

SEMINAR

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“DNA Structural Transitions and Transcriptional Regulation in *E. coli*”

Separation of the two strands of the DNA duplex is a necessary step in the initiation of transcription. So the occurrences and locations of duplex strand openings must be stringently controlled in vivo. Although these openings commonly are regulated by enzymatic processes, any event that alters the stability of the duplex can affect the ease of opening. In particular, negative DNA superhelicity can destabilize the duplex, causing its strands to separate at specific positions where the thermodynamic stability is low. Because superhelical stresses couple together the transition behavior of all sites that experience them, this process is much more complex than thermal denaturation.

We have developed computational methods to predict the destabilization properties of superhelical DNA molecules having any specified base sequence. The energy and conformational parameters used in this analysis are all taken from experimental measurements, so there are no free parameters in this model. Yet when it is used to analyze specific DNA sequences, the results of this method are in quantitatively precise agreement with experimental measurements of the locations and extents of local strand separations. This justifies its use to predict the duplex destabilization properties of other DNA base sequences, on which experiments have not been performed.

We have completed the analysis of stress-induced duplex destabilization (SIDD) in the complete *E. coli* genome. We find that destabilization is not uniform. A relatively small number of sites are significantly destabilized, while approximately 80% of the genome remains as stable as it would be in the relaxed condition. The destabilized sites are strongly clustered in intergenic regions, and specifically in regions that contain promoters. A statistical analysis shows that the most strongly destabilized sites are overrepresented in promoters by about 30 standard deviations beyond what would be expected at random, and are underrepresented in coding regions, also by about 30 standard deviations. Not all promoters are destabilized, however, only a subset. The genes with destabilized 5' flanks tend to encode proteins that function in the transition between environmental conditions.

This approach also has proven useful in illuminating the role of SIDD in specific mechanisms of regulation. Here I will describe one example, that of the initiation of transcription from the *ilvGMEDA* operon of the *ilv* regulon. We have found a new, DNA supercoiling-dependent regulatory mechanism that coordinates the basal level of expression of this with the nutritional and environmental states of the cell. This is accomplished by an IHF binding-mediated translocation of superhelical energy from an upstream supercoiling-induced DNA duplex destabilized (SIDD) site to the downstream promoter site. This mechanism provides local superhelical energy to the promoter regions to amplify promoter activity over the entire range of global physiological superhelical densities in response to cellular energy charge, which in turn is correlated with the nutritional and environmental growth state of the cell.

Date: Thursday, April 3rd

Time: 2:10 - 3:00pm

Location: 1652 Gilman Hall

Presented by the L. H. Baker Center for Bioinformatics and Biological Statistics and IGERT
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