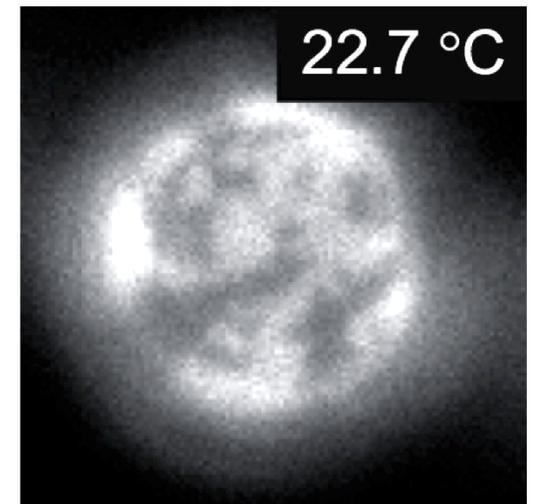# Ising models in membranes, and critical droplets in DNA: Statistical physics in biology

James P. Sethna, Bryan Daniels, Ben Machta, Eshan Mitra, Stefanos Papanikolaou, Michelle Wang, Barbara Baird, Sarah Veatch

I. Ising criticality in cell membranes

II. Plectoneme nucleation rate

22.7 °C

I. Ising Criticality in Cell Membranes

Ben Machta, Sarah Veatch, Stefanos Papanikolaou, JPS

- Baird: Living cell membranes, when detached from the cell, undergo a phase separation near body temperature

    (liquid ordered / liquid disordered)
- Sarah Veatch: This is a continuous transition in the Ising universality class.
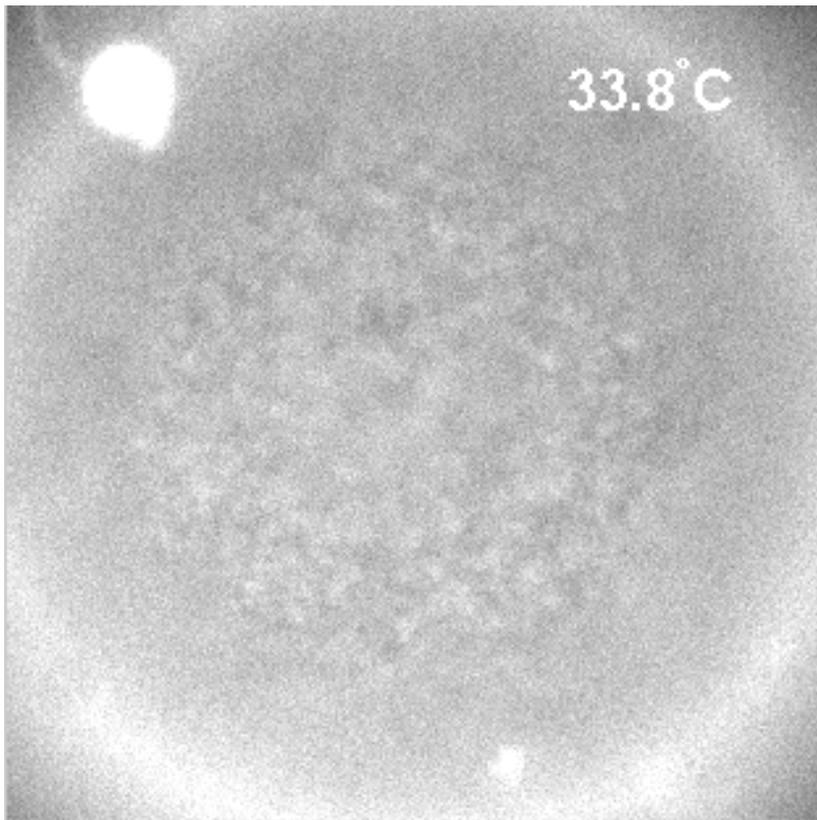- Connections with "lipid rafts"?

Why don't intact cells undergo phase separation?

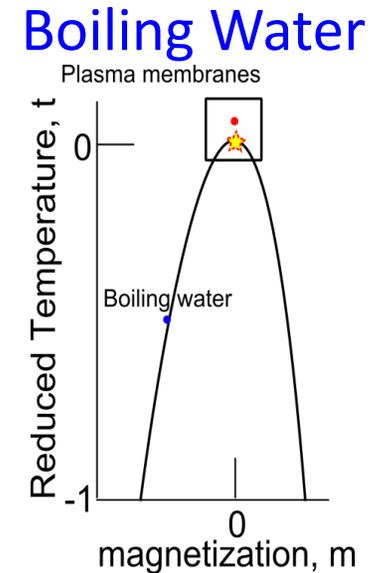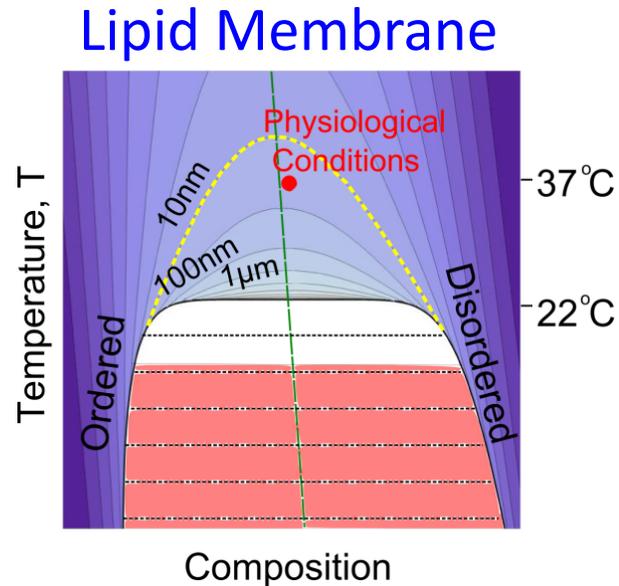Why should cells want to be near a critical point?
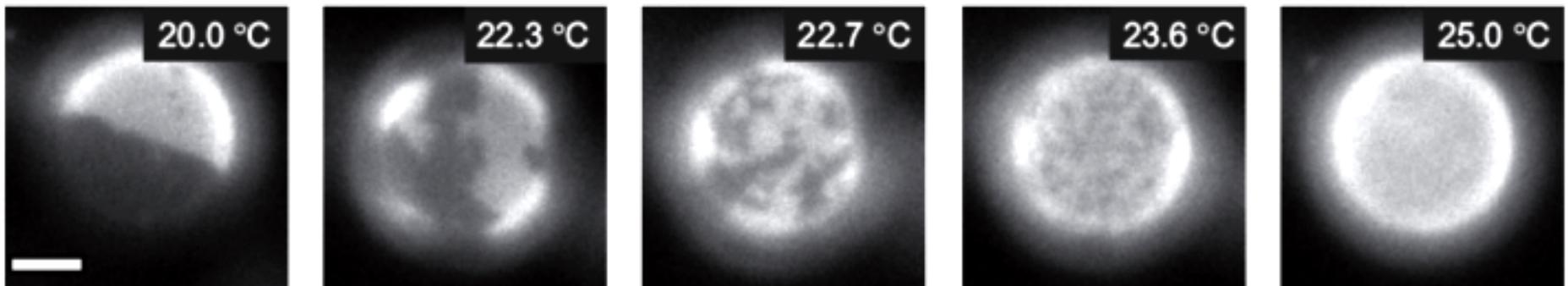
Why criticality is a surprise
Cells are carefully tuned

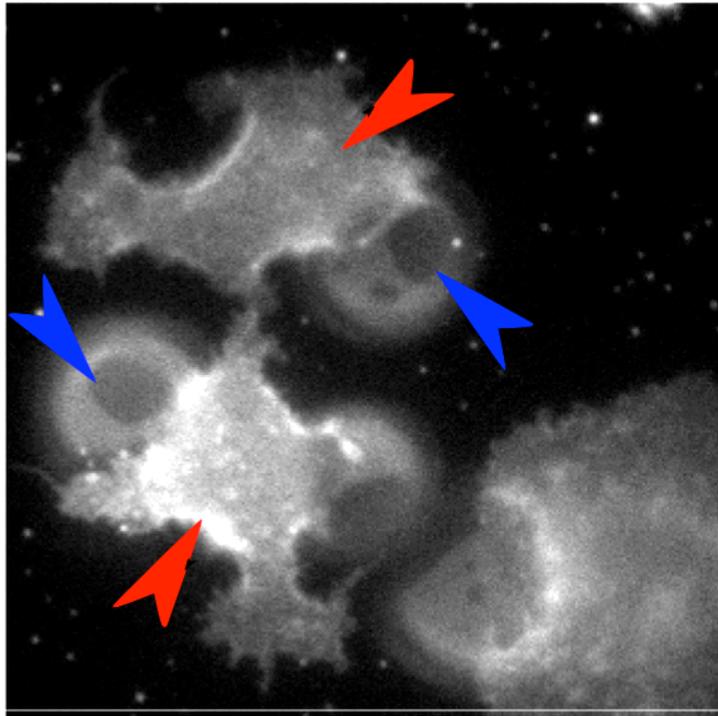**Lipid Membrane**

Boiling Water

Model (non-cell) membrane

How close are cells to critical?
- Body temperature (37°C) is 1.05 T_c
- Fraction near 50/50 (M=0)
- Correlation length ~20nm
  (twenty times lipid size) at 37°C
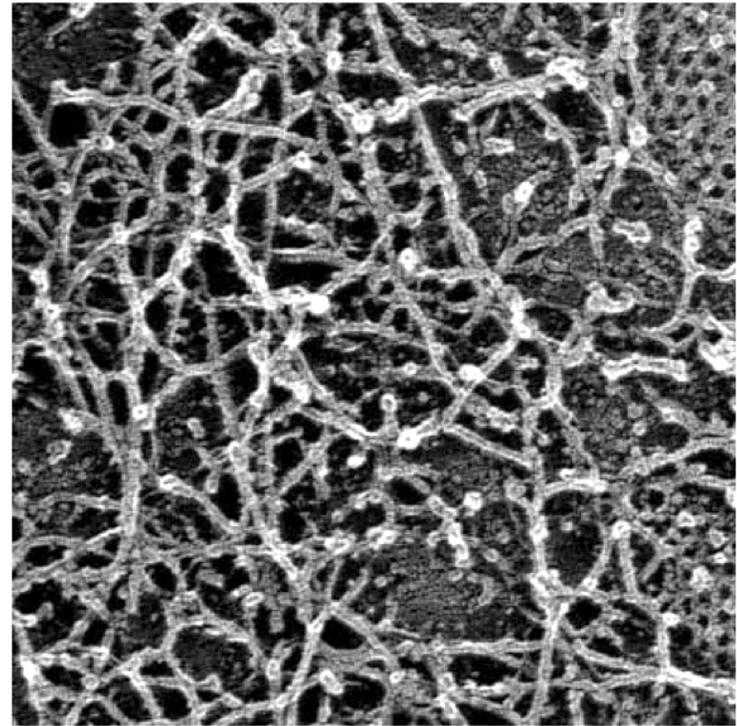- Sharp contrast with boiling water

Why don't intact cells phase separate?
The cytoskeleton as a random field
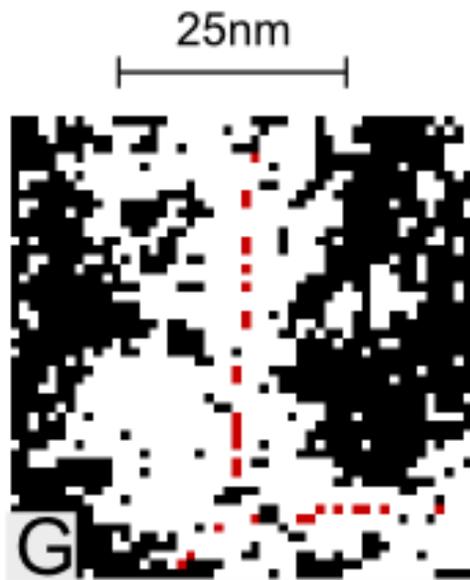

Red: Intact cells
Blue: Blebs, detached from cytoskeleton

Cytoskeleton underneath the cell membrane, attached by protein anchors that may favor one phase over the other
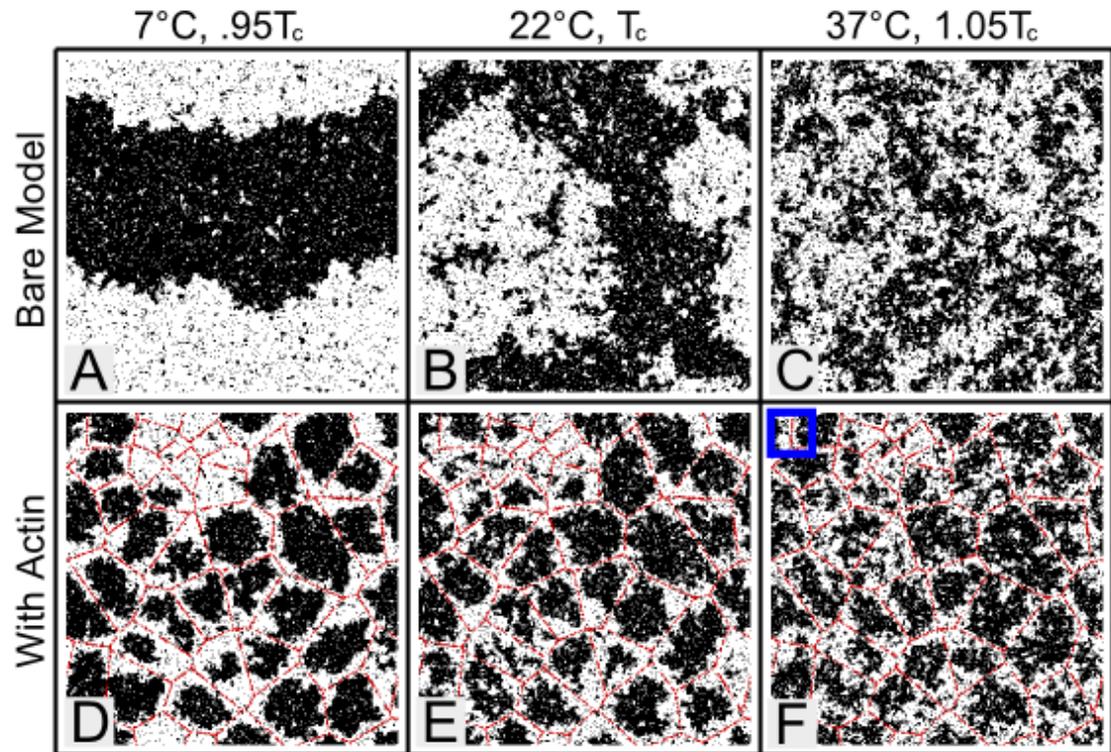
Our model
Connections to anomalous protein diffusion

25nm

7°C, .95T_c   22°C, T_c   37°C, 1.05T_c

Bare Model

A   B   C

With Actin

D   E   F

Protein anchors as "pickets" in a fence along cytoskeleton

Random field destroys phase separation in 2D

Puddles are formed when picket spacing < ξ, large compared to proteins

"Confined" and "unconfined" proteins families explained by 'black'-loving proteins stuck in puddles

Why should cells want to be near critical?
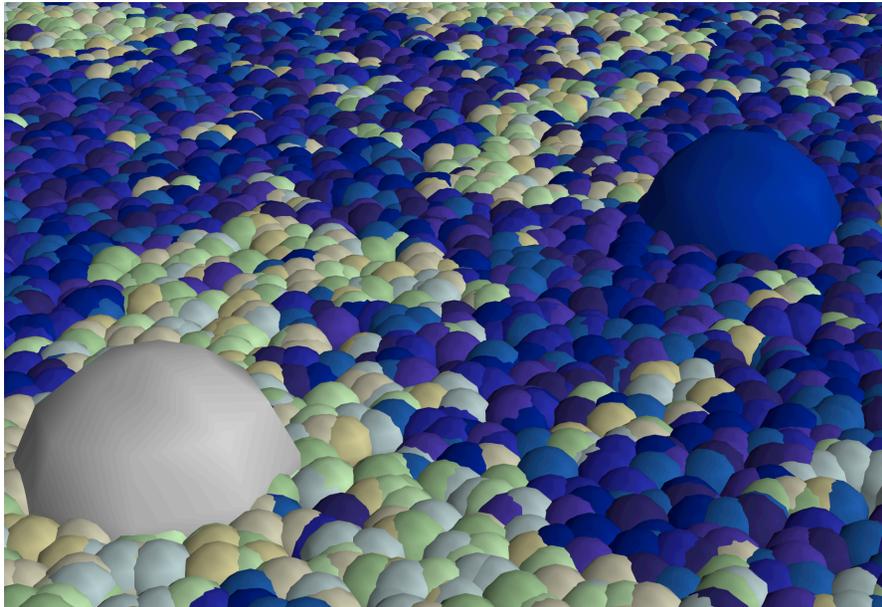## Superstructures and receptor clustering

- Assembling a large structure from 'white' proteins costs much less free energy when the correlation length ξ is large.
- Near phase separation allows for easier clustering of "black" and "white"-loving proteins without complete segregation.

a FcεRI signalling
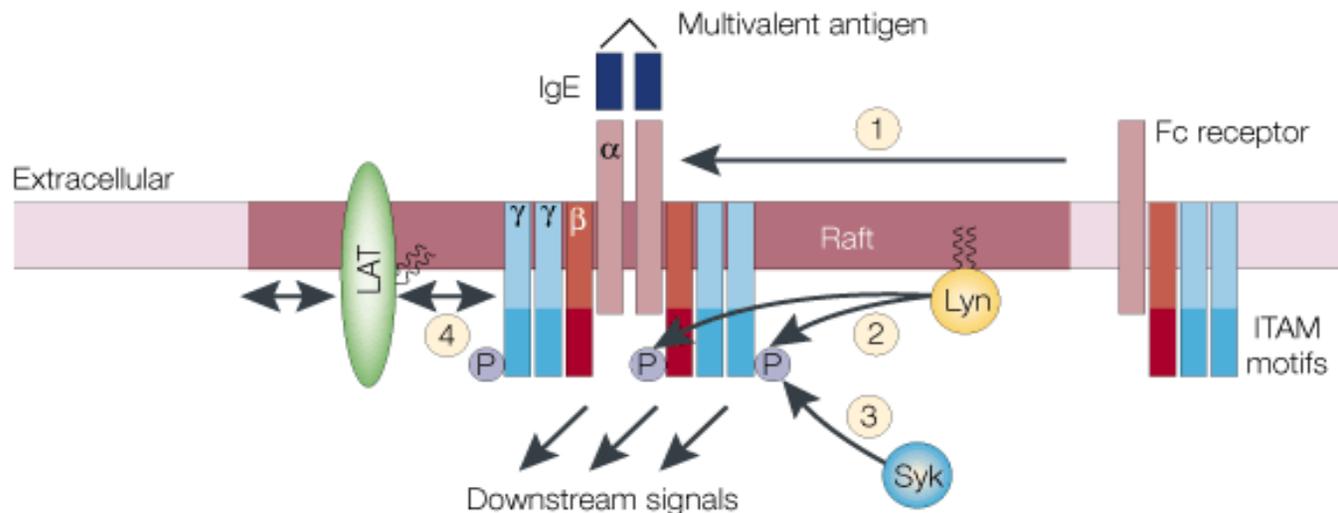
Using Ising fluctuations to communicate
Long-range Casimir forces between proteins

Conformal field theory
(Dedekind and Jacobi elliptic fcts)
agrees with Monte Carlo
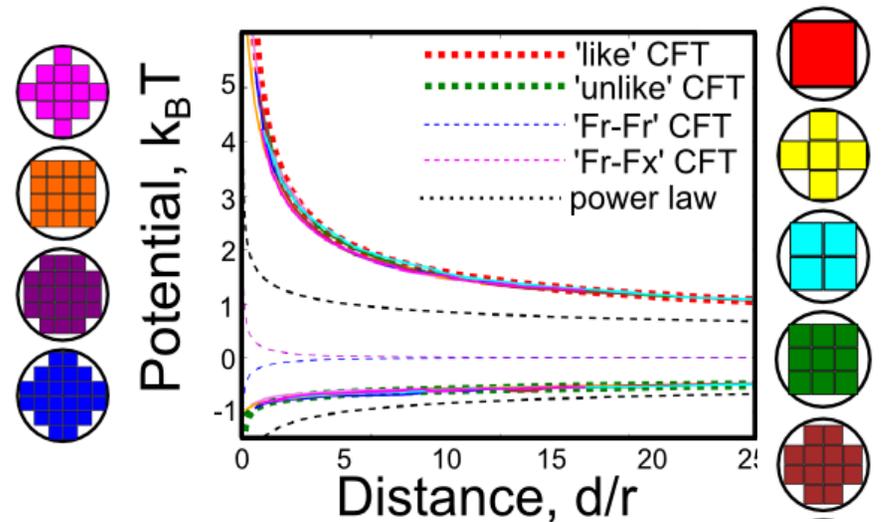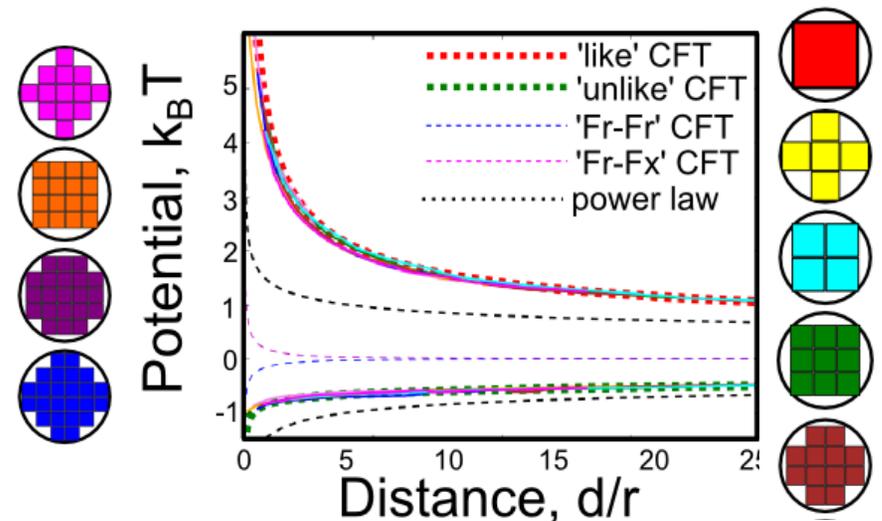
Proteins prefer 'up' or 'down'
Power-law lipid puddles
Puddle overlap gives attraction/ repulsion
Long range $r^{-1/4}$
Too weak to cluster

II. Plectoneme Formation

Bryan Daniels
Scott Forth, Chris Deufel, Maxim Sheinin, Michelle Wang
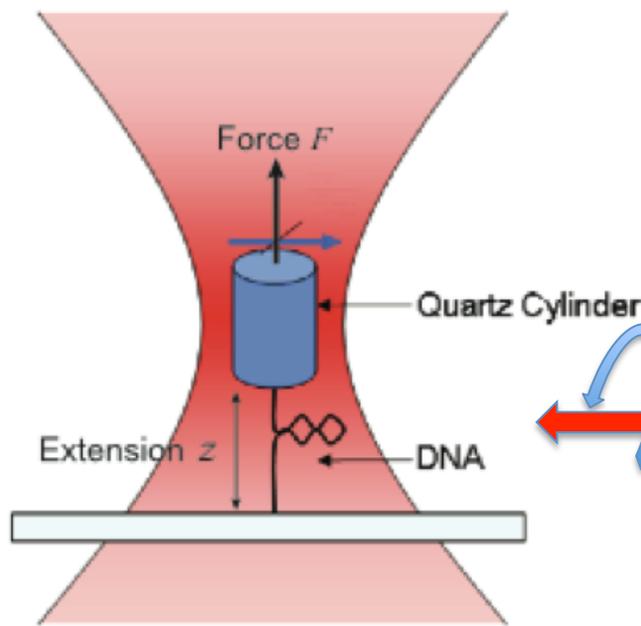
Note: Magnetic tweezers, RNA: Jan Lipfert here

Force F

Quartz Cylinder

Extension z

DNA

Linking number

K

F

Tension Force
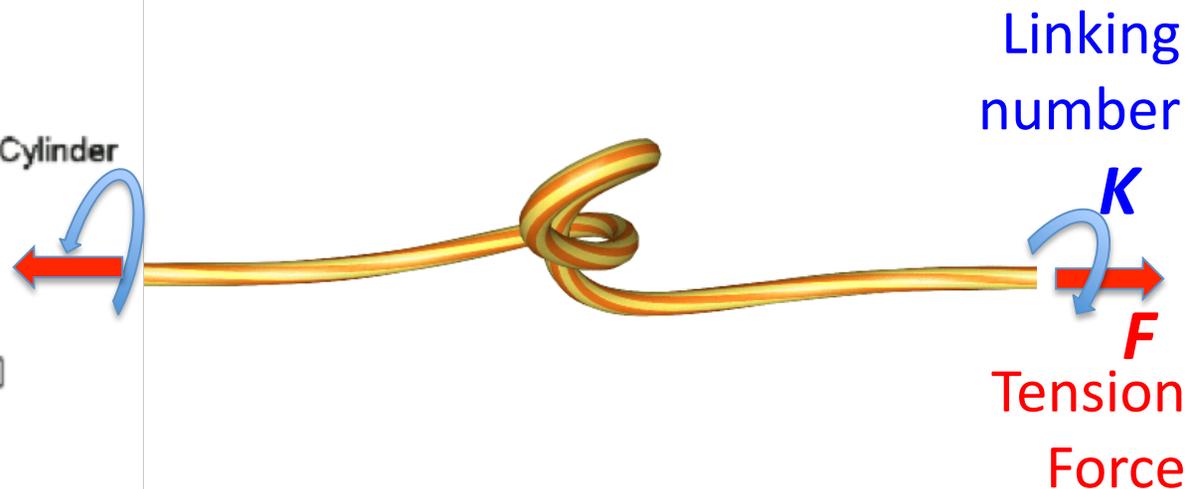
When DNA is overtwisted, it forms a supercoiled state called a **_plectoneme_**, similar to those formed by ropes, garden hoses, and telephone cords

Plectonemes: Particle or Phase?
Analogies in chemistry and physics
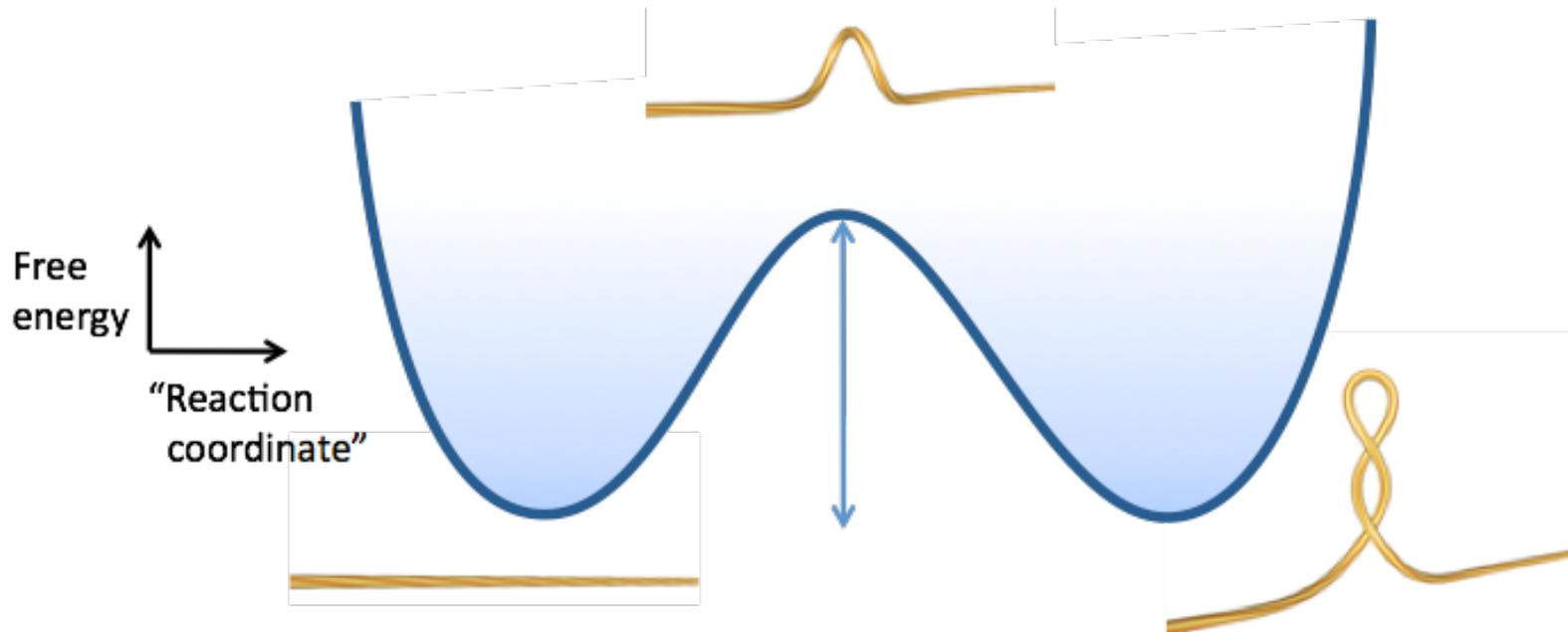
- Formation by crossing a free energy barrier. Reaction rate theory
- Nucleation of plectoneme 'helical' droplet from 'straight' phase (like raindrop nucleation)
- Double-well potential energy along reaction coordinate

(Note: No true phase transitions in 1D)

Plectoneme Nucleation Rate

Bryan Daniels, Wang Group

Thermal Rate $\Gamma = \Gamma_0 \, exp(-B/k_B T)$

Challenges:
• Dependence usually barrier dominated
Biology barriers are few $k_B T$
• Nucleation often involves atomic-scale interfaces
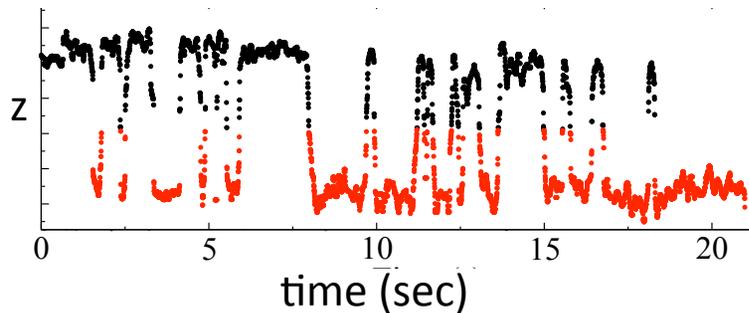DNA well described by continuum elastic model
• Nucleation dominated by disorder (raindrops on salt and dust particles)
DNA disorder (base sequence) under experimental control!
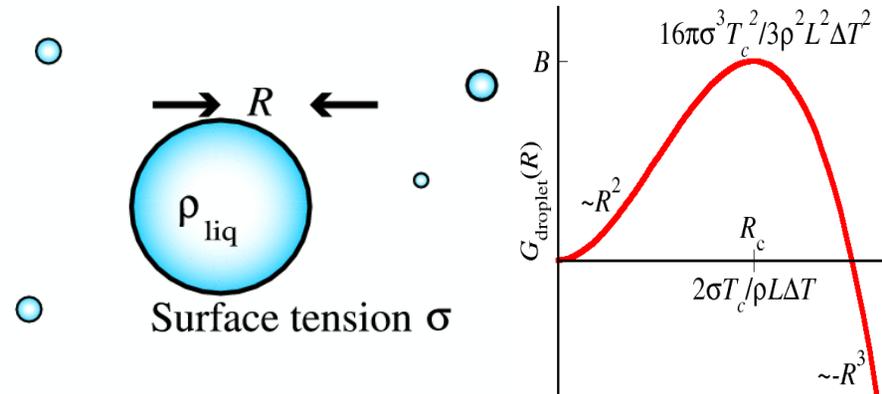
• Langer, 1968: Critical droplet theory of thermal nucleation rate from imaginary part of free energy
• Coleman: Instantons for quantum nucleation
• Chemistry: transition state theory
• Langer & Ambegaokar, 1967, supercurrent decay in thin wires (Error in Γ_0 of 10^{10}, still agreed w/expt. Fixed by Halperin & McCumber)
• Ising models, polyacetylene, raindrops, metallurgy, …

The energy barrier
Experiment and theory

Extension z / time (sec)

Histogram of Extensions $\rho(z)$

Effective potential (log ρ)
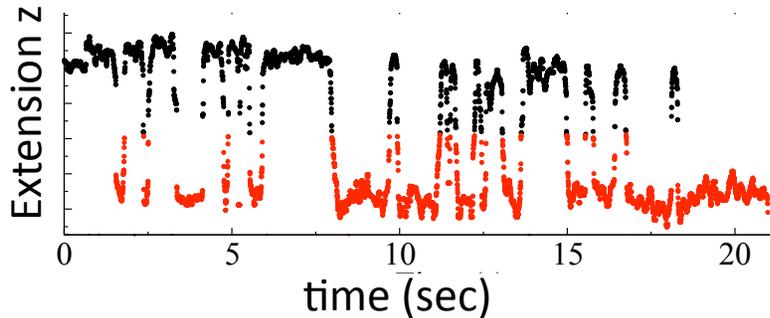
Wang experimental conundrum:
- Transition rate ~1 Hz
- Theoretical energy barrier ~ 5.5 k_BT (soliton)
- Experimental free energy barrier ~2 k_BT

Our motivation:
Usually rates of 1/sec correspond to 20k_BT barriers (Γ_0 ~ 10^{13} Hz). Why such a small prefactor?
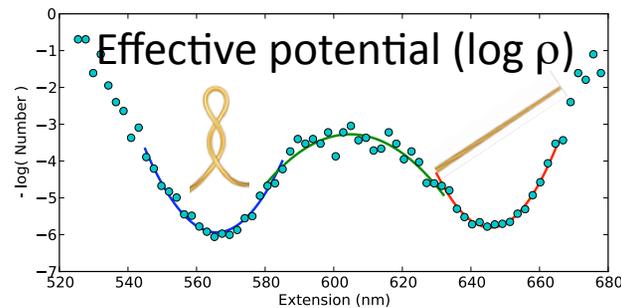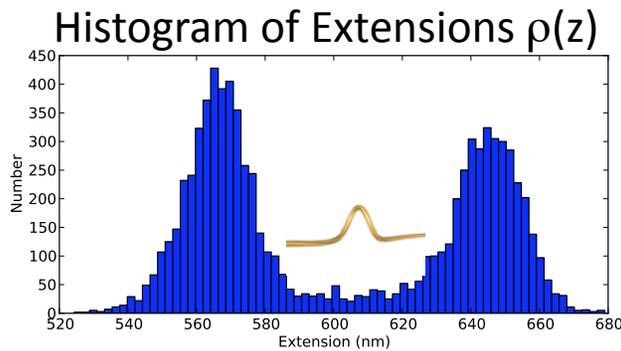
In the end, we do calculate a small prefactor Γ_0 ~ 10^5 Hz, but the actual rate depends on the response of the measuring apparatus
Problems with worm-like chain model?

Critical droplet / transition state theory
Estimating the prefactor

$$k_{\text{hopping}} = \boxed{\begin{array}{c} \text{negative eigenvalue of} \\[4pt] M_{ij} H^{\text{saddle}}_{jk}/2\pi \end{array}} \times \boxed{2\pi (L/\ell_0) J_s J_\phi \frac{\beta}{2\pi} \sqrt{\frac{\det H_{\text{straight}}}{|\det' H_{\text{saddle}}|}} e^{-(E^*_{\text{saddle}} - E_{\text{straight}})/kT}}$$
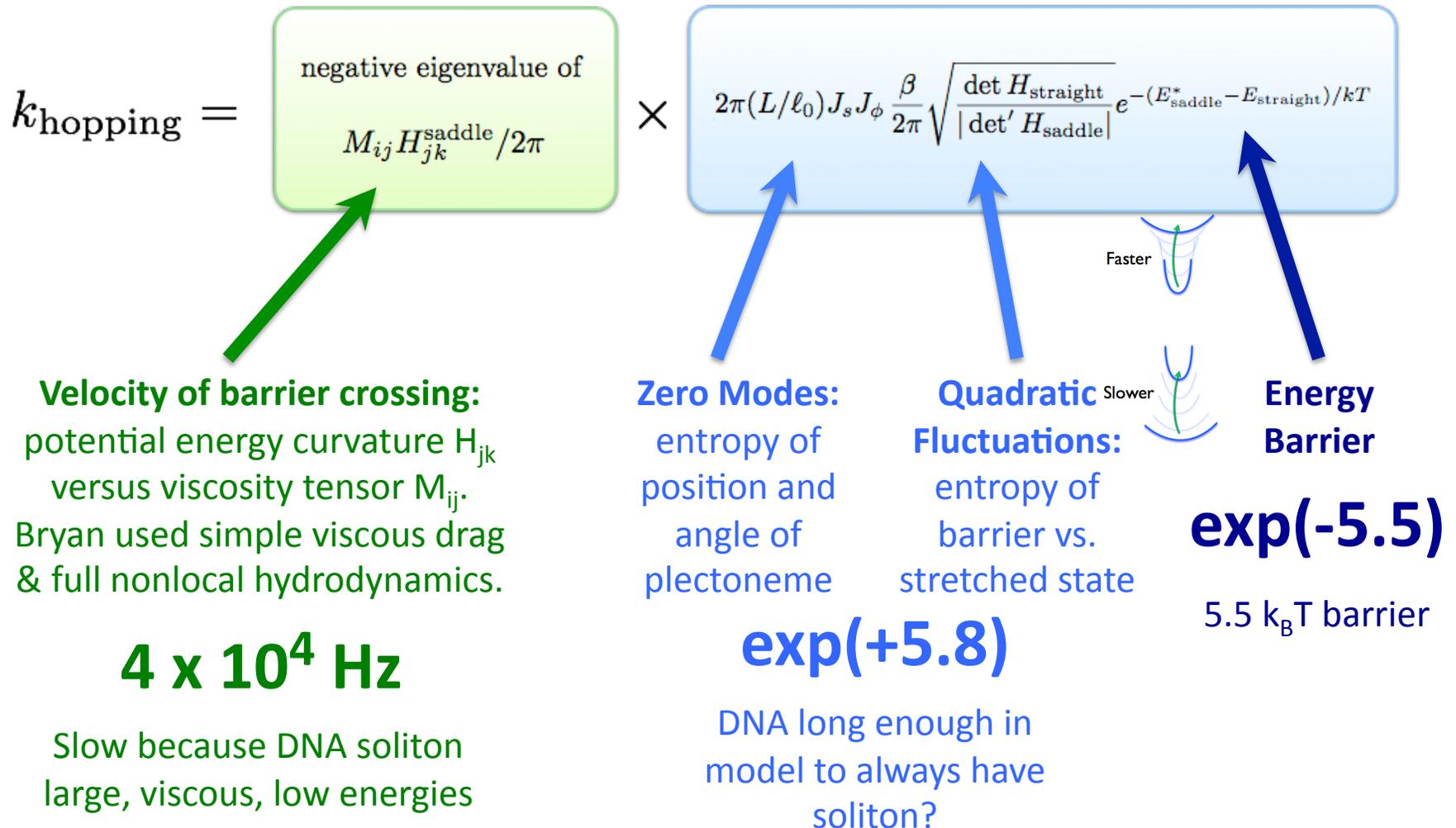
Faster

Slower

Velocity of barrier crossing:
potential energy curvature H_{jk}
versus viscosity tensor M_{ij}.
Bryan used simple viscous drag
& full nonlocal hydrodynamics.

Zero Modes:
entropy of
position and
angle of
plectoneme

Quadratic
Fluctuations:
entropy of
barrier vs.
stretched state

Energy
Barrier

exp(-5.5)

5.5 $k_B T$ barrier

4×10^4 Hz

Slow because DNA soliton
large, viscous, low energies

exp(+5.8)

DNA long enough in
model to always have
soliton?

Disorder
## Nucleotide sequence-dependence

- DNA is not intrinsically straight at zero temperature (P. Nelson, 1999); level of disorder not well known
- Natural bends produce nucleation sites: less entropy, but lower energy
- Natural bends slow down untwisting: slower prefactor
- Bryan finds the disordered saddle points using numerical searches & perturbation theory
- New free energy barrier larger (entropy no longer wins for short chains)
- Predicted rate largely unchanged (just outside feasible range using current techniques)
- Jan Lipfert's RNA results suggest something missing in model (even slower rates, similar elastic properties: problems in wormlike chain?)

Ising models in membranes, and critical droplets in DNA: Statistical physics in biology
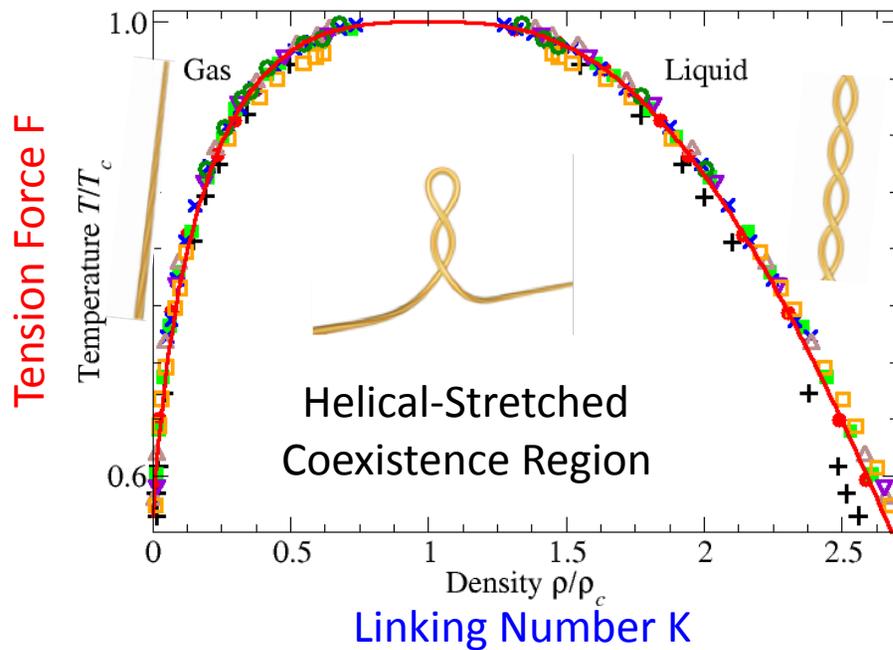
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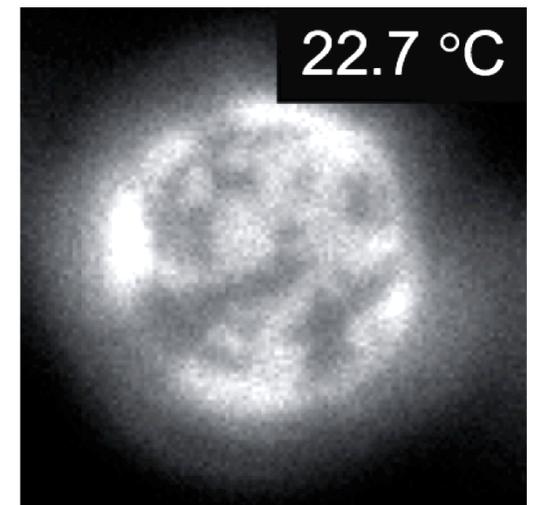
Plectoneme as phase: Marko

Two-phase coexistence at constant linking number

Just as a liquid evaporates to fill an expanding volume without change of pressure at constant temperature, so the plectoneme grows to absorb increasing linking number without changing the torque at constant external force.
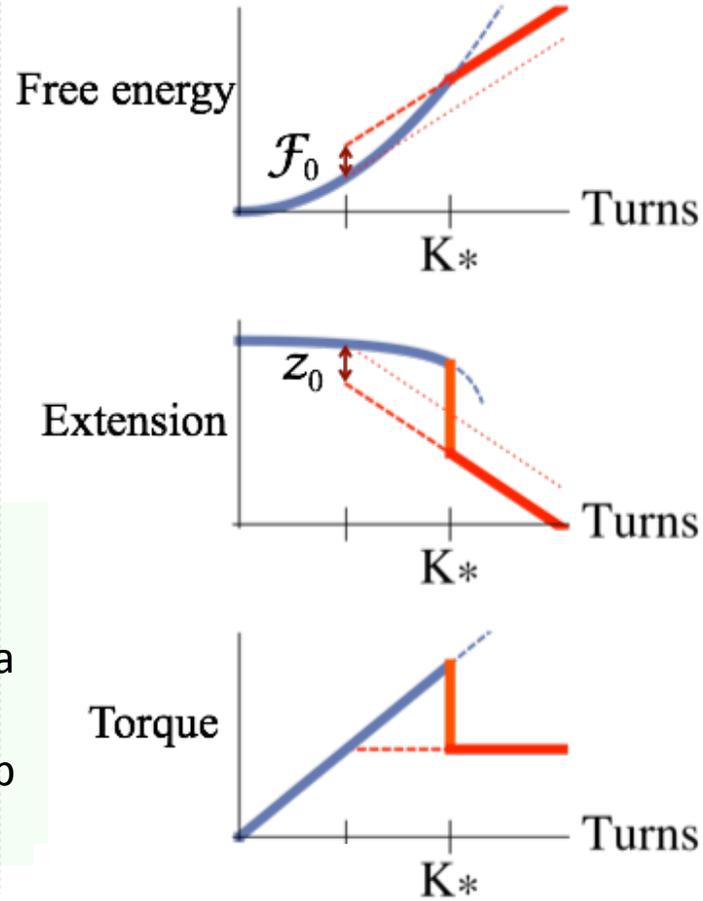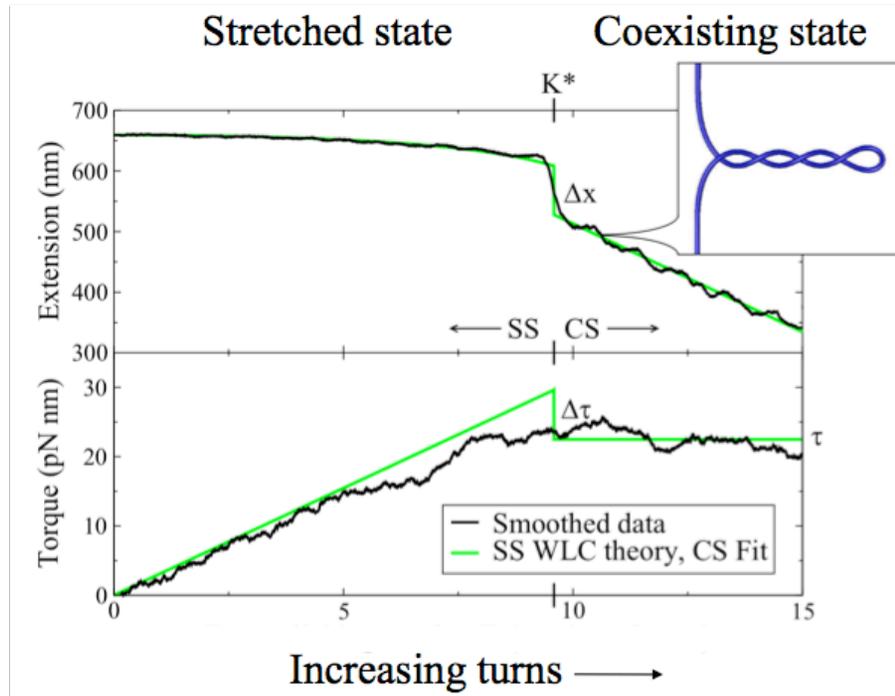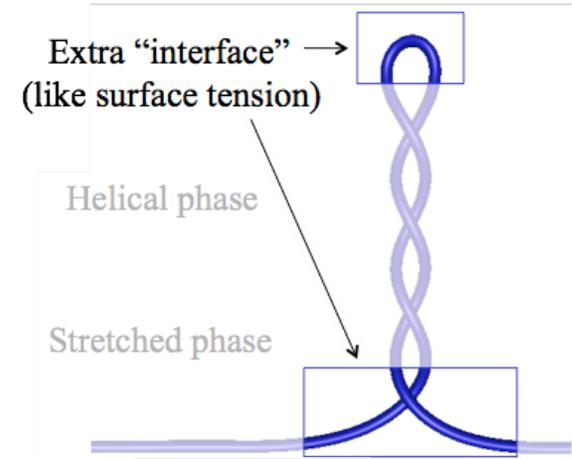
Without interface (Marko)
[Linear]

Free energy — Turns — K_*

Extension — Turns — K_*

Torque — Turns — K_*
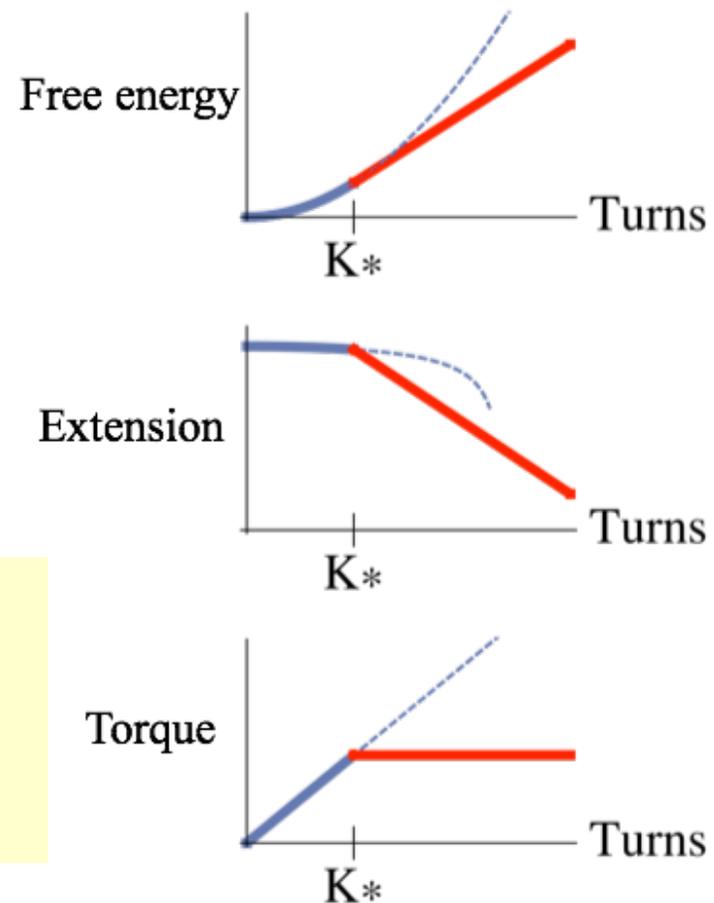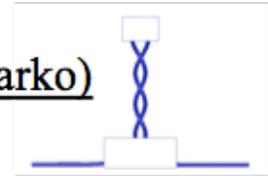
Extension and torque jumps
## Including the interfacial energies

Just as the nucleation of a gas bubble (impeded by surface tension) causes an initial jump in the volume, so Wang group's experiments showed a jump in the extension that we explain using the extra energy and length contributions of the cap and foot of the plectoneme.

Complete description
Using experiment to predict experiment

The helical phase is completely characterized by two numbers: the torque τ and the length change per linking number q.

The "interface" is described by two numbers: the extra free energy $\mathcal{F}_0$ and extra length z_0.
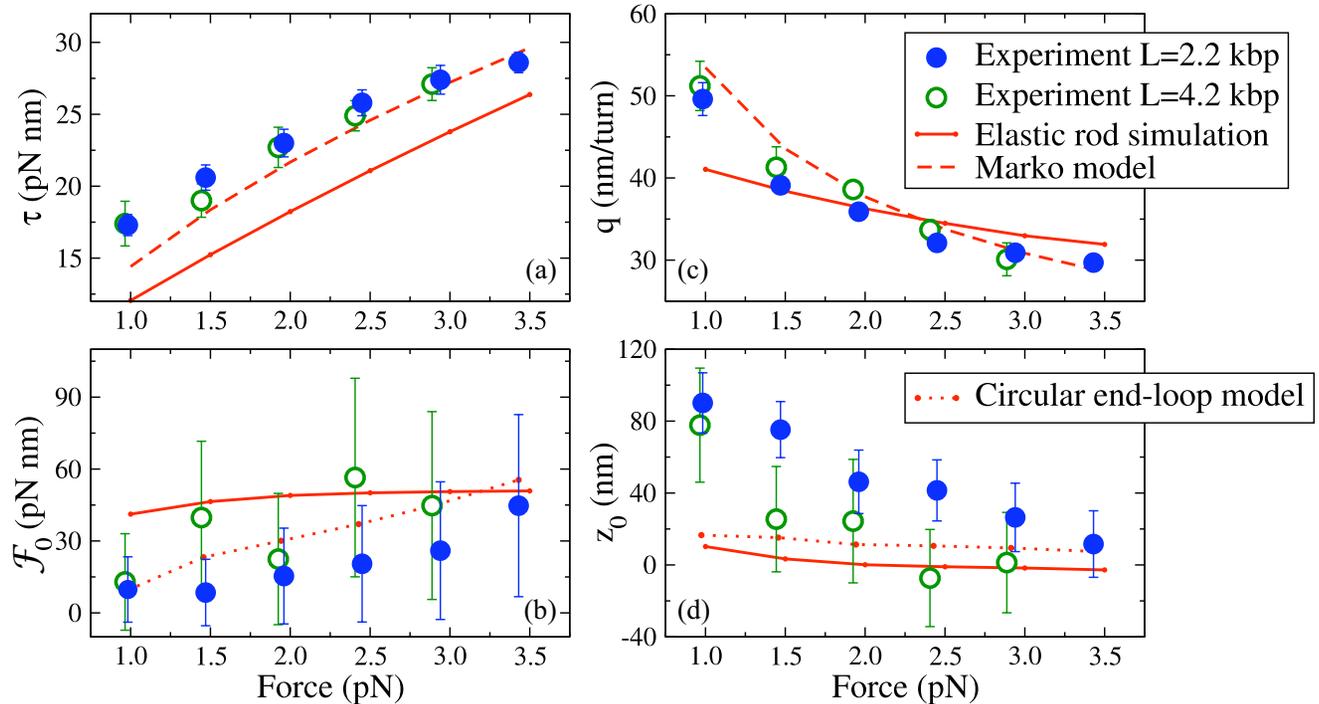
All four of these can be extracted from experiment, and used to predict the extension jump size and location (next slide).

Any theoretical calculation can be characterized by these four numbers (our elastic rod, Schiessel's similar simulations, Monte Carlo, etc.)

Our elastic rod simulations failed to accurately describe Wang's experiments

Predictions for Wang's experiments
Elastic rod model predicts strong length dependence

Using the experimental numbers for τ, q, $\mathscr{F}_0$ and z_0, and incorporating the entropy of translations, we find good agreement with the length dependence observed in the extension jump, and predicted a torque jump that we later measured.
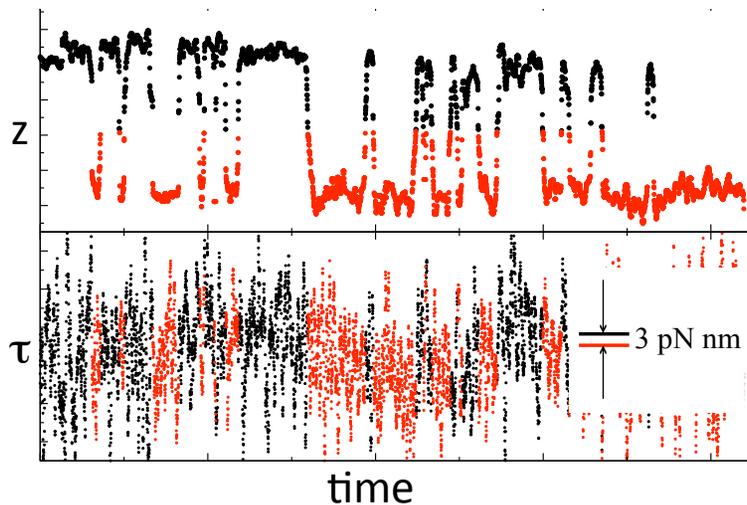
By chopping the torque based on the extension z, we measure $\Delta\tau$
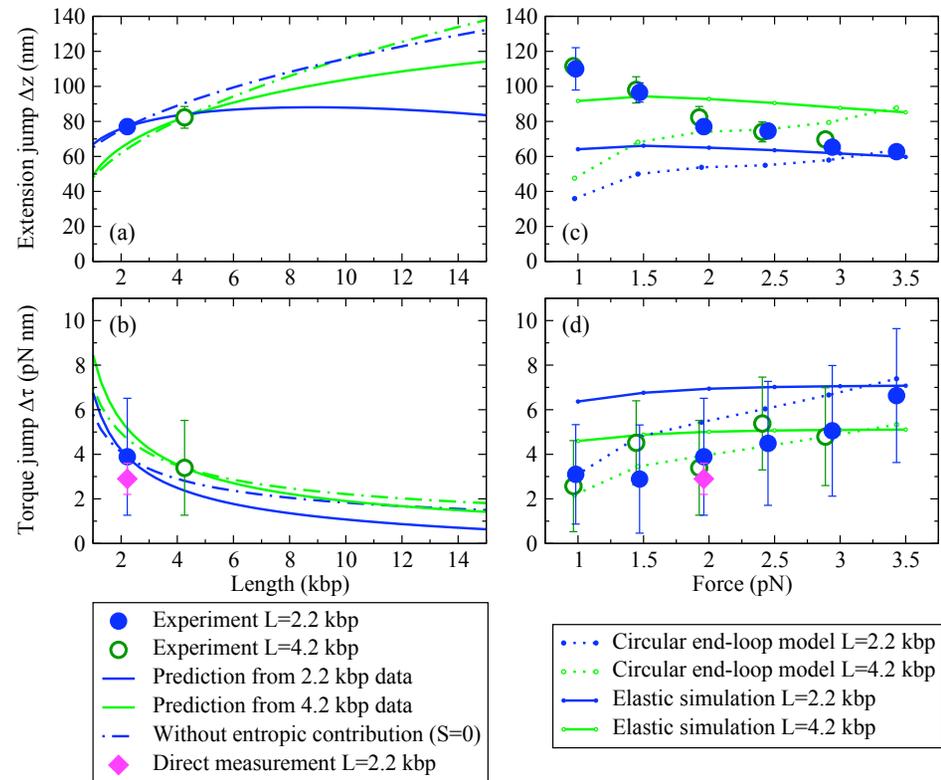
The elastic rod simulations, however, predict a substantial increase in Δz with DNA length, which is not observed. (Schiessel checking if his elastic rod model works better.)