

the minimally frustrated stable states, biological networks can robustly establish cell types and regulate cell fate choice between these types. The number of commonly observed cell fates is thus limited to the number of expression patterns in these minimally frustrated stable states. The minimal frustration property distinguishes stable states corresponding to canonical cell types from other possible stable states of the biological network. In contrast, while a random network may have a collection of stable states with an expression pattern similar to that of a canonical cell type, these stable states will in no way be special as compared to the numerous other stable states the random network can exhibit.

Cancer cells exhibit very noisy gene expression which may be driven by the overexpression of certain genes [31–33], corrupted epigenetic regulation [34], or by metabolic re-programming [35]. Our results suggest that given the

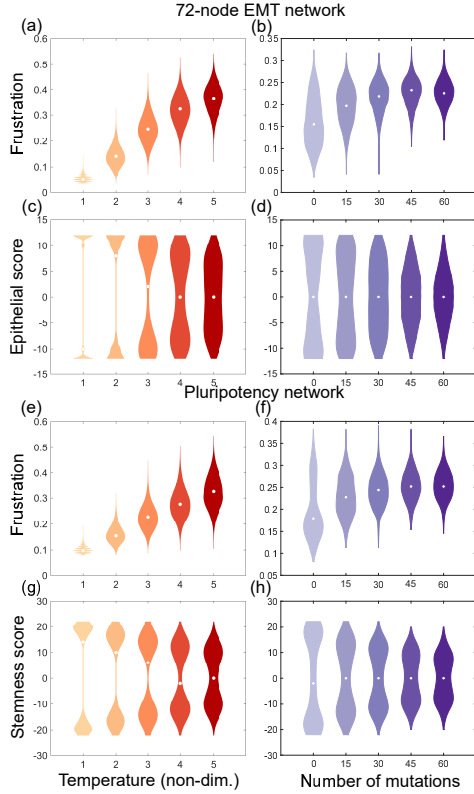


FIG. 3. (Color online) High frustration states are increasingly occupied under noisy dynamics or if the biological network accumulates mutations. (a), (e) Frustration of observed biological network states under noisy node dynamics. The dynamics become more and more noisy as the pseudo-temperature is increased. (b), (f) Frustration of observed states when mutations are introduced into biological networks (without noise in the network dynamics). (c), (d) Epithelial scores of observed states under different levels of noise in the network dynamics (c) and when the network is mutated (d). (g), (h) Stemness scores of observed states under different levels of noise (g) and when the network is mutated (h). The white circle in each violin indicates the median.

high gene expression noise, cancer cells must frequently exhibit ambiguous cell fate choices. Such behavior has been reported across cancer subtypes, and non-canonical phenotypic states in cancer cells have been shown to be associated with disease aggressiveness. For example, hybrid epithelial-mesenchymal cells, reported across cancer types, have been implicated in the metastatic aggressiveness of solid tumors [22]. Also, populations of small cell lung cancer cells treated with anti-cancer drugs have been shown to enrich for hybrid neuroendocrine-mesenchymal cells [16]. Lowering of network frustration upon deletion from the EMT network of factors known to stabi-

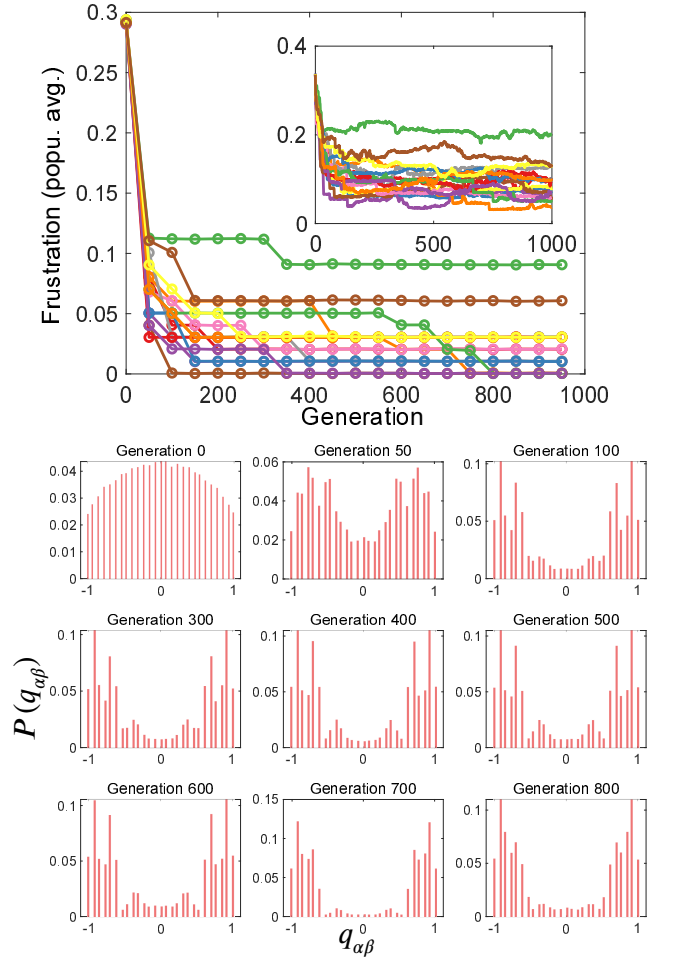


FIG. 4. (Color online) Evolution of biological behavior by a population of random networks under selection for networks with low frustration states. (Top) Frustration of the least frustrated observed state averaged over the networks in a population of 500 networks. Different curves indicate independent simulation runs. (Inset) State frustration averaged over the end states of simulations starting from 50 random initial conditions for each network followed by averaging over the networks in the population. The initial population of 500 random networks was generated from the 26-node EMT network. (Bottom)  $P(q_{\alpha\beta})$  at different time points during the evolution simulation, shown for one of the simulation runs.