Distinguishing deterministic from stochastic processes in feedback systems

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The activity of cellular regulatory networks is jointly governed by deterministic nonlinear system dynamics and noise. The prediction of system behavior is facilitated if the system is described first in deterministic terms, which is then supplemented with noise. However, it is often difficult to measure them separately. This is particularly true for positive feedback systems, which commonly underlies bistable cell fate determination. Both noise and deterministic nonlinearities jointly determine how fast the transition between two cell fates is. To separate the underlying stochastic and deterministic effects, we opened feedback loops. The resulting open loop function revealed the deterministic components; in particular how promoter cooperativity and protein dimerization shape nonlinear deterministic response. Next we measured noise using single molecule detection of RNA molecules in the cell. Combining the two measurements, we could predict the transition rates between cell fates. They indicate that having low molecule number accelerates the transitions while protein dimerization stabilizes each cell fate. Thus, through bypassing the effect of noise, feedback opening can help distinguish the molecular basis of deterministic and stochastic mechanisms that control cell fate determination and reprogramming.