

Reconstruction of epithelial-to-mesenchymal transition dynamics from single cell genomics data reveals parallel transition paths

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An important open question in epithelial-to-mesenchymal transition (EMT) is whether the transition proceeds through linear or multiple parallel paths¹. To address this question, one needs to trace how a cell changes over time. Single cell RNA seq (scRNA-seq) has been widely used in studying EMT, but the destructive nature of the technique makes it challenging to extract dynamical information. In a more general context it is a grand challenge in the single cell field to reconstruct equations of motion of the underlying gene regulatory networks (GRN) that regulate cellular dynamics and cell fate decision². To address this challenge, our lab has developed Dynamo, a machine-learning based analytical framework to reconstruct single cell dynamical equations³. The framework is able to estimate RNA kinetic parameters from a wide range of scRNA-seq data, reconstruct continuous vector field functions, which govern cell state evolution, and contain quantitative information on gene regulations. The framework also allows in silico screening of gene perturbations to modulate cell fate transitions such as EMT/MET. We applied this computational framework to a MCF10A scRNA-seq data, a human mammary epithelial cell line, where cells were treated with several increasing doses of TGF β . With this framework, we analyzed how an external factor, the various doses of TGF β , alters stability of different EMT phenotypes. Utilizing the reconstructed vector fields from each dose of TGF β , we identified parallel EMT transition paths (Fig. 1), which also agreed with our live cell imaging studies using A549 cells^{4,5}. Currently, we are integrating scRNA-seq analysis and live cell imaging platforms for screening combinatorial EMT-interfering drugs.

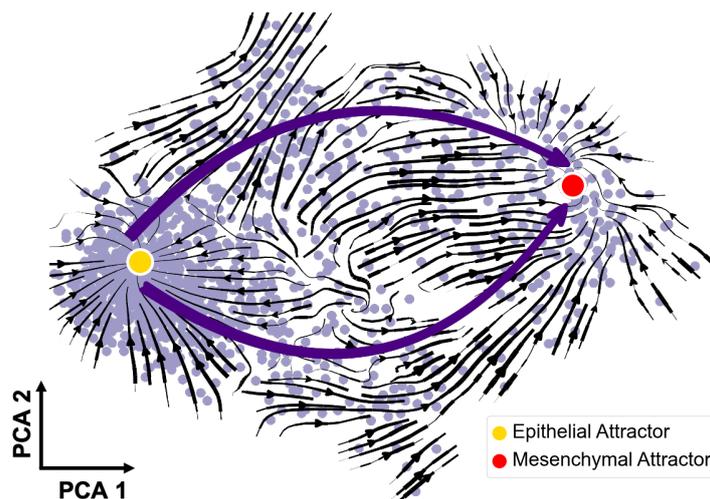


Figure 1: Parallel EMT transition paths between epithelial to mesenchymal state

Two parallel pathways emerge in the 12.5 ng/ml dose of TGF β vector field, transitioning from the epithelial to mesenchymal attractor.

References

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