Modeling Demonstrates that Gene Circuit Architecture Controls Phenotypic Variability in a Bacterial Persistence Network

Background

Bacterial persistence is a non-inherited bet-hedging mechanism where a subpopulation of cells enters a dormant state, allowing those cells to survive environmental stress such as treatment with antibiotics. Persister cells are not mutants; they are formed by natural stochastic variation in gene expression. Understanding how regulatory architecture influences the level of phenotypic variability can help us explain how the frequency of persistence events can be tuned.

Results

We present a model of the regulatory network controlling the HipBA toxin-antitoxin system from *Escherichia coli*. Using a biologically realistic model we first determine that the persistence phenotype is not the result of bistability within the network. Next, we develop a stochastic model and show that cells can enter persistence due to random fluctuations in transcription, translation, degradation, and complex formation. We then examine alternative gene circuit architectures for controlling *hipBA* expression and show that networks with more noise (more persisters) and less noise (fewer persisters) are straightforward to achieve. Thus, we propose that the gene circuit architecture can be used to tune the frequency of persistence, a trait that can be selected for by evolution.

Conclusions

We developed deterministic and stochastic models describing how the regulation of toxin and antitoxin expression influences phenotypic variation within the population. Persistence events are the result of stochastic fluctuations in toxin levels that cross a threshold, and their frequency is controlled by the regulatory topology governing gene expression.