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Electrostatics, statistical mechanics, and dynamics of DNA

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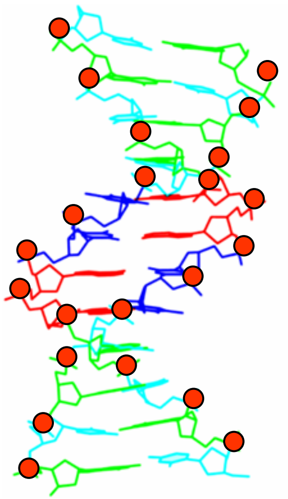
September 2007

DNA electrostatics



- DNA is *negatively charged* at the phosphate groups giving rise to *self-repulsion*
- Charge is screened by counterions in the solvent: for weak charges use Debye-Hückel energy

$$\Phi = \sum_{i<j} \frac{\delta_i \delta_j e^{-\kappa r_{ij}}}{4\pi\varepsilon_0 \varepsilon_w r_{ij}} \qquad r_{ij} = \left| \mathbf{r}_i - \mathbf{r}_j \right|$$

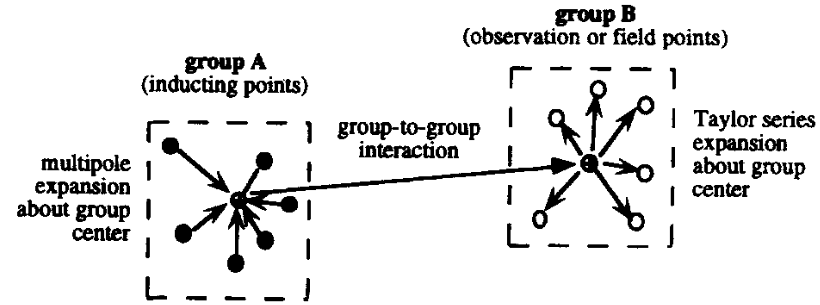
- κ = Debye screening parameter (depends on salt concentration)
- δ = effective charge of each phosphate group is reduced by 74% due to counterion condensation
  [see Manning, Q Rev Biophys 11 (1978) 179-246; Westcott, J Chem Phys 107 (1997) 3967-3980]

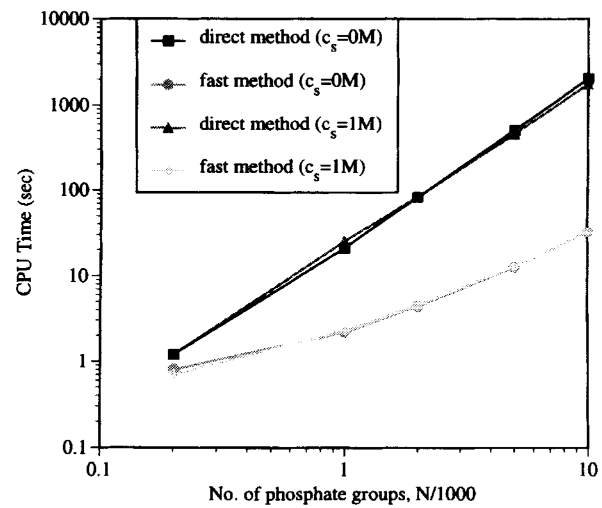
Other possible treatments:

- *hard-core repulsion* [e.g., Vologodskii & Cozzarelli, Biopolymers 35 (1995) 289-296]
- *nonlinear Poisson-Boltzman equation* [e.g., Shkel, J Phys Chem B 104 (2000) 5161-5170]

Multipole Expansion

- For N charges the computation of electrostatic energy is of order $O(N^2)$
- Speedup is possible using *multipole expansion:*
  Interaction energy of distant charges is replaced by interaction energy of their multipole approximations
- In addition, fast method speeds up the calculation by adaptive hierarchical subdivision of the region of computation – complexity reduced to O(N)





[Fenley et al., J Comp Chem 17 (1996) 976-991]

Open problems

The contribution of electrostatics to DNA rigidity and structure is not fully understood

- To what extent is electrostatics responsible for DNA stiffness?
- How is intrinsic curvature of DNA related to variations in backbone charges?

[Hud & Plavec, Biopolymers 69 (2003) 144-159]

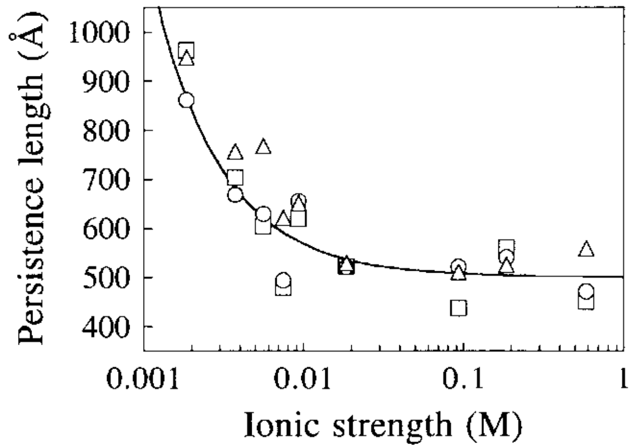


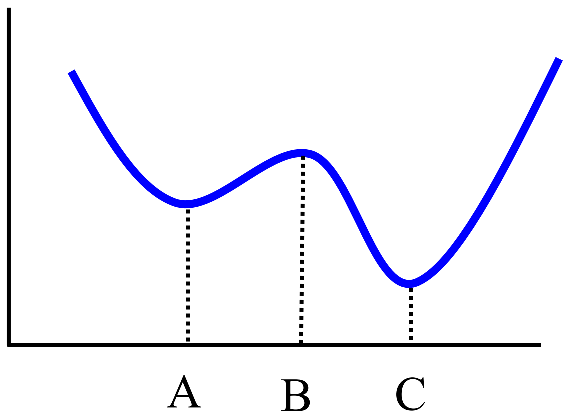
FIG. 5. Dependence of persistence length (P) on monovalent (Na^+) ionic strength. Points are from Table 1: □, *inextensible* WLC; ○, strong-stretching limit; △, *extensible* WLC. Line calculated from Eq. **3** with P_o = 500 Å.

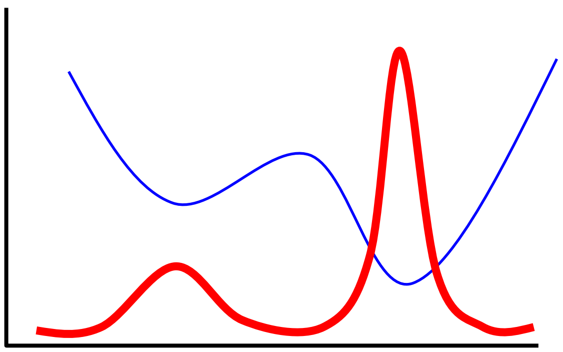
[Bauman et al., PNAS 94 (1997) 6185-6190]

Thermal fluctuations in DNA

DNA fluctuates = samples configuration space

Probability of a configuration ≈ – exp (Energy/kT)





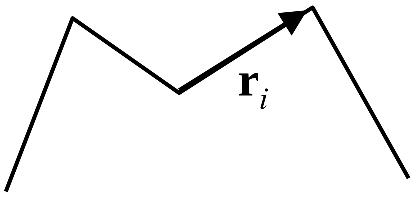
Mechanics:
Global and local minimizers
Unstable equilibria
Normal modes of vibration

Statistical mechanics:
Probability distribution
Free energy
Relaxation time
Mean time of transition

Freely jointed chain model

- N segments of length l (Kuhn length ~ 100nm for DNA) with random, uncorrelated orientations

$$\langle \mathbf{r}_i \rangle = 0, \quad \langle \mathbf{r}_i \cdot \mathbf{r}_j \rangle = l^2 \delta_{ij}$$



- End-to-end vector

$$\mathbf{R} = \sum_{i=1}^{N} \mathbf{r}_i$$

- In the limit of large N, the radial distribution function is Gaussian

$$\langle |\mathbf{R}|^2 \rangle = \sum_{i=1}^{N} \sum_{j=1}^{N} \langle \mathbf{r}_i \cdot \mathbf{r}_j \rangle = Nl^2$$

$$P(\mathbf{R}) = \left(\frac{3}{2\pi N l^2} \right)^{\frac{3}{2}} \exp\left(-\frac{3|\mathbf{R}|^2}{2Nl^2} \right)$$

[Doi & Edwards, *Theory of Polymer Dynamics,* 1986]

Wormlike chain model

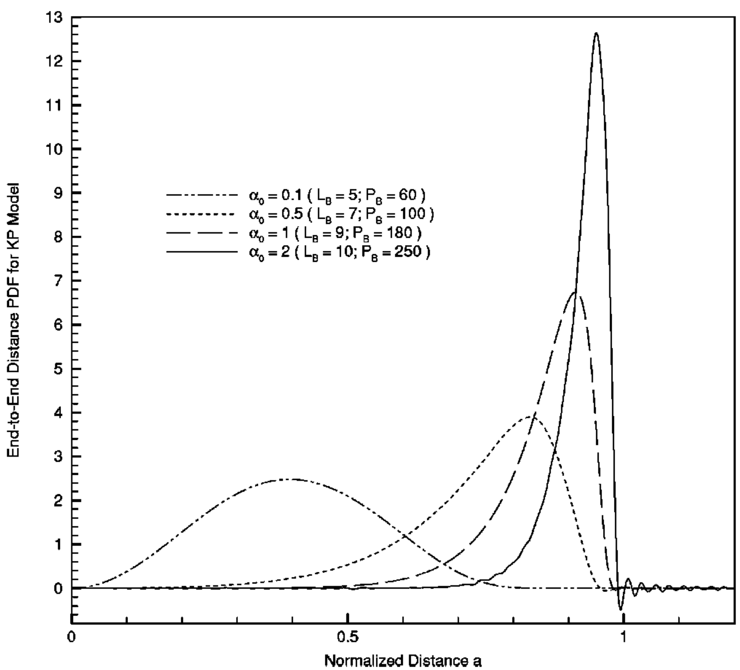
- Accounts for bending rigidity of the polymer
- Elastic energy (continuum description) $$E(\mathbf{x}(.)) = \frac{1}{2}\int_0^L A\kappa(s)^2\, ds$$
- Orientation correlation function (P = A/kT, persistence length ~ 50nm) $$< \mathbf{t}(s)\cdot\mathbf{t}(\bar{s}) >= \exp\left(-\frac{|s-\bar{s}|}{P}\right)$$
- End-to-end vector $$\mathbf{R} = \mathbf{x}(L) - \mathbf{x}(0) = \int_0^L \mathbf{t}(s)ds$$
- Mean square end-to-end distance

$$< |\mathbf{R}|^2 >= 2P\left(L - P(1 - e^{-L/P})\right) = \begin{cases} 2P(L-P) & L >> P \\ L^2(1 - L/3P) & L << P \end{cases}$$

- Radial distribution function can be found approximately using expansions or by numerical calculation

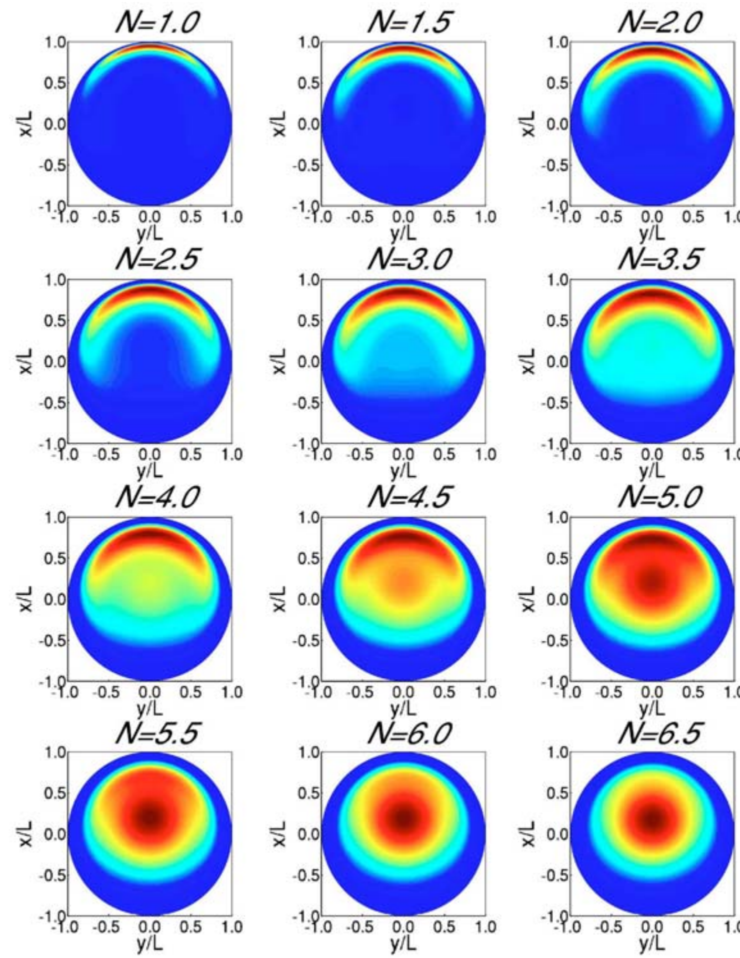
[Kratky & Porod, Rec Trav Chim Pays-Bas 68 (1949) 1106-1123;
Landau & Lifshitz, *Statistical Physics*, 1958]

Radial distribution function



[Chirikjian & Wang, PRE 62 (2000) 880-892]

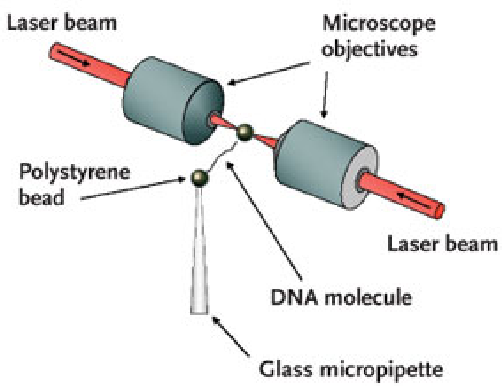
Distribution of chain end location in 2D
N = L/(2P)

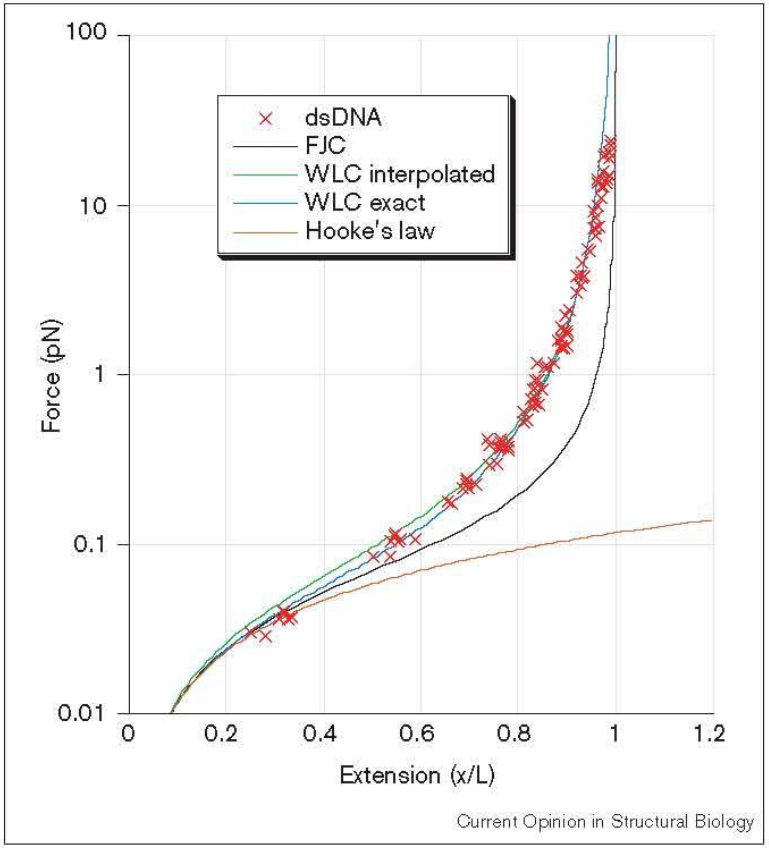


[Spakowitz & Wang, PRE 72 (2005)]

DNA stretching

Single molecule of DNA is stretched in an optical or magnetic trap





Mean end-to-end distance obeys approximately

$$\frac{FP}{kT} = \frac{1}{4}\left(1 - \frac{x}{L}\right)^{-2} - \frac{1}{4} + \frac{x}{L}$$

[Marko & Siggia, Macromolecules 28 (1995) 8759-8770]

[Smith, Finzi, Bustamante, Science 258 (1992) 1122-1126; Bustamante et al. Curr Opin Struct Bio 10 (2000) 279-285]

Helical wormlike chain

- Accounts for bending and twisting rigidity (important for supercoiling)

$$E(\mathbf{x}(.), \Delta\Omega(.)) = \frac{1}{2}\int_0^L A\kappa(s)^2 + C\Delta\Omega(s)^2\, ds$$

- Free energy of supercoiling

$$G(\Delta Lk) = -kT \ln Z(\Delta Lk)$$

$$Z(\Delta Lk) = Q^{-1} \int_{Wr+Tw=\Delta Lk} \exp\left(-\frac{E(\mathbf{x}(.), \Delta\Omega(.))}{kT}\right) d\mathbf{x}(.)\, d\Delta\Omega(.)$$

- Approximate and numerical solutions

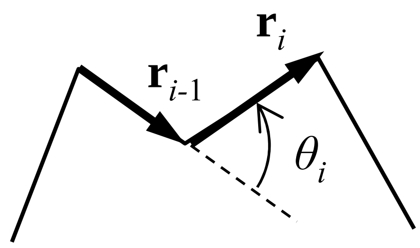
[Shimada & Yamakawa, Macromolecules 17 (1984) 689-698;
Marko & Siggia, Macromolecules 28 (1995) 8759-8770;
Moroz & Nelson, PNAS 94 (1997) 14418-14422;
Bouchiat & Mezard, Phys Rev Lett 80 (1998) 1556-1559;
Chirikjian & Wang, Phys Rev E 62 (2000) 880-892;
Zhang & Crothers, Biophys J 84 (2003) 136-153; …]

- Monte Carlo sampling

[Frank-Kamenetskii et al., Nature 258 (1975) 398-402;
Levene & Crothers, J Mol Biol 189 (1986) 61-72;
Gebe et al, Biophys J 68 (1995) 619-633; …]

Monte Carlo sampling of closed DNA

- DNA is divided into N rigid subunits of length l
- Bending energy $E_b = \alpha \sum_{i=1}^{N} \theta_i^2$
- Twisting energy $$E_t = \frac{2\pi^2 C}{L}(\Delta Lk - Wr)^2$$

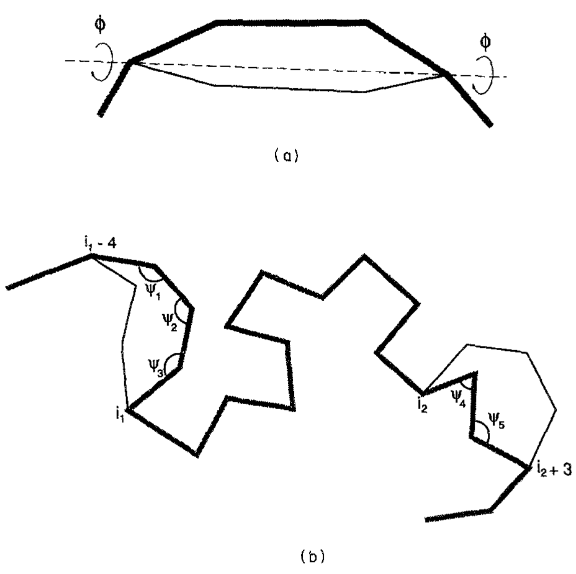


Algorithm

1. Displace the molecule by a move
2. Check for excluded volume and knot type
3. Compute energy
4. Accept new configuration in accord with Metropolis criterion

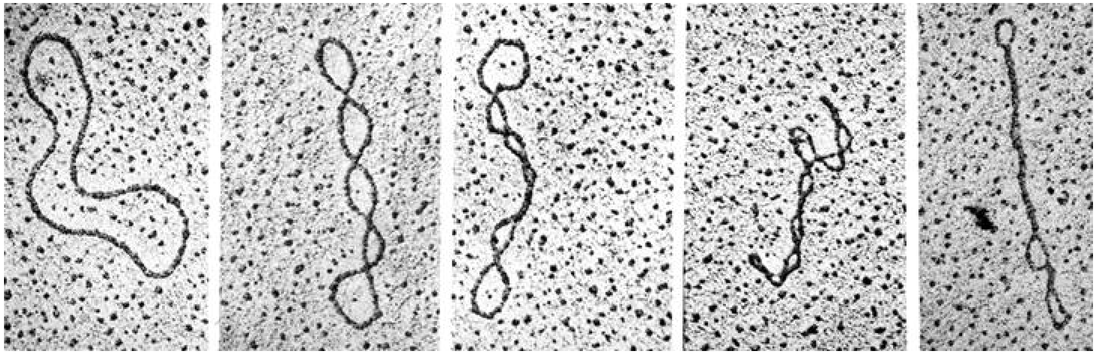
$$P_{accept} = \max\{1, \exp((E_{old} - E_{new})/kT)\}$$

Crankshaft and reptation moves



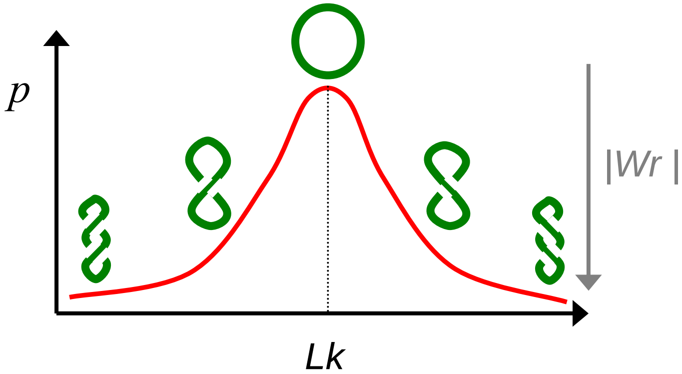
[Vologodskii et al, J Mol Biol 227 (1992) 1224-1243]

Supercoiling



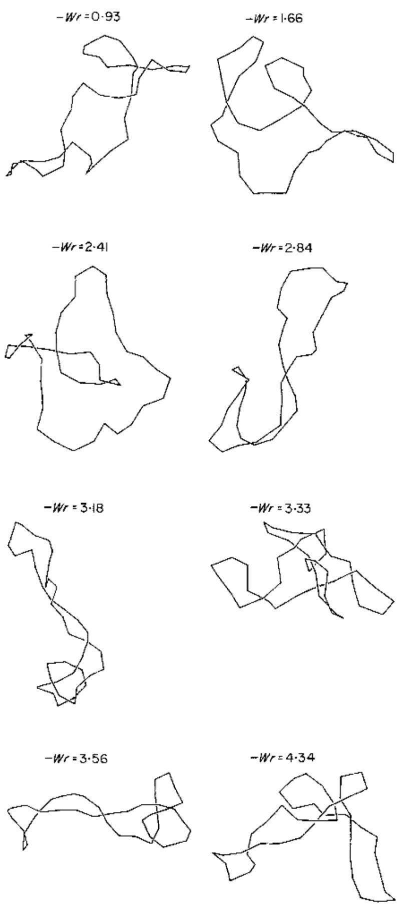
- *Topoisomers* – molecules with different *Lk* (same knot type)
- Distribution of *Lk* is roughly Gaussian

$$G(Lk) \cong K(N)(Lk - Lk_0)^2$$

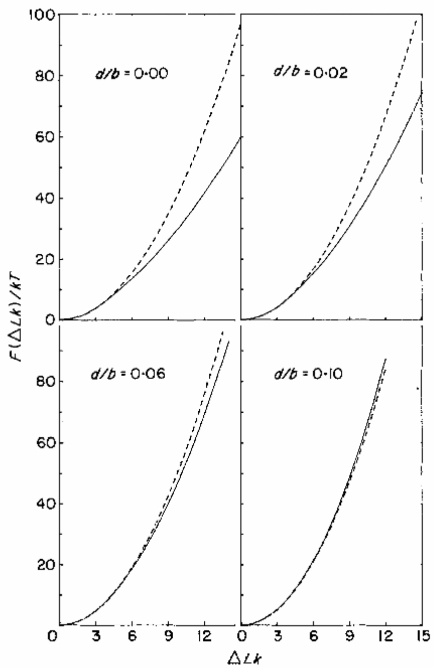


[Vinograd & Lebowitz, J Gen Physiol 49 (1966) 103-125;
Shore & Baldwin, J Mol Biol 170 (1983) 957-1008;
Horowitz & Wang, J Mol Biol 173 (1984) 75-91]

Monte Carlo simulations of supercoiling

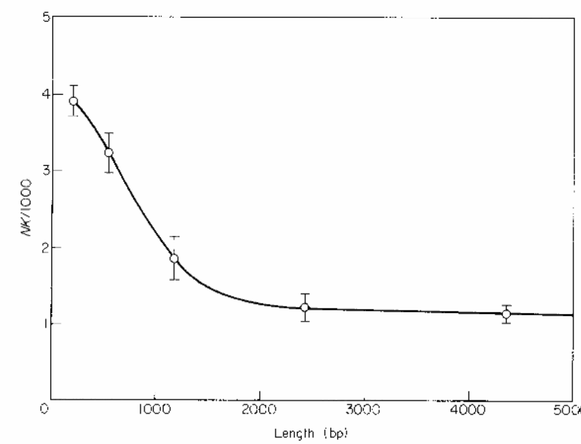


Example configurations
L = 2650bp, d/l = 0.02



Dependence of free energy on Lk and d/*l*

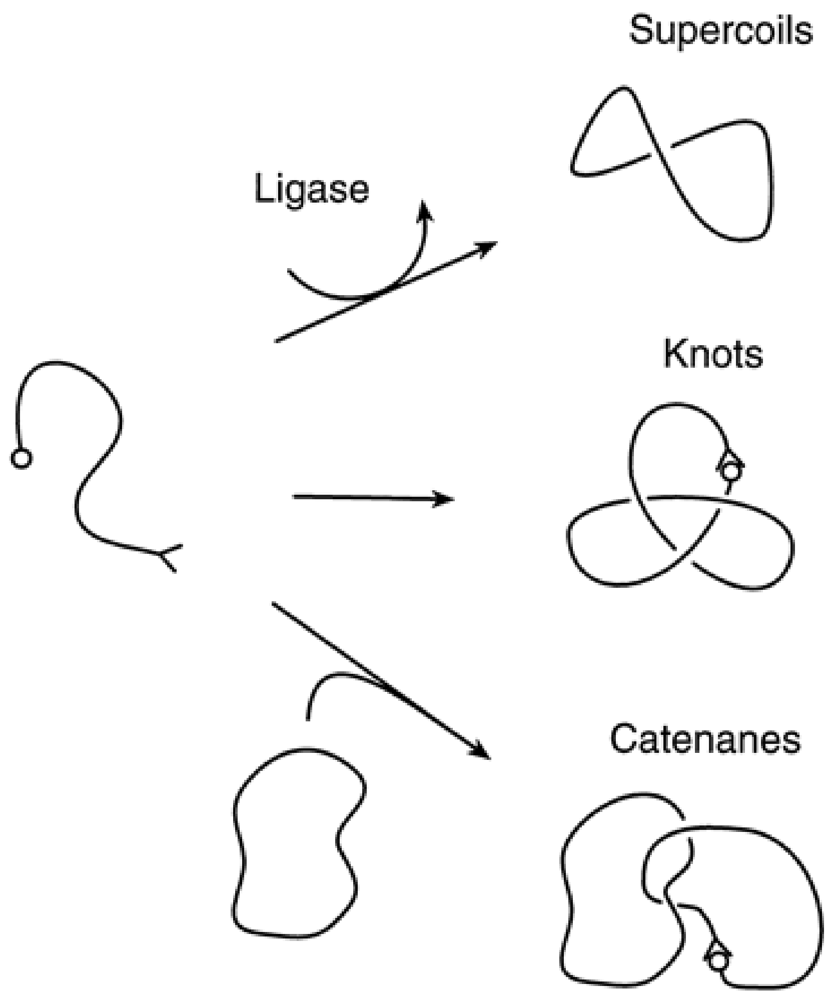
$$G(Lk) \cong K(N)(Lk - Lk_0)^2$$



Dependence of the coefficient K on N

[Klenin et al, J Mol Biol 217 (1991) 413-419]

DNA cyclization experiment



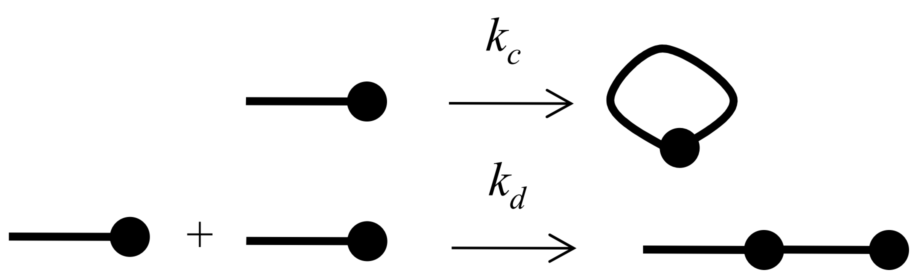
Ring closure probability

Ring closure probability – probability that the ends of a freely fluctuating open DNA will approach each other in a proper orientation

$$P = P(\mathbf{r}=0)\ \ P(\mathbf{t}^{+}\cdot\mathbf{t}^{-}=1\,|\,\mathbf{r}=0)\ \ P(\mathbf{d}^{+}\cdot\mathbf{d}^{-}=1\,|\,\mathbf{t}^{+}\cdot\mathbf{t}^{-}=1\ \&\ \mathbf{r}=0)$$

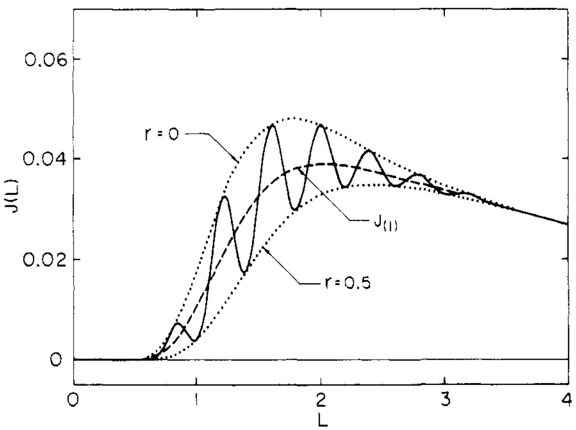
• P is related to the *Jacobson-Stockmayer factor* $J = K_c/K_d$ (ratio of cyclization to dimerization equilibrium constants) as $P = J\,N_A/(4\pi)$

• J can be measured for DNA as the ratio of cyclization to dimerization rate constants

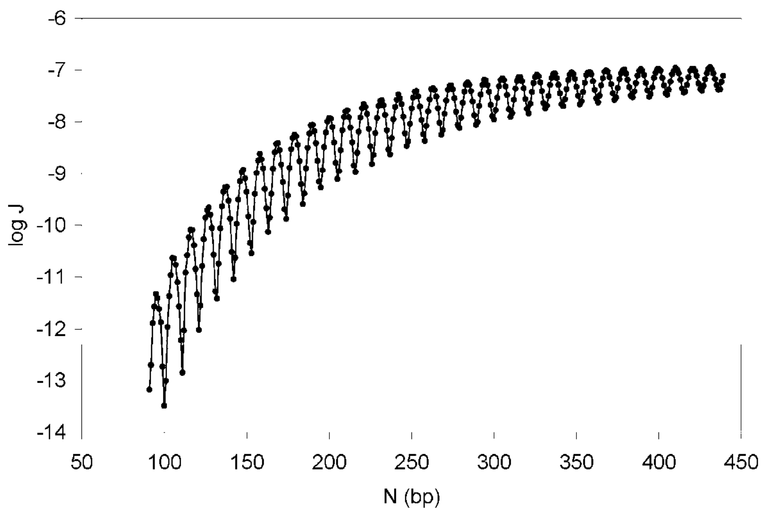


[Shore et al, PNAS 78 (1981) 4833-4837]

Typical dependence of *J* on *N*



[Shimada & Yamakawa, Macromolecules 17 (1984) 689-698]



[P_B = 147bp, P_T = 206bp, h = 10.5 bp/turn]

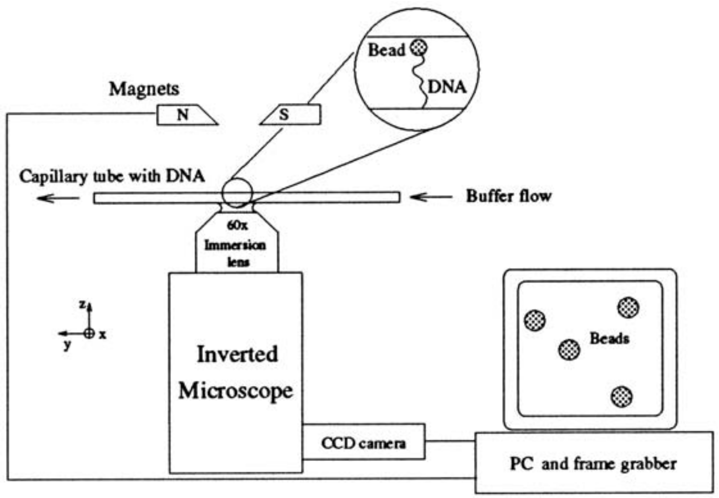
- The *J* vs *N* curve depends on bending rigidity, twisting rigidity, and helical repeat; DNA cyclization can be used to measure these properties

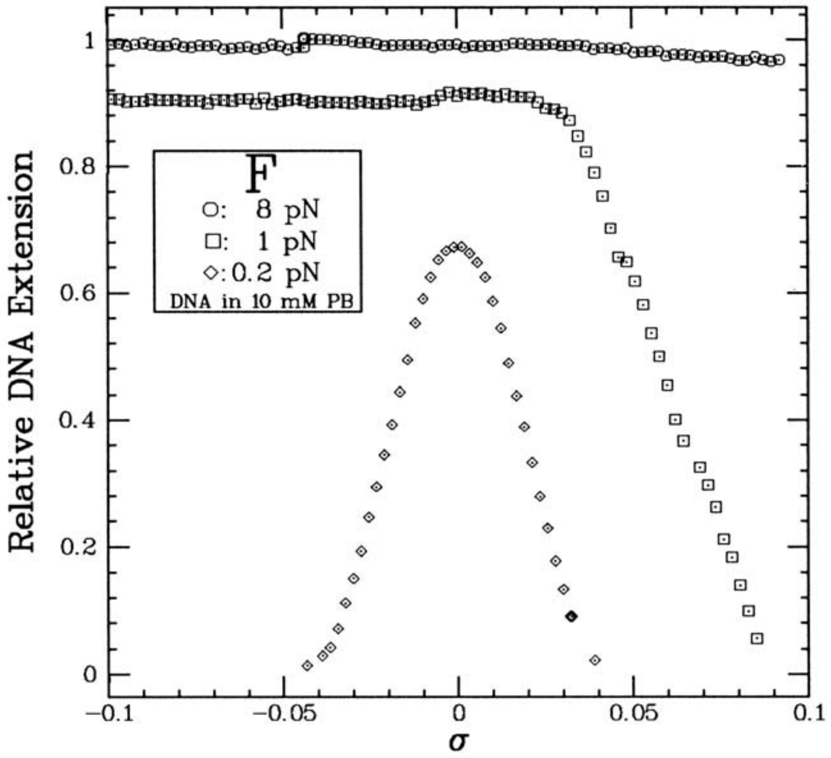
  [Crothers et al, Methods Enzymol 212 (1992) 3-29]

- Cyclization experiments can be used to demonstrate the presence and magnitude of protein induced bends in DNA

  [Kahn & Crothers et al, J Mol Biol 276 (1998) 287-309]

DNA twisting



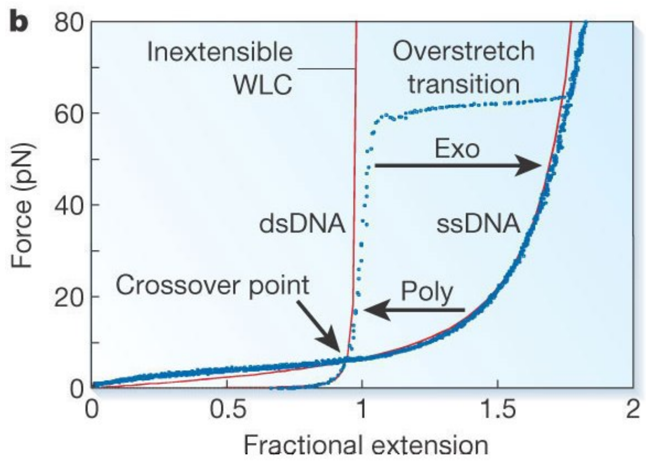


Curves reproduced theoretically by approximate or numerical solution of WLC

[Strick, Allemand, Bensimon, Croquette, Biophys J 74 (1998) 2016-2028]

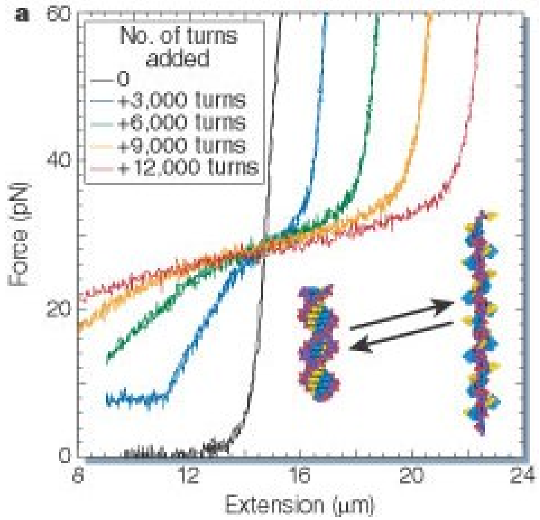
Stretching and twisting defects

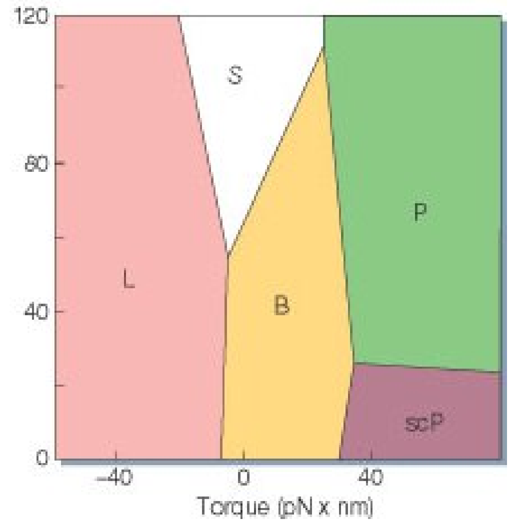
overstretching



[from Bustamante et al., Nature **421** (2003) 423-427]

Over/under-twisting
& stretching

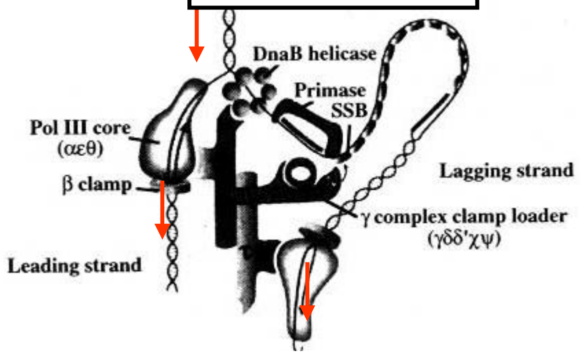




[Sarkar et al., PRE **63** (2001)]

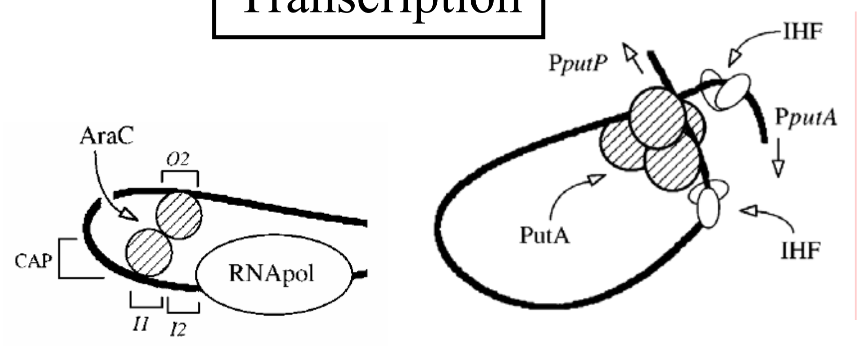
DNA looping

Replication



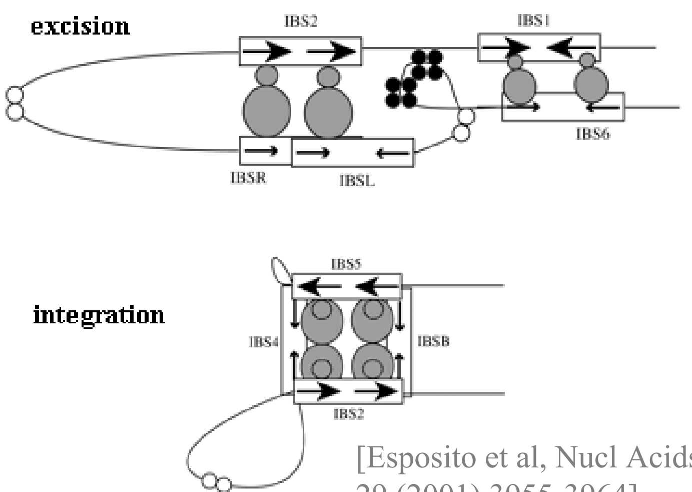
[Hingorani & O'Donnell, Curr Org Chem 4 (2000) 887-913]

Transcription



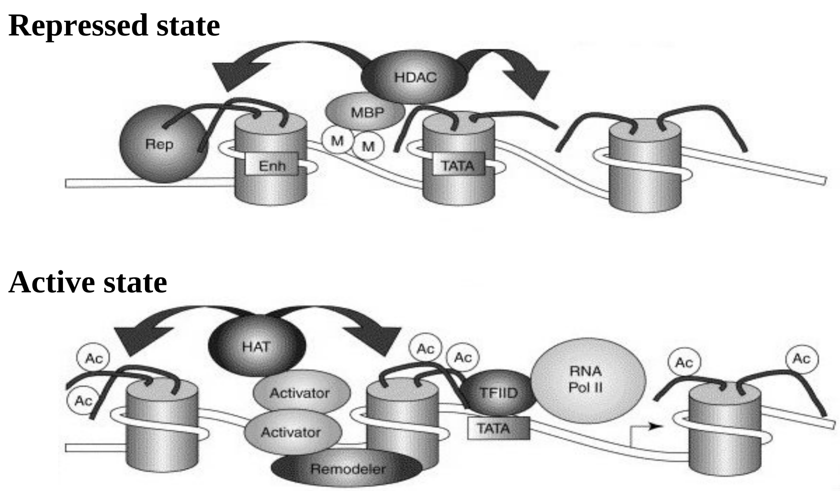
[J. Perez-Martin & V. de Lorenzo, Ann Rev Microbiol 51 (1997) 593-628]

Recombination



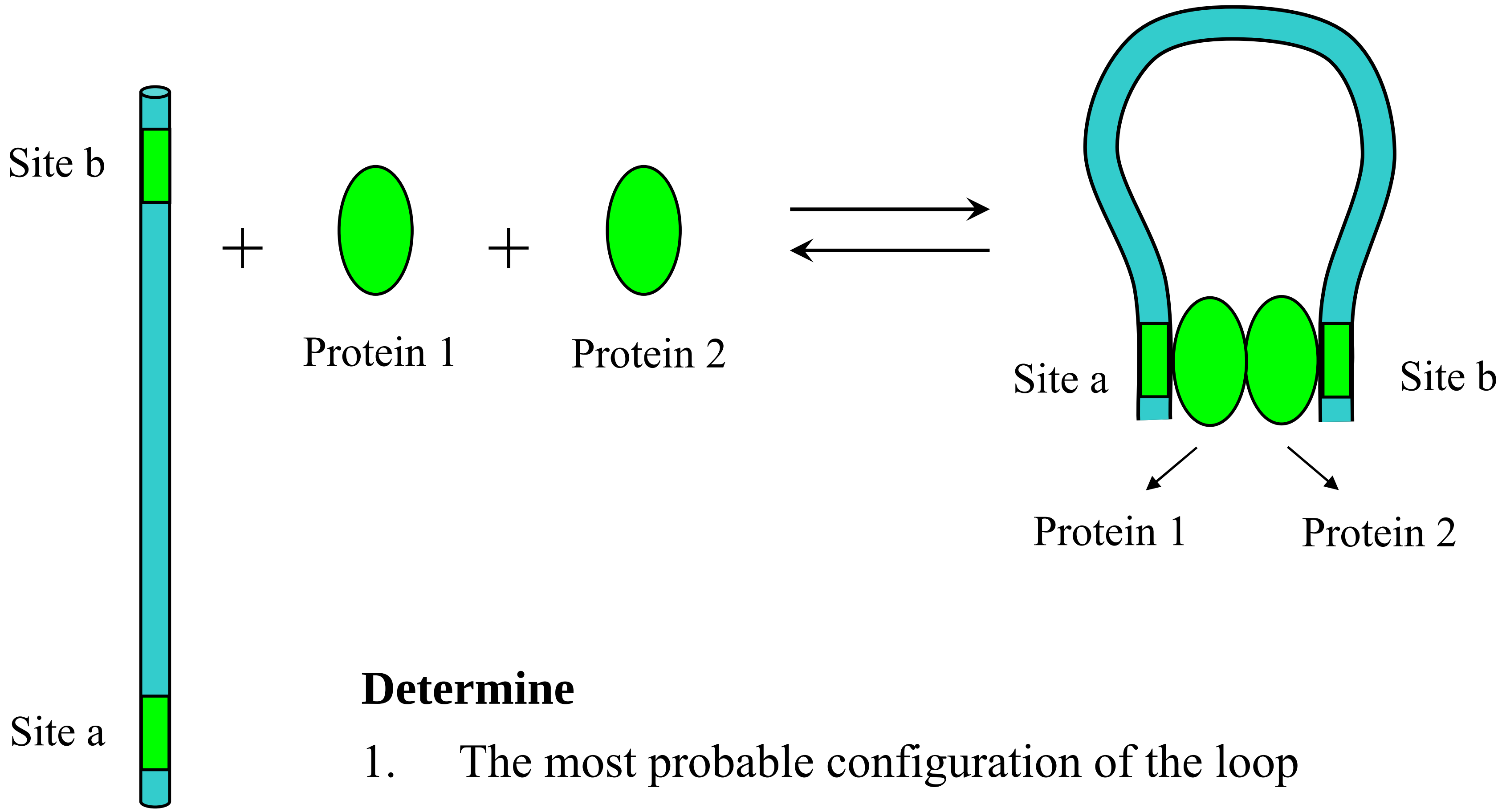
[Esposito et al, Nucl Acids Res 29 (2001) 3955-3964]

Chromatin remodeling



[Cairns, Trends Biochem Sci 23 (1998) 20-25]

Basic problem – DNA looping



Determine

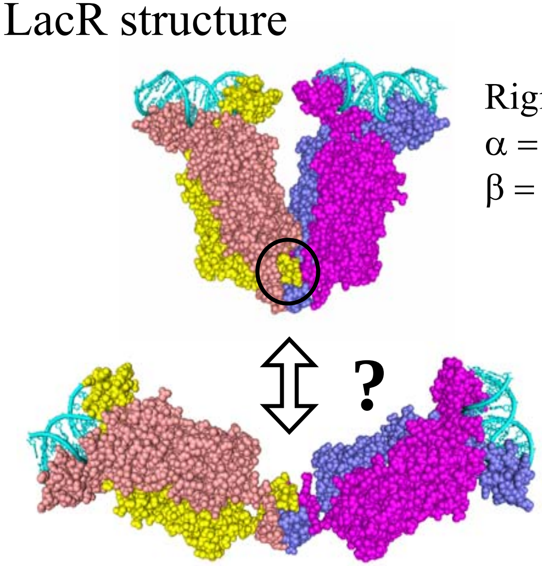
1. The most probable configuration of the loop
2. The probability of loop formation

Configuration of LacR-induced DNA loop

Sequence

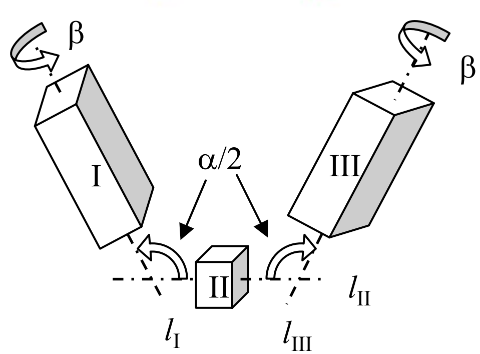
```
-82                    -61.5                         -35                        -10       +1        +11
 |                      \/                            |                          |         |         |
GGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATT

<---------O3--------><-------CAP-------->                <----> . . . RNAP. . . .<---->      <---------O1-------->
```

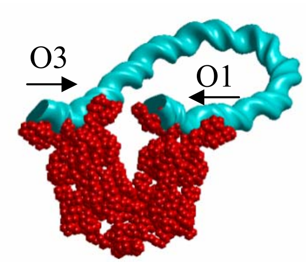
LacR structure



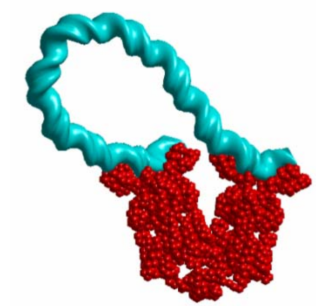
Rigid V-shape
α = 34°
β = 33°

Flexible
α, β free to change

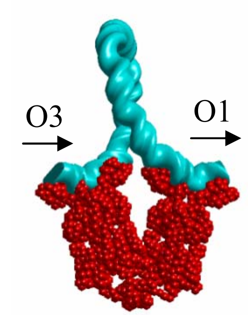




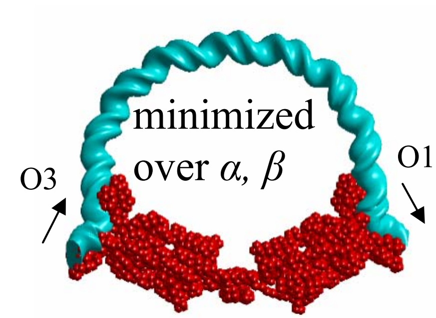
A1
ΔG = **31.8** *kT*



A2
32.9 *kT*



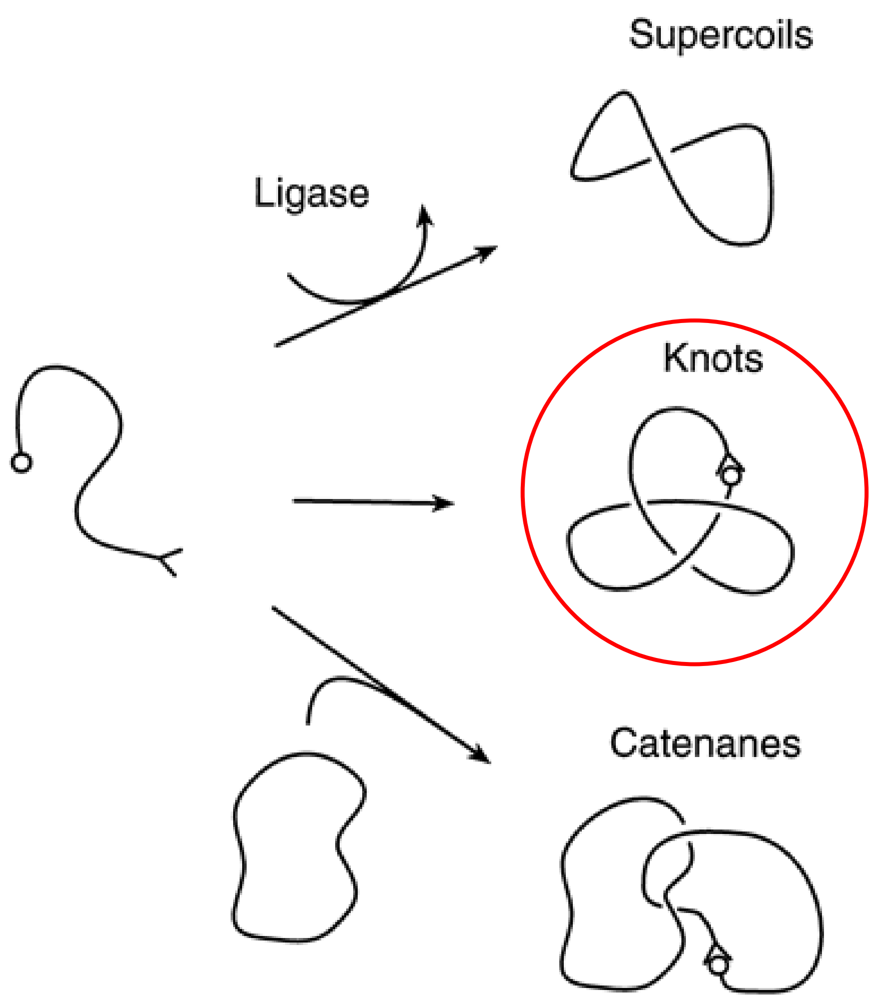
P1
38.6 *kT*



P1^{f}
24.7-32.3 *kT*

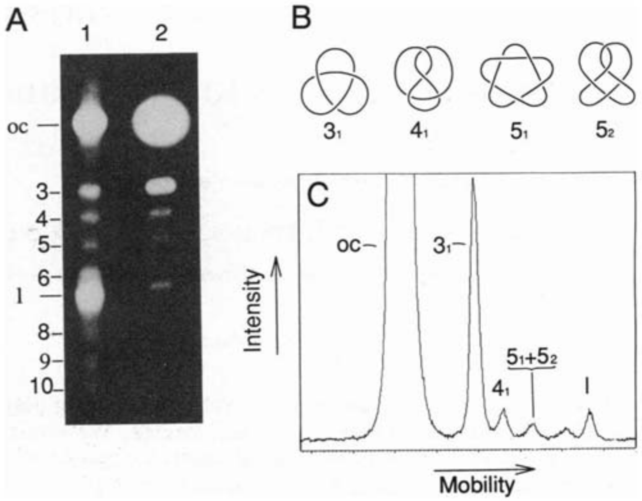
[Swigon et al, PNAS 103 (2006) 9879-9884]

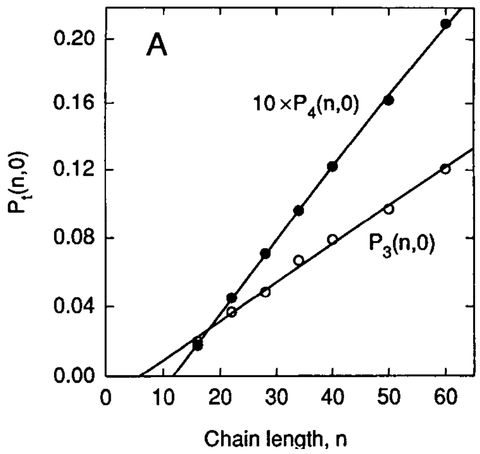
DNA cyclization experiment

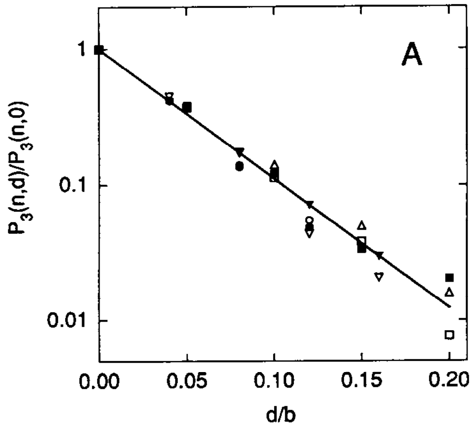


Distribution of knots

- P decreases with increasing knot complexity
- P increases linearly with chain length
- P decreases exponentially with effective diameter *d*







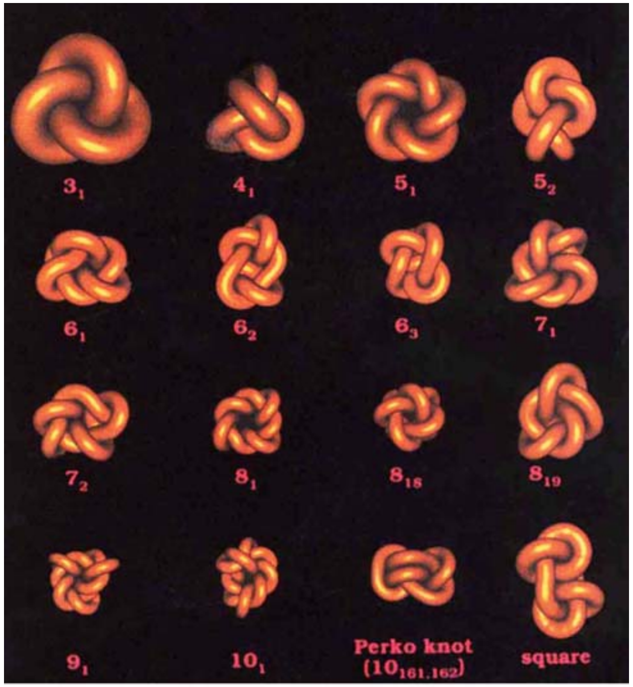
[Rybenkov, Cozzarelli, Vologodskii, PNAS 90 (1993) 5307-5311]

Ideal knot representation

Ideal knot = a geometric representation of a knot type that maximizes rope length/diameter ratio

Proportional quantities

- Axis length/diameter ratio
- Average crossing number
- Mean average crossing number of fluctuating knot
- Migration distance of DNA knot in gel electrophoresis



[Katritch et al, Nature Lett 384 (1996) 142-145; Stasiak et al, Nature 384 (1996) 122]

Dynamics of DNA

Basic model structure

- Continuum
- Discrete

Physics

- Elasticity – bending and twisting
- Electrostatics
- Hydrodynamic interactions

Dynamics

- Classical (acceleration, no fluctuations)
- Langevin (acceleration plus fluctuations)
- Brownian (diffusion)

Classical rod dynamics

- Axial curve $\mathbf{r}(s,t)$
- Directors $\mathbf{d}_i(s,t)$ $\quad \mathbf{d}_3 = \mathbf{r}_t$
- Curvature vector $\mathbf{d}_{i,s} = \kappa \times \mathbf{d}_\iota$
- Spin vector $\mathbf{d}_{i,t} = \omega \times \mathbf{d}_\iota$

$$\omega_s - \kappa_t = \kappa \times \omega$$

- Dynamical equations

$$\mathbf{F}_{ss} = \mathbf{d}_{3,tt}$$

$$\mathbf{M}_s + \mathbf{d}_3 \times \mathbf{F} = \mathbf{d}_1 \times \mathbf{d}_{1,tt} + \mathbf{d}_1 \times \mathbf{d}_{1,tt}$$

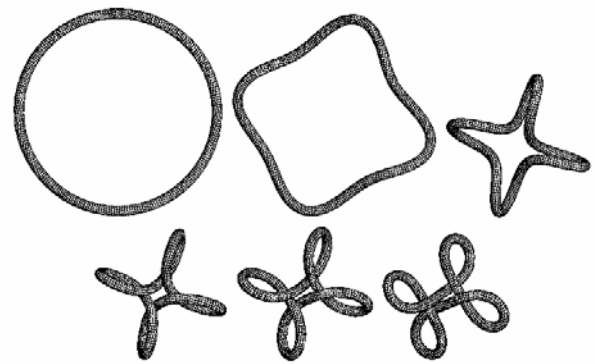
- Constitutive equation

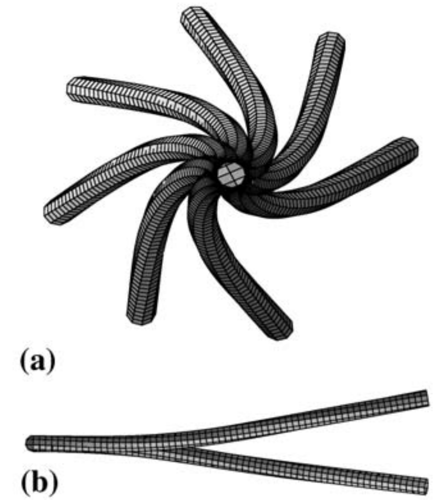
$$\mathbf{M} = \kappa_1 \mathbf{d}_1 + \kappa_2 \mathbf{d}_2 + \Gamma \kappa_3 \mathbf{d}_3$$

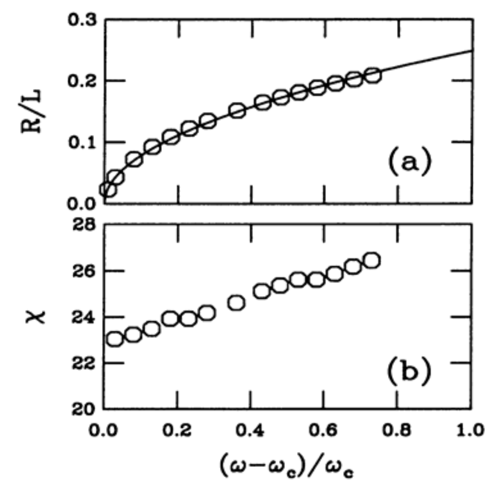
Describes

- Traveling waves
  [Coleman et al, Arch. Rational Mech Anal. 121 (1993) 339-359]
- Collapse of linear twisted DNA to plectonemic loop
  [Goriely & Tabor, Proc R Soc Lond A 454 (1998) 3183-3202]

Inclusion of *viscous drag* enables the study of the collapse of a twisted DNA circle and whirling of a twisted linear segment







[Klapper, J Comp Phys 125 (1996) 325-337]

[Wolgemuth et al, Phys Rev E 84 (2000) 1623-1626]

Langevin dynamics

- DNA is represented by N connected beads with centers at $\mathbf{X}_i$
- Total energy is a sum of stretching, bending, twisting, and electrostatic energy

$$E = E_S + E_B + E_T + E_C$$

- Langevin equation

$$m_i \ddot{\mathbf{X}}_i(t) + \gamma m_i \dot{\mathbf{X}}_i(t) + \frac{\partial E(t)}{\partial \mathbf{X}_i} = \mathbf{R}_i(t)$$

- $\mathbf{R}_i$(t) = random force acting on i-th bead

$$\left\langle \mathbf{R}_i(t) \right\rangle = 0, \quad \left\langle \mathbf{R}_i(t) \mathbf{R}_j(t)^T \right\rangle = 0, \quad \left\langle \mathbf{R}_i(t) \mathbf{R}_i(t')^T \right\rangle = 2\gamma k T m_i \delta(t - t')$$

[Ramachandran & Schlick, Phys Rev E 51 (1995) 5188-6203]

Brownian dynamics

- DNA is represented by N connected beads with centers at $\mathbf{X}_i$
- Total energy is a sum of stretching, bending, twisting, and electrostatic energy

$$E = E_S + E_B + E_T + E_C$$

- One-step BD algorithm

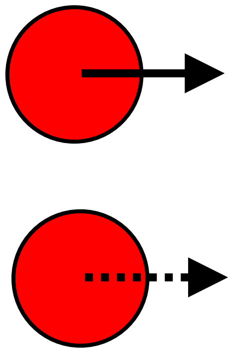
$$\mathbf{X}_i(t+\Delta t) = \mathbf{X}_i(t) - \frac{\Delta t}{kT}\sum_j \mathbf{D}_{ij}(t)\frac{\partial E(t)}{\partial \mathbf{X}_j} + \mathbf{R}_i(t)$$

- $\boldsymbol{D}_{ij}$ = diffusion tensor, accounts for hydrodynamic coupling and random motion coupling between beads i and j
- $\mathbf{R}_i$ = random displacement $\quad \langle \mathbf{R}_i(t) \rangle = 0, \quad \left\langle \mathbf{R}_i(t)\mathbf{R}_j(t)^T \right\rangle = 2\Delta t \mathbf{D}_{ij}(t)$

[e.g., Allison et al, Macromolecules 23 (1990) 1110-1118;
Chirico & Langowski, Biopolymers 34 (1994) 415-433;
Heath et al, Macromolecules 29 (1996) 3583-3596]

Rotne-Prager tensor

- Stokes approximation for hydrodynamic coupling of spherical particles
- Inter-particle location vector $\mathbf{r}_{ij} = \mathbf{X}_i - \mathbf{X}_j$

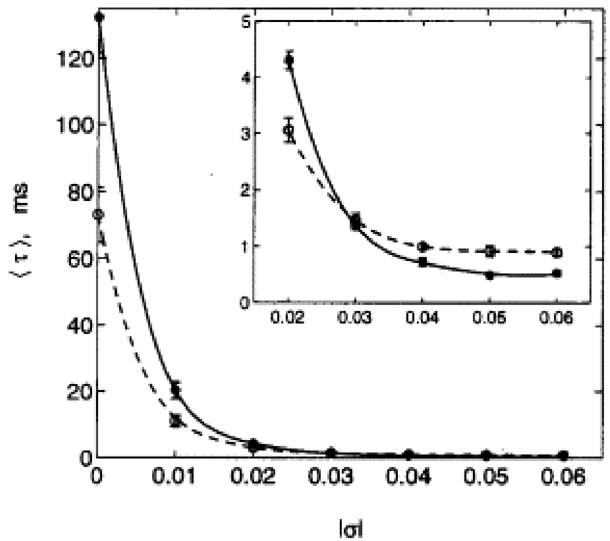


$$\mathbf{D}_{ii} = \frac{kT}{6\pi\eta a}\mathbf{I}$$

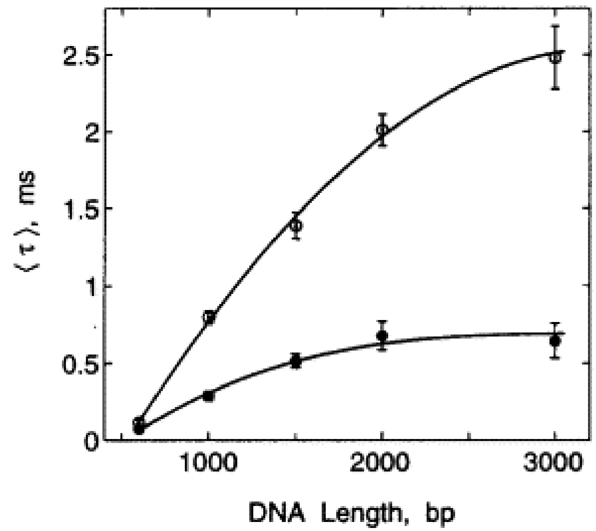
$$\mathbf{D}_{ij} = \frac{kT}{8\pi\eta r_{ij}}\left[\left(\mathbf{I} + \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}^T}{r_{ij}^2}\right) + \frac{a^2}{2r_{ij}^2}\left(\frac{1}{3}\mathbf{I} - \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}^T}{r_{ij}^2}\right)\right]$$

- For DNA pick a = 1.78 nm

Site juxtaposition in supercoiled DNA

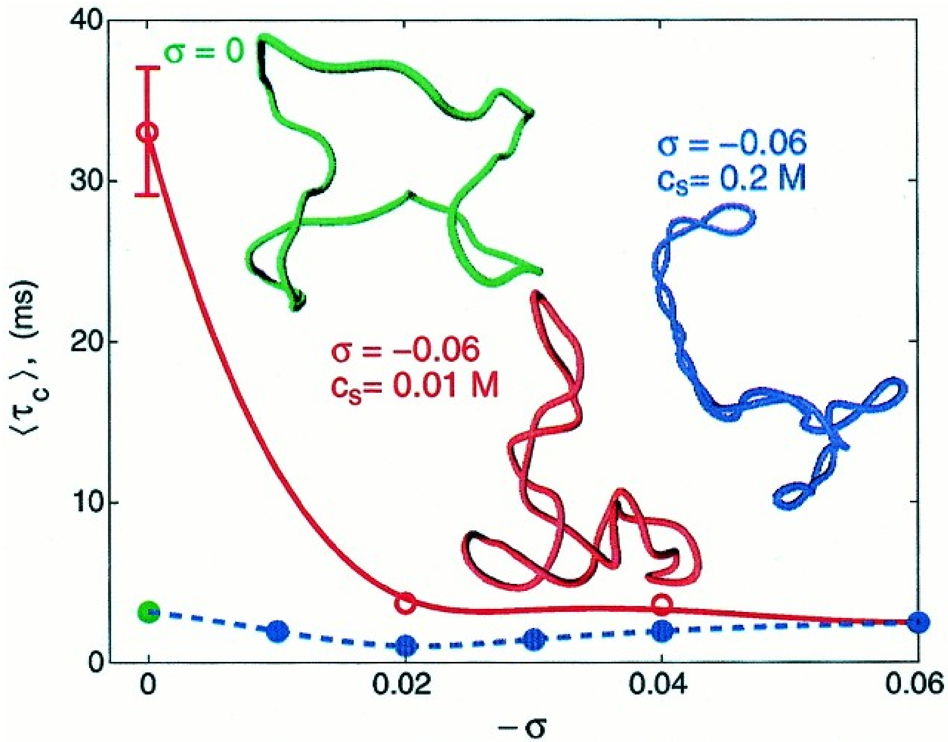


The average collision time of two sites as a function of DNA superhelix density. DNA is 1500 bp in length, site separation 300 bp (•) and 600 bp (○).



Dependence of the average time of juxtaposition of two sites on the length of supercoiled DNA. Superhelix density is −0.03 (○) and −0.06 (•), site separation is 600 bp.

[Jian, Schlick, Vologodskii, J.Mol.Biol 284 (1998) 287-296]



Effect of supercoiling on the juxtaposition time. Data were obtained for 3-kb DNA and 600-bp separations between the chosen sites along the chain contour.

[Huang, Schlick, Vologodskii, PNAS 98 (2001) 968-973]

Summary

- Electrostatic contribution to DNA behavior is complex
- Worm-like chain model reproduces results of DNA supercoiling, knotting, and closure experiments with great accuracy
- Single molecule DNA stretching and twisting experiments provide unprecedented amount of detail on DNA behavior
- Study of DNA loop formation and its role in gene regulation requires accurate knowledge of sequence-dependence of DNA elasticity.

Challenges

- Incorporate accurate electrostatic treatment into WLC, solve for short lengths
- Incorporate in vitro effects of crowding and random protein binding
- Dynamics in the presence of electrostatics

Other important topics

- Supercoiling induced DNA denaturation – relation to gene regulation
- Role of DNA looping in gene regulation
- Anomalous cyclization of specific short DNAs; DNA kinking and melting
- Effects of proteins on DNA supercoiling and/or knotting
- Knot localization
- Distribution of knots at fixed Lk
- Probability of unknotting by strand passage in the presence of intrinsic bends
- Stability of elastic rod equilibria using conjugate point theory
- Global curvature and self-contact
- Bifurcation of rods subject to various end conditions
- Charge distribution and electrostatic potential calculation
- Normal mode analysis of discrete and continuum models

Further reading

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- Bustamante, Bryant, Smith, *Ten years of tension*, Nature 421 (2003) 423-427
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- Olson, *Simulating DNA at low resolution*, Curr Opin Struct Biol 6 (1996) 242-256
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- Vologodskii & Cozzarelli, *Conformational and thermodynamic properties of supercoiled DNA,* Ann Rev Biophys Biomol Struct 23 (1994) 609-643
- Wang, *DNA Topoisomerases*, Ann Rev Biochem 65 (1996) 635-692
- J.H. White, *An introduction to the geometry and topology of DNA structure*. In: Mathematical Methods for DNA Sequences, CRC, Boca Raton, Florida (1989), pp. 225–253.