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Title: DNA Dynamically directs Its Own Transcription Initiation

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*Abstract of presentation to be given at the 5th **international conference on Biological Physics**, Chalmers Conference Center, Gothenburg, Sweden, 22-27 August, 2004.*

DNA Dynamically Directs Its Own Transcription Initiation

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Initiation of DNA gene transcription requires a transient opening in the double helix at the transcriptional start site. It is generally assumed that the location of this "transcriptional bubble" is determined by sequence-specific protein binding, and that the energy required for unwinding the double helix comes from torsional strain. Physical twisting should cause DNA to open consistently in weakly bonded A/T rich stretches, however, simple base-pairing energetics alone can not account for the variety of observed transcriptional start sites. Applying the Peyrard-Bishop nonlinear cooperativity model to DNA, we are able to predict that thermally-induced DNA bubbles, similar in size to transcription bubbles, form at specific locations on DNA promoters. These predicted openings agree remarkably well with experiment, and that they correlate exactly with known transcription start sites and important regulatory sites on three different promoters. We propose that the sequence-specific location of the transcriptional start site is predetermined by the inherent opening patterns of specific DNA sequences. As DNA bubble formation is independent of protein binding, it appears that DNA is not only a passive carrier of information, but its dynamics plays an important role in directing the transcription and regulation of the genes it contains.

DNA Directs Its Own Transcription

K. Ø. Rasmussen

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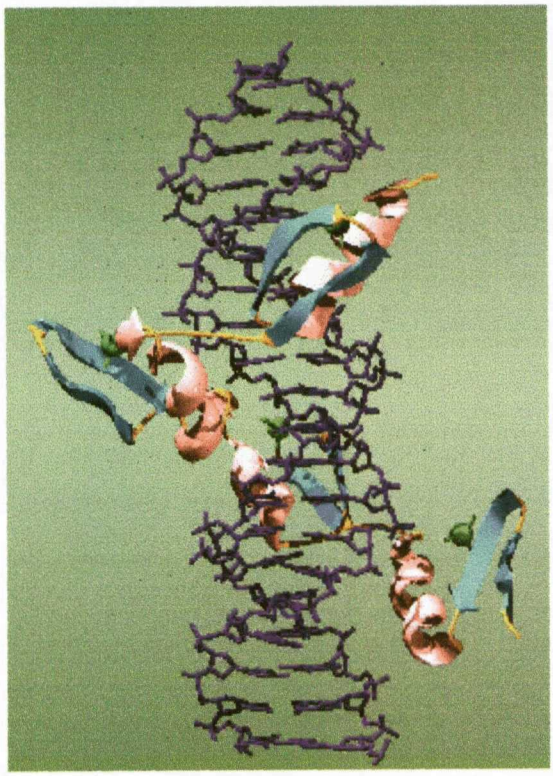

Collaborators:

G. Kalosakas, LANL

A. R. Bishop, LANL

A. Usheva, Harvard Medical School

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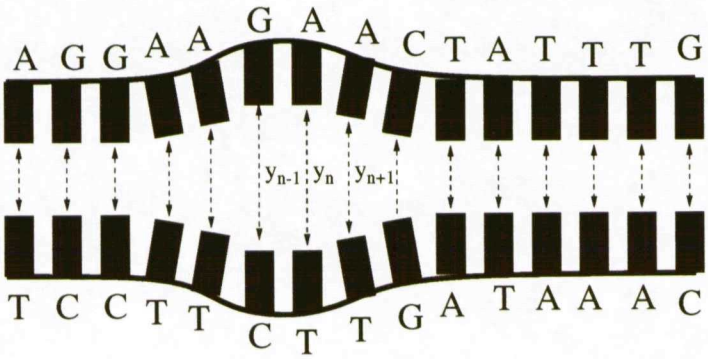
"Peyrard-Bishop" Model

M. Peyrard and A.R. Bishop, PRL. **62**, 2755 (1989); T. Dauxois, M. Peyrard, and A. R. Bishop, PRE **47**, R44 (1993).



Coherent openings

"bubbles"

$$H = \sum_n \left[\frac{1}{2} m \dot{y}_n^2 + V(y_n) + W(y_n, y_{n-1})\right]$$

Base pair potential: $V(y_n) = D_n \left(\exp\left[-a_n y_n\right] - 1\right)^2$

Neighbor coupling:

$$W(y_n, y_{n-1}) = \frac{k}{2}\left(1 + \rho \exp\left[-\beta(y_n + y_{n-1})\right]\right) \times (y_n - y_{n-1})^2$$

$$m\frac{d^2 y_n}{dt^2} = -V'(y_n) - W'(y_n, y_{n-1}) - W'(y_{n+1}, y_n) - m\gamma\frac{dy_n}{dt} + f_n(t)$$

$D_n = 0.05eV, \quad a_n = 4.2A^{-1}$ for AT base pair

$D_n = 0.075eV, \quad a_n = 6.9A^{-1}$ for GC base pair

A. Campa and A. Giansanti, PRE **58**, 3585 (1998).

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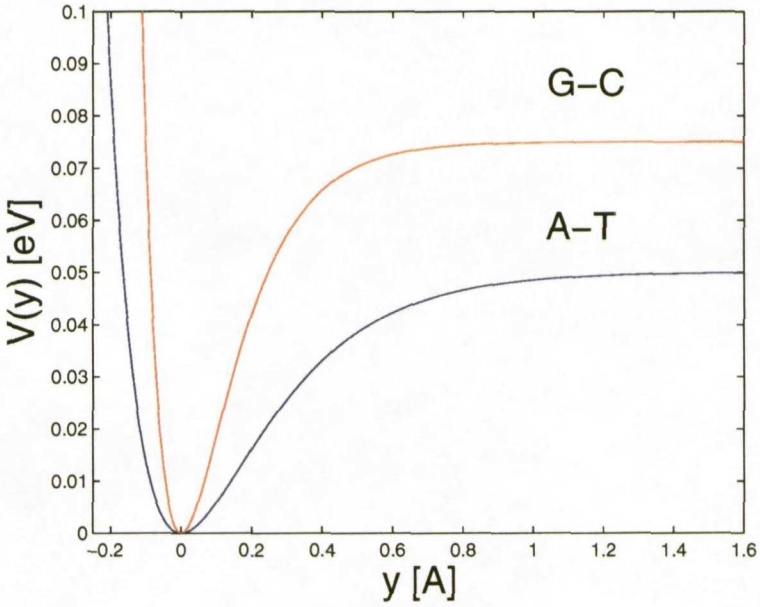
Base pair potential



P5 Sequence

```
   (-45)        β                                  (-20)      γ
5'-GTGGC CATTTAGGGT ATATATGGCC GAGTGAGCGA
          GCAGGATCTC CATTTTGACC GCGAAATTTG AACG-3'
                   (+1)  α                          (+24)
```

AdMLP Sequence

```
   (-62)                                  (-40)          γ
5'-GC CACGTGACCA GGGGTCCCCG CCGGGGGGGT ATAAAAGGGG
      GCGGACCTCT GTTCGTCCTC ACTGTCTTCC GGATCGCTGT CCAG-3'
             β                  (+1)  α                  (+24)
```

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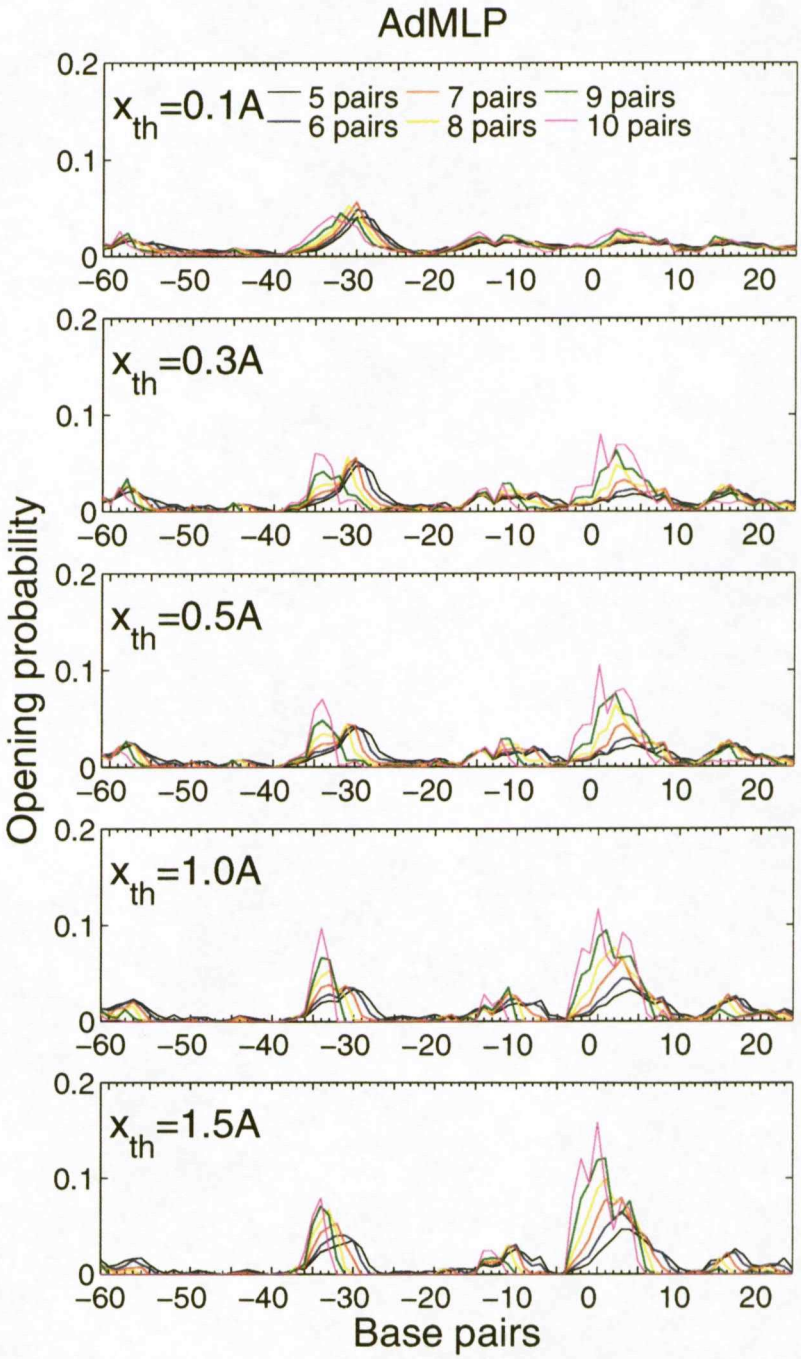
Simulated Opening Statistics

Langevin MD; Kalosakas & Rasmussen



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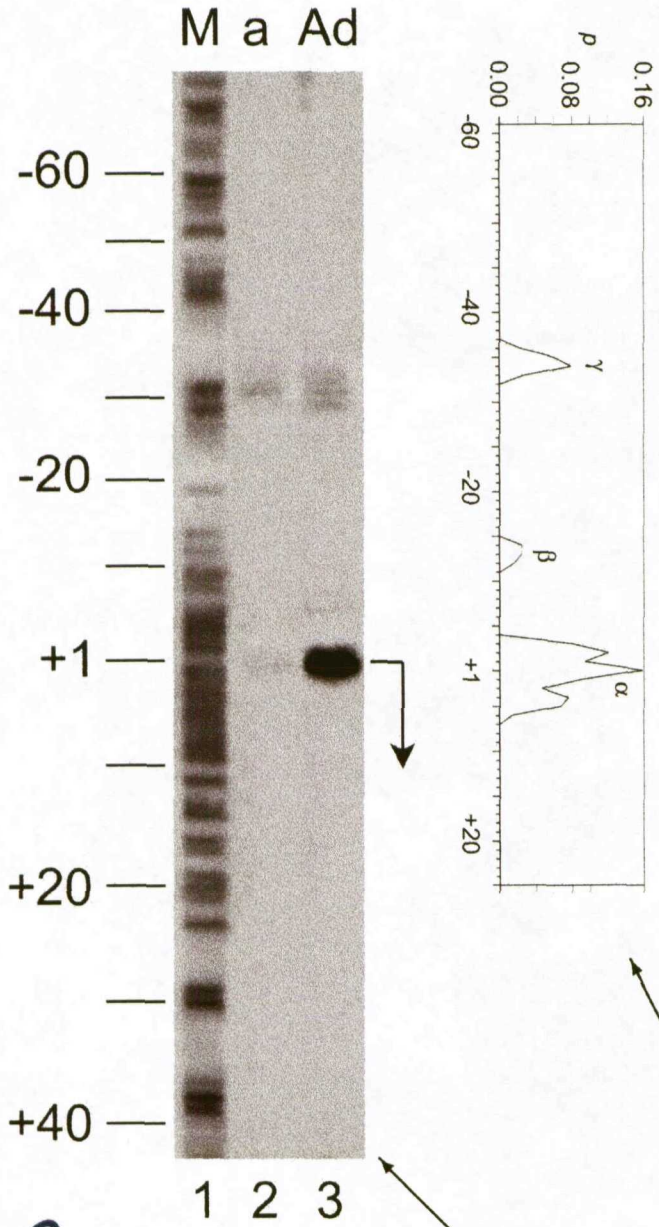
Comparison to transcription experiments

Sequencing Gel Experiment;

Choi *et al.*, Nucleic Acids Res. **32**, 1589 (2004)

AdMLP transcription



Simulation of PB model

Transcription Activity Lane

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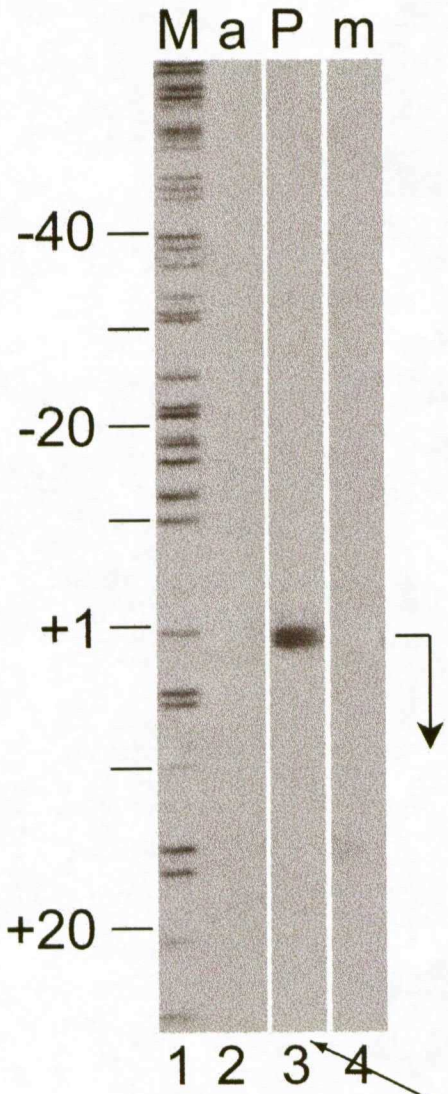
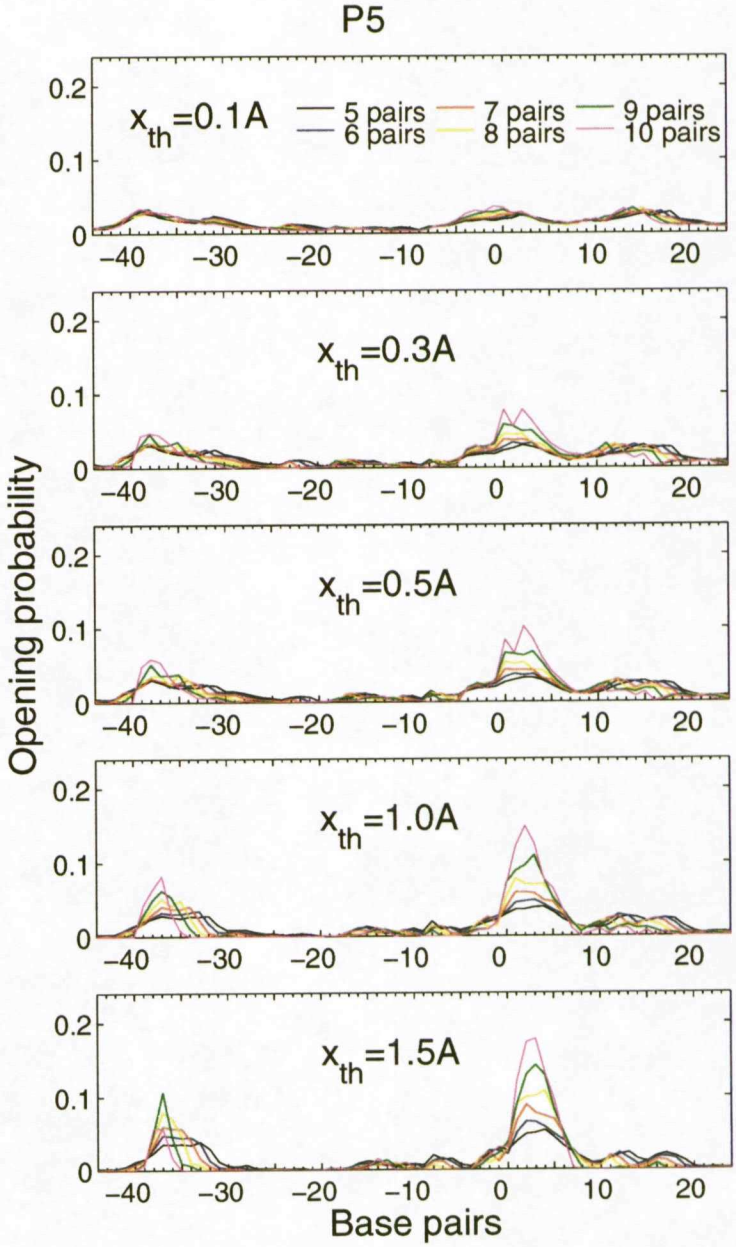
Comparison to transcription experiments

P5 transcription





Transcription Activity Lane

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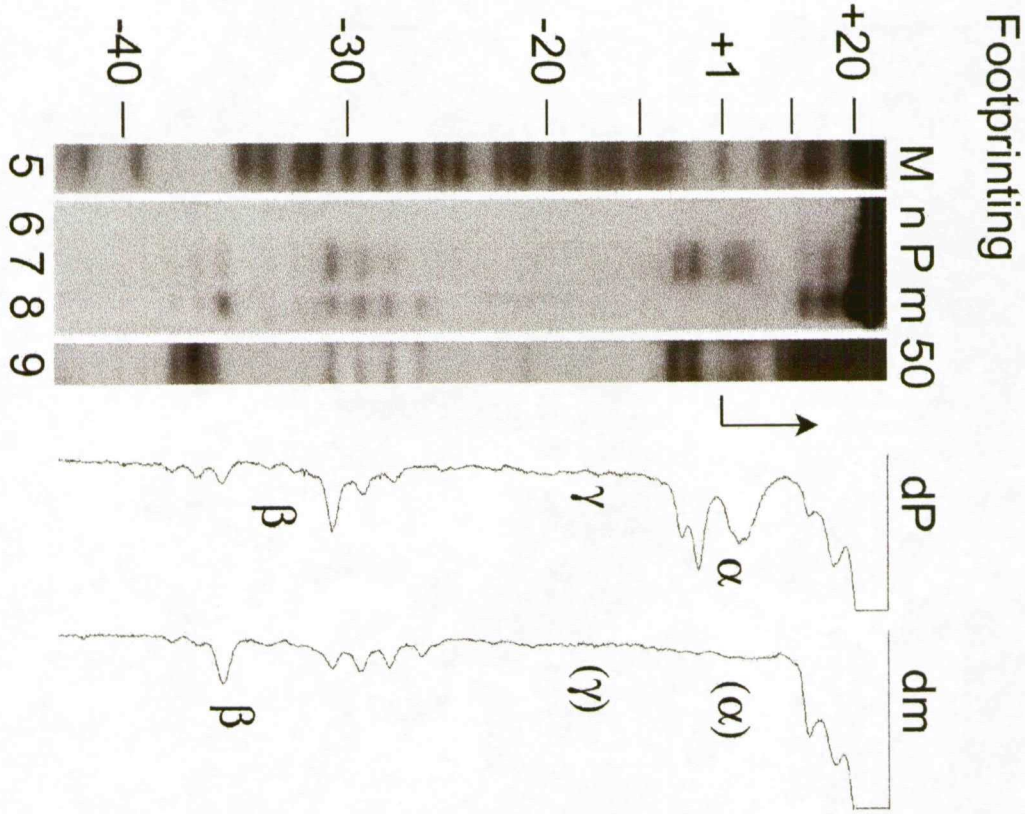
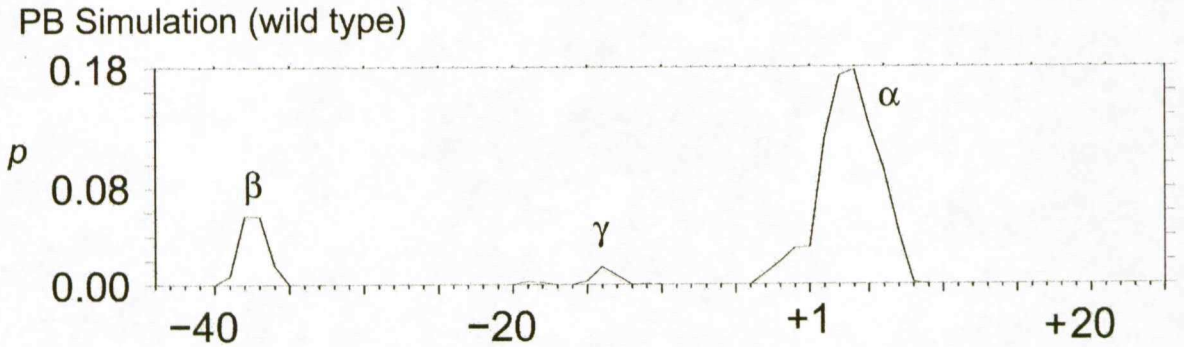
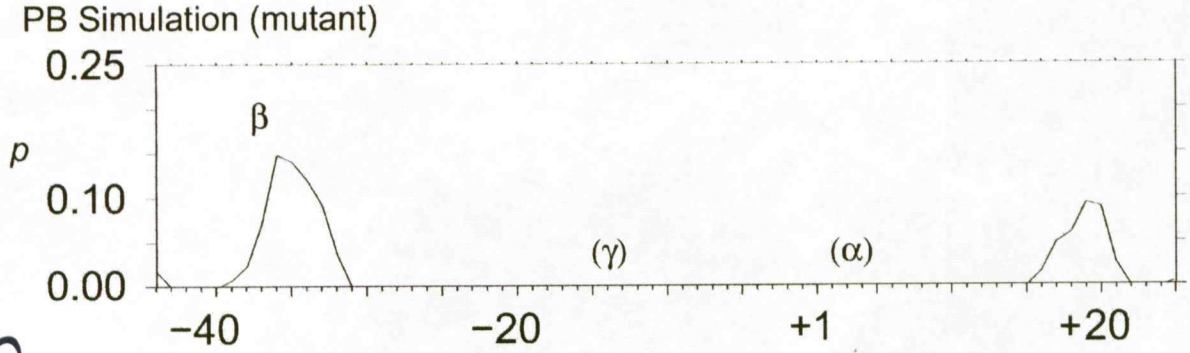
FOOTPRINTING EXPERIMENTS VS. SIMULATIONS







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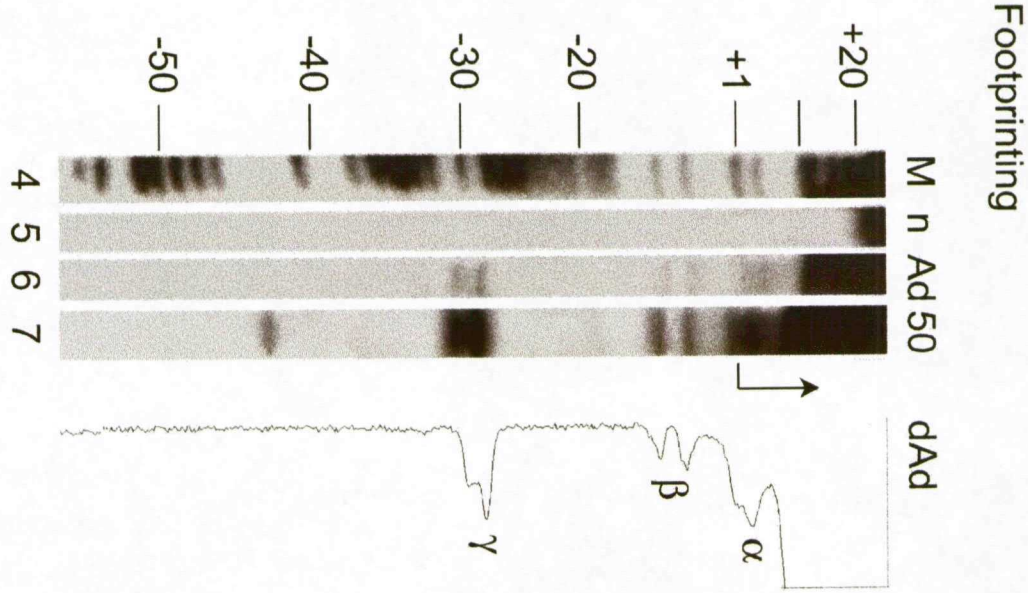
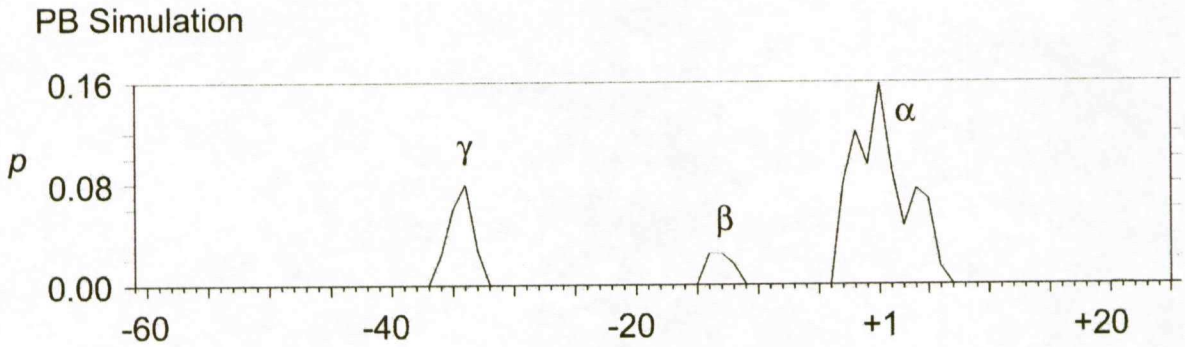
FOOTPRINTING VS. SIMULATIONS for AdMLP





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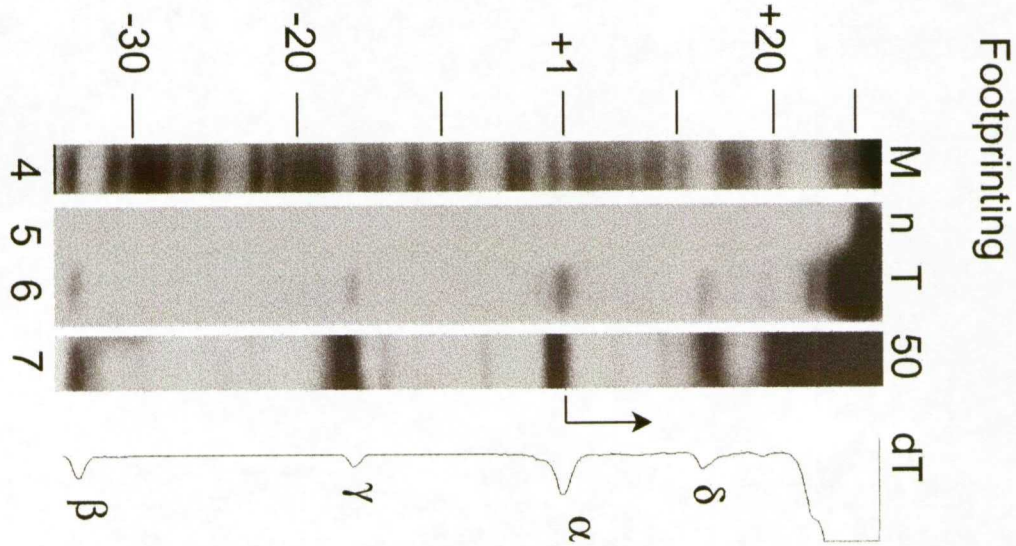
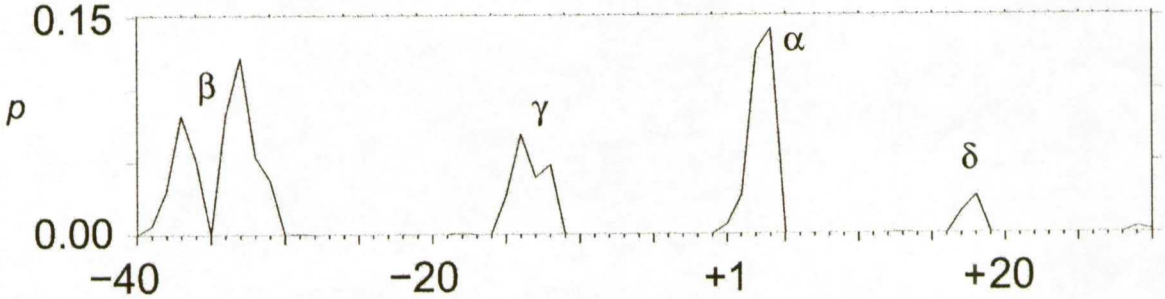


B PB Simulation

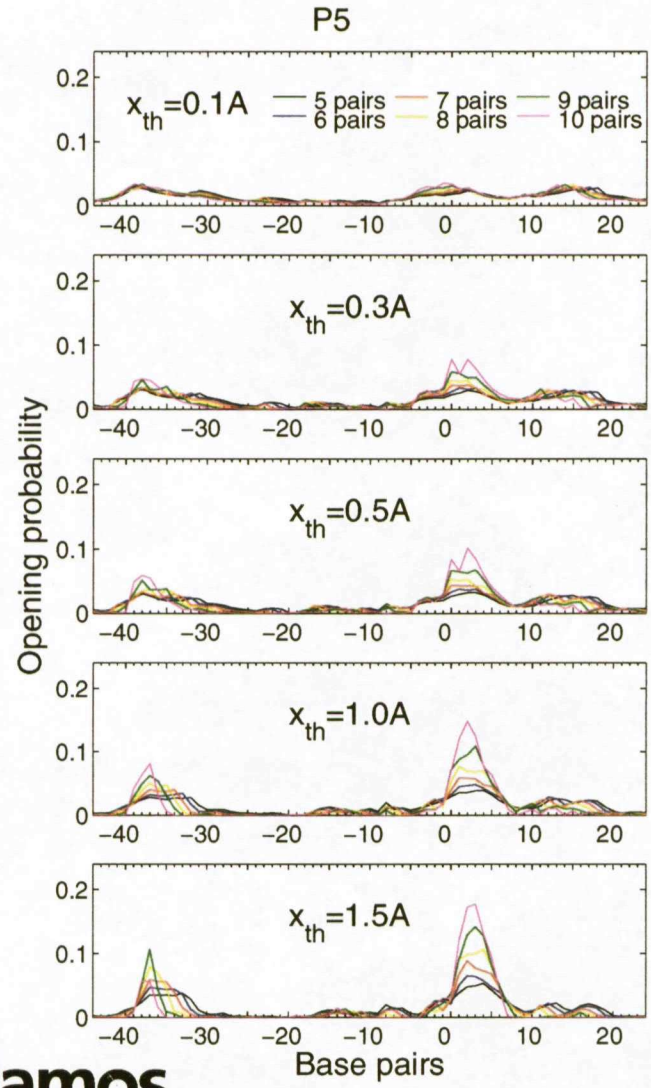


INTERPLAY OF NONLINEAR COOPERATIVITY & DISORDER

Same sub-sequence different dynamics

P5 Sequence

```
(-45)      β                                  (-20)     γ
5'-GTGGC CATTTAGGGT ATATATGGCC GAGTGAGCGA
          GCAGGATCTC CATTTTGACC GCGAAATTTG AACG-3'
                    (+1)  α                          (+24)
```



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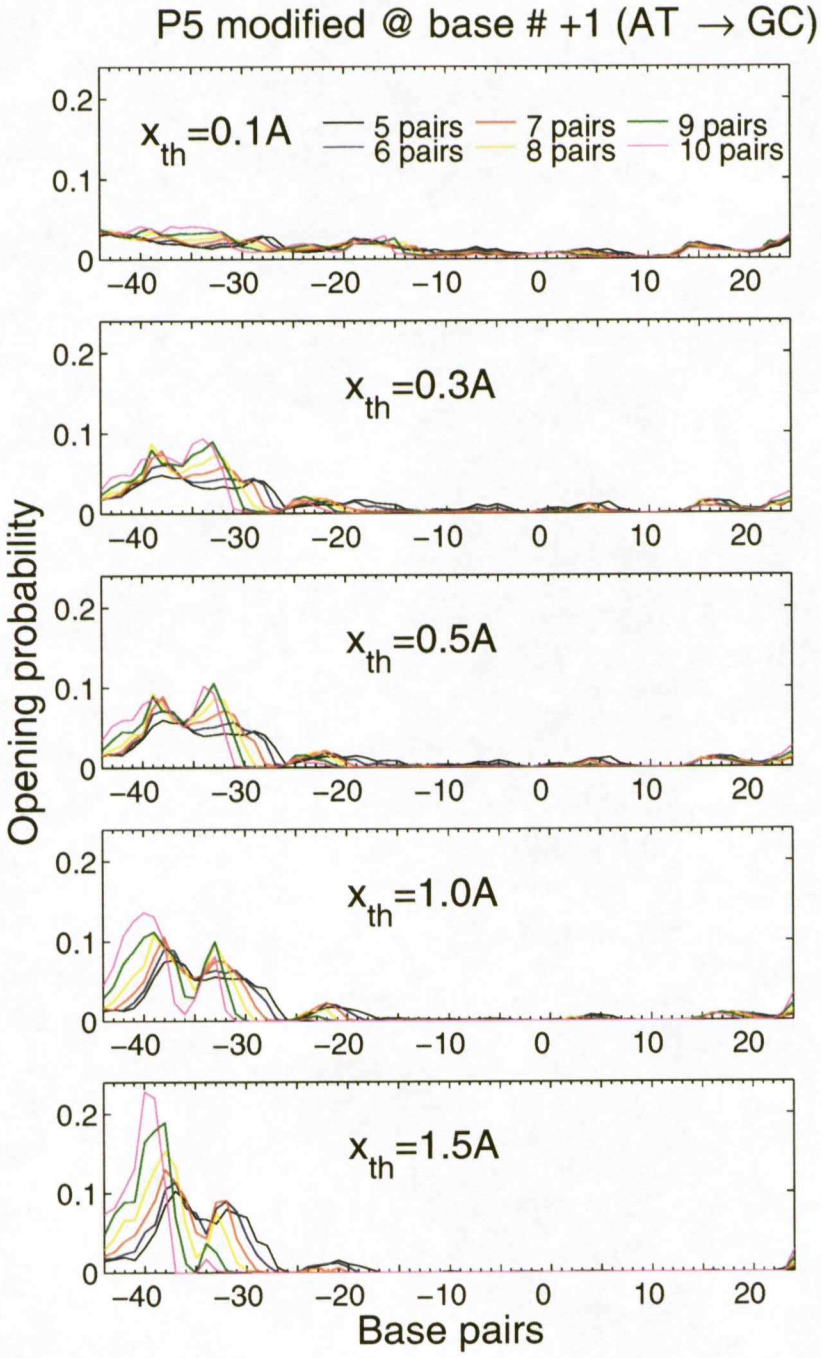
Modified at base pair # +1: Suppresses Transcription



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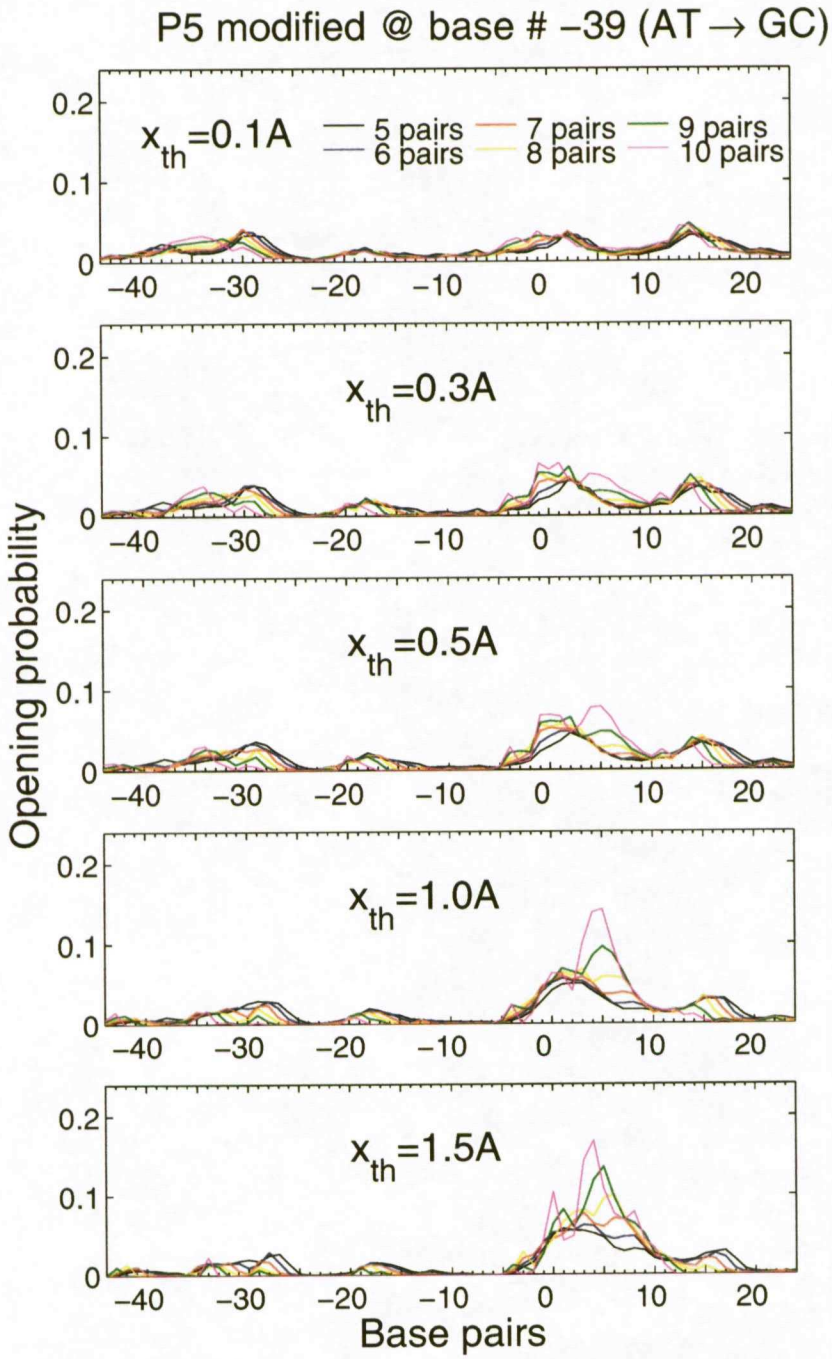
Modified at base pair # -39: Suppresses Transcription



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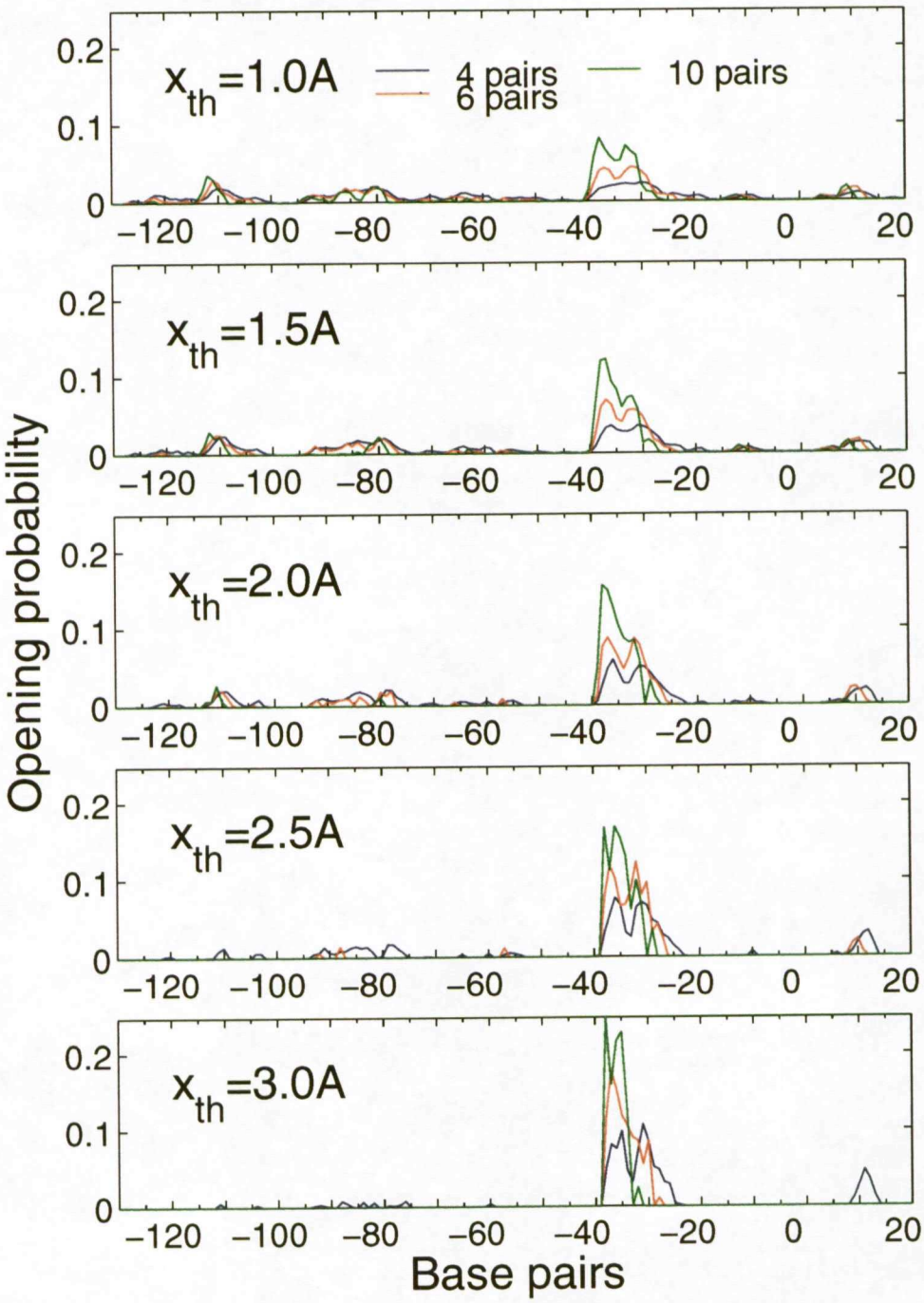
Human Promoter Sequence (alpha-actin (hSMA))



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Conclusions

- PB model captures correct dynamics in the melting precursor nucleation regime
- Major bubble formation sites agrees with transcription initiation sites
- Minor bubble formation sites appears to identify important protein binding sites.
- Demonstrated the importance of dynamics an not just structure
- Indications that DNA not only carries information, but also actively directs it own transcription.