

Continuous Modeling of Cellular Trajectories in The Alzheimer's Brain

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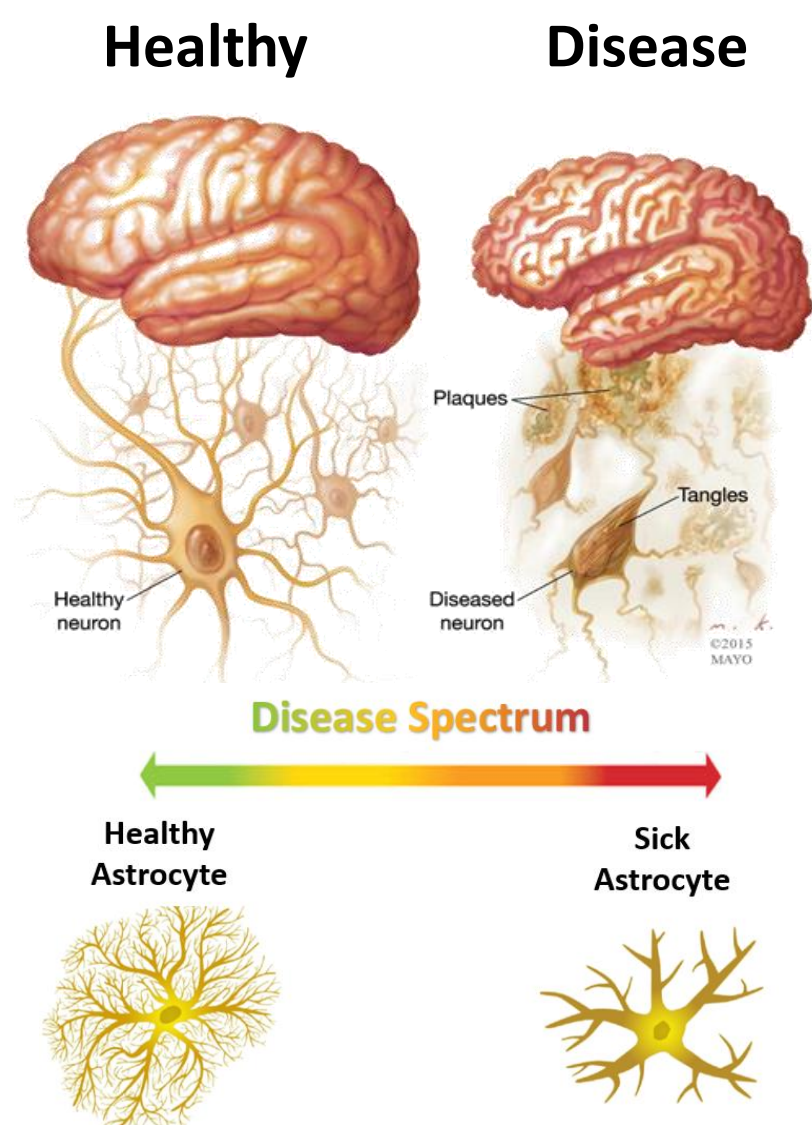
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1. Alzheimer's Disease

Alzheimer Disease (AD) is a progressive neurodegenerative disease that affects millions of people around the world, and the most common form of dementia. As of 2021, an estimated 6.2 million Americans age 65 and older are living with AD and yet, we lack an effective treatment.

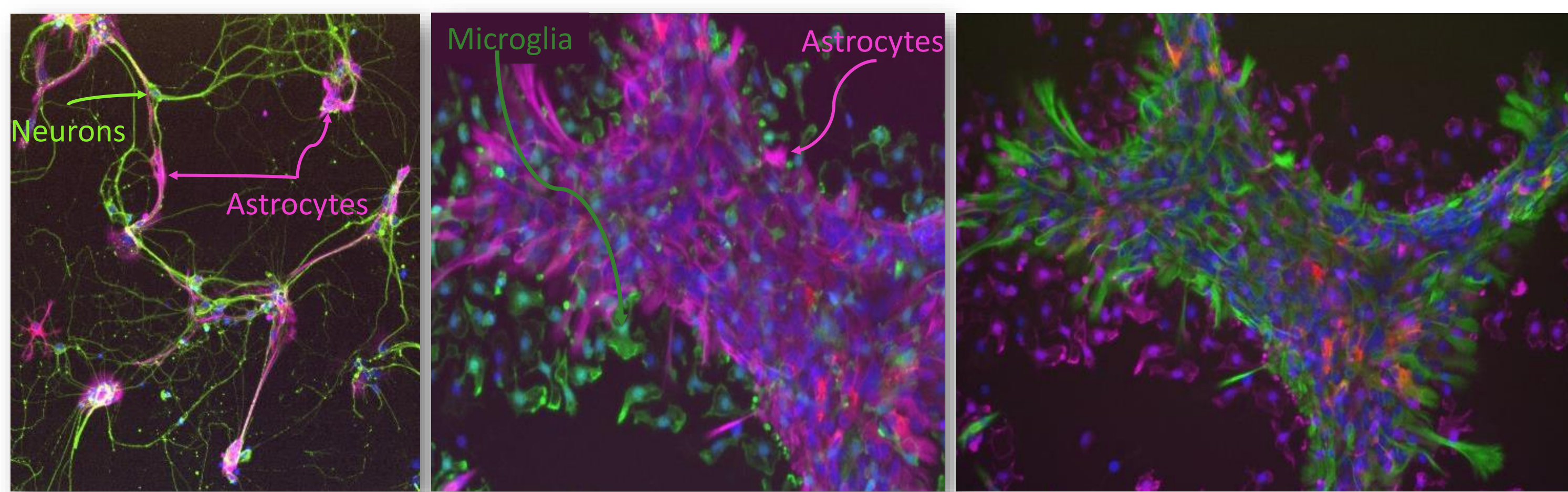
The AD pathology is characterized by severe degeneration of neurons. In addition, we also see that AD patients exhibit an abnormal aggregation of proteins, specifically, amyloid- and neurofibrillary tangles, which are neurotoxic and causes synapse damage.

Traditional research of AD focused on the damage and degeneration of neurons in the brain, whilst more recent work, from our lab and others, showed multiple cell types are changing in AD brains beyond neurons. For example, our lab has been able to show that Astrocytes have appeared to change their cellular state along changes with AD.

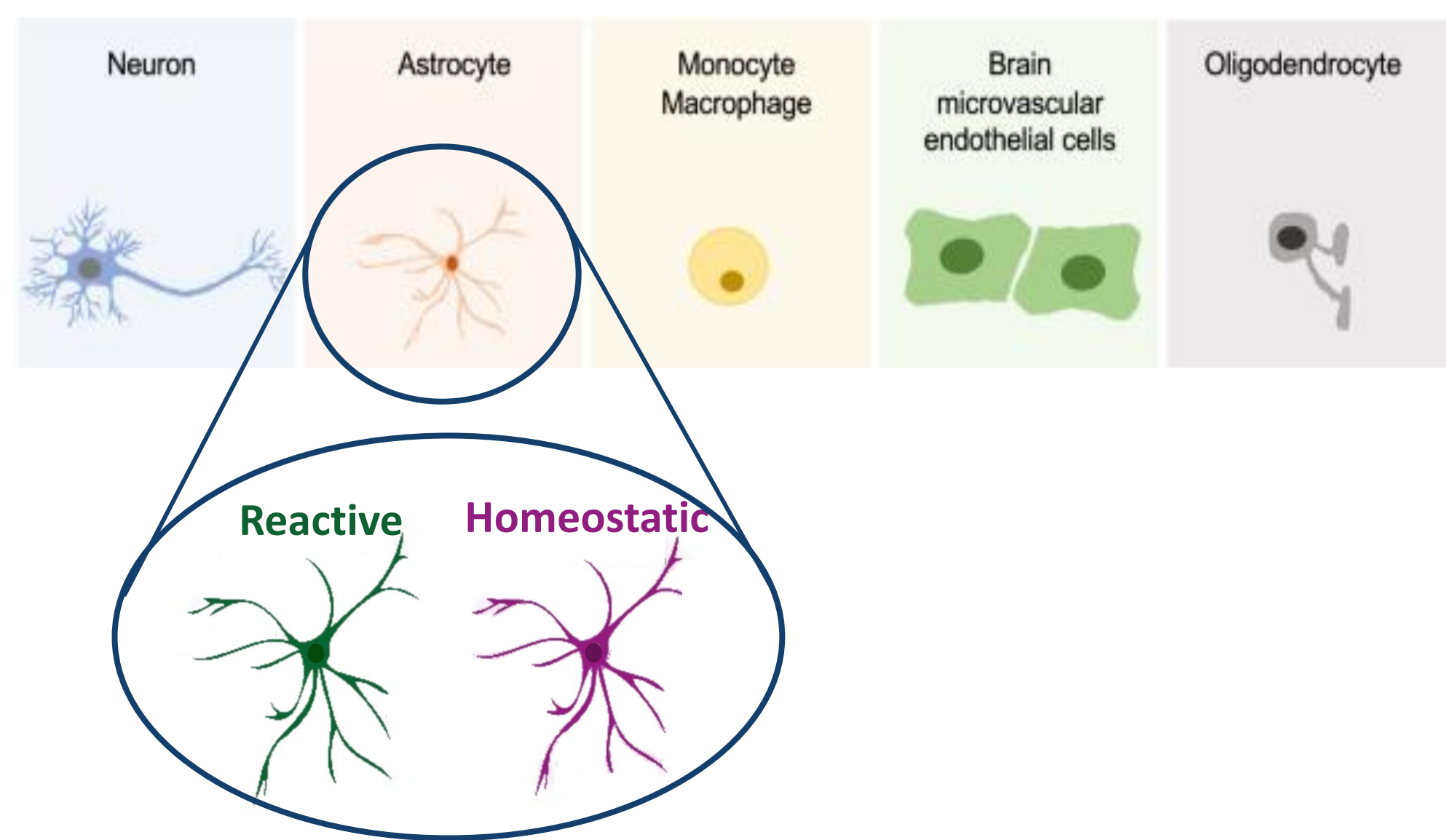


2. The Cellular Landscape of The Human Brain is Diverse

Different Cell Types In the Human Brain

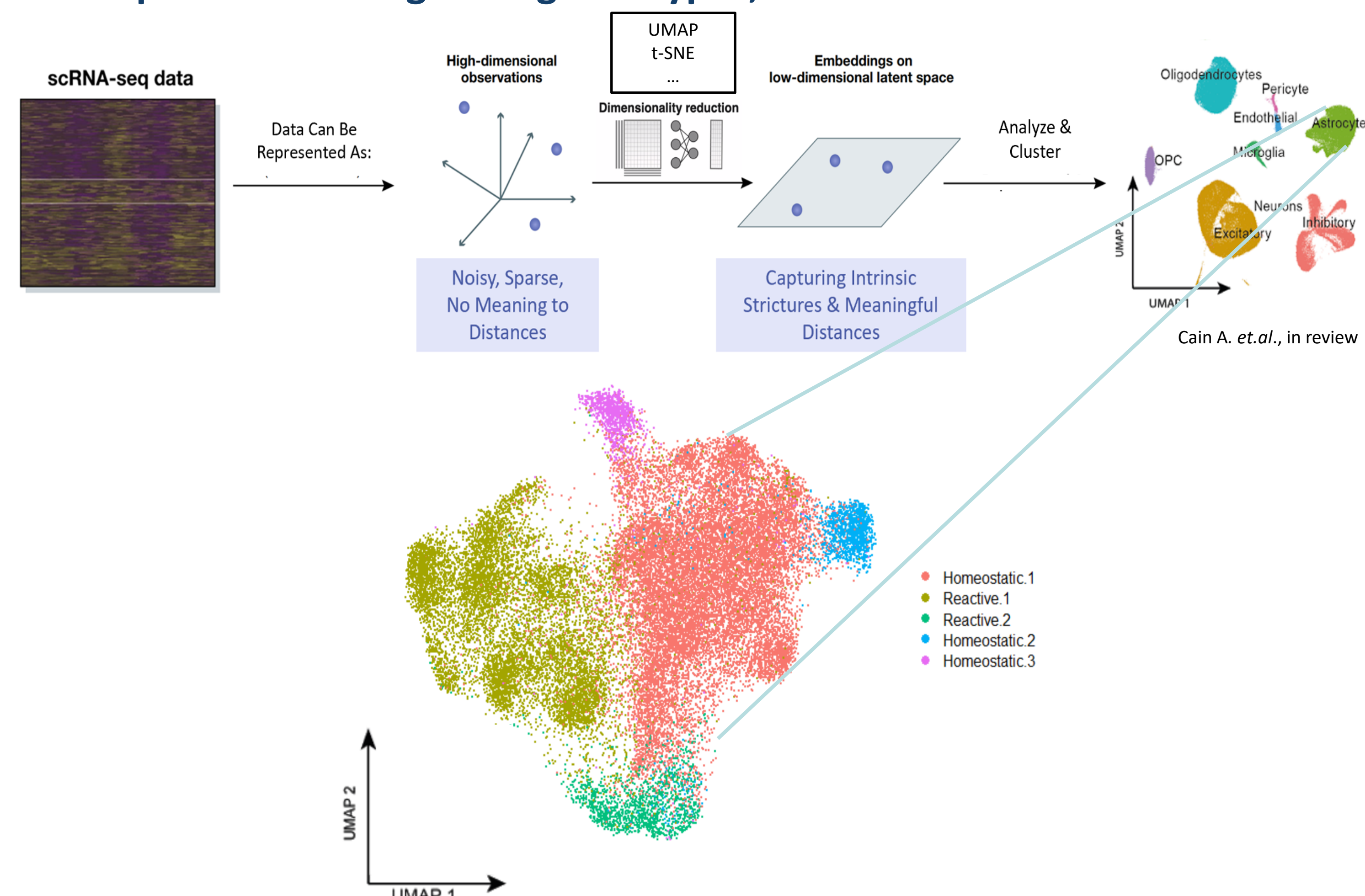


Different Cell States In the Human Brain



Credit: Hodaya Vrabel,
Bio-Imaging Facility
Silberman Institute of
Life Science

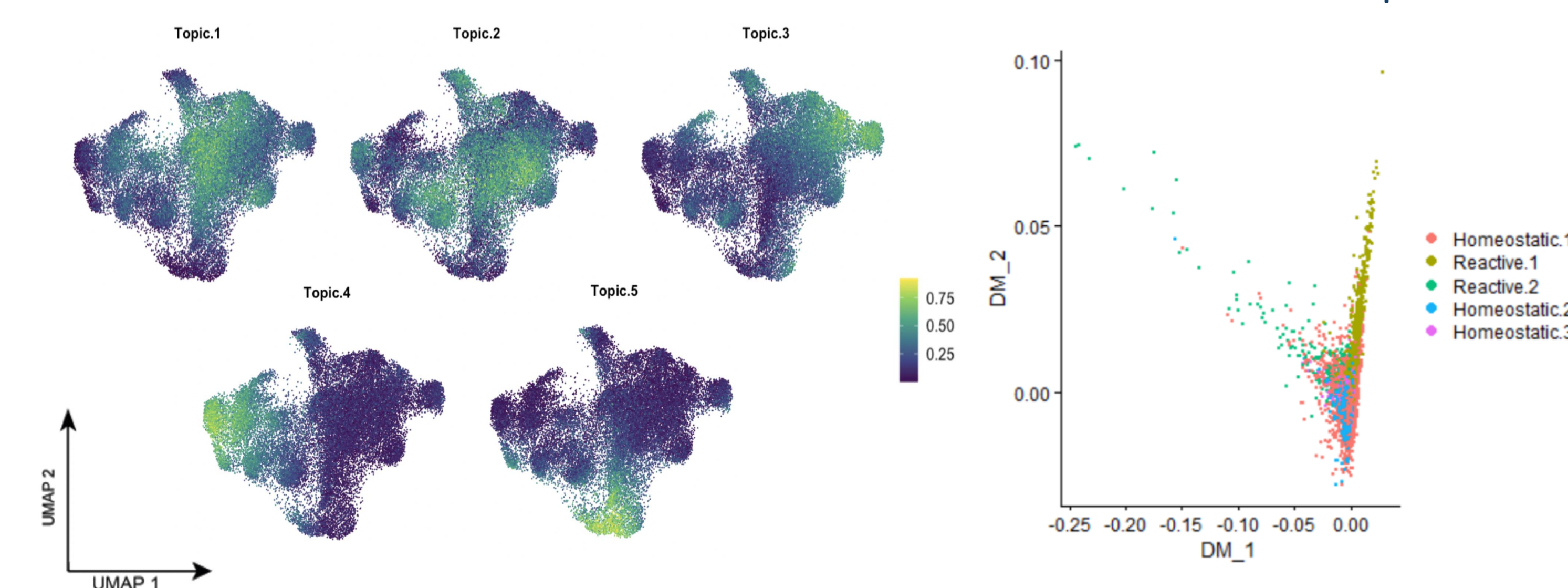
3. Standard Pipeline of Single Nucleus RNA Sequencing (sNuc-seq) Is Capable Of Distinguishing Cell Types, But Fails to Reveal Cell States



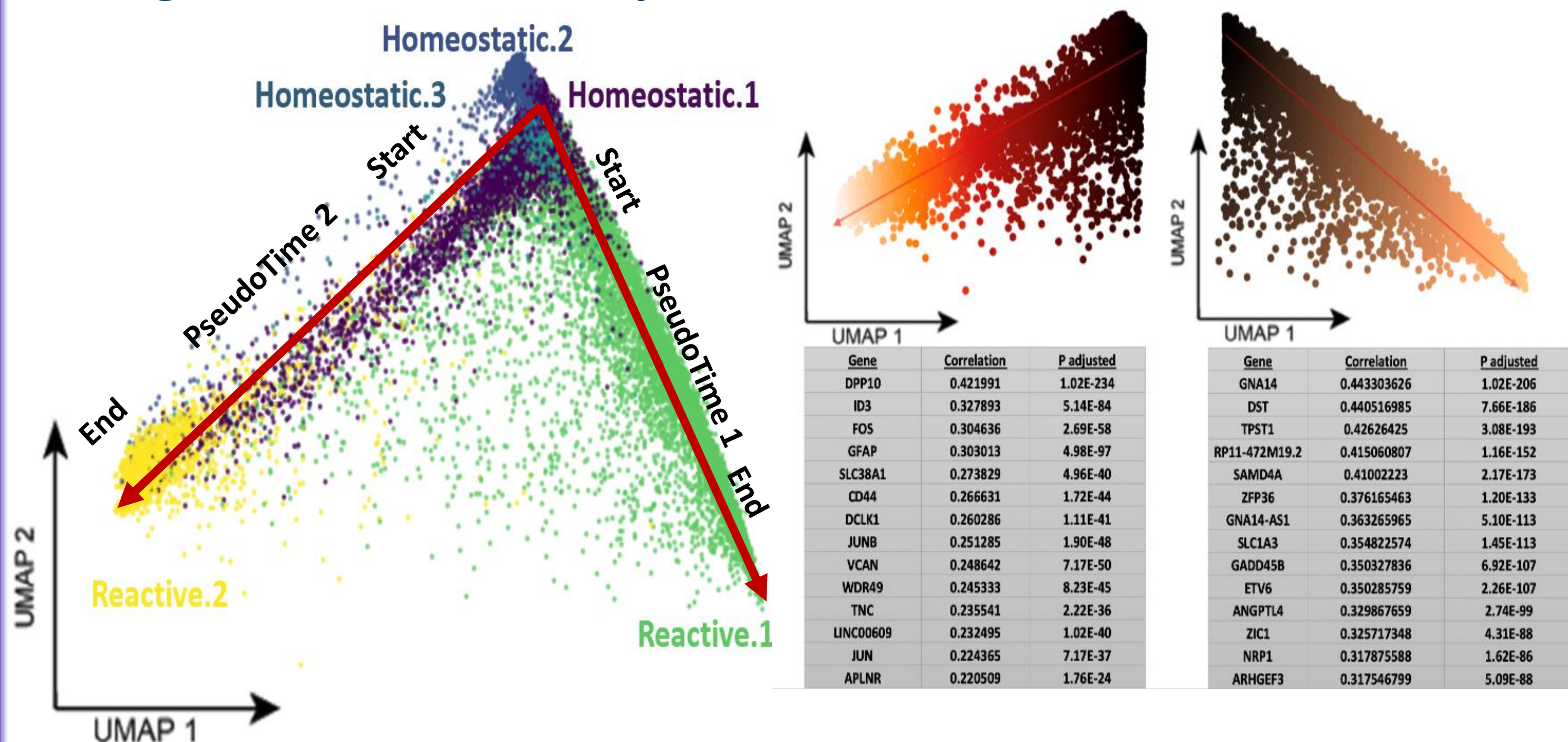
4. Classical Techniques Are Able to Provide Some Insight, But Ultimately Cannot Describe Cell States Transitions

Topic Modeling

Diffusion Maps



5. Under Gaussian Output Metric UMAP Algorithm Can Reveal Trajectories



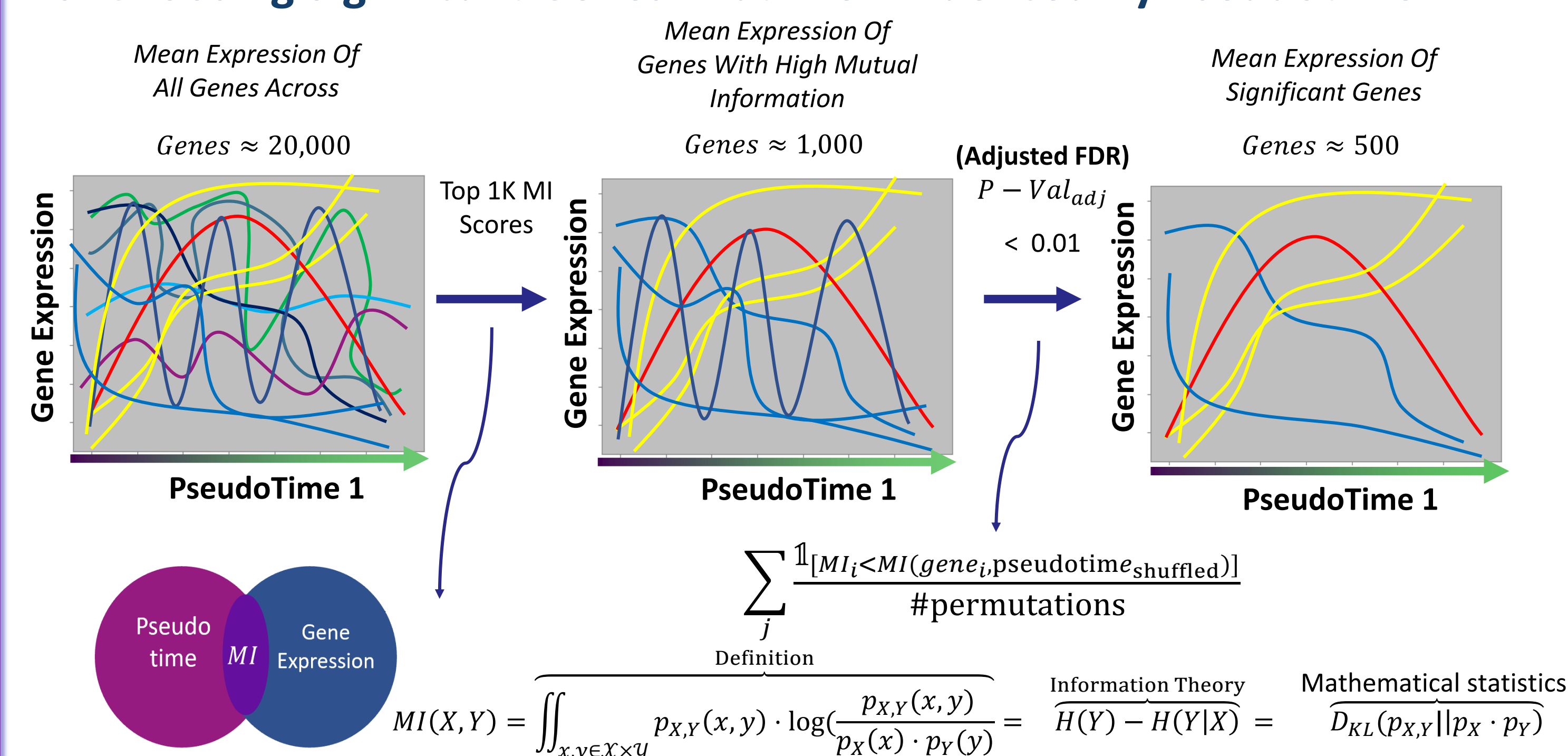
Gaussian Metric:

Consider the space formed by 2d-Gaussian distributions: Let G be a metric space over \mathbb{R}^d with the following metric: $d: \mathbb{R}^d \times \mathbb{R}^d \rightarrow \mathbb{R}^d$ s.t $\forall f, g \in \mathbb{R}^d - f, g$ are gaussians

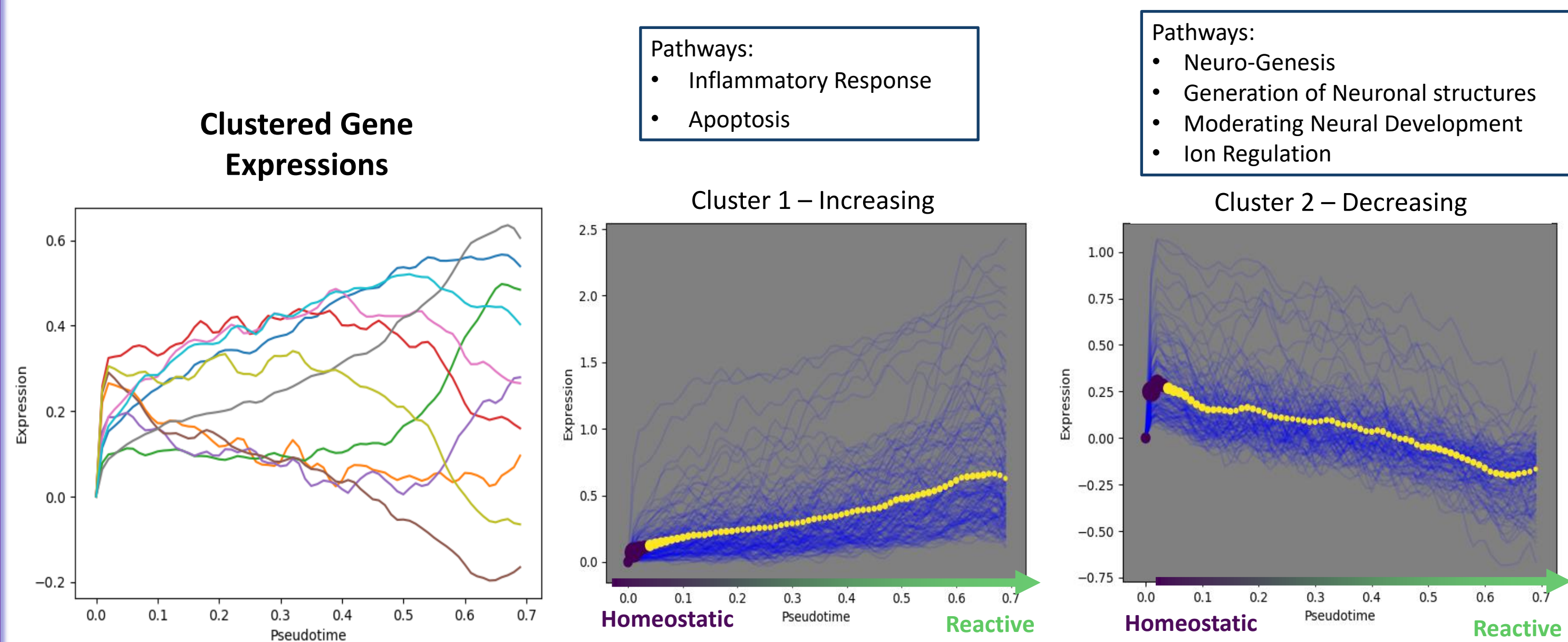
we measure the distance between two Gaussians by the negative log of the inner product between the PDFs.

$$d(f, g) = -\log(\langle f, g \rangle) = -\log\left(\int_{-\infty}^{\infty} f(x) \cdot g(x) dx\right)$$

6. Choosing Significant Genes That Are Influenced By Pseudotime



7. Clustering Significant Genes Reveals Cellular Expression Programs



8. Proposed Model To Be Capture More Complex Structures

