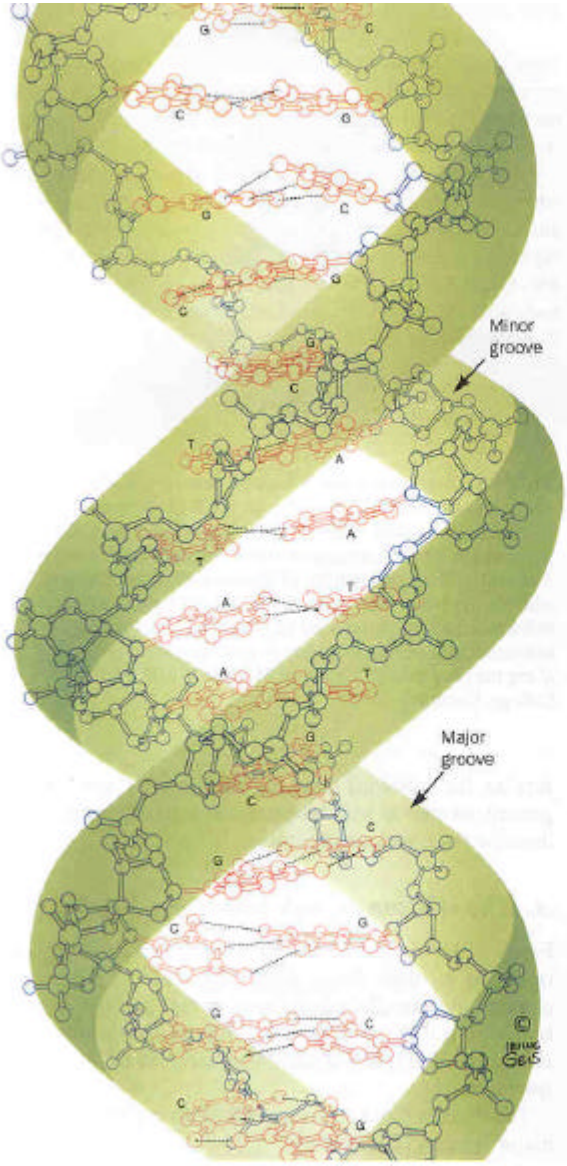
DNA Melting

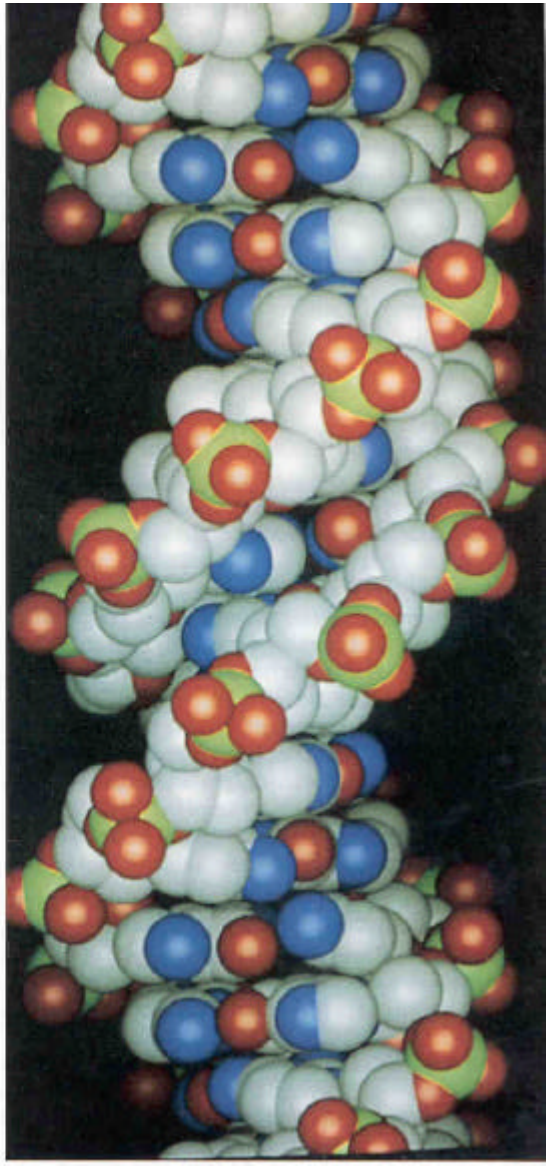
D. Poland and H.A. Scheraga, *Theory of helix-coil transitions in biopolymers*, 1970

R.M. Wartell and A.S. Benight, *Phys. Rep.* **126**, 67 (1985)

http://www.biophys.uni-duesseldorf.de/POLAND/poland.html

http://www.bioinformatics.org/meltsim/





B-type double helix

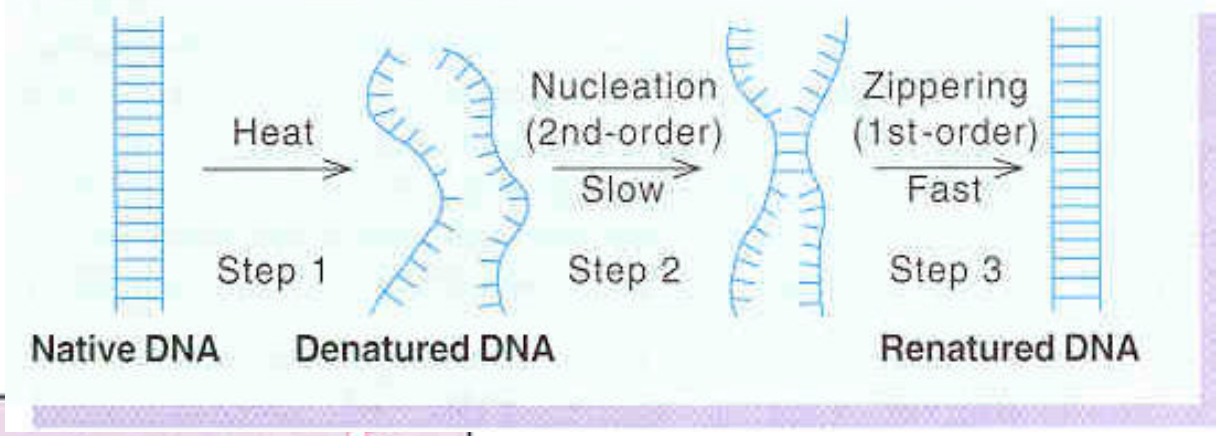
right-handed

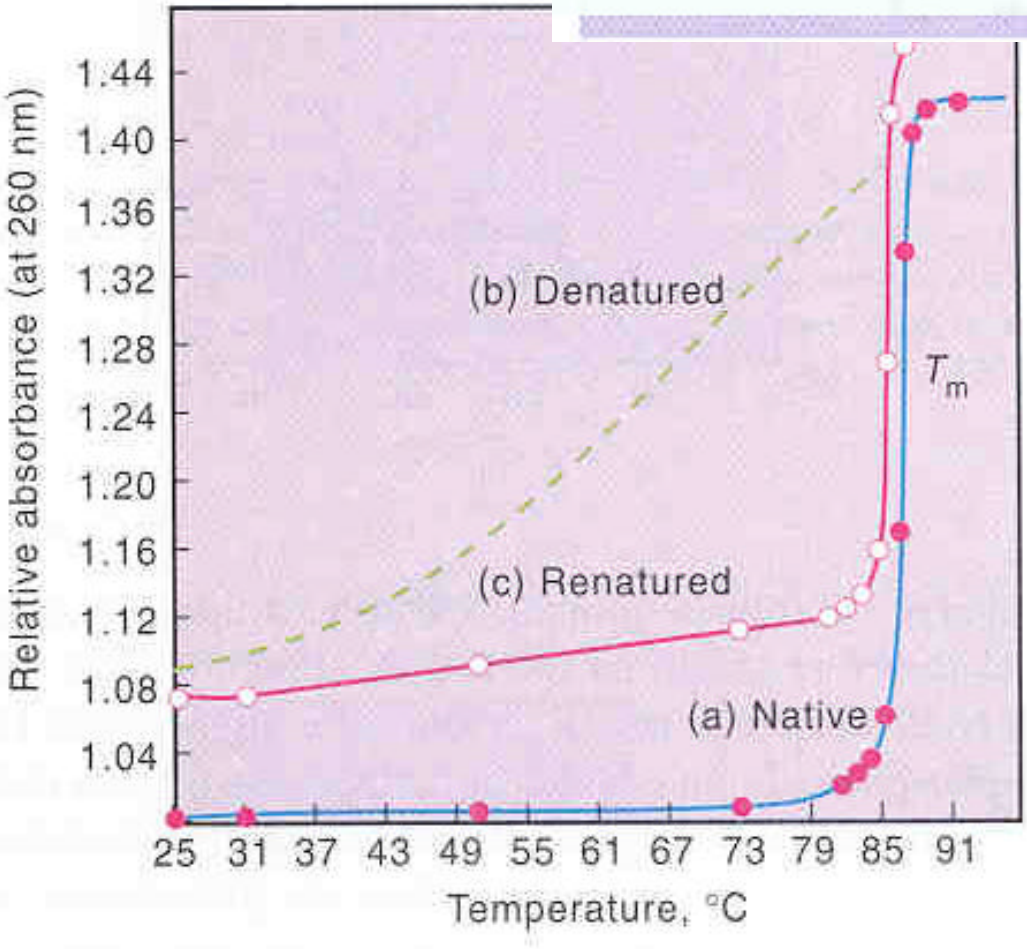
pitch spacing = 34 Å

residues per turn =10

Denature Transition

Careful experimental studies since 1960's

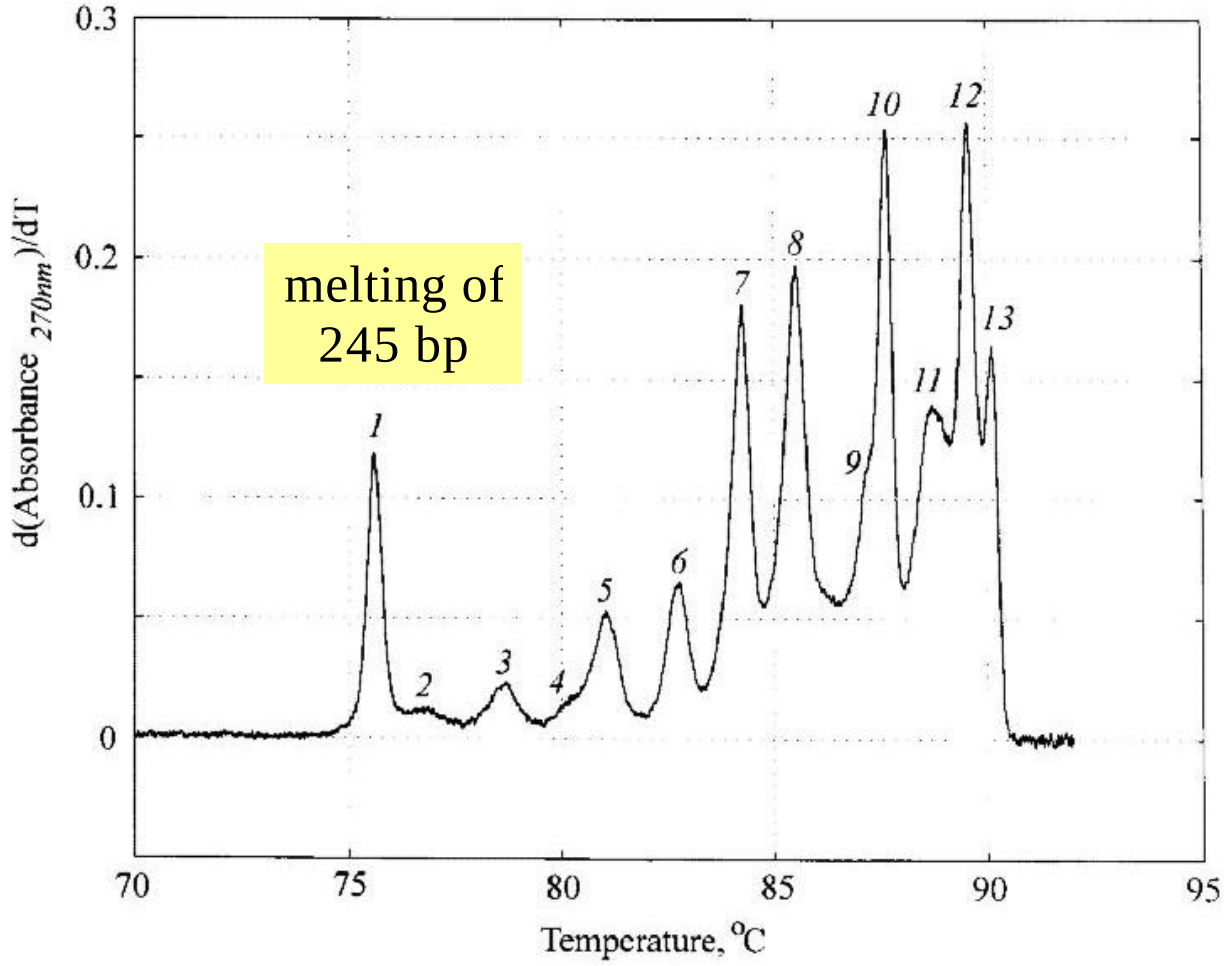




Main tool: UV absorption

40% enhancement upon pair breaking

Melting curves



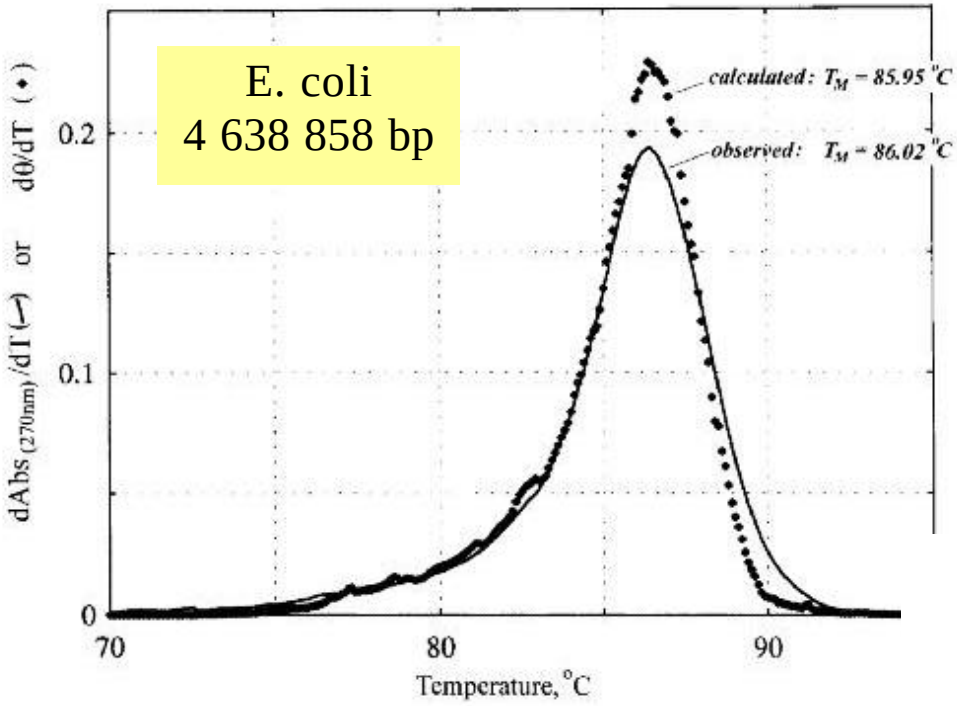
pN/MCS-13 DNA
4662 bp
0.0745 M-Na^+

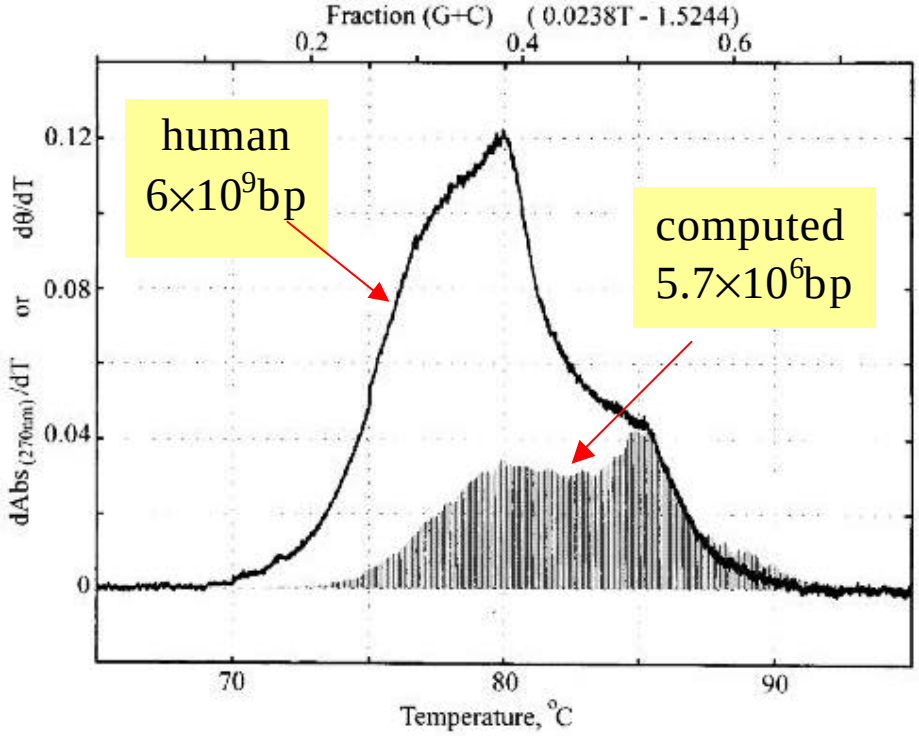
multistep melting!

peak width: ~0.5°C

Source: R. D. Blake et al, *Bioinformatics*, **15**, 370 (1999)

melting curves of long chains





General features of melting curves from experimental studies

- Short chains (<300 bp or so):

  — single peak with a width 0.3-0.7ºC

  — peak position depends on relative A-T and G-C contents

$$T_M = 42 \cdot (G + C) + 64^{\circ}\mathrm{C} \quad \text{at } 0.0745\mathrm{M\ Na}^{+}$$

- Medium-sized chains (a few thousand bps)

  well resolved peaks spanning over 15ºC or so

- Long chains (more than one million bps)

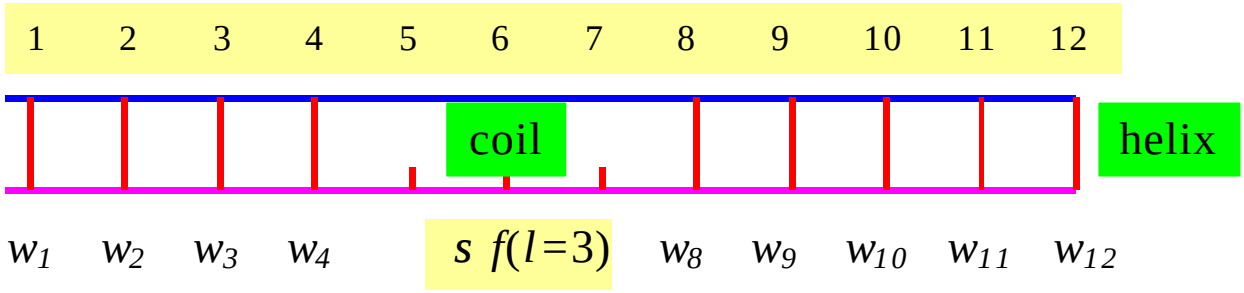
  single melting peak spanning over 15ºC or so

  sensitive to compositional variations

Theoretical Issues

- Why is the melting of individual domains so sharp?
- What is the nature of the transition for very long chains?

The pair stacking model



Ingredients:

- open/close for each bp represented by an Ising variable
- each closed pair has a weight w_i (random field)
- each loop of l open pairs has a weight $s * f(l)$ (ferromagnetic coupling)

  s : loop initiation factor, typically 10^{-5}

  $f(l)$: excess loop entropy, power-law function l^{-b}

	5' i 3' / 3' j 5'	$\frac{dT_{ij}}{d\log[Na^+]}$ °C/°K	$T_{ij}^{1.0M\text{-}Na+}$ °C	°K	$T_{ij}^{0.0745M\text{-}Na+}$ °C	$\Delta H_{ij}^{a)}$	$\Delta S_{ij}^{b)}$
1	A·T / T·A	21.00	81.85	355.01	58.23	8.00	22.53
2	T·A / A·T	20.11	86.72	359.88	64.10	8.31	24.64
3	A·T / A·T	19.78	89.08	362.24	66.77	8.45	24.86
4	G·C / A·T	17.76	99.49	372.65	79.51	9.13	24.50
5	C·G / A·T	17.10	103.18	376.34	83.94	9.36	24.87
6	A·T / G·C	16.87	104.43	377.59	85.45	9.44	25.00
7	A·T / C·G	16.21	107.96	381.12	89.72	9.67	25.37
8	G·C / G·C	14.18	118.49	391.65	102.50	10.34	27.52
9	C·G / G·C	13.20	124.54	397.70	109.69	10.72	26.95
10	G·C / C·G	13.20	124.61	397.77	109.76	10.72	26.95

a) kcal·mol ij^{-1}.
b) cal·mol ij^{-1}-deg^{-1}.

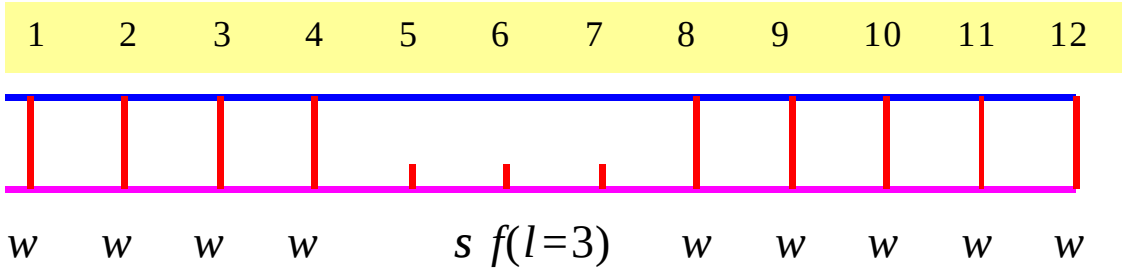
R. D. Blake et al,

Bioinformatics **15**, 370 (1999)

helix to coil entropy increase:

$\Delta S \simeq 12.5 k_B$ / bp

Homopolymer Unbinding (excluding sliding entropy)



Excess free energy of a loop:

$$\Delta G / k_B T \simeq -\ln\left[s\ f(l)\right] - 2\ln l + l \ln w$$

$$= -(2-b)\ln l - \ln s - l\left[a \frac{\Delta T}{T_M}\right]$$

$b > 2$: large loops unfavorable $\Rightarrow$ 1st order transition

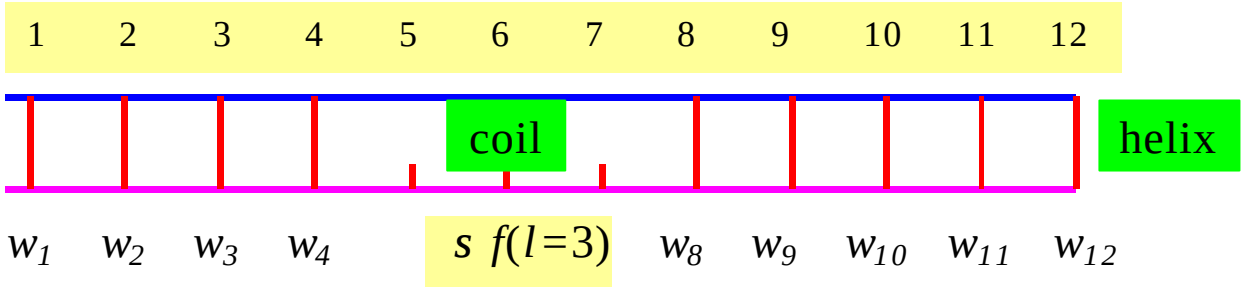
$b < 2$: loops of sufficiently large size are excited $\Rightarrow$ continuous transition

Width of the transition region:

minimum loop size: $l_c \simeq s^{-1/(2-b)} \simeq 10^{20}\,\text{bp}$ for $b = 1.75$ (SAW)

transition region: $\Delta T \simeq T_M / a l_c = 360\text{K}/(12.5\times 10^{20}) \simeq 3\times 10^{-19}\,\text{K}$

Heteropolymer Unbinding



Simple case: $f(l)=1$ or $b=0$ $\Rightarrow$ 1D random field Ising model

solved exactly by Lehman and McTague (*J. Chem. Phys.* **49**, 3170 (1968))

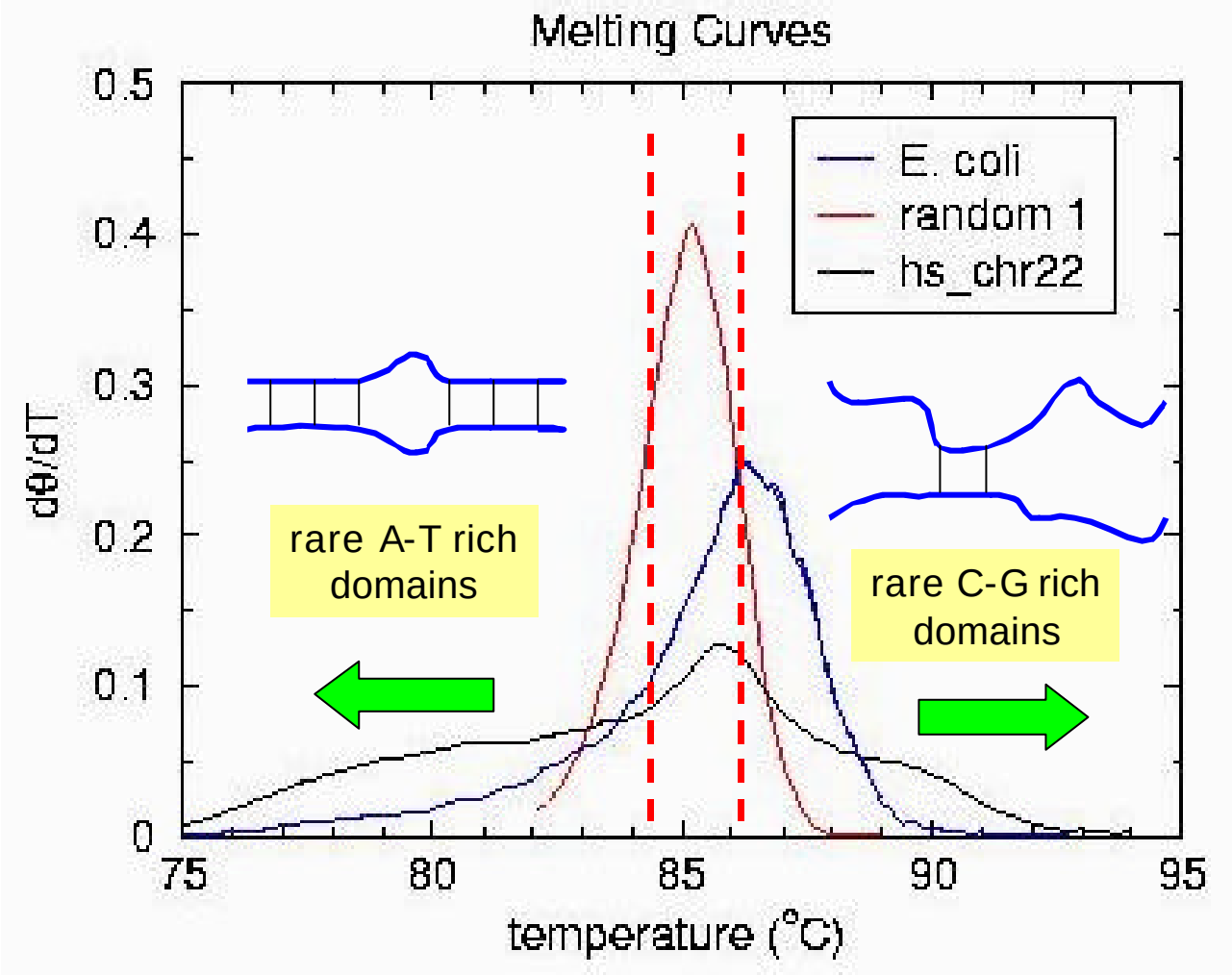
Heuristics: $$\Delta G / k_B T \simeq -\ln s - l\left[a\frac{\Delta T}{T_M}\right] + \left[c_{AT}(1-c_{AT})l\right]^{1/2}\left[a\frac{T_{AT}-T_{GC}}{T_M}\right]e$$

minimal loop size: $$l_c \simeq \left[\frac{2T_M \ln s}{a(T_{AT}-T_{GC})}\right]^2 \simeq 250\text{bp}$$

$e \in N(0,1)$

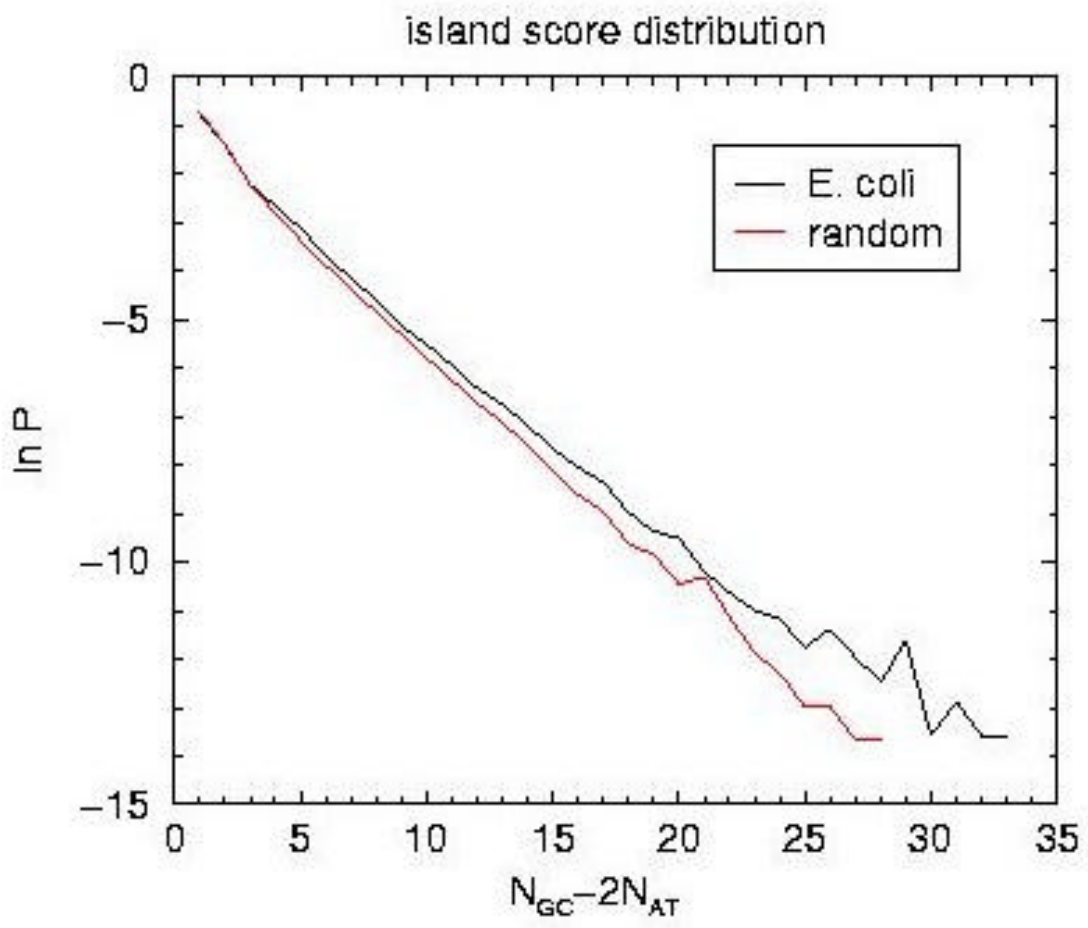
melting of each segment: $$\Delta T \simeq \frac{T_M}{a\ l_c} \simeq 0.12\text{K}$$

Hard case: loop entropy + sequence heterogeneity



Reduced enthalpy of a helical segment of length $N = N_{AT} + N_{GC}$ at T=92°C:

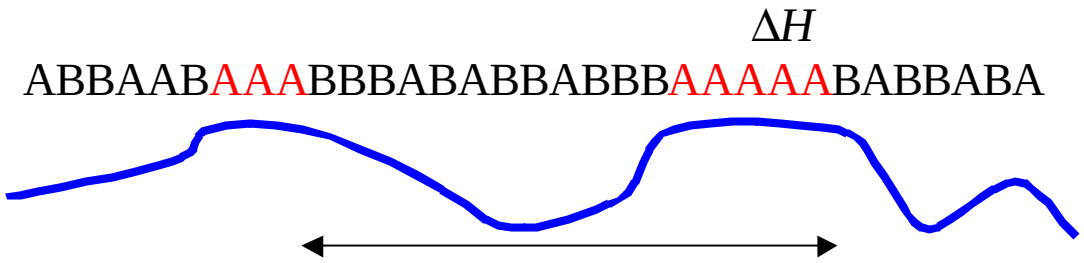
$$x = \Delta H / k_B T = -0.48 \times (N_{GC} - 2N_{AT})$$



$$P(x) \sim \exp(qx)$$

$$q = 0.97$$

Why is this important?



Exponential tail: $P(x) = A\exp(qx), \quad x = \Delta H / k_B T$

Energy gain: finding best contact in a segment of length L,

$\Rightarrow \quad \Delta H_m / k_B T \approx -\frac{1}{q}\ln(AL)$

Loop entropy cost: $\Delta s / k_B \approx b \ln L - \ln s$

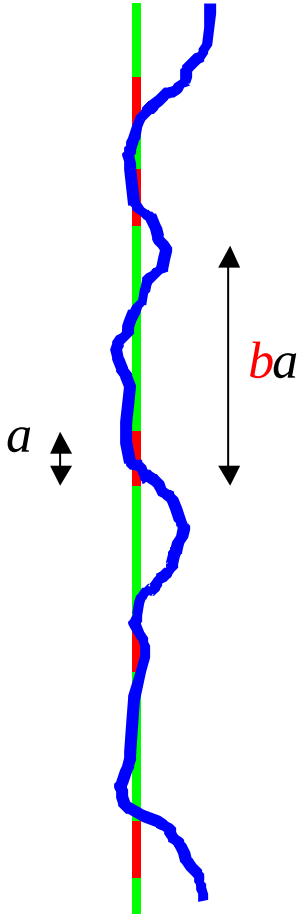
$\Rightarrow \quad \Delta G / k_B T \approx \left(b - \frac{1}{q} \right) \ln L - \ln s - \frac{1}{q} \ln A$

Transition: $q = q_c = 1/b$

$\Rightarrow \quad x \sim \exp(-const./|T - T_C|^{1/2})$ Kosterlitz-Thouless!

Real-space RG

L.H. Tang and H. Chaté, PRL **86**, 830 (2001)



Basic idea: coarse-graining along the chain

$\Downarrow$

renormalization of contact interactions

w = Boltzmann weight of a contact at scale a

$\tilde{w}$ = Boltzmann weight of a contact at scale ba

RG transformation:

$$1+\tilde{w}=\frac{1}{b^b}\prod_{i=1}^{b}(1+w_i)+1-\frac{1}{b^b}$$

$\Downarrow$

$$P(x)\to\tilde{P}(\tilde{x})$$

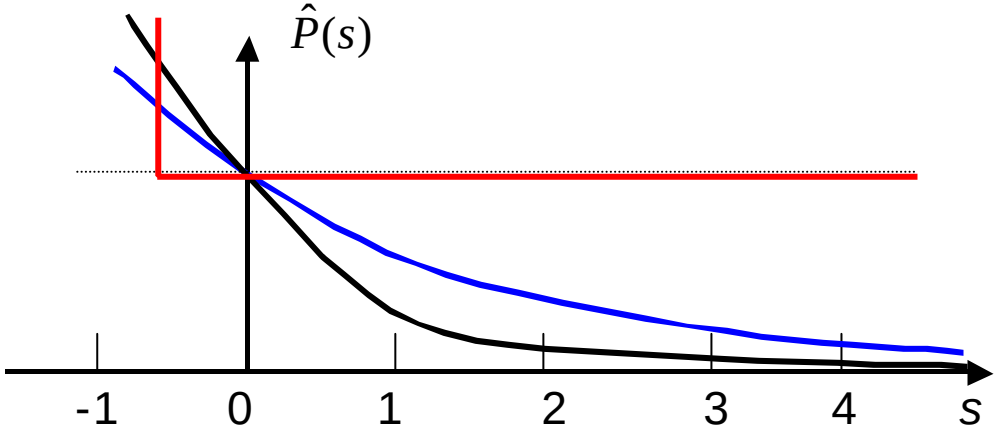
$b = \exp(dl) \to 1,$

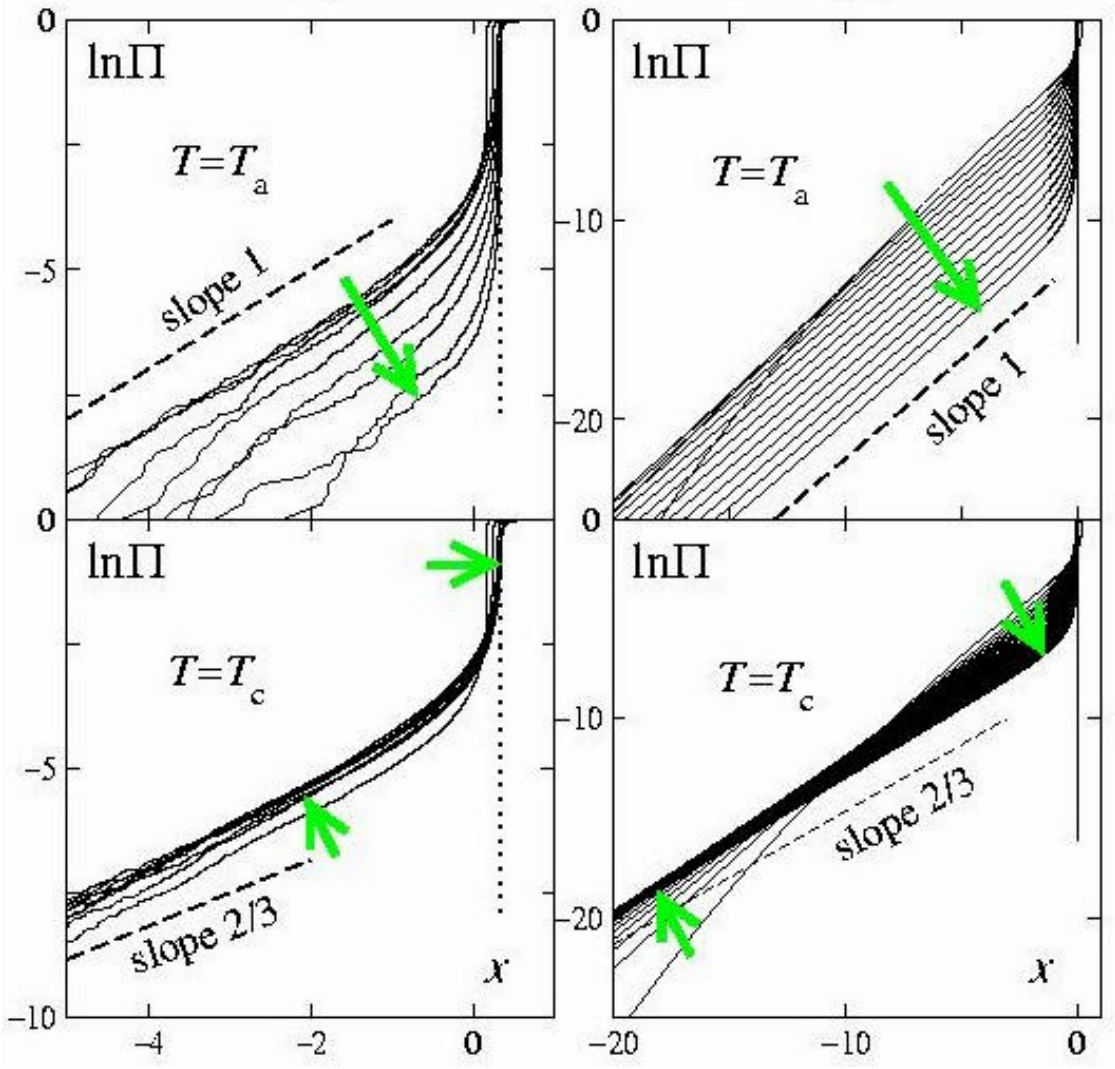
Laplace transform $\hat{P}(s) = \int_{-\infty}^{0} dx \exp(sx) P(x)$

Functional low equation

$$d\hat{P}(s)/dl = \hat{P}\ln\hat{P} + b\ \ s\left[\hat{P}(s) - \hat{P}(s+1)\right]$$

Infinitely many fixed-point solutions:





1+1 directed polymer

Berker lattice

Parametrization

$$P(x) = (1-A)d(x) + Aq\exp(qx)$$

typical repulsive

rare attractive

Kosterlitz-Thouless RG: including multiple “contacts, ” etc.

$$\frac{dq}{dl} = -\tfrac{1}{2} qA$$

$$\frac{dA}{dl} = (1 - qb)A + \frac{2-q}{2q} A^2$$