Modeling acute myeloid leukemia from RNA sequencing data in a continuum of differentiation states

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Abstract

Here we present a mathematical model of movement in a reduced dimensional space representing states of cellular differentiation. We motivate this work with recent examples that demonstrate a continuum of cellular differentiation using **single cell RNA sequencing data** (scRNA-Seq) to characterize cellular states in a high-dimensional space, which is then mapped into lower dimensions with dimension reduction techniques. We represent trajectories in the differentiation space as a graph, and model directed and random movement on the graph with PDEs. We present a **PDE model** of hematopoeisis parameterized with publicly available scRNA-Seq data and use it to simulate the pathogenesis of acute myeloid leukemia (AML). The model predicts the emergence of cells in novel intermediate states of differentiation consistent with immunophenotypic characterizations of a mouse model of AML.

Introduction

Recent advance of single cell RNA sequencing (scRNA-Seq) technologies has enabled a new, high-dimensional definition of cell states, that are in the order of 20,000 protein encoding genes that compose the transcriptome. Dimension reduction techniques, e.g., principal component analysis (PCA), diffusion maps (DM) and t-distributed stochastic neighbor embedding (t-SNE), are commonly used to map this 20,000 dimensional data into a lower dimensional space.

This process has revealed a continuum of cell phenotypes, with intermediate states connecting canonical cell states, for example, the process is in hematopoietic cell differentiation. While normal hematopoiesis is long thought to occur through stepwise differentiation of hematopoietic stem cells following a tree-like hierarchy of discrete states (Figure 1A), recent advances in scRNA-Seq technologies now allow resolution of single cell heterogeneity and reconstruction of differentiation trajectories as differentiation occurs as a continuous process, which can be mapped into a continuum of cellular and molecular phenotypes (Figure 1B).

Figure 1A

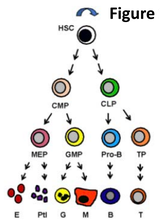
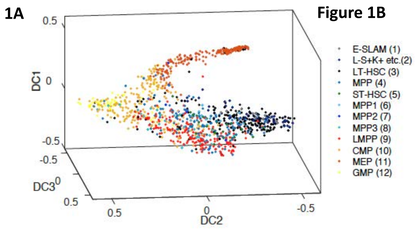


Figure 1B



Model

Dimension reduction technique & Pseudotime ordering

We consider Hematopoetic stem cell differentiation scRNA-Seq data processed with **diffusion mapping** (Nestorowa et al. 2016a) and **diffusion pseudotime** (Haghverdi et al. 2016) to map the data a lower dimensional **continuum** space for the purpose of analyzing cell transition probabilities and inferring trajectories within the reduced space.

PDE model on the graph on the reduced space

$$\frac{\partial u_k}{\partial t} = -\frac{\partial}{\partial x}\left(V_k(x)u_k\right) + R_k(x)u_k + \frac{D_k(x)}{2w_k(x)}\frac{\partial}{\partial x}\left(w_k(x)\frac{\partial u_k}{\partial x}\right), \qquad x \in e_k = \overline{a_k b_k},$$

The model is defined on a **graph** that is identified after clustering the reduced data with classical discrete cell states. The advantage is that we can use the well-known properties of the classical cell states.

An **advection-reaction-diffusion** equation is modeled **on the graph**.

advection term: differentiation rate,
reaction term: growth rate (abnormal proliferation/apoptosis),
diffusion term: phenotypic instability.

The terms can be interpolated using the classical cell state properties.
The boundary condition on the nodes preserve the cell flow.

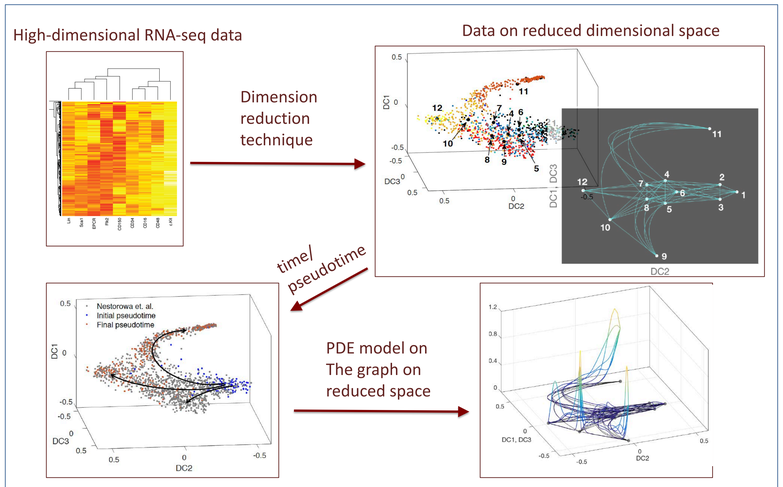
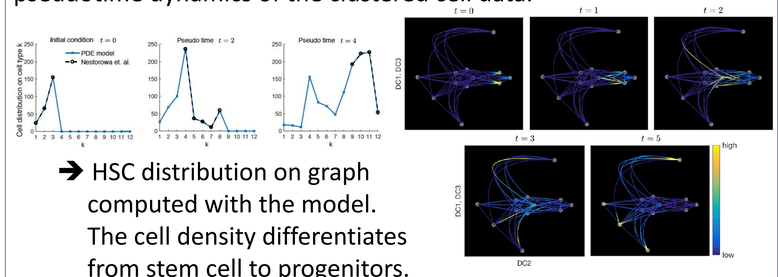


Figure 2. Flow chart of our modeling process: The chart organizes steps taken toward constructing the PDE model. First, high-dimensional data such as single cell RNA-Sequencing (scRNA-Seq) are represented in 2- or 3-dimensional space through one of many dimension reduction techniques. Then, temporal events (pseudotime trajectories) are inferred from the dimension reduced reduced data. We then use the reduced dimension representation and pseudotime trajectories to model ow and transport in the reduced space. The hematopoetic cell data is from Nestorowa et al. (2016a).

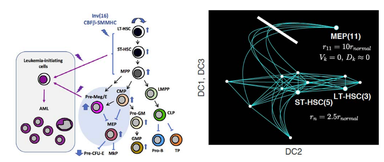
Results

Normal condition: The model parameters are fitted to model the pseudotime dynamics of the clustered cell data.

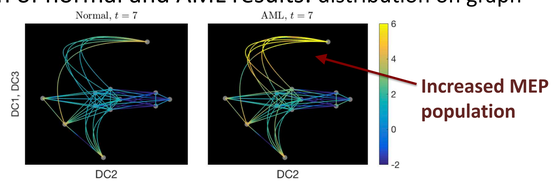


➔ HSC distribution on graph computed with the model. The cell density differentiates from stem cell to progenitors.

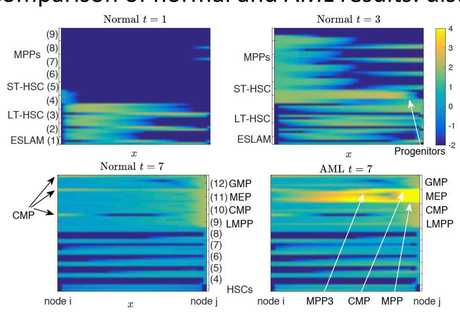
AML condition: blocked flow to MEP and increased proli-ferations in MEP/HSCs.



Comparison of normal and AML results: distribution on graph



Comparison of normal and AML results: distribution on edges



HSC transfers to the differentiated progenitor cells.

The model predicts mixed CMP-MEP cell type that is observed during AML progression exhibit an MEP-like immunophenotype with a CMP-like functional readout (Kuo et al. 2006).

Conclusions

PDE model of HSC differentiation and AML is developed on the reduced diffusion component space using scRNA-Seq data.
The model predicts the emergence of novel intermediate cell states of differentiation in AML condition that is consistent with immunophenotypic characterizations of a mouse model of AML.

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Reference

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