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Gene expression dynamics during cell differentiation: Cell fates as attractors and cell fate decisions as bifurcations[1]

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During development of multicellular organisms, multipotent stem and progenitor cells undergo a series of hierarchically organized "somatic speciation" processes consisting of binary branching events to achieve the diversity of discretely distinct differentiated cell types in the body. Current paradigms of genetic regulation of development do not explain this discreteness, nor the time-irreversibility of differentiation. Each cell contains the same genome with the same $N(\sim 25{,}000)$ genes and each cell type k is characterized by a distinct stable gene activation pattern, expressed as the cell state vector $S_k(t) = \{x_{k1}(t),.. \; x_{ki}(t),.. \; x_{kN}(t)\}$, where x_{ki} is the activation state of gene i in cell type k. Because genes are engaged in a network of mutual regulatory interactions, the movement of $S_k(t)$ in the N-dimensional state space is highly constrained and the organism can only realize a tiny fraction of all possible configurations S_k. Then, the trajectories of S_k reflect the diversifying developmental paths and the mature cell types are high-dimensional attractor states. Experimental results based on gene expression profile measurements during blood cell differentiation using DNA microarrays are presented that support the old idea that cell types are attractors. This basic notion is extended to treat binary fate decisions as bifurcations in the dynamics of networks circuits. Specifically, during cell fate decision, the metastable progenitor attractor is destabilized, poising the cell on a 'watershed state' so that it can stochastically or in response to deterministic perturbations enter either one of two alternative fates. Overall, the model and supporting experimental data provide an overarching conceptual framework that helps explain how the specifics of gene network architecture produces discreteness and robustness of cell types, allows for both stochastic and deterministic cell fate decision and ensures directionality of organismal development.

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