BT5340: Protein Folding and Stability

Assignment 2

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Zimm-Bragg model:

The central idea of this model is that the probability that a monomer j is in state C(coil) or H(helix) depends on whether the neighboring monomer j-1 is in C or H.

Monomer state		Zimm-Bragg Statistical weight for j
j-1	j	
C	C	q(C|C) = 1
H	C	q(C|H) = 1
C	H	q(H|C) = σs
H	H	q(H|H) = s

Expressing the same as a matrix, we have

$$G = \begin{bmatrix} q(C|C) & q(H|C) \\ q(C|H) & q(H|H) \end{bmatrix} = \begin{bmatrix} 1 & \sigma s \\ 1 & s \end{bmatrix}$$

The statistical weight vector of the first monomer can be expressed as

$q_1 = [q(C),\ q(H)]$

To get the statistical weights of a 2 two monomer sequence we multiply G with q_1.

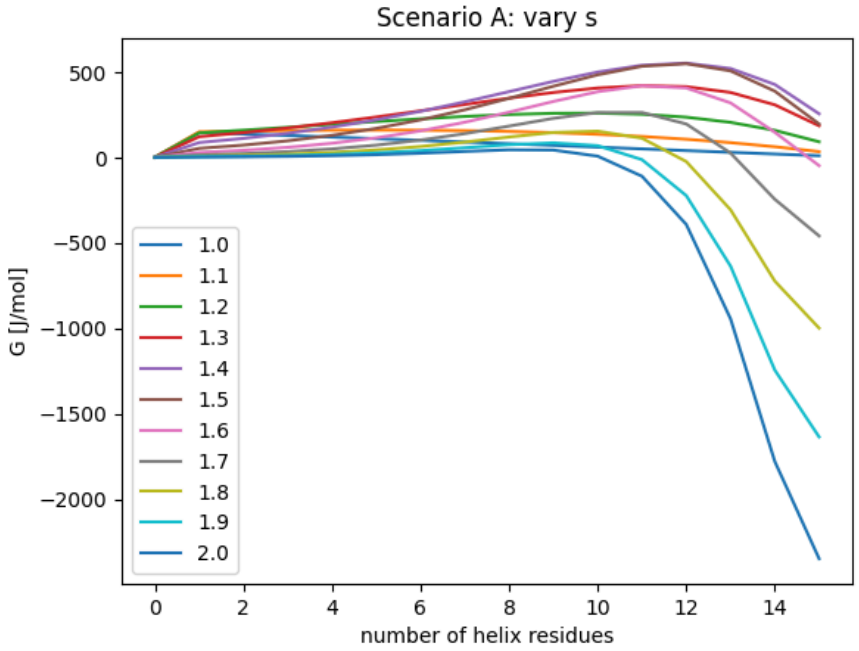
$q_2 = q_1 G.$

$\Rightarrow q_2 = [1 + \sigma s,\ \sigma s + \sigma s^2]$

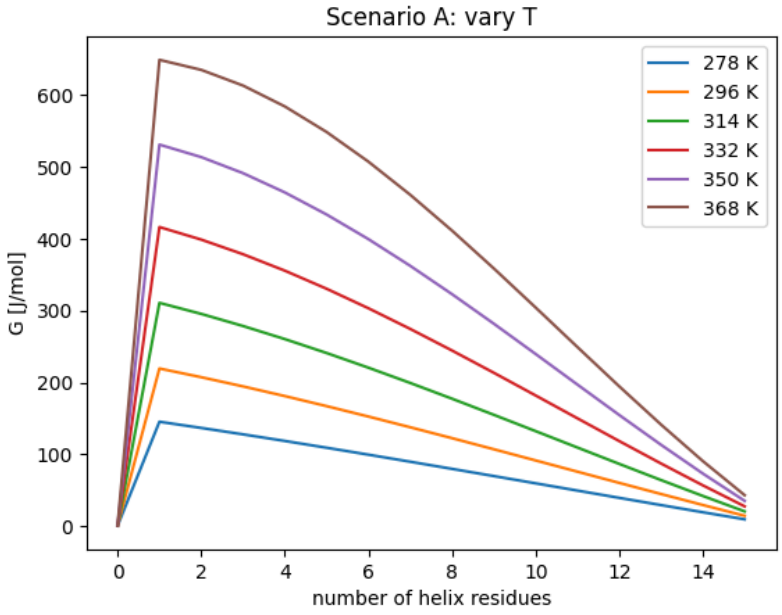
Similarly for 15 residue sequence we have,

$q_{15} = q_1 G^{14}$

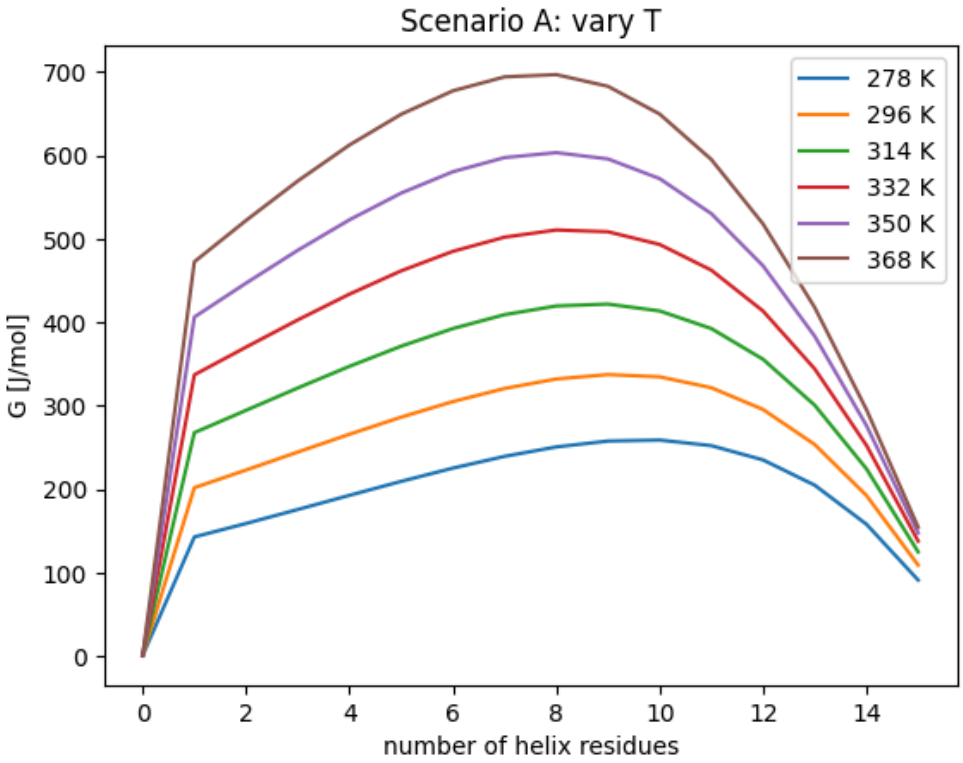
We have probed the problem of helix-coil transition for a 15 residue peptide using Zimm-Bragg model with a $\sigma = 10^{-3}$. The free energy vs no. of helical residues plot for a range of s values greater than 1(Scenario A) for T = 278K is given below.



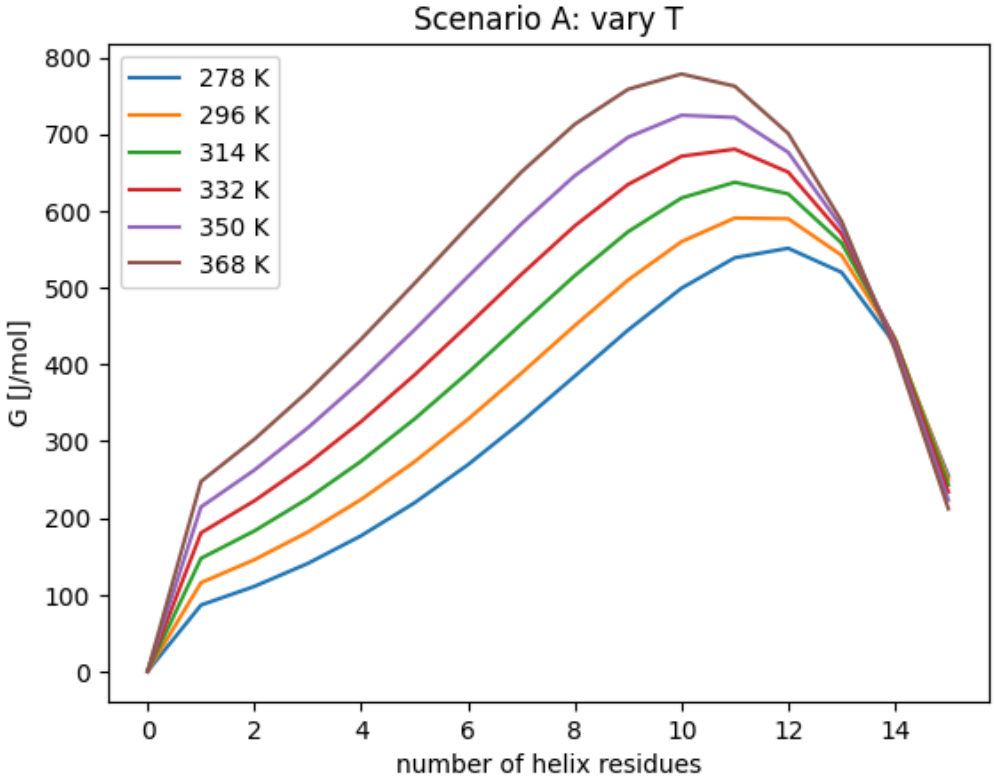
This shows that to achieve 12 helical residues at s = [1.0, 1.5], the free energy change is positive and as s increases further the free energy change quickly falls off to negative values. For varying temperatures the free energy vs no. of helix residues plot looks as follows:



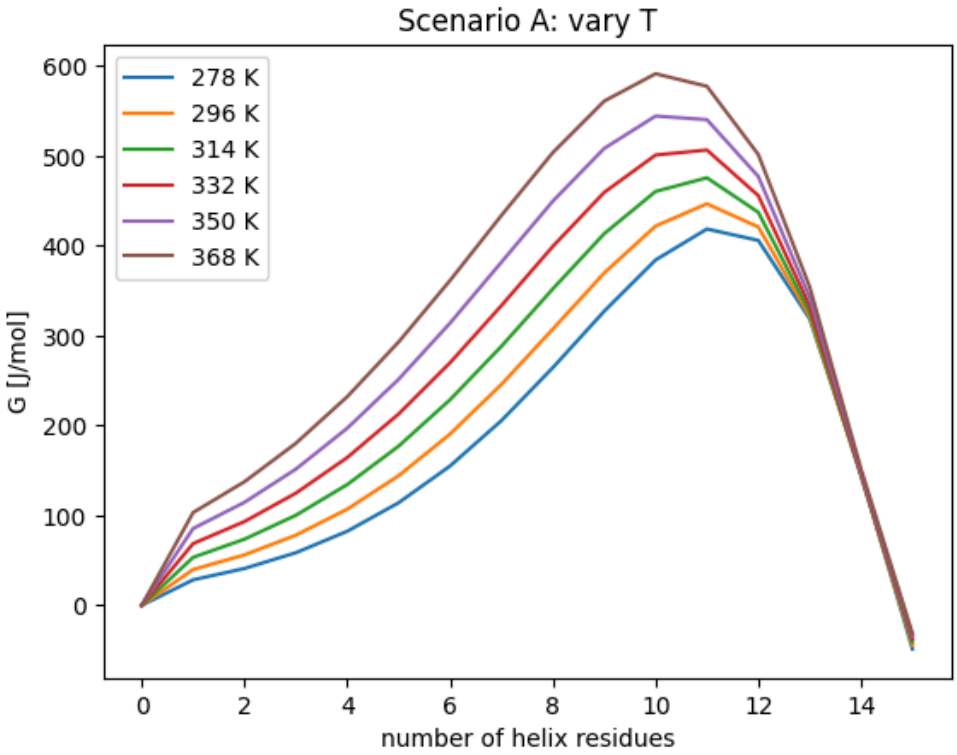
s=1.0


Scenario A: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
500
600
700
0
2
4
6
8
10
12
14

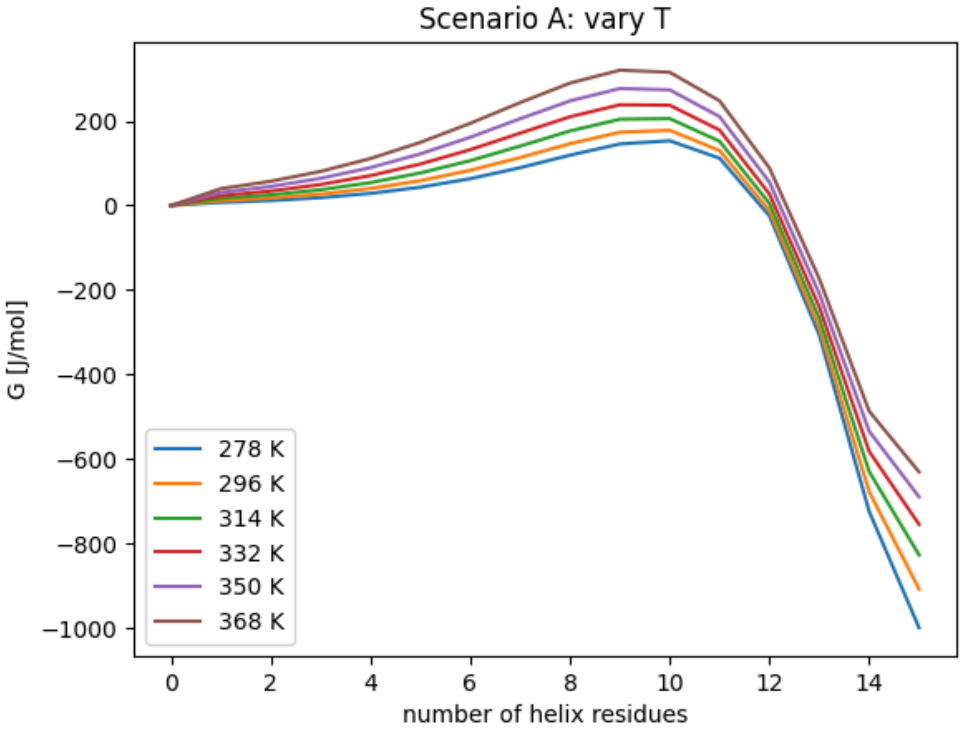
s=1.2


Scenario A: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
500
600
700
800
0
2
4
6
8
10
12
14

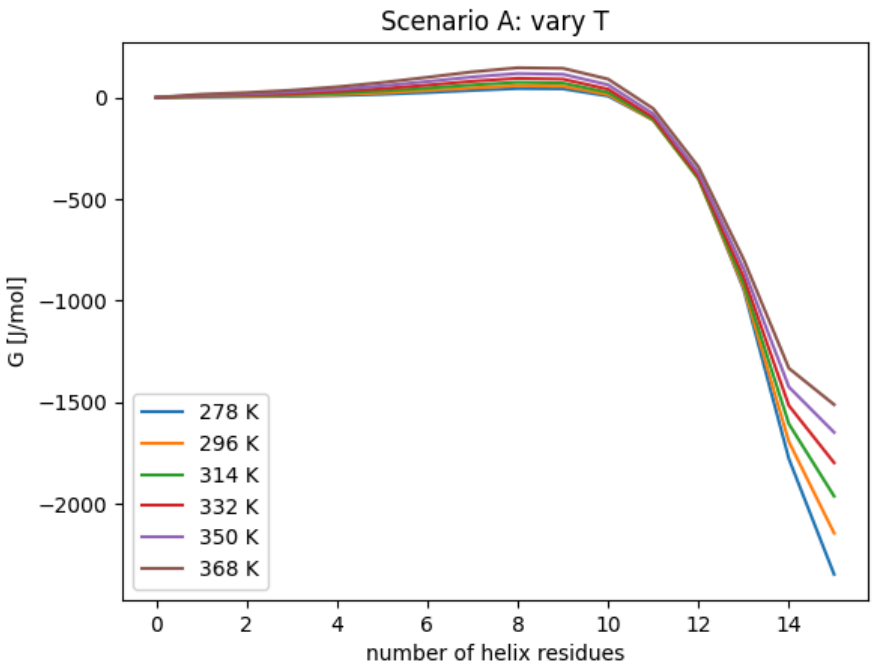
s=1.4


Scenario A: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues

s=1.6


Scenario A: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues

s=1.8

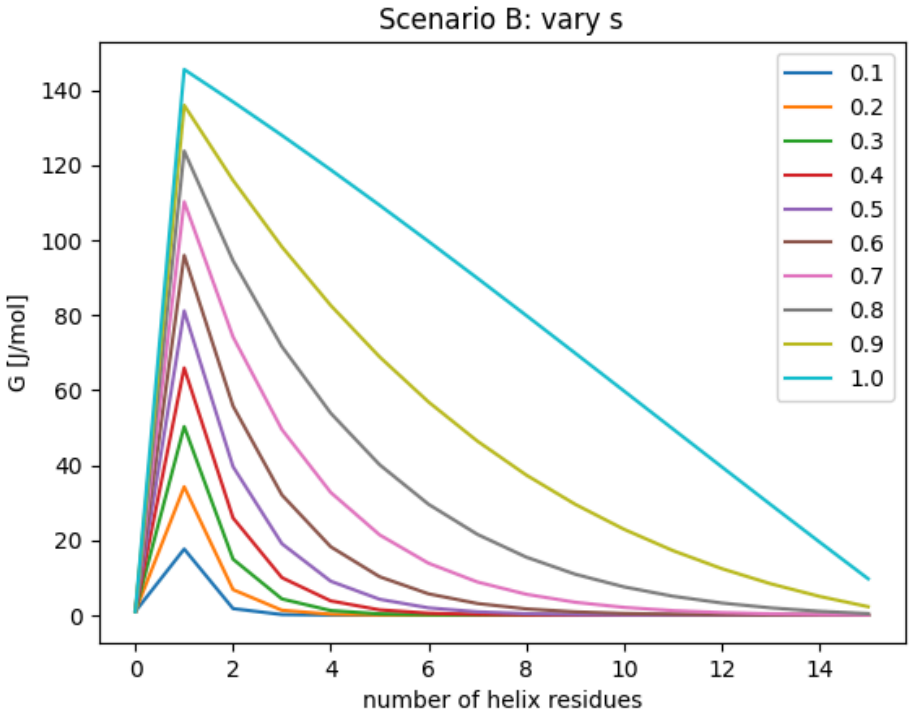


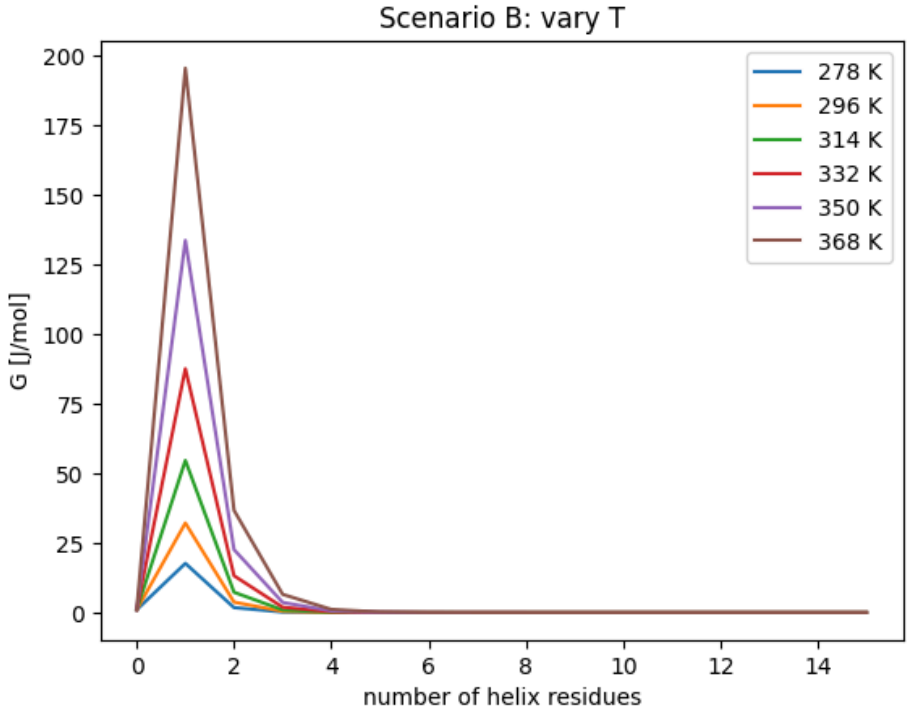
s = 2.0

It can be seen that the free energy peaks at n = 1 for s = 1.0, the peak moves right (rightmost being n = 12) and increases in magnitude as s increases to 1.5. After that it moves left (stopping at n = 8) and decreases in magnitude, it even goes into negative values after the peak. The peak is the free energy barrier that has to be crossed in order to have favourable ΔG for the process. Since it is decreasing we can conclude that the helical state is thermodynamically favourable.

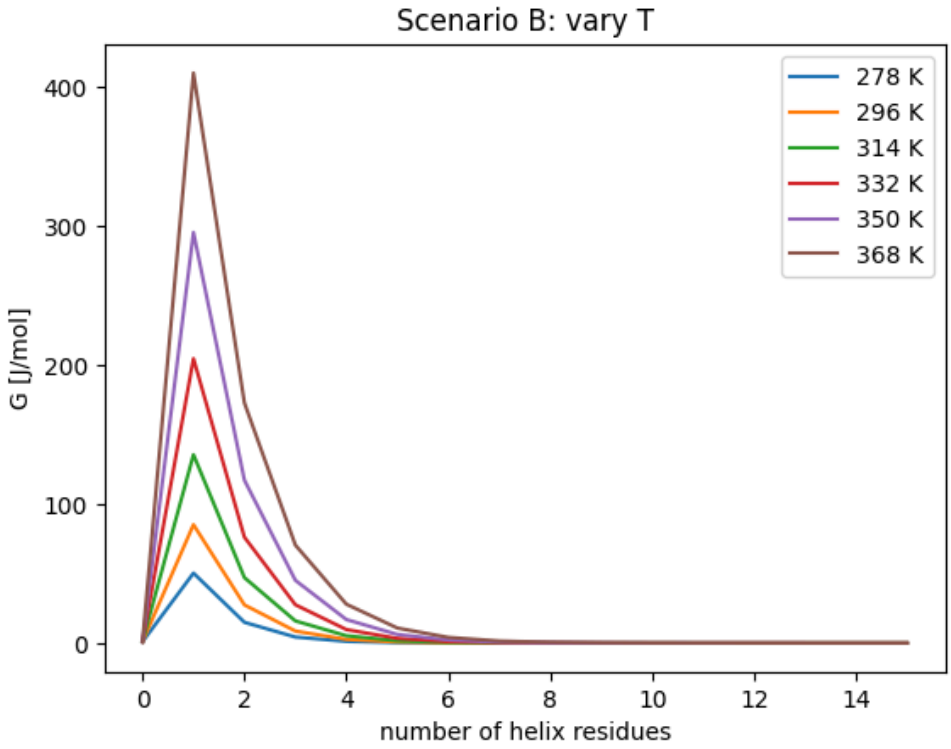
It can be seen in all plots that an increase in temperature increases the energy barrier. Supporting the fact that the folding process is not favourable at higher temperatures.

The same plots for s < 1 (Scenario B) are as follows.

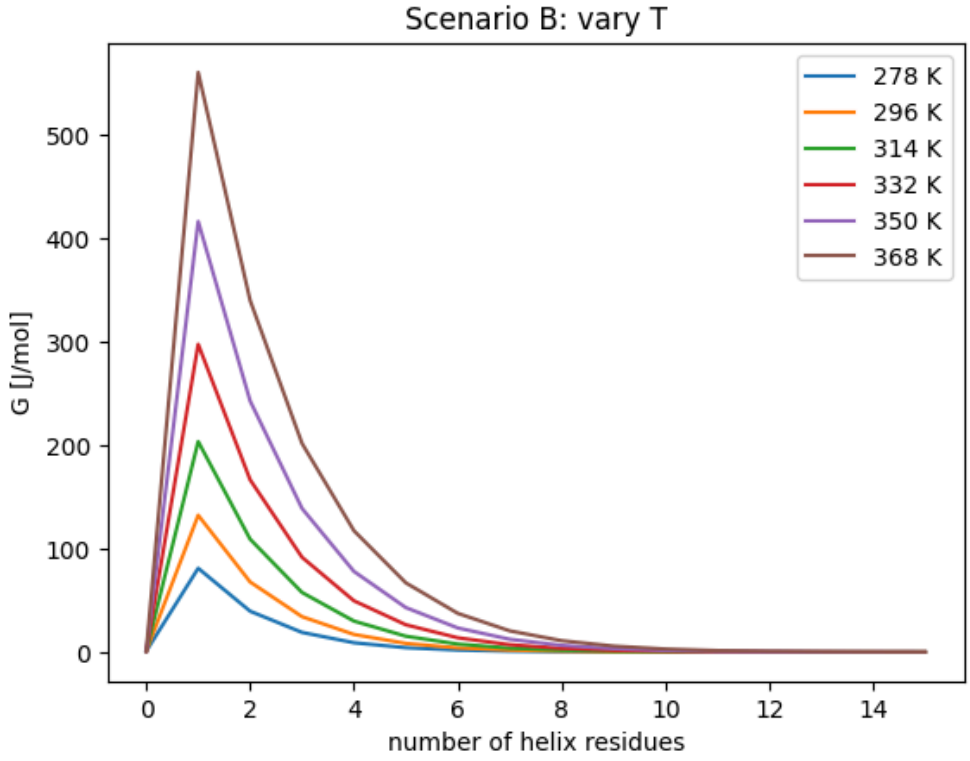




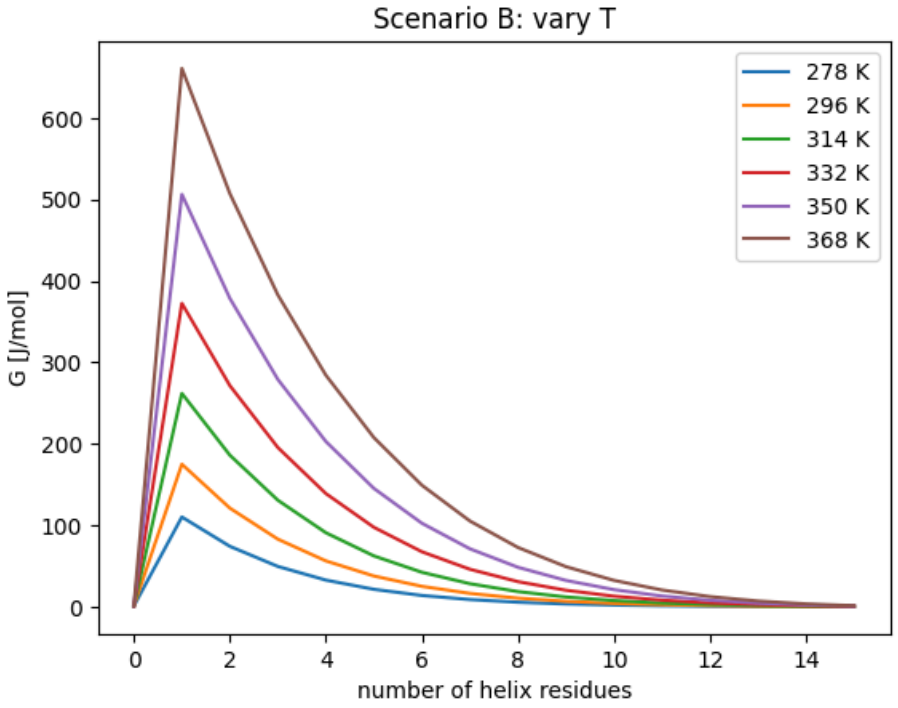
s=0.1


Scenario B: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
0
2
4
6
8
10
12
14

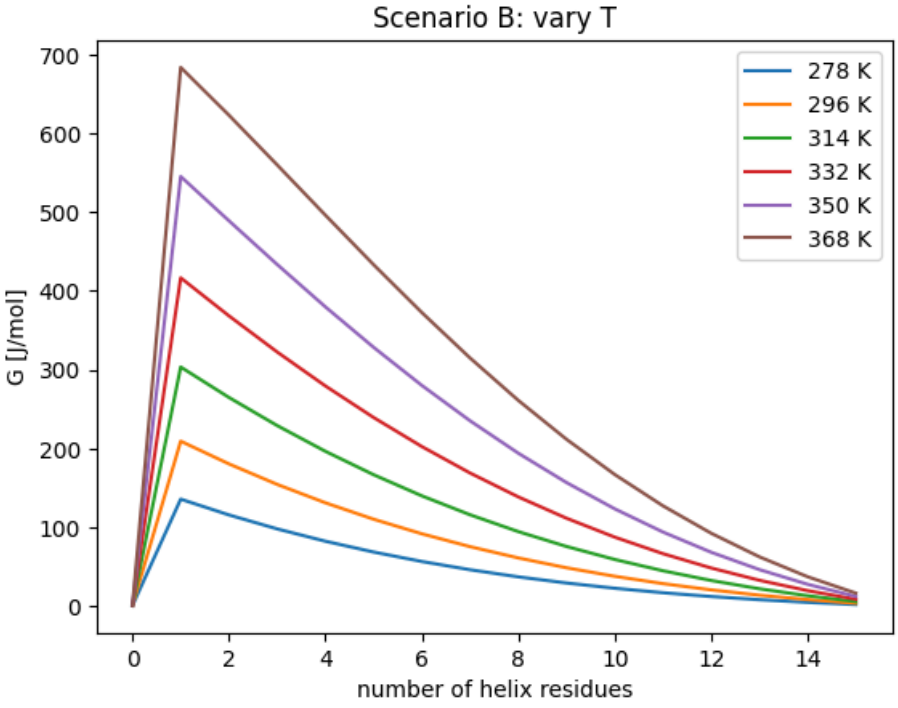
s=0.3


Scenario B: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
500
0
2
4
6
8
10
12
14

s=0.5

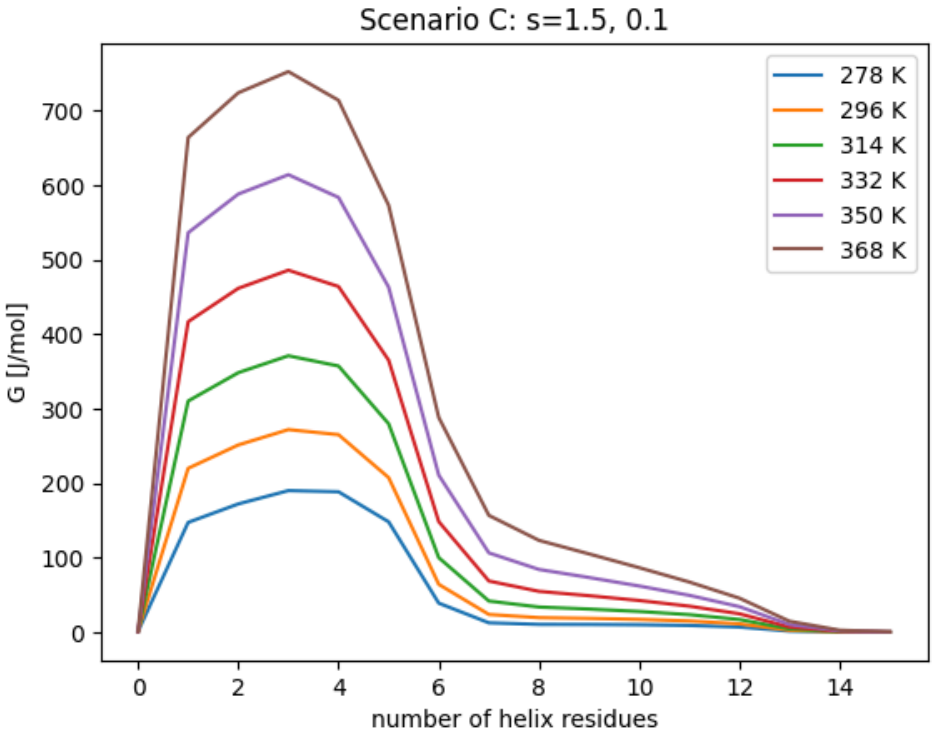

Scenario B: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
500
600
0
2
4
6
8
10
12
14

s=0.7


Scenario B: vary T
278 K
296 K
314 K
332 K
350 K
368 K
G [J/mol]
number of helix residues
0
100
200
300
400
500
600
700
0
2
4
6
8
10
12
14

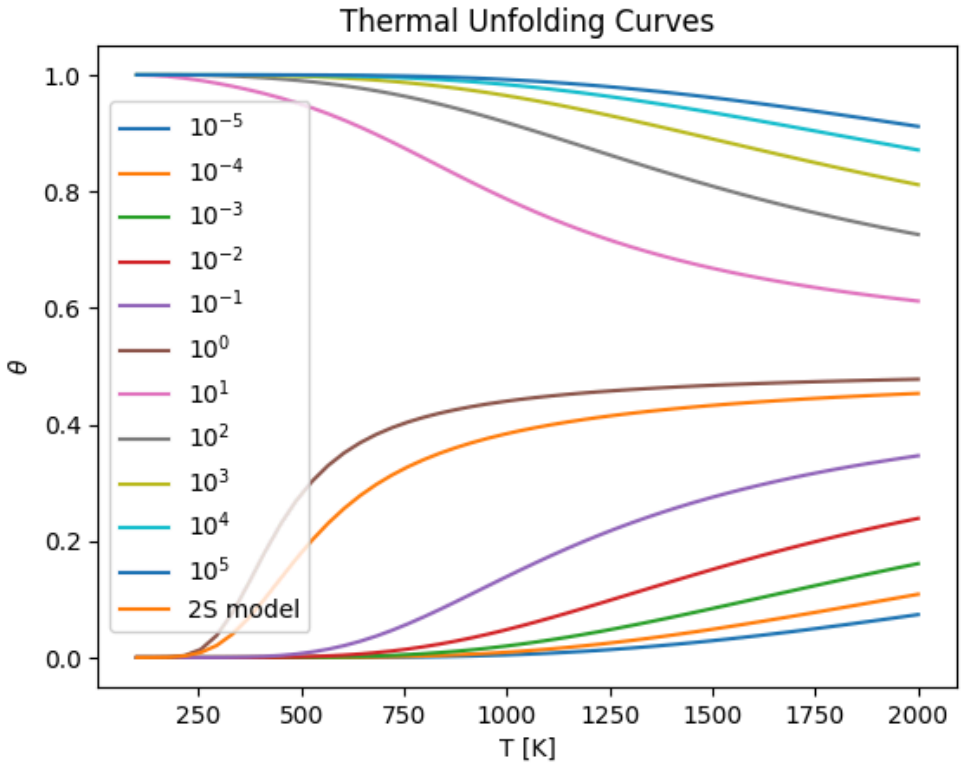
s=0.9

It can be seen in the above plots how the free energy varies with no. of helix residues(n). Unlike scenario A, here the peak is at n = 1 for all the s values. The initial peak occurs due to difficulty in nucleating the peptide with helical residue. The magnitude of the peak however increases from 200 J/mol to 700 J/mol as s increases from 0.1 to 0.9. However it is seen that the peak falls in a slower manner compared to its ascent, which is opposite of what is observed in scenario A where the ascent is slower then the descent. Here the ΔG is at best zero, which indicates that folding is not a favourable process in these conditions.
For scenario C,



For scenario C, there is also the possibility that the helix can transition back into coil. Here the peak is at n = 3 and it does increase in magnitude with temperature. The movement of the peak can be observed by changing the s values in the shared notebook.

Thermal unfolding curves:



The above is a plot of fractional helicity vs temperature. Melting temperature is defined as the temperature at which the fractional helicity reaches 0.5. We see that only two curves reach 0.5 fractional helicity s = 1 and the 2s curve. The melting temperature for s = 1 is 759.18K and for the 2s model it is 1146.94K.

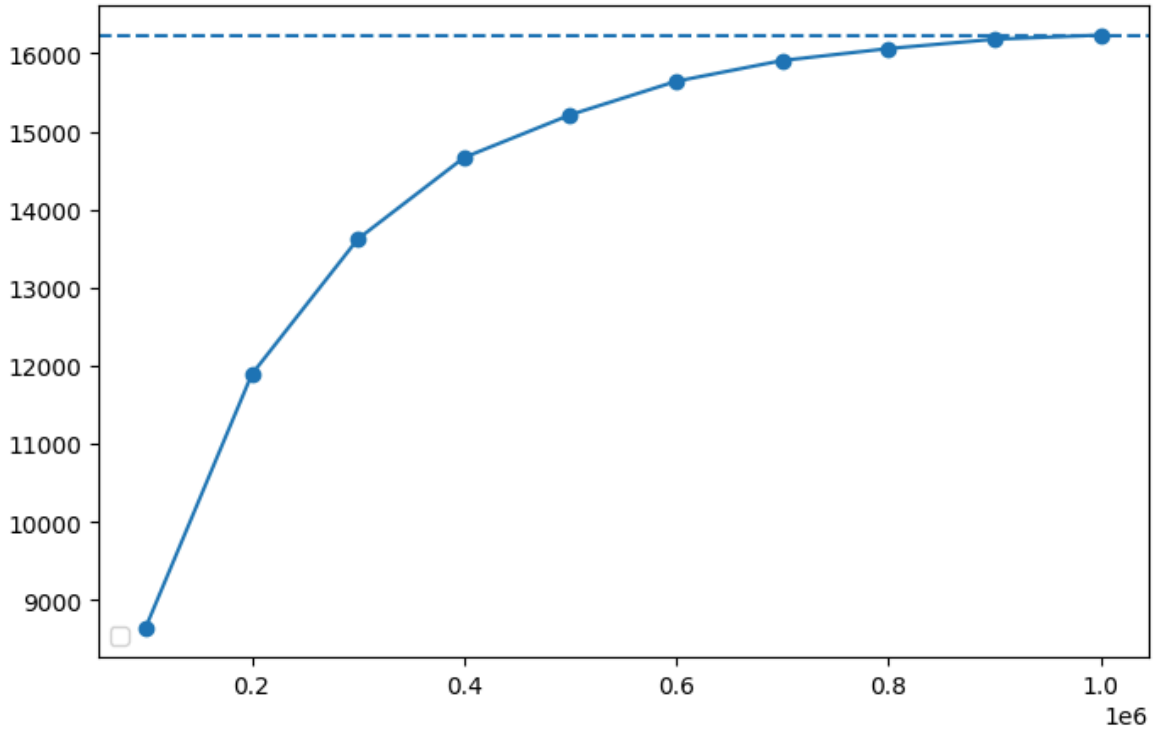
Monte Carlo simulation:

We performed a monte carlo simulation on a 15 residue peptide, each residue can be in folded helix form or in unfolded coil form. Coil was represented by 0 and helix by 1, we simulated the peptide using a list containing 1s and 0s. Starting from a list of 15 zeros, a residue at a random position underwent transition. The decision of making a transition from current state to a valid next state was done using the metropolis criterion(MC). The statistical weights used for applying the MC were calculated using the Zimm Bragg's model. Values used for the simulation are s = 2 and $\sigma = 10^{-3}$.

Predicting the microscopic routes available:
Starting from a fully unfolded state, the first residue to flip into a helix can be any one of the 15 residues .Once that happens, the only allowed moves are to extend the helix to either the left or the right end according to SSA. To reach full helicity , we to have convert the remaining 14 residues from coil (0) to helix (1).The remaining 14 residues can be added to the left or the right of the existing helix residues .Since each of the 14 residue has 2 choices(0/1), the total number of possible routes are = 2^14 = 16384.

Here we assume that only one residue is allowed to undergo a transition from a coil to helical state at a given step.also during each transition of a residue from coil to helix the ΔG change is negative as per the Zimm Bragg model.hence we can infer that there are a total 16384 unique routes for a 15 residue protein to fold.

The following is a plot of no. of routes explored vs no. of simulations.



It can be seen that the graph converges to the value which is predicted.

References:

1. https://pubs.aip.org/aip/jcp/article/38/4/934/207167/On-the-Helix-Coil-Equilibrium-in-Polypeptides
2. https://onlinelibrary.wiley.com/doi/10.1002/prot.21492
3. Book : Molecular driving forces: Statistical thermodynamics in chemistry and biology/ Ken A Dill