Homework 3

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problem1. What are FET fusion proteins? What are the possible mechanisms of FET fusion proteins in transcription regulation.

solution.

1.

FET (FUS/EWSR1/TAF15) fusion proteins are a special part of the transcription factors involved in the formation of transcriptional aggregates. Members of the FET protein family are RNA-binding proteins, but chromosomal translocations can form new fusion proteins, which have been found in many patients with sarcoma and leukemia.

In this class of fusion proteins, the N-terminal is derived from the low complexity domain (LCD) of the FET protein family, while the C-terminal is mainly derived from the DNA binding domain (DBD) of the ETS protein family.

2.

It may be that the phase transition characteristic of FET protein enables related transcription factors to have pro-tumor functions.

EWS, FUS, and TAF15 are RNA-binding proteins whose structure consists of an intrinsically disordered, low-complexity, prion-like, SYGQ-rich N-terminal

trans-activation domain, followed by three arginine-rich and glycine (RGG) -rich repeats of varying lengths. RGG1 and RGG2 are separated by RNA recognition motifs containing 87 amino acids, and RGG2 and RGG3 are separated by zinc finger domains 20. The EWS transactivation domain, encoded by the first seven exons of EWSR1, is largely silent in wild-type proteins, but becomes highly active and inhibited by RGG repeats after C-terminal region loss due to chromosomal translocation, which is consistent with their activation after replacement by fusion partners. Prion-like domains have phase transition properties, defined as the ability of a biological system to undergo phase or state changes, which may include a transformation from a solution of proteins to a fluid-like compartment of phase separation that makes up membraneless organelles.

Further research showed that the N-terminus of the fusion protein could bind to the C-terminal domain (CTD) of RNA polymerase II (Pol II), thereby improving the transcription level of downstream genes and possibly inducing cancer. In 2018, Robert Tjian's research group found that the FET family fusion protein WS-FLI1 forms aggregates in the nucleus and can recruit RNA polymerase 4. In 2021, Zhi Qi and Pilong Li 's research group discovered loci-specific phase separation of FET fusion oncoproteins promoting gene transcription.

problem2. How to explain the data on the AFS experiment?

solution.

The worm-like chain (WLC) model in polymer physics is used to describe the behavior of polymers that are semi-flexible: fairly stiff with successive segments pointing in roughly the same direction, and with persistence length within a few orders of magnitude of the polymer length.

I use this model to fit the data.

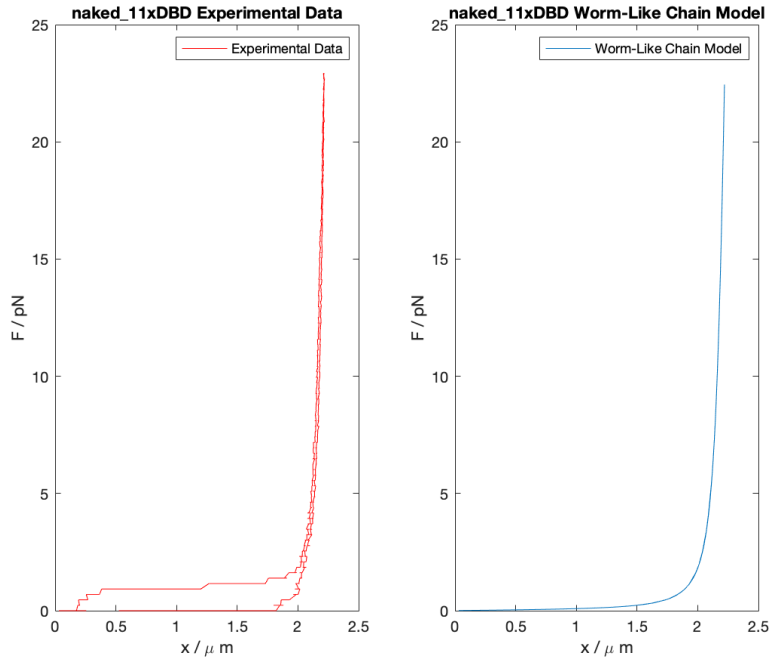

图 1: Naked DNA

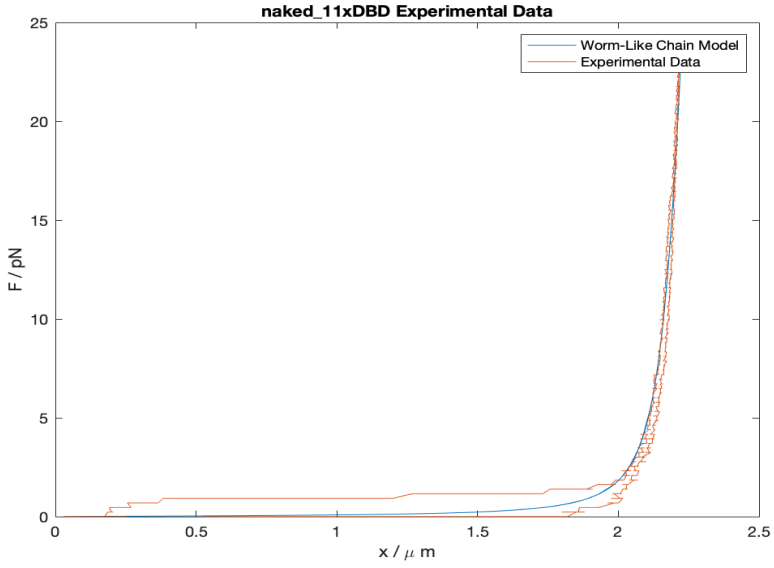

图 2: Naked DNA

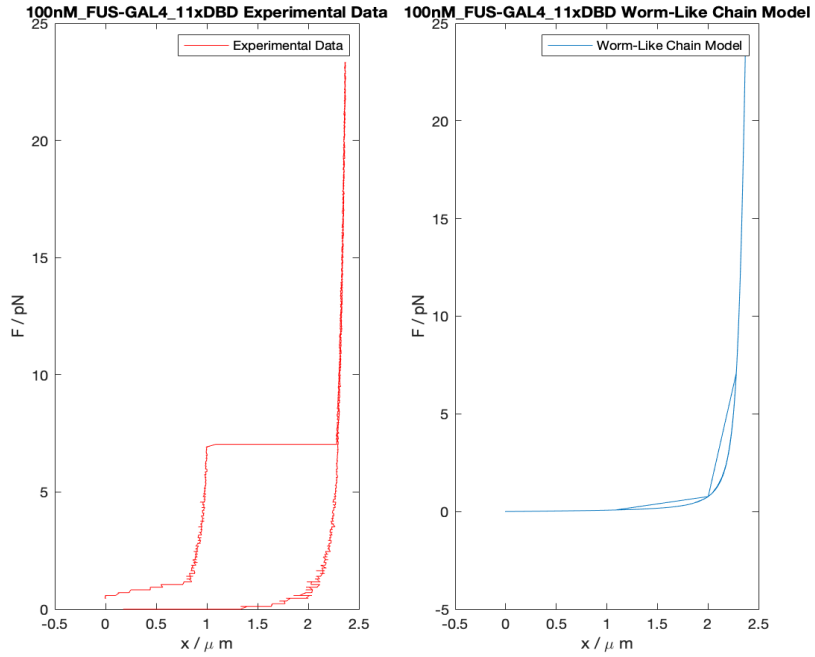

图 3: DNA with motif

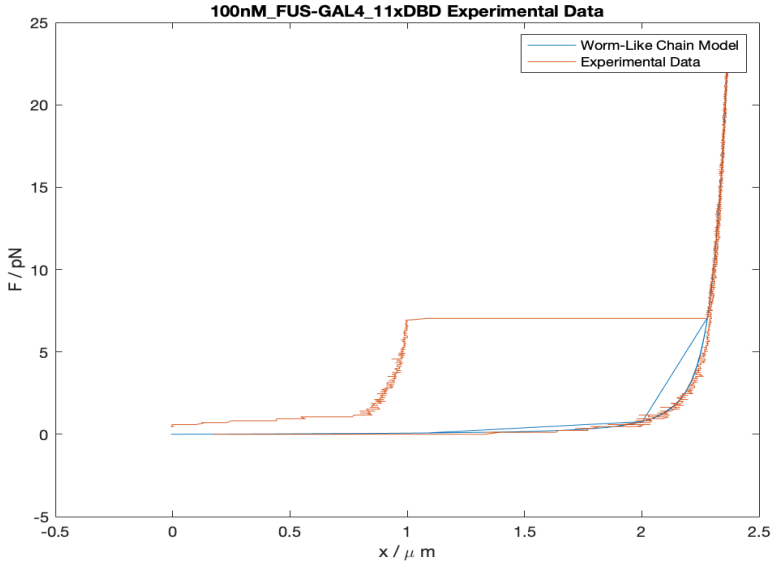

图 4: DNA with motif

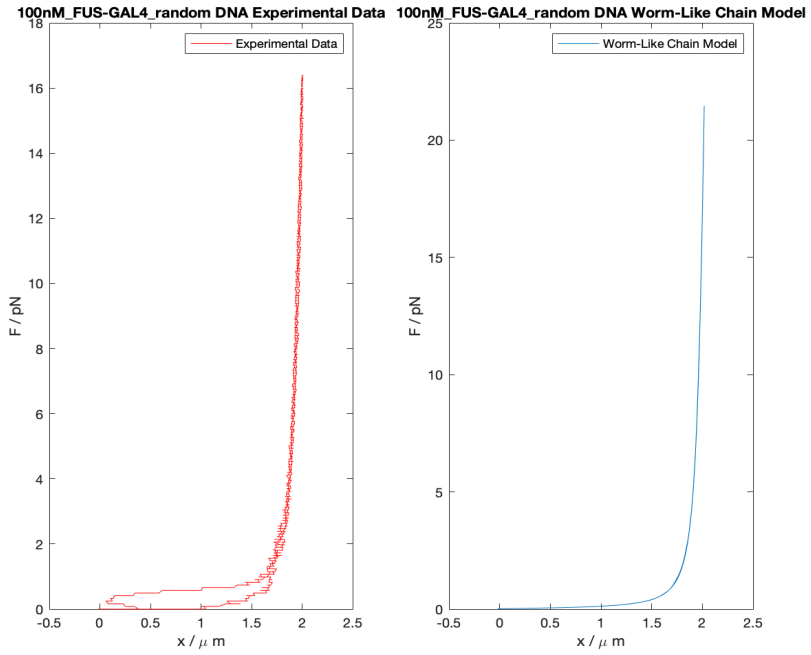

图 5: random DNA

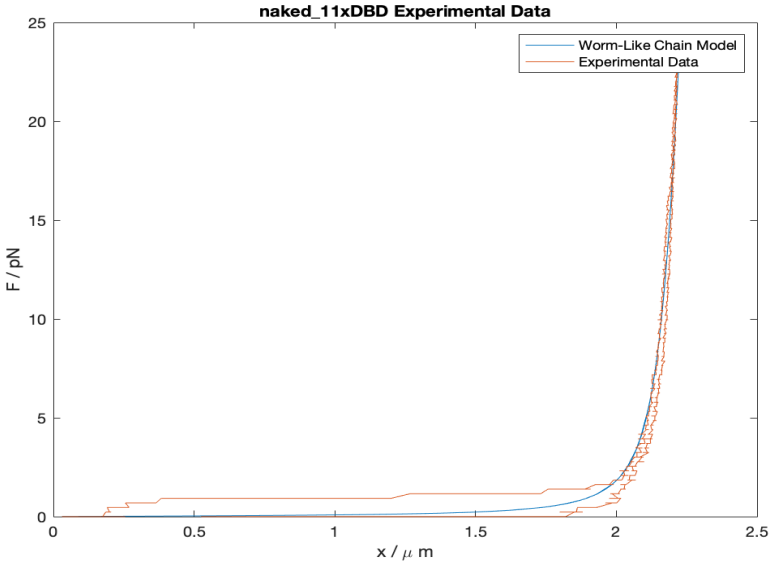

图 6: random DNA

The Naked DNA data matches the Worm-Like Chain Model predictions very well . For motif on DNA, there are many FUS-GAL4 protein aggregations that bind to it. Apply force to it, when force reaches a certain value(7.5 pN), it enters a platform. As the force increases, proteins on it fall off and return to the state of Naked DNA.We can calculate the extra work required for the proteins to fall off the DNA from the area enclosed by this curve.

In theory ,when there is no motif (random DNA) on DNA, proteins bind randomly. As F changes, the corresponding x gradually changes (no platform appears), it means that the proteins on the DNA fall off gradually.

However, in fact, for this data, the data of random DNA is very similar to naked DNA, which indicates that this protein hardly bind to random DNA.

Reference

[1]Sizemore GM, Pitarresi JR, Balakrishnan S, Ostrowski MC. The ETS family of oncogenic transcription factors in solid tumours. Nat Rev Cancer. 2017 Jun;17(6):337-351.

[2]Chong S, Dugast-Darzacq C, Liu Z, Dong P, Dailey GM, Cattoglio C, Heckert A, Banala S, Lavis L, Darzacq X, Tjian R. Imaging dynamic and selective low-complexity domain interactions that control gene transcription. Science. 2018 Jul 27;361(6400):eaar2555.

[3]Zuo L, Zhang G, Massett M, Cheng J, Guo Z, Wang L, Gao Y, Li R, Huang X, Li P, Qi Z. Loci-specific phase separation of FET fusion oncoproteins promotes gene transcription. Nat Commun. 2021 Mar 5;12(1):1491.

[4]Schwartz J C, Cech T R, Parker R R. Biochemical properties and biological functions of FET proteins[J]. Annu Rev Biochem, 2015, 84: 355-379.