Conference on Atomistic Simulations of Biomolecules:
towards a Quantitative Understanding of Life Machinery

Stability of Biopolymers in Aqueous Solution. GMPC Approach

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OUTLINE

- Biopolymers, helix-coil transition,

- Generalized Model of Polypeptide Chain (GMPC)
  1. Base model
  2. Model containing solvent (water)
  3. Reduced parameters
  4. Transition point

- Transition point for GMPC with solvent and ligand

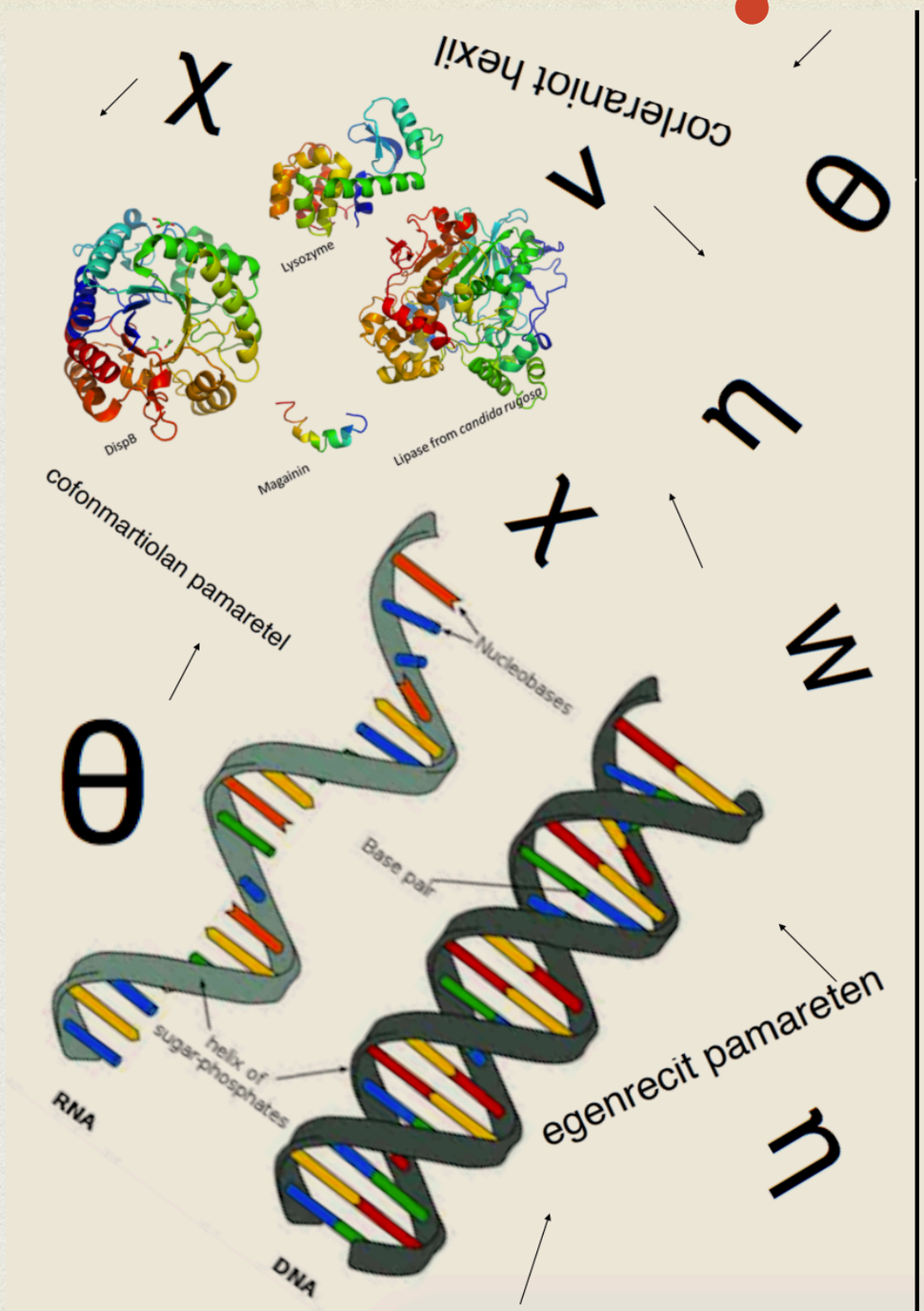
- Experimental data

- New results
  1. Hamiltonian
  2. Parameters' redefinition
  3. Conclusion

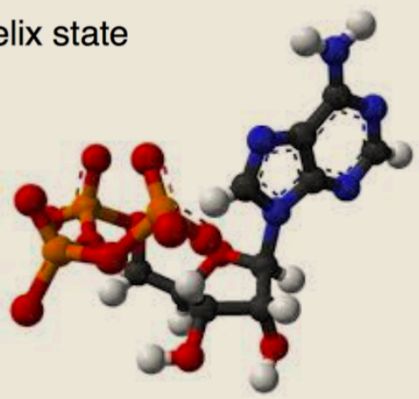
ENRICO FERMI

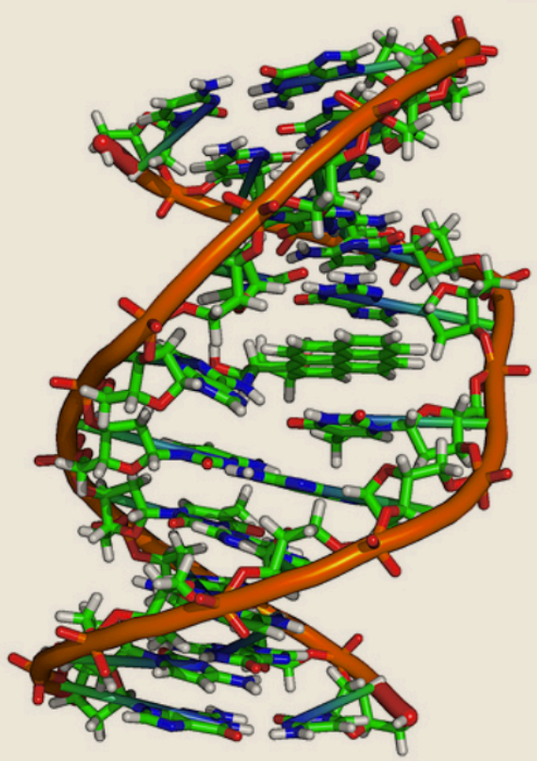
This is the main idea of Fermi theory of β decay

MOTIVATION FOR OUR GROUP



W	→	energetic parameter
Q	→	conformational parameter
θ	→	helicity degree
χ	→	correlation length
η	→	fraction of joints
v	→	average length of helix state
…		… …





https://web.stanford.edu/class/cs279/lectures/lecture2.pdf

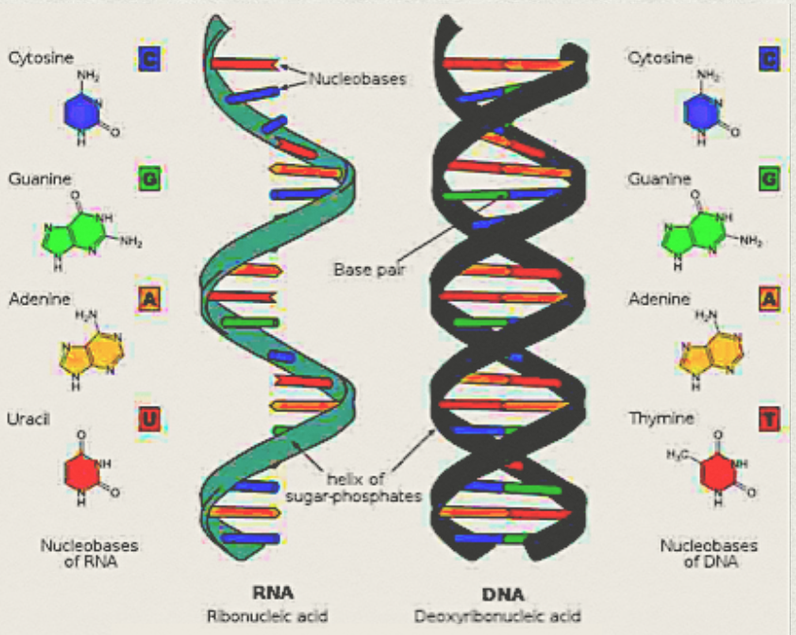
http://edtech2.boisestate.edu/jonfreer/502/jigsaw.html

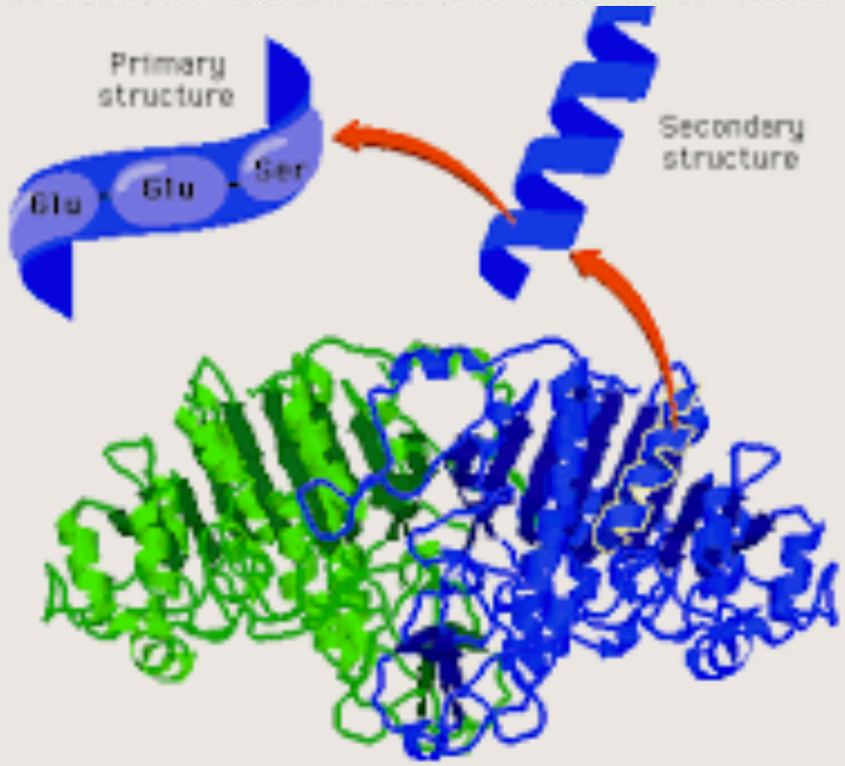
BIOPOLYMERS

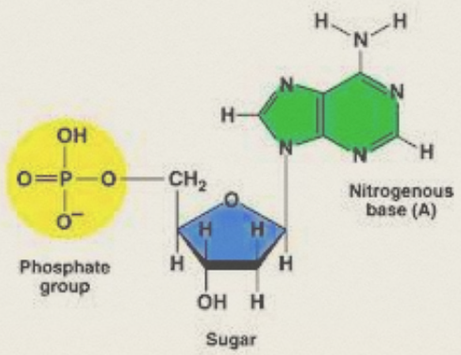
DNA, RNA, Proteins

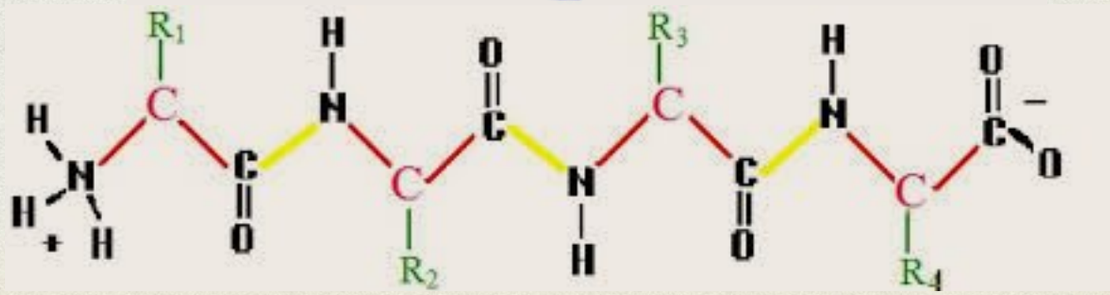
↓ ↓ ↓

polynucleotides, polypeptides



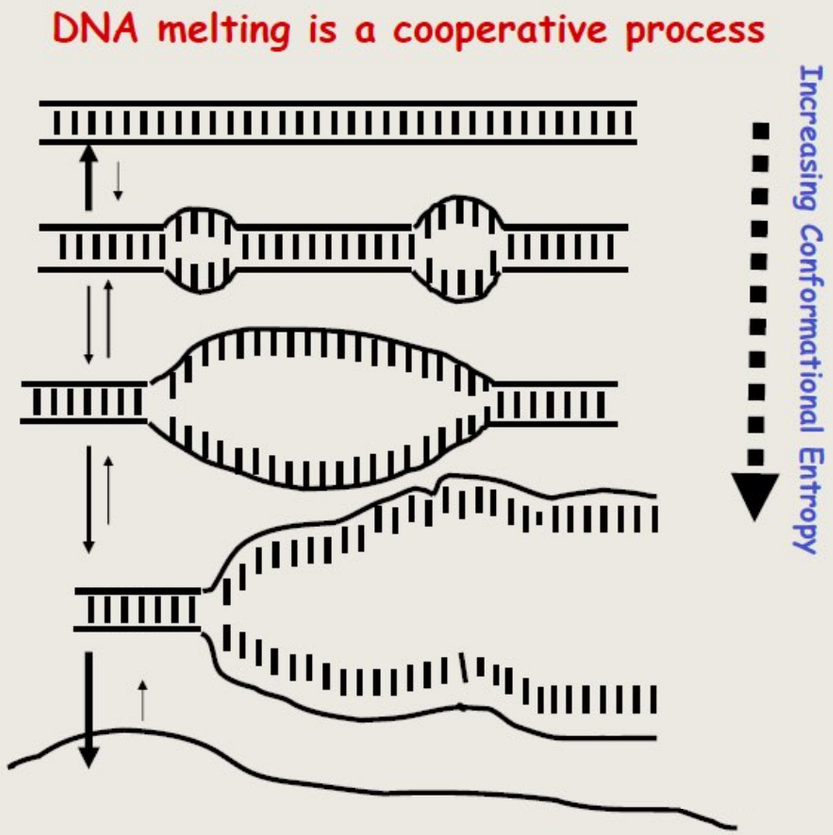


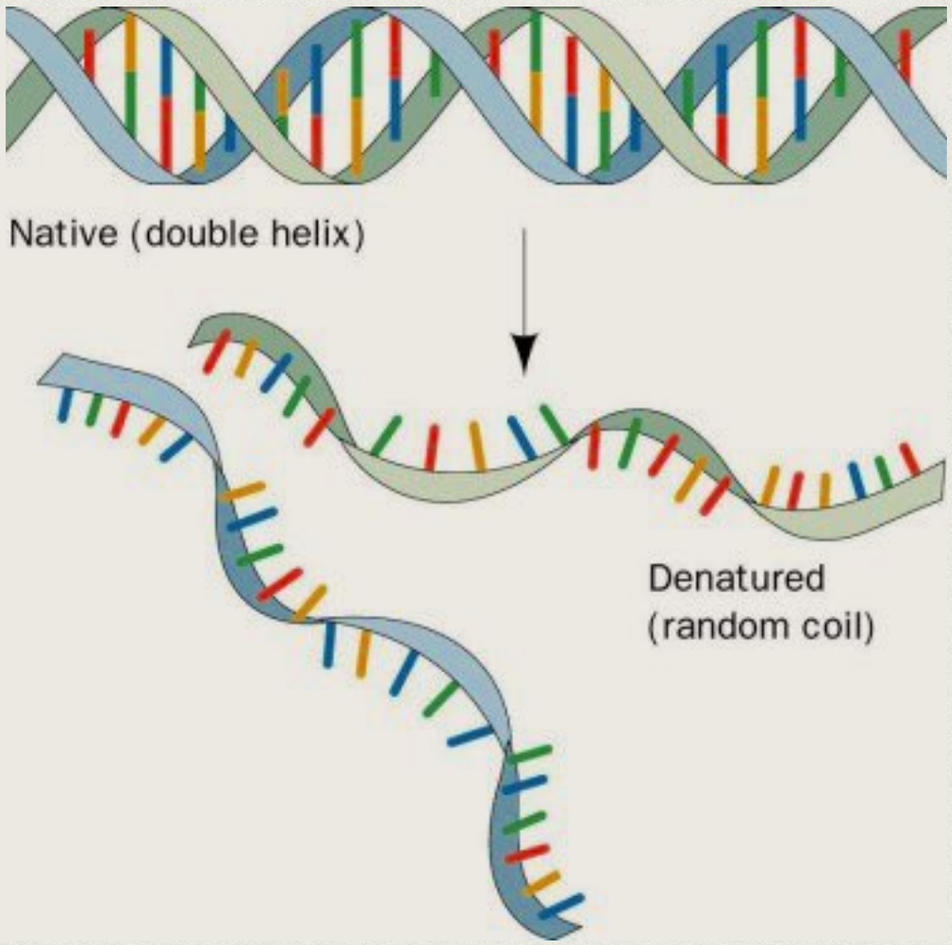




http://www.differencebetween.net/science/difference-between-dna-and-rna/

HELIX-COIL TRANSITION





https://chimmeral.wordpress.com/2014/04/11/dna-divorce-lets-get-denatured

http://www.wikiwand.com/en

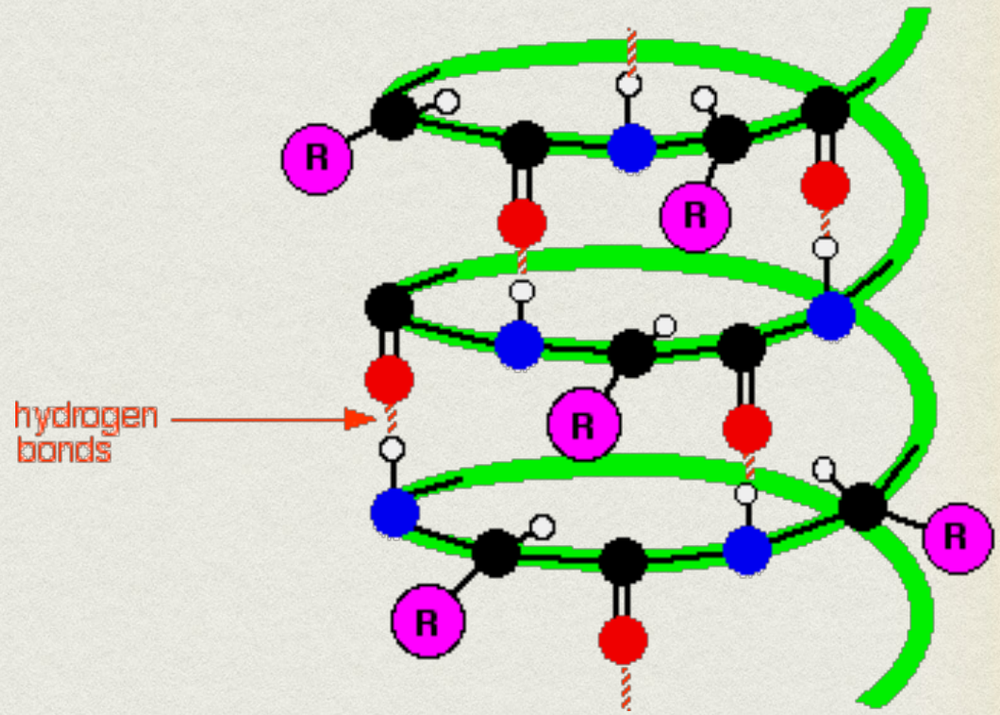
GMPC

- GMPC is a microscopic model, which describes helix-coil transition in biopolymers (DNA, RNA, proteins).

- In these systems conformations are correlated over some dimensional range Δ.

- Conformations are discrete and all of them have the same statistical weight.

- The Hamiltonian uses pure molecular microscopic parameters



http://www.chemguide.co.uk/organicprops/aminoacids/proteinstruct.html

BASE MODEL

$$-\beta H = J \sum_{i=1}^{N} \prod_{j=0}^{\Delta-1} \delta(\gamma_{i+j}, 1) = J \sum_{i=1}^{N} \delta_i^{\Delta}$$

$\gamma_i = 1, \ldots, Q$

$$J = \frac{U}{kT}$$

$$G = \begin{bmatrix} W & 1 & 0 & 0 & . & . & . & 0 \\ 0 & 0 & 1 & 0 & 0 & . & . & 0 \\ 0 & 0 & 0 & 1 & 0 & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & 0 & . & . & Q-1 \\ 1 & 1 & 1 & 1 & 1 & . & . & Q-1 \end{bmatrix}$$

$$\lambda^{\Delta-1}(\lambda - W)(\lambda - Q) = (W-1)(Q-1)$$

$$Z = TrG^N = \lambda_1^N$$

Model parameters:

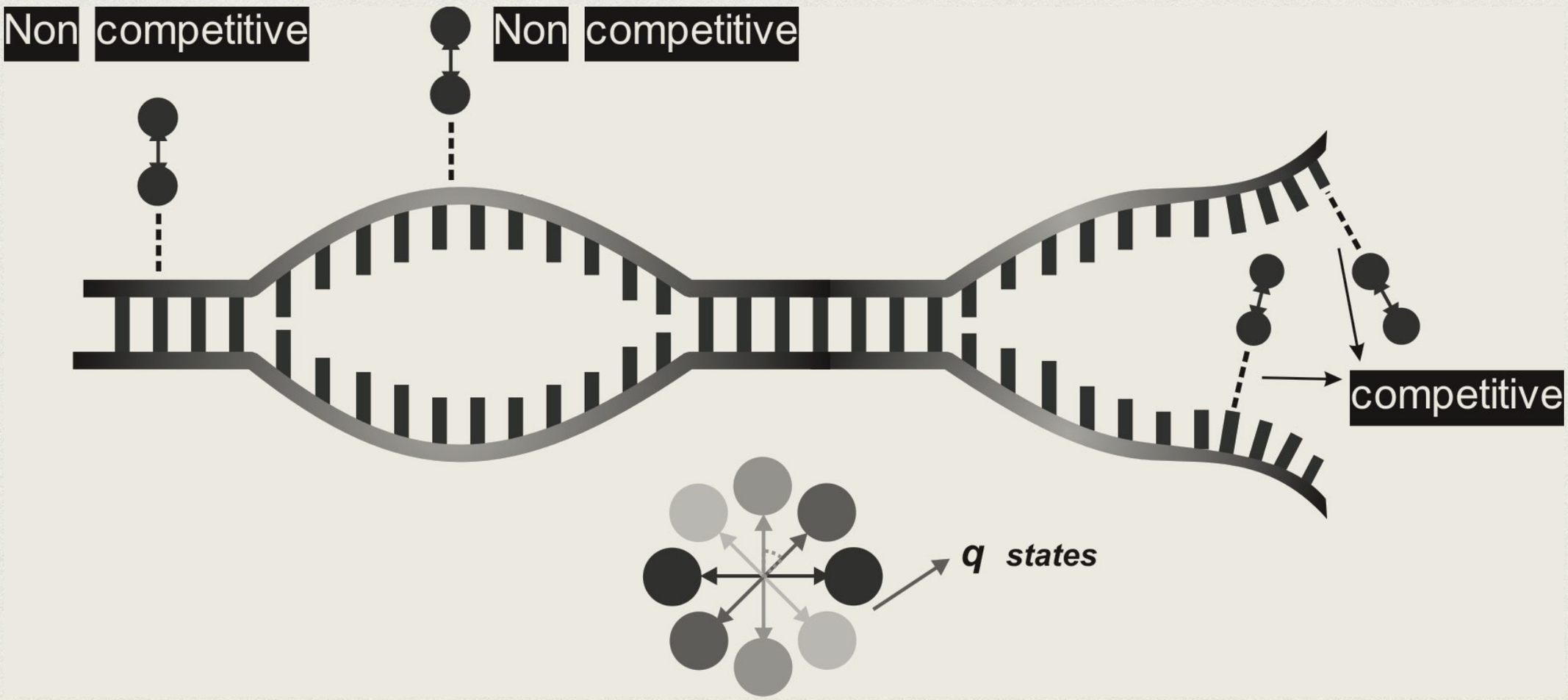
- The energy U of hydrogen bond formation
- The discrete number Q of possible conformations of each repeated unit
- Number of repeated units Δ fixed by one hydrogen bond.

$$W = e^{\frac{U}{T}}$$

$$F = -kT \ln Z = -NkT\lambda_1$$

MODEL WITH SOLVENT

However the basic model is far from reality.
The main thing is interactions with solvent.

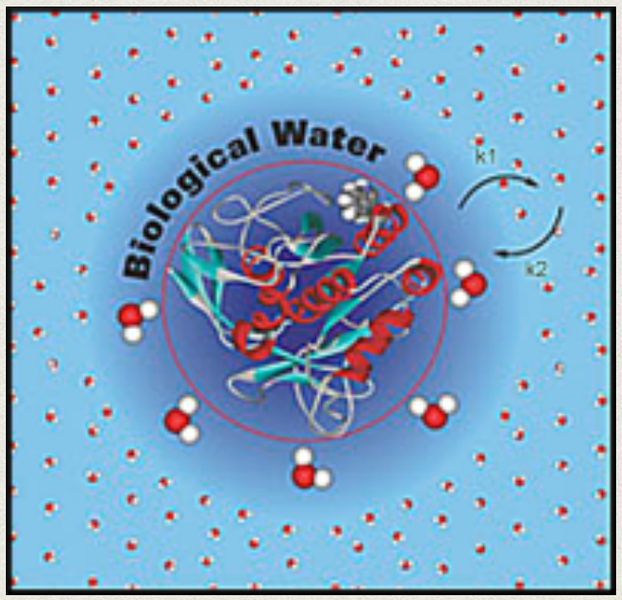


http://bimanbagchi.com/hydration.html

HAMILTONIAN OF THE MODEL OF BIOPOLYMERS INTERACTING WITH SOLVENT

$$-\beta H_S = J\sum_{i=1}^{N}\delta_i^{\Delta} + I_{st}\sum_{i=1}^{N}\delta_i^{\Delta}\,\delta(S_i^{st},1) + I_{dst}\sum_{i=1}^{N}(1-\delta_i^{\Delta})\,\delta(S_i^{dst},1) + I_h\sum_{i=1}^{N}\delta_i^{1}\,\delta(\mu_i,1) + I_c\sum_{i=1}^{N}(1-\delta_i^{1})\,\delta(\nu_i,1)$$

basic competitive non-competitive



PARTITION FUNCTION

$$Z=\sum_{\{\gamma_i=1\}}^{Q}\sum_{\{s_i^{st}\}}^{q_s^{st}}\sum_{\{s_i^{dst}\}}^{q_s^{dst}}\sum_{\{\mu_i=1\}}^{q_s^{h}}\sum_{\{\nu_i=1\}}^{q_s^{c}}\prod_{i=1}^{N}e^{-\beta H}$$

$$\nu_i = 1,\dots,q_s^c$$

$$\mu_i = 1,\dots,q_s^h$$

$$s_i^{dst} = 1,\dots,q_s^{dst}$$

$$s_i^{st} = 1,\dots,q_s^{st}$$

$$\gamma_i = 1,\dots,Q$$

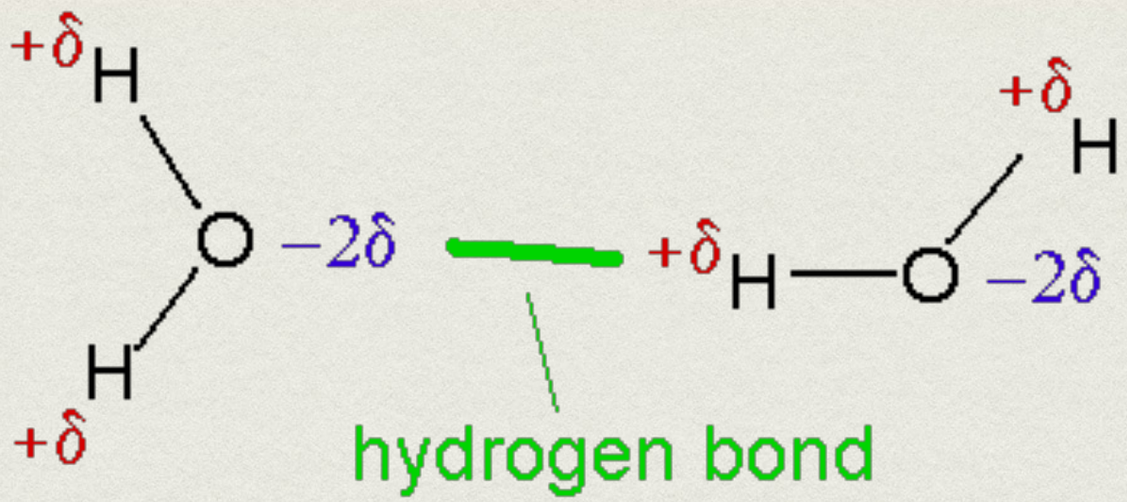
REDEFINITION OF PARAMETERS

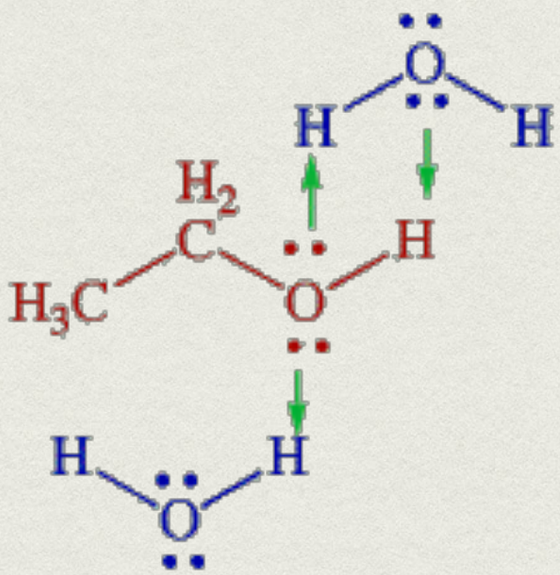
$$\tilde{W} = e^{J} \frac{\left(e^{I_s^{st}} + q_s^{st} - 1 \right)^{2m}}{\left(e^{I_s^{dst}} + q_s^{dst} - 1 \right)^{2m}}$$

$$\tilde{Q} = 1 + (Q-1) \frac{\left(e^{I_s^{c}} + q_s^{c} - 1 \right)}{\left(e^{I_s^{h}} + q_s^{h} - 1 \right)}$$

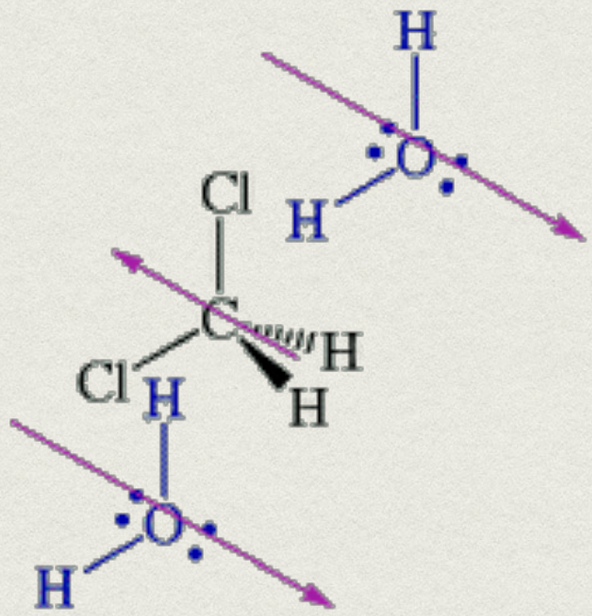
$2m$: number of spin variables required to describe the interaction between solvent molecule and each repeated unit.

INTERACTIONS WITH WATER





Hydrogen bonds



Other interactions

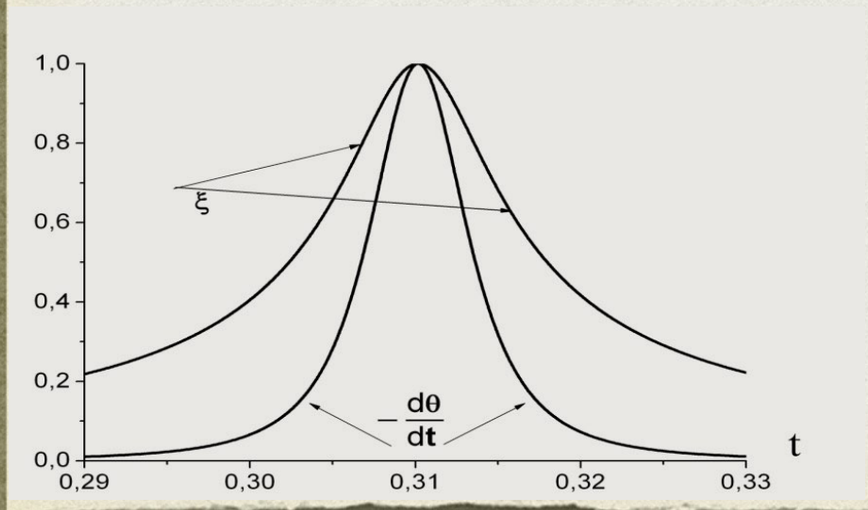
http://witcombe.sbc.edu/water/chemistrystructure.html

TWO MAIN PARAMETERS

W Q

$$\theta = \frac{\partial \ln \lambda_1}{\partial J} = \frac{W}{\lambda_1}\frac{\partial \lambda_1}{\partial W}$$

$$\xi = \ln^{-1}\left(\frac{\lambda_1}{\lambda_2}\right)$$

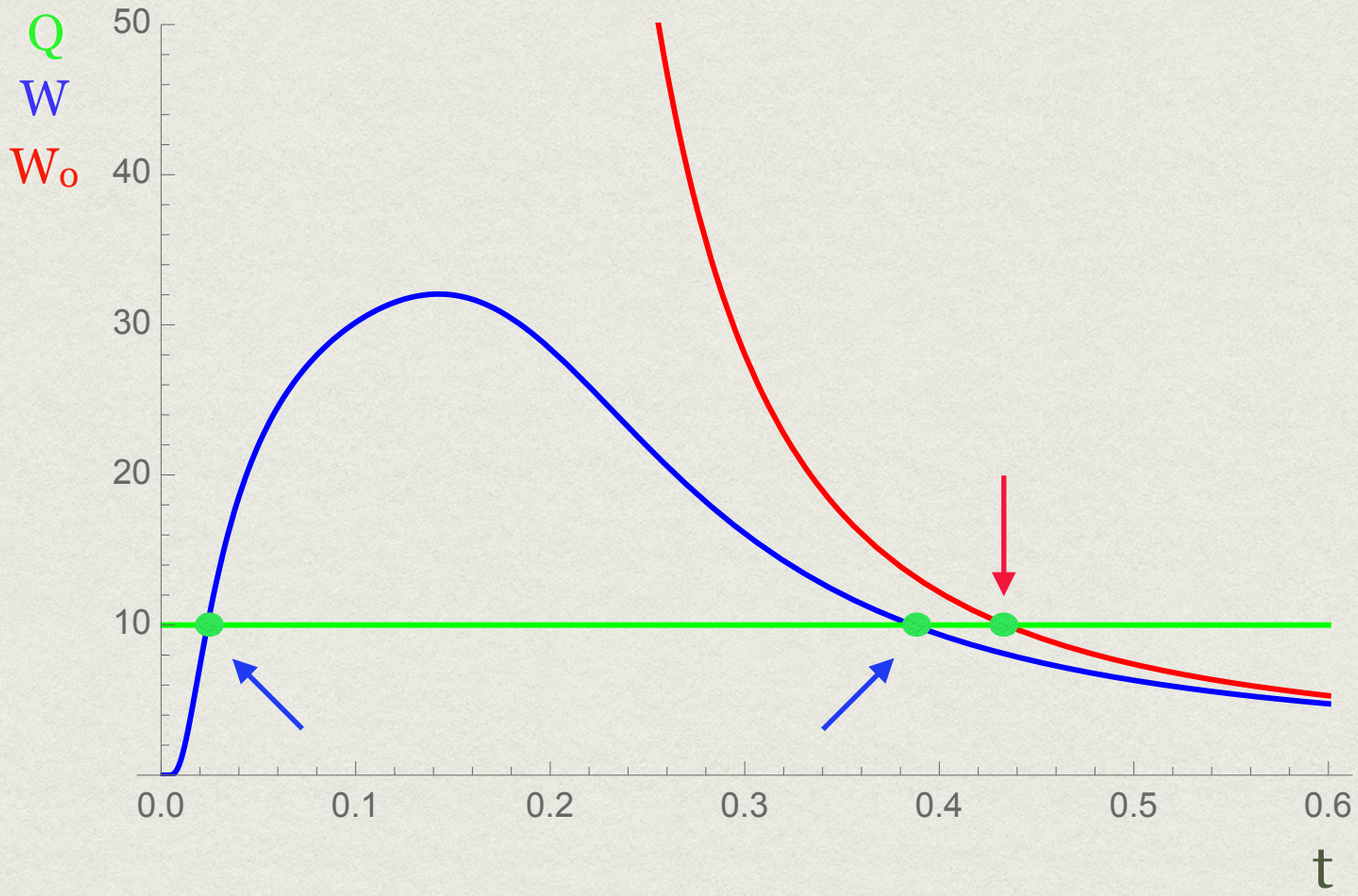


$$\eta = \theta \cdot \frac{(1-W)}{\lambda_1}$$

$$\nu = \frac{\theta}{\eta}$$

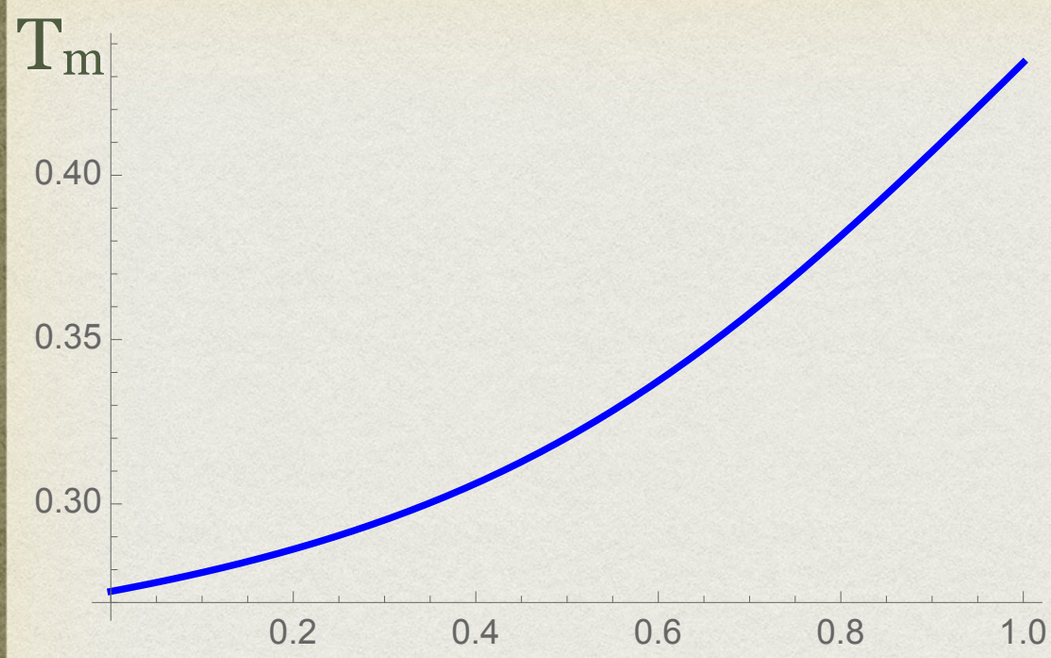
TRANSITION POINT

W: energetic parameter for model with solvent
W_o: energetic parameter for base model
Q: conformational parameter

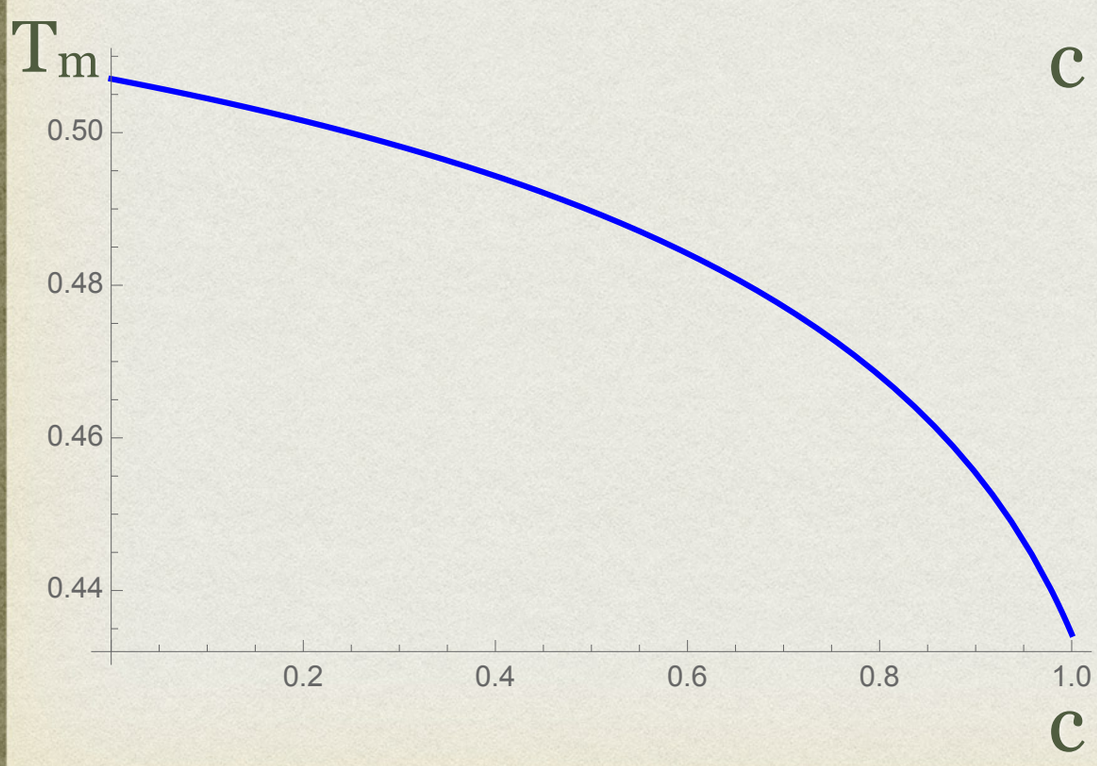


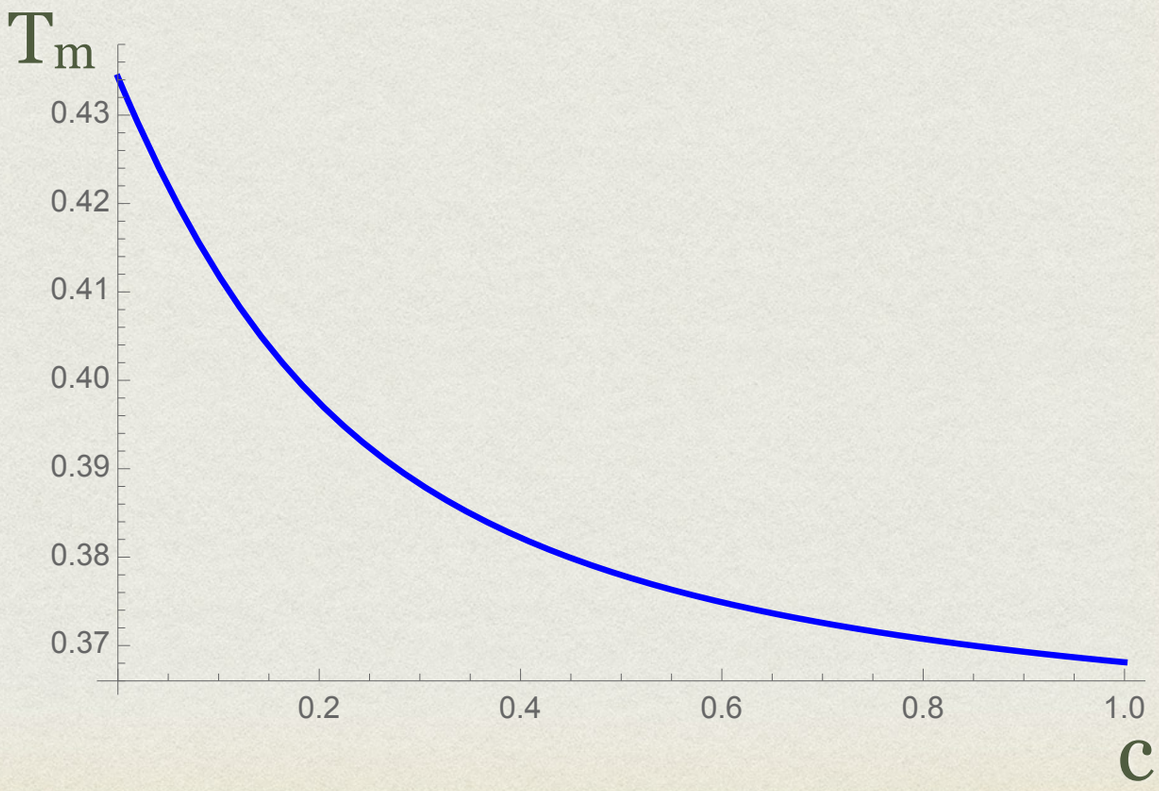
W = Q

MELTING TEMPERATURE



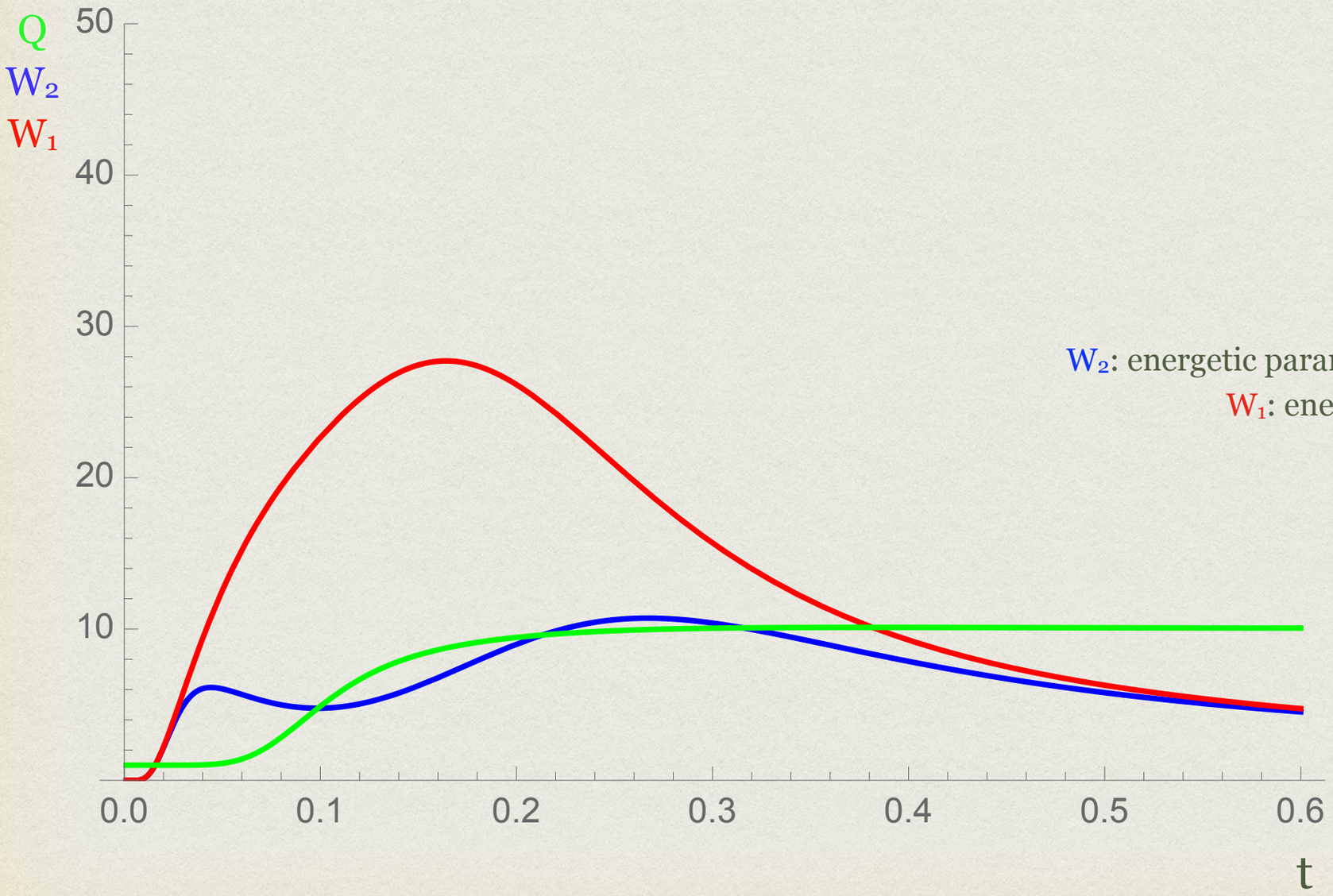
W = Q





GMPC FOR BIOPOLYMERS INTERACTING WITH SOLVENT AND LIGAND

$$-\beta H = J \sum_{i=1}^{N} \delta_i^{\Delta} - \beta H_S(s_{st}, s_{dst}, s_h, s_c)\, \delta(f > m) - \beta H_L(l_{st}, l_{dst}, l_h, l_c)\, \delta(f \le m)$$



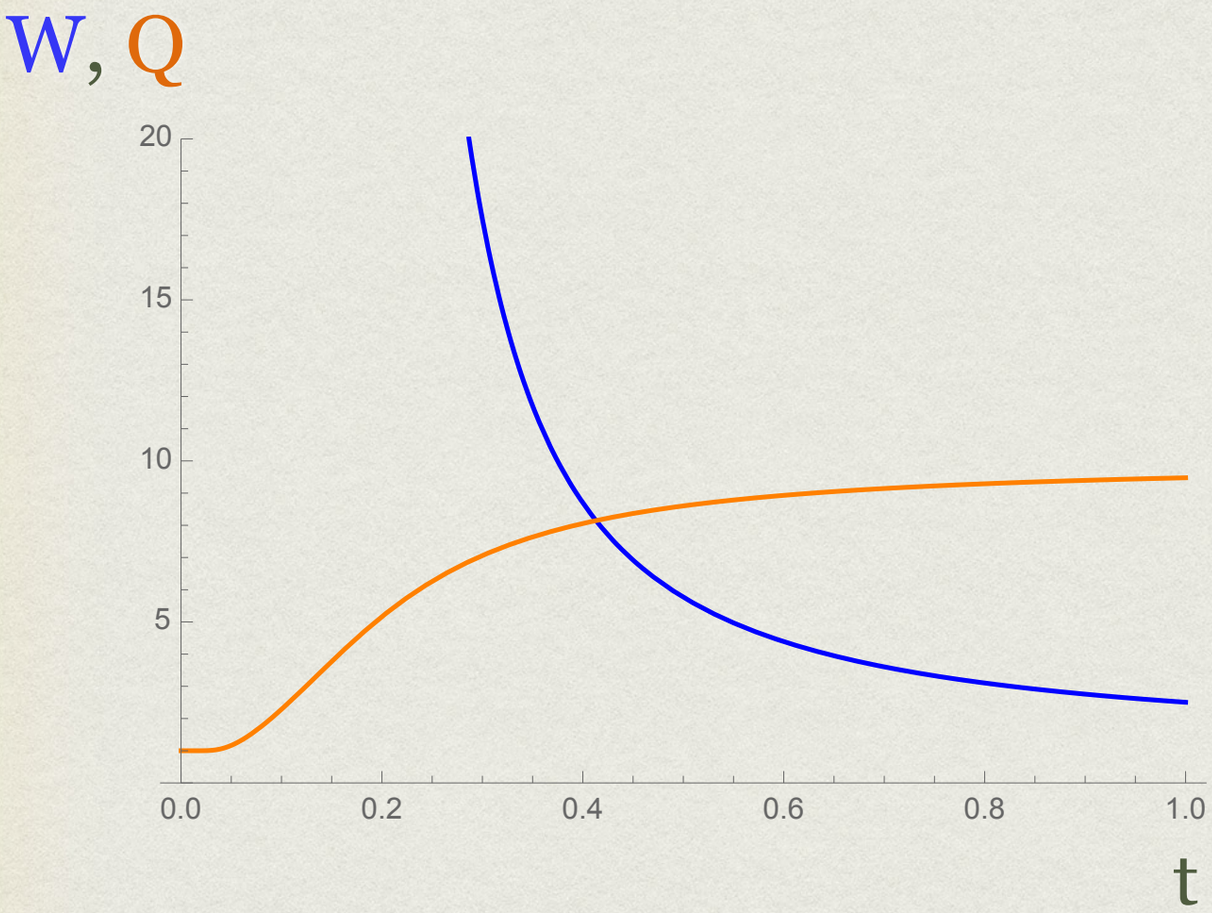
W_2: energetic parameter for model with solvent and ligand

W_1: energetic parameter for model with solvent

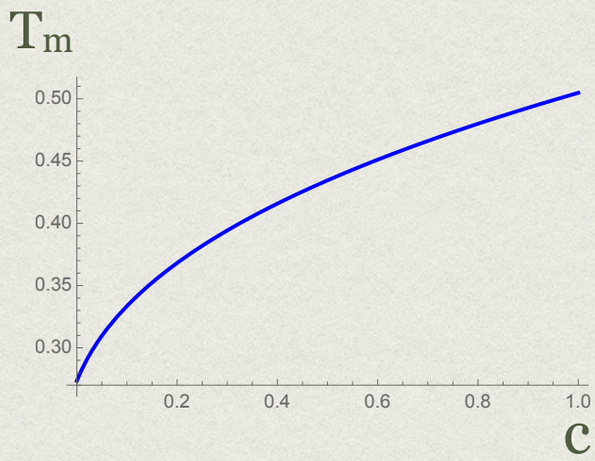
Q: conformational parameter

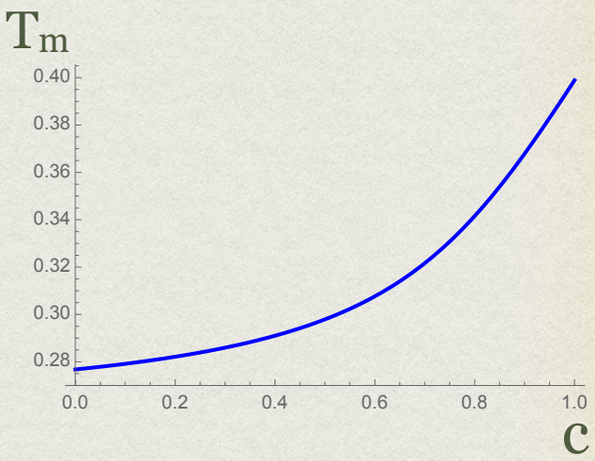
MELTING TEMPERATURE

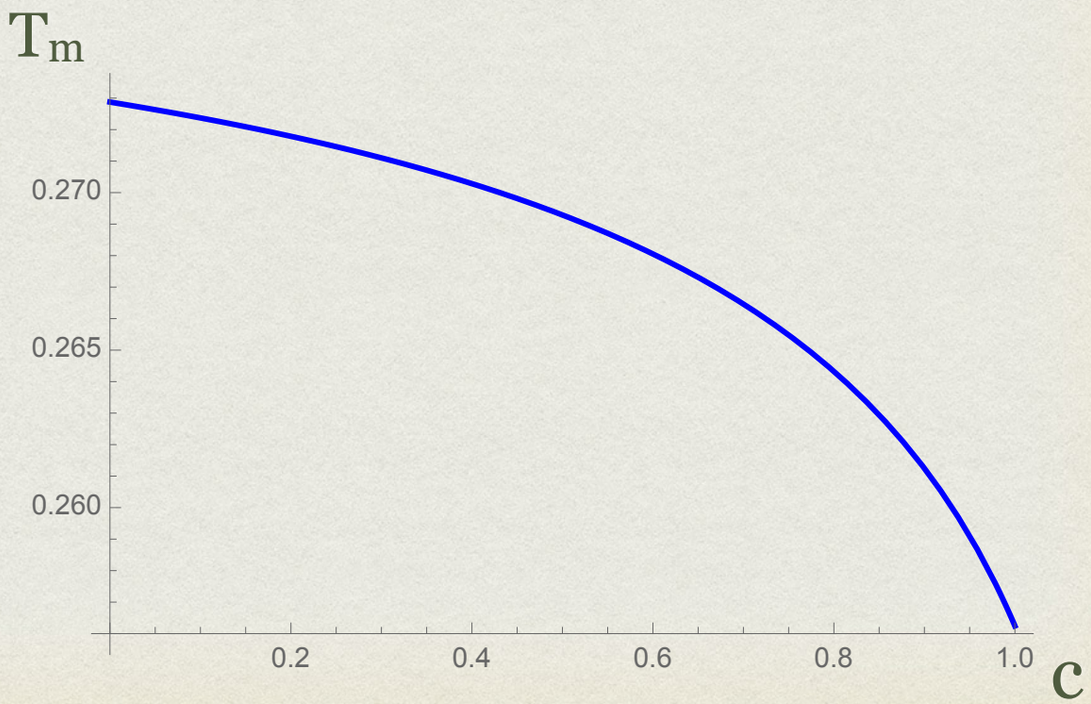
Interactions with both solvent and ligand



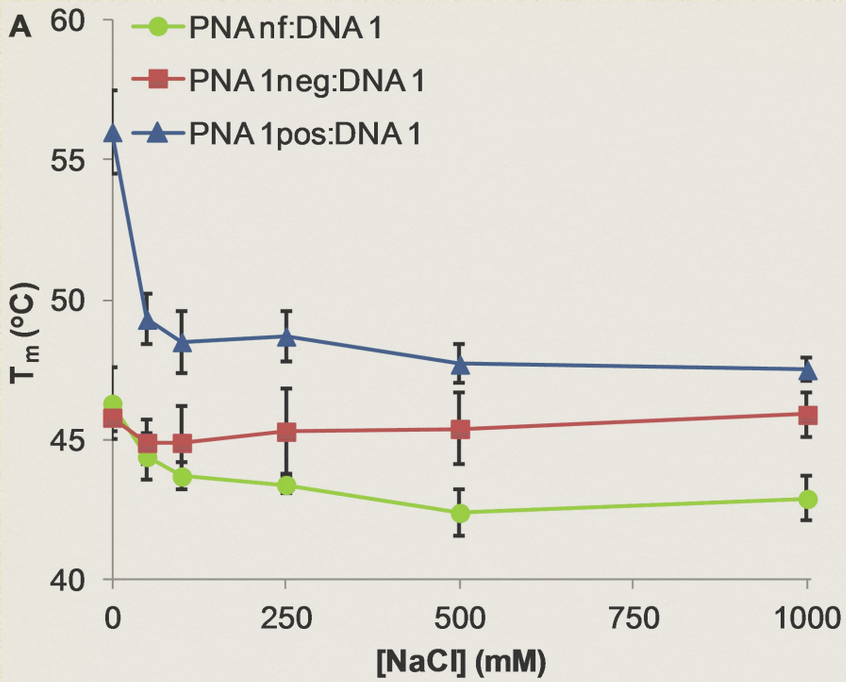
$$c\,(W_L - Q_L) + (1 - c)\,(W_S - Q_S) = 0$$

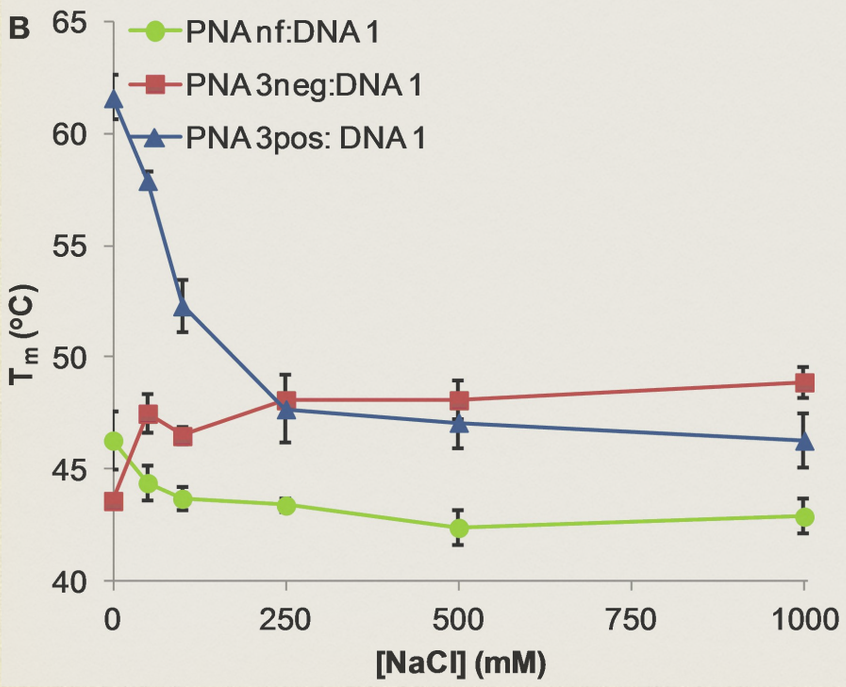


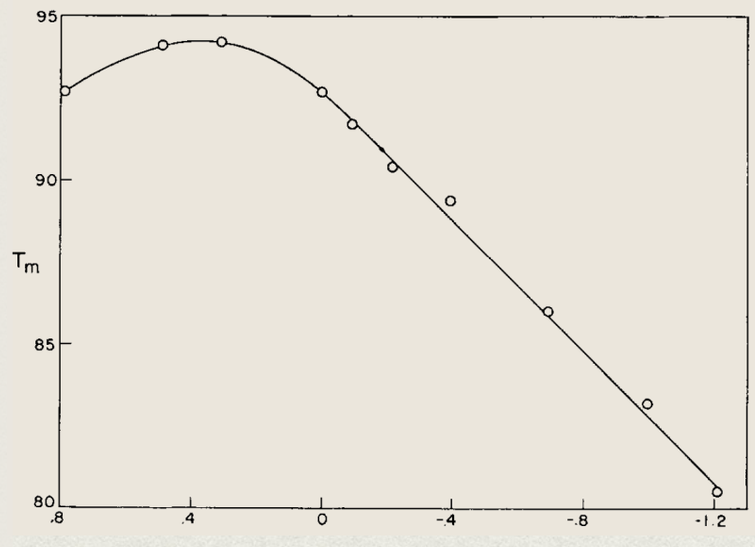




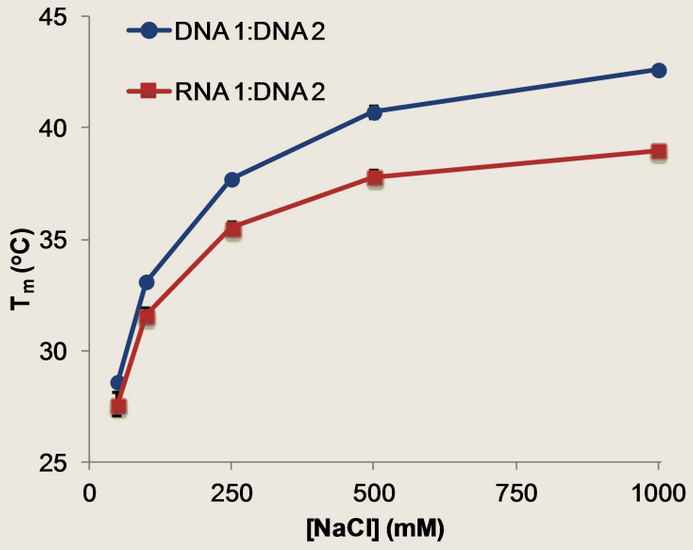
EXPERIMENTAL DATA

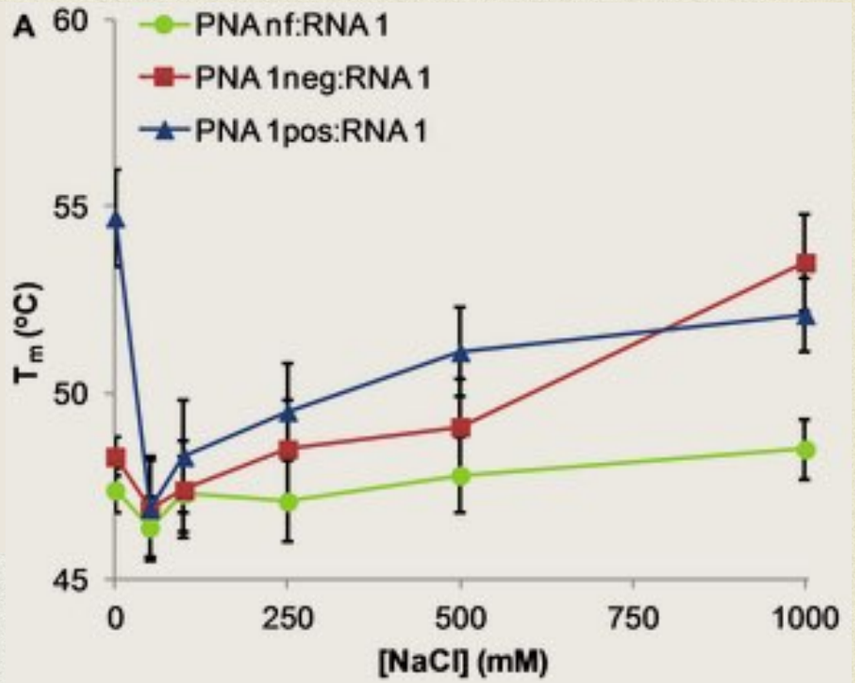


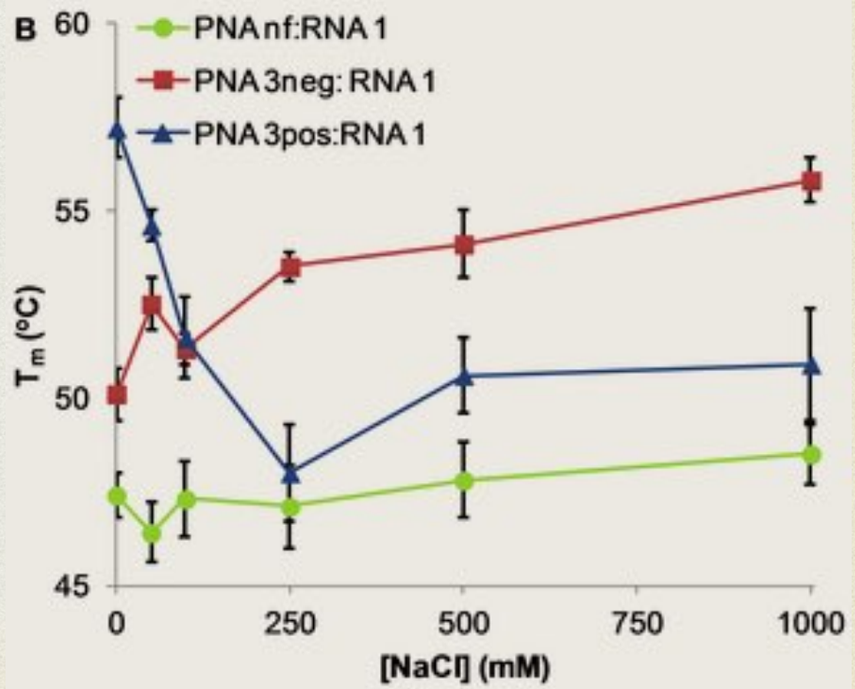




The T_m of D. pneumonia DNA was determined in CsCl solutions having concentrations up to 6M.







HAMILTONIAN OF INTERACTIONS IN DIFFERENT BINDING SIDES

$$-\beta H = -\beta H_0 - \beta H_L \cdot H\left(p - f_i^L\right) - \beta H_S \cdot H\left(f_i^S - p\right)$$

$$H(x) = \begin{cases} 0, & x<0 \\ 1, & x\geq 0 \end{cases}$$

Heaviside function

$$G = \begin{bmatrix} \widetilde{W} & 1 & 0 & 0 & . & . & . & 0 \\ 0 & 0 & 1 & 0 & 0 & . & . & 0 \\ 0 & 0 & 0 & 1 & 0 & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & 0 & . & . & \widetilde{Q}-1 \\ 1 & 1 & 1 & 1 & 1 & . & . & \widetilde{Q}-1 \end{bmatrix}$$

REDUCED ENERGETIC AND CONFORMATIONAL PARAMETERS

$$\tilde{W}=e^{J}\frac{\left(1-c+c\cdot R_{st}^{L}\,R_{h}^{L}\right)\cdot\left(c+(1-c)\cdot R_{st}^{S}\,R_{h}^{S}\right)}{\left(1-c+c\cdot R_{dst}^{L}\,R_{h}^{L}\right)\cdot\left(c+(1-c)\cdot R_{dst}^{S}\,R_{h}^{S}\right)}$$

$$\tilde{Q}-1=(Q-1)\,\frac{\left(1-c+c\cdot R_{dst}^{L}\,R_{c}^{L}\right)\cdot\left(c+(1-c)\cdot R_{dst}^{S}\,R_{c}^{S}\right)}{\left(1-c+c\cdot R_{dst}^{L}\,R_{h}^{L}\right)\cdot\left(c+(1-c)\cdot R_{dst}^{S}\,R_{h}^{S}\right)}$$

TRANSITION POINT

$$\tilde{W} = \tilde{Q}$$

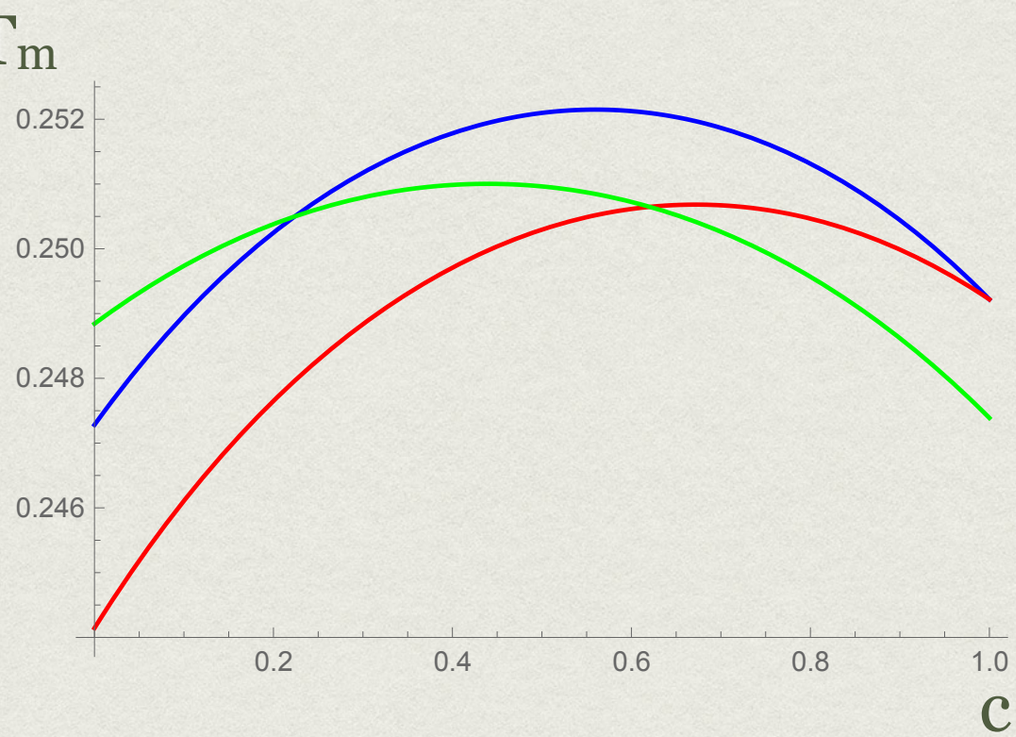
$$e^{J}\left(1 - c + c \cdot R_{st}^{L}\, R_{h}^{L}\right) \cdot \left(c + (1 - c) \cdot R_{st}^{S}\, R_{h}^{S}\right) =$$

$$= (Q\text{-}1)\left(1 - c + c \cdot R_{dst}^{L}\, R_{c}^{L}\right) \cdot \left(c + (1 - c) \cdot R_{dst}^{S}\, R_{c}^{S}\right) + \left(1 - c + c \cdot R_{dst}^{L}\, R_{h}^{L}\right) \cdot \left(c + (1 - c) \cdot R_{dst}^{S}\, R_{h}^{S}\right)$$

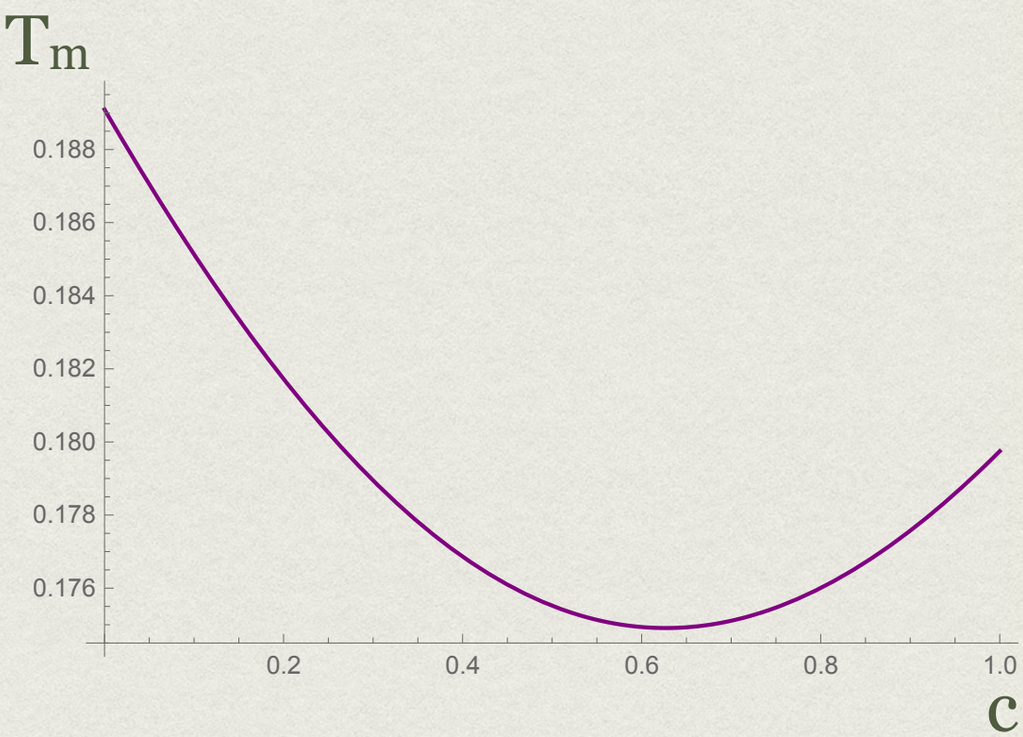
SIMPLEST CASES

$$-\beta H = \sum_{i=1}^{N} \left[J\,\delta_i^{\Delta} + I_L \delta_i^{\Delta} H\left(p - f_i^{L}\right) \delta(l_i, 1) + I_S \delta_i^{\Delta} H\left(f_i^{S} - p\right) \delta(s_i, 1) \right] \qquad (1)$$

$$-\beta H = \sum_{i=1}^{N} \left[J\,\delta_i^{\Delta} + I_L \left(1-\delta_i^{\Delta}\right) H\left(p - f_i^{L}\right) \delta(l_i, 1) + I_S \left(1-\delta_i^{\Delta}\right) H\left(f_i^{S} - p\right) \delta(s_i, 1) \right] \qquad (2)$$

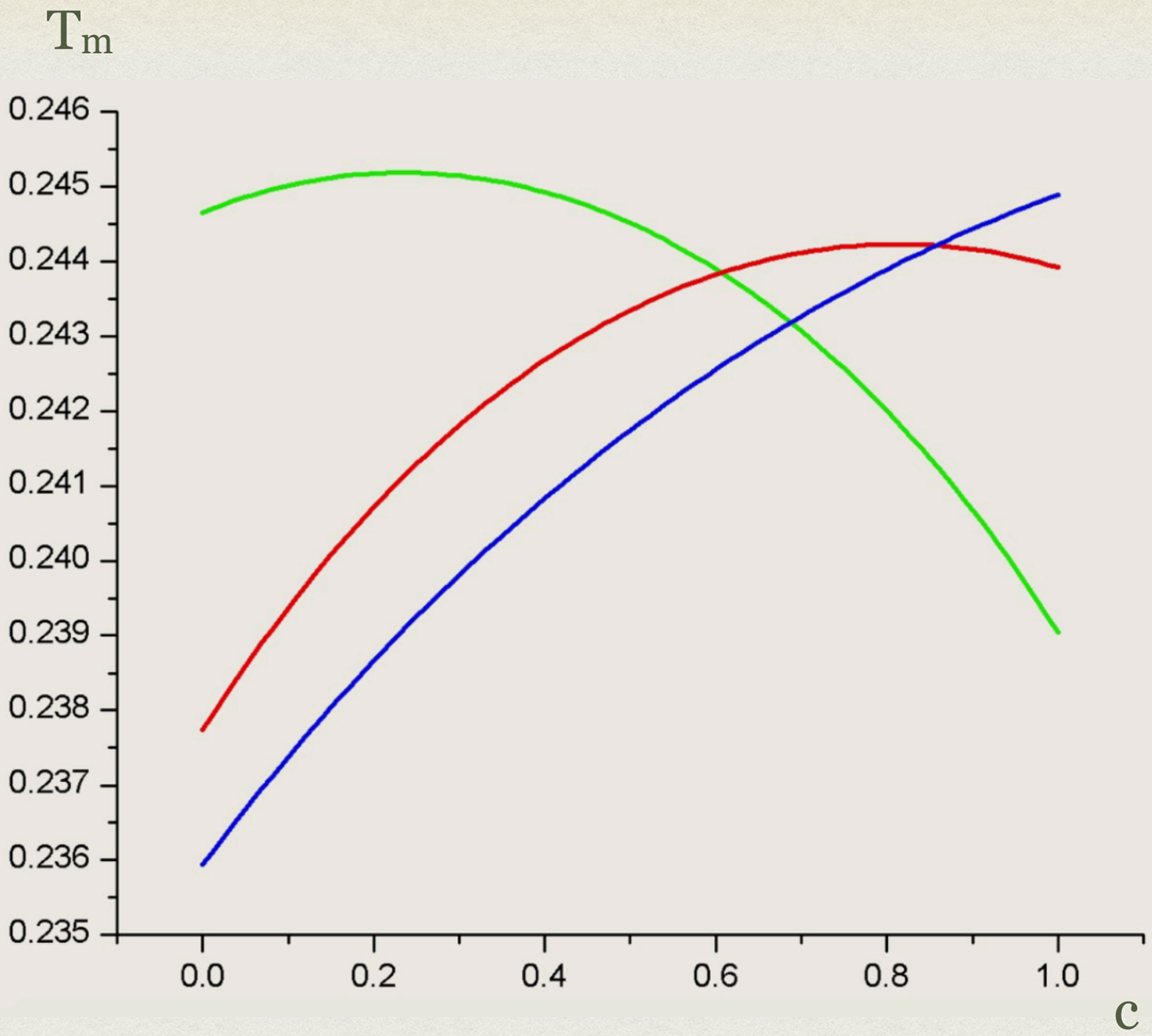


Dependence of normalized temperature of the helix-coil transition from the concentration for the model with Hamiltonian (1) at 1. α_L=0.48, α_S=0.5, *Q=91*, 2. α_L=0.55, α_S=0.5, *Q=100*, 3. α_L=0.55, α_S=0.53, *Q=86.4*.



Dependence of normalized temperature of the helix-coil transition from the concentration for the model with Hamiltonian (2) at 1. α_L=0.51, α_S=0.45, *Q=100*.

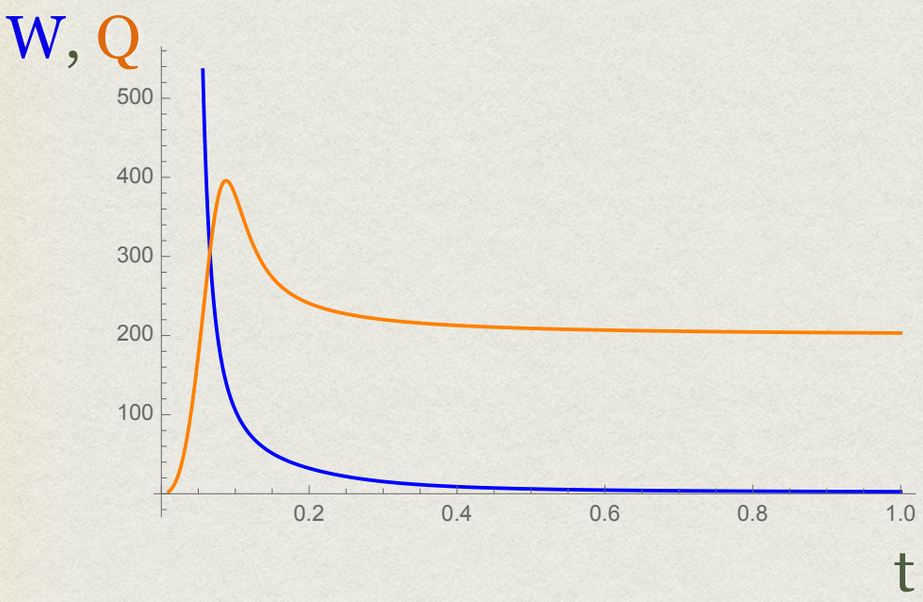
NON-MONOTONE AND MONOTONE BEHAVIORS

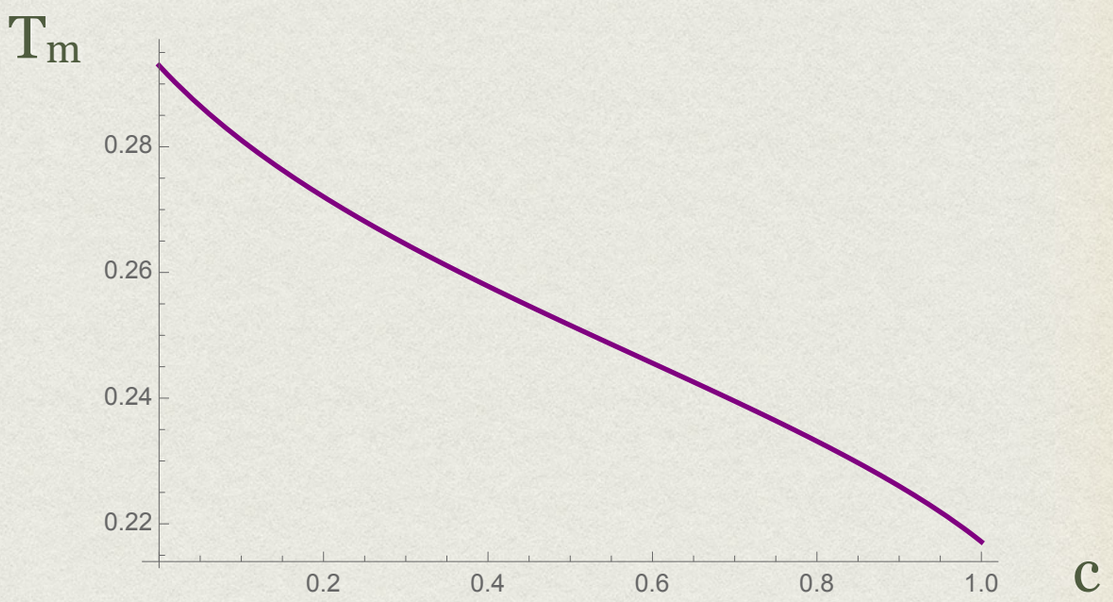


Dependence of normalized temperature of the helix-coil transition from the concentration for the model with Hamiltonian (1) at 1. α_L=0.438, α_S=0.502, *Q=100*, 2. α_L=0.494, α_S=0.425, *Q=100*, 3. α_L=0.42, α_S=0.296, *Q=86.4*.

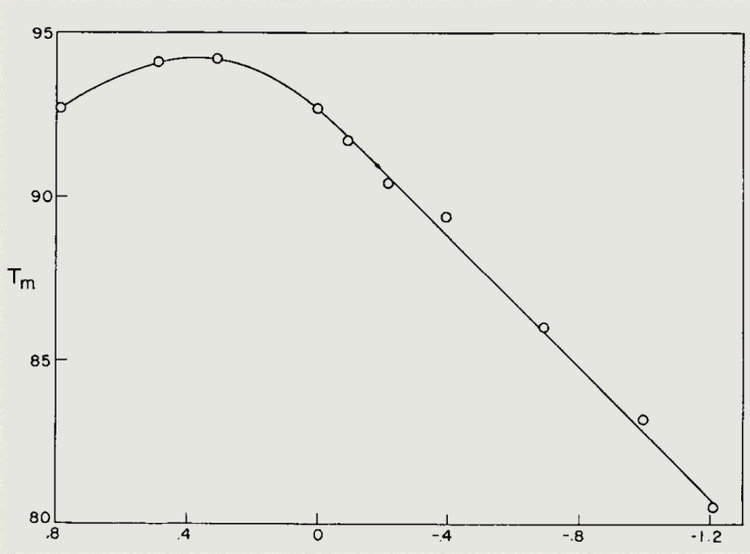
NON-MONOTONE BEHAVIOR

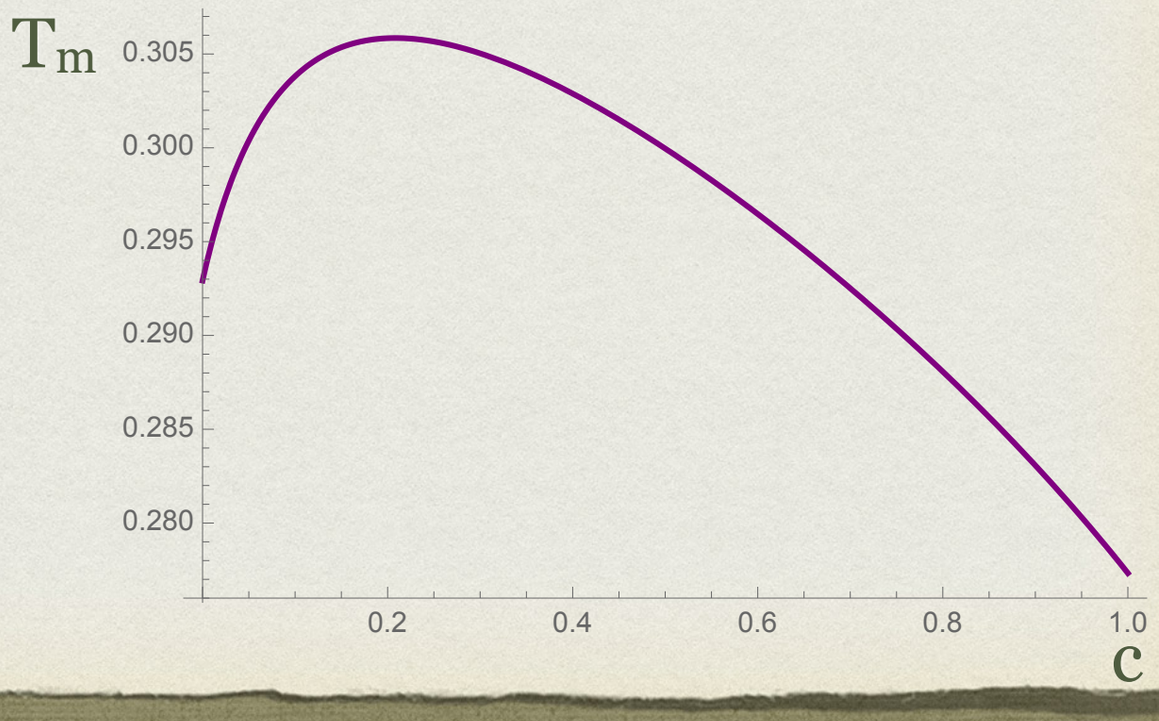
$$-\beta H = -\beta H_0 - \beta H_L \cdot H\left(p - f_i^L\right) - \beta H_S \cdot H\left(f_i^S - p\right)$$



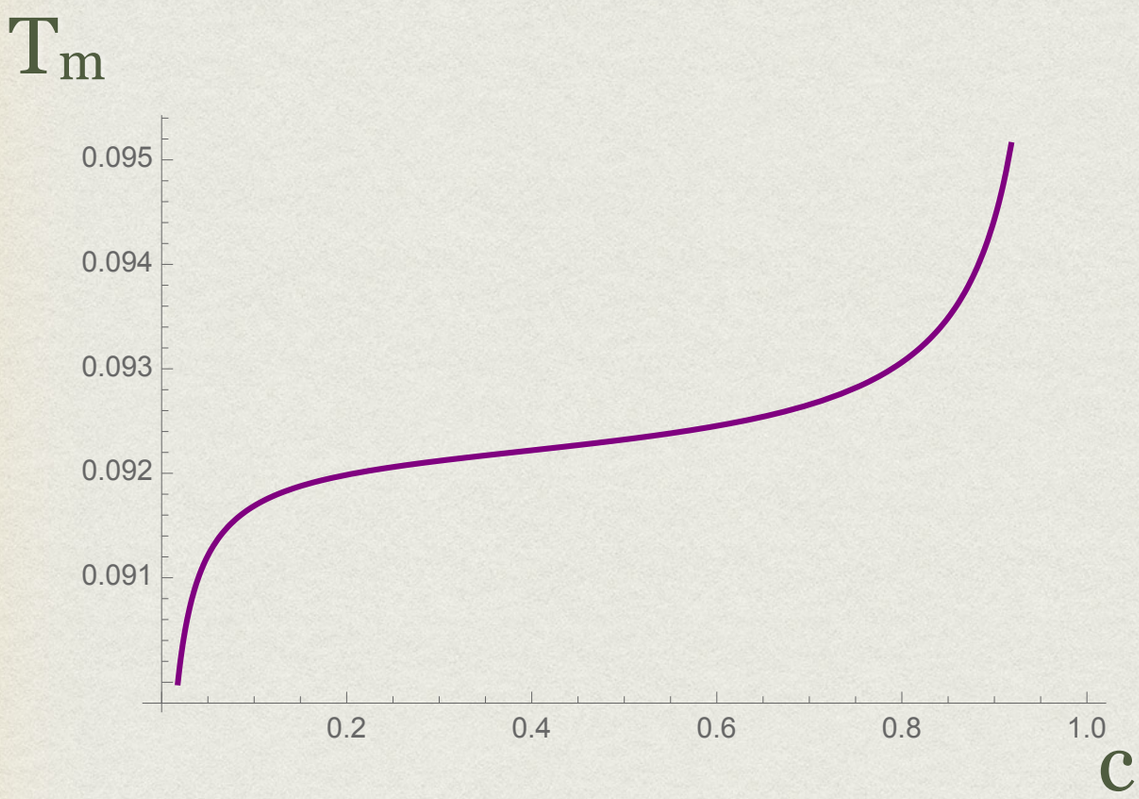


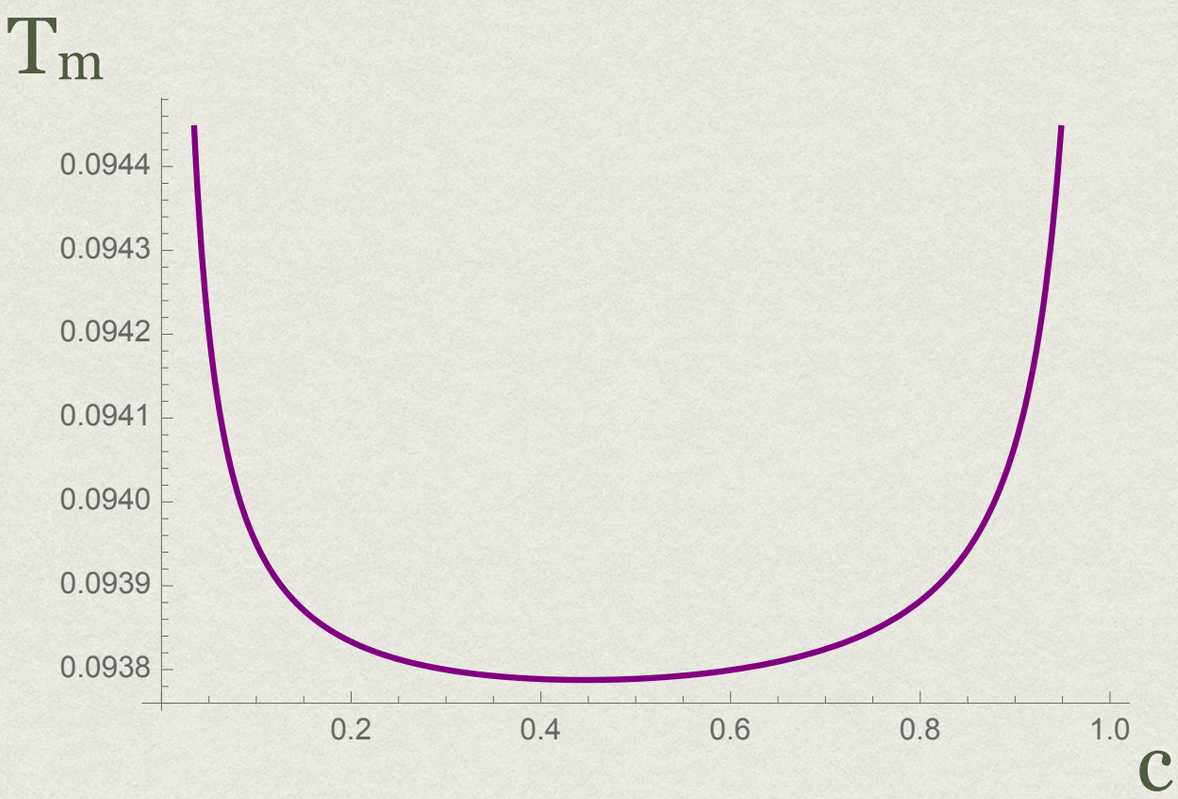
The T_m of D. pneumonia DNA was determined in CsCl solutions having concentrations up to 6M.





MORE COMPLICATED CASES





CONCLUSIONS

- GMPC allows to find microscopic parameters of biological systems if energetic and conformational parameters are defined.
- With last updates, GMPC qualitatively describes the stability of biopolymers in various solutions in both monotone and non-monotone cases.
- In all the models corresponding to the stabilization of helical structure, the helix-coil transition point passes through maximum, in the contrary, the transition point passes through the minimum, for the models stabilizing coiled conformation.
- The changes in regime of helical state stability is not always connected with competition of stabilizing and destabilizing interactions of blend's components, but can be result of both components cumulative effect.
- All the result are qualitative. Although, they are close to some experimental results, we need to do numerical adjustments, to be able to describe real systems more completely.

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THANK YOU