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Epigenetic landscapes explain partially reprogrammed cells and identify key reprogramming gene ALEX LANG, HU LI, JAMES COLLINS, PANKAJ MEHTA, Boston University — A common metaphor for describing development is a rugged epigenetic landscape where cell fates are represented as attracting valleys resulting from a complex regulatory network. Here, we introduce a framework for explicitly constructing epigenetic landscapes that combines genomic data with techniques from physics, specifically Hopfield neural networks. Each cell fate is a dynamic attractor, yet cells can change fate in response to external signals. Our model suggests that partially reprogrammed cells (cells found in reprogramming experiments but not in vivo) are a natural consequence of high-dimensional landscapes and predicts that partially reprogrammed cells should be hybrids that coexpress genes from multiple cell fates. We verify this prediction by reanalyzing existing data sets. Our model reproduces known reprogramming protocols and identifies candidate transcription factors for reprogramming to novel cell fates, suggesting epigenetic landscapes are a powerful paradigm for understanding cellular identity.

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