INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Phenotypic Plasticity of Cells in Epithelial-Mesenchymal Transition: An Experimental and Mathematical Study

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SHORT ABSTRACT

Phenotypic plasticity or phenotypic state transition is the potential of cells to switch between different phenotypes of the cell. We investigated the phenotypic plasticity in Epithelial-Mesenchymal Transition (EMT) at the phenomenon-level using EGF-induced EMT of MDA-MB-468 cells as an experimental system. We defined phenotypic states in terms of the morphology of MDA-MB-468 cells: Cobble, Spindle, and Circular. Using quantitative image analysis, we captured state transition dynamics and developed a mathematical method to estimate state transition trajectories. Our analysis showed that the dominant, reversible state transition path is Cobble $\vdash\!\!\rightarrow$ Circular $\vdash\!\!\rightarrow$ Spindle $\vdash\!\!\rightarrow$ Cobble. We also showed an ultrasensitive on/off switch involving phospho-EGFR controls the state transition dynamics in these cells. Further, we used the same experimental system to investigate the effect of background noise on cell state transition. We introduced background noise by using suboptimal doses of TGF-β1. TGF-β1 alone did not induce any state transition in these cells. We used statistical analysis and information theory-based methods to understand the effects of TGF-β1 on EGF-induced state transition. Our analysis showed that TGF-β1 exerted a positive synergistic influence to push cells towards Spindle and Cobble states but, at the same time, increased the noise in the process. In this work, we classified cells based on morphology. We cannot isolate the cell types based on shape for further gene expression studies. Techniques like Quantitative PCR (qPCR) generates ensemble-averaged data. In our current work, we developed a mathematical tool to estimate cell-type-specific gene expression by deconvoluting the qPCR data of a mixed population of cells. Our algorithm is generic and can be used to deconvolute any population-level data (like qPCR, Western Blot) when the distribution of subpopulations is known.

In this thesis, we used the EGF-induced EMT of MDA-MB-468 cells as an experimental system. However, the physical concepts and mathematical approaches developed in this work are generic and can be used for any other cellular phenomenon involving phenotypic state transition.

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