# Mesoscopic modeling of DNA: the statistical physics of melting, unzipping and hairpin formation

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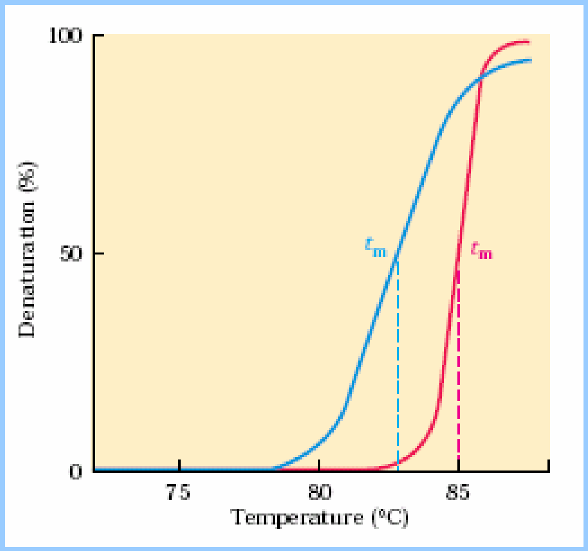
# Outline (“Biological physics”)

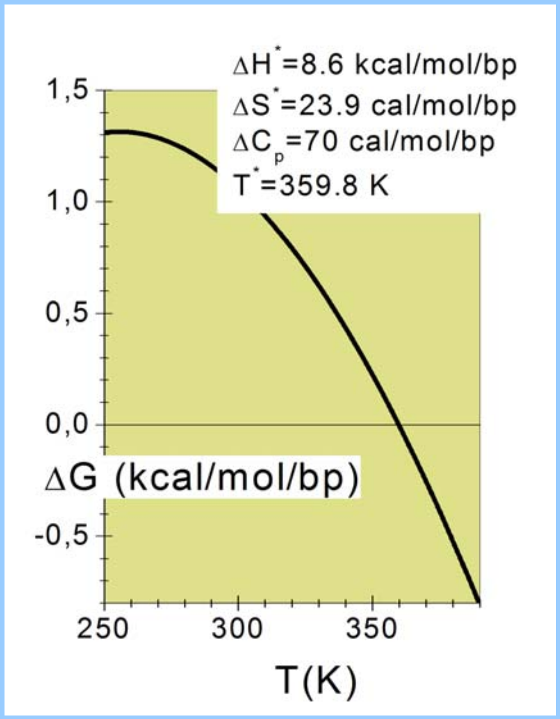
- **DNA „melting“ & „unzipping“**
- **mesoscopic modeling (discrete / continuum)**
- **thermodynamic behavior („true“ phase transition in 1-D system)**
- **small systems (DNA „hairpins“), dynamics!**

# DNA denaturates (heat, pH)



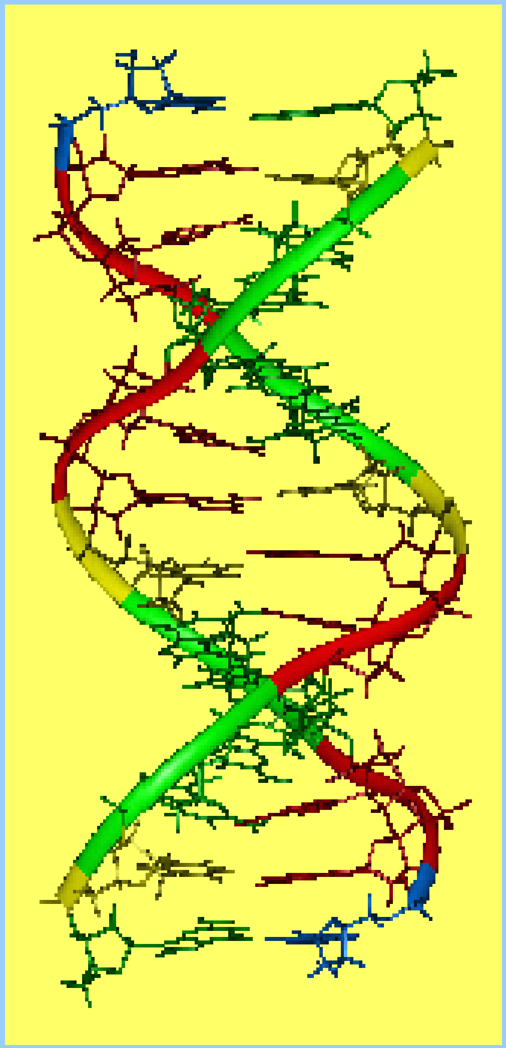

**duplex unbinds into 2 single strands**
**no breaking of covalent bonds**

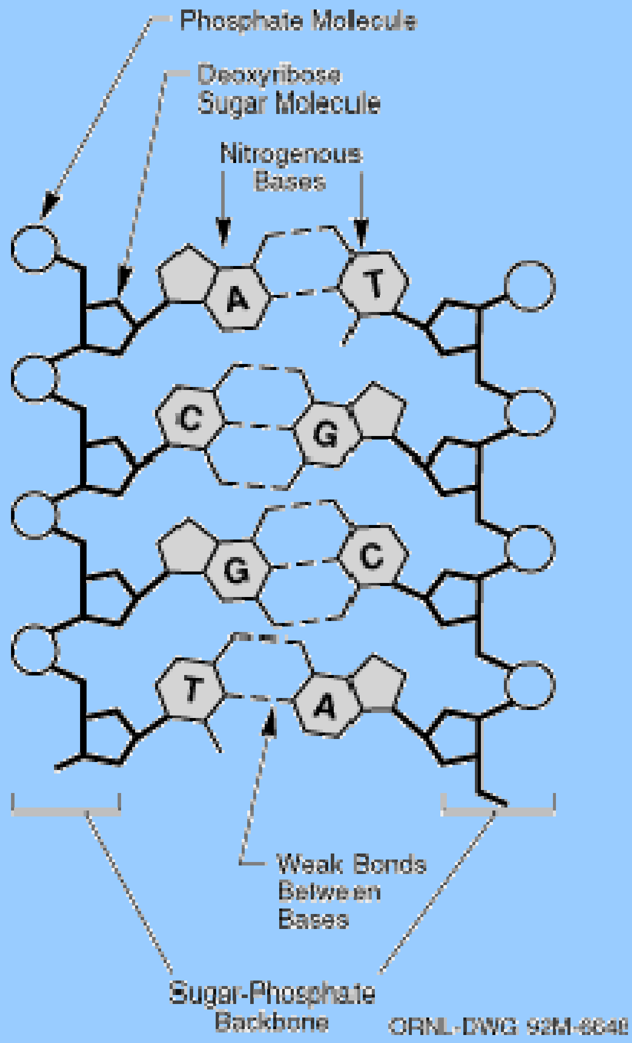
**detect e.g. change in UV absorption**

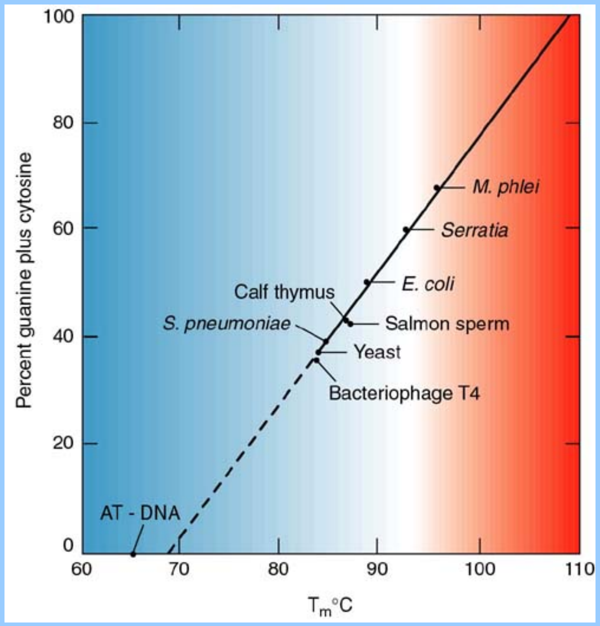



**macroscopic thermodynamics**
**interpreted as 1st order transition**
**ΔH = 6-12 kcal/mole/bp**

# The role of structure

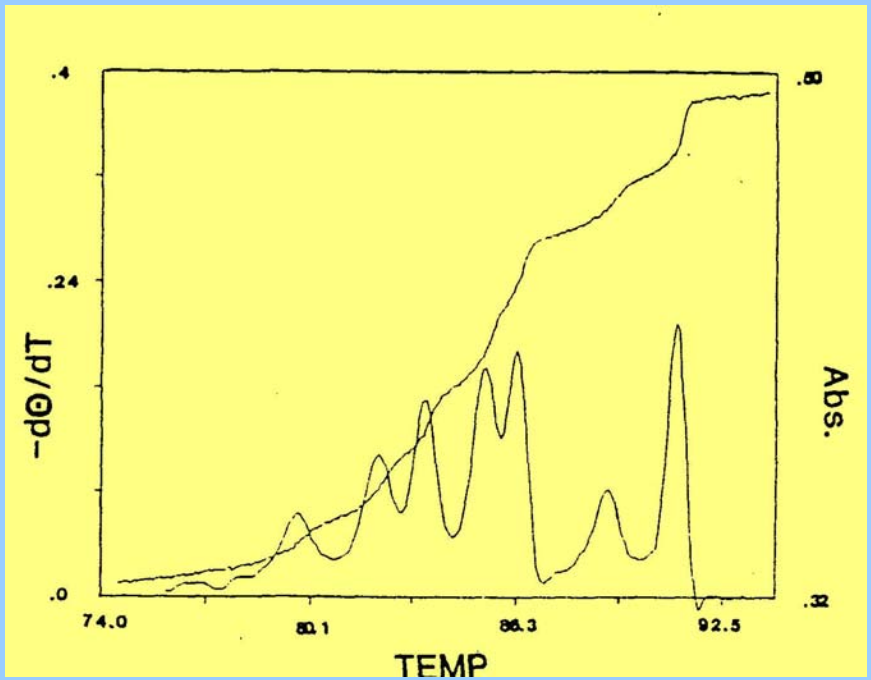





- **G-C: 3 H-Bonds**
- **A-T: 2 H-Bonds**

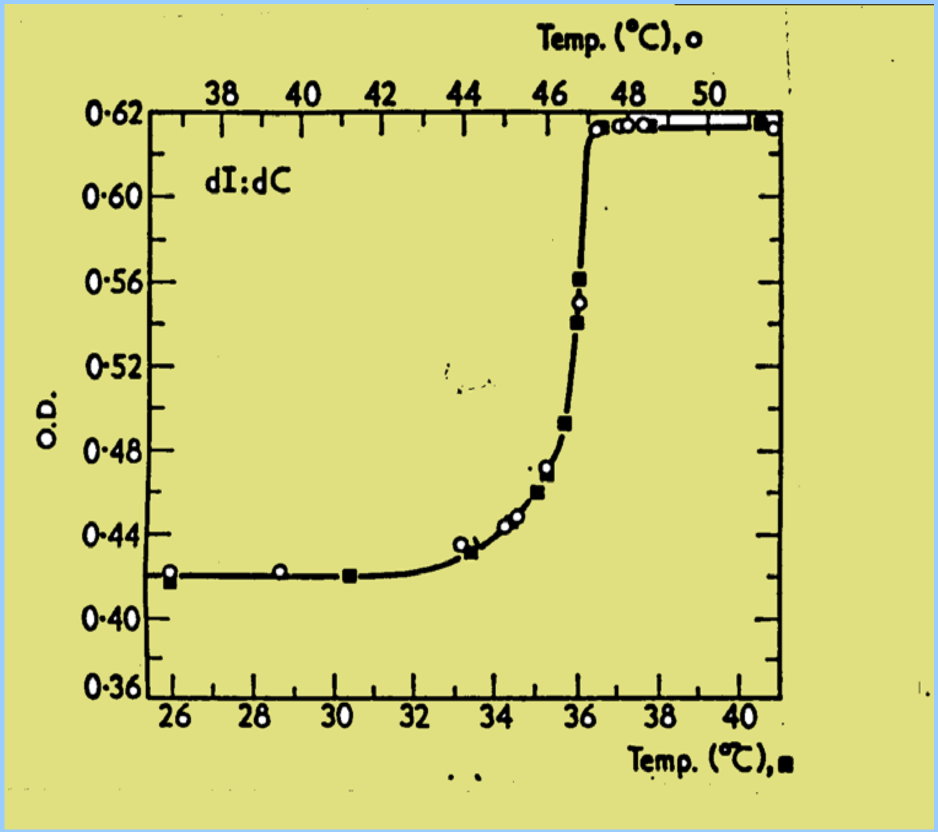
# fine structure of melting curve




1630 bp Hinf I Restriction Endonuclease DNA fragment of the plasmid pBR322

- fragment-specific peaks („fingerprinting“)
- multistep melting

# Synthetic polynucleotides




- „homogeneous“ DNA ($10^3$ - $10^4$ identical BP´s)
- $\Delta T/T_m = O(10^{-3})$
- still not $N \rightarrow \infty$ !

Inman & Baldwin, J. Mol. Biol. **8,** 452 (1964)

# (discrete) mesoscopic modeling: helices & loops

**BP unit: helical / unbound („Ising“ 2-state model)**

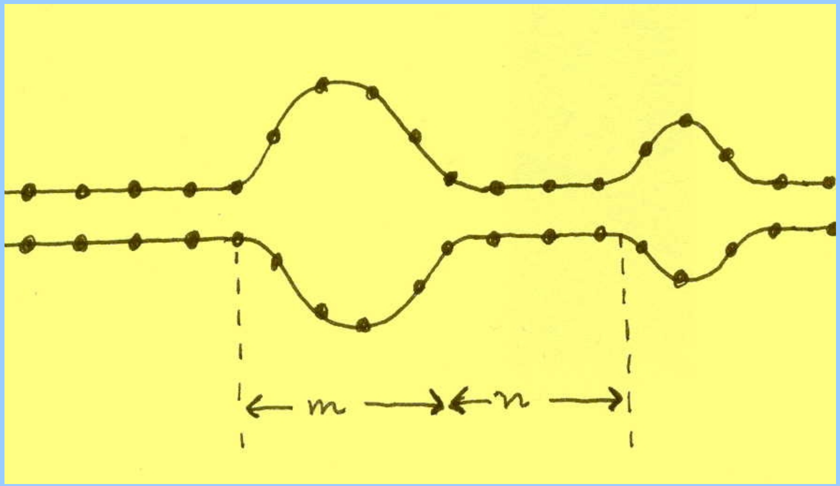
**Helix nucleation** $\sigma << 1$

**growth** $s = s_0 e^{-\varepsilon/T} \approx 1$

$p_n = \sigma s^n$

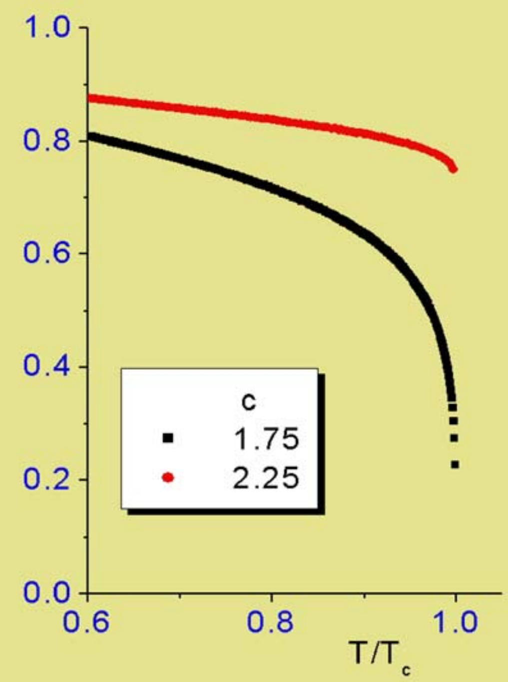
**Loop Entropy!** $q_m = \dfrac{b^m}{m^c}$

$P_{n,m} = z\, p_n q_m$




Poland & Scheraga, JCP **45,** 1464 (1966)

# Order parameter: Helix%




helix fraction vs. T

- c<1 no phase transition
- 1<c<2 2. Order
- c>2 1. Order

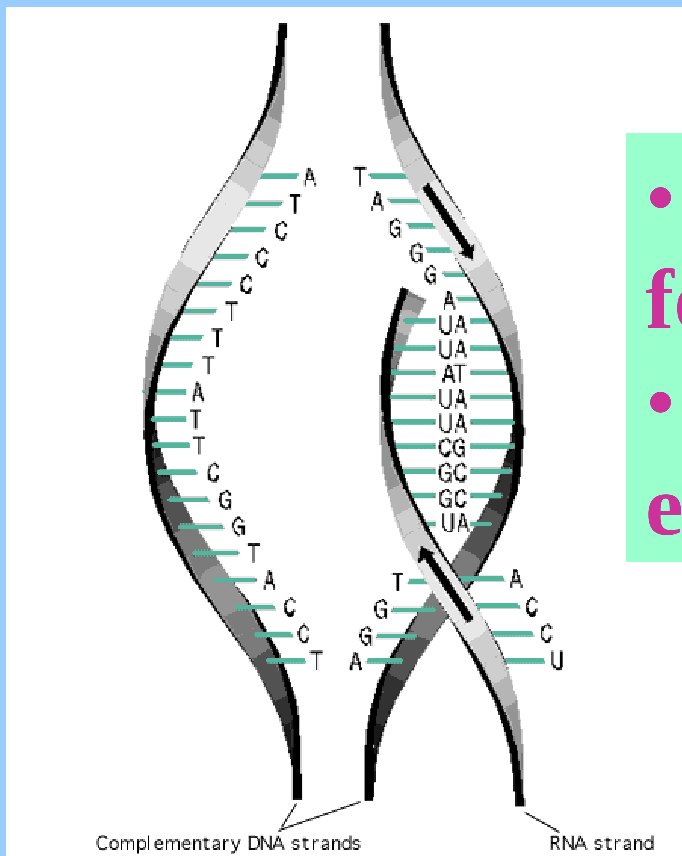
$$c = d/2 \; (=1.5)\, \mathrm{RW}$$

$$c = 1.75 \; \mathrm{SAW}[1]$$

$$c = 2.1[2]$$

[1] Fisher , JCP (1966)
[2] Kafri et al, PRL (2000)

# Not just thermodynamics!




- **local denaturation essential for transcription to mRNA**
- **BP- lifetime (Imino-p exchange) : $\tau_{BP} \approx$ 10 msec**

PS model:

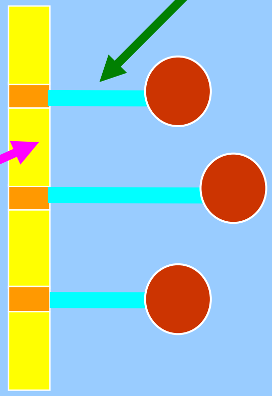
- > 0 probability
- no dynamics!

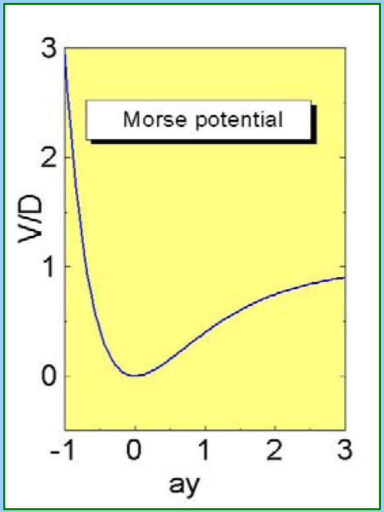
# Mesoscopic (lattice-dynamical) modeling

**1 degree of freedom / base pair (bp separation)**

$y_n$

$V(y)$






$$W(y_n, y_{n-1}) = \frac{1}{2} k \left(y_n - y_{n-1}\right)^2$$

**stacking-interaction (nonlinear spring)**

$$H_P = \sum_n W\left(y_n, y_{n-1}\right) + V(y_n)$$

Peyrard & Bishop PRL **62,** 2755 (1989)
Dauxois, Peyrard & Bishop PRE (1991)

# Exact Thermodynamics (TI)

**partition fn.**

$$Z_P = \int dy_1 \ldots dy_n \;\; e^{-H_P(\{y\})/T}$$

$$= \int dy_1 \ldots dy_n \;\; K(y_1, y_2) \ldots K(y_{N-1}, y_N)$$

**kernel**

$$K(x,y) = e^{-W(x,y)/T} \; e^{-V(x)/T}$$

**Transfer Integral Eq.**
**(non Hilbert-Schmidt!)**

$$\int_{-\infty}^{+\infty} dy \, K(x,y) \; \phi_\nu(y) = \Lambda_\nu \phi_\nu(x)$$

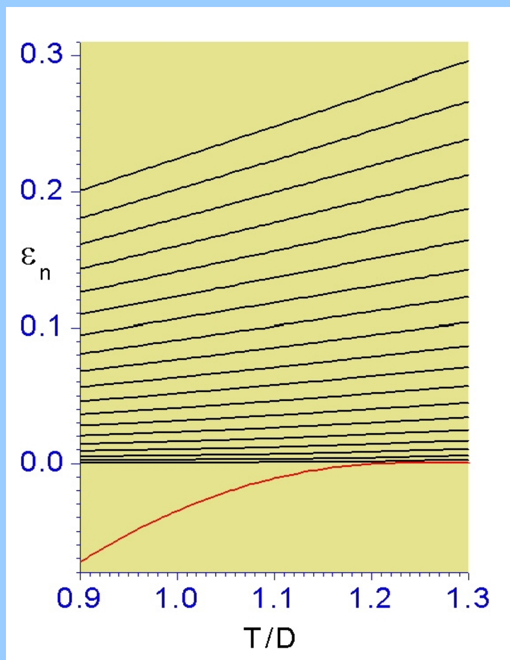
$$\Lambda_0 \geq \Lambda_1 \geq \ldots$$

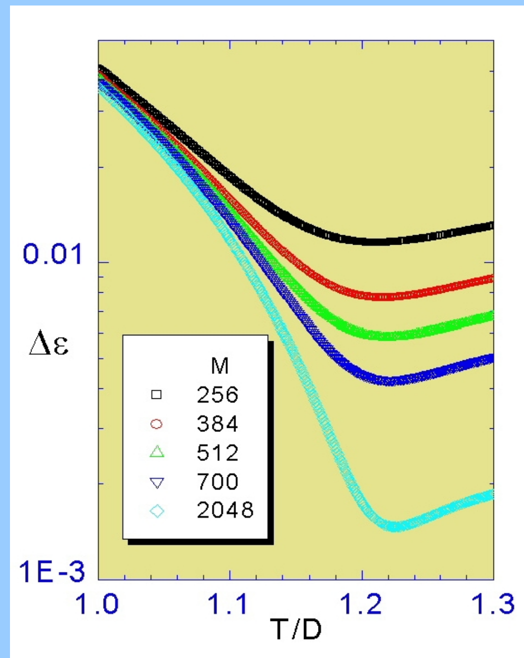
**free energy**

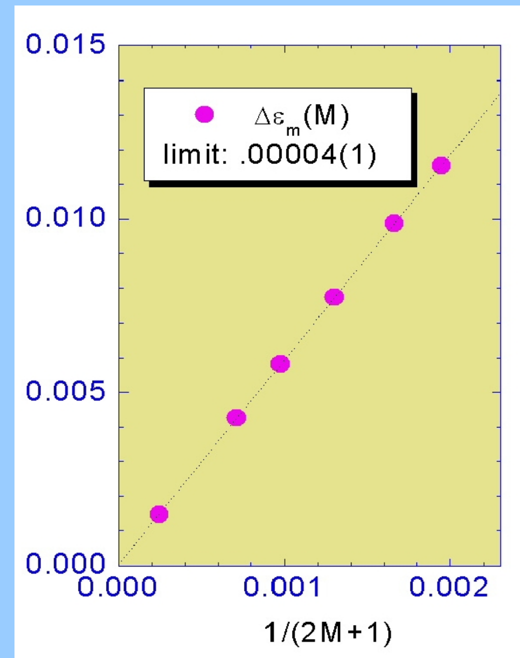
$$Z_P = \sum_\nu \Lambda_\nu^N \approx \Lambda_0^N$$

$$f = -\frac{1}{N} T \ln Z_P \approx -T \ln \Lambda_0 \equiv \varepsilon_0$$

# Spectrum of TI-eq. (ρ=0, num.)



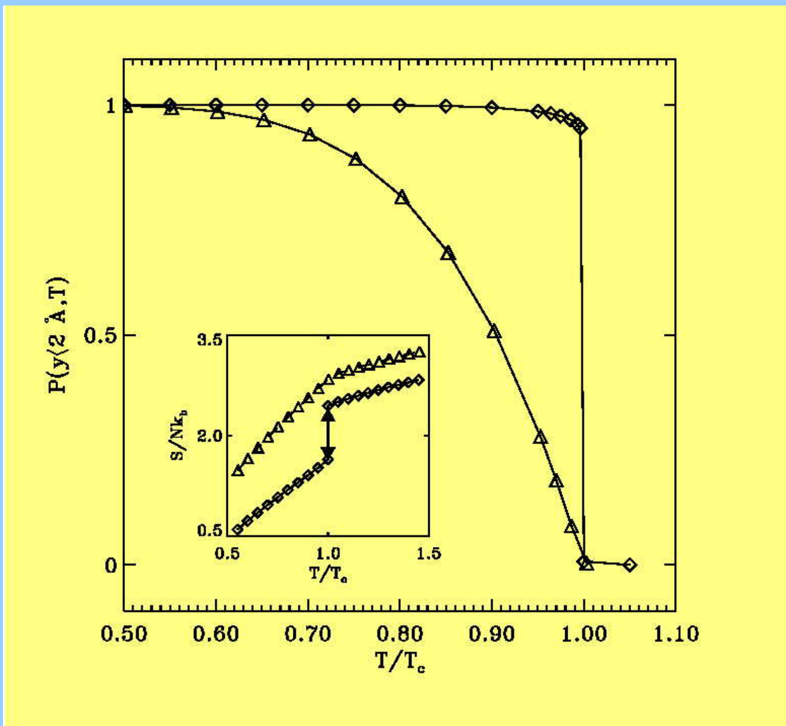

$$\Delta\varepsilon \equiv \varepsilon_1 - \varepsilon_0 \propto \xi^{-1} \rightarrow 0$$

**finite-size scaling „proof“:**
**exact phase transition**

$$\propto \left(T_c - T\right)^2$$

N. Th., PR E **68**, 026109 (2003)

# Order of Phase Transition?




**helix fraction vs. $T/T_c$**

**inset: entropy**

$$P(y < y_0 \;, T) \propto (T_c - T) \quad , \; \rho = 0$$

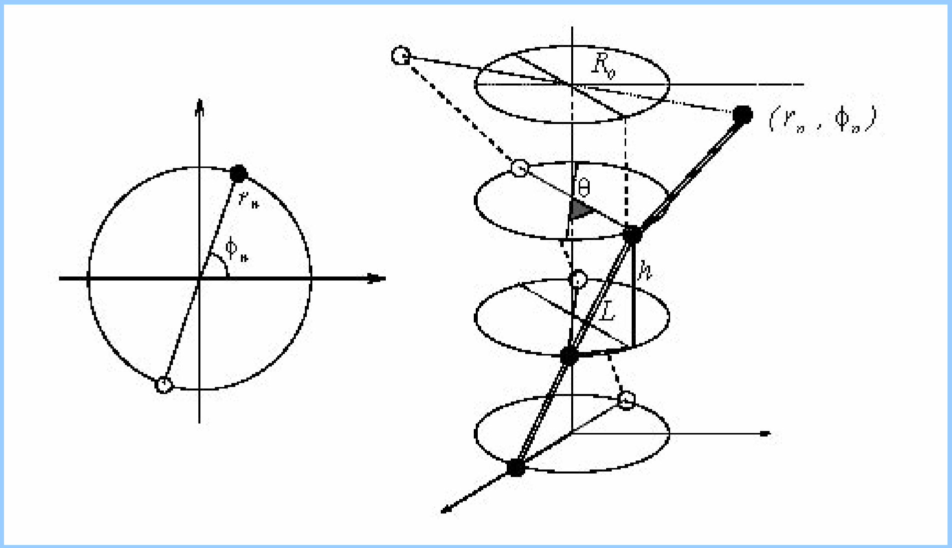
$$\to const \;, \; \rho = 1$$

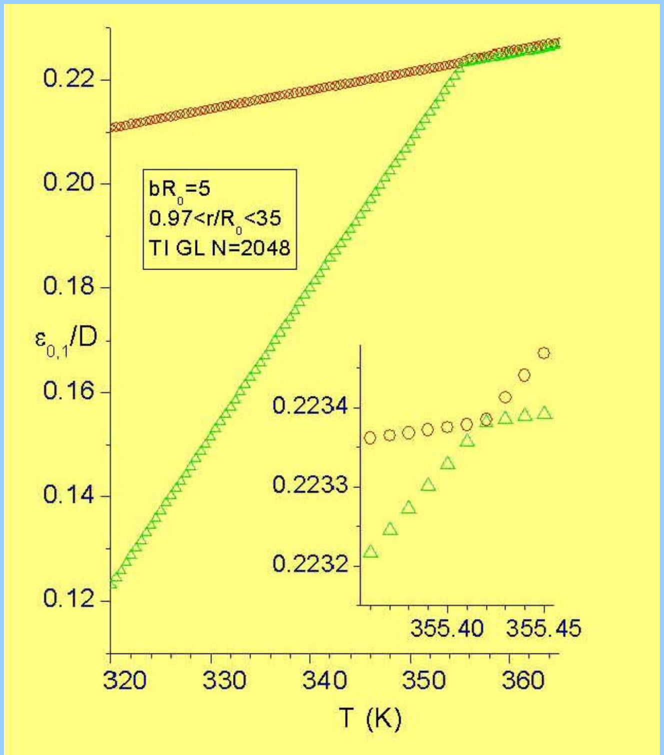
**nonlinear stacking interaction**

**⇒ *effectively* 1st order**

Th., Dauxois & Peyrard, PRL **85**, 26 (2000)

# Helicoidal version




BPs on fixed planes, 2 DoF / BP

- also *effectively* 1st order
- $\Delta T_{crossover} < 0.003$ K

$$\Delta\varepsilon \propto e^{-const/(T_c - T)} \quad , \quad \rho = 0$$
$$\approx (T_c - T) \quad , \quad \rho = 1$$

Barbi, Lepri, Peyrard & Th., PR E **68,** 061909 (2003)

# Phase transitions in 1D?

- **Exact** statements about phase transitions in 1D - not allowed, on general physical (Landau) or mathematical (van Hove & extensions) grounds. Exceptions?
- **Mathematical**: singular integral equations (?)
- **Physical***: Energy vs. Entropy balance of the interface, (domain wall, DW) . Quantitative. Predicts $T_c$ .

* N. Th., Physica D **216**, 185 (2006)

# Nonlinear equilibrium structures

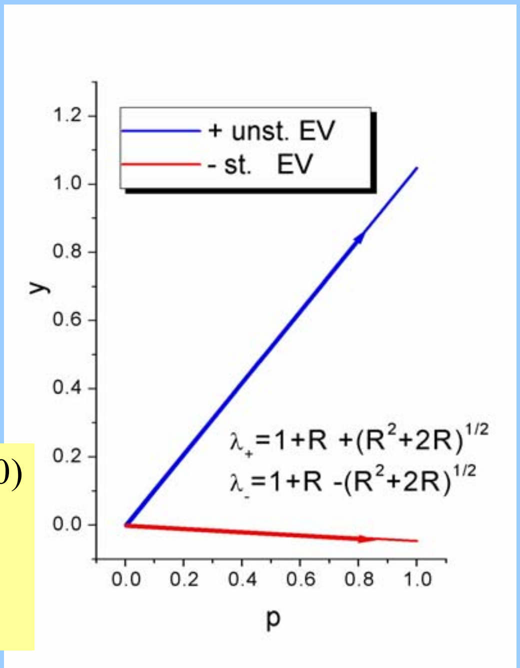
$$H_P = \sum_{n=0}^{N} \frac{1}{2R}\left(y_{n+1} - y_n\right)^2 + V(y_n)$$

$R >> 1$

Th., Peyrard & MacKay,
PRL **93**, 258101 (2004)

$$\left.\frac{\delta H}{\delta y_n}\right|_{\{\dot{y}_j = 0\}} = 0 \quad \forall n$$

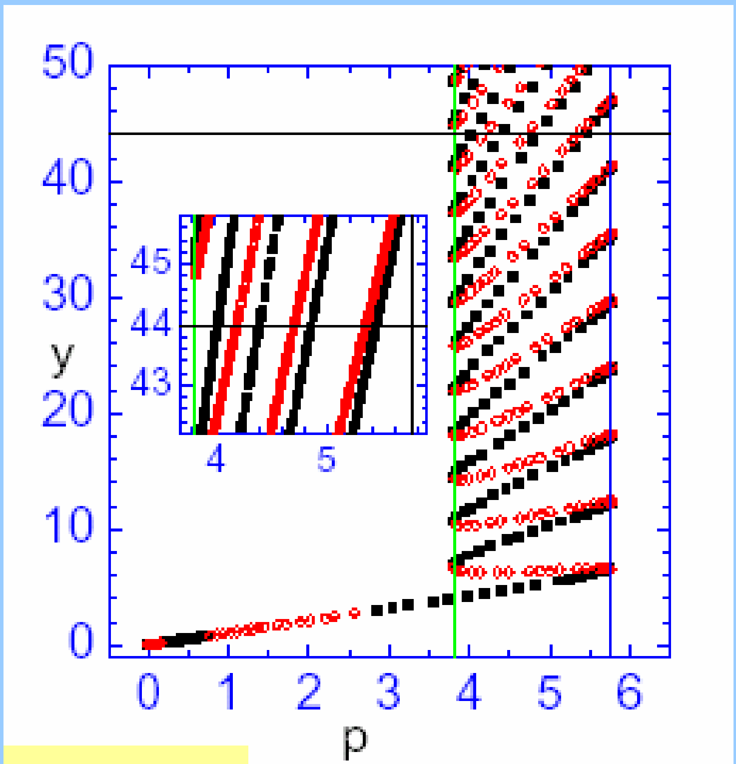
$$\left.\begin{aligned} p_{n+1}^{(\alpha)} &= p_n^{(\alpha)} + RV'(y_n^{(\alpha)}) \\ y_{n+1}^{(\alpha)} &= y_n^{(\alpha)} + p_{n+1}^{(\alpha)} \end{aligned}\right|$$




hyperbolic fixed point $^{(0)}$

$$y_n^{(0)} = p_n^{(0)} = 0 \qquad \forall n$$

# The HFP´s unstable manifold




$$y_0 = 0$$
$$y_{N+1} = L$$

$$A_{mn}^{(\alpha)} = \left. \frac{\partial^2 H}{\partial y_n \partial y_m} \right|_{\{y_i = y_i^{(\alpha)}\}}$$

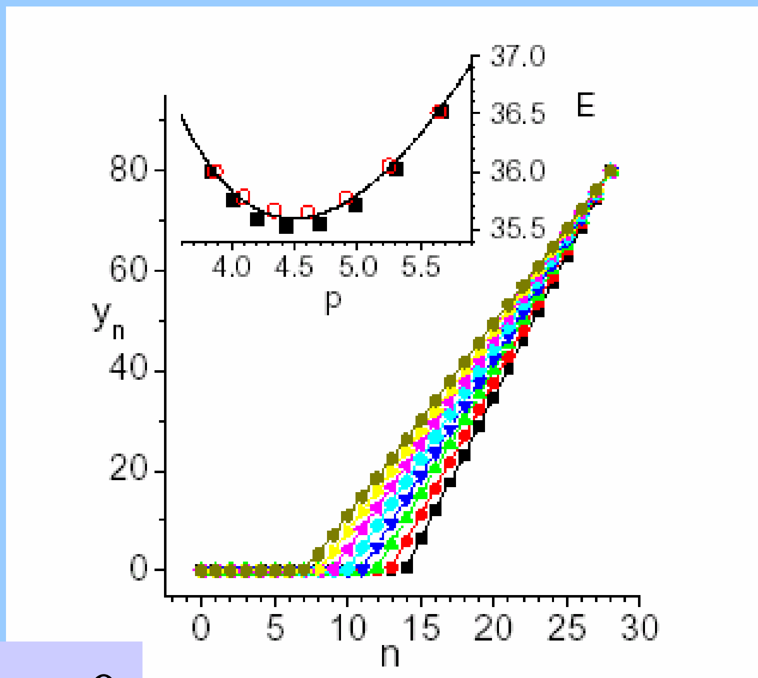
$$A^{(\alpha)} b_\nu^{(\alpha)} = \Lambda_\nu^{(\alpha)} b_\nu^{(\alpha)}$$

$(i)$ $\Lambda_\nu^{(\alpha)} > 0 \quad \nu = 1, 2, \cdots, N$ min(black)

$(ii)$ $\Lambda_\nu^{(\alpha)} > 0 \quad \nu = 2, \cdots, N$

$\Lambda_\nu^{(\alpha)} < 0, \ \nu = 1,$ saddles (red)

# Domain Walls (DW)




$$E(p,L) \approx N_{unbound}\left(1+\frac{p^2}{2R}\right)$$

$$N_{unbound} \approx L/p$$

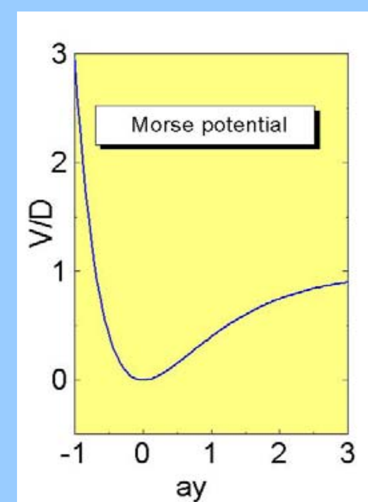
global energy min at

$$E^*(L) \approx 2L/p^*$$

$$p^* = (2R)^{1/2}$$

$$y_0 = 0$$

$$y_{N+1} = L$$



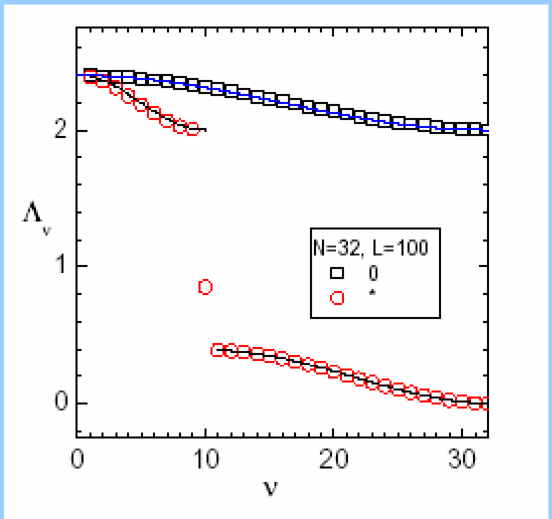

- „interpolates" between 2 equilibria
- 2nd equilibrium is at infinity!
- cf. phonon spectra

# DW spectra → thermodynamics

$$H^{(\alpha)}(\{\psi\}) = E^{(\alpha)} + \frac{1}{2}\sum_{m,n} A^{(\alpha)}_{mn}\psi_m\psi_n + \cdots$$

$$Z_N^{(\alpha)} = \int_{-\infty}^{\infty}\prod_{j=1}^{N} d\psi_j \; e^{-H^{(\alpha)}(\{\psi\})/T}$$

$$\approx e^{-E^{(\alpha)}/T}\prod_{\nu}\left\{\frac{2\pi T}{\Lambda_\nu^{(\alpha)}}\right\}^{1/2}$$




$$\Delta G(L,T) = -T\lim_{N\to\infty}\ln\left\{\frac{Z_N(L)}{Z_N(0)}\right\}$$

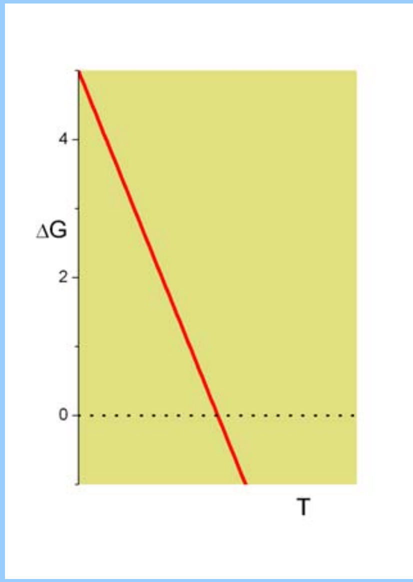
$$\frac{Z_N(L)}{Z_N(0)} \approx e^{-E^{*}/T}\prod_{\nu}\left\{\frac{\Lambda_\nu^{(0)}}{\Lambda_\nu^{(*)}}\right\}^{1/2}$$

# DW entropy vs energy balance

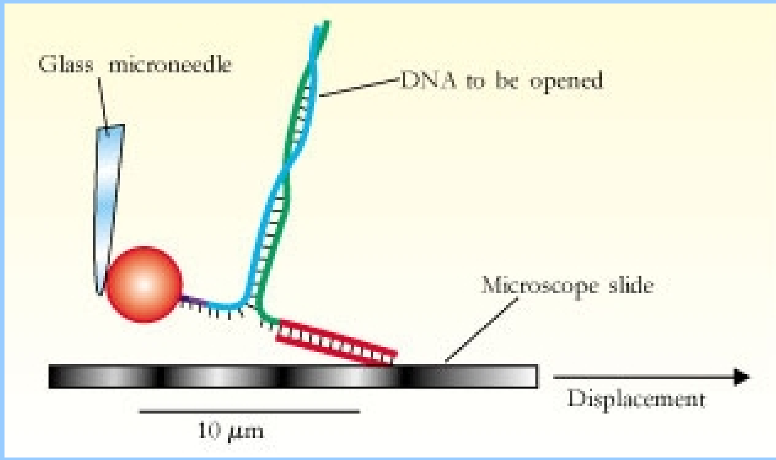
$$\Delta G \approx E^* - T\Delta S \propto L$$

$$f(T) = \left(\frac{\partial \Delta G}{\partial L}\right)_T = \frac{2 - T\sigma}{p^*}$$

*(unzipping force)*




Th., Peyrard & MacKay (PRL, 2004)



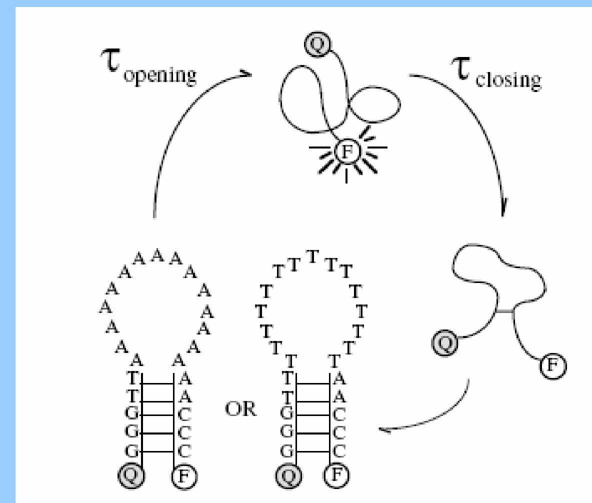

DW thermally stable at high T (entropic effect)

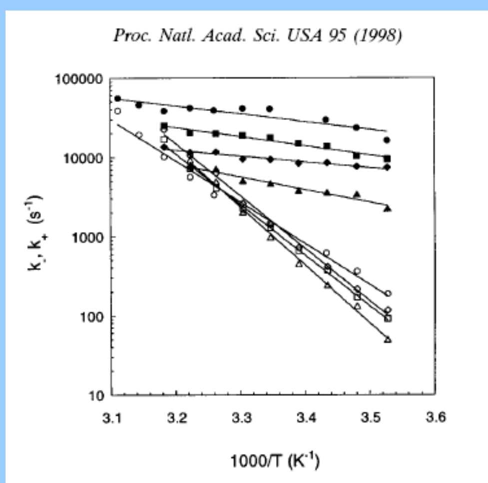
cf. expt: Essevat-Roulet, Bockelmann & Heslot, PNAS **94,** 11935 (1997)

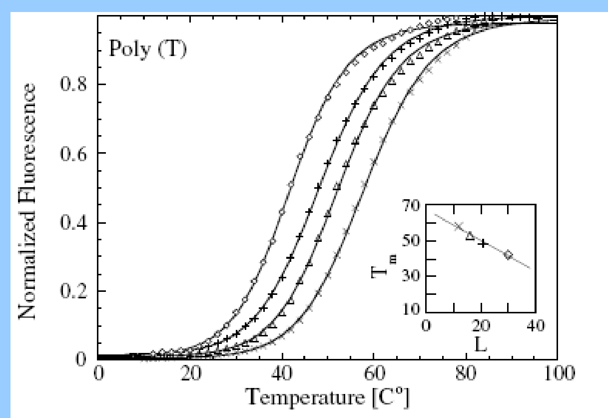
# DNA hairpins (expt)

**DNA single strand with complementary ends**
**<u>GGGTT</u> ... <u>AACCC</u>**

**DNA beacon: fluorophore & quencher attached to hairpin ends.**
**Closed: quencher suppresses fluorescent signal**



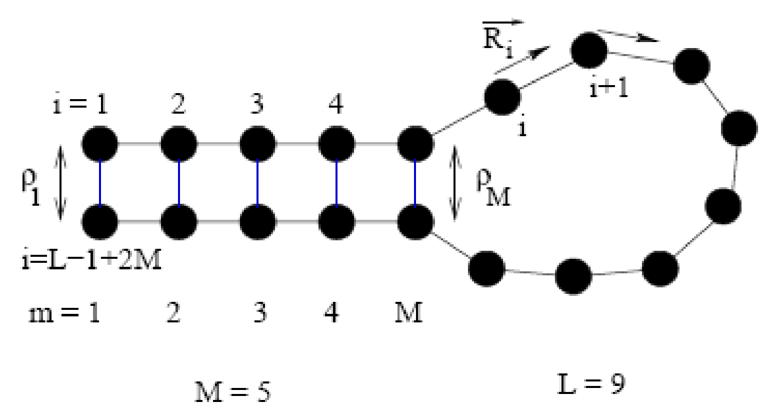



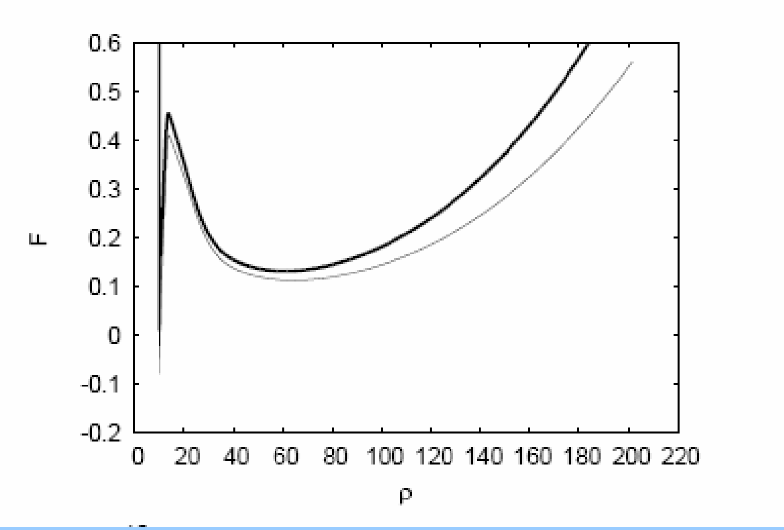

**Melting profiles**
**Conformational dynamics**
**e.g. long opening,**
**short closing times,**
**details (length, sequence)**

Goddard et al (PRL, 2000)
Bonnet et al (PNAS, 1998)

# DNA beacons (model calculation)

**polymer chain (rigidity) + DNA modeling**

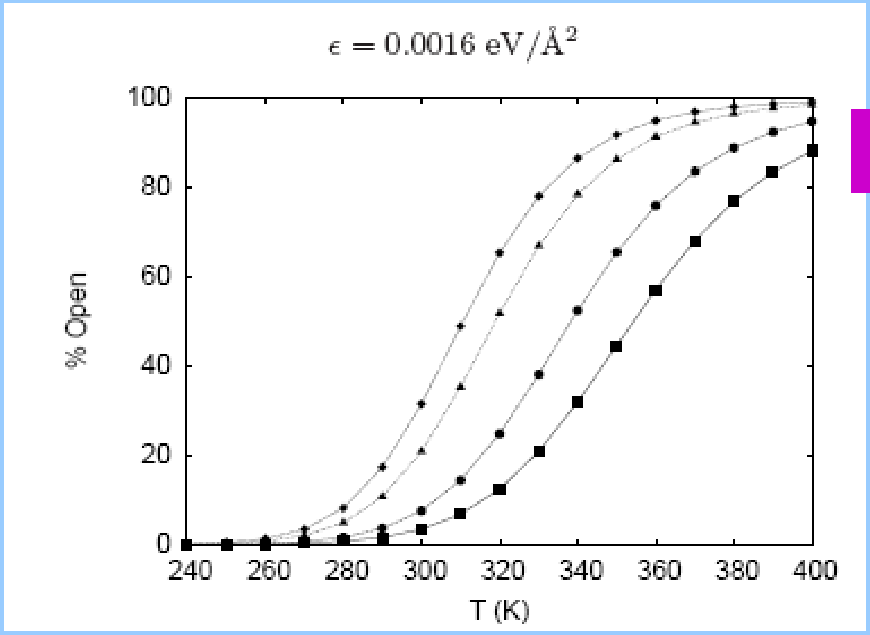


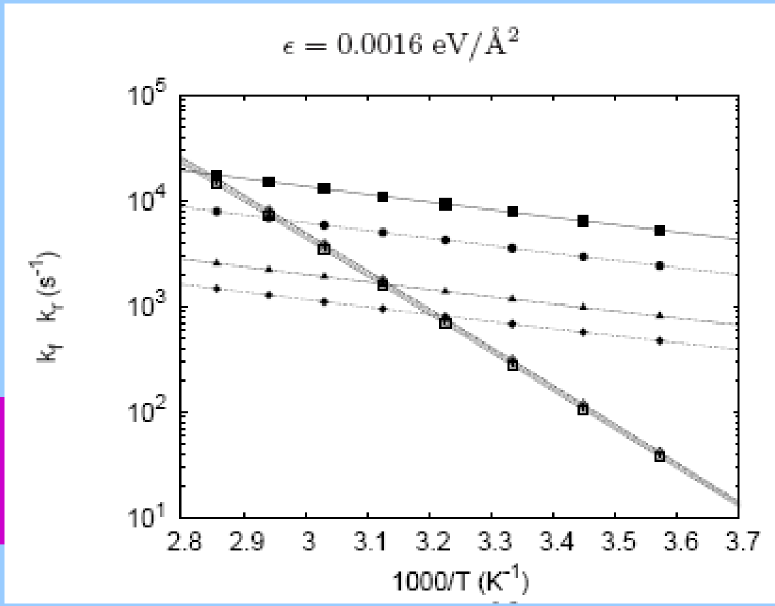

- **effective integration over „fast“ degrees of freedom**
- **Q-F distance: „reaction coordinate“ (energy landscape)**
- **Dynamics: overdamped Fokker-Planck**

Errami, Peyrard & Th., EPJ E **23**, 397 (2007)

# DNA beacons (model calculation)




**melting profiles**




**opening rates (slow)**
**closing rates (fast, L-dependent)**

# Conclusions

• thermal & mechanical DNA denaturation share many of the properties of genuine thermodynamic phase transitions (1D).

• both processes can be understood in terms of the formation and entropic stablity of an interface (DW).

• underlying lattice dynamical modeling can be succesfully applied to finite objects (e.g. hairpins).

# Collaborators

- M. Peyrard (ENS-Lyon)
- T. Dauxois (ENS-Lyon)
- R.S. MacKay (Warwick)
- S. Lepri (Firenze)
- J. Errami (ENS-Lyon)