Subtle Interplay of Stochasticity and Deterministic Dynamics Pervades an Evolutionary Plausible Genetic Circuit for *Bacillus subtilis* Competence

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Short Abstract **—** We study the behavior a plausible competence core regulatory gene circuit for which the order of net negative regulation of the competence master regulator gene through an intermediate gene is reversed, and for which positive auto-regulation on that intermediate gene has been added.

Keywords **— Nonlinear dynamics, Stochasticity, Competence, Bacillus subtilis, Genetic circuit**

HERE, we study the interplay of stochastic and deterministic dynamics in an evolutionary plausible candidate core genetic circuit for *Bacillus subtilis* competence. This circuit was hypothesized based on the one studied by [1] using the approach and methods of [2]. Briefly, competence is a state of the *Bacillus subtilis* bacterium during which import of exogenous DNA from the environment and its incorporation into the cell's genome is possible for stochastically distributed periods of time. The molecular machinery that allows this is controlled by two genes, ComK and ComS. When ComK is up-regulated, competence is achieved. ComK positively auto-regulates itself. Also, in wild-type bacteria, ComK negatively regulates itself through ComS in the following specific order: first negatively onto ComS followed by positively back onto ComK [3-5]. In [1] it was shown both theoretically and verified experimentally that an alternative wiring of the basic core regulatory circuit in which the negative regulation order of ComK via an intermediate gene called MecA is reversed, i.e. implemented by first positively up-regulating MecA then followed by down-regulation of ComK, results in an impaired phenotype. For this mutant circuit, excursions in competence are less variable in duration, thus spoiling the circuit's ability to efficiently sample a randomly changing evolutionary environment. Here, we consider the same reverse-wiring circuit, but study the impact of adding positive auto-regulation onto the intermediary gene that we call MecA*.

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Specifically, we studied the delivery of phenotype under varying biochemical noise conditions. We find that high biochemical noise would not necessarily be detrimental to the circuit's ability to deliver the competence phenotype. This is due to an unexpected built-in robustness in the circuit that we further investigate. This robustness allows the circuit to function even in the presence of a single fixed point in the dynamics, contrary to naïve expectations that would call for three fixed points.

Also, we find that seemingly subtle deterministic dynamical features of the regulation –the occurrence of unstable and stable limit cycles- , while in the presence of biochemical noise, would result in distinctive new observables. We make specific predictions in the shape and features of the distribution of time duration of competence excursions. The shape of the distribution is thus correlated with the regulatory topology.

We also conduct mathematical analyses of the system's stability at the fixed points, and we then derive some general model-independent consequences. The mathematical features of importance are eigenvector directions and orthogonality, crossing angle of nullclines, and the position of the crossing location.

Finally, we also show how imperfect time-scale separation in the system would result in observables detrimental to the phenotype.

In conclusion, we offer some perspectives on how Nature could have harnessed these features for selection.

References

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