Modelling DNA Hairpins

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Outline

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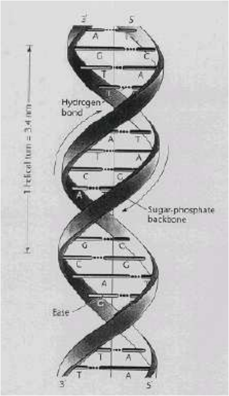
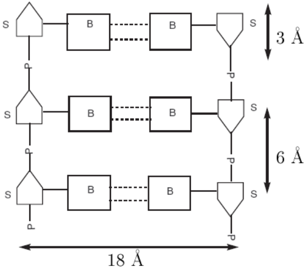
Structure and conformation

- DNA is a very long helicoidal molecule composed of two chains of desoxyribonucleotides:

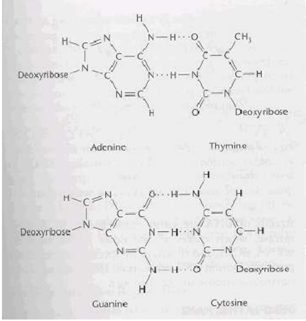




(W. Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag)

Structure and conformation

- A nucleotide is composed of three molecular parts
  - A cyclic sugar (desoxyribose)
  - A purine or a pyrimidine base: Adenine-Guanine-Cytosine-Thymine
  - A phosphate linked to the sugar



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Properties

- The stability of DNA results from various interactions
  - Hydrogen bonding between complementary bases
  - Stacking interaction between base-pairs
- Melting of DNA
  $\longrightarrow$ The two strands of the DNA can be dissociated by **heat**
  $\longrightarrow$ The melting can be followed by the UV absorbance measurement

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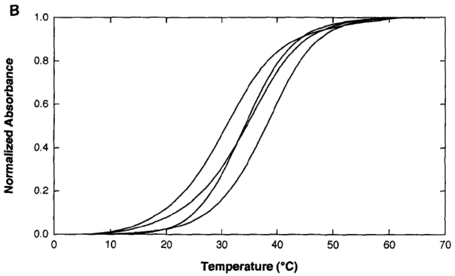
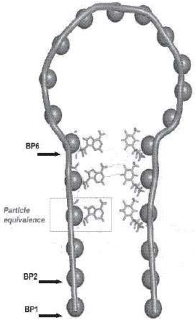


DNA Hairpins

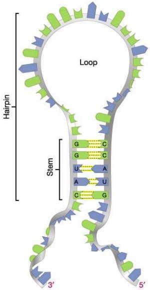
- Single Strands of DNA with complementary bases at its two ends
  $\longrightarrow$ 5'-CCCAA-$(N)_n$-TTGGG-3'
- Schematic secondary structure



(S. Cuesta-López *et al*, Eur. Phys. J. E **16**, 235-246)

Interest

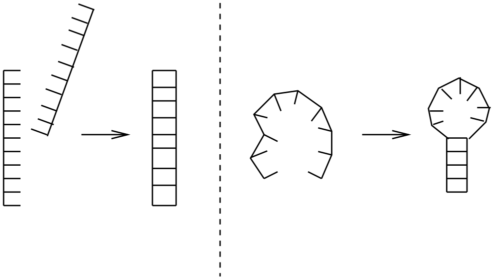
- Biological interest
  - Loop formation is a first step in the folding of the RNA



  - DNA hairpins provide very sensitive probes for short DNA sequences

Interest

- Physical interest
  - DNA hairpins are simple systems for the understanding of the self-assembly of DNA

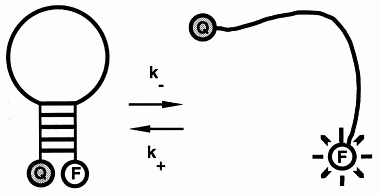


  - Modelling the fluctuations of hairpins is more challenging than the thermal denaturation of DNA
    $\rightarrow$ it is not simply the reverse process of its opening

Outline

Measurement Principle

- Molecular Beacons (G. Bonnet *et al*, Proc. Natl. Acad. Sci. USA **95**, 8602-8606)
  → Oligonucleotides with a fluorophore and a quencher attached at its two ends: 5’-CCCAA-(N)$_n$-TTGGG-3’



- Fluorescence Resonance Energy Transfer
  - The conformational state is directly reported by the fluorescence
  - The fraction of open beacons can be measured

$$f(T) = \frac{I(T) - I_c}{I_0 - I_c}$$

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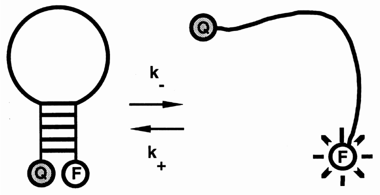

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  - The conformational state is directly reported by the fluorescence
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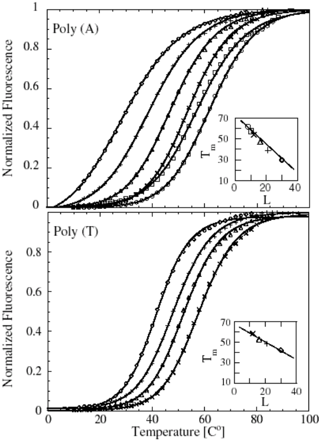
Results

- Melting curves for different loop sequences



- The melting temperature T_m decreases with the loop length
- The decay is most important for poly(A)
- T_m is higher for a poly(T) than a poly(A)-loop

Measurement principle

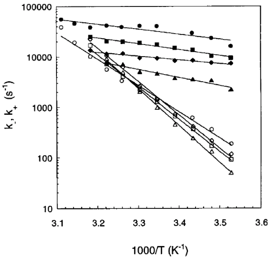
- **F**luorescence **C**orrelation **S**pectroscopy
  $\longrightarrow$ Measurement of the autocorrelation function that gives the sum of the kinetic rates k_- and k_+
- The equilibrium constant gives the ratio of the kinetic rates

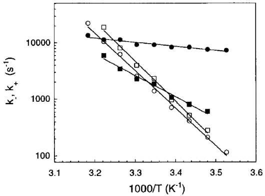
$$K(T) = \frac{f(T)}{1 - f(T)}$$

$$K(T) = \frac{k_-(T)}{k_+(T)}$$

Results

- Rates of opening and closing in Arrhenius plot

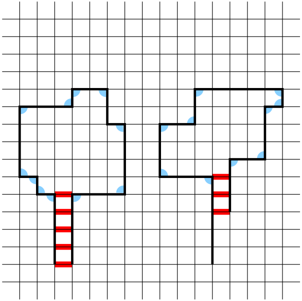




- Kinetics of opening do not depend on the loop sequence
- The rate of closing decreases with the loop length
- The activation energy is only affected by the nature of the loop

Outline

Description of the model



(S. Cuesta-López, J. Errami, F. Falo, and M. Peyrard, J. Biol. Phys. **31**, 273-301)

- Total energy of the chain

$$E = n_A E_A + \frac{1}{2}\sum_{j=1}^{n_s}\sum_{j'=1}^{n_s} e(j,j')$$

$$e(j,j') = \delta(t_j - t_{j'})\delta(d_{jj'} - 1)a(j)a(j')E_{\mathrm{HB}}(t_j)$$

- **Hydrogen** bonds between complementary bases

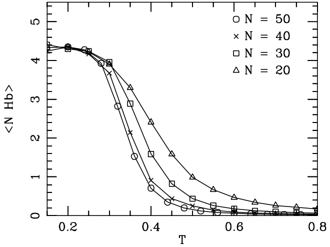
$$E_{\mathrm{HB}} < 0$$

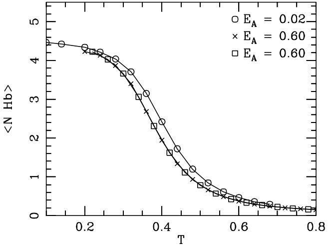
- **Flexibility** of the chain and stacking interaction

$$E_A > 0$$

Thermodynamics of the opening-closing transition

- Transition in the abscence of mismatch





  - The melting temperature T_m decreases with the loop length
    → Good agreement with the experiments
  - The melting temperature T_m decreases with the increase of the rigidity
    → The effect is too small to model (T)-loop and (A)-loop

- Role of the mismatches

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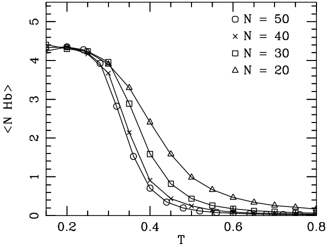

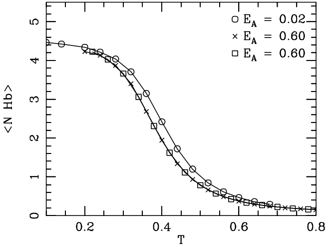

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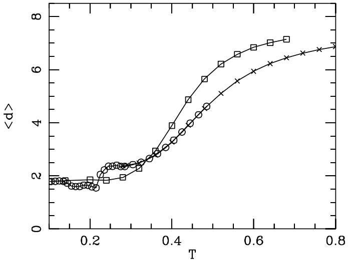
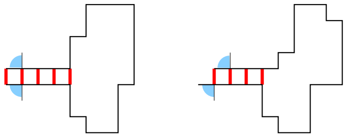




- The melting curve is smoother
- The melting curve shows an aditional fairly sharp kink
  → The mismatched closings are metastable states

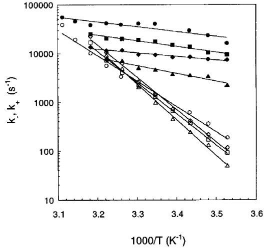
Kinetics of opening and closing

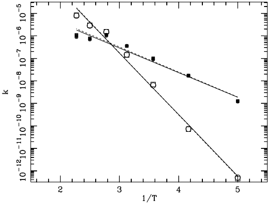
- Chemical equilibrium between closed and open states

$$\frac{d[C]}{dt} = -k_o[C] + k_{cl}[O]$$
$$\frac{d[O]}{dt} = +k_o[C] - k_{cl}[O]$$

$$k_o = \frac{1}{\tau}\frac{1}{1+K_e} \qquad k_{cl} = \frac{1}{\tau}\frac{K_e}{1+K_e}$$

$\rightarrow$ Studying the opening of the hairpins we can also get the kinetics of closing





Discussion

- Thermodynamic and kinetic results are in qualitative agreement with respect to the experiments

- No quantitative comparisons are possible
  - There is not enough degrees of freedom in the model
  - The difference between poly(T) and poly(A) is not well described
  - To get good statisitcs the calculation could become very long

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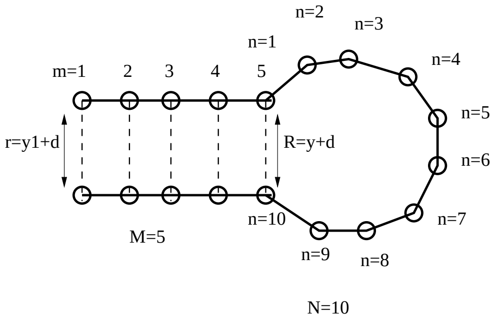
Outline

Presentation of the model

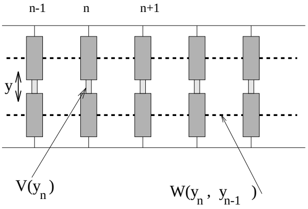
- The model of the hairpin contains two parts
  - The loop which is treated as a polymer in three dimensions
  - The stem which is an extension of the ends of the loop with additional interactions: PBD-model

(J. Errami, N. Theodorakopoulos and M. Peyrard, *Modelling DNA beacons at the mesoscopic scale*, submitted to European Physical Journal E)



PBD-Model for melting

- PBD model



- Modelling the interactions at the scale of the base
  - Hydrogen bonding between complementary bases

$$V(y_n) = D\left(e^{-ay_n} - 1\right)^2$$

  - Coupling between consecutive base-pairs

$$W(y_n, y_{n-1}) = \frac{K}{2}\left[1 + \rho e^{-\alpha(y_n + y_{n-1})}\right](y_n - y_{n-1})^2$$

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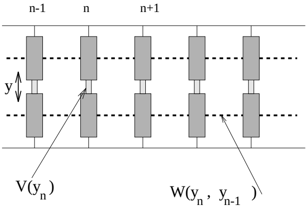

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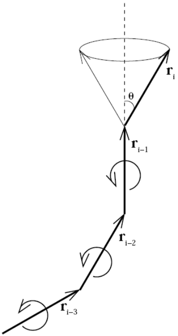
Freely Rotating Chain



The root mean square distance scales as $\sqrt{N}$ for large N

$$\left\langle \mathbf{R}^2 \right\rangle = Nl^2 \frac{1+\cos\theta}{1-\cos\theta}$$

The chain has a “stiffness”

$$\lim_{N\to\infty} \langle \mathbf{R}\cdot\mathbf{u}_0 \rangle \equiv l_p = \frac{l}{1-\cos\theta}$$

→ It also corresponds to the correlation length in the continuum limit approximation

End-to-end distance probability distribution

$\mathbf{R}$ scales as $\sqrt{N}$ for large N

→ The probability distribution is Gaussian for large N

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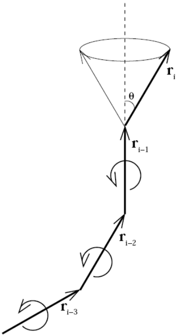

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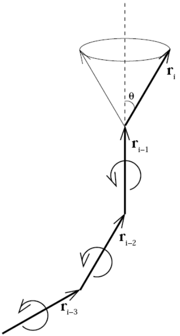

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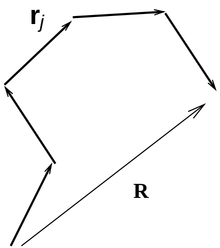
Kratky-Porod Chain (KP)



Hamiltonian of the chain

$$H = -\epsilon \sum_{j=1}^{N-1} \left(\mathbf{r}_j \cdot \mathbf{r}_{j+1} - l^2 \right)$$

The persistence length depends on the temperature

$$l_p = -\frac{l}{\ln\left[\coth b - \frac{1}{b}\right]} \approx lb = l \times \frac{\epsilon l^2}{k_B T}$$

No analytical expression for the end-to-end probability distribution
$\rightarrow$ Powerful numerical calculation in terms of a finite sum of Bessel functions

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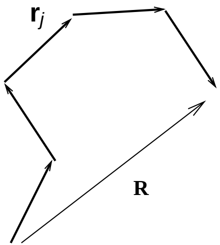

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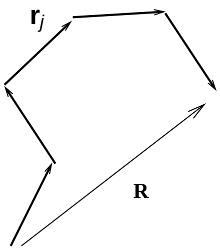

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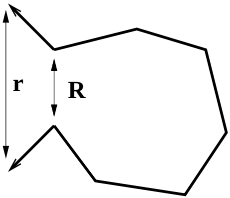
Growth of a polymer chain $S(r|R)$



Probability of the growth chain $P_{N+2}(r)$
$\rightarrow$ derived from $P_N(R)$

$$\int_0^\infty dRP_N(R)S(r|R) = P_{N+2}(r) \quad \forall r, N$$

The conditional probability distribution $S(r|R)$

$$\int_0^\infty drS(r|R) = 1 \quad \forall R$$

Distribution of the added bond vectors assumed to be **Gaussian**

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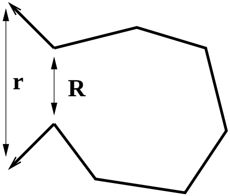

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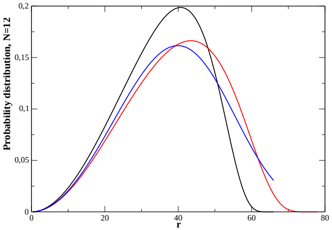
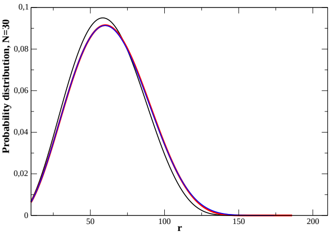
Conditional probability distribution $S(r|R)$

Effective Gaussian approach
$\rightarrow$ Approximate $P_N(R)$ by a Gaussian chain that gives the correct **persistence length**
The Gaussian approximation can be rough for small N but quite good for the extention of the chain





Partition function

- Construction of the reduced partition function of the hairpin
  - Partition function of a chain for a given end-to-end distance R

$$Z_N(R) = Z_N^{\text{tot}} P_N(R)$$

  - Suppose that we add one bond at each end

$$Z_{N+2}(r_{M-1}) = P_{N+2}(r_{M-1}) Z_{N+2}^{tot}$$

  - Introducing the S function

$$Z_{N+2}(r_{M-1}) = Z_{N+2}^{tot} \int dr_M S(r_{M-1}|r_M) P_N(r_M)$$

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Partition function

- Construction of the reduced partition function of the hairpin
  - Then we put the additional interactions according to the PBD model

$$Z_{N+2}(r_{M-1}) = Z_{N+2}^{tot} \, e^{-\beta V(r_{M-1})} \int dr_M \; e^{-\beta(W(r_{M-1},r_M)+V(r_M))} S(r_{M-1}|r_M) P_N(r_M)$$

  - Finally we extend the process to the hairpin

$$Z(r) = Z_{\mathrm{loop}(N+2(M-1))} e^{-\beta V(r)} \times \int_0^{+\infty} \prod_{i=2}^{M} dr_i \prod_{i=2}^{M} S(r_{i-1}|r_i) e^{-\beta[V(r_i)+W(r_{i-1},r_i)]} P_N(r_M)$$

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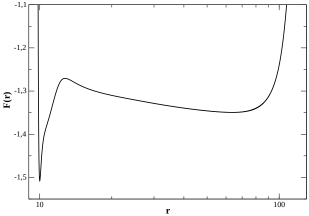
Melting curves

- Free energy landscape

$$F(r) = -k_b T \ln\ Z(r)$$



$\rightarrow$ The shape of $F(r)$ justifies the image of the two-state system

- Melting curves

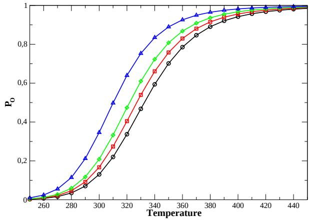
$$f = \frac{K_{eq}}{1+K_{eq}} = \frac{\frac{P_O}{P_C}}{1+\frac{P_O}{P_C}} = P_O = \frac{\int_{r_c}^{+\infty} drZ(r)}{\int_0^{+\infty} drZ(r)}$$

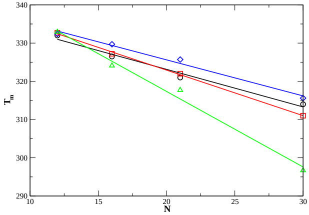
FRC Model

- Melting curves equivalent to poly(T)

k=0.025 eV.$Å^{-2}$, α=6.9 $Å^{-1}$, $\delta = 0.35$, $\rho = 5$. D=0.112 eV, $\theta = 50°$,○: N=12: □: N=16; ◇: N=21; △: N=30

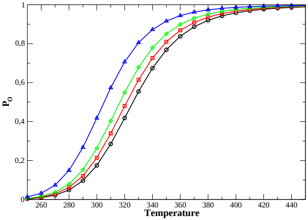
□: D=0.112 eV, $\theta = 50°$;
◇: D=0.119 eV, $\theta = 45°$;
△: D=0.100 eV, $\theta = 64°$

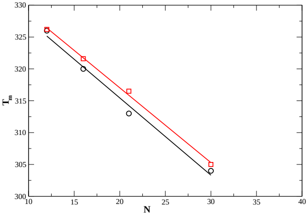




FRC model

- Melting curves equivalent to poly(A)
  D=0.112 eV, k=0.025 eV.Å^{-2}, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$,
  $\theta = 48°$, ○: N=12; □: N=16; ◇: N=21; △: N=30

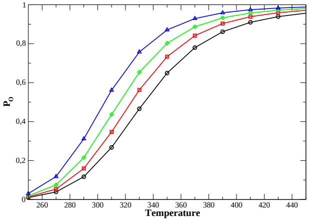


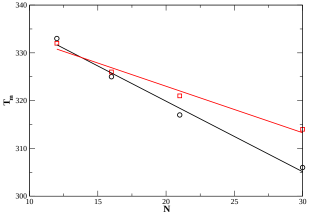


N	$\theta = 50°$, $\frac{\Delta P}{\Delta T} T_m$	$\theta = 48°$, $\frac{\Delta P}{\Delta T} T_m$	Poly(T) (Exp)	Poly(A) (Exp)
12	3.6	3.7	11	9
16	3.7	3.8	11	8.5
21	3.7	3.8	11	8.5
30	3.9	4.0	11	7.5

KP model

- Melting curves equivalent to poly(T)
  D=0.107 eV, *k*=0.025 eV.Å^{-2}, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$, ϵ $=$ 0.0018 *eV*.Å^{-2}. •: N=12; □: *N*=16; ◇: *N*=21; △: *N*=30

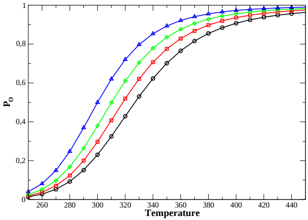


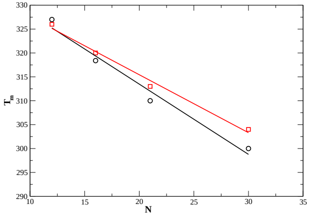


N	ϵ=0.0018 eV.Å^{-2}, $\frac{\Delta P}{\Delta T} T_m$	Poly(T) (Exp), $\frac{\Delta P}{\Delta T} T_m$
12	3.2	11
16	3.4	11
21	3.45	11
30	3.8	11

KP model

- Melting curves equivalent to poly(A)
  D=0.107 eV, k=0.025 eV.Å^{-2}, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$, $\epsilon = 0.00195$ eV.Å^{-2}; ●: N=12; □: N=16; ⋄: N=21; △: N=30





N	ϵ=0.00195 eV.Å^{-2}, $\frac{\Delta P}{\Delta T} T_m$	Poly(A) (Exp), $\frac{\Delta P}{\Delta T} T_m$
12	3.25	9
16	3.45	8.5
21	3.6	8.5
30	3.8	7.5

Theoretical predictions

- Transition state theory

$$\mathbf{C} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{T} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{O}$$

$$k_{op}^{-1} = k_1^{-1} + \frac{\bar{C}_C}{\bar{C}_O} k_{-2}^{-1}$$

$$k_{cl}^{-1} = k_{-2}^{-1} + \frac{\bar{C}_O}{\bar{C}_F} k_1^{-1}$$

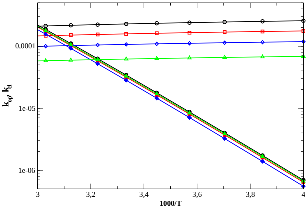
  - The system is evolving on a one-dimensional free energy surface

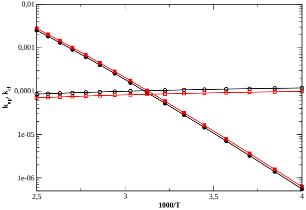
$$k_{op}^{-1} = Z_C \int_{-\infty}^{+\infty} dr \, \frac{e^{-\beta F(r)} J^2(r)}{D(r)} = \frac{Z_C}{Z_O} k_{cl}^{-1}$$

$$J(r) = \begin{cases} \int_{-\infty}^{r} dx \, \frac{e^{-\beta(F(x)-F(r))}}{Z_C} & \forall\, r < r_T \\ \int_{r}^{+\infty} dx \, \frac{e^{-\beta(F(x)-F(r))}}{Z_O} & \forall\, r > r_T \end{cases}$$

FRC model

- Rates of opening and closing
  D=0.112 eV, k=0.025 eV.Å^{-2}, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$.
  Left: $\theta = 50°$; $\bullet$: N=12; $\square$: N=16; $\diamond$: N=21; $\triangle$: N=30.
  Right: N=21, black: $\theta = 50°$, red:$\theta = 48°$





	E_{op}, model	E_{cl}, model	E_{op}, exp	E_{cl}, exp
Poly(T)	11.5	-0.33	32	3.4
Poly(A)	11.5	-0.33	32	17.4

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  D=0.107 eV, k=0.025 eV.Å^{-2}, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$.
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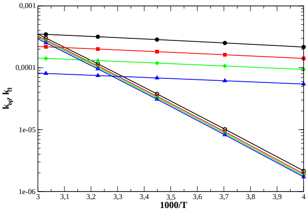
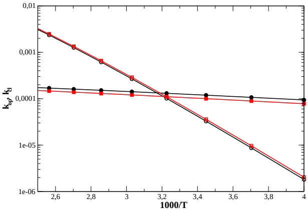
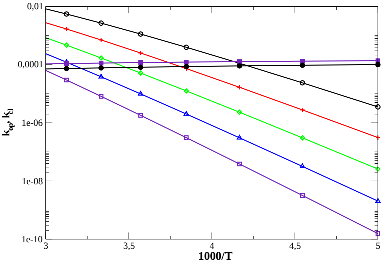
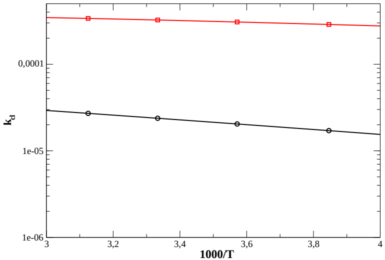




	E_{op}, model	E_{cl}, model	E_{op}, exp	E_{cl}, exp
Poly(T)	10	+1	32	3.4
Poly(A)	10	+1	32	17.4

- Effect of D and ϵ on the kinetics





○: D=0.08 eV; □: D=0.09 eV; ◇: D=0.10 eV; △: D=0.11 eV, ×: D=0.12 eV

○: ϵ=0.0040 eV.Å^{-2}, □: ϵ=0.0010 eV.Å^{-2}

Discussion

- Thermodynamics
  - We are able to describe the dependance of T_m with the loop length for poly(T) and poly(A)
  - We get too large transition widths
- Kinetics
  - Our results are in qualitative agreements with the experiments
  - We can describe the kinetics of poly(T)
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- We have studied the self assembly of DNA Hairpins with two models
- Lattice model
  - The results are qualitatively good
  - It helps us in the understanding of the physics of the system
- PBD-Polymer model
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- Microscopic model
  →Modelling of all the interactions between the atoms
  - Potential describing the stretching of covalent bonds

$$k_{\mathrm{bond}}\left(r-r_0\right)^2$$

  - Potential of angular rigidity

$$k_f\left(\theta-\theta_0\right)^2$$

  - Potential of torsion

$$k_g(1+\cos\phi)$$

  - Lennard-Jones potential for non-bonding interactions

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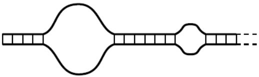
- Poland-Scheraga model
  - Model consists on an alternating sequence of ordered and unordered states



  - The ordered state is energetically favoured over an unordered state

$$\rightarrow \quad w = \exp\left(-\frac{\epsilon}{k_B T}\right)$$

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- The phase transition is governed by the value of c

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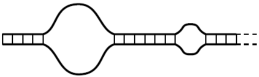

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$$\rightarrow\ w = \exp\left(-\frac{E}{k_b T}\right)$$

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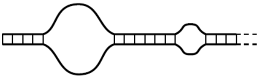

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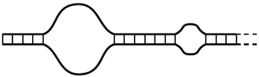

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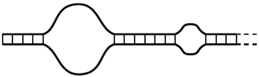

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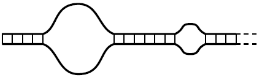

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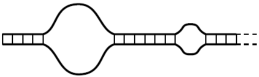

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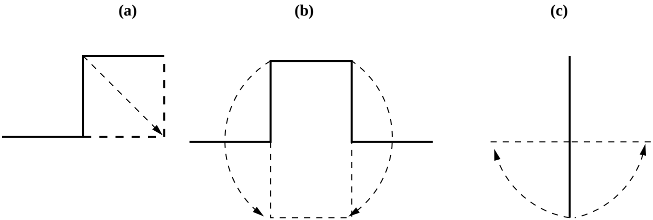
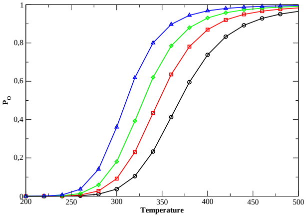
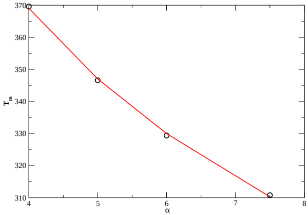
- Monte Carlo simulation in the canonical ensemble
  - Minimization of the Free Energy
    $\rightarrow$ Find the **Thermodynamic** properties of the system
  - Try to deduce the **Kinetics** using MC-step
    $\rightarrow$ Selection of local motions of the chain



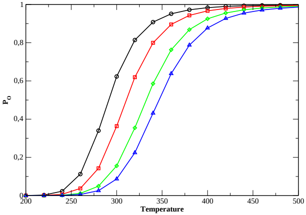
- Effect of the width of the Morse potential
  D=0.112 eV, k=0.025 eV.Å^{-2}, $\delta = 0.35$, $\rho = 5$, $\theta = 50^\circ$ and N=21. $\bullet$: α=4.0 Å^{-1}; $\square$: α=5.0 Å^{-1}; $\diamond$: α=6.0 Å^{-1}; $\triangle$: α=7.5 Å^{-1}

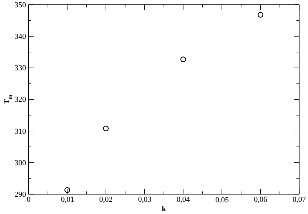




a (Å^{-1})	$S \neq 1$, $\frac{\Delta P}{\Delta T} T_m$
4	3.4
5	3.5
6	3.8
7.5	4.1

- Effect of the rigidity of the stem
  D=0.112 eV, α=6.9 Å^{-1}, $\delta = 0.35$, $\rho = 5$, $\theta = 50°$ and N=21. ●: k=0.010 eV.Å^{-2}; □: k=0.020 eV.Å^{-2}; ⋄: k=0.040 eV.Å^{-2}; △: k=0.060 eV.Å^{-2}





k(eV.Å^{-2})	$S \neq 1$, $\frac{\Delta P}{\Delta T} T_m$
0.01	4.1
0.020	4
0.040	3.8
0.06	3.7