Competing Timescales in a model of Protein Binding to DNA

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1. DNA can be overstretched

A single DNA molecule can be overstretched producing a plateau at 65pN. This can be explained by a structural change of the DNA.

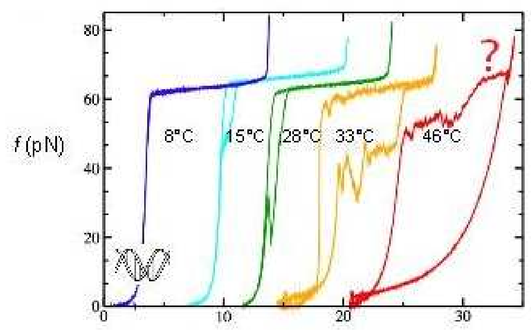

FIGURE 1: Experimental force-extension curves of single DNA molecule under different temperatures. [1]

2. Simulation of discrete model

Previously a discrete statistical mechanics model was used. The DNA chain is represented as a series of discrete basepairs or sites, see Figure 4.

The simulation can produce results similar to those seen in Figure 1:

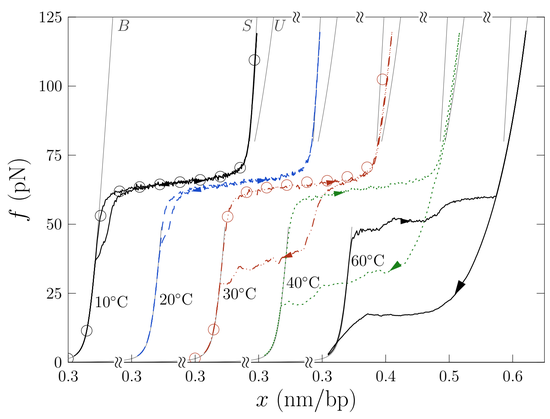

FIGURE 2: Simulation results to show effect on temperature on pulling and relaxation of DNA chain. Distinct hysteresis occurs which is dependent on the temperature [2]

References

[1] Hanbin Mao, J. Ricardo Arias-Gonzlez, Steve Smith, Ignacio Tinoco Jr. and Carlos Bustamante *Temperature Control Methods in a Laser-tweezers System,* Biophysical Journal 89:1308-1316 (2005)

[2] Stephen Whitelam, Sander Pronk and Phillip L. Geissler *There and (Slowly) Back Again: Entropy-Driven Hysteresis in a Model of DNA Overstretching,* Biophysical Journal 94:2452-2469 (2008)

[3] Andy Sischka, Katja Toensing, Rainer Eckel, Sven David Wilking,y Norbert Sewald,y Robert Ros, and Dario Anselmetti *Molecular Mechanisms and Kinetics between DNA and DNA Binding Ligands,* Biophysical Journal 88:404-411 (2005)

3. Proteins change the overstretching curves

The aim of this project was to use the previous model and introduce the effect of protein binding. Overstretching experiments are greatly affected by proteins.

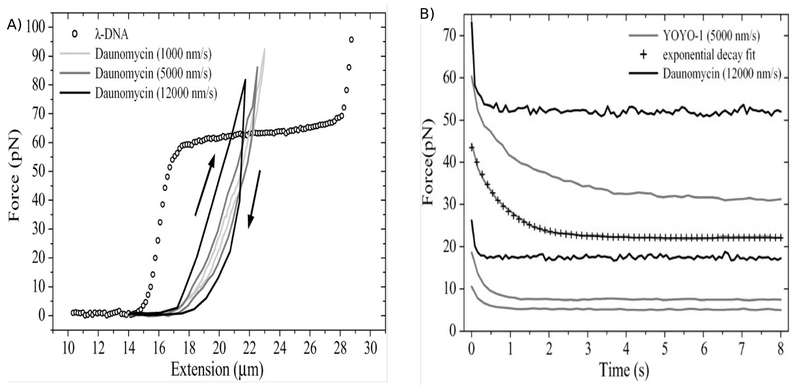

FIGURE 3: A) shows the effect of protein on the DNA molecule force-extension curve. B) shows an experiment in which the DNA molecule is pulled to a high force and then allowed to relax. [3]

4. Adding protein to the model

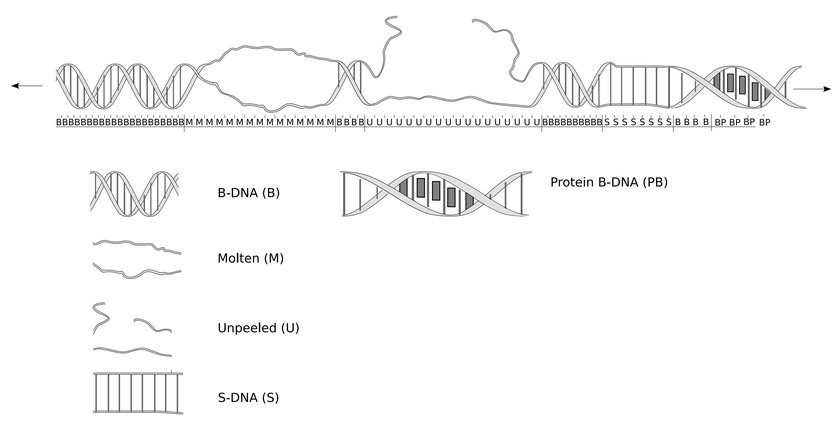

FIGURE 4: Diagram of the possible states in our model. The protein may bind to any state but its effect is neutral unless binding to the helical form (B)

- Protein is introduced by allowing discrete binding events during the simulation.
- Events governed by binding rate, $\Gamma^0_{\text{protein}}$ and binding energy ϵ_{PB}.
- Protein-bound B-Form is longer than the unbound form.
- Protein binding energy is 0 for all but B-form

5. Setting parameters

Parameters of model set by comparing to experimental data. Pulling to high force sets our protein binding rate and binding energy:

$$\Gamma^0_{\text{protein}} = 1000 \times \Gamma^0_{\text{DNA}}$$

$$\epsilon_{\text{PB}} = 3k_{\text{B}}T$$

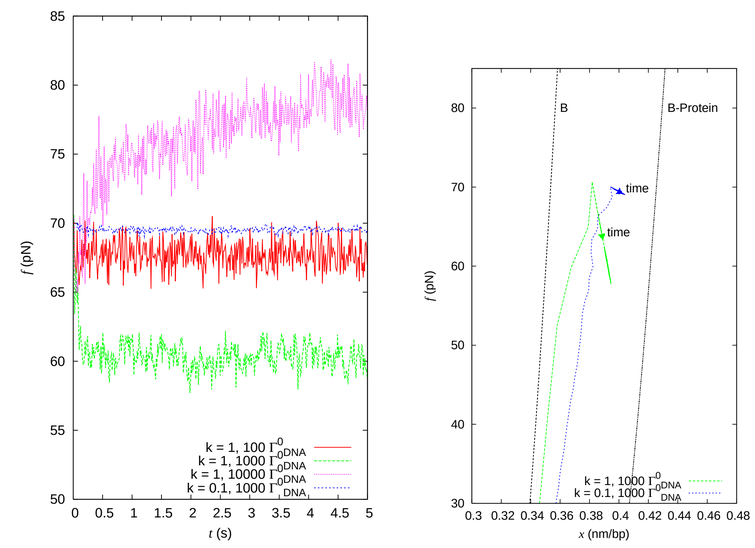

FIGURE 5: Simulation results (mimicking Figure 3(B)) for pulling to a maximum force of 70pN and then stopping with different protein binding rates. Molecule relaxes along a line with gradient equal to spring constant. Results set model parameters based on experiment

6. Equilibrium is not enough

Equilibrium considerations are not enough to explain Figure 3(A). Competing timescales of protein binding and changes in structure are needed.

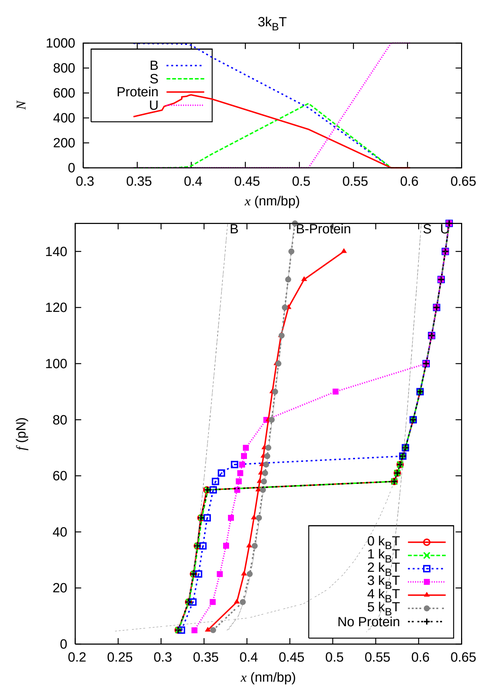

FIGURE 6: Equilibrium plot of several different protein binding energies at a temperature of 20°C and a nick in the DNA chain.

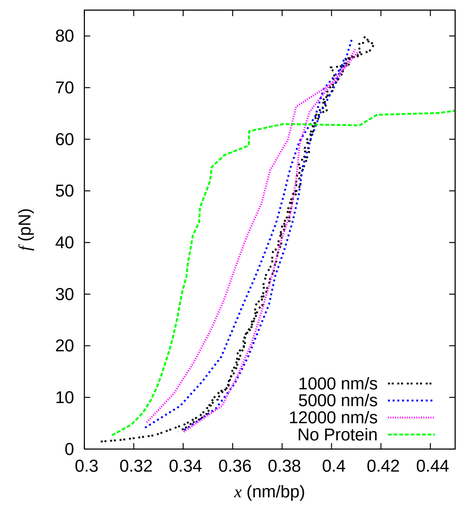

FIGURE 7: Dynamic simulation of pulling and relaxing the DNA with different pulling rates at 20°C with 1 nick. The protein binding energy was fixed. Banana shape is reproduced as seen in Figure 3(A)