Dynamics of cell fate decision-making in *Bacillus subtilis*

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The dynamics of cell fate decision-making during multipotent differentiation are poorly understood. We simultaneously measured the activities of competing differentiation programs (sporulation and competence) in single cells of the model organism *Bacillus subtilis*. This approach revealed that sporulation and competence programs progress independently towards the final precise decision point. Engineered artificial crosslinks between competence and sporulation circuits revealed that cell fate outcome is determined by temporal race between the key players of the two differentiation programs. Modeling suggests that variable progression towards a switch-like decision might represent a general strategy to maximize adaptability and robustness of cellular decision-making.

***Keywords* — Cell fate decision-making, single-cell differentiation dynamics, temporal competition, molecular race**

Under changing extracellular conditions, cells must be able to make reliable decisions, but also be flexible to adapt to such changes. To understand how cellular decision-making meets these requirements, we quantitatively measured gene expression dynamics and protein localization events in single cells of the model organism *Bacillus subtilis* during sporulation [1]. Results revealed that sporulation proceeded through reversible and noisy steps towards the final irreversible decision point. Mathematical population models suggest that such combination of opposite dynamic behaviors maximizes both adaptability and robustness of cellular decision-making under unpredictably fluctuating environmental conditions [2].

Multiple differentiation circuits can become active and interact in the same cell. How cells reach a specific cell fate choice among other possibilities during multipotent differentiation is a fundamental, yet poorly resolved question. To address this question, we simultaneously measured activities of the competing sporulation and competence programs in single cells of *B. subtilis* [3,4]. This approach revealed that, surprisingly, competence and sporulation programs could act independently in the same cell without affecting each other up to the final decision point. This finding was confirmed by the discovery of cells in a conflicted state when, despite the expression of key competence regulator ComK [5], they ultimately progressed to sporulation. Measurements of gene expression dynamics in these cells revealed key differences in the relative timing between competing differentiation programs. To investigate the role of relative timing in cell fate outcome, we altered it by engineering artificial cross-regulatory links between the sporulation and competence genetic circuits. Results favor a simple model for cellular decision-making that does not require intricate cross-regulatory systems prior to the decision. Rather, cell fate choice appears to be the outcome of a "molecular race" between independently progressing differentiation programs that compete in time [6]. This temporal competition mechanism provides a simple, yet efficient way to generate mutually exclusive cell fates.

Investigation of the biological benefits and limitations of such strategy opens a promising venue for future studies. Additionally, we will address the influence of transient competence events on the dynamics of sporulation.

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