Breathing Signature of the Core Promoter

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We report our finding that the introduction of a few mismatched bases (artificial "bubble template") at the transcription start site allows bidirectional transcription even in the absence of any transcription factors. We establish the correlation between experimentally determined DNA gene transcription regulation sites and the theoretically determined thermally induced coherent openings (bubbles) of the double-stranded DNA at these sites. Our analysis suggests a complex dynamic picture of DNA promoter regions, where different regulatory sites may be distinguishable by the details of their dynamic behavior.

***Keywords* — DNA, promoters, local dynamics, bubbles, transcription.**

I. Transcription Bubble

From a structural perspective, RNA polymerase require single-stranded DNA, i.e. the formation of a 'transcriptional bubble' at the transcriptional start site (TSS) to initiate transcription [1]. Eukaryotic transcription initiation often proceeds from a negatively supercoiled template in the absence of helicases [2–5], suggesting spontaneous local melting of double-stranded (ds)DNA as a key feature of promoter sequences. Furthermore, the introduction of a few mismatched bases to permanently unzip the DNA at the start site allows transcription in the absence of supercoiling [5,6].

We attempt to better establish the connection between DNA bubbles and transcription through the following simulations and experiments.

II. Simulations

Since localized breathing of the double strand is the dynamical mechanism of bubble generation it is reasonable to expect some local enhancement of the breathing dynamics to be a common feature of the TSS, in order to assist the formation of the transcriptional bubble. Previously we have demonstrated a correlation between TSS location, single strand nuclease sensitivity, and transient dsDNA strand separation [7], as well as correlation between enhanced bubble formation and various transcription binding sites [8]. In search of distinguishing dynamic features of gene promoter TSS sequences, we performed molecular dynamic simulations, based on the Peyrard-Bishop-Dauxois model [9,10] of eight experimentally characterized mammalian core promoters [11]. From the generated dynamical trajectories we extracted three distinct dynamic characteristics: bubble probability, bubble lifetime, and the average strand separation. The calculated dynamical profiles suggest that thermal fluctuations commonly induce relatively large, long-lived bubbles at the transcription start site [11].

III. Experiments

Experimentally, we demonstrated that human RNA polymerase (RNAP) II performs bidirectionally transcription in the absence of any transcription factors, if an artificial long-lived bubble of length more than 5 base pairs is introduced at the start site of the Adeno-associated virus P5 promoter [11]. This transcriptional data together with the previously published results by us and others [2-7], clearly suggests that most likely local DNA melting is sufficient to enable bidirectional transcription by RNAP II alone.

IV. Conclusions

Our data, suggest that each promoter exhibits distinct DNA dynamic characteristics, i.e. spontaneous local openings, which are likely to be recognized and engaged by the transcriptional machinery, and may then be amplified, stabilized, or suppressed by DNA-protein interactions as part of gene transcriptional regulation.

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This work was funded by NIH grant GM071482, and supported by DOE

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