Population Dynamics Epithelial-Mesenchymal heterogeneity in Cancer Cells

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Epithelial-Mesenchymal heterogeneity in cancer has been widely characterized *in vitro, in vivo,* and *in silico* over the past two decades, owing to its connections with the tumor-initiating program, drug resistance, and metastasis. However, little is known about how this heterogeneity emerges spontaneously. Here, we present noise or fluctuations in copy number doubling during the cell cycle and later partitioning of EMT-inducing transcription factor SNAIL at cell division among the daughter cells as a possible mechanism of spontaneous state transition. Our in-silico model explained observed bulk-level and single-cell clonal behavior reported in PMC42-LA breast cancer cells.

Keywords **—** asymmetric cell division; epithelial-mesenchymal heterogeneity; epithelial-mesenchymal plasticity; population dynamics**.**

I. Introduction

Intra-tumor heterogeneity refers to cells with different functional characteristics within a tumor and remains a significant bottleneck in cancer therapy [1]. This heterogeneity can be of genetic or non-genetic origins [2]. Studies on clonal cell populations reveal the non-genetic heteroheneity among cells, which often harbor fractions of cells with enhanced fitness in unpredicted environments such as drug treatment [3]. Therefore, understanding the mechanism leading to cell-cell variability can help design better therapeutic strategies.

One of the canonical forms of heterogeneity is along the Epithelial-Mesenchymal axis, where the count of distinct states depends on the size of the bio-markers set [4,5]. Further, spontaneous state transition has been reported both in-vitro and in-vivo [4,5]. However, less is known about the mechanism behind these state transitions.

Here, we propose asymmetric partitioning of Epithelial-Mesenchymal Transition (EMT) inducing transcription factor (TF) among daughter cells that can cause spontaneous switching. Our results corroborate observations made in PMC42-LA breast cancer cells [4].

II. Results

We built on an existing population dynamics model accounting for cell division and death of cells from three subpopulations – Epithelial , Hybrid, and Mesenchymal [6]. The phenotype is ascribed to a cell depending on molecular levels of components in the underlying gene regulatory network [7]. A cell division event introduces variability in the levels of SNAIL among the daughter cells due to its imperfect partitioning. This asymmetric may cause spontaneous state switching in daughter cells. The noise/fluctuation accounted here is considered normally distributed and proportional to the parent cell's SNAIL copy number. Below results are from such a formalism based model:

1. The dominance of Epithelial cells in population over time irrespective of initial subpopulations fraction.
2. Effect of starting with different subpopulations fraction, heterogeneous doubling time, and noise levels on the rate of attaining high E fraction.
3. Probability of phenotypic switching in a cell division and rate of phenotypic switching - we show that switching probability in a cell division and switching rates are a function of the cell's position on the E-M axis (level of Snail). Also, there is a skew in the switching rates of E and M cells.
4. Heterogeneity in subpopulations fraction among single-cell clones at initial times - we simulate the model starting with a single cell of either E, E/M, or M type. We observe that each single-cell clones after two weeks have distinct subpopulations fractions. This variability was highest in single M cell clones.

III. Conclusion

The population dynamics model capturing phenotypic switching at cell division can explain experimental observations reported on PMC42-LA breast cancer cells - 1) the maintenance of the Epithelial dominant state and 2) variation in phenotype fractions among single-cell clones.

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