Supplementary Information: *In silico* design of misfolding resistant proteins: the role of structural aspect of competing conformational ensemble for optimization of frustration

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The expressions for the stability gaps; Δ_1 , Δ_2 , Δ_3 and Δ_4 can be given as

$$\Delta_1 = E_f - \langle En_1 \rangle \tag{S1}$$

$$\Delta_2 = E_f - \langle En_2 \rangle \tag{S2}$$

$$\Delta_3 = E_f - \langle En_3 \rangle \tag{S3}$$

$$\Delta_4 = E_f - \langle En_4 \rangle \tag{S4}$$

Here, all terms have the same meaning as described in the manuscript.

For Eq. 19, there is a set of 2732 transcendental equations which determines the Lagrange undetermined multipliers. The variational functionals, V_1 , is maximized with respect to 2600 (= 130 × 20) site identity monomer probabilities, $\omega_i(\alpha)$. This gives a set of 2600 nonlinear equations. Thus, equation 1 to 2600 are differential equations and the general form of this is expressed below,

$$\frac{\partial V_1}{\partial \omega_i(\alpha)} = \frac{\partial}{\partial \omega_i(\alpha)} (S - \lambda_{norm} f_{norm} - \lambda_1 \Delta_1 - \lambda_2 \Delta_2)$$

There are 130 normalization equations (equation 2601 to 2730) and can be obtained from Eq. 17. The general form of this is expressed below,

$$-1+\sum_{\alpha=1}^{m}\omega_i(\alpha)=0$$

Equations 2731 and 2732 are for foldability criteria Δ_1 and Δ_2 respectively. Thus, there are a set of 2732 (=2600+130+1+1) nonlinear transcendental equations for Eq. 19. Similarly, for Eq. 20 to Eq. 24 there is a set of 2732 transcendental equations each.

DEGREE OF FRUSTRATION IN DESIGNED SEQUENCES

Presence of frustration is an important aspect of protein folding and stability. The sections 3.3.3 and 3.3.4 provide insightful information about frustration in the designed sequences. Here, the Monte Carlo designed sequences corresponding to each method are analyzed for their degree of frustration at the target conformation based on the developed potential. It is already stated in the manuscript that the developed

TABLE S1. Attribution of degree of frustration to the amino acids at
the target structure based on developed potential.

Rank	Degree of frustration
1	0
2	+1
3	+2
4	+3
5	+4
6	+5

potential has specific potential values for each of the 20 amino acids at each of the six structural contexts, k=1, 2, 3, 4, 5, and 6. For the calculation of degree of frustration, first for an amino acid, α at i^{th} site in a designed sequence, the structural context of that site in the target structure is determined. Next, the potential values of an amino acid, α are ranked from least to highest across all structural contexts. Based on this ranking, the degree of frustration are assigned to the amino acid, α at i^{th} site of the target structure (refer to Table S1). Then, structural context of amino acid, α at i^{th} site of the target is matched with its structural context in the potential and the corresponding degree of frustration is attributed. This is repeated for each amino acid in the designed sequence. Finally the total degree of frustration for each designed sequence is calculated by adding all these frustration values. The following equations are used to calculate degree of frustration, $F_s^i(\alpha)$ of an amino acid, α of a sth sequence at ith site of the target structure; total degree of frustration, $F_s^{tot}(\alpha)$ in the whole sequence and its average, $F_s^{avg}(\alpha)$ where N=130.

$$F_{s}^{i}(\alpha) = \begin{cases} 0, & \text{if k is at rank 1} \\ +1, & \text{if k is at rank 2} \\ +2, & \text{if k is at rank 3} \\ +3, & \text{if k is at rank 4} \\ +4, & \text{if k is at rank 5} \\ +5, & \text{if k is at rank 6} \end{cases}$$

$$F_s^{tot}(\alpha) = \sum_{i=1}^N F_s^i(\alpha)$$
$$F_s^{avg}(\alpha) = \frac{F_s^{tot}(\alpha)}{N}$$

In section 3.3.3, it is shown that among the design methods, method M_4 designs more frustrated sequences. Moreover, it

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Method	Sl. No. of Sequence in TSR	Total Frustration	Average of Total Frustration
	1	247	
	2	265	
M_2	3	264	252.8
	4	251	
	5	237	
	1	214	
	2	217	
M_3	3	216	213.8
	4	211	
	5	211	
	1	246	
	2	244	
M_4	3	246	244.8
	4	246	
	5	242	
	1	231	
	2	218	
M_5	3	224	225.4
	4	229	
	5	225	
	1	192	
	2	217	
M_6	3	226	209.2
	4	195	
	5	216	
	1	239	
	2	262	
M_7	3	274	258.2
	4	252	
	5	264	

TABLE S2. Determination of degree of frustration of the designed sequences at the target structure based on developed potential.



Fig. S1. Plot of degree of frustration for the sequences designed using method M_2, M_3, M_4, M_5, M_6 and M_7 .

is also shown that the method M_4 is successful in designing sequences which are highly frustrated and specifically destabilize the non-native conformations. From Table S2 and Fig. S1, it can be seen that all the methods designs frustrated sequences. However, the average degree of frustration for the sequences designed by method M_4 is 244.8. Although this average degree of frustration is not highest, however, this is in between the two extremes 209.2 (method M_6) and 258.2 (method M_7). This result indicates that method M_4 designs frustrated sequence. It is also shown in the section 3.2.1 and 3.3.1 that method M_4 designs more stable sequences in terms of percentage of Monte Carlo steps populated in the target state ensemble. This observation has bolstered our previous findings that method M_4 designs frustrated, however, stable sequences at the target structure.

Self consistent mean field theory provides sequences in the form site identity monomer probabilities. Therefore, distribution graphs (Fig. S2(a)- S2(t)) are plotted for the comparison of site-identity monomer probabilities of some sequences designed by the methods M_2 , M_4 and M_7 . The comparison is done between two DSG methods M_2 , M_4 and method M_7 . The two DSG methods are chosen based on the percentage of Monte Carlo steps population in the target state ensemble, method M_2 having the lowest percentage of Monte Caro steps population and method M_4 with its highest value (see Table 5). While method M_7 is having lowest percentage of Monte Carlo steps population among all methods. A distribution plot, say Fig. S2(a), shows the monomer probabilities of alanine at all 130 residue sites of the sequences designed by the three selected methods M_2 , M_4 and M_7 . Similar distribution graphs are plotted for the remaining amino acid residues showing their monomer probabilities at each of the 130 sites. Since only generalized conclusion can be drawn from the method applied here for designing sequences, it is difficult to comment whether a specific residue will be conserved at particular site of the target structure.





(b)







Asparagine

Ma

- M₇

0.12

0.10







(e)



(i)



(j)



(k)

(h)



(l)



Fig. S2. Distribution plot of site-identity monomer probability vs. residue sites for the sequences corresponding to lowest foldability values designed by methods M_2 , M_4 , and M_7 .



Method	Sequence in TSR	Number of refolding	Steps in target(%)	Average of steps in target (%)
	$\Delta_1 = -1.2805$	7674	63.57	
	$\Delta_3 = -6.8465$			
	$\Delta_1 = -1.2806$	7654	46.75	
	$\Delta_3 = -6.8283$			
M_2	$\Delta_1 = -1.2806$	7644	47.25	54.73
	$\Delta_3 = -6.8307$			
	$\Delta_1 = -1.2806$	7674	63.57	
	$\Delta_3 = -6.8313$			
	$\Delta_1 = -1.2806$	7666	52.51	
	$\Delta_3 = -6.8376$			
	$\Delta_1 = -1.2105$	7643	56.07	
	$\Delta_4 = -13.2776$	B (10)		
	$\Delta_1 = -1.2105$	7649	56.16	
	$\Delta_4 = -13.2782$		56.04	55.01
<i>M</i> ₃	$\Delta_1 = -1.2106$	/644	56.34	55.91
	$\Delta_4 = -13.2768$	7(42	56.16	
	$\Delta_1 = -1.2106$	7642	56.16	
	$\Delta_4 = -13.2775$	7()(54.92	
	$\Delta_1 = -1.2105$	/626	54.82	
	$\Delta_4 = -13.2708$	7655	74 78	
	$\Delta_2 = -4.1328$	7033	/4./8	
	$\Delta_3 = -6.7501$	7655	73 48	
	$\Delta_2 = -4.1327$ $\Lambda_2 = -8.7395$	7055	75.48	
M_4	$\Delta_3 = -6.7595$	7654	73 /0	73.96
	$\Delta_2 = -4.1525$ $\Lambda_2 = -8.7372$	7054	75.49	75.70
	$\frac{\Delta_3 = 0.7572}{\Delta_2 = -4.1508}$	7655	73.48	
	$\Delta_2 = -8.7470$	1055	75.40	
	$\Delta_3 = -4.1555$	7654	74 57	
	$\Delta_2 = -8.7147$	7001	71.07	
	$\Delta_2 = -3.1738$	7660	56.01	
	$\Delta_4 = -13.4279$	1000	20101	
	$\Delta_2 = -3.1734$	7684	68.08	
	$\Delta_4 = -13.4176$			
M ₅	$\overline{\Delta_2} = -3.1736$	7678	68.45	62.40
5	$\Delta_{4}^{2} = -13.4195$			
	$\Delta_2 = -3.1737$	7675	55.26	
	$\Delta_4 = -13.4120$			
	$\Delta_2 = -3.1737$	7684	64.22	
	$\Delta_4 = -13.4462$			
	$\Delta_3 = -7.0678$	7668	61.41	
	$\Delta_4 = -13.2386$			
	$\Delta_3 = -7.0645$	7655	66.42	
	$\Delta_4 = -13.2442$			
M_6	$\Delta_3 = -7.0623$	7688	70.38	66.33
	$\Delta_4 = -13.2155$			
	$\Delta_3 = -7.0647$	7662	63.49	
	$\Delta_4 = -13.2221$			
	$\Delta_3 = -7.0638$	7697	69.97	
	$\Delta_4 = -13.2105$			
	Δ=-6.2101	7526	68.05	
	$\Delta = -6.2102$	7108	60.41	
M_7	Δ=-6.2103	7609	64.69	64.65
	$\Delta = -6.2104$	7664	59.81	
	$\Delta = -6.2105$	7378	70.27	

TABLE S3. Results of Monte Carlo simulations on the sequences designed by Monte Carlo simulation method.

Method Squaresc in TSk Number of sites A ₂ =1.2805 (54) (30) (31) (55) A ₄ =0.8465 [26,15] [23,07] [23,84] [20,23] [23,07] [23,84] [20,23] A ₄ =-6.8283 [23,84] [20,23] [23,07] [23,84] [20,23] [23,07] [23,84] [20,23] [23,07] [23,84] [20,23] [23,07]				Class		
$M_2 = \frac{13}{4.6} + \frac{12.00}{7.10} + \frac{12.00}{1.2.34} + \frac{12.00}{1.2.$	Method	Sequence in		Number of sites		
$M_2 = \frac{1-3}{4,a^{a-1},2805} (34) (30) (31) (35) \\ A_3 = -2.806 (31) (28) (30) (31) \\ A_4 = -6.823 (23,42) (29,23) (23,07) (23,44) (26,52) \\ A_4 = -1.2806 (23,37) (24,47) (23,38) (26,15) (23,17) (23,47) (23,48) \\ A_4 = -2.806 (24,38) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17) (23,47) (25,48) (26,15) (23,17$		TSR		Percentage (%)		
$M_2 = \begin{array}{c} \begin{array}{c} A_1 = -6.3865 & (34) & (30) & (3) & (35) \\ \hline A_1 = -0.2806 & (31) & (38) & (30) & (31) \\ \hline A_2 = -6.3233 & (23.84) & (29.23) & (23.07) & (23.84) \\ \hline A_2 = -6.3233 & (23.84) & (29.23) & (23.07) & (23.84) \\ \hline A_2 = -6.3870 & (25.38) & (24.15) & (23.07) & (23.58) \\ \hline A_2 = -6.3870 & (25.38) & (26.15) & (23.07) & (25.38) \\ \hline A_1 = -6.3876 & (25.38) & (21.15) & (23.07) & (23.07) & (25.38) \\ \hline A_1 = -6.3876 & (25.38) & (23.14) & (22.30) & (28.46) \\ \hline A_2 = -6.3876 & (22.38) & (23.84) & (22.30) & (28.46) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (28) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (21.53) & (27) & (35) \\ \hline A_1 = -1.2195 & (40) & (21.53) & (27) & (35) \\ \hline A_1 = -1.2175 & (40) & (21.53) & (27) & (35) \\ \hline A_1 = -1.2175 & (40) & (21.53) & (27) & (35) \\ \hline A_2 = -1.2775 & (15) & (22.30) & (18.46) & (270) \\ \hline A_2 = -1.2775 & (15) & (22.30) & (18.46) & (270) \\ \hline A_2 = -1.2776 & (15) & (22.30) & (12.31) & (23.14) & (23.14) \\ \hline A_2 = -1.3776 & (37) & (35) & (25) & (29) \\ \hline A_2 = -1.527 & (26.15) & (22.30) & (19.23) & (23.31) & (23.41) \\ \hline A_2 = -3.7372 & (26.15) & (22.30) & (19.23) & (23.31) & (23.41) \\ \hline A_2 = -3.747 & (26.15) & (21.53) & (12.53) & (22.5) & (29) \\ \hline A_2 = -1.4176 & (11.53) & (22.5) & (33) & (38) \\ \hline A_2 = -3.747 & (26.15) & (27.5) & (23) & (23) & (23) \\ \hline A_2 = -3.747 & (26.15) & (27.5) & (23) $			1–3	4-6	7–10	11-20
$M_2 = \frac{A_3 = -6.8465}{A_3 = -1.2806} (26.15] (23.07] (23.84] (29.23) A_3 = -6.8233 (23.84] (29.23] (23.07] (23.84] A_4 = -2.8266 (3.3) (34) (30) (31) A_5 = -6.8307 (25.38] (26.15] (23.07] (23.07] (23.64] A_4 = -1.2066 (3.3) (31) (29.07] (21.07] (20.07] A_5 = -6.8313 (26.15] (23.07] (23.07] (23.07] (29.07] A_5 = -6.8370 (25.38] (23.344] (22.301] (24.07] (26.07) A_5 = -6.8370 (25.38] (23.344] (22.301] (26.07] (26.07) A_4 = -1.2105 (40) (28) (27) (35) A_4 = -1.2106 (40) (28) (27) (23) (23) (24) (36) A_5 = -1.1213 (41) (29) (24) (36) A_5 = -1.1258 (46) (28) (28) (27) (23) (29) A_5 = -4.1528 (46) (28) (28) (23) (23) (23) (23) (24) (36) A_5 = -4.1528 (46) (28) (28) (23) (23) (23) (23) (23) (24) (24) (36) A_5 = -4.1528 (46) (28) (28) (23) (23) (23) (23) (23) (23) (23) (23$		$\Delta_1 = -1.2805$	(34)	(30)	(31)	(35)
$M_2 \\ M_2 $		$\Delta_3 = -6.8465$	[26.15]	[23.07]	[23.84]	[26.92]
$M_2 = \begin{array}{ccccccc} M_2 = \begin{array}{cccccccc} M_2 = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_1 = -1.2806$	(31)	(38)	(30)	(31)
M2 A ₁ =-1.2866 (3) <th(3)< th=""> (3) (3) <th(< td=""><td></td><td>$\Delta_3 = -6.8283$</td><td>[23.84]</td><td>[29.23]</td><td>[23.07]</td><td>[23.84]</td></th(<></th(3)<>		$\Delta_3 = -6.8283$	[23.84]	[29.23]	[23.07]	[23.84]
$M_4 = \frac{A_3 = -6.807}{A_3 = -1.2806} (23.28) (26.15) (23.07) (23.07) (25.38) A_4 = -1.2806 (34) (30) (30) (30) (35) A_4 = -1.2806 (33) (31) (23.07) (27.09) A_4 = -1.2806 (23.381 (23.841 (22.30) (28.46) A_4 = -1.2105 (40) (28) (27) (35) A_4 = -1.32782 (30.761 (22.39) (20.00) (26.92) A_4 = -1.32782 (30.761 (22.39) (20.00) (26.92) A_4 = -1.32783 (30.761 (22.39) (20.00) (26.92) A_4 = -1.32783 (30.761 (22.39) (20.00) (26.92) A_4 = -1.32783 (30.761 (21.53) (20.761 (26.92) A_4 = -1.32783 (31.53) (22.30) (18.461 (27.69) A_4 = -1.32783 (31.53) (22.30) (18.461 (27.69) A_4 = -1.32784 (31.53) (22.30) (18.461 (27.69) A_4 = -1.32784 (31.53) (22.30) (18.461 (27.69) A_4 = -1.32785 (36.92) (21.53) (19.21) (22.30) A_4 = -1.3278 (48) (28) (25) (29) (A_4 = -1.3278 (46) (28) (29) (25) (29) A_4 = -1.3278 (46) (28) (29) (20) (30) A_4 = -1.3278 (46) (28) (29) (20) (30) A_4 = -1.3278 (47) (29) (23) (29) (A_4 = -1.3476 (16.92) (21.53) (19.23) (23.07) A_4 = -1.3476 (16.92) (21.53) (19.23) (23.07) A_4 = -1.3476 (31.53) (29) (29) (29) (A_4 = -1.3477 (26.15) (21.53) (19.23) (23.07) (A_4 = -1.34279 (26.15) (21.53) (29) (39) (A_4 = -1.3427 (33) (27) (31) (32) (A_4 = -1.3427 (33) (27) (33) (39) (A_4 = -1.3426 (31.53) (20.66) (23) (39) (A_4 = -1.3426 (31.53) (20.66) (23) (31) (A_4 = -1.3426 (29) (29.23) (21.53) (23) (39) (A_4 = -1.3426 (31.53) (20.76) (27) (23) (39) (A_4 = -1.3426 (29) (29) (29) (23) (33) (39) (41) (A_4 = -6.2103 (29) (29) (29) (23) (33) (31) (41) (42.50 (29) (29) (29) (33) (31) (41) (42.50 (29) (29) (29) (33) (31) (41) (42.50 (29) (29) (29) (33) (31) (41) (42.5$	M_2	$\Delta_1 = -1.2806$	(33)	(34)	(30)	(33)
$M_{4} = \frac{A_{3} = -6.813}{A_{3} = -6.813} = \frac{(26.15)}{(25.15)} = \frac{(23.07)}{(23.07)} = \frac{(23.07)}{(22.09)} = \frac{(23.07)}{(27)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(29)} = \frac{(23.07)}{(21.53)} = \frac{(23.07)}{(27)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27.07)} = \frac{(23.07)}{(25.53)} = \frac{(27.07)}{(27.07)} = \frac{(23.07)}{(25.57)} = \frac{(27.07)}{(27.07)} = \frac{(27.07)}{(25.57)} = \frac{(27.07)}{(27.07)} = \frac{(27.07)}{($		$\Delta_3 = -6.8307$	[25.38]	[26.15]	[23.07]	[25.38]
$M_{5} = \frac{A_{3} = -6.8313}{A_{3} = -1.2806} (33) (31) (2307) (23.07) (27.69) (37) (35) (37) (35) (37) (38.46) (37) (38.46) (37) (38.46) (37) (38.46) (37) (38.46) (37) (38) (37) (37) (38) (37) (3$		$\Delta_1 = -1.2806$	(34)	(30)	(30)	(36)
$M_{1} = -1.2806 (33) (31) (29) (37) \\ A_{1} = -1.2105 (40) (28) (27) (35) \\ A_{1} = -1.2105 (40) (29) (20) (20) (26.92) \\ A_{1} = -1.2106 (40) (29) (20) (20) (26.92) \\ A_{1} = -1.2106 (40) (28) (27) (35) \\ A_{1} = -1.2106 (41) (29) (24) (27) (35) \\ A_{1} = -1.2105 (41) (29) (24) (26) (27) (35) \\ A_{1} = -1.2105 (41) (29) (24) (26) (27) (35) \\ A_{1} = -1.2105 (41) (29) (24) (26) (27) (35) (21) (27) (26) (21) (27) (26) (21) (27) (26) (21) (27) (26) (21) (27) (2$		$\Delta_3 = -6.8313$	[26.15]	[23.07]	[23.07]	[27.69]
$M_{5} = -6.8376 [25.38] [23.84] [22.30] [23.46] \\ A_{4} = -13.2165 (40) (28) (27) (55) \\ A_{4} = -13.2776 [30.76] [21.53] [20.76] [26.92] \\ A_{4} = -13.2782 [30.76] [21.53] [20.76] [26.92] \\ A_{4} = -13.2788 [30.76] [22.30] [20.00] [26.92] \\ A_{4} = -13.2788 [30.76] [22.30] [20.00] [26.92] \\ A_{4} = -13.2788 [30.76] [22.30] [20.00] [26.92] \\ A_{4} = -13.2788 [30.76] [21.53] [20.77] [26.92] \\ A_{4} = -13.2788 [31.53] [22.30] [26.76] [26.92] \\ A_{4} = -13.2788 [31.53] [22.30] [26.76] [26.92] \\ A_{4} = -13.2788 [31.53] [22.30] [26.76] [27.93] \\ A_{4} = -8.7561 [36.92] [21.53] [19.23] [22.30] \\ A_{2} = -4.1528 (48) (28) (25) (27) \\ A_{4} = -4.7395 [36.92] [21.53] [19.23] [22.30] \\ A_{2} = -4.1528 (48) (28) (25) (25) (29) \\ A_{2} = -4.7470 [36.92] [21.53] [19.23] [22.30] \\ A_{2} = -4.1528 (47) (25) (33) (33) (38) \\ A_{2} = -4.1528 (47) (25) (33) (33) (38) \\ A_{2} = -4.1528 (47) (25) (33) (33) (38) \\ A_{2} = -4.1528 (47) (25) (33) $		$\Delta_1 = -1.2806$	(33)	(31)	(29)	(37)
$M_{3} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_3 = -6.8376$	[25.38]	[23.84]	[22.30]	[28.46]
$M_{5} = \begin{array}{c c c c c c c c c c c c c c c c c c c $		$\Delta_1 = -1.2105$	(40)	(28)	(27)	(35)
$M_{3} = (1, 2105) (40) (28) (27) (35) (26.52) (36) (37) (21.53) (20.76) (26.92) (36) (37) (37) (37) (37) (37) (37) (37) (37$		$\Delta_4 = -13.2776$	[30.76]	[21.53]	[20.76]	[26.92]
$M_3 = M_4 = -13.2782 [30.76] [21.53] [20.76] [26.92] (26) (35) A_4 = -13.2768 [30.76] [22.30] (20.00] [26.92] A_4 = -1.3.2768 [30.76] [21.53] [20.76] [26.92] A_4 = -13.2775 [30.76] [21.53] [20.76] [26.92] A_4 = -13.2775 [30.76] [21.53] [20.76] [26.92] A_4 = -13.2775 [30.76] [21.53] [19.23] [22.30] A_4 = -4.1528 (48) (28) (25) (29) (25) (29) A_4 = -4.1528 (48) (28) (24) (30) A_4 = -4.1523 (47) (29) (25) (29) (25) (29) A_4 = -4.1523 (47) (29) (25) (29) (23) (23.0) A_4 = -4.1523 (47) (29) (25) (29) (43) (23.0) A_4 = -4.1523 (47) (29) (25) (29) (43) (23.0) A_4 = -4.1523 (47) (29) (25) (29) (43) (23.0) A_4 = -4.1523 (47) (29) (25) (29) (43) (23.0) A_4 = -4.1523 (47) (29) (25) (29) (43) (23.0) A_4 = -4.1523 (47) (28) (25) (29) (43) (23.0) A_4 = -4.1525 (47) (28) (25) (33) (38) (23.0) A_4 = -4.157 (36.15] (21.53] (19.23] (22.30) A_4 = -4.157 (36.15] (21.53] (19.23] (22.30) A_4 = -4.157 (36.15] (21.53] (19.23] (22.30) A_4 = -1.34126 (31.53] (20.01] (23.34] (24.61] A_4 = -1.34126 (21.23.0] (19.23] (20.76] (20.76] (20.76] (20.76] A_4 = -1.34126 (21.23.0] (20.76] (20.76] (20.76] (20.76] A_4 = -1.34120 (20.23] (20.76] (20.76] (20.76] (20.23) A_4 = -1.34120 (20.23] (20.76] (20.76] (20.76] (20.23) A_4 = -1.34120 (20.23] (20.76] (20.76] (20.76] (20.23) A_4 = -1.34120 (20.23) (20.76] (20.76] (20.76] (20.23) A_4 = -1.34120 (20.23) (20.76] (20.76] (20.23) (30) A_4 = -1.34120 (20.23) (20.76] (20.76] (20.76] (20.23) (30) A_4 = -1.32210 (20.23) (20.76] (20.76] (20.76] (20.23) (30) A_4 = -1.32210 (20.30) (20.76] (20.76] (20.76] (20.76] (20.44) A_4 = -1.32210 (20.30) (20.76] (20.76$		$\Delta_1 = -1.2105$	(40)	(28)	(27)	(35)
$M_3 \qquad \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_4 = -13.2782$	[30.76]	[21.53]	[20.76]	[26.92]
$M_{4} = -13.2768 [30.76] [22.30] [20.00] [26.92] A_{4} = -13.2775 [30.76] [21.53] [20.76] [26.92] A_{4} = -13.2775 [30.76] [21.53] [22.30] [18.46] [27.69] A_{4} = -13.2768 [31.53] [22.30] [18.46] [27.69] A_{2} = -4.1528 (48) (23) (25) (29) A_{2} = -8.7561 [36.92] [21.53] [19.23] [22.30] A_{2} = -8.7572 [48] (48) (28) (23) (24) (30) A_{2} = -4.7395 [36.92] [21.53] [19.23] [22.30] A_{2} = -4.7395 [36.92] [21.53] [19.23] [22.30] A_{2} = -4.7372 [36.15] [22.30] (19.23] [22.30] A_{2} = -4.7372 [36.15] [22.30] (19.23] [22.30] A_{2} = -4.1525 (47) (29) (25) (29) A_{3} = -8.740 [36.92] [21.53] [19.23] [22.30] A_{2} = -4.1555 (47) (28) (25) (29) A_{3} = -8.7147 [36.15] [21.53] [19.23] [23.07] A_{2} = -3.1738 (34) (25) (33) (38) A_{4} = -13.4279 [26.15] [19.23] [23.07] A_{4} = -3.1736 (34) (25) (33) (38) A_{4} = -13.4176 [31.53] [20.00] [23.844] [24.61] A_{4} = -13.4176 [31.53] [20.00] [23.844] [24.61] A_{4} = -13.4176 [31.53] [20.00] [23.844] [24.61] A_{4} = -13.4120 [29.23] [20.76] [20.76] [20.76] [20.33 A_{4} = -13.4120 [29.23] [20.76] [20.76] [20.76] [20.33 A_{4} = -13.4120 [29.23] [20.76] [20.76] [20.76] [20.76] A_{4} = -13.221 [22.30] [19.23] [20.76] [20.76] [20.76] [20.76] A_{4} = -13.221 [22.30] [20.76] [20.76] [20.76] [20.76] [20.76] A_{4} = -13.221 [22.30] [20.76] [20.76] [20.76] [20.76] A_{4} = -13.2105 [20.92] [21.63] [20.76] [21.53] [23.84] A_{4} = -6.2101 (24) (28) (35) (35) (36) A_{4} = -13.2105 [20.92] [21.69] (30.76] [23.84] A_{4} = -6.2103 (22) [20.7] [23.9] (30.76] [23.84] A_{4} = -6.2103 (22) [20.7] [23.9] (30.76] [23.84] A_{4} = -6.2103 (22) [20.7] [23.9] (30.76] [23.84] [33.53] A_{4} = -6.2103 (22) [20.7] [20.7] [23.83] [$	M_3	$\Delta_1 = -1.2106$	(40)	(29)	(26)	(35)
$M_{5} = \begin{array}{c c c c c c c c c c c c c c c c c c c $		$\Delta_4 = -13.2768$	[30.76]	[22.30]	[20.00]	[26.92]
$M_{5} = \frac{A_{4} = -13.27/5}{A_{4} = -1.2703} (41) (29) (24) (26) (24) (36) (25) (27) (2$		$\Delta_1 = -1.2106$	(40)	(28)	(27)	(35)
$M_{4} = \frac{\Lambda_{4} = -1.2103}{\Lambda_{2} = -1.32768} (31) (22) (22) (23) (18) (41) (25) (29) (23) (23) (25) (29) (24) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (29) (26) (25) (25) (29) (26) (25) (25) (29) (26) (25) (25) (29) (26) (25) (25) (29) (26) (25) (25) (29) (26) (25) (25) (29) (26) (26) (26) (26) (26) (26) (26) (26$		$\Delta_4 = -13.2775$	[30.76]	[21.53]	[20.76]	[26.92]
$M_{4} = \frac{A_{4}^{=-1.5,268} (31,3)}{A_{4}^{=-4.1528} (48)} (28) (25) (25) (29)}{A_{3}^{=-8.7561} (36,92) (21,53] (19,23] (12,30)}{A_{2}^{=-4.1527} (48)} (28) (24) (30)}{A_{2}^{=-8.7395} (36,92) (21,53] (18,46] (23,07)}{A_{2}^{=-4.1527} (48)} (28) (25) (25) (29)}{A_{2}^{=-8.7372} (36,15] (22,30) (19,23) (22,30)}{A_{2}^{=-4.1555} (47) (28) (25) (25) (29)}{A_{2}^{=-4.1555} (47) (28) (25) (25) (29)}{A_{2}^{=-4.1555} (47) (28) (25) (25) (29)}{A_{2}^{=-4.1555} (47) (28) (25) (33) (38)}{A_{2}^{=-3.1738} (34) (25) (33) (38)}{A_{2}^{=-3.1738} (34) (25) (33) (38)}{A_{2}^{=-3.1738} (41) (26) (31) (33) (38)}{A_{2}^{=-3.1734} (41) (26) (31) (33) (38)}{A_{2}^{=-3.1737} (38) (27) (27) (27) (38)}{A_{2}^{=-3.1737} (38) (27) (27) (27) (38)}{A_{2}^{=-3.1737} (42) (25) (25) (29) (34)}{A_{2}^{=-13.4120} (29,23) (25) (29) (34)}{A_{2}^{=-13.420} (29,23) (25) (29) (34)}{A_{2}^{=-13.420} (29,23) (25) (29) (34)}{A_{2}^{=-13.420} (29,23) (25) (29) (34)}{A_{2}^{=-13.420} (29,23) (20,76) (20,76) (29,23) (22,15)}{A_{2}^{=-3.1737} (42) (25) (25) (29) (34)}{A_{2}^{=-13.420} (29,23) (29) (25) (32) (29) (34)}{A_{2}^{=-13.420} (35) (35) (38) (25) (32) (32)}{A_{2}^{=-13.2420} (35) (35) (38) (25) (32) (32) (34)}{A_{2}^{=-13.2420} (35) (25) (32) (27) (37) (37) (36) (23) (39)}{A_{2}^{=-13.2420} (35) (28) (27) (37) (37) (37) (36) (28) (27) (37) (37) (37) (36) (28) (27) (37) (37) (37) (36) (28) (27) (37) (37) (37) (36) (28) (28) (35) (36) (28) (31) (37) (37) (37) (36) (28) (35) (36) (28) (31) (37) (37) (37) (37) (36) (28) (35) (36) (28) (31) (37) (37) (37) (37) (36) (28) (35) (36) (28) (31) (37) (37) (37) (37) (36) (26) (28) (35) (31) (37) (37) (37) (37) (37) (36) (28) (35) (36) (28) (31) (37) (37) (37) (37) (37) (36) (28) (35) (36) (28) (31) (37) (37) (37) (37) (37) (37) (37) (37$		$\Delta_1 = -1.2103$	(41)	(29)	(24)	(36)
$M_4 = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_4 = -13.2768$	[31.53]	[22.30]	[18.46]	[27.69]
$M_4 = \frac{\lambda_3 = -8.7501}{\lambda_2 = -4.1527} (48) (28) (24) (30) (24) (30) (23) (23) (25) (29) (25) (25) (29) (25) (25) (29) (25) (26) (26) (26) (26) (26) (26) (26) (26$		$\Delta_2 = -4.1528$	(48)	(28)	(25)	(29)
$M_{4} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_3 = -8.7561$	[36.92]	[21.53]	[19.23]	[22.30]
$M_4 = \frac{\lambda_3 = -8.795}{\lambda_3 = -4.1523} = \frac{(1+3.5)}{(1+7)} = \frac{(1+3.5)}{(2-9)} = \frac{(1+3.5)}{(2-5)} = \frac{(1+3.5)}{(2-9)} = \frac{(2-5)}{(2-9)} = \frac{(2-5)}{(2-5)} =$		$\Delta_2 = -4.1527$	(48)	(28)	(24)	(30)
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	14	$\Delta_3 = -8.7395$	[36.92]	[21.53]	[18.46]	[23.07]
$M_{5} = \frac{A_{3} = -8, 742}{A_{2} = -4, 1508} (48) (25) (19, 23) (12, 23) (22, 30) (25) (29) (21, 53] (19, 23) (22, 30) (23, 32) (24, 31) (25) (21, 32) (25, 31) (24, 32) (25, 31) (24, 32) (25, 31) (25$	M_4	$\Delta_2 = -4.1523$	(47)	(29)	(25)	(29)
$M_{5} = \frac{\Lambda_{2}^{2=4,1306}}{\Lambda_{2}^{2=4,1306}} \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_3 = -8.7372$	[30.15]	[22.30]	[19.23]	[22.30]
$M_{2} = -4.155 \qquad (47) \qquad (28) \qquad (21.53) \qquad (19.23) \qquad (22.5) \qquad (30) \\ \Delta_{3} = -8.7147 \qquad [36.15] \qquad (21.53) \qquad (19.23) \qquad (23.07) \\ \Delta_{2} = -3.1738 \qquad (34) \qquad (25) \qquad (33) \qquad (38) \\ \Delta_{4} = -13.4279 \qquad [26.15] \qquad (19.23) \qquad (25.58) \qquad (29.23) \\ \Delta_{2} = -3.1734 \qquad (41) \qquad (26) \qquad (31) \qquad (32) \\ \Delta_{4} = -13.4176 \qquad [31.53] \qquad (200) \qquad (23.84] \qquad (24.61) \\ \Delta_{4} = -3.4736 \qquad (37) \qquad (31) \qquad (34) \qquad (28) \\ \Delta_{4} = -13.4195 \qquad [28.46] \qquad (23.84] \qquad (26.15] \qquad (21.53) \\ \Delta_{2} = -3.1737 \qquad (38) \qquad (27) \qquad (27) \qquad (38) \\ \Delta_{4} = -13.4195 \qquad [29.23] \qquad [20.76] \qquad (20.76] \qquad (29.23) \\ \Delta_{4} = -13.44102 \qquad [29.23] \qquad (20.76] \qquad (20.76] \qquad (29.23) \\ \Delta_{4} = -13.4462 \qquad [32.30] \qquad (19.23) \qquad (22.30) \qquad (26.15] \\ \Delta_{4} = -7.0678 \qquad (35) \qquad (38) \qquad (25) \qquad (32) \\ \Delta_{4} = -13.2422 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (17.69) \qquad (30.00) \\ \Delta_{4} = -13.2442 \qquad [31.53] \qquad (20.76] \qquad (28) \qquad (27) \qquad (37) \\ \Delta_{4} = -13.2105 \qquad (26.92] \qquad (29) \qquad (32) \qquad (34) \\ \Delta_{4} = -13.2105 \qquad (26.92] \qquad (27.69] \qquad (21.53) \qquad (26.15] \\ \Delta_{3} = -7.0647 \qquad (42) \qquad (22) \qquad (32) \qquad (34) \\ \Delta_{4} = -13.2105 \qquad (26.92] \qquad (27.69] \qquad (21.53) \qquad (23.84] \\ \Delta_{4} = -6.2101 \qquad (24) \qquad (28) \qquad (35) \qquad (41) \\ \Delta_{4} = -6.2103 \qquad (22) \qquad (34) \qquad (35) \qquad (41) \\ (40) \qquad (43) \\ \Delta_{4} = -6.2103 \qquad (22) \qquad (34) \qquad (35) \qquad (44) \\ (23.07] \qquad (17.69] \qquad (30.76] \qquad (28.46] \\ \Delta_{4} = -6.2104 \qquad (30) \qquad (16) \qquad (40) \qquad (44) \\ (23.07] \qquad (12.30) \qquad (30.76] \qquad (33.84) \\ \Delta_{4} = -6.2104 \qquad (30) \qquad (16) \qquad (29) \qquad (33) \qquad (39) \\ (40) \qquad (41) \\ (22.30) \qquad (22.30) \qquad (23.30 \qquad (29) \qquad (25.38] \qquad (30.00) \\ (37.6) \qquad (37.$		$\Delta_2 = -4.1508$	(48)	(28)	(25)	(29)
$M_{5} = \frac{M_{3}^{2-4,1733}}{M_{2}^{2-3,1738}} \begin{pmatrix} (47) \\ (36,15] \\ (21,53] \\ (21,53] \\ (22,38] \\ (44) \\ (25) \\ (33) \\ (33) \\ (38) \\ (34) \\ (25) \\ (31) \\ (32) \\ (32) \\ (34) \\ (32) \\ (34) \\ (32) \\ (34) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (34) \\ (34) \\ (28) \\ (32) \\ (34) \\ (34) \\ (34) \\ (28) \\ (32) \\ (34) \\ (34) \\ (34) \\ (34) \\ (28) \\ (32) \\ (34) \\ (34) \\ (34) \\ (34) \\ (28) \\ (32) \\ (34) \\ (34) \\ (34) \\ (34) \\ (28) \\ (32) \\ (34) \\ (35) \\ (35) \\ (38) \\ (25) \\ (29) \\ (34) \\ (34) \\ (34) \\ (35) \\ (34) \\ (34) \\ (35) \\ (34) \\ (35) \\ (35) \\ (36) \\ (35) \\ (36) \\ (37$		$\Delta_3 = -8.7470$	[30.92]	(28)	(25)	(20)
$M_{5} = \frac{\Lambda_{3}^{6,1/4}}{\Lambda_{4}^{13,4279}} \begin{bmatrix} [24,51] \\ [25] \\ [33] \\ [43] $		$\Delta_2 = -4.1333$	(47)	(28)	(23)	(30)
$M_{5} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_3 = -6.7147$	(24)	(25)	(22)	(28)
$M_{5} = \frac{\lambda_{4} = -13.4279}{\lambda_{4} = -13.4176} [21.53] [22.53] [23.84] [24.61] [24.61] [23.84] [24.61$		$\Delta_2 = -3.1738$	(34)	(23)	(55)	(38)
$M_{5} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_4 = -13.4279$	(41)	(26)	(21)	(22)
$ M_5 \qquad \begin{array}{c c c c c c c c c c c c c c c c c c c $		$\Delta_2 = -3.1734$	(41)	[20]00]	(31)	(32)
$M_{5} = \begin{array}{ccccccccccccccccccccccccccccccccccc$	М-	$\Delta_4 = -13.4170$	(37)	(31)	(34)	(28)
$M_{7} = \begin{bmatrix} \frac{\Delta_{4} = -13.4125}{\Delta_{2} = -3.1737} & [120.40] & [120.43] & [120$	1115	$\Delta_2 = -3.1730$ $\Delta_4 = -13.4195$	[28,46]	[23.84]	[26,15]	(28)
$M_{7} = \begin{bmatrix} \Delta_{2} - 5.1737 & (39) & (27) & (27) & (39) \\ \Delta_{4} - 13.4120 & [29.23] & [20.76] & [20.76] & [29.23 \\ \Delta_{2} - 3.1737 & (42) & (25) & (29) & (34) \\ \Delta_{4} - 13.4462 & [32.30] & [19.23] & [22.30] & [26.15] \\ \Delta_{3} - 7.0678 & (35) & (38) & (25) & (32) \\ \Delta_{4} - 13.2386 & [26.92] & [29.23] & [19.23] & [24.61] \\ \Delta_{3} - 7.0645 & (41) & (27) & (23) & (39) \\ \Delta_{4} - 13.2142 & [31.53] & [20.76] & [17.69] & [30.00] \\ \Delta_{3} - 7.0647 & (42) & (22) & (32) & (34) \\ \Delta_{4} - 13.2155 & [29.23] & [21.53] & [20.76] & [28.46] \\ \Delta_{3} - 7.0647 & (42) & (22) & (32) & (34) \\ \Delta_{4} - 13.2155 & [29.23] & [16.92] & [24.61] & [26.15] \\ \Delta_{3} - 7.0638 & (35) & (36) & (28) & (31) \\ \Delta_{4} - 13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \Delta_{4}13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \Delta_{4}13.2105 & [26.92] & [27.69] & [30.76] & [28.46] \\ \Delta_{4}6.2101 & (24) & (28) & (35) & (43) \\ \hline M_{7} & \frac{18.46}{\Delta} & [21.53] & [26.92] & [33.07] \\ \hline \Delta_{4} - 6.2102 & (30) & (23) & (40) & (37) \\ \hline - & & & & & & & & & & & & & & & & & &$		$\Delta_4 = -13.4195$	(38)	(27)	(27)	(38)
$M_{7} = \begin{bmatrix} A_{4} = -13.4120 & [23.2] & [20.76$		$\Delta_2 = -3.1737$ $\Delta_4 = -13.4120$	[20 23]	[20,76]	[20,76]	(38)
$M_{7} = \begin{bmatrix} A_{2} = 3.1462 & [32.30] & [19.23] & [22.30] & [26.15] \\ A_{3} = -7.0678 & (35) & (38) & (25) & (32) \\ A_{4} = -13.2386 & [26.92] & [29.23] & [19.23] & [24.61] \\ \hline A_{3} = -7.0645 & (41) & (27) & (23) & (39) \\ A_{4} = -13.2442 & [31.53] & [20.76] & [17.69] & [30.00] \\ \hline A_{3} = -7.0623 & (38) & (28) & (27) & (37) \\ A_{4} = -13.2155 & [29.23] & [21.53] & [20.76] & [28.46] \\ \hline A_{3} = -7.0647 & (42) & (22) & (32) & (34) \\ \hline A_{4} = -13.2211 & [32.30] & [16.92] & [24.61] & [26.15] \\ \hline A_{3} = -7.0638 & (35) & (36) & (28) & (31) \\ A_{4} = -13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \hline A_{4} = -6.2101 & (24) & (28) & (35) & (43) \\ \hline A_{4} = -6.2102 & (30) & (23) & (40) & (37) \\ \hline A_{4} = -6.2103 & (22) & (34) & (33) & (41) \\ \hline A_{4} = -6.2103 & (22) & (34) & (33) & (41) \\ \hline A_{4} = -6.2104 & (30) & (16) & (40) & (44) \\ \hline A_{4} = -6.2105 & (29) & (29) & (33) & (39) \\ \hline A_{4} = -6.2105 & (29) & (29) & (33) & (39) \\ \hline \end{bmatrix}$		$A_2 = -3.1737$	(42)	(25)	(29)	(34)
$M_{7} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1$		$\Delta_2 = -134462$	[32 30]	[19 23]	[22 30]	[26,15]
$M_{6} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\frac{\Delta_4 - 13.1102}{\Delta_2 - 7.0678}$	(35)	(38)	(25)	(32)
$M_{6} = \begin{bmatrix} 1, 1, 2, 3 \\ \hline A_{3} = -7.0645 \\ \hline A_{4} = -13.2442 \\ \hline A_{3} = -7.0623 \\ \hline A_{4} = -13.2155 \\ \hline A_{4} = -13.2221 \\ \hline A_{3} = -7.0647 \\ \hline A_{4} = -13.2221 \\ \hline A_{3} = -7.0638 \\ \hline A_{4} = -13.2105 \\ \hline A_{4} = -6.2101 \\ \hline A_{4} = -6.2102 \\ \hline A_{5} = -6.2103 \\ \hline A_{5} = -6.2103 \\ \hline A_{5} = -6.2104 \\ \hline A_{5} = -6.2105 \\ \hline A_{5} $		$\Delta_4 = -13.2386$	[26.92]	[29.23]	[19,23]	[24 61]
$M_{6} = \begin{bmatrix} \Delta_{4} = -13.2442 & [31.53] & [20.76] & [17.69] & [30.00] \\ \Delta_{3} = -7.0623 & (38) & (28) & (27) & (37) \\ \Delta_{4} = -13.2155 & [29.23] & [21.53] & [20.76] & [28.46] \\ \Delta_{3} = -7.0647 & (42) & (22) & (32) & (34) \\ \Delta_{4} = -13.2221 & [32.30] & [16.92] & [24.61] & [26.15] \\ \Delta_{3} = -7.0638 & (35) & (36) & (28) & (31) \\ \Delta_{4} = -13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \hline & & & & & & & & & & & & & & & & & &$		$\Delta_4 = -7.0645$	(41)	(27)	(23)	(39)
$M_{6} = M_{6} = \frac{1}{\Delta_{3} = -7.0623} (38) (28) (27) (37) (37) (44) (42) (22) (32) (34) (44) (42) (22) (32) (34) (44) (44) (43) (35) (36) (28) (31) (26.15) (26.92) (27.69) (21.53) (23.84) (28) (31) (24) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (35) (43) (28) (28) (35) (43) (28) (28) (35) (43) (28) (28) (35) (43) (28) (28) (35) (43) (28) (28) (35) (43) (28) (28) (28) (28) (28) (28) (28) (28$		$\Delta_4 = -13.2442$	[31,53]	[20.76]	[17.69]	[30 00]
$M_{7} = \begin{bmatrix} \Delta_{4} = -13.2155 & [29.23] & [21.53] & [20.76] & [28.46] \\ \hline \Delta_{4} = -13.2121 & [32.30] & [16.92] & [24.61] & [26.15] \\ \hline \Delta_{4} = -13.2221 & [32.30] & [16.92] & [24.61] & [26.15] \\ \hline \Delta_{4} = -13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \hline \Delta_{4} = -6.2101 & (24) & (28) & (35) & (43) \\ \hline \Delta_{4} = -6.2102 & (30) & (23) & (40) & (37) \\ \hline \Delta_{4} = -6.2103 & (22) & (34) & (33) & (41) \\ \hline \Delta_{4} = -6.2103 & (22) & (34) & (33) & (41) \\ \hline \Delta_{4} = -6.2104 & (30) & (16) & (40) & (44) \\ \hline \Delta_{4} = -6.2105 & (29) & (29) & (33) & (39) \\ \hline \Delta_{4} = -6.2105 & (29) & (29) & (33) & (39) \\ \hline \Delta_{4} = -6.2105 & (29) & (22.30] & [25.38] & [30.00] \\ \hline \end{bmatrix}$	Μc	$\frac{\Delta_4^2}{\Delta_2^2} = -7.0623$	(38)	(28)	(27)	(37)
$M_7 \qquad \begin{array}{c c c c c c c c c c c c c c c c c c c $	1110	$\Delta_4 = -13.2155$	[29,23]	[21,53]	[20,76]	[28,46]
$M_{7} = \begin{bmatrix} \Delta_{4} = -13.221 & [32.30] & [16.92] & [24.61] & [26.15] \\ \Delta_{3} = -7.0638 & (35) & (36) & (28) & (31) \\ \Delta_{4} = -13.2105 & [26.92] & [27.69] & [21.53] & [23.84] \\ \Delta_{4} = -6.2101 & (24) & (28) & (35) & (43) \\ & & [18.46] & [21.53] & [26.92] & [33.07] \\ \Delta_{2} = -6.2102 & (30) & (23) & (40) & (37) \\ & & [23.07] & [17.69] & [30.76] & [28.46] \\ & & & [16.92] & [26.15] & [25.38] & [31.53] \\ \hline \Delta_{2} = -6.2104 & (30) & (16) & (40) & (44) \\ & & & [23.07] & [12.30] & [30.76] & [33.84] \\ \hline \Delta_{2} = -6.2105 & (29) & (29) & (33) & (39) \\ & & & [22.30] & [22.30] & [22.30] & [25.38] & [30.00] \\ \hline \end{bmatrix}$		$\Delta_{2} = -7.0647$	(42)	(22)	(32)	(34)
$M_{7} = \begin{array}{c ccccccccccccccccccccccccccccccccccc$		$\Delta_4 = -13.2221$	[32.30]	[16.92]	[24.61]	[26,15]
$M_{7} = \begin{array}{c ccccccccccccccccccccccccccccccccccc$		$\Delta_3 = -7.0638$	(35)	(36)	(28)	(31)
$M_{7} = \begin{array}{ccccccccccccccccccccccccccccccccccc$		$\Delta_4 = -13.2105$	[26.92]	[27.69]	[21.53]	[23.84]
$M_7 \qquad \begin{array}{c ccccccccccccccccccccccccccccccccccc$		Δ=-6.2101	(24)	(28)	(35)	(43)
$M_7 \qquad \begin{array}{c ccccccccccccccccccccccccccccccccccc$			[18.46]	[21.53]	[26.92]	[33.07]
$M_{7} \qquad \boxed{\begin{array}{ccccccccccccccccccccccccccccccccccc$		Δ=-6.2102	(30)	(23)	(40)	(37)
$ M_7 \qquad \begin{array}{c ccccccccccccccccccccccccccccccccccc$		-	[23.07]	[17.69]	[30.76]	[28.46]
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	M_7	Δ=-6.2103	(22)	(34)	(33)	(41)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$,		[16.92]	[26.15]	[25.38]	[31.53]
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Δ=-6.2104	(30)	(16)	(40)	(44)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		-	[23.07]	[12.30]	[30.76]	[33.84]
[22.30] [22.30] [25.38] [30.00]		Δ=-6.2105	(29)	(29)	(33)	(39)
			[22.30]	[22.30]	[25.38]	[30.00]

TABLE S4. Comparison of the sequences designed by Monte Carlo simulation method with the sequences designed by mean field method. (**Bold figures in black color indicates class**; number of sites in parentheses are in blue color; percentages in brackets are in magenta color.)

		Class	A.v.o.m.o.c.
Mathad	Saguanga in	Class Number of sites	Average
Methou	TSD	Percentage (%)	over the $parcentage(\%)$
	ISK	1_3	percentage(10)
	$\Delta_1 = -1.2805$	(34)	
	$\Delta_{1} = -6.8465$	[26.15]	
	$\Delta_1 = -1.2806$	(31)	
	$\Delta_3 = -6.8283$	[23.84]	
M_2	$\Delta_1 = -1.2806$	(33)	25.38
2	$\Delta_3 = -6.8307$	[25.38]	
	$\Delta_1 = -1.2806$	(34)	
	$\Delta_3 = -6.8313$	[26.15]	
	$\Delta_1 = -1.2806$	(33)	
	$\Delta_3 = -6.8376$	[25.38]	
	$\Delta_1 = -1.2105$	(40)	
	$\Delta_4 = -13.2776$	[30.76]	
	$\Delta_1 = -1.2105$	(40)	
	$\Delta_4 = -13.2782$	[30.76]	
M_3	$\Delta_1 = -1.2106$	(40)	30.91
	$\Delta_4 = -13.2768$	[30.76]	
	$\Delta_1 = -1.2106$	(40)	
	$\Delta_4 = -13.2775$	[30.76]	
	$\Delta_1 = -1.2103$	(41)	
	$\Delta_4 = -13.2768$	[31.53]	
	$\Delta_2 = -4.1528$	(48)	
	$\Delta_3 = -8.7561$	[36.92]	
	$\Delta_2 = -4.1527$	(48)	
14	$\frac{\Delta_3 = -8.7395}{4.1522}$	[36.92]	26.61
M_4	$\Delta_2 = -4.1523$	(47)	30.01
	$\frac{\Delta_3 = -8.7372}{4.1509}$		
	$\Delta_2 = -4.1508$	(48)	
	$\frac{\Delta_3 = -6.7470}{\Delta_2 = -4.1555}$	(47)	
	$\Delta_2 = -4.1555$	(47)	
	$\Delta_3 = -6.7147$	(34)	
	$\Delta_2 = -3.1738$	[26,15]	
	$\Delta_4 = -13.4279$ $\Delta_2 = -3.1734$	(41)	
	$\Delta_2 = -134176$	[31,53]	
M5	$\frac{24}{\Delta_2 = -3.1736}$	(37)	29.53
	$\Delta_4 = -13.4195$	[28,46]	
	$\Delta_2 = -3.1737$	(38)	
	$\Delta_4 = -13.4120$	[29.23]	
	$\Delta_2 = -3.1737$	(42)	
	$\Delta_4^2 = -13.4462$	[32.30]	
	$\Delta_3 = -7.0678$	(35)	
	$\Delta_4 = -13.2386$	[26.92]	
	$\Delta_3 = -7.0645$	(41)	
	$\Delta_4 = -13.2442$	[31.53]	
M_6	$\Delta_3 = -7.0623$	(38)	29.38
	$\Delta_4 = -13.2155$	[29.23]	
	$\Delta_3 = -7.0647$	(42)	
	$\Delta_4 = -13.2221$	[32.30]	
	$\Delta_3 = -7.0638$	(35)	
	$\Delta_4 = -13.2105$	[26.92]	
	$\Delta = -6.2101$	(24)	
		[18.46]	
	Δ=-6.2102	(30)	
		[23.07]	
M_7	$\Delta = -6.2103$	(22)	20.76
		[16.92]	
	$\Delta = -6.2104$	(30)	
		[23.07]	
	$\Delta = -6.2105$	(29)	
		[22.30]	

TABLE S5. The averages over the percentage of number of sites belonging to class 1–3 for each method. (**Bold figures indicate class**; number of sites in parentheses are in blue color; percentages in brackets are in magenta color.)

Method	Sequence in	Number of sites with	Percentage(%)	Average over the
	TSR	same k as in target		percentage(%)
	$\Delta_1 = -1.2805$	28	21.53	
	$\Delta_3 = -6.8465$			
	$\Delta_1 = -1.2806$	28	21.53	
	$\Delta_3 = -6.8283$			
M_2	$\Delta_1 = -1.2806$	29	22.30	21.99
-	$\Delta_3 = -6.8307$			
	$\Delta_1 = -1.2806$	28	21.53	
	$\Lambda_2 = -6.8313$			
	$\Delta_1 = -1.2806$	30	23.07	
	$\Delta_1 = -6.8376$	50	25.07	
	$\frac{23-0.0570}{1-1.2105}$	36	27.69	
	$\Delta_1 = -1.2103$	50	27.09	
	$\Delta_4 = -13.2770$	26	27.60	
	$\Delta_1 = -1.2105$	30	27.69	
	$\Delta_4 = -13.2782$	28	20.46	20.21
M_3	$\Delta_1 = -1.2106$	37	28.46	28.31
	$\Delta_4 = -13.2768$			
	$\Delta_1 = -1.2106$	37	28.46	
	$\Delta_4 = -13.2775$			
	$\Delta_1 = -1.2103$	38	29.23	
	$\Delta_4 = -13.2768$			
	$\Delta_2 = -4.1528$	26	20.00	
	$\Delta_3 = -8.7561$			
	$\Delta_2 = -4.1527$	26	20.00	
	$\Delta_3 = -8.7395$			
M_4	$\Delta_2 = -4.1523$	27	20.76	20.30
7	$\Delta_3 = -8.7372$			
	$\frac{-5}{\sqrt{2}} = -4.1508$	26	20.00	
	$\Lambda_2 = -8.7470$		20100	
	$\Delta_3 = -4.1555$	27	20.76	
	$\Lambda_2 = -8.7147$	2,	20.70	
	$\Delta_3 = 0.7147$	22	25.38	
	$\Delta_2 = -5.1758$	55	25.58	
	$\Delta_4 = -13.4279$	24	2(15	
	$\Delta_2 = -5.1/54$	34	20.15	
	$\Delta_4 = -13.41/6$	22	25.20	05.04
M_5	$\Delta_2 = -3.1/36$	33	25.38	25.84
	$\Delta_4 = -13.4195$			
	$\Delta_2 = -3.1737$	34	26.15	
	$\Delta_4 = -13.4120$			
	$\Delta_2 = -3.1737$	34	26.15	
	$\Delta_4 = -13.4462$			
	$\Delta_3 = -7.0678$	36	27.69	
	$\Delta_4 = -13.2386$			
	$\Delta_3 = -7.0645$	36	27.69	
	$\Delta_4 = -13.2442$			
M_6	$\Delta_3 = -7.0623$	35	26.92	27.38
-	$\Delta_4 = -13.2155$			
	$\Delta_3 = -7.0647$	36	27.69	
	$\Delta_4 = -13.2221$			
	$\Delta_2 = -7.0638$	35	26.92	
	$\Lambda_4 = -13\ 2105$		20.72	
	<u>A6 2101</u>	30	23.07	
	A = 6.2101	30	23.07	
M_	$\Delta = -0.2102$	22	23.07	21.52
1117	$\frac{\Delta = -0.2103}{\Lambda = 6.2104}$	23	17.09	21.33
	$\frac{\Delta = -0.2104}{\Lambda = 0.2107}$	20	20.70	
	$\Delta = -6.2105$	30	23.07	

TABLE S6. Comparison of Monte Carlo designed sequences with the target sequence based on structural context similarity.

Method	Sequence in TSR	Average Percentage of structural context similarity over unfolded	Average over the percentage(%)
	1 2005	conformations(%)	
	$\Delta_1 = -1.2805$	16.80	
	$\Delta_3 = -0.8403$	16.41	
	$\Delta_1 = -1.2800$ $\Delta_2 = -6.8283$	10.41	
Ma	$\Delta_3 = -0.8283$ $\Delta_1 = -1.2806$	16.61	16 84
1112	$\Delta_1 = -6.8307$	10.01	10.01
	$\Delta_1 = -1.2806$	16.80	
	$\Delta_3 = -6.8313$		
	$\Delta_1 = -1.2806$	17.59	
	$\Delta_3 = -6.8376$		
	$\Delta_1 = -1.2105$	20.46	
	$\Delta_4 = -13.2776$		
	$\Delta_1 = -1.2105$	20.60	
	$\Delta_4 = -13.2782$		••••
M_3	$\Delta_1 = -1.2106$	21.12	20.94
	$\Delta_4 = -13.2768$	21.12	
	$\Delta_1 = -1.2100$ $\Delta_2 = -13.2775$	21.12	
	$\frac{\Delta_4 = -13.2775}{\Delta_1 = -1.2103}$	21.41	
	$\Delta_{4} = -13.2768$	21.11	
	$\Delta_2 = -4.1528$	14.21	
	$\Delta_3 = -8.7561$		
	$\Delta_2 = -4.1527$	14.28	
	$\Delta_3 = -8.7395$		
M_4	$\Delta_2 = -4.1523$	15.03	14.51
	$\Delta_3 = -8.7372$		
	$\Delta_2 = -4.1508$	14.19	
	$\Delta_3 = -8.7470$	14.04	
	$\Delta_2 = -4.1555$	14.84	
	$\Delta_3 = -8./14/$	20.40	
	$\Delta_2 = -5.1/38$	20.40	
	$\frac{\Delta_413.4279}{\Lambda_23.1734}$	18 75	
	$\Delta_2 = -134176$	10.75	
M5	$\frac{\Delta_4 = 13.1170}{\Lambda_2 = -3.1736}$	19.41	19.46
	$\Delta_4 = -13.4195$		19110
	$\Delta_2 = -3.1737$	20.28	
	$\Delta_4 = -13.4120$		
	$\Delta_2 = -3.1737$	18.49	
	$\Delta_4 = -13.4462$		
	$\Delta_3 = -7.0678$	21.96	
	$\Delta_4 = -13.2386$	20.20	
	$\Delta_3 = -7.0645$	20.29	
M	$\Delta_4 = -13.2442$	22.86	21.70
MG	$\Delta_3 = -7.0025$ $\Delta_3 = -13.2155$	22.80	21.79
	$\Delta_4 = -15.2155$	22.22	
	$\Delta_3 = -132221$	22.27	
	$\Delta_3 = -7.0638$	21.60	
	$\Delta_4 = -13.2105$		
	Δ=-6.2101	19.53	
	Δ=-6.2102	17.81	
M_7	Δ=-6.2103	14.73	17.75
	Δ=-6.2104	17.93	
	$\Delta = -6.2105$	17.75	

TABLE S7. Determination of structural context (k) similarity between the k of Monte Carlo designed sequences and the k of unfolded conformations.

					Bins of structural context			
Method	Sequence in				similarity percentage			
	TSR				Number of non-native			
					conformations			
		0–5	5-10	10-15	15-20	20-25	25-30	30-100
	$\Delta_1 = -1.2805$	6	2047	68914	154633	46660	302	14
	$\Delta_3 = -6.8465$							
	$\Delta_1 = -1.2806$	2	1925	77713	160209	32456	263	8
	$\Lambda_2 = -6.8283$	-	1720	,,,,,	100202	02100	200	0
Ma	$\Delta_3 = 0.0205$ $\Delta_1 = -1.2806$	2	2121	75956	151677	42624	186	10
1112	$\Delta_1 = -6.8307$	2	2121	15750	1910//	12021	100	10
	$\Delta_3 = 0.0307$ $\Delta_1 = -1.2806$	6	2030	68003	154637	46574	312	15
	$\Delta_1 = 1.2000$ $\Delta_2 = -6.8313$	0	2037	00775	154657	40574	512	15
	$\frac{\Delta_3 = 0.0315}{\Delta_1 = -1.2806}$	2	842	51760	149938	69019	988	27
	$\Delta_1 = 1.2000$ $\Delta_2 = -6.8376$	2	042	51700	147750	0)01)	200	21
	$\Delta_3 = 0.0570$	0	331	18353	90368	13/03/	20376	114
	$\Delta_1 = -1.2105$ $\Delta_2 = -13.2776$	0	551	10555	90508	154054	29370	114
	$\Delta_4 = -13.2770$	0	283	16056	87/35	136081	30785	136
	$\Delta_1 = -1.2103$ $\Delta_2 = -13.2782$	0	265	10950	87455	150981	50785	150
М.	$\Delta_4 = -13.2782$	0	202	12012	77717	120100	41041	424
11/13	$\Delta_1 = -1.2100$	0	265	13912	///1/	139199	41041	424
	$\Delta_4 = -13.2706$	0	202	12012	77717	120100	41041	424
	$\Delta_1 = -1.2100$	0	265	13912	///1/	139199	41041	424
	$\Delta_4 = -13.2773$	0	256	12474	74442	122297	50407	1520
	$\Delta_1 = -1.2103$	0	230	15474	74442	152587	50497	1320
	$\Delta_4 = -15.2708$	10	11242	157150	07207	(1(9	177	21
	$\Delta_2 = -4.1528$	18	11545	15/152	97387	0408	1//	31
	$\Delta_3 = -8.7561$	1.4	10500	155570	00550	((12)	170	- 24
	$\Delta_2 = -4.1527$	14	10599	155573	99552	6642	172	24
	$\Delta_3 = -8.7395$	2	57()	120140	100700	12720	170	
M_4	$\Delta_2 = -4.1523$	3	5766	130149	123732	12728	173	25
	$\Delta_3 = -8.7372$	10	11(50	157057	0(402	(224	175	- 21
	$\Delta_2 = -4.1508$	18	11659	15/956	96403	6334	175	31
	$\Delta_3 = -8.7470$	17	7102	127200	115790	12000	107	20
	$\Delta_2 = -4.1555$	17	/185	137299	115782	12080	187	28
	$\Delta_3 = -8.7147$	0	2(2	17202	99001	142507	22029	265
	$\Delta_2 = -3.1/38$	0	363	17392	88901	143527	22028	365
	$\Delta_4 = -13.4279$	16	1077	26665	122005	102157	0515	01
	$\Delta_2 = -3.1/34$	10	1077	30003	123095	103157	8545	21
14	$\Delta_4 = -13.41/0$	(907	26500	110015	122010	11200	10
M5	$\Delta_2 = -3.1/30$	0	807	26509	110915	123019	11302	18
	$\Delta_4 = -13.4193$	2	249	10157	01455	141026	20592	06
	$\Delta_2 = -3.1/3/$	2	348	18157	91455	141936	20582	96
	$\Delta_4 = -13.4120$	(1106	41071	12(219	0(200	6040	27
	$\Delta_2 = -3.1/3/$	0	1120	418/1	120218	90388	6940	27
	$\Delta_4 = -13.4462$	2	202	0077	50051	147701	55025	1707
	$\Delta_3 = -7.0678$	2	303	8877	58851	14//21	55035	1/8/
	$\Delta_4 = -13.2386$		(10	10565	00771	122220	2(000	240
	$\Delta_3 = -7.0645$	6	648	19565	92771	133238	26000	348
	$\Delta_4 = -13.2442$	1	205	5.405	27500	154006	71(00	2470
<i>M</i> ₆	$\Delta_3 = -7.0623$	1	205	5425	37508	154336	/1622	3479
	$\Delta_4 = -13.2155$		455	0.407	50(12	142120	(2002	2022
	$\Delta_3 = -7.0647$	/	455	9407	52643	143138	63903	3023
	$\Delta_4 = -13.2221$	4	241	0010	(2020	150(07	44600	1070
	$\Delta_3 = -7.0638$	4	341	9919	63939	152687	44608	1078
	$\Delta_4 = -13.2105$	7	547	10(10	112410	125100	5755	40
	$\Delta = -6.2101$	1	54/	18619	112418	135190	5/55	40
м	$\Delta = -0.2102$	4	1105	44245	130045	/0238	919	20
I VI 7	$\Delta = -6.2103$	1/	049/	138236	120908	0/01	135	22
	$\Delta = -6.2104$	/	/64	3/980	15/644	/4680	1460	41
	$\Delta = -0.2105$	2	1135	44407	153360	/3116	531	19

TABLE S8. Binning of number of non-native conformations according to their percentage of structural context similarity. (Bins of structural context similarity percentage are in blue color; number of non-native conformations are in black color)

TABLE S9. Similarity of misfolded structures to the native structure.

Method	Average similarity of misfolded structures to
	the native structure
<i>M</i> ₂	93.19%
<i>M</i> ₃	93.10%
M_4	93.53%
<u>M</u> 5	93.11%
M_6	93.08%
M_7	92.79%