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Network dynamical systems approach to decipher fundamental principles in cell fate transitions

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Cells fate transitions orchestrated by exceedingly intricate networks of transcription factors is pivotal to development, differentiation, and unfortunately, to diseases such as metastasis of carcinomas. Therefore, understanding the principles governing cell fate transitions is critical for elucidating developmental processes, and phenotypic plasticity leading to non-genetic tumor heterogeneity. By employing gene regulatory networks (GRNs) underlying epithelial-mesenchymal transition, a cell fate transition program enabling reversible fate transitions between epithelial, mesenchymal, and hybrid cell states, we explore the dynamic interplay between network topology, combination, and cellular phenotypes.

We show that topological features of GRNs, such as positive/negative feedback loops and their connectedness, cohesion and consistency of interactions, can provide firsthand insights about the emergent dynamics and eventually the cellular phenotypes enabled by the complex networks.

Further, our mathematical models of specific two-component network architectures reveal that cooperativity and logic underlie robust phenotypic switches, enabling cells to exhibit both hysteretic (abrupt) and smooth, continuous state transitions. These behaviors, analogous to differentiation, trans-differentiation, and reprogramming, reflect an underlying dynamic epigenetic landscape. Furthermore, we explored the role of intrinsic and extrinsic signals in modulating fate transitions, uncovering how network logic and signal asymmetry contribute to cellular reprogramming and differentiation.

Our results show that fate transitions during signal induction is subject to logic and different logics can steer cell to different fates. Taken together, our findings highlight that network features and the combinatorial logic can reveal crucial information to understanding the evolutionary principles of fate transitions in development and carcinomas.

These findings unravel potential ways for developing more targeted cancer therapies aimed at disrupting the adaptive potential of metastatic cells as well

as implementing logic for engineering cell fates for therapeutic applications in synthetic biology and regenerative medicine.

Keywords: regulatory networks, cell fate decisions, cancer metastasis, network dynamical systems

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