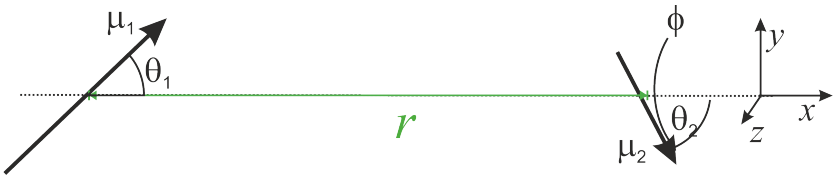
Problem set 7

Due December 8, 2026

1. Consider two point dipoles with moments μ_1 and μ_2, respectively, at distance r, making angles θ_1 and θ_2, respectively, with the line linking them and the second one rotated counterclockwise by ϕ from the plane of the first dipole and the linking line when looking from dipole 1 to dipole 2, as in the picture below.



   (a) Based on the general formula of dipole-dipole interaction energy

$$E = \frac{1}{4\pi\varepsilon_0 r^3}\left[\boldsymbol{\mu}_1 \bullet \boldsymbol{\mu}_2 - 3\left(\boldsymbol{\mu}_1 \bullet \hat{\mathbf{r}}\right)\left(\boldsymbol{\mu}_2 \bullet \hat{\mathbf{r}}\right)\right]$$

   where $\hat{\mathbf{r}}$ is the unit vector of the direction from dipole 1 to dipole 2 and ε_0 is the the dielectric permeability of the vacuum, demonstrate that the energy can be expressed as

$$E = -\frac{\mu_1\mu_2}{4\pi\varepsilon_0 r^3}\left(2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos\phi\right)$$

   The suggested coordinate system to carry out calculations is shown on the right side of the picture but it is not obligatory.

   (b) Derive the formula for the cumulant expansion of the potential of mean force of the interaction of two dipoles averaging over θ_1, θ_2, and ϕ, up to the second order. The general formula is below.

$$W = -k_B T \ln\left\langle \exp\left(-\frac{E}{k_B T}\right)\right\rangle = \langle E\rangle - \frac{1}{2k_B T}\left(\langle E^2\rangle - \langle E\rangle^2\right) + \ldots$$

   Is the average dipole interaction energy long- or short-range?

2. (a) Get the structure of the N-terminal domain of staphylococcal protein A (a three-helix bundle) from the Protein Data Bank (PDB; `https://www.rcsb.org/`; the 1BDD entry). Take the first structure of the NMR-determined ensemble.

   (b) Using the Miyazawa-Jernigan contact free-energy table quoted below (S. Miyazawa, R.L. Jernigan, *Macromolecules*, **1985**, 18, 534-552) and also in numerical form in file `eij_mj85.dat` available from the course web page, compute the sum of residue-residue contact energies of the protein. Use the following formula:

$$E = \sum_{i=1}^{N} \sum_{j=1}^{i-1} \begin{cases} e_{ij} & d_{C_i^\alpha C_j^\alpha} \leq 7\text{Å} \\ 0 & \text{otherwise.} \end{cases}$$

   where e_{ij} is the energy from the table corresponding to the types of the residues with indices i and j and $d_{C_i^\alpha C_j^\alpha}$ is the distance between the α-carbon atoms of the respective residues. Take the values of the energies from the diagonal and upper diagonal of the table (these values are in `eij_mj85.dat`).

Table V
Contact Energies in RT Units: e_{ij} for Upper Half and Diagonal and e_{ij}' for Lower Half

e_{ij}

	CYS	MET	PHE	ILE	LEU	VAL	TRP	TYR	ALA	GLY	THR	SER	GLN	ASN	GLU	ASP	HIS	ARG	LYS	PRO
CYS	-5.44	-5.05	-5.63	-5.03	-5.03	-4.46	-4.76	-3.89	-3.38	-3.16	-2.88	-2.86	-2.73	-2.59	-2.08	-2.66	-3.63	-2.70	-1.54	-2.92
MET	0.70	-6.06	-6.68	-6.33	-6.01	-5.52	-6.37	-4.92	-3.99	-3.75	-3.73	-3.55	-3.17	-3.50	-3.19	-2.90	-3.31	-3.49	-3.11	-4.11
PHE	0.52	-0.22	-6.85	-6.39	-6.26	-5.75	-6.02	-4.95	-4.36	-3.72	-3.76	-3.56	-3.30	-3.55	-3.51	-3.31	-4.61	-3.54	-2.83	-3.73
ILE	0.80	-0.18	0.14	-6.22	-6.17	-5.58	-5.64	-4.63	-4.41	-3.65	-3.74	-3.43	-3.22	-2.99	-3.23	-2.91	-3.76	-3.33	-2.70	-3.47
LEU	0.59	-0.09	0.06	-0.16	-5.79	-5.38	-5.50	-4.26	-3.96	-3.43	-3.43	-3.16	-3.09	-2.99	-2.91	-2.59	-3.84	-3.15	-2.63	-3.06
VAL	0.73	-0.02	0.14	0.00	-0.01	-4.94	-5.05	-4.05	-3.62	-3.06	-2.95	-2.79	-2.67	-2.36	-2.56	-2.25	-3.38	-2.78	-1.95	-2.96
TRP	0.67	-0.63	0.12	0.19	0.11	0.13	-5.42	-4.44	-3.93	-3.37	-3.31	-2.95	-3.16	-3.11	-2.94	-2.91	-4.02	-3.56	-2.49	-3.66
TYR	0.60	-0.12	0.25	0.41	0.19	0.04	-3.55	-2.85	-2.50	-2.48	-2.30	-2.53	-2.47	-2.42	-2.25	-3.33	-2.75	-2.01	-2.80	
ALA	0.59	0.29	0.31	-0.05	0.19	0.10	0.03	0.18	-2.51	-2.15	-2.15	-1.89	-1.70	-1.44	-1.51	-1.57	-2.09	-1.50	-1.10	-1.81
e_{ij}' GLY	0.64	0.37	0.79	0.55	0.56	0.50	0.43	0.36	0.19	-2.17	-2.03	-1.70	-1.54	-1.56	-1.22	-1.62	-1.94	-1.68	-0.84	-1.72
THR	0.70	0.16	0.52	0.23	0.33	0.38	0.26	0.15	-0.04	-0.09	-1.72	-1.59	-1.59	-1.51	-1.45	-1.66	-2.31	-1.97	-1.02	-1.66
SER	0.61	0.22	0.61	0.42	0.48	0.42	0.50	0.21	0.11	0.13	0.00	-1.48	-1.37	-1.31	-1.48	-1.46	-1.94	-1.22	-0.83	-1.35
GLN	0.43	0.30	0.56	0.33	0.25	0.24	-0.01	-0.31	0.00	-0.01	-0.29	-0.18	-0.89	-1.36	-1.33	-1.26	-1.85	-1.85	-1.02	-1.73
ASN	0.93	0.33	0.67	0.91	0.70	0.91	0.39	0.10	0.61	0.32	0.14	0.23	-0.13	-1.59	-1.43	-1.33	-2.01	-1.41	-0.91	-1.43
GLU	1.23	0.43	0.50	0.47	0.58	0.49	0.36	-0.06	0.34	0.45	0.00	-0.15	-0.30	-0.04	-1.18	-1.23	-2.27	-2.07	-1.60	-1.40
ASP	0.54	0.61	0.59	0.68	0.79	0.71	0.28	0.01	0.16	-0.05	-0.32	-0.23	-0.33	-0.06	-0.16	-0.96	-2.14	-1.98	-1.32	-1.19
HIS	0.48	1.11	0.21	0.75	0.44	0.48	0.08	-0.17	0.55	0.53	-0.06	0.19	-0.02	0.18	-0.29	-0.26	-2.78	-2.12	-1.09	-2.17
ARG	0.71	0.23	0.58	0.48	0.43	0.38	-0.16	-0.28	0.44	0.10	-0.42	0.21	-0.72	0.07	-0.79	-0.80	-0.04	-1.39	-0.06	-1.85
LYS	1.11	-0.15	0.53	0.34	0.20	0.45	0.15	-0.31	0.08	0.18	-0.23	-0.15	-0.65	-0.19	-1.08	-0.90	0.24	0.57	0.13	-0.67
PRO	0.40	-0.49	0.29	0.23	0.42	0.10	-0.36	-0.43	0.03	-0.04	-0.21	-0.02	-0.69	-0.04	-0.22	-0.11	-0.19	-0.56	-0.15	-1.18

e_{rr} -2.34 e_{1r} -3.36 -4.22 -4.37 -4.17 -3.93 -3.49 -3.82 -2.91 -2.36 -2.06 -2.04 -1.81 -1.75 -1.70 -1.74 -1.67 -2.41 -1.92 -1.23 -1.89

e_r' -3.18 e_1' -4.00 -4.91 -5.12 -4.88 -4.65 -4.17 -4.36 -3.24 -2.82 -2.34 -2.30 -2.07 -1.98 -1.90 -1.94 -1.81 -2.75 -2.18 -1.50 -2.22

   Assuming that the structure does not change upon mutation, compute the sums of the contact energies of the Y15W mutant of protein A and the other mutants summarized in the table below that contain other mutations in addition to Y15W (the Y15W mutant being the reference), the denaturation free energies of which (ΔG_{D-N}) were determined by Sato and Fersht (*J. Mol. Biol.*, **2007**, 372, 264-267):

Mutation	ΔG_{D-N} [kcal/mol]
Y15W	$\mathbf{4.99 \pm 0.12}$
N12A	5.15 ± 0.07
A13G	3.17 ± 0.02
F14A	4.42 ± 0.06
L20A	2.32 ± 0.02
N29A	5.29 ± 0.03

You can also use the other data of the fourth [ΔG_{D-N}(0M)] column of Table 4 of the above reference. Compare the differences of ΔG_{D-N} of the Y15W (reference) mutant with those of the contact energies. Note that not a complete sum of contact energies must be computed in order to compute the differences. Comment on the differences between the experimental and the estimated values. If you decide to use all data from Table 4 of the paper by Sato and Fersht, determine the correlation between the calculated and the experimental values.