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Nitrogen-fixing cyanobacteria are tuned for evolvability

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Cyanobacteria produce a significant fraction of the oxygen on the environment and, together with archaea, they fix atmospheric nitrogen used by all other organisms. One of the first forms of multicellular organisms on Earth are filamentous cyanobacteria, which constitute a paradigmatic model organism of the transition between unicellular and multicellular living forms. The genus *Anabaena* forms colonies with cells arranged in one-dimensional filaments; under nitrogen-limiting conditions some cells can differentiate into a nitrogen-fixing heterocysts, forming regular patterns to effectively provide nitrogen for the colony.

By combining genetic, metabolic and morphological features, a mathematical model was recently proposed to understand the regulation of heterocyst differentiation in *Anabaena PCC 7120* [1]. The model quantitatively reproduced the appearance and dynamics of this pattern, allowing to explore the impact of different factors like fixed-nitrogen diffusion, cell division, or stochasticity on pattern formation.

In this contribution we analyze a simplified version of the previous model, using the minimal gene regulatory mechanisms for heterocyst pattern formation at early stages (Fig. 1). Early pattern formation involves mechanisms of local autoactivation and long-range inhibition, governed by the genes *hetR*, and *patS*, respectively.

The analysis of our model (see Fig. 2) for two-cell filament shows that the wild type genotype is poised very close to a critical point in the parameter space, a so-called codimension 2 bifurcation. The proximity of the wild type genotype to the critical point is also supported by stochastic simulations with 50 cell-filaments using the same simplified model.

This result suggests that small variations in the genotype would be enough to produce big qualitative changes in phenotypes, since the wild type lies close to all the different kinds of phenotypes available to the system.

Furthermore, the proximity to the critical point suggests that the regulatory machinery of heterocyst differentiation has optimized evolvability, in the sense that small changes in the genotype, that can be produced in different ways by small mutations, are enough to adapt the system to permanent changes in environmental conditions.



Fig. 1. Minimal model of the genetic network involved in heterocyst pattern formation at early stages. This network includes mechanisms of local autoactivation via HetR dimers and long-range inhibition governed by PatS, that is able to bind and inhibit HetR dimers and also to diffuse between cells (blue dashed arrows).



Fig. 2. Two-dimensional bifurcation diagram for two different parameters. The curves for the three types of bifurcations divide the parameter space into different phenotypes of our two-cell system: *heterogeneous* in yellow, *bistable* in grey and *homogeneous* in blue. The wild-type value for the pair of parameters is represented as an asterisk.

J. Muñoz-García and Saúl Ares, Proc. Natl. Acad. Sci. U.S.A 113, 6218-6223 (2016).