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Does It Really Matter: The Role of Volume Exclusion and DNA Looping in Lambda Prophage Induction

The genetic switch of the lambda prophage from lysogeny to lytic growth is robust to fluctuations in repressor/activator protein concentrations and alterations in operator site sequences. For example, recent studies have shown that the sequences of the three operator sites of the lambda switch can be interchanged or made equal to each other and, in some instances, have little impact on the behavior of the system (Bakk, Little). Mathematical models rooted in statistical mechanics have both contributed to our understanding of the dynamical and equilibrium behavior of this switch and provided some insight on the source of its robust behavior, but they are nonetheless based upon incorrect physical model of the system. These models, the most popular of which have been proposed by Gary Ackers, were unfortunately proposed prior to the discovery of the role of looping in control of the lambda prophage's gene expression and, additionally, they do not account for molecular crowding in the cell. I propose to construct my own thermodynamic model of the lambda phage genetic switch using a methodology similar to Ackers but counting states using the style of Bintu, et al. This model will account for DNA looping and allow for the investigation of molecular crowding's impact on prophage induction. It is my hope that this model will help explain why the system is robust to the genetic and concentration perturbations mentioned above and that accounting for looping provides behavioral predictions more accurate to experimental observations than those of Acker's model. I will meet these objectives as follows: 1, reproduce the result of Gary Ackers using the methodology referenced above; 2, evaluate the impact of molecular crowding on Ackers's result; 3, introduce looping into the model. These models will be analyzed using the programs Mathematica and MatLab.

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John W. Little, Donald P. Shepley and David W. Wert **Robustness of a gene regulatory circuit** The EMBO Journal 15:4299-307 (1999)

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