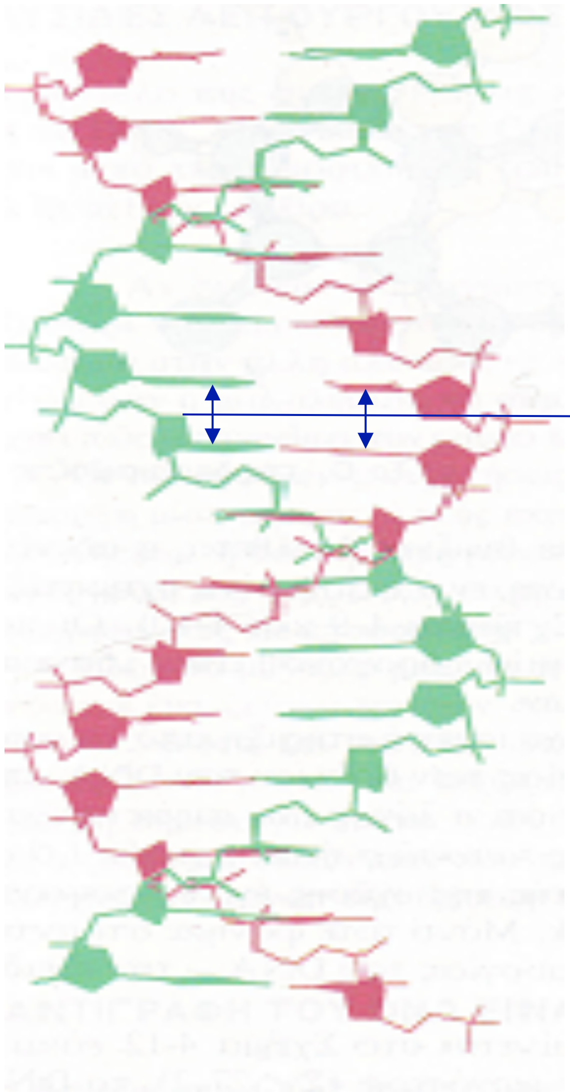
Complex dynamics of a nonlinear Hamiltonian model of DNA

George Kalosakas

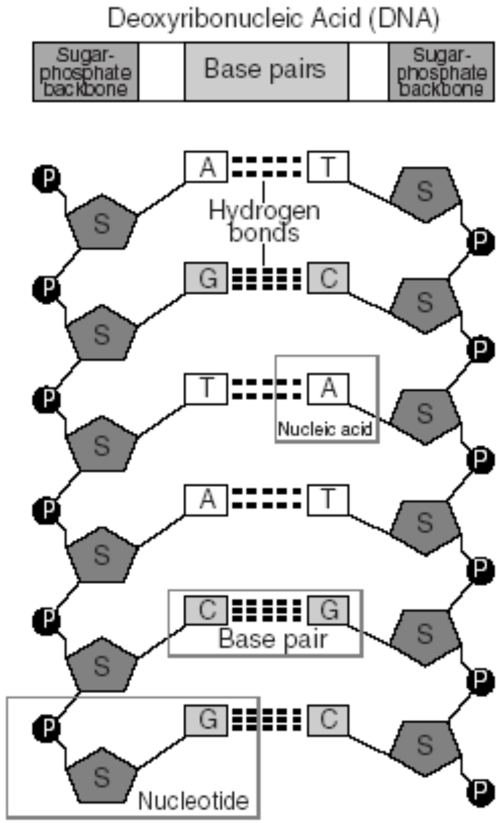
Department of Materials Science
University of Patras
Greece

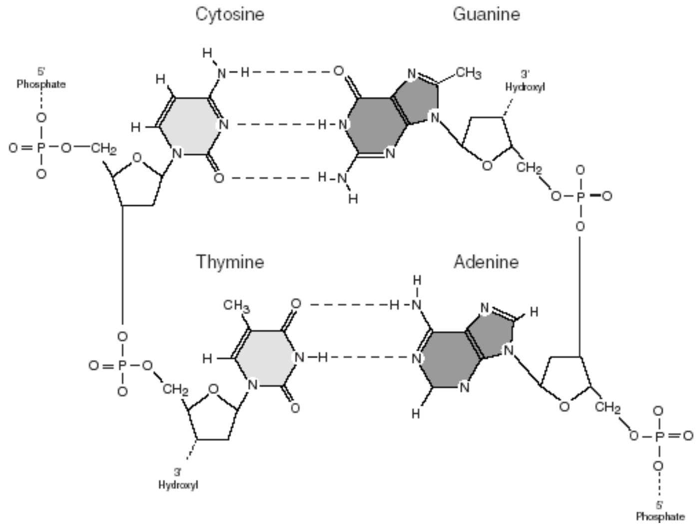
DNA structure



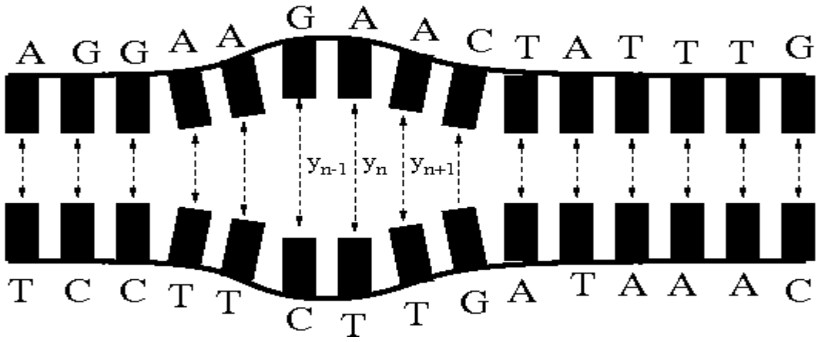
overlap of π molecular orbitals (made up by p_z atomic orbitals).

Stacking interaction.





Peyrard-Bishop-Dauxois (PBD) Model



Peyrard, Bishop, *Phys. Rev. Lett.* ***62***, 2755 (1989)

Dauxois, Peyrard, Bishop, *Phys. Rev. E 47*, R44 (1993)

A coarse-grained model, grouping the nucleotides in one unit

$$H = \sum_n \left[\frac{1}{2} m \dot{y}_n^2 + V(y_n) + W(y_n, y_{n-1}) \right]$$

base pair potential: $$V(y_n) = D_n \left(e^{-a_n y_n} - 1 \right)^2$$

π-stacking interaction: $$W(y_n, y_{n-1}) = \frac{k}{2} \left[1 + \rho e^{-\beta(y_n + y_{n-1})} \right] (y_n - y_{n-1})^2$$

Parameter values [from Campa, Giansati, *Phys. Rev. E* **58**, 3585 (1998)]

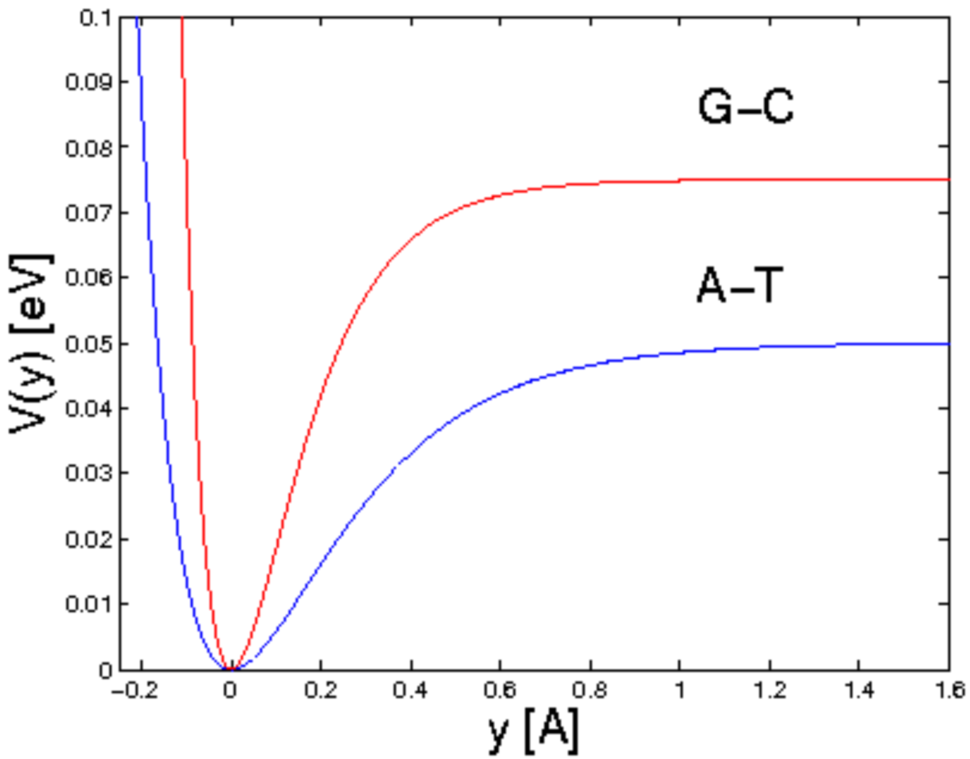
$$V(y_n) = D_n\left(e^{-a_n y_n} - 1\right)^2$$

A-T base pair:

$$D_n = 0.05 eV, \quad a_n = 4.2 A^{-1}$$

G-C base pair:

$$D_n = 0.075 eV, \quad a_n = 6.9 A^{-1}$$



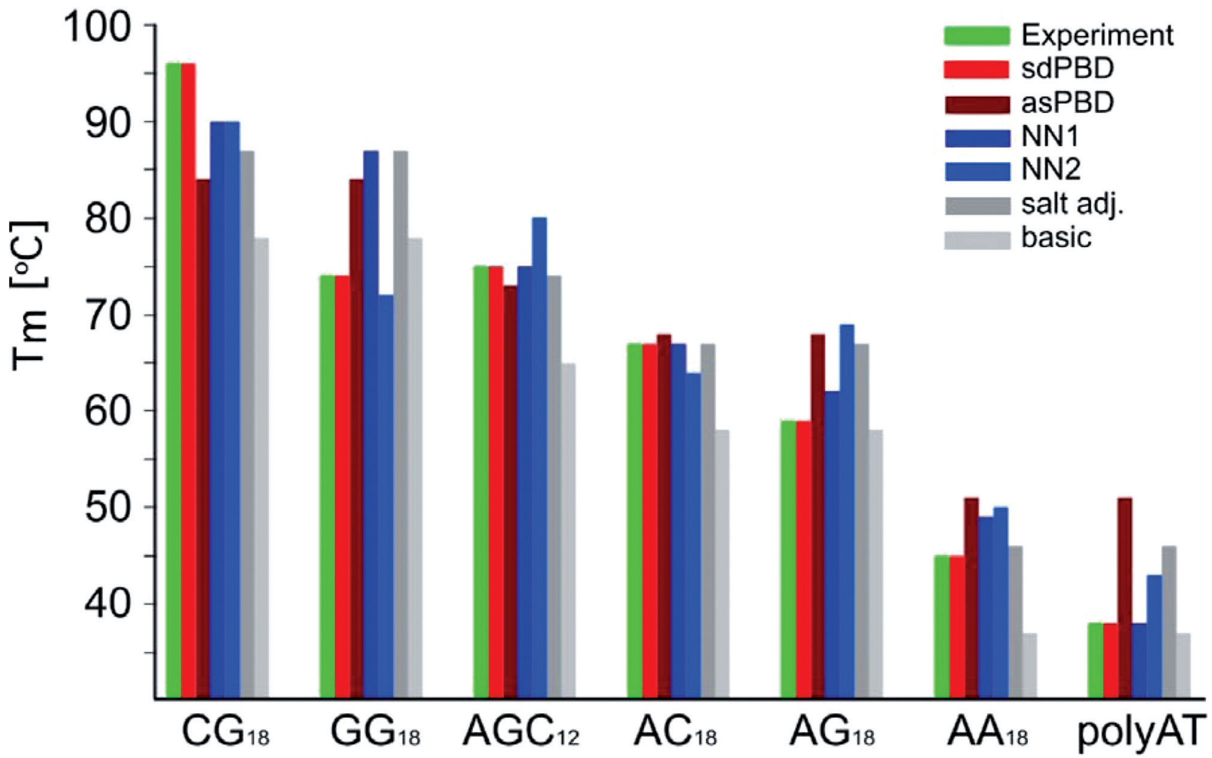
$$W(y_n, y_{n-1}) = \frac{k}{2}\left[1 + \rho e^{-\beta(y_n + y_{n-1})}\right](y_n - y_{n-1})^2$$

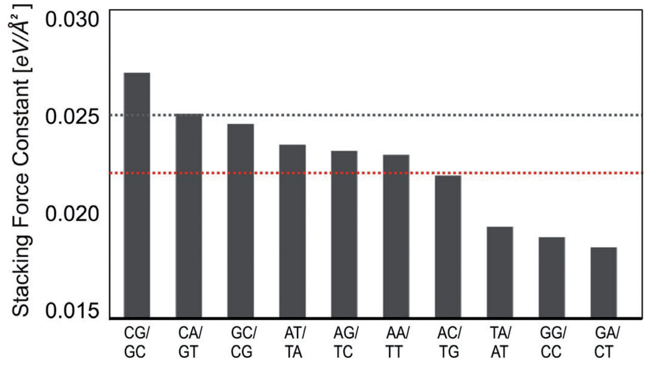
$$k = 0.025 eV/A^2, \quad \rho = 2, \quad \beta = 0.35 A^{-1}$$

$$m = 300 a.m.u.$$

(nucleotide mass)

Improvement of the PBD model: sequence dependent stacking parameters





Homogeneous and periodic DNA sequences exhibit large deviations in melting temperatures

dsDNA	Melting Temperature, T_m (°C)	Stacking constant
$(G)_{36}.(C)_{36}$	74	k_{GG}
$(GC)_{18}.(GC)_{18}$	96	k_{GC}, k_{CG}
$(AC)_{18}.(GT)_{18}$	67	k_{AC}, k_{CA}
$(AG)_{18}.(CT)_{18}$	59	k_{AG}, k_{GA}
$(A)_{36}.(T)_{36}$	45	k_{AA}
$(AGC)_{12}.(GCT)_{12}$	75	k_{AG}, k_{GC}, k_{CA}
poly(AT).poly(AT)[a]	38[a]	k_{AT}, k_{TA}

Alexandrov, Gelev, Monisova, et al., *Nucleic Acids Res. 37*, 2405 (2009)

Successes of the PBD Model

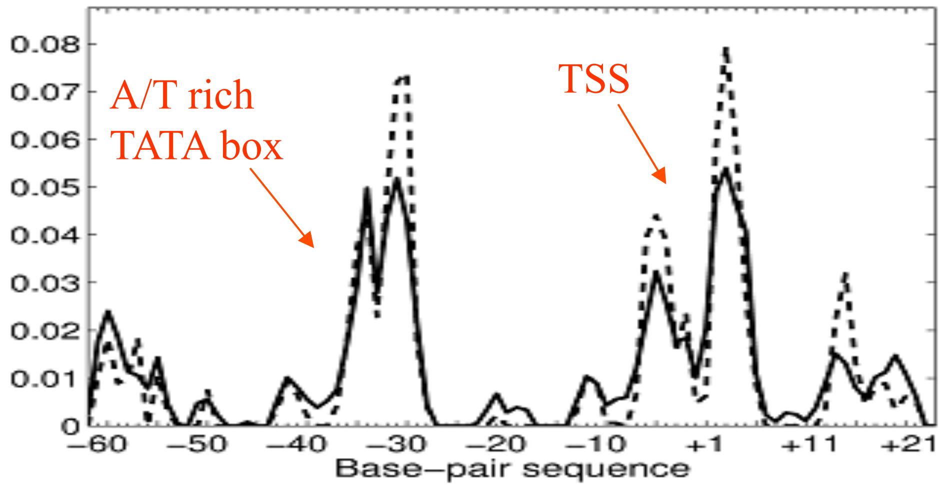
- Predicts a sharp melting (denaturation) transition of long DNA chains.
  Dauxois, Peyrard, Bishop, *Phys. Rev. E 47*, R44 (1993)
- Quantitatively reproduces melting curves of short heterogeneous and periodic DNA segments (20-40bp).
  Campa, Giansati, *Phys. Rev. E* ***58***, 3585 (1998)
  Alexandrov, Gelev, Monisova, et al., *Nucleic Acids Res. 37*, 2405 (2009)
- Provides the characteristic multi-step melting observed in single heterogeneous DNA molecules.
  Cule, Hwa, *Phys. Rev. Lett. 79*, 2375 (1997)
- Accurately predicts the position of large base pair openings due to thermal fluctuations in DNA gene promoter sequences (at functionally relevant sites).
  Choi, Kalosakas, Rasmussen, et al., *Nucleic Acids Res. 32*, 1584 (2004)
  Alexandrov, Gelev, Yoo, et al., *PLoS Comput. Biol. 5*, e1000313 (2009)
  Apostolaki, Kalosakas, *Phys. Biol. 8*, 026006 (2010)
  Huang, Lindblad, *J. Biol. Eng. 7*, 10 (2013)
- Guides the design of promoter variants controlling transcriptional activity through genetic engineering.
  Alexandrov, Gelev, Yoo, et al., *Nucleic Acids Res. 38*, 1790 (2010)

Positions of large thermal openings in viral gene promoters

Adenovirus Major Late Promoter

-62 -40
5' -GC CACGTGACCA GGGGTCCCCG CCGGGGGGGT ATAAAAGGGG
GCGGACCTCT GTTCGTCCTC ACTGTCTTCC GGATCGCTGT CCAG- 3'
-20 +1 +24

→ S1 nuclease selectively cleaves ssDNA.
→ Sufficiently sensitive reaction with *relatively large openings* of ds DNA

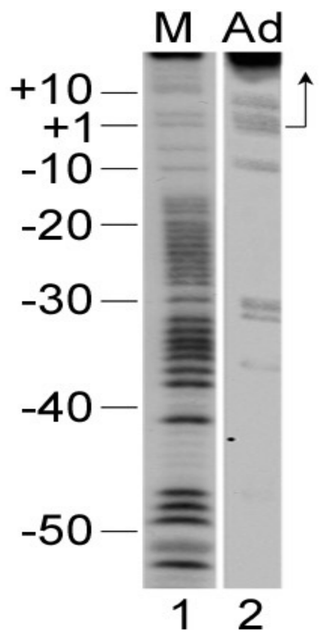


PBD
MD simulations
T=300K

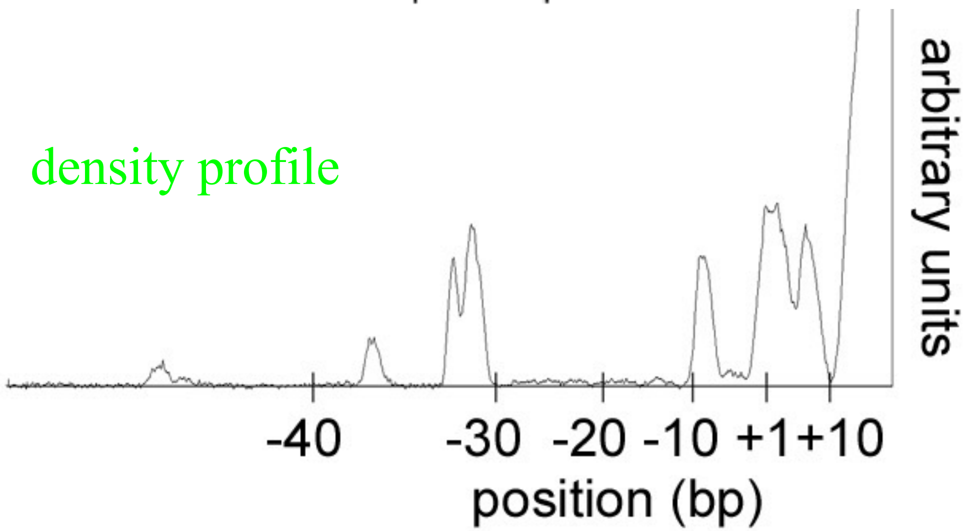
width: 10 bp

threshold:
2.1 A (thick)
1.4 A (dotted)

S1 nuclease cleavage reactions

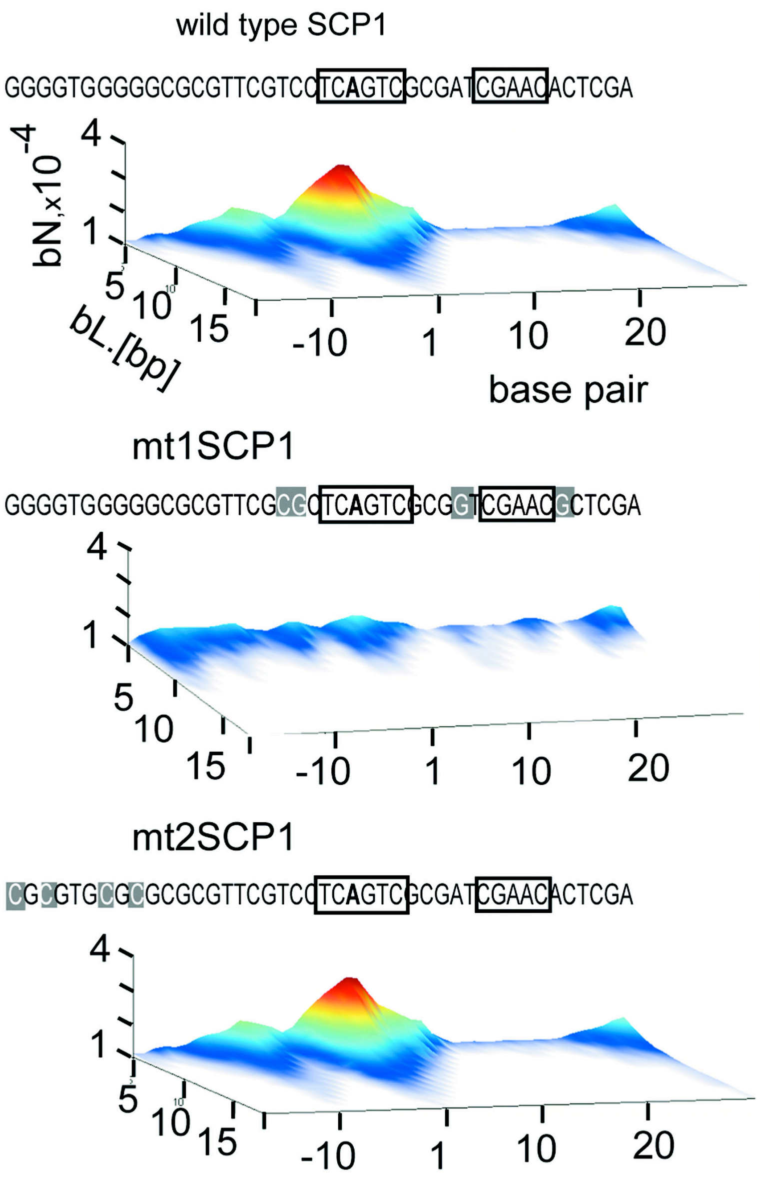


density profile



Choi, Kalosakas, Rasmussen, et al., *Nucleic Acids Res.* ***32***, 1584 (2004)
Kalosakas, Rasmussen, Bishop, et al., *Europhys. Lett.* ***68***, 127 (2004)

Separate contributions of DNA dynamics and TF binding to transcriptional activity



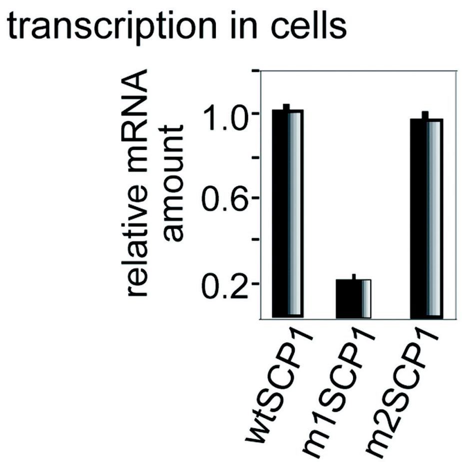
SCP1 (artificially constructed) superpromoter

EPBD
LMD simulations
T=300K

various widths

threshold: 3.5 A

Gel shift reactions confirm that TF binding is unaffected by the mutants



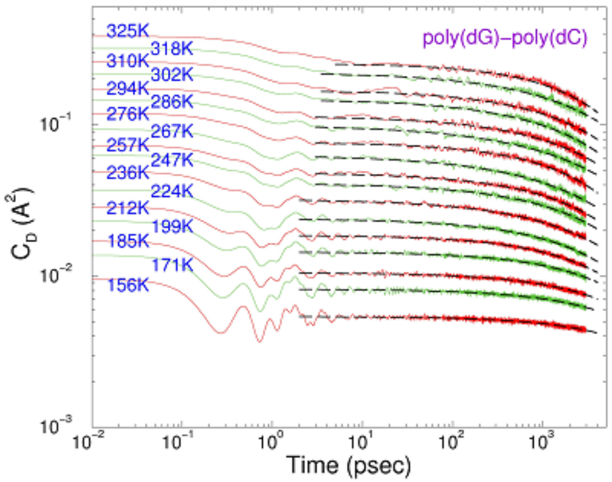
Suppression of TSS bubble
→ decrease in promoter activity
(independent of TF binding)

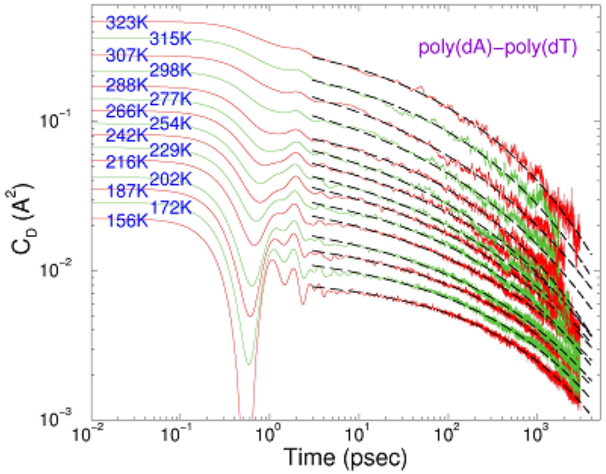
Alexandrov, Gelev, Yoo, et al., *Nucleic Acids Res. **38***, 1790 (2010)

Non-Exponential Decay of Fluctuations

Local displacement autocorrelation function

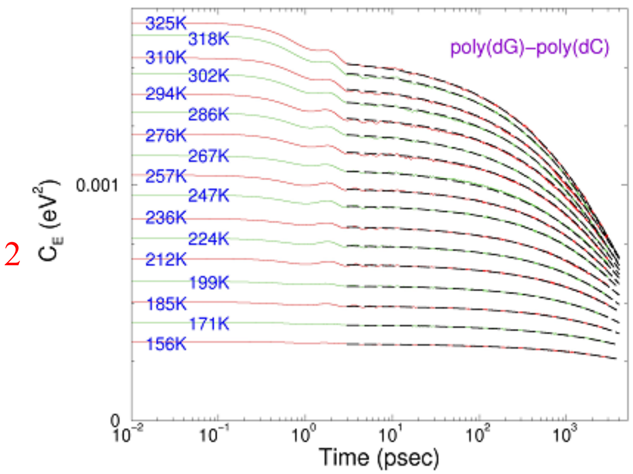
$$C_D(t) = \langle y_n(t) y_n(0) \rangle - \langle y_n \rangle^2$$

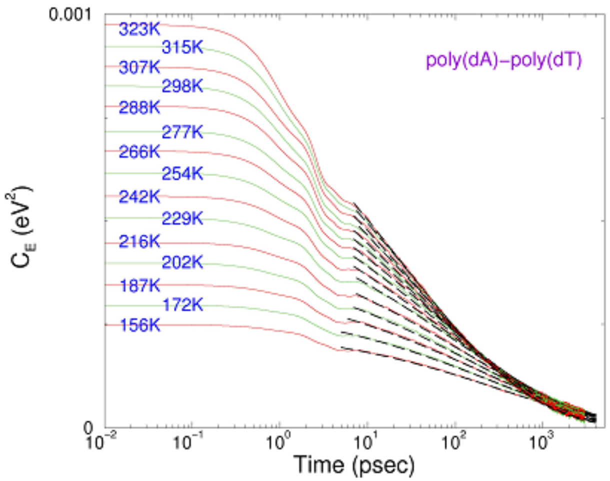




Local energy autocorrelation function

$$C_E(t) = \langle E_n(t) E_n(0) \rangle - \langle E_n \rangle^2$$





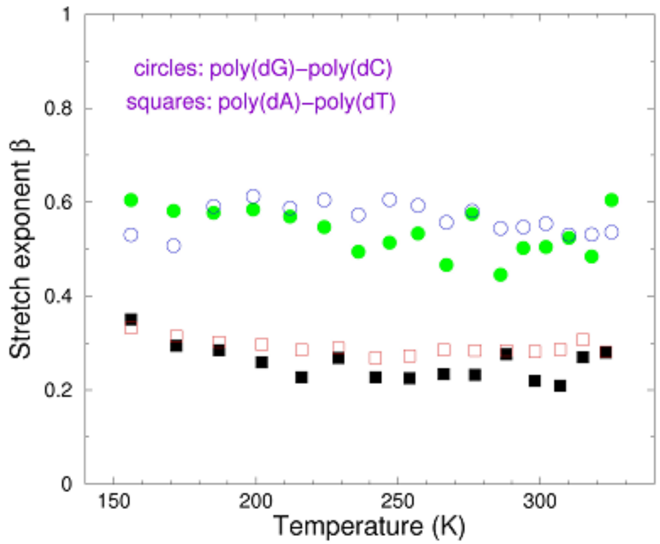
Kalosakas, Ramsussen, Bishop,
Chem. Phys. Lett. ***432***, 291 (2006)

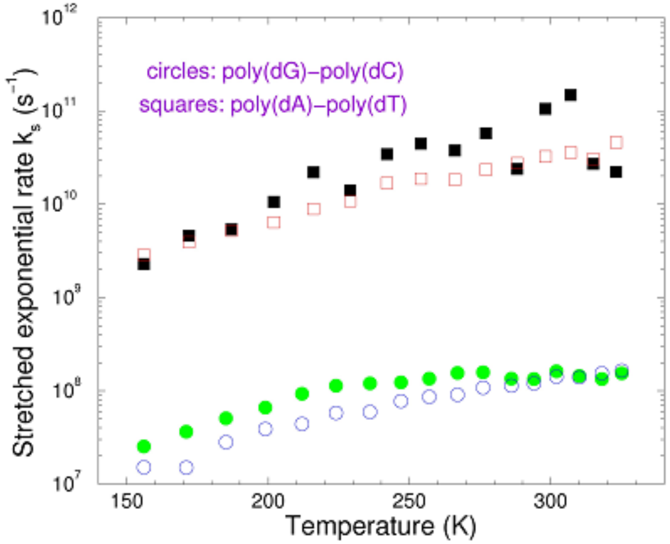
Slow fluctuations: $C_0 \cdot e^{-(k_s t)^{\beta}}$

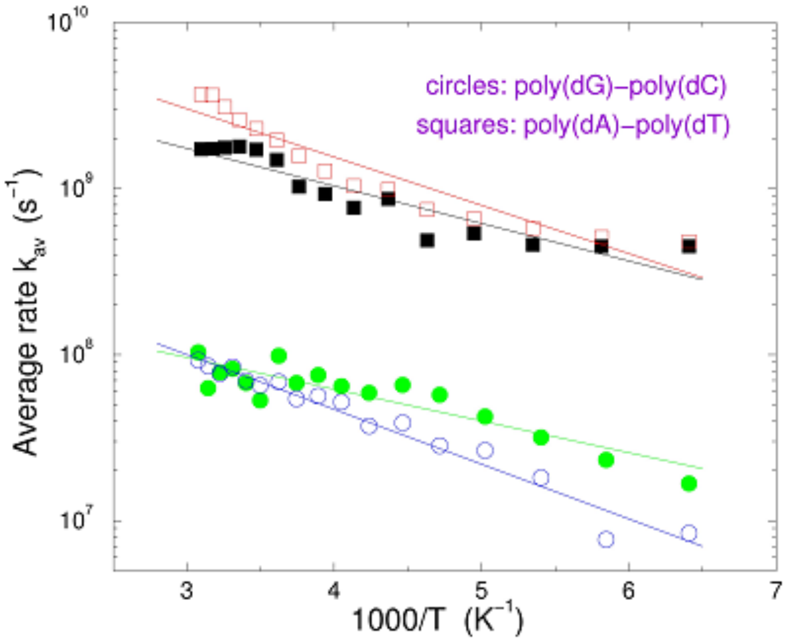
Quantifying the stretched exponential parameters

$$C_0 \cdot e^{-(k_s t)^{\beta}}$$

filled symbols --> C_D
open symbols --> C_E







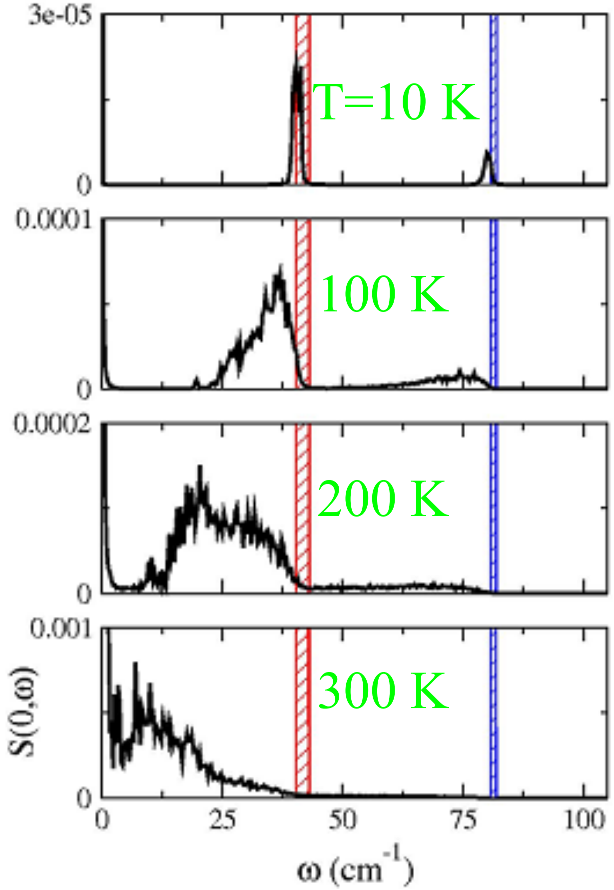
Arrhenius plot for the average rate

$$k_{av} = k_s \frac{\beta}{\Gamma(1/\beta)}$$

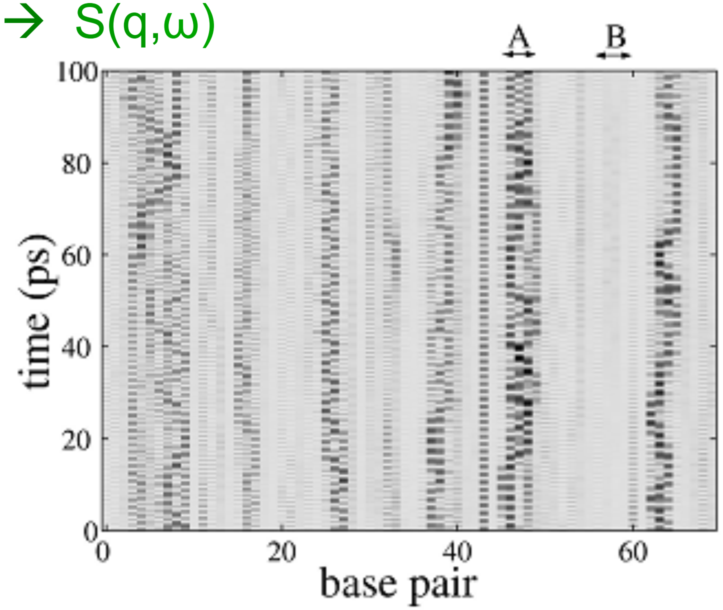
Activation energies 4-6 kJ/mol

T-dependent Structure Factor

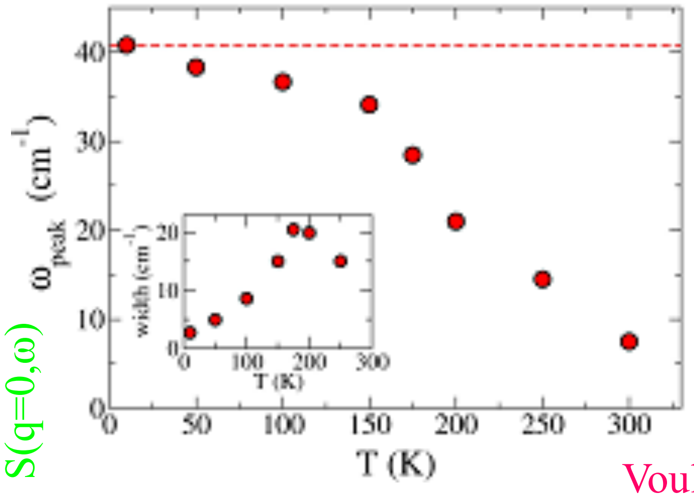
Time evolution of a thermalized T7 bacteriophage sequence (~70bp) → S(q,ω)

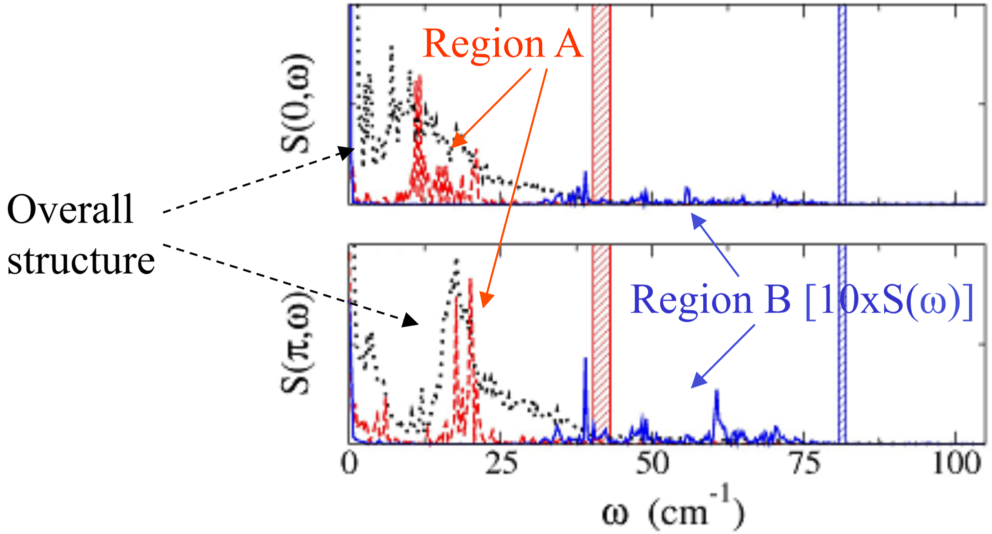


Density plot of base-pair stretchings at T=300 K



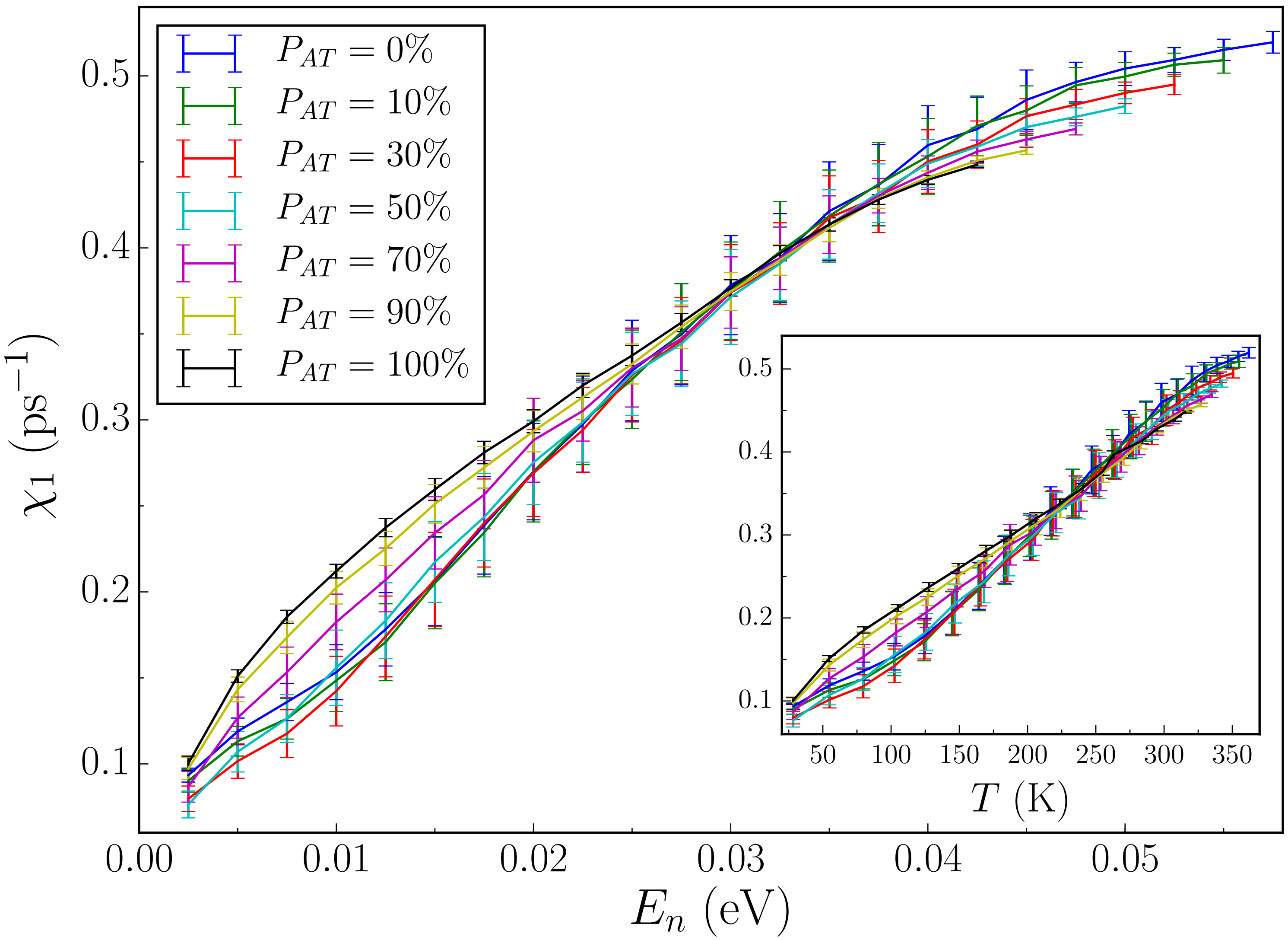
Position of the peak of S(q=0,ω)





Voulgarakis, Kalosakas, Ramsussen, Bishop, *Nano Lett. 4*, 629 (2004)

Lyapunov exponents of heterogeneous DNA sequences



Hillebrand, Kalosakas, Schwellnus, Skokos, *Phys. Rev. E* ***99***, 022213 (2019)

Charge-Lattice interactions

$$H = H_{PBD} + H_{tight-binding} + H_{coupling}$$

$$H_{tight-binding} = -t\sum_n \left(C_n^+ C_{n+1} + C_n^+ C_{n-1}\right)$$

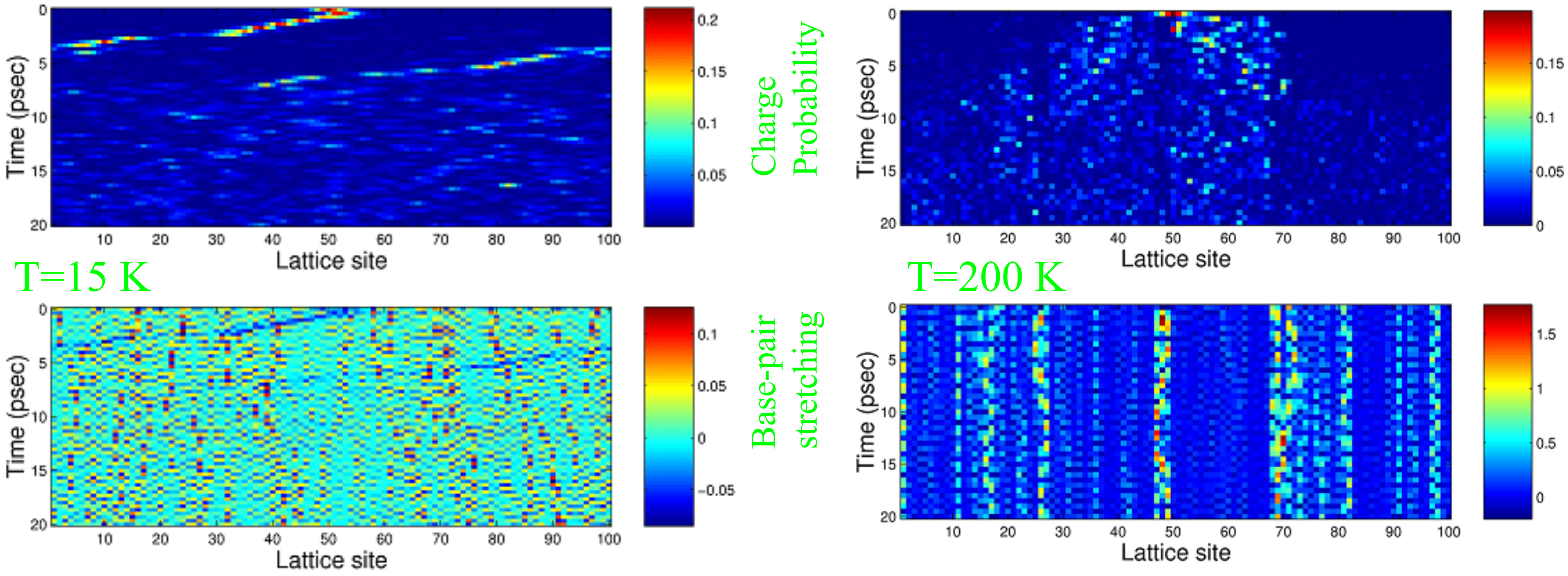
$$H_{coupling} = H_{Holstein} = \chi \sum_n y_n C_n^+ C_n$$

Semiclassical equations:

$$i\hbar \frac{d\Psi_n}{dt} = -t\left(\Psi_{n+1} + \Psi_{n-1}\right) + \chi y_n \Psi_n$$

$$m\frac{d^2 y_n}{dt} = -V'(y_n) - W'(y_n, y_{n-1}) - W'(y_{n+1}, y_n) - \chi\,|\Psi_n|^2$$

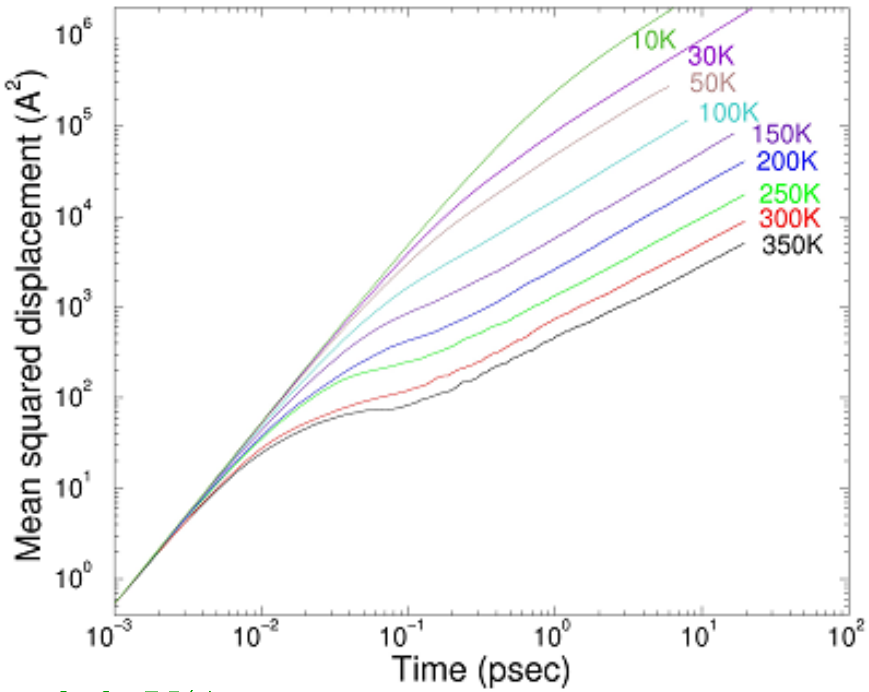
Komineas, Kalosakas, Bishop, *Phys. Rev. E* ***65***, 061905 (2002)



χ=0.6 eV/A, t=0.1 eV, initial condition: ground state at T=0 K (~20 sites polaron)

Kalosakas, Ramsussen, Bishop, *J. Chem. Phys.* ***118***, 3731 (2003)

Anomalous diffusion at higher T due to vibrational hot spots



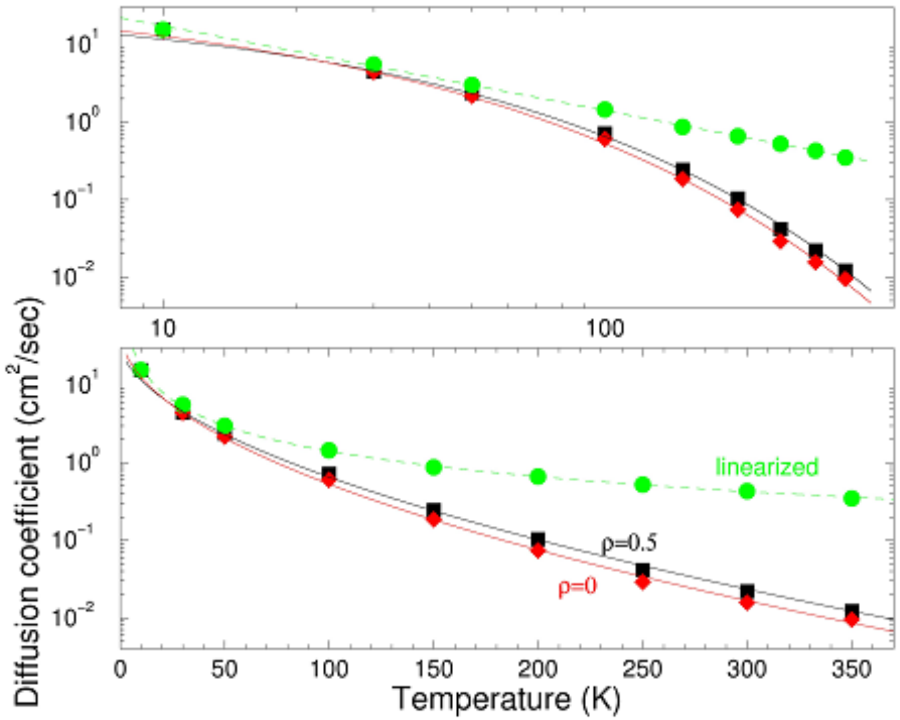
initial wavefunction localized at the site n_0 $\Psi_n(t=0)=\delta_{n,n_0}$

$$x^2(t)=\sum_n (nl)^2\left|\Psi_n(t)\right|^2-(n_0 l)^2$$

Anomalous diffusion (sublinear diffusion and a plateau) at higher T

χ=0.6 eV/A,
t=0.1eV

$$\langle x^2\rangle = 2D\cdot t$$ for large t

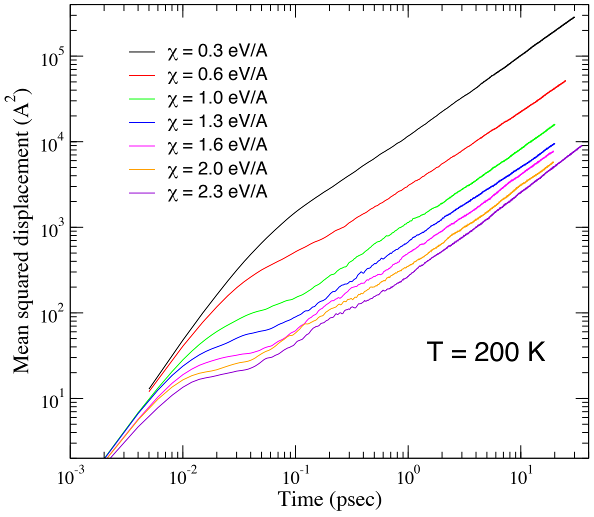


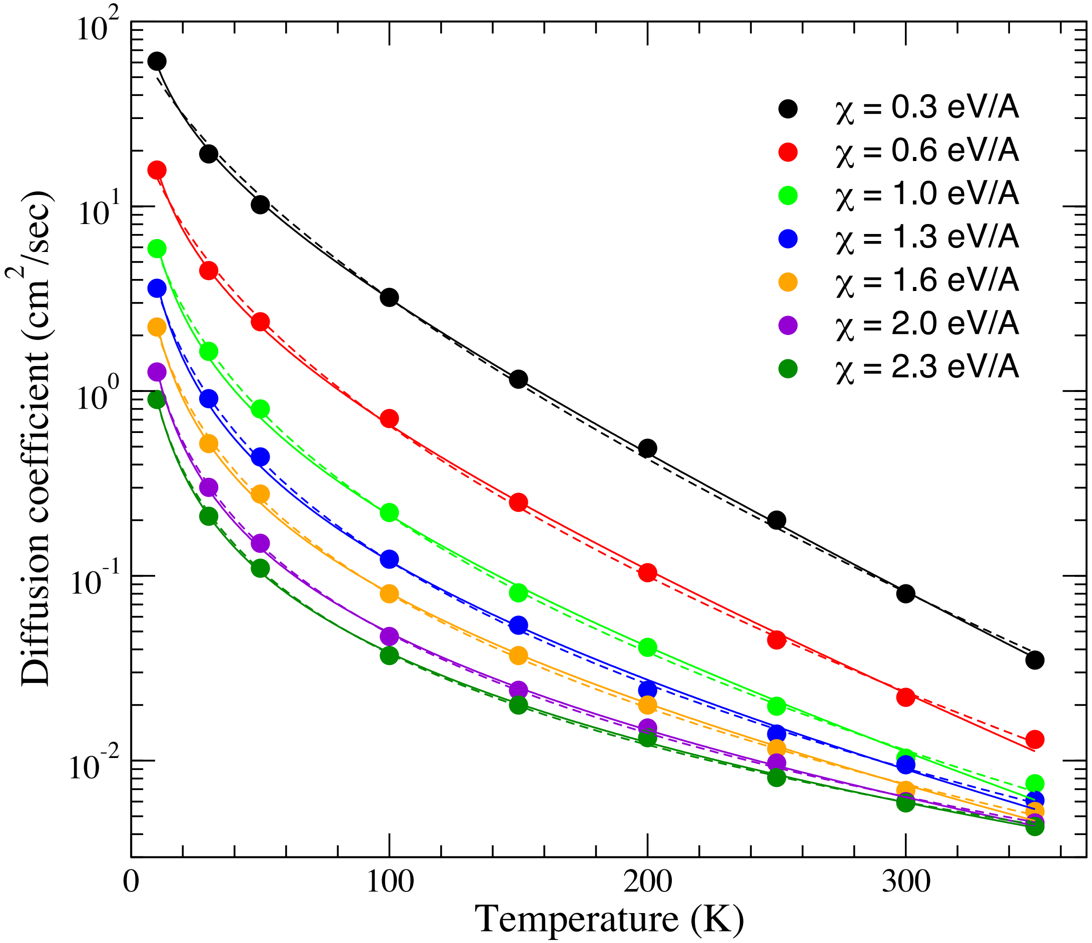
Nonlinear on-site interaction: modified exponential law

Linearized case: power law

Kalosakas, Ngai, Flach, *Phys. Rev. E. 71*, 061901 (2005)

Dependence of D(T) on the electron-phonon coupling constant





$$D(T) = C\frac{\exp(-T/T_1)}{T^p} \qquad (1)$$

$$D(T) = c \cdot \exp\left[-(T/T_0)^\beta\right] \qquad (2)$$

Solid lines: Eq. (1)   Dashed lines: Eq. (2)

Kalosakas, *Phys. Rev. E* ***84***, 051905 (2011)

Collaborators

A.R. Bishop, K.O. Rasmussen, P. Maniadis
Theoretical Division, Los Alamos Natl. Lab., USA

C.H. Choi, A. Usheva
Dept. of Medicine, Harvard Medical School, USA

N.K. Voulgarakis
Washington State Univ., USA

S. Komineas
Applied Mathematics Dept., Univ. of Crete, Greece

Ch. Skokos, M. Hillebrand
Mathematics & Applied Maths, Univ. of Cape Town, South Africa