Critical high-dimensional state transitions in cell populations or why cancers follow the principle "What does not kill me makes me stronger"[1]

SUI HUANG, Institute for Systems Biology

Transitions between high-dimensional attractor states in the quasi-potential landscape of the gene regulatory network, induced by environmental perturbations and/or facilitated by mutational rewiring of the network, underlie cell phenotype switching in development as well as in cancer progression, including acquisition of drug-resistant phenotypes. Considering heterogeneous cell populations as statistical ensembles of cells, and single-cell resolution gene expression profiling of cell populations undergoing a cell phenotype shift allow us now to map the topography of the landscape and its distortion. From snapshots of single-cell expression patterns of a cell population measured during major transitions we compute a quantity that identifies symmetry-breaking destabilization of attractors (bifurcation) and concomitant dimension-reduction of the state space manifold (landscape distortion) which precede critical transitions to new attractor states. The model predicts, and we show experimentally, the almost inevitable generation of aberrant cells associated with such critical transitions in multi-attractor landscapes: therapeutic perturbations which seek to push cancer cells to the apoptotic state, almost always produce "rebellious" cells which move in the "opposite direction": instead of dying they become more stem-cell-like and malignant. We show experimentally that the inadvertent generation of more malignant cancer cells by therapy indeed results from transition of surviving (but stressed) cells into unforeseen attractor states and not simply from selection of inherently more resistant cells. Thus, cancer cells follow not so much Darwin, as generally thought (survival of the fittest), but rather Nietzsche (What does not kill me makes me stronger).