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Control of lineage stability and its role in resolving cell fates ARYEH WARMFLASH, University of Chicago, AARON DINNER, University of Chicago — We synthesize experimental data from recent studies to construct a computational model for the gene regulatory network that governs the development of immune cells and use it to explain several surprising results. At the heart of the model is a cross-antagonism between the macrophage-promoting factor Egr and the neutrophil-promoting factor Gfi. This module is capable of giving rise to both graded and bistable responses. Increasing the concentrations of these factors forces the system into the bistable regime in which cells can decide stochastically between fates. This bistable switch can be used to explain cell reprogramming experiments in which a gene associated with one cell fate is induced in progenitors of another. In one such experiment, C/EBPα, a neutrophil promoting factor, was induced in B cell progenitors which then differentiated to macrophages. Our model shows that if C/EBPα is induced early, it can induce differentiation to a neutrophil. In B cell progenitors, however, the bistable switch is already in a macrophage promoting state. Thus, expression of C/EBPα cannot activate the neutrophil pathway, but it can repress the B cell pathway and promote macrophage differentiation.

Aryeh Warmflash
University of Chicago

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