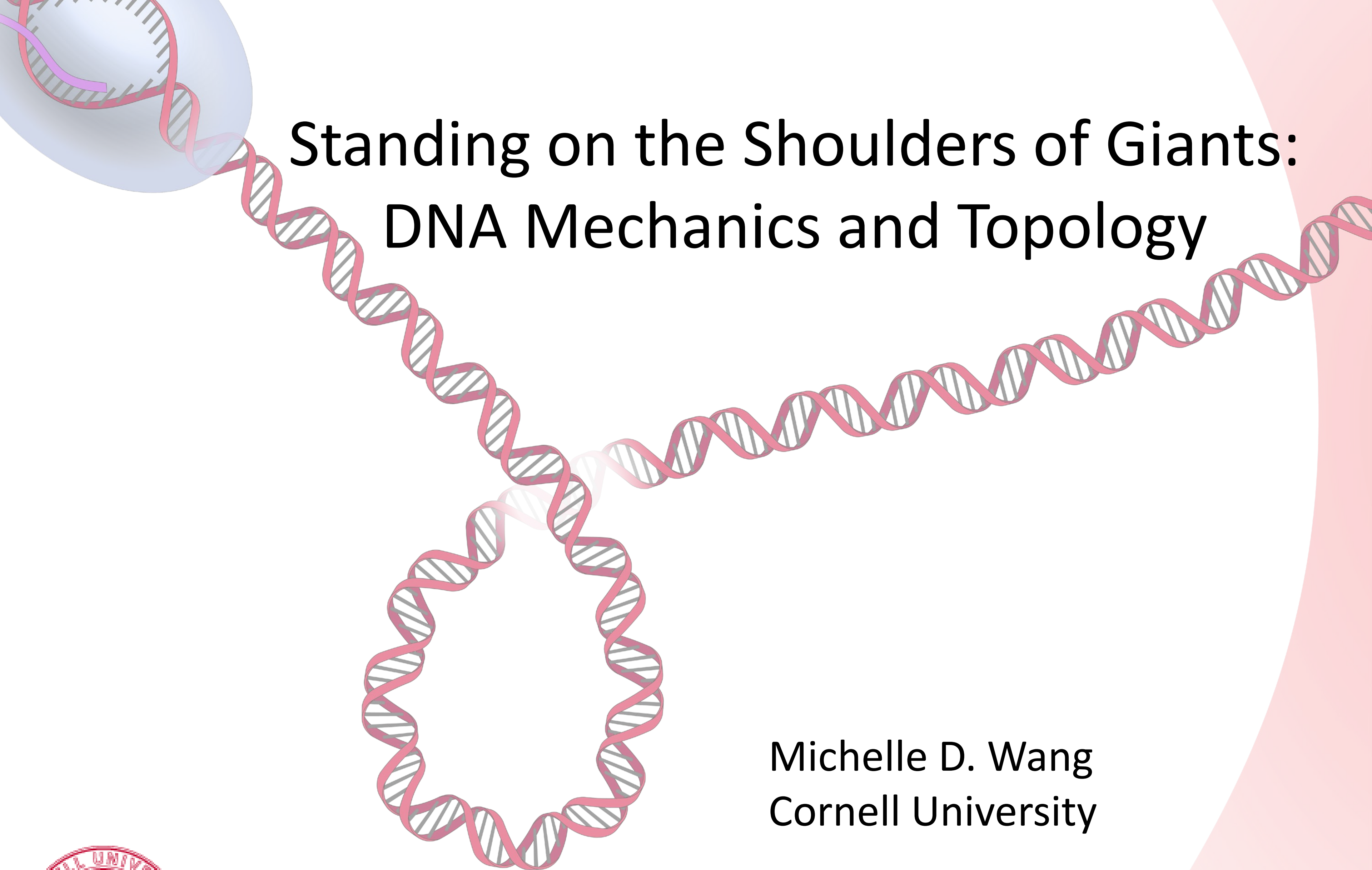
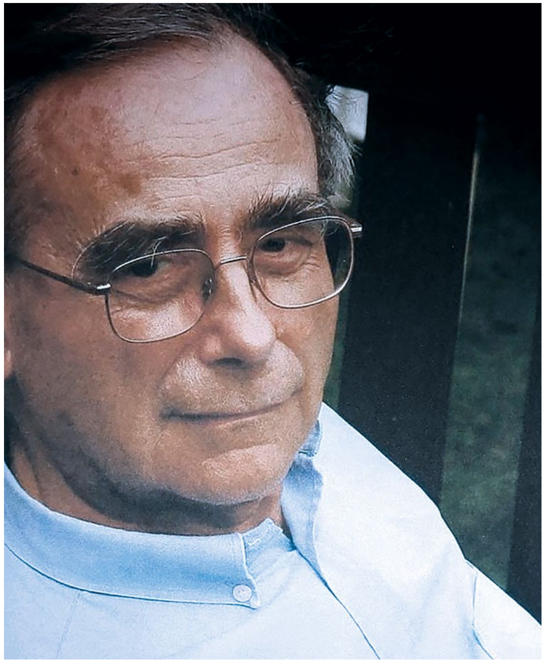


# Standing on the Shoulders of Giants: DNA Mechanics and Topology

Michelle D. Wang
Cornell University



Claude Bouchiat

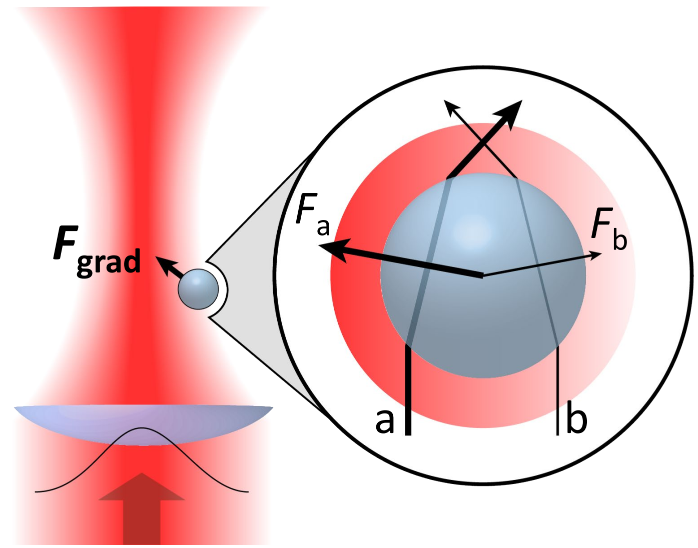
May 16, 1932
to
November 25, 2021

Qing-Yue Wang

February 27, 1933
to
January 12, 2022

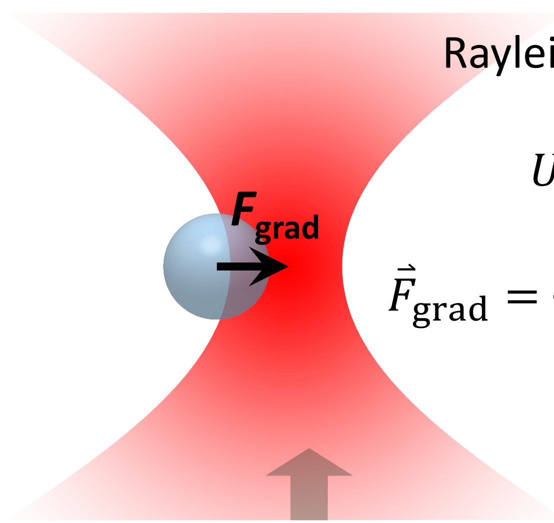
# Optical Trapping


Arthur Ashkin, Gérard Mourou, and Donna Strickland




## Arthur Ashkin

- Discovered optical gradient force in 1970 (Askkin, PRL, 1970).
- Co-winner of 2018 Nobel Prize in Physics for the invention of optical tweezers and their applications to biological systems.
- Enabled 1997 Nobel Prize in Physics for the laser cooling and trapping of atoms, and the 2001 Nobel Prize in Physics for achieving Bose-Einstein condensation using magneto-optical traps to cool atoms.



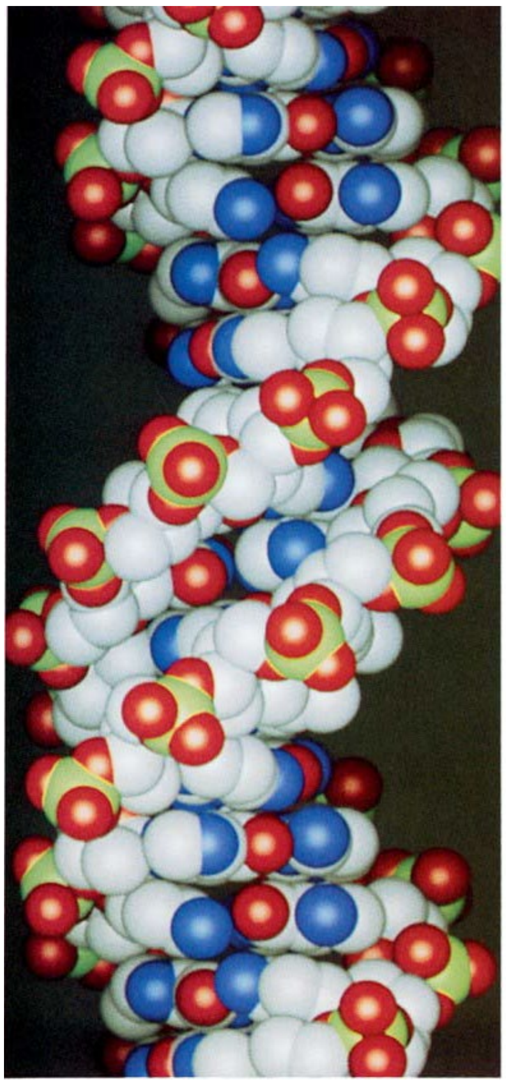

Rayleigh Regime (r<<λ)

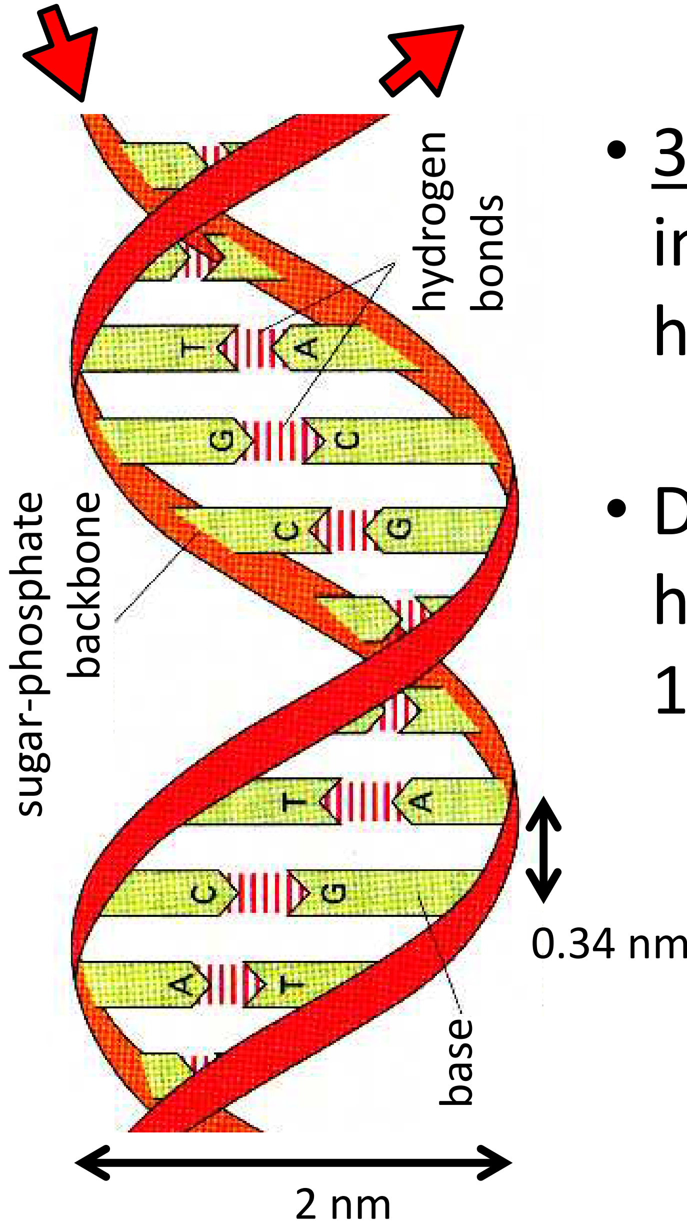
$$U = -\frac{1}{2}\vec{p}\cdot\vec{E}$$

$$\vec{F}_{\text{grad}} = \frac{1}{2}\nabla(\vec{p}\cdot\vec{E}) \propto \nabla(E^2)$$

Killian et al., Cell, 2018

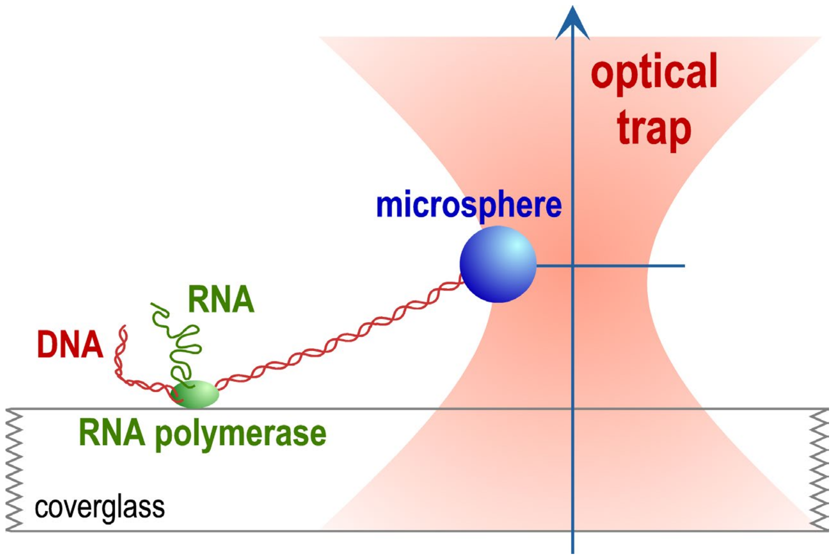
# DNA: The Genetic Code

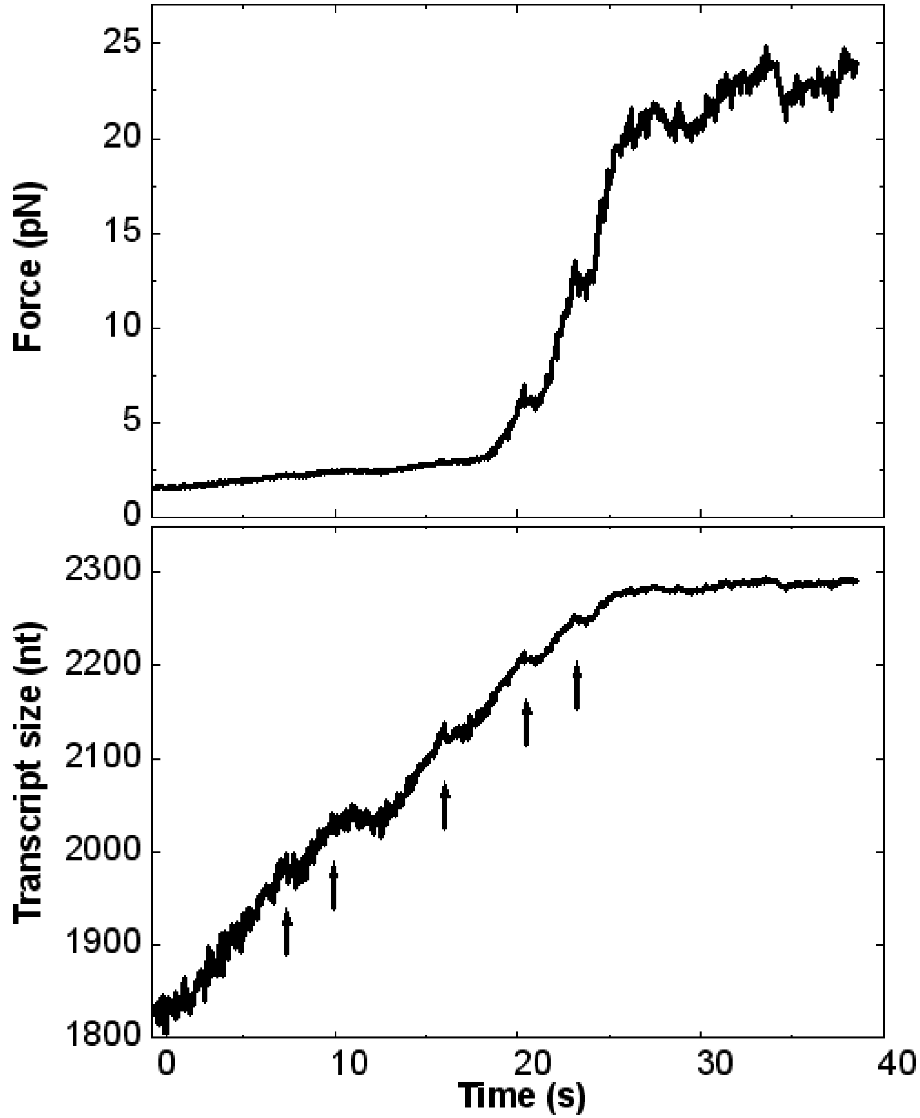





- <u>3.2 billion</u> base pairs in 23 chromosomes in human (1.1 meters!)
- DNA is a chiral double helix (right-handed, 10.6 bp/turn)

# *E. coli* RNA Polymerase Generates ~ 25 pN



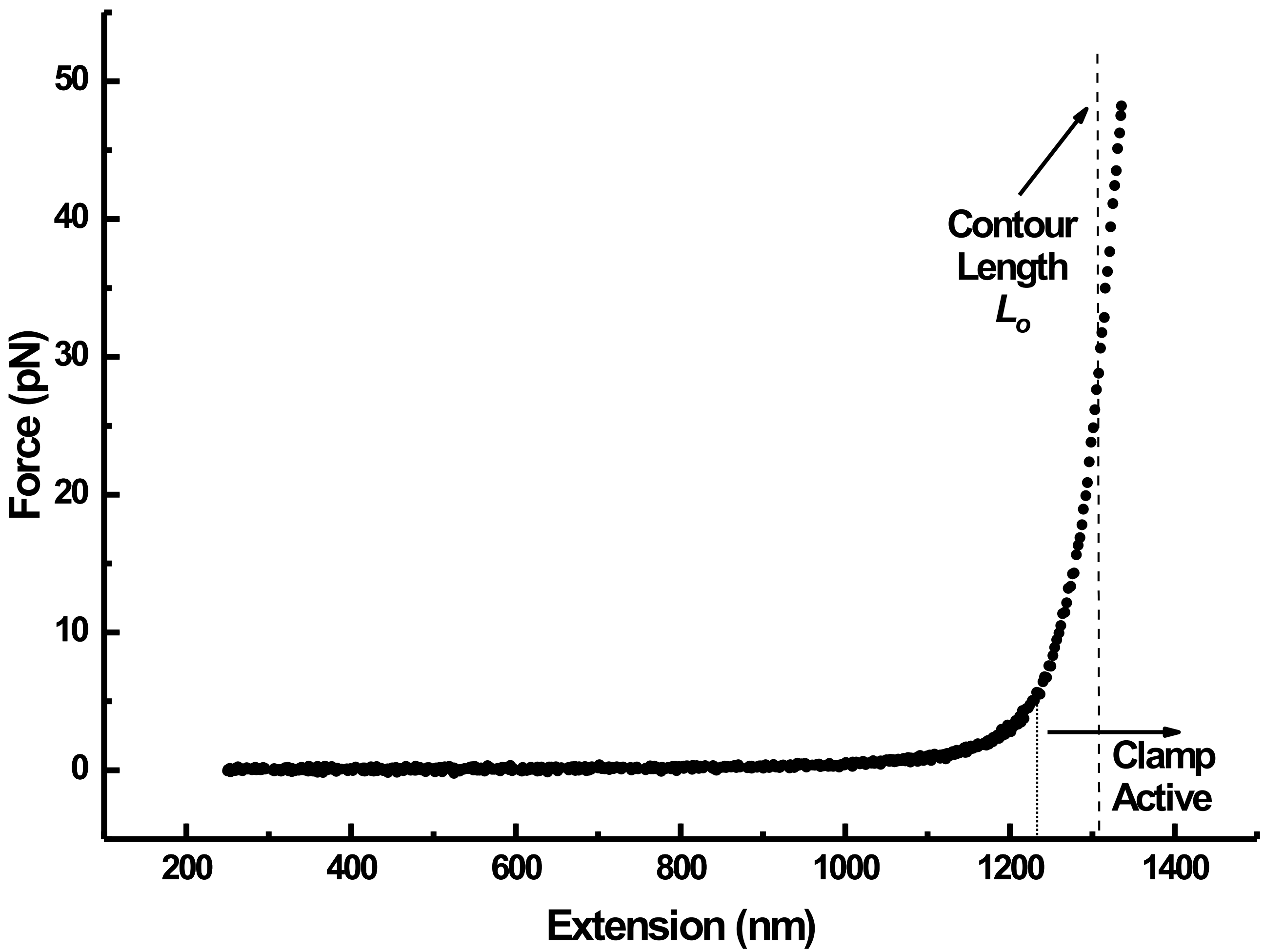

- RNAP position on DNA is monitored via the bead.
- RNAP is a powerful motor.

Wang et al., Science, 1998
Yin et al., Science, 1995

Biophysical Journal Volume 72 March 1997 1335–1346

# Stretching DNA with Optical Tweezers

Michelle D. Wang,* Hong Yin,# Robert Landick,§ Jeff Gelles,# and Steven M. Block*



*Macromolecules* **1995,** *28,* 8759–8770 **87**

# Stretching DNA

**John F. Marko***

*Center for Studies in Physics and Biology, The Rockefeller University, 1230 York Avenue, New York, New York 10021-6399*

**Eric D. Siggia**

*Laboratory of Atomic and Solid State Physics, Clark Hall, Cornell University, Ithaca, New York 14853-2501*

*Received May 9, 1995; Revised Manuscript Received September 18, 1995*[⊗]

## Marko-Siggia Worm-Like-Chain (WLC) Model – interpolation expression:

$$F = \frac{k_{\mathrm{B}}T}{A}\left[\frac{z}{L} + \frac{1}{4(1 - z/L)^2} - \frac{1}{4}\right]$$

bending persistence length

## Modified Marko-Siggia Worm-Like-Chain (WLC) Model – interpolation expression:

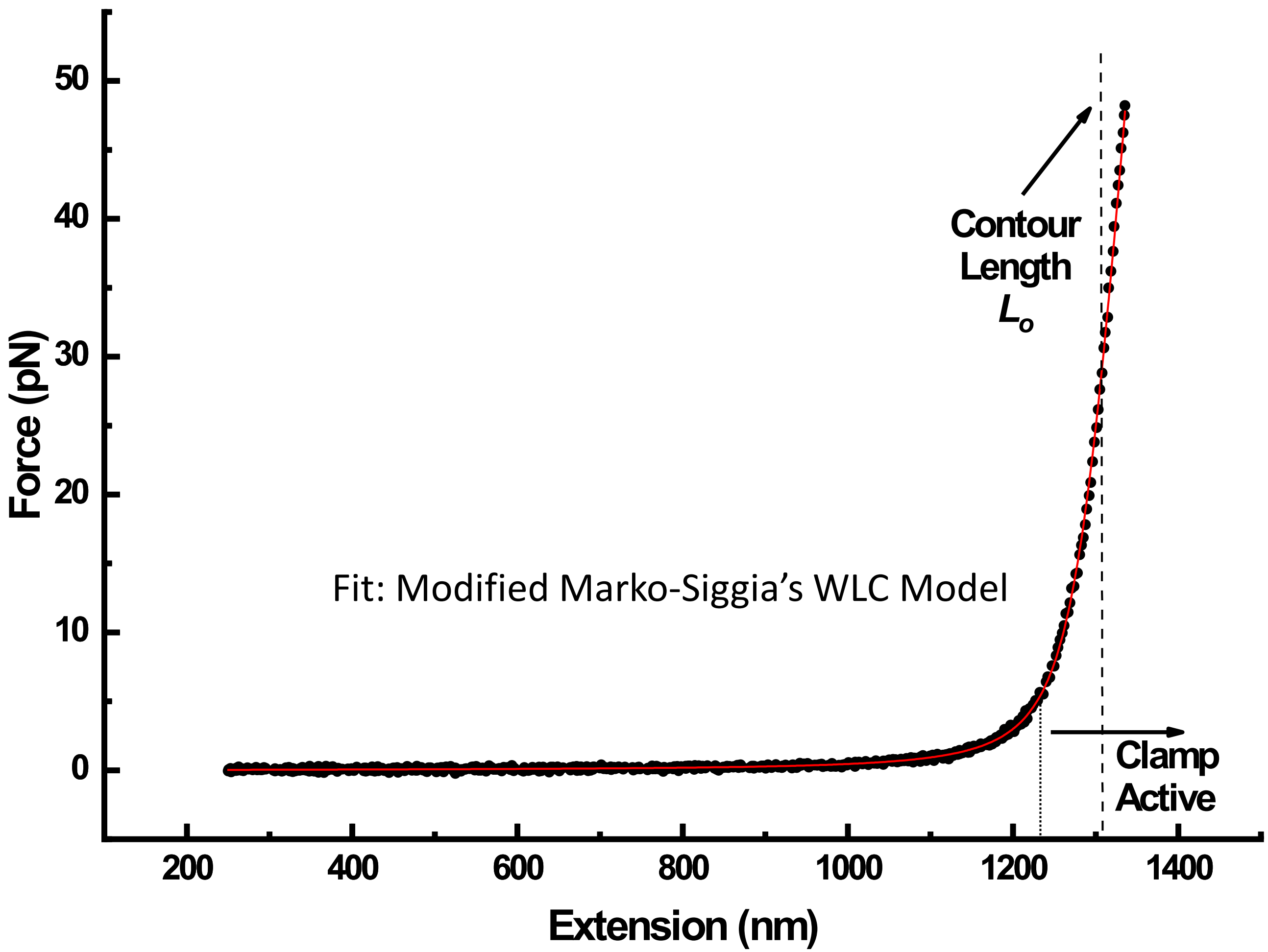
$$F = \frac{k_{\mathrm{B}}T}{A}\left[\frac{z}{L} + \frac{1}{4(1 - z/L + F/K_o)^2} - \frac{1}{4} - \frac{F}{K_o}\right]$$

stretch modulus

Biophysical Journal Volume 72 March 1997 1335–1346

# Stretching DNA with Optical Tweezers

Michelle D. Wang,* Hong Yin,# Robert Landick,§ Jeff Gelles,# and Steven M. Block*



Biophysical Journal Volume 76 January 1999 409–413

# Estimating the Persistence Length of a Worm-Like Chain Molecule from Force-Extension Measurements

C. Bouchiat,* M. D. Wang,# J.-F. Allemand,§ T. Strick,§ S. M. Block,¶ and V. Croquette§

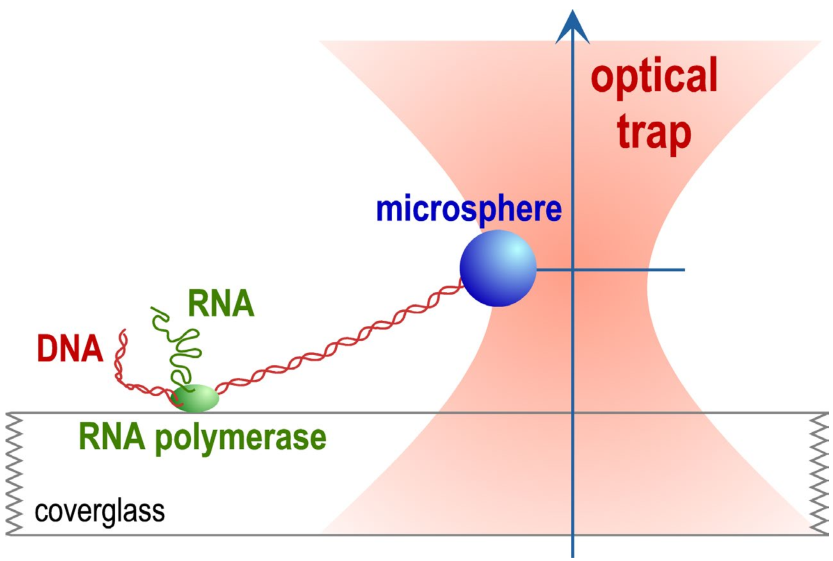
Bouchiat model: MS interpolation formula with 7th order polynomial:

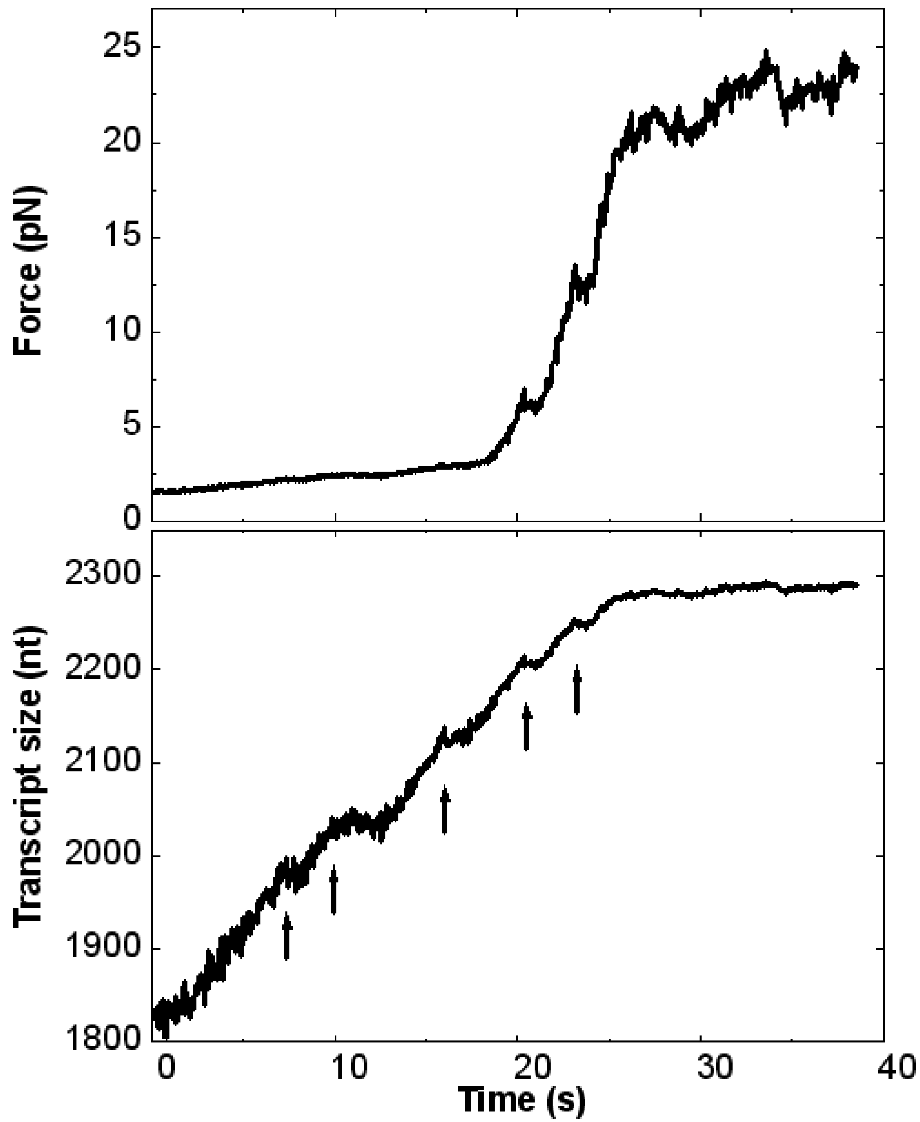
$$F = \frac{k_B T}{A}\left[\frac{z}{L} + \frac{1}{4(1-z/L)^2} - \frac{1}{4} + \sum_{i=2}^{7} a_i \left(\frac{z}{L}\right)^i\right]$$

$$a_2 = -\,0.5164228$$
$$a_3 = -\,2.737418$$
$$a_4 = +\,16.07497$$
$$a_5 = -\,38.87607$$
$$a_6 = +\,39.49944$$
$$a_7 = -\,14.17718$$

constants

# *E. coli* RNA Polymerase Generates ~ 25 pN

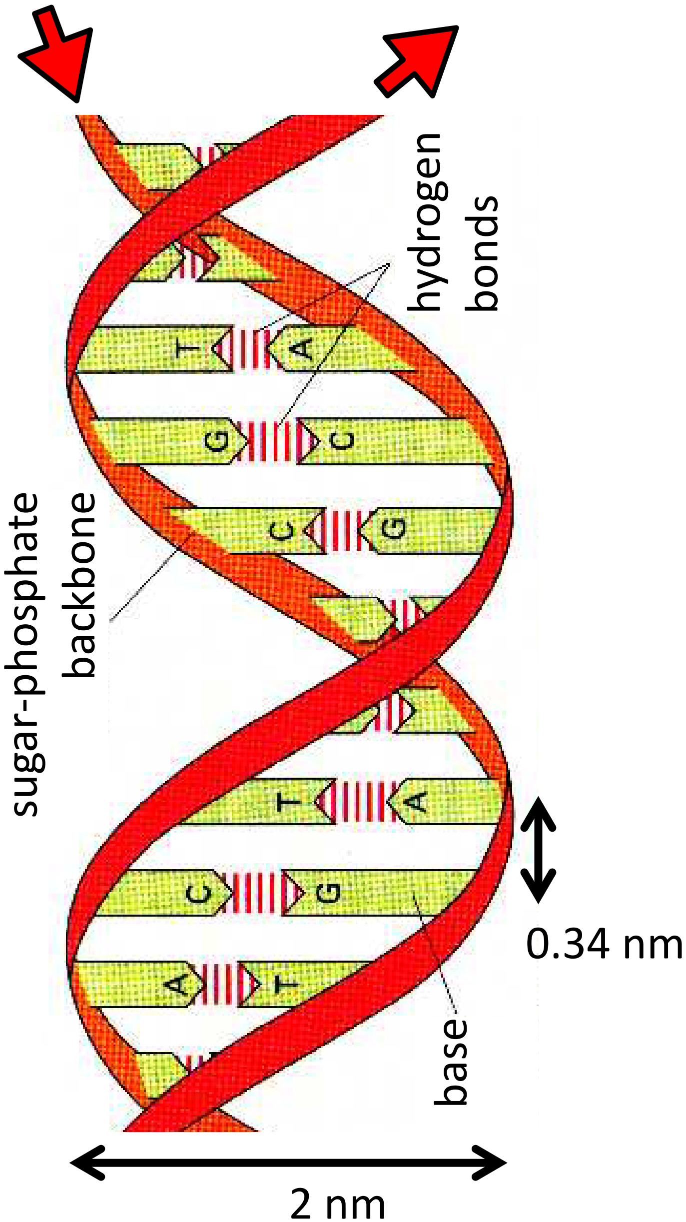



- RNAP position on DNA is monitored via the bead.
- RNAP is a powerful motor.

Wang et al., Science, 1998
Yin et al., Science, 1995

# The Right-Handed Double Helix



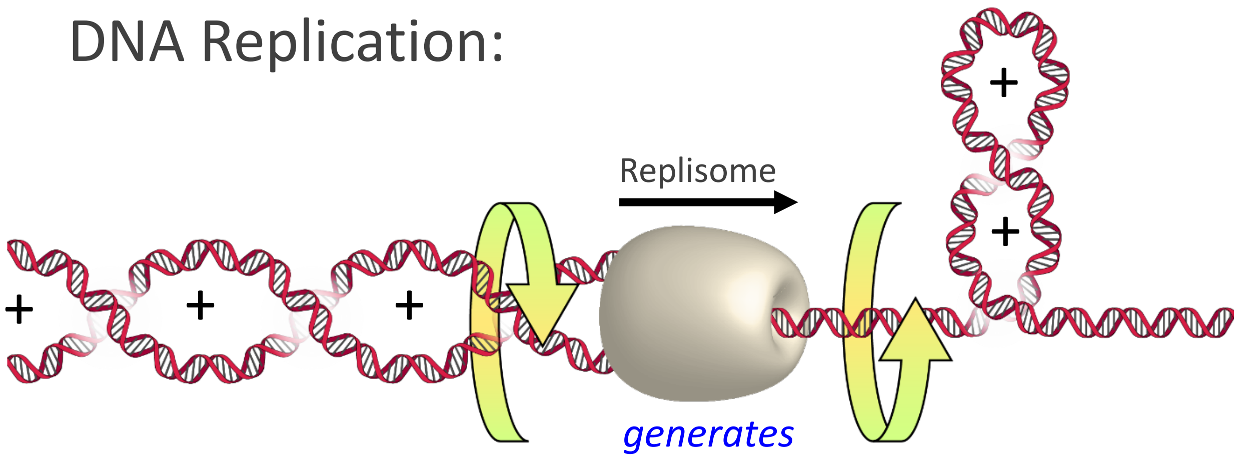

"The difficulty is a **topological** one… the two chains **must be untwisted**… the difficulty of untwisting is a **formidable** one."

Watson & Crick, Cold Spring Harb Symp Quant Biol, 1953

Watson & Crick, Nature, 1953
Wilkins, Stokes,& Wilson, Nature, 1953
Franklin & Gosling, Nature, 1953

# Translocation and Rotation Are Coupled

DNA Replication:

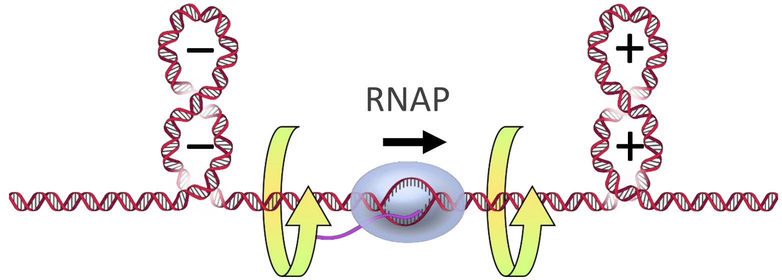



Forth et al., Ann. Rev. Biophys., 2013

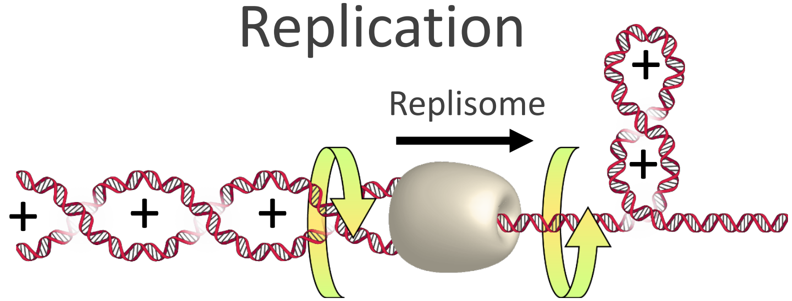
| | Translocation | | Rotation |
|---|---|---|---|
| DNA replicated:<br>10.5 bp (helical pitch) | 3.5 nm | ⟷ | 1 turn |
| DNA replicated:<br>Your lifetime: | $10^{16}$ m (light year) | ⟷ | $10^{25}$ turns |

# Inherent Motor Capacity

## Transcription




## Replication




Remove roadblocks
Remodel DNA structure & topology
Navigate collisions with other motors

⟷

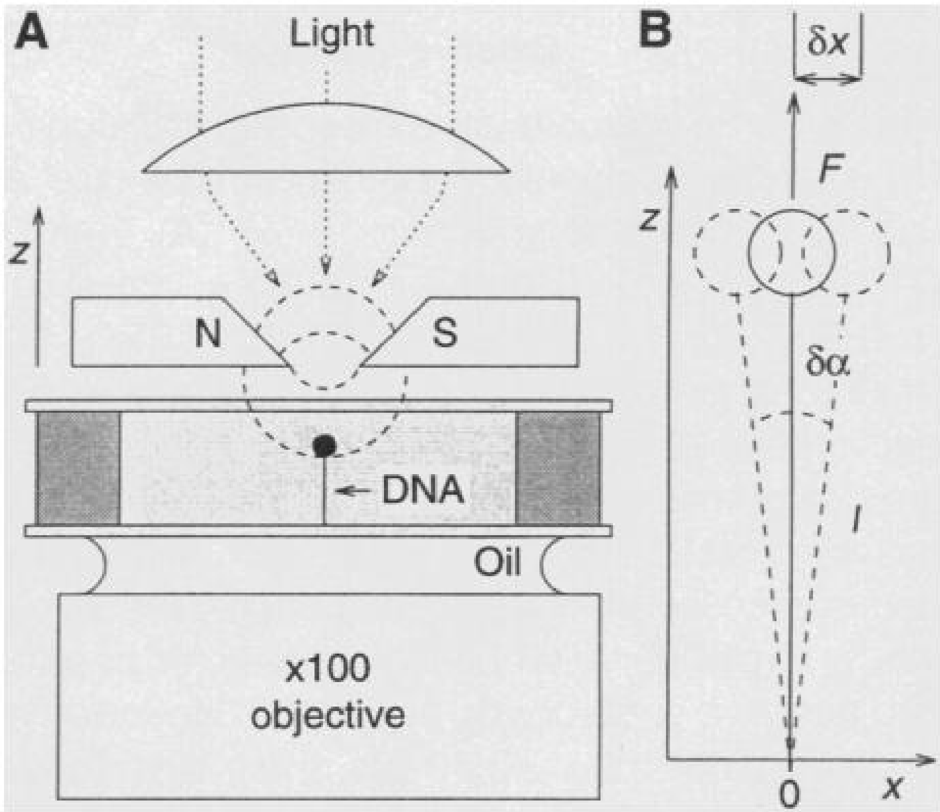
**Force** Resistance to translocation

**Torque** Resistance to rotation

Science, 1996

# The Elasticity of a Single Supercoiled DNA Molecule

T. R. Strick, J.-F. Allemand, D. Bensimon, A. Bensimon, V. Croquette

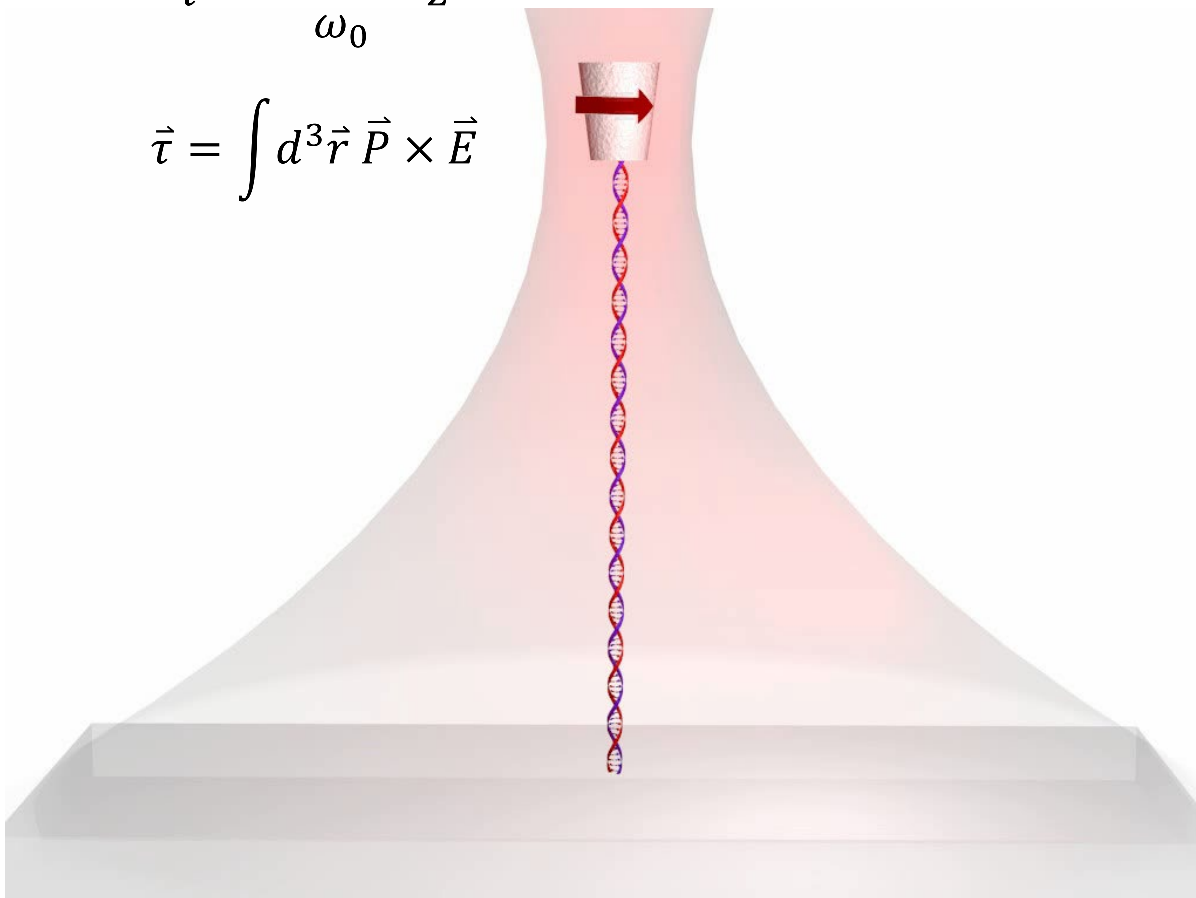


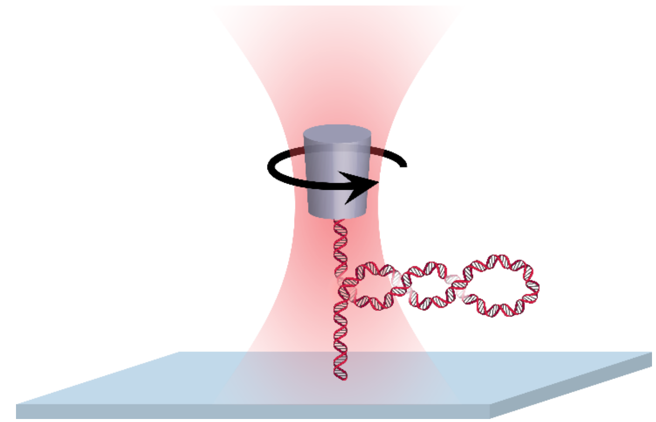

Optical rotation: Dholakia, Padgett, Heckenberg, Rubinsztein-Dunlop

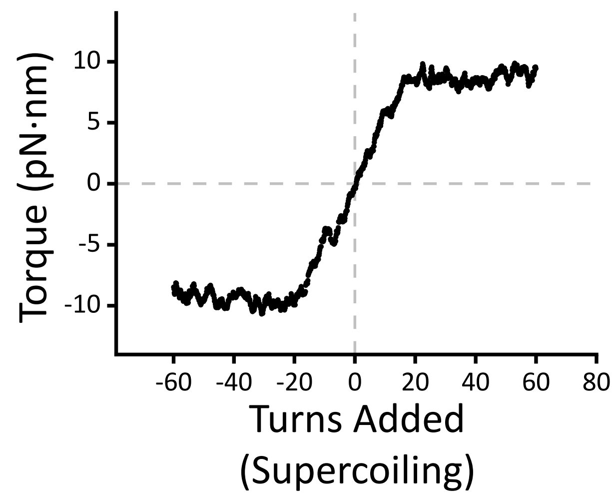
# The Angular Optical Trap (AOT)

$$\vec{\tau} = \frac{P_{\mathrm{R}} - P_{\mathrm{L}}}{\omega_0}\hat{z}$$

$$\vec{\tau} = \int d^3\vec{r}\,\vec{P} \times \vec{E}$$



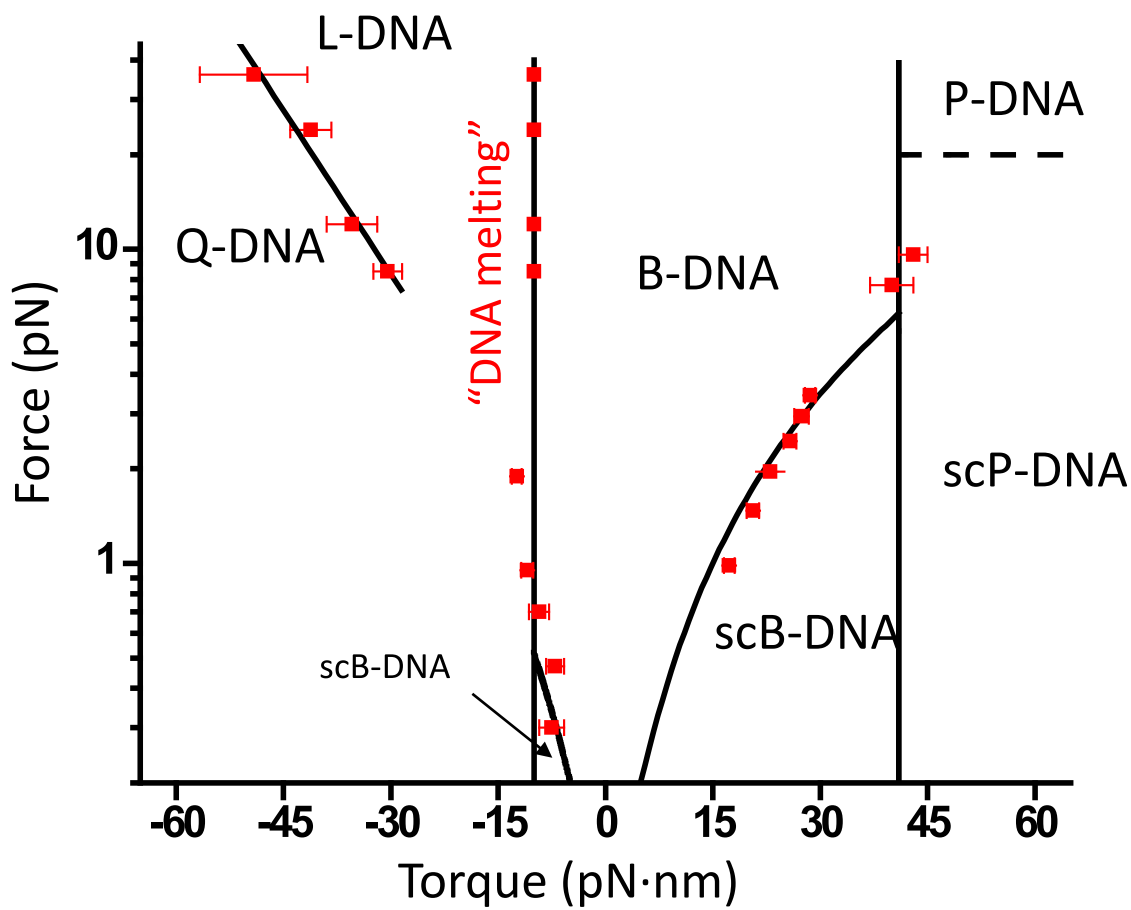





- Torque and rotation
- Force and displacement

La Porta & Wang, Phys Rev Lett, 2004
Deufel et al., Nat Methods, 2007
Forth et al., Phys Rev Lett, 2008
Sheinin et al., Phys Rev Lett, 2011
Le et al., Cell, 2019
Gao et al., Phys Rev Lett, 2021

# DNA Phase Diagram




- Bending modulus
- Twist modulus
- Stretch modulus
- Twist-stretch coupling modulus

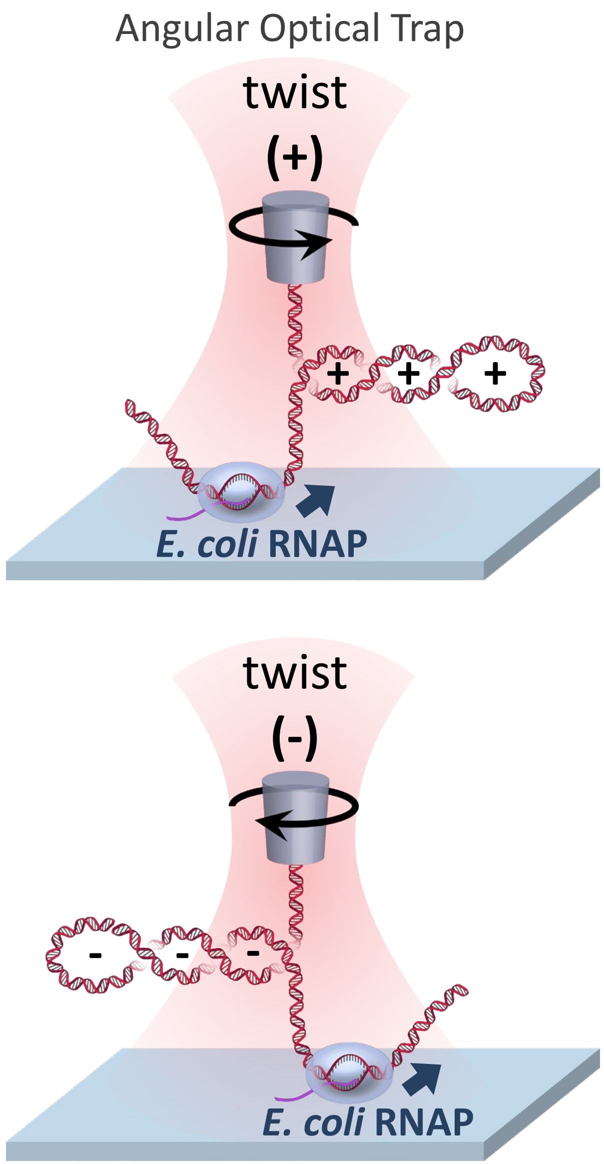
<u>Theory</u>

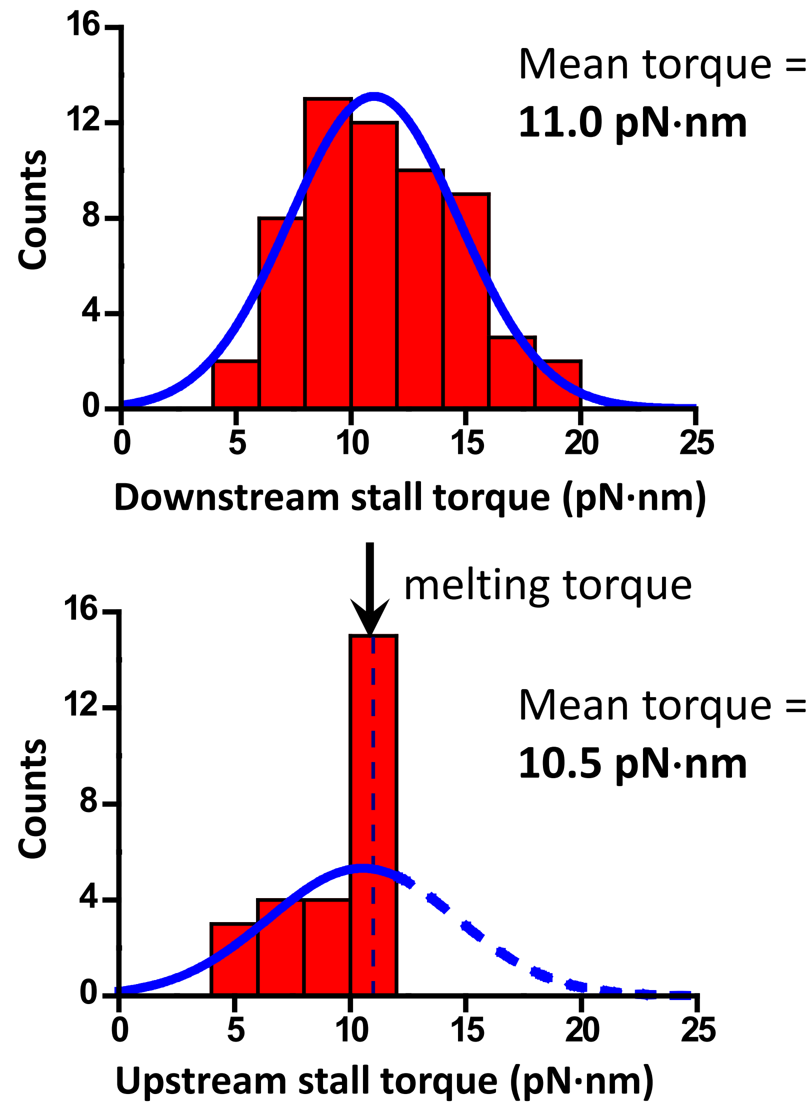
Marko & Siggia, Science, 1994
Moroz & Nelson, PNAS, 1997
Bouchiat & Mézard, Phys. Rev. Lett., 1998
Leger et al., Phys. Rev. Lett., 1999
Sarkar et al., Phys. Rev. E, 2001
Marko, Phys. Rev. E, 2007
Marko & Neukirch, Phys. Rev. E, 2013

<u>Our AOT data</u>

Deufel et al., Nature Methods, 2007
Forth et al., Phys. Rev. Lett., 2008
Daniels et al., Phys. Rev. E., 2009
Sheinin et al., Phys. Chem. Chem. Phys., 2009
Sheinin et al., Phys. Rev. Lett., 2011.
Xiang et al., Phys. Rev. Lett., 2021

# How does a Motor Protein Work against Torsional Stress?



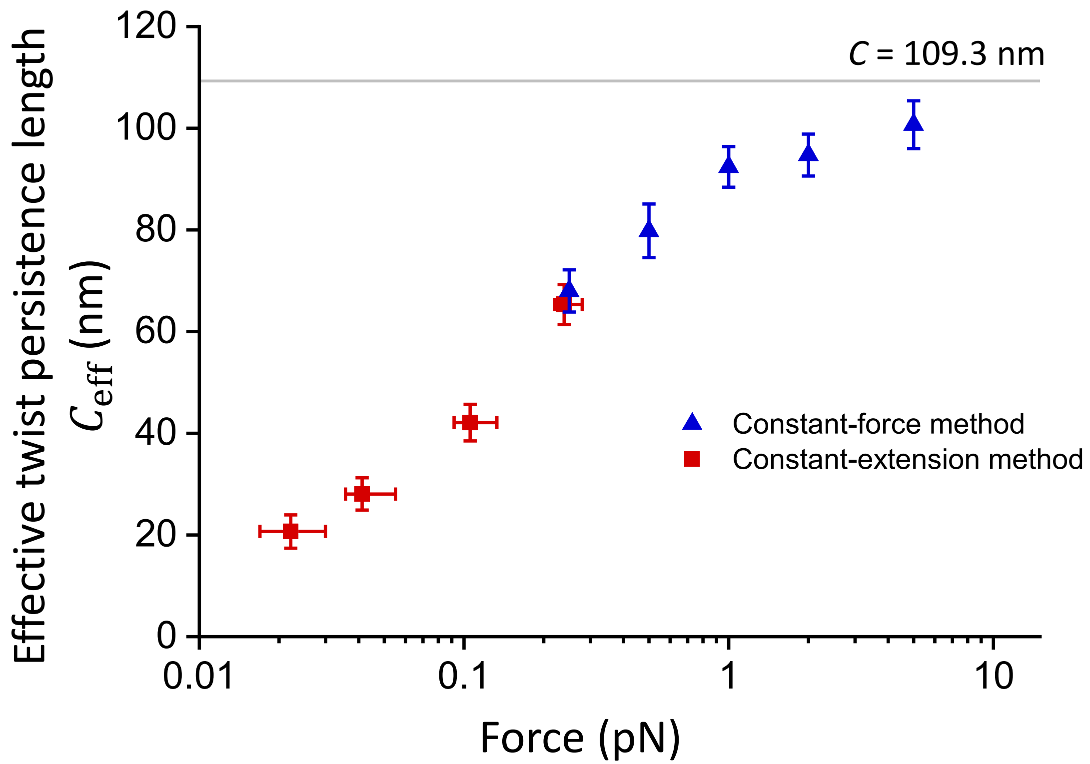

Ma et al., Science, 2013

PHYSICAL REVIEW LETTERS **127,** 028101 (2021)

Editors' Suggestion　Featured in Physics

# Torsional Stiffness of Extended and Plectonemic DNA

Xiang Gao,[1,2] Yifeng Hong,[3] Fan Ye,[1,2] James T. Inman,[1,2] and Michelle D. Wang[1,2,*]



# Moroz-Nelson (MN) Theory

*Proc. Natl. Acad. Sci. USA*
Vol. 94, pp. 14418–14422, December 1997
Biophysics

**Torsional directed walks, entropic elasticity, and DNA twist stiffness**

J. DAVID MOROZ AND PHILIP NELSON*

$$C_{\mathrm{eff}}(F)^{-1} = C^{-1} + \left(4A\sqrt{\frac{AF}{k_{\mathrm{B}}T}}\right)^{-1}$$

Modified-MN theory

$$C_{\mathrm{eff}}(F) = C\left(1 - \frac{C}{4A}\sqrt{\frac{k_B T}{AF}}\right)$$

Marko-Modified

Not valid at low forces

PHYSICAL REVIEW LETTERS **127,** 028101 (2021)

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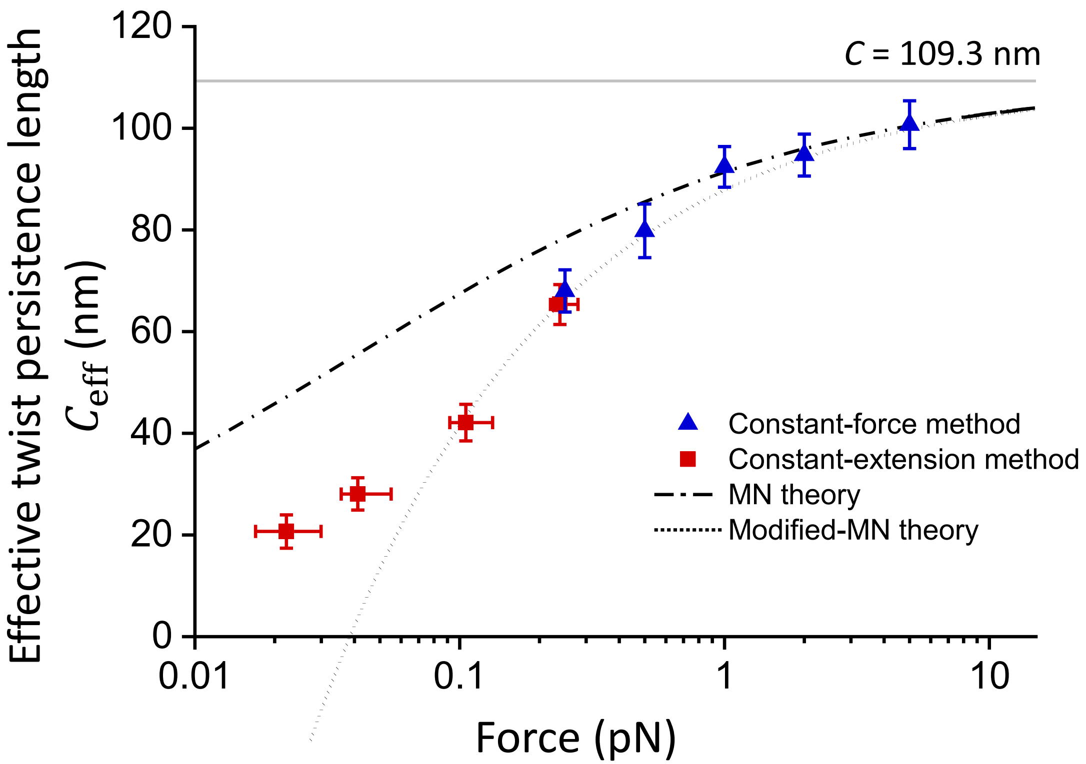


# Bouchiat-Mezard (BM) Theory

VOLUME 80, NUMBER 7 PHYSICAL REVIEW LETTERS 16 FEBRUARY 1998

## Elasticity Model of a Supercoiled DNA Molecule

C. Bouchiat and M. Mézard
*Laboratoire de Physique Théorique de l'Ecole Normale Supérieure,* 24 rue Lhomond, 75231 Paris Cedex 05, France*
(Received 5 June 1997)

Eur. Phys. J. E **2**, 377–402 (2000)

THE EUROPEAN PHYSICAL JOURNAL E
EDP Sciences


## Elastic rod model of a supercoiled DNA molecule

C. Bouchiat[1,a] and M. Mézard[1,2]

# SOS to Marc

Reply from Marc on September 14, 2021:

…. I have not been working on these topics for years, and I am not sure how useful I can be, but I am certainly willing to talk with you and try to help clarify some issues in the paper.

# Understanding the BM Theory

$$\frac{E_{\rm bend}}{k_{\rm B}T} = \frac{A}{2}\int_0^L \left(\frac{d\hat{t}}{ds}\right)^2 ds = \frac{A}{2}\int_0^L (\dot{\phi}^2 \sin^2\theta + \dot{\theta}^2) ds$$

$$\frac{E_{\rm twist}}{k_{\rm B}T} = \frac{C}{2}\int_0^L \Omega_3^2 ds = \frac{C}{2}\int_0^L \left(\dot{\psi} + \dot{\phi}\cos\theta\right)^2 ds$$

$$\frac{E_{\rm stretch}}{k_{\rm B}T} = -\int_0^L \frac{F\cos\theta}{k_{\rm B}T} ds$$

$$Z(\theta_1, \phi_1, \psi_1, s_1 | \theta_0, \phi_0, \psi_0, s_0) = \int D(\theta, \phi, \psi) \exp\left(-\frac{E_{\rm RLC}}{k_{\rm B}T}\right)$$

$$\langle \theta_1, \phi_1, \psi_1, s_1 | \theta_0, \phi_0, \psi_0, s_0 \rangle = \int D(\theta, \phi, \psi) \exp\left(-i\int_{t_0}^{t_1} dt L(t)\right) = \langle \theta_1, \phi_1, \psi_1 | \exp\left(-i(t_1 - t_0)\widehat{H}\right) | \theta_0, \phi_0, \psi_0 \rangle,$$

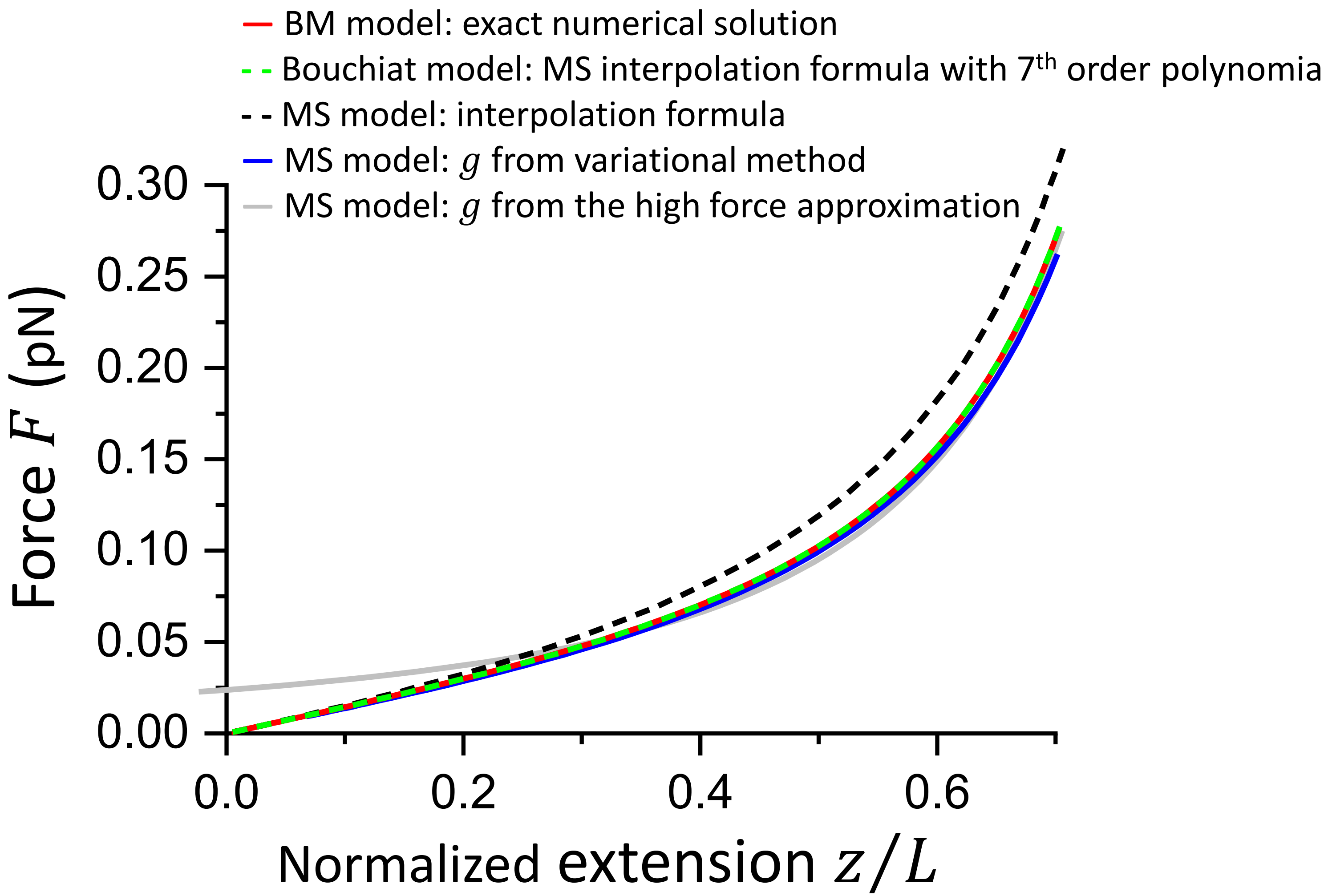
Convert the calculation of the partition function to an eigenvalue problem of the Schrödinger equation of a quantum mechanical symmetric top:

$$\widehat{H} = -\frac{1}{2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial}{\partial\theta}\right) + \left[-\frac{FA}{k_{\rm B}T}\cos\theta - \frac{\tau^2}{2(k_{\rm B}T)^2}\cdot\frac{1-\cos\theta}{1+\cos\theta}\cdot\frac{I_1(A\sin^2\theta/b)}{I_0(A\sin^2\theta/b)}\right]$$

$$\widehat{H}\Psi_0(\theta) = \boldsymbol{\epsilon_0}\Psi_0(\theta).$$

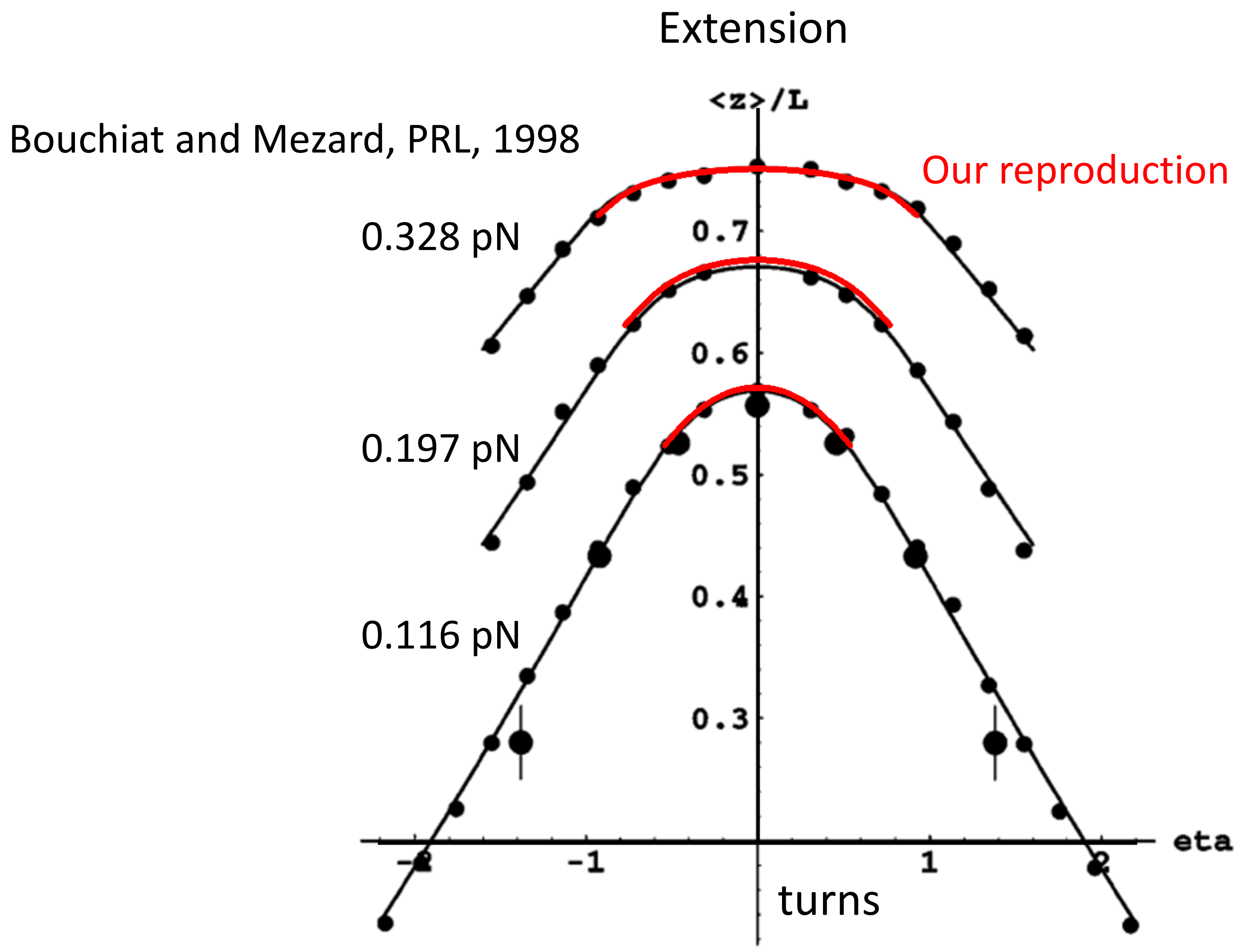
$$\cdots \longrightarrow \boldsymbol{C_{\rm eff}\ (F)}$$

# Sanity Check 1 – Zero Torsion Limit




Gao et al., PRL, 2021

# Sanity Check 2 – Hat Curves




Gao et al., PRL, 2021

PHYSICAL REVIEW LETTERS 127, 028101 (2021)

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# Torsional Stiffness of Extended and Plectonemic DNA

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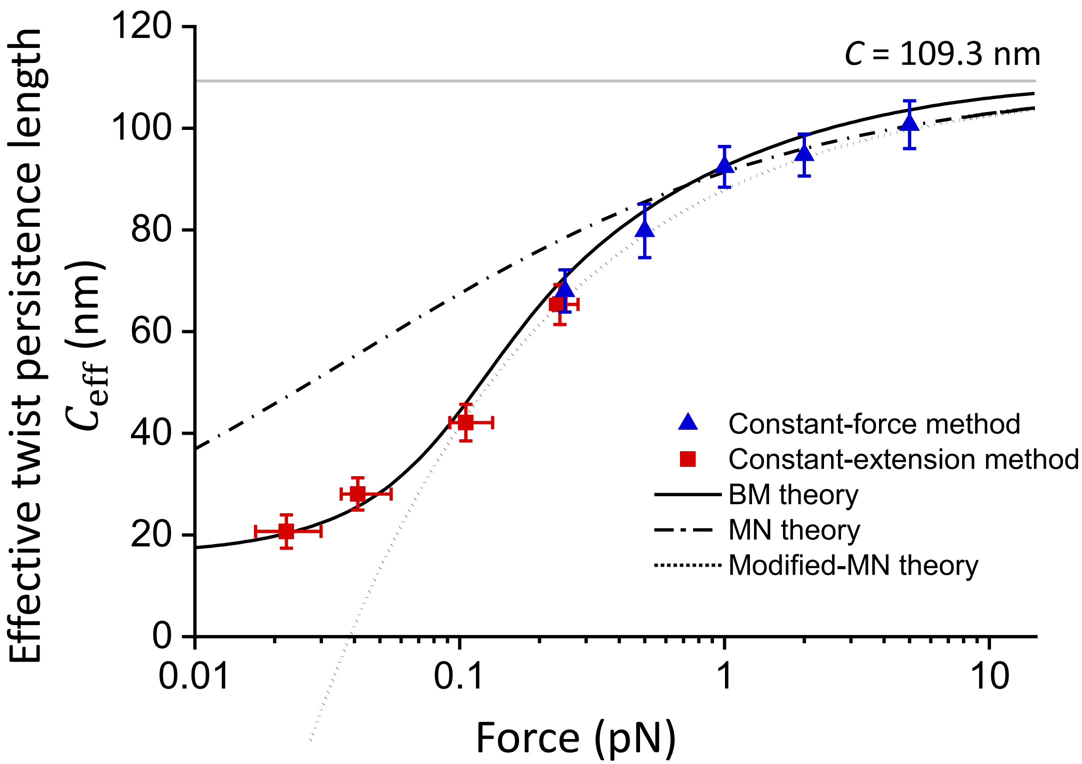
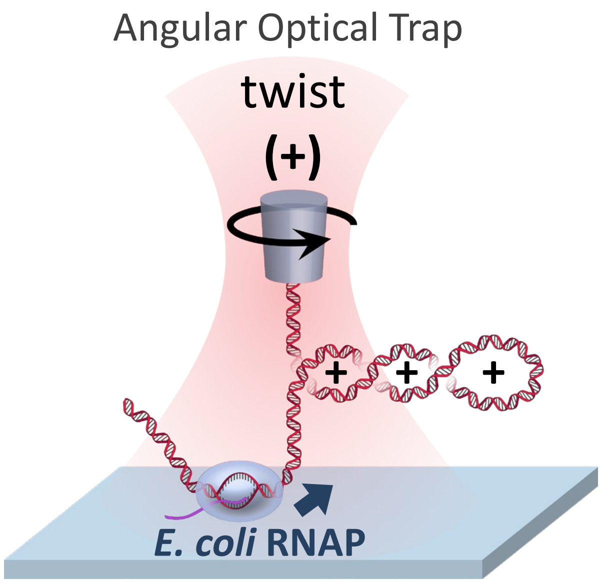


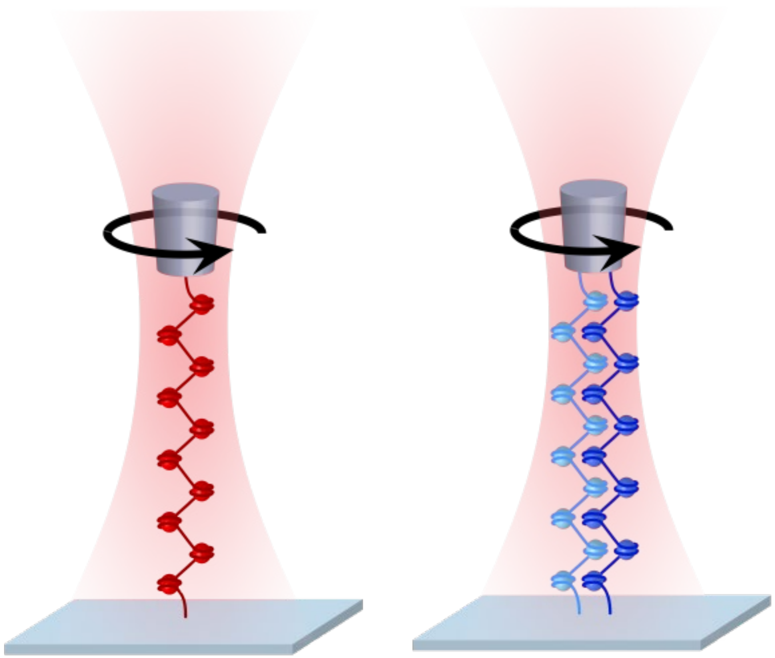
# Torsion of Fundamental Processes on DNA

## Transcription




Ma et al., Science, 2013
Ma et al., PNAS, 2019

## Chromatin



Le, et al., Cell, 2019

… standing on the shoulders of giants

NSF

hhmi

NATIONAL INSTITUTES OF HEALTH

CORNELL UNIVERSITY FOUNDED A.D. 1865