lize hybrid epithelial-mesenchymal cells (shown in Supplemental Material [20], Fig. S4) further bolsters the evidence for a connection between non-canonical phenotypic states and high frustration in biological networks. Our model thus provides a new perspective on how noise in the dynamics of regulatory networks in cancer cells can contribute towards the failure of anti-cancer therapies—noise can facilitate the emergence of cancer cells that exhibit non-canonical phenotypic states. Additionally, accumulation of mutations in biological networks, another characteristic associated with cancer progression, will also promote aberrant cell fate choice. Both noisy gene expression and accumulation of mutations have been shown to be key contributors to intra-tumoral heterogeneity, with significant implications for the failure of anti-cancer therapies [36]. Estimation of network frustration from cancer cell gene expression data will be a direct test of the role of cell fates associated with high frustration states in disease aggressiveness.

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