Quantitative modeling of a restriction-modification gene switch in bacteria

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Restriction-modification (R-M) switches present rudimental immunological systems in bacteria. As a part of a joint experimental and theoretical work, we *i)* developed a thermodynamic model of control of R-M genes by the control protein *ii)* modeled dynamics of the establishment of R-M system in a bacterial host.

***Keywords* — Restriction-modification systems, transcription regulation, control protein, biophysical modeling**

I. Background

Type II restriction-modification systems consist of two transcription units, one encoding for methylase (M), and another encoding for the control protein (C) and the restriction endonuclease (R). The endonuclease recognizes and cuts specific DNA sequences, while the methylase protects the same DNA sequence from cleavage by the endonuclease by methylating them. C proteins coordinate expression of R and M genes by binding to the operator sequence upstream of CR genes and regulating their expression. Type II R-M genes are often plasmid encoded and can spread from one bacterial host to another, thus propagating through bacterial populations [1].

We combine theoretical and experimental study [2] in order to answer two questions: *i)* What is the mechanism of transcription control of CR genes by C protein. *ii)* What are dynamical properties of the system, and what is the relationship between the system architecture and its biological function during establishment in a bacterial host.

II. Results

Operator sequence upstream of CR genes contains two C protein-binding sites, one of which acts as activator and the other as repressor of transcription. However, experiment shows that in the absence of RNA polymerase both C protein binding sites are simultaneously occupied at all C protein concentrations, raising a question of how activated transcription is achieved.

We propose a model by which RNA polymerase can displace C protein from the promoter proximal binding site, and quantitatively model dependence of CR transcription activity from protein concentration and biophysical parameters of the system. The model shows a very good agreement with the experimental data, both in the case of mutant and wild-type promoter sequences. The alternative models (with the same number of fit parameters), do not agree well with the data.

We next developed dynamical model of establishment of the R-M system in bacterial host, based on the quantitative model of transcription control by C protein described above. We show that the system has a stable equilibrium state, and consequently analyze the dynamics of the equilibrium establishment when a plasmid carrying the R-M system enters bacterial host. The analysis shows that the endonuclease is synthesized with a significant delay with respect to methylase and that the transition form ON to OFF state of the endonuclease is exhibited in a narrow time interval. These dynamical properties turn out to be insured by several (largely redundant) properties of systems architecture and mechanism of transcription control by C protein.

III. Conclusion

Since destruction of host DNA by restriction endonuclease would lead to death of both host and a plasmid carrying R-M system, preventing this is likely a major selection pressure on the system architecture. We therefore argue that that the dynamical properties inferred from our study are a consequence of the requirement to produce enough methylase and protect host DNA before significant endonuclease synthesis begins. In summary, we here developed a biophysical model capable of accurately describing transcriptional control of R-M system and relate modeled dynamical properties of the system with its presumed biological function.

References

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