Mechanical control of Gene Expression.

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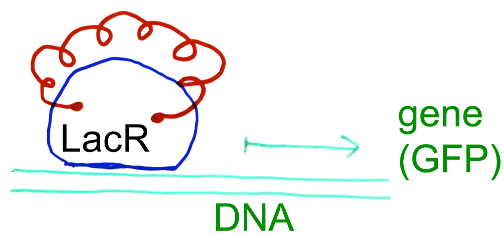
Regulating gene expression is fundamental for metabolism, development, and disease. In addition, gene expression represents one of the most remarkable chemical amplifiers of the cell. One well-studied genetic switch is the Lac operon, which regulates the genes required for lactose metabolism in bacteria. When the Lac repressor protein (LacR) is bound to its operator site on the bacterial DNA, transcription of downstream genes is shut off. LacR is allosterically controlled by the inducer allolactose, which causes LacR to fall off the DNA, allowing transcription.

We plan to mechanically control the LacR using a molecular spring to externally control its conformation. We anticipate that a large enough mechanical stress exerted by the molecular spring at an opportune location on the surface of the protein will deform the repressor substantially and cause it to fall off the operator site, activating transcription. Initially, measurements will be obtained in vitro, but we also aim to develop a system which can be used in the cell. One interesting feature is that in this system, a chemical process is turned *on* by mechanical stress.

We are trying to mechanically activate transcription in the manner depicted in the cartoon. Under tension, the molecular spring attached to the LacR induces a conformational change which causes the LacR to fall off the DNA, initiating transcription.



LacR binds DNA as a tetramer and as a dimer. The dimer bound to a short DNA sequence is shown here, together with one possible location for the application of the mechanical stress (arrows).