The best of both worlds: Combining deep learning and modeling for time-series single-cell RNA-sequencing data

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Deep learning techniques are powerful and flexible tools for identifying complex structure from data. Yet, they represent a black-box algorithmic modeling culture that is sometimes considered as distinct from classical statistical modeling based on the assumption of an underlying explicit data-generating model. However, integrating the two modeling paradigms and combining their respective advantages can open up new routes for model building and statistical methods development.

In this spirit, we present an application for modeling of trajectories in time-series single-cell RNA-sequencing (scRNA-seq) data from neuronal development: Such time-resolved scRNA-seq data promises insights into mechanisms controlling differentiation and cell fate decisions at the level of individual cells. Yet, at each time point, a different, heterogeneous sample of cells from diverse types and developmental stages is obtained, complicating the identification of specific developmental trajectories across multiple time points.

To address this challenge, we propose a modeling approach that integrates neural network-based dimension reduction with inference of the temporal dynamics. More specifically, we use a deep learning approach to infer a low-dimensional, latent representation of gene expression. In this latent space, we optimize an explicit dynamic model to describe cell type-specific trajectories by alternating between assigning cells into groups based on the current dynamic model predictions, and matching the predicted and true distributions in each group using a quantile-based loss function.

Empirically, we show that this approach allows for inferring distinct developmental trajectories despite the lack of one-to-one correspondence between cells at different time points. Jointly optimizing the neural network for dimension reduction and the dynamic model allows for learning an improved low-dimensional representation specifically adapted to the underlying dynamics.

The approach thus more broadly exemplifies the potential of combining different modeling paradigms, such as neural networks and dynamic modeling, to address complex modeling challenges, such as the joint identification of developmental trajectories and a suitable dimension reduction from time-series scRNA-seq data.