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Differentiation at the single cell level: slow, noisy, and out of control

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Transient differentiation allows genetically identical cells to generate dynamical phenotypic diversity in a homogeneous environment. In Bacillus subtilis, competence is a transient state associated with the capability for DNA uptake from the environment. Individual genes and proteins underlying differentiation into the competent state have been elucidated, but it is unclear how these genes interact dynamically in individual cells to control both entry into competence and return to vegetative growth. Here we show that transient differentiation can be understood in terms of excitable behavior of the underlying genetic circuit. Using quantitative fluorescence time-lapse microscopy, we directly observed the activities of multiple circuit components simultaneously in individual cells. We analyzed the resulting data in terms of a mathematical model. A core module containing positive and negative feedback loops controls both entry into, and exit from, the competent state. Reengineering the competence network to bypass the negative feedback loop specifically blocks exit from competence converting the excitable system into a bistable one. These results show that a simple genetic circuit combines stochastic and deterministic elements to support transient differentiation through excitability.