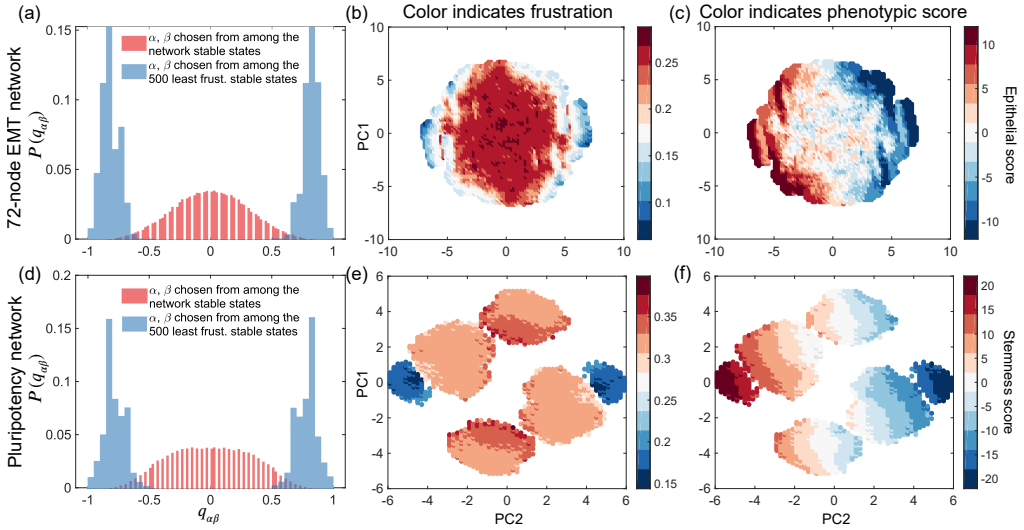

FIG. 2. Minimally frustrated stable states of biological networks define canonical cell types. (a), (d) $P(q\quad)$ is bimodal for the minimally frustrated stable states of both the 72-node EMT network and the pluripotency network. (b), (c), (e), (f) Principal component-representation of the 200000 observed stable states of the 72-node EMT network and of the pluripotency network. In each case, we included 100000 least frustrated and 100000 most frustrated stable states. In (c), a high, positive score indicates an epithelial phenotype while a low, negative score indicates a mesenchymal phenotype. In (f), a high, positive score indicates a stem cell phenotype while a low, negative score indicates a di erentiated phenotype. Clusters with extreme values of the phenotypic scores represent canonical cell types. See Supplemental Material [20], section II (d) for details of how the scores were defined.

species in cells has recently been shown to inhibit such co-presentation [23–25].

E ect of noise in network dynamics.— So far, we have neglected stochasticity in our analyses. Noise in gene expression can have significant implications for cellular function [26]. We defined a pseudo-Hamiltonian $H = -\sum_{i,j} J_{ij} s_i s_j$ and used the finite-temperature Metropolis Monte Carlo algorithm [27, 28] to probe network behavior under noisy dynamics (for details of the simulations, see Supplemental Material [20], section II (e)). As node dynamics become increasingly noisy, biological networks become more and more likely to exhibit states with high frustration (Fig. 3 (a) and 3 (e); also see Supplemental Material [20], Fig. S5 (a)-(c), and S6). Functionally, this manifests as more and more cells in a population presenting with ambiguous cell fate choices (Fig. 3 (c) and 3 (g)).

E ect of network mutations.— Another scenario in which cells presenting ambiguous cell fate choices are frequently observed in our modeling framework is if the biological network becomes mutated (Fig. 3 (b) and 3 (f); also see Supplemental Material [20], Fig. S5 (d)-(f), and S7). We observed that the studied biological networks are relatively robust, and it is only after a signifivant number of mutations have accumulated that a significant fraction of cells in the population start exhibiting non-canonical phenotypic states. Since high frustration stable states are far more numerous than minimally frustrated stable states, cell-to-cell variation in network states will be higher when cells exhibit high frustration.

Emergence of biological characteristics in random networks.— Under selection for networks with low frustration states, a population of randomized 26-node EMT networks can evolve to exhibit the behavior reported herein for the corresponding biological network (Fig. 4; see Supplemental Material [20], section II (f) for details of the simulation). This includes existence of minimally frustrated stable states that are frequently encountered when starting from random initial conditions (Fig. 4 (Top)) and a bimodal $P(q\quad)$ when , pairs are sampled from among the minimally frustrated stable states (Fig. 4 (Bottom)). That such an evolutionary process is feasible lends crucial support to the hypothesis that the existence of minimally frustrated stable states is a feature that has been acquired by complex biological networks over evolutionary time. Finally, preliminary data suggests that one can relax the assumption of a Boolean modeling framework without changing any of the conclusions (see Supplemental Material [20], section II (g), Fig. S8, S9 (b), and S9 (d)).

Discussion— In the energy landscape description of protein folding [29, 30], existence of minimally frustrated structural conformations distinguishes biological proteins from random heteropolymers. Here, we have shown that the existence of minimally frustrated stable states similarly distinguishes biological regulatory networks from random networks. These minimally frustrated stable states represent canonical cell types and because most random initial conditions dynamically evolve to one of