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DECIDING FATE IN ADVERSE TIMES: SPORULATION AND COMPETENCE IN *Bacillus subtilis*

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Bacteria serve as systems biology central arena for understanding how networks of genes and proteins process information and control cellular behaviors. When soil bacteria *Bacillus subtilis* is exposed to stress, it exhibits a remarkable variety of different phenotypes. This shows that cells with the same genome and under similar environment can still decide for different fates. This decision depends on stochastic fluctuations inside and outside of the cell, and is guided by signals that the bacteria send and receive. Here we focus in the decision of *B. subtilis* between two specialized phenotypes: competence and sporulation. Competence is a transient differentiated state where the cell can import DNA from the medium for genetic variation. It is a path cells might decide to follow while preparing for sporulation, an irreversible decision of surviving adversities by forming a resilient spore.

In recent years much effort has been devoted to investigations of specific bacteria gene circuits as functioning modules. The next challenge is integrative modeling of the operation of complex cellular networks composed of many such modules. Here, a tractable integrative model of the sophisticated decision-making signal transduction system that determines the cell fate between sporulation and competence is presented. This provides an understanding of how information is sensed and processed to reach "informative" decision in the context of the cell state and signals from other cells.

The sporulation module (Spo0A dynamics) is modeled as a timer whose clock rate is adjusted by a stress-sensing unit. Different stress signals are integrated into a phosphorelay ending in the activation of sporulation master regulator Spo0A. The interplay between the sporulation and competence modules is mediated via the Rap assessment system and the AbrB-Rok decision module, creating an opportunity for competence within a specific window of the sporulation timer. From the colony's perspective, the Rap system has a balancing and synchronizing effect, accelerating sporulation and competence in cells which are behind schedule. This makes the probability to enter competence more uniform

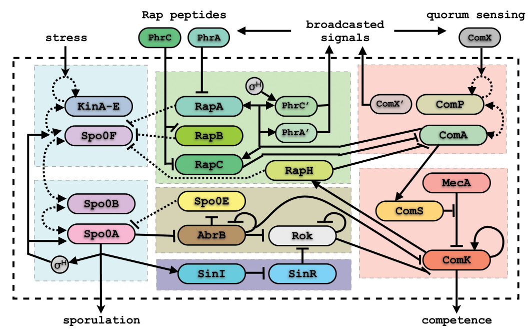

Figure 1 – The sporulation-competence signal transduction network. The sporulation module is shown on the left (blue) and the competence module is shown on the right (red). The two main modules interact via the Rap communication and information processing module (green), the AbrB-Rok decision module (brown) and the SinR-SinI commitment unit (purple). The input and output signals are represented by the wide solid lines that cross the cross the outer black envelope. Solid lines indicate positive (with arrow head) and negative (with perpendicular bar) transcription regulation or (in)activation upon binding, and the dashed line represent phosphorylation (with arrow head) or dephosphorylation (with perpendicular bar).

throughout the colony, and synchronizes the sporulation progression (clock rates).

The competence module (ComK dynamics) is modeled as a stochastic switch whose transition rate is controlled by a quorum-sensing unit. Transitions into competence can be formulated as an activation problem - a threshold concentration has to be crossed by fluctuations in the ComK level for the transition into competence to happen. The situation can be mapped to the escape problem of a particle over a potential barrier under the effect of noise. With the kinetic rate equation for the concentration of ComK $dk/dt = F(k,s)$, we can define a potential $U(k,s) = -\int F(k,s)dk$. The probability per unit time of escape into competence τ^{-1} is then proportional to $exp[-\Delta U(s)/\epsilon]$, where ϵ is the effective noise.

A special AbrB-Spo0A-Spo0E part of the decision module regulates the clock rate of the sporulation timer. Since Spo0A is inhibited by Spo0E which is inhibited by AbrB which is inhibited by Spo0A*, these three genes form a spe-

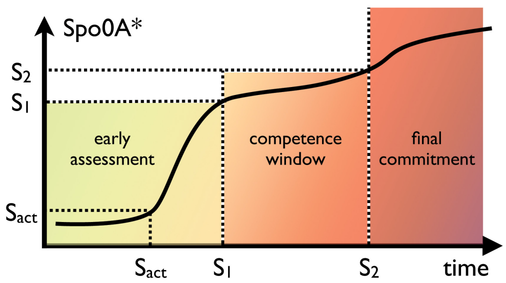

Figure 2 – Dynamical behavior of Spo0A* as function of time for constant stress level, showing the different stages of the decision process.

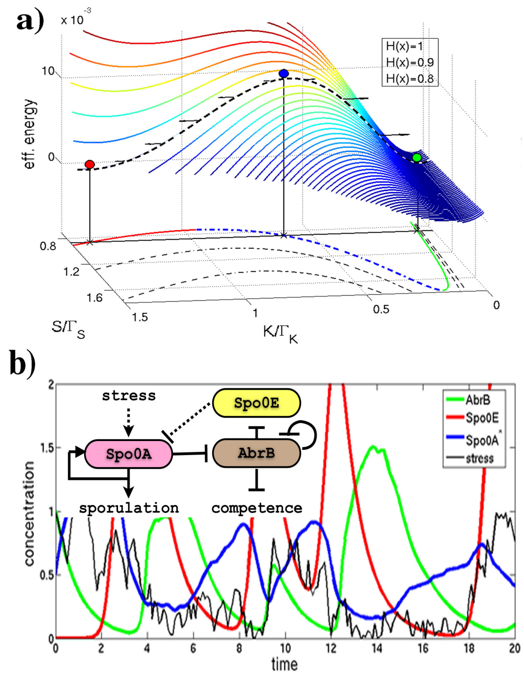

Figure 3 – (a) The function of the competence switch when ComS acts as a control parameter. We illustrate the effective potential $U(k, s)$ and nulcline (equilibrium solution) as function of the control parameter s. The green segment corresponds to the vegetative state and the red segment corresponds to the competent state. (b) Repressilator-like circuit regulating both sporulation and competence. The response of the system for a noisy input signal can show great alternation of the species involved, being responsible for phenotypical variation.

cial repressilator circuit. Ordinarily, this circuit simply leads to a decrease in the rate of accumulation of Spo0A* when AbrB is sufficiently inhibited. We also found that this repressilator circuit can lead to an "undecided" frustrated state in which the values of AbrB exhibit large dynamical oscillations and fluctuations. Since the AbrB dynamics in the frustrated state is sensitive to the cell conditions, on the colony level the AbrB-Spo0A circuit may play an important role in generating variability among the colony.

In general, the colony level problem is to understand the collective sporulation-competence decision, given the repertoire of individual cells, based on their complex and intricate cellular signal transduction systems and genetic circuits. Each cell has its own microenvironment and hence behaves differently than other cells in the colony. Also it is clear that cells often behave stochastically as it has been carefully established in our previous study of the competence process, where genetic noise is necessary to drive some cells (at least temporarily) into the competent state. It may very well be the case that stochastic behavior at the single cell level and cell variability have important functional role as they are necessary to drive optimum behavior of the colony as a whole. In the context of game theory, this is referred to as a mixed strategy.

References

[1] López D, Vlamakis H, Kolter R (2009) Generation of multiple cell types in *Bacillus subtilis*. *FEMS Microbiol Rev* **33**:152-163

[2] López D, Kolter R (2010) Extracellular signals that define distinct and coexisting cell fates in *Bacillus subtilis*. *FEMS Microbiol Rev* **34**:134-149

[3] Kashtan N, Alon U (2005) Spontaneous evolution of modularity and network motifs. *Proc Natl Acad Sci U S A* **102**:13773-8

[4] Burbulys D, Trach KA, Hoch JA (1991) Initiation of sporulation in *B. subtilis* is controlled by a multicomponent phosphorelay. *Cell* **64**:545-52

[5] Fujita M, Losick R (2005) Evidence that entry into sporulation in *Bacillus subtilis* is governed by a gradual increase in the level and activity of the master regulator Spo0A. *Genes Dev* **19**:2236-44

[6] Süel GM, Garcia-Ojalvo J, Liberman LM, Elowitz MB (2006) An excitable gene regulatory circuit induces transient cellular differentiation. *Nature* **440**:545-50

[7] Süel GM, Kulkarni RP, Dworkin J, Garcia-Ojalvo J, Elowitz MB (2007) Tunability and noise dependence in differentiation dynamics. *Science* **315**:1716-9

[8] Schultz D, Ben Jacob E, Onuchic JN, Wolynes PG (2007) Molecular level stochastic model for competence cycles in *Bacillus subtilis*. *Proc Natl Acad Sci U S A* **104**:17582-7