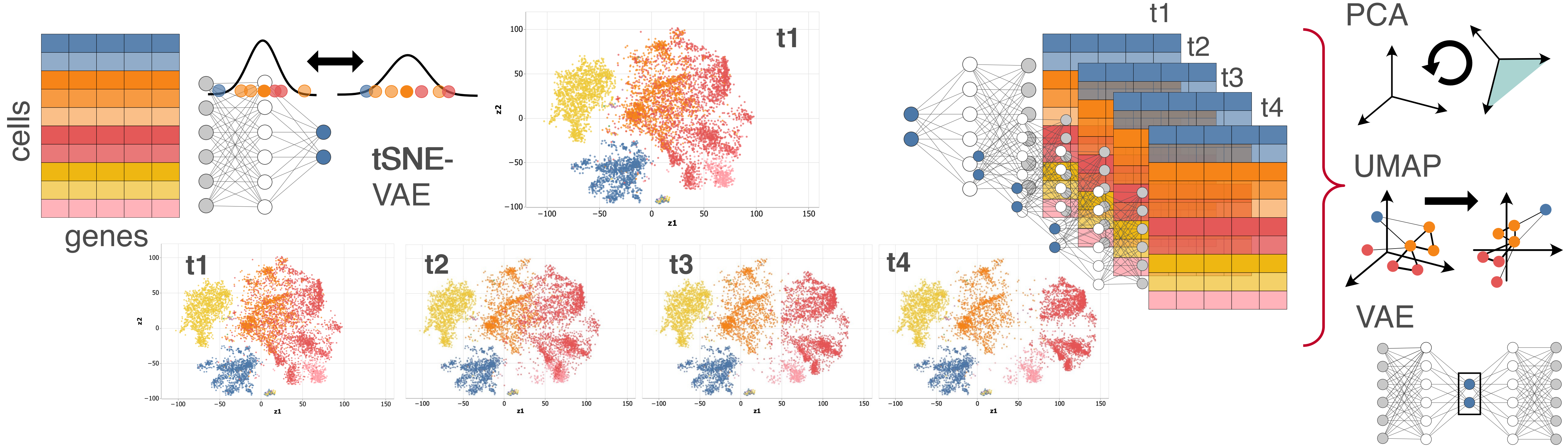

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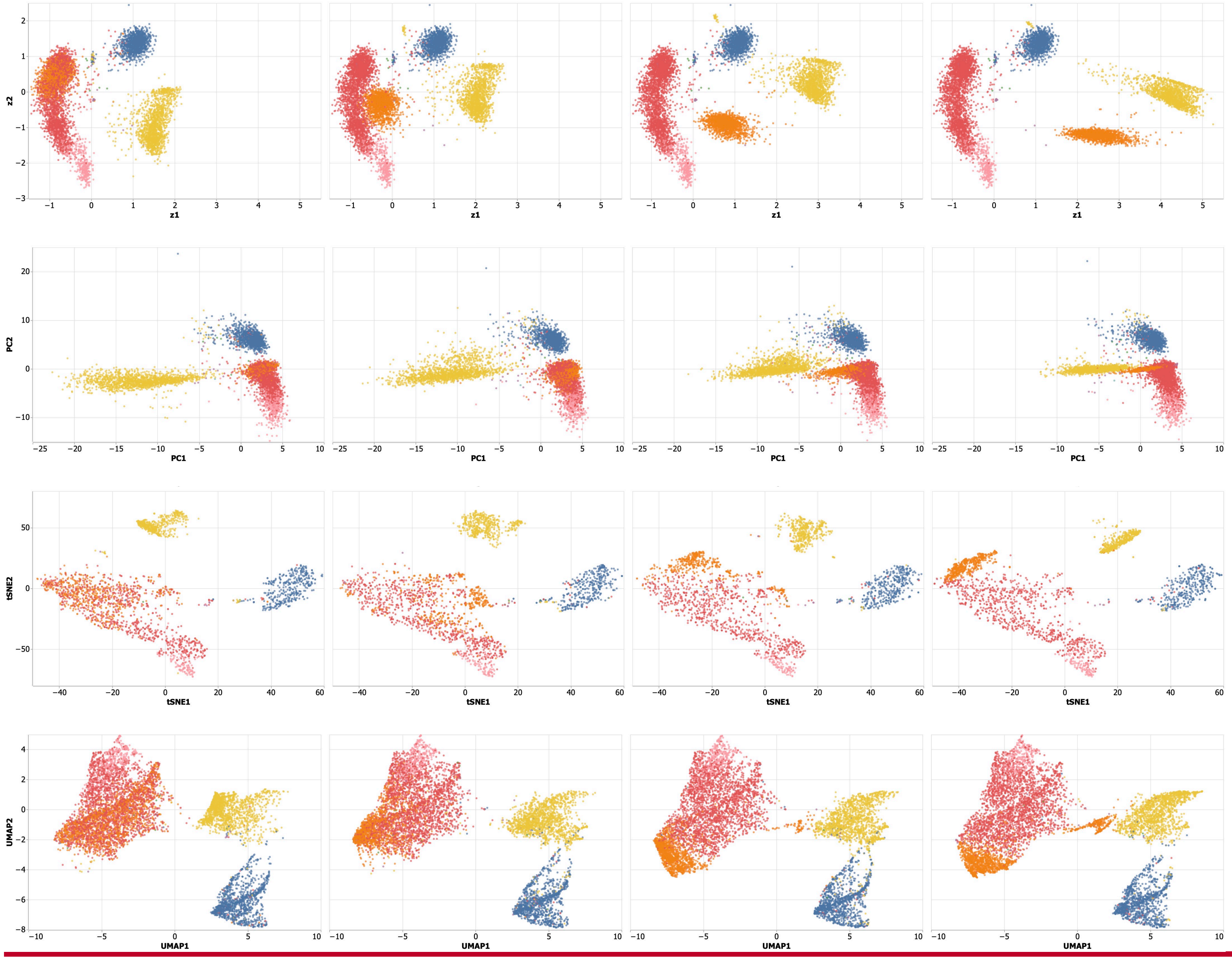
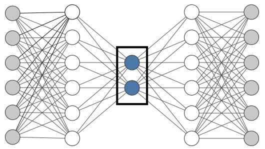
5. Apply PCA, UMAP and the VAE on the synthetic high-dimensional time-series data

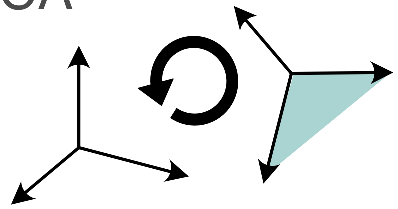
Results: Cluster spreading + rotation



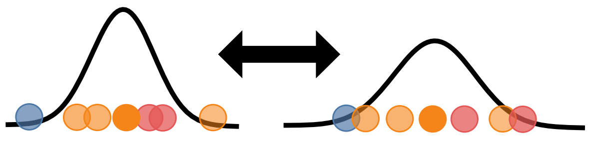
Orignal trans-
formation in the
VAE latent space



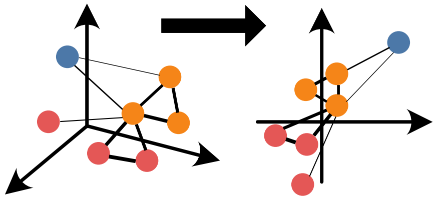
PCA



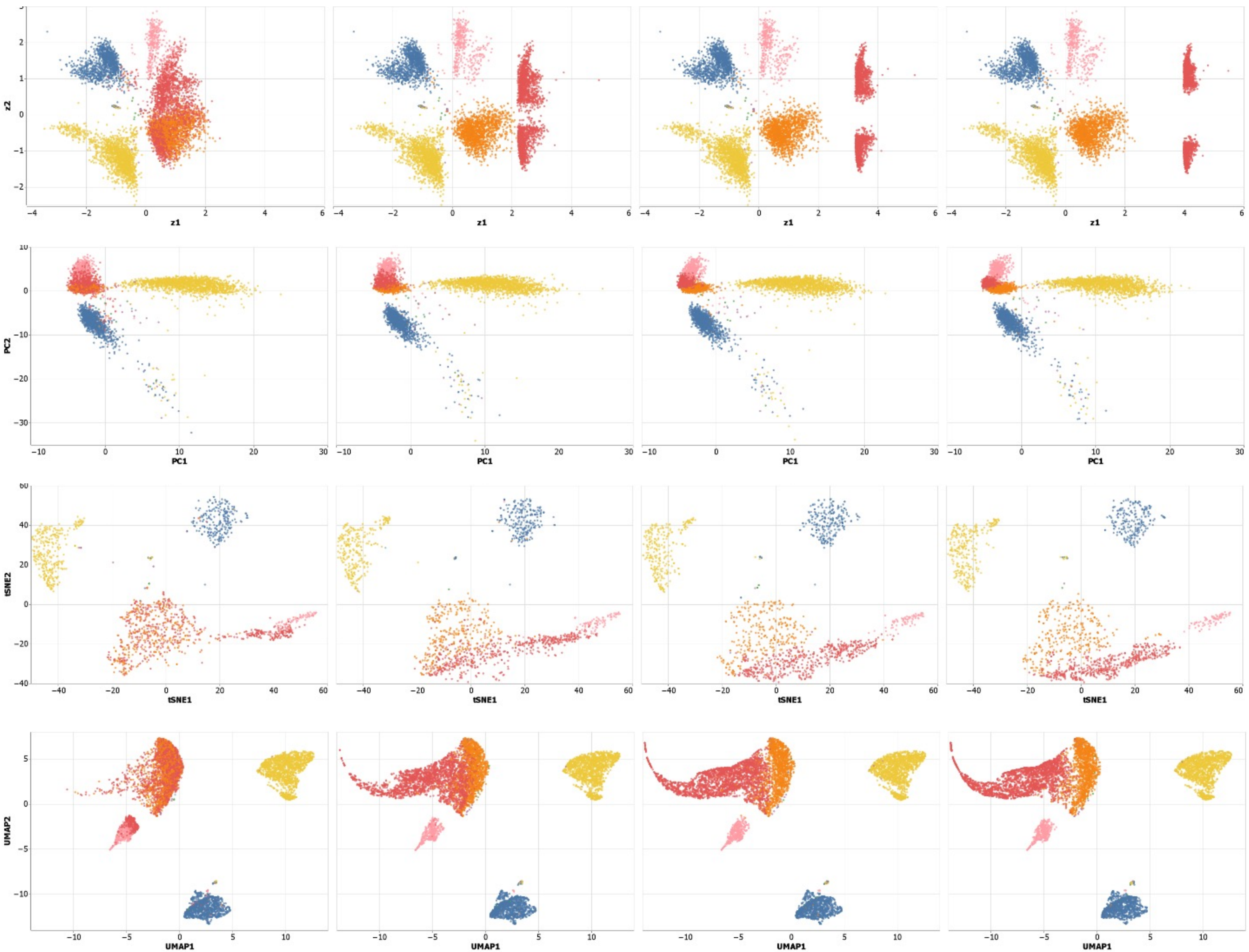
tSNE



UMAP



Results: Cluster division in VAE space



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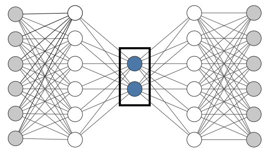

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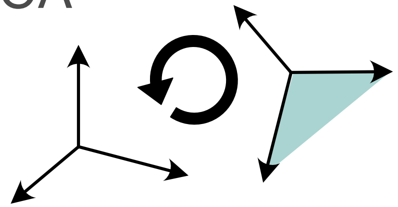
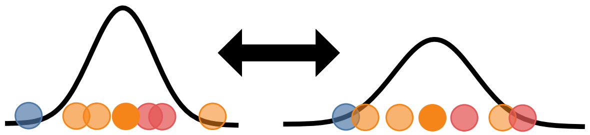
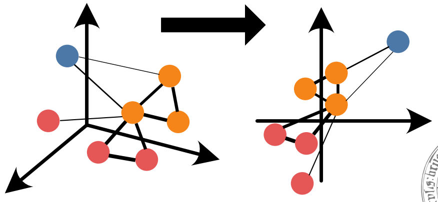


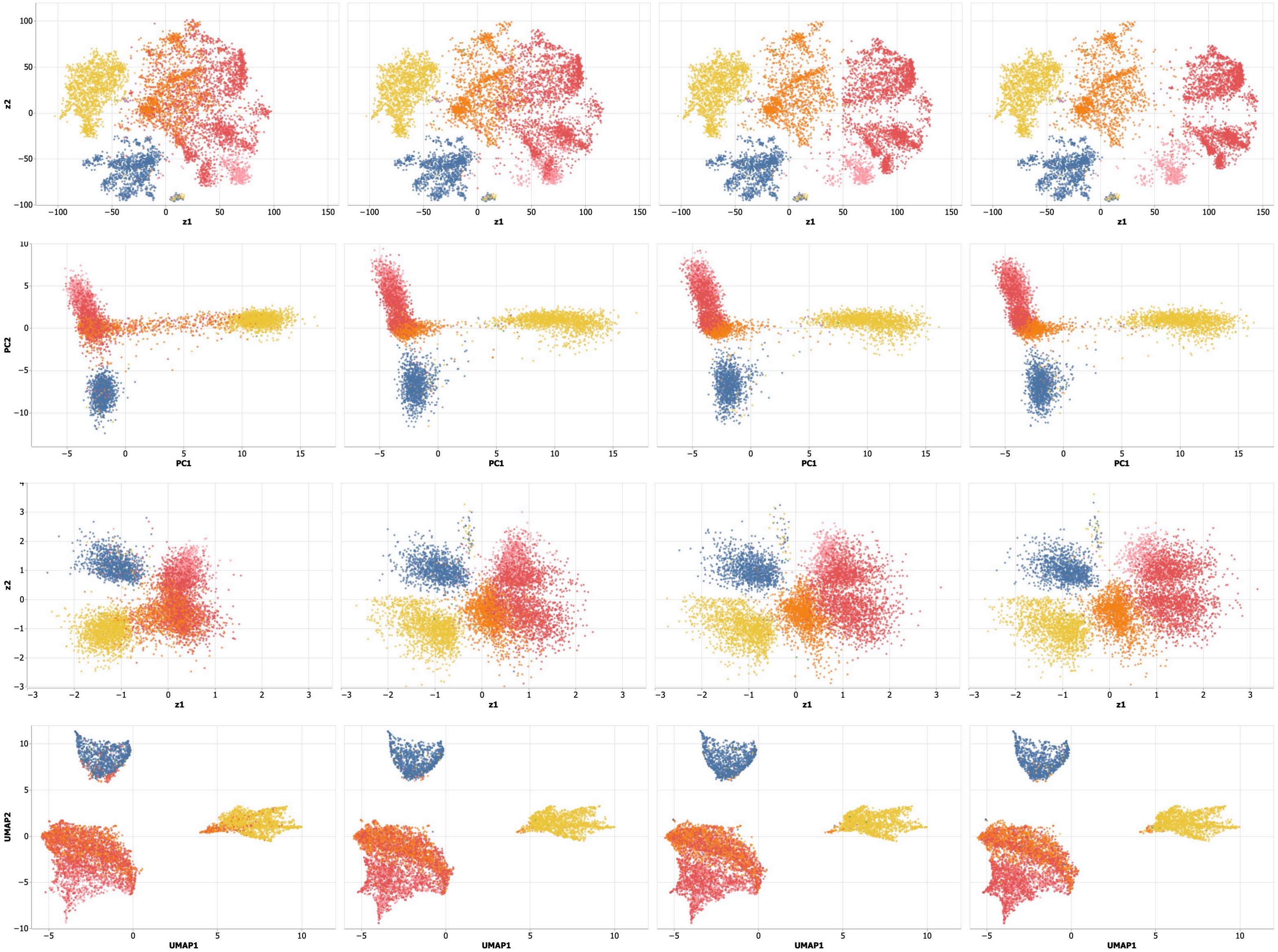
tSNE



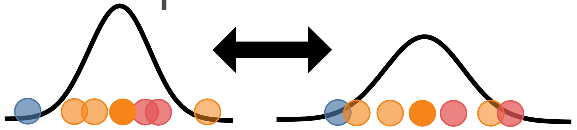
UMAP



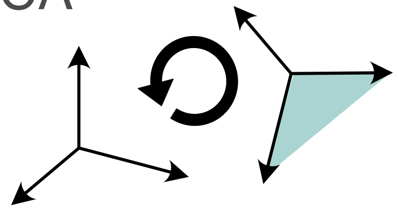
Results: Cluster division in tSNE space



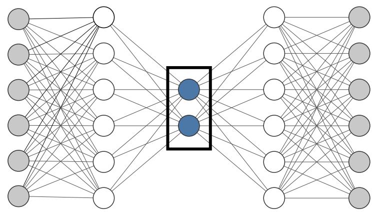
Orignal transformation in tSNE space



PCA



VAE



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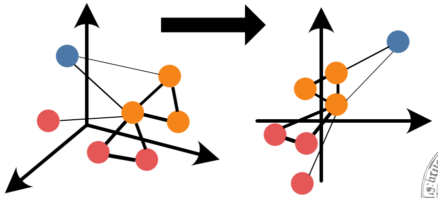
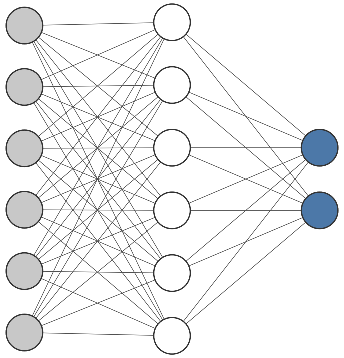
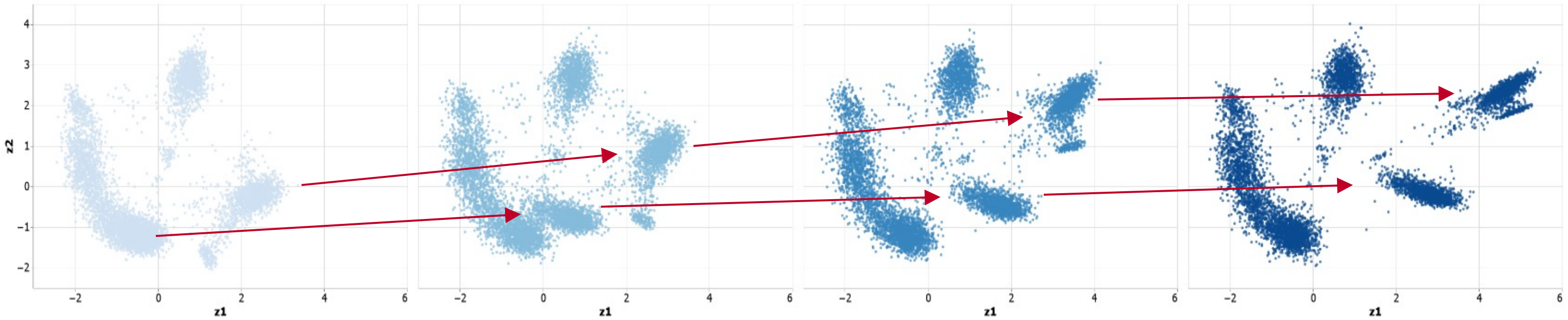


More than meets the eye…

- Popular dimension reduction techniques are not specifically designed to capture temporal patterns and do not necessarily reflect underlying dynamics
- Different dimension reduction methods have different perspectives on temporal devlopment patterns
- → Use these insights to design dimension reduction techniques that explicitly respect time structure
- → Have some explicit model for the temporal dynamics and let the model and the dimension reduction "talk to each other"

f_{encoder} ⟺ f_{dynamics}

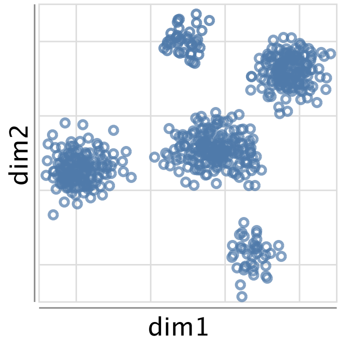




Why deep learning?

Neural networks can easily be combined with other explicit models

$x \in \mathbb{R}^p$ | tSNE algorithm | $z \in \mathbb{R}^2$



no explicit function f_{tSNE}

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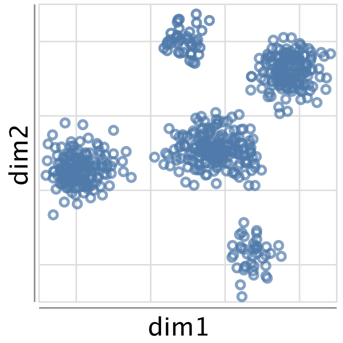
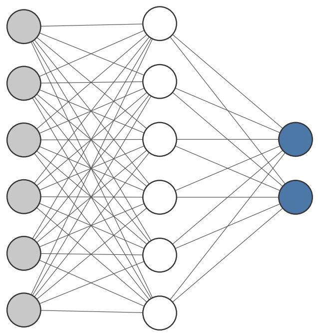
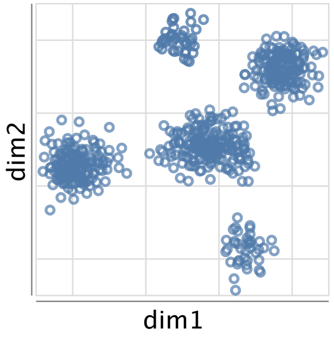
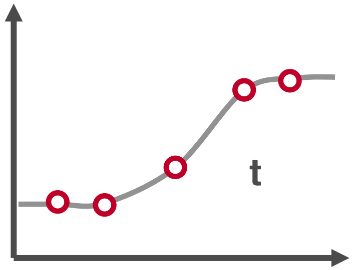


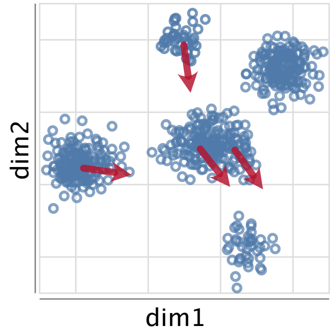
no explicit function f_{tSNE}

$x \in \mathbb{R}^p$ → VAE encoder f_{enc} → $z \in \mathbb{R}^2$ → dynamic model f_{dyn} → $z^{t_1}, z^{t_2}, \ldots \in \mathbb{R}^2$









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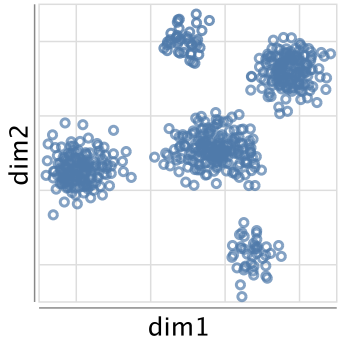

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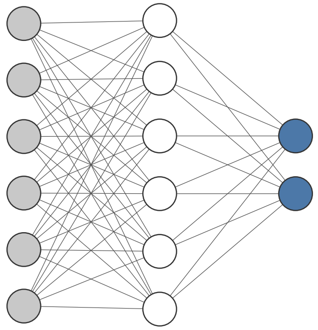
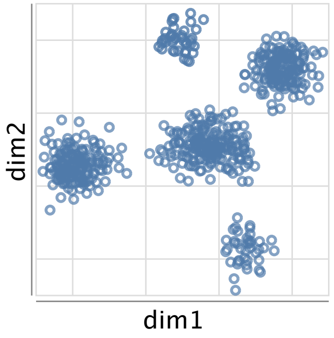
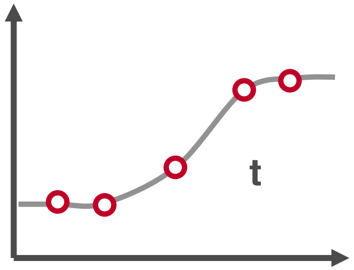
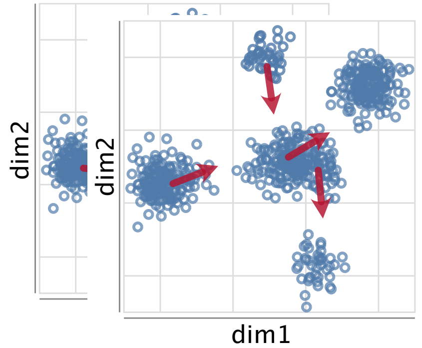
Define $\mathrm{loss}(x; \theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}})$ and minimize w.r.t. $\theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}}$

$\frac{\partial}{\partial \theta_{\mathrm{dyn}}} \mathrm{loss}$ ← $\frac{\partial}{\partial \theta} \mathrm{loss}(x; \theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}})$





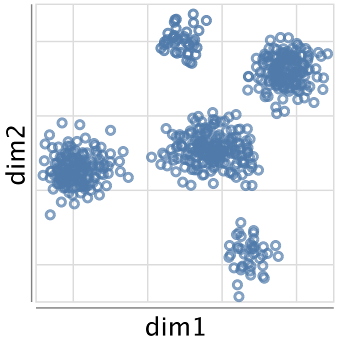




Why deep learning?

Neural networks can easily be combined with other explicit models

$x \in \mathbb{R}^p$ — tSNE algorithm — $z \in \mathbb{R}^2$

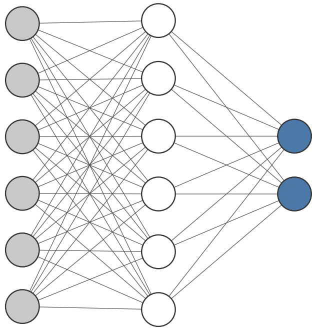


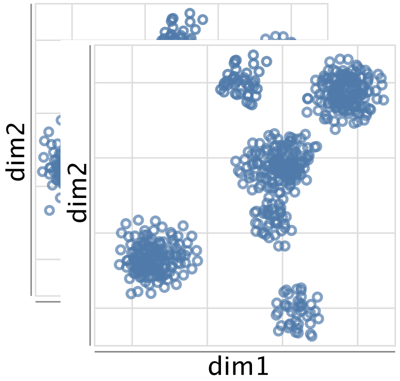
no explicit function f_{tSNE}

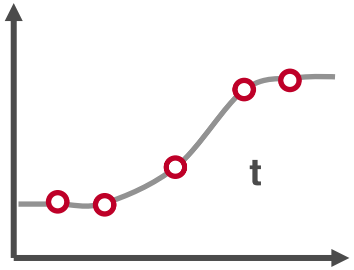
$x \in \mathbb{R}^p$ → VAE encoder f_{enc} → $z \in \mathbb{R}^2$ → dynamic model f_{dyn} → $z^{t_1}, z^{t_2}, \ldots \in \mathbb{R}^2$

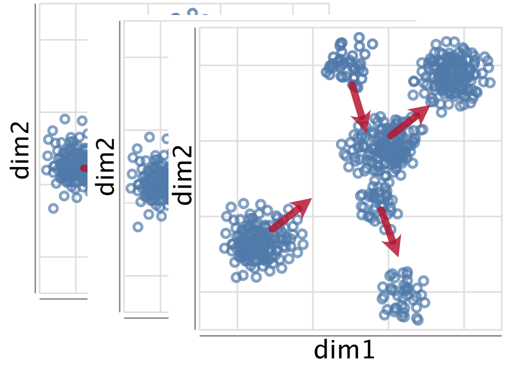
Define $\mathrm{loss}(x; \theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}})$ and minimize w.r.t. $\theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}}$

$\frac{\partial}{\partial \theta_{\mathrm{enc}}} \mathrm{loss}$ ← $\frac{\partial}{\partial \theta_{\mathrm{dyn}}} \mathrm{loss}$ ← $\frac{\partial}{\partial \theta} \mathrm{loss}(x; \theta_{\mathrm{enc}}, \theta_{\mathrm{dyn}})$









Differentiable programming to get the best of both worlds

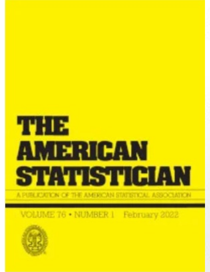
If you can program it, you can estimate the model parameters!

```julia
using Zygote

function loss(x, θ_enc, θ_dec, θ_dyn)
    z = VAE.enc(x, θ_enc)
    z' = dynamic_model(z, θ_dyn)
    x' = VAE.dec(z', θ_dec)
    lossval = ...
    return lossval
end

params = params(θ_enc, θ_dec, θ_dyn)
optimizer = ADAM(η)

for steps in 1:nsteps
    ∇loss = gradient(θ -> loss(x, θ...), params)
    update!(optimizer, params, ∇loss)
end
```

Zygote

Yann LeCun
January 5, 2018 ·

OK, Deep Learning has outlived its usefulness as a buzz-phrase.
Deep Learning est mort. Vive Differentiable Programming!



Statistical Practice

Using Differentiable Programming for Flexible Statistical Modeling

Maren Hackenberg, Marlon Grodd, Clemens Kreutz, Martina Fischer, Janina Esins, Linus Grabenhenrich, Christian Karagiannidis & Harald Binder ...show less

Received 07 Dec 2020, Accepted 17 Oct 2021, Accepted author version posted online: 09 Nov 2021, Published online: 21 Dec 2021

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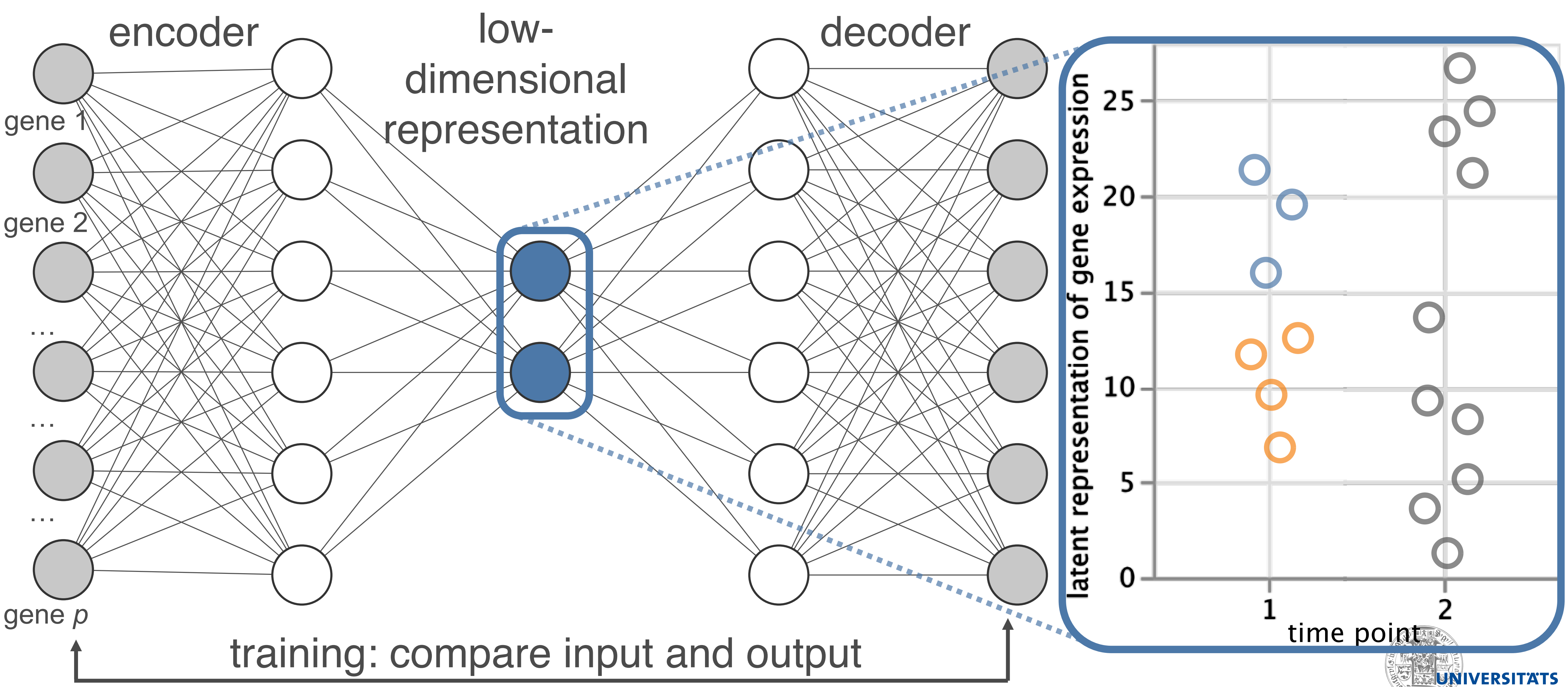
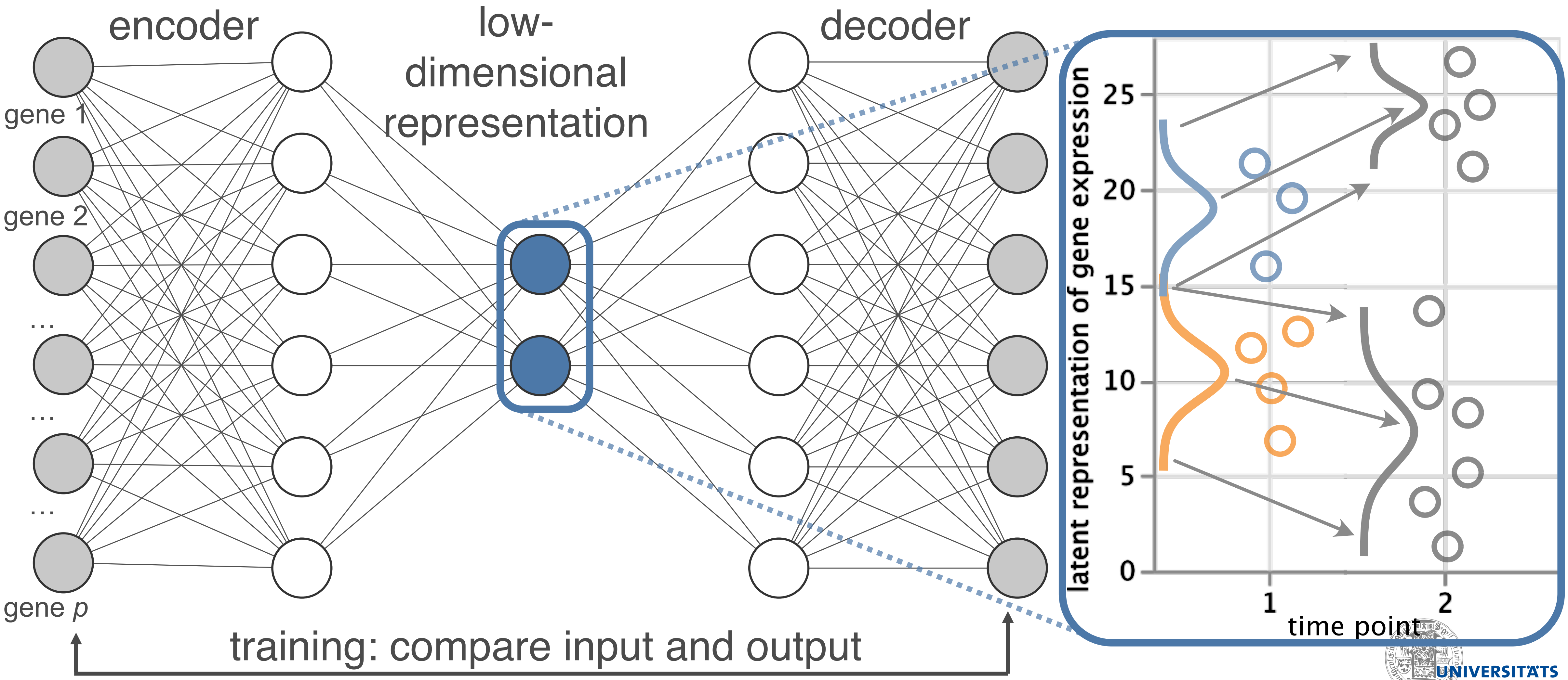
Combining VAEs with dynamic modeling for time-series single-cell RNA-sequencing

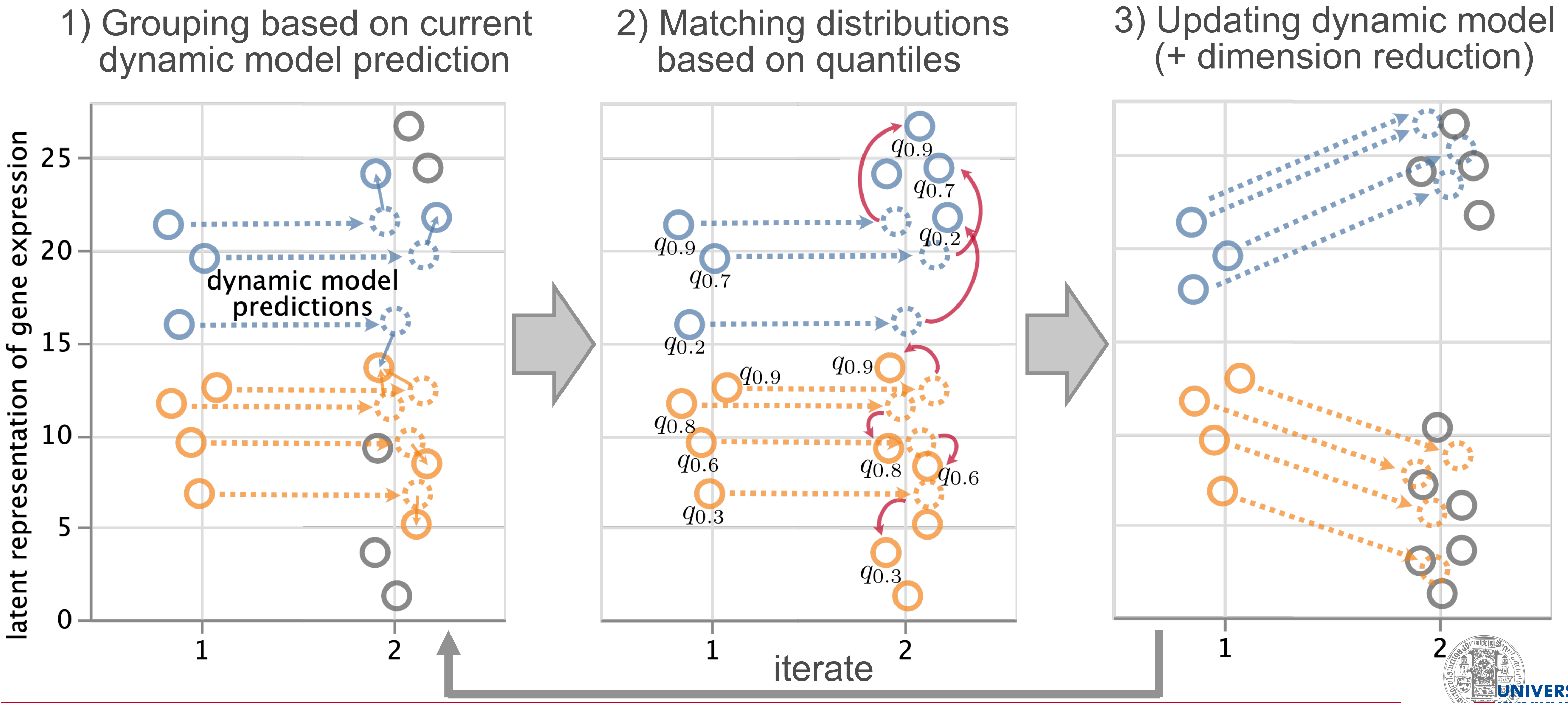


Combining VAEs with dynamic modeling for time-series single-cell RNA-sequencing



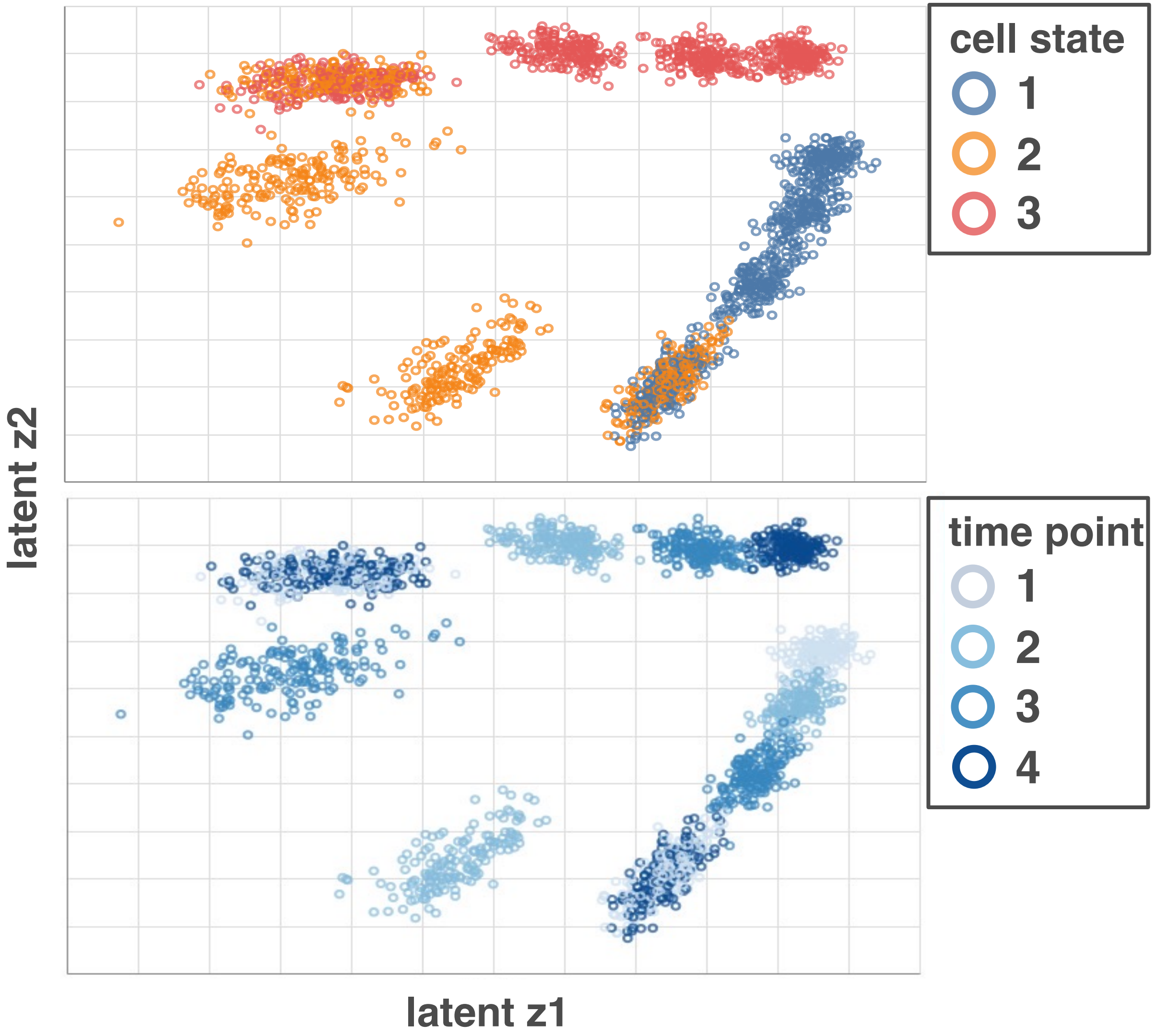
Modeling trajectories in a low-dimensional space

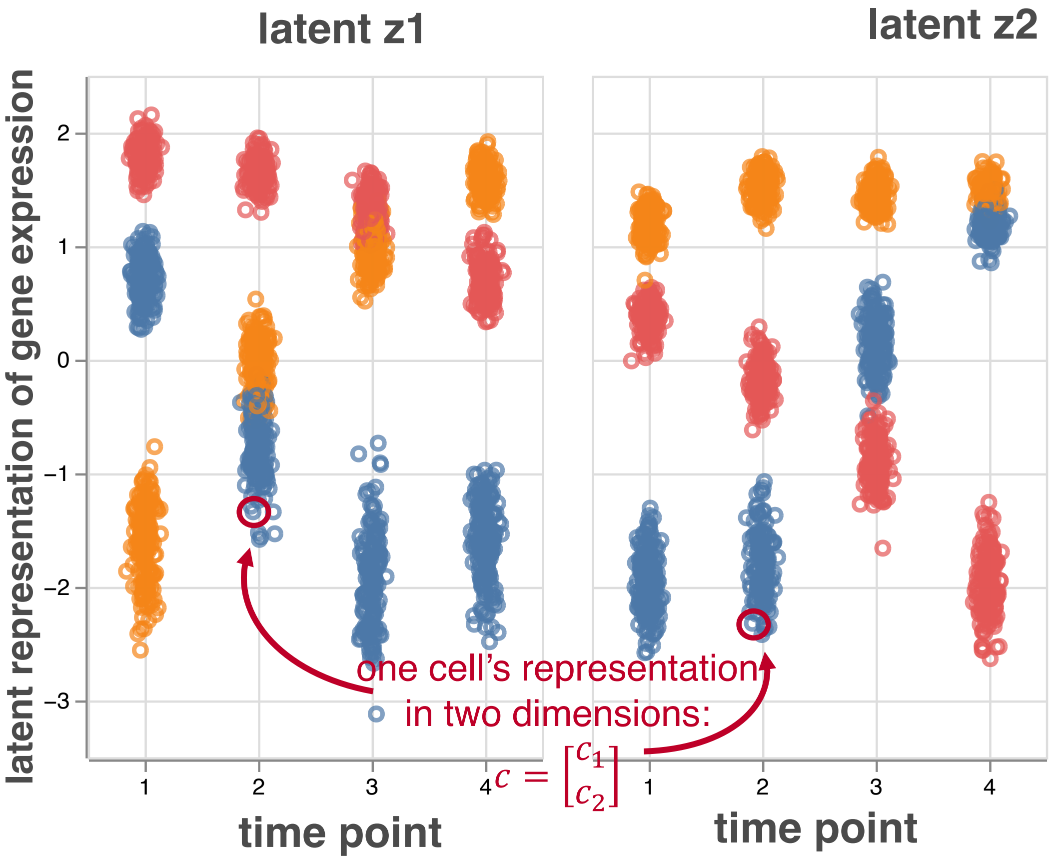
Iteratively optimize a dynamic model for describing trajectories in an EM framework



Simulating time-series scRNA-seq count data

Count data simulated with the `splatter` R package

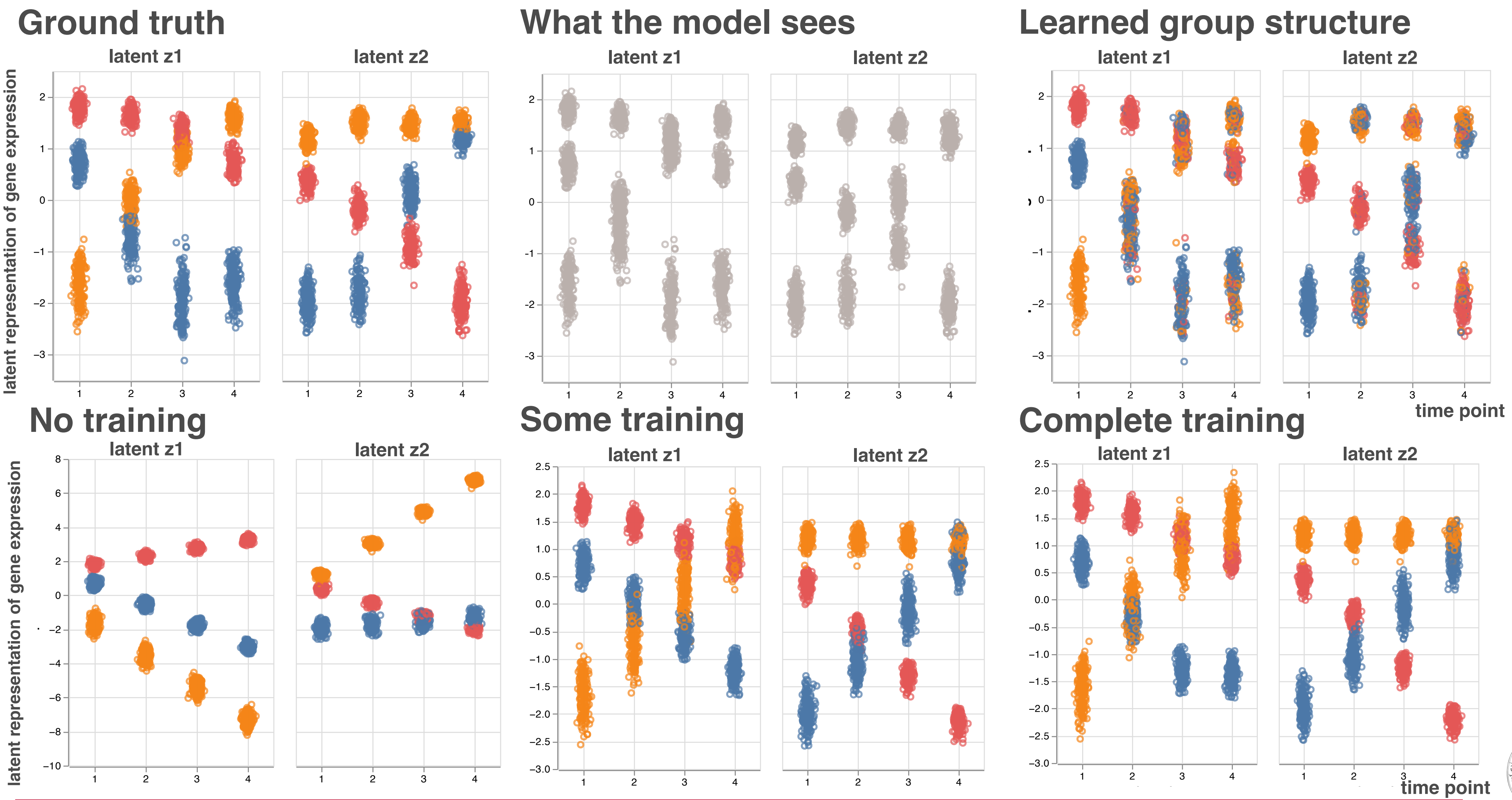




Each cell (circle) appears twice: dimension 1 of its low-dimensional representation in the left panel, dimension 2 in the right panel

Simulation study results

The dynamic model simultaneously infers underlying trajectories and cell states



VAE represen-tation of original data

Model predictions

Summary

- **time-series single-cell RNA-seq is promising…**
  - study highly-resolved subgroups of cells
  - understand group-specific developmental trajectories
- **… but also implies specific challenges:**
  - find a suitable dimension reduction that reflects temporal patterns
  - link groups of cells across time despite no one-to-one correspondence
- using **deep learning**-based approaches and combining them with dynamic **modeling** can help to address these challenges

Thanks to…

Harald Binder

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Martin Treppner

Kiana Farhadyar

Sara Al-Rawi

Moritz Hess

Göran Köber

Camila Fullio

Tanja Vogel

And thanks to you for listening!

Questions?

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