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Evolutionary optimization of negative and co-operative autoregulation in RK2 plasmids

The central control operon of the RK2 plasmid is negatively and co-operatively autoregulated by dimers of two global plasmid regulators, KorA and KorB. Several roles for negative feedbacks in biosystems have been proposed by many researchers, and these roles include reduction of noise, increased robustness, speeding of response time and reducing burden on host. In this work, we seek to explain the evolutionary adaptation of the RK2 central control operon in terms of these proposed roles, using comparative analyses of the wild type system with a progression of simpler systems. We used a stochastic, multi-scale model that includes negative and co-operative gene autoregulation of the central control operon of the plasmid, plasmid replication and host cell growth and division. Keeping track of an RK2 plasmid line, we can observe the dynamics of protein abundance from entry of the plasmid into a naive host through to steady state. The comparative analyses between the regulation in models of the wild type central control operon and models with simpler, adequate architectures show a speed up of response time and a decrease in burden for the host, indicated by a decrease in the number of produced mRNAs. In comparison, minimal increased robustness and reduction of internal noise in steady state of bacterial growth phase were observed in these anayses. We conclude that possible reasons for evolution of the complex negative feedback regulation of the RK2 central control operon are the optimization of fast response times and reduced burden to host, and that it is unlikely that this regulatory system has evolved to reduced noise or increase robustness.