A Variational Model for Oligomer-Formation Process of GNNQQNY Peptide from Yeast Prion Protein Sup35

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Supporting Materials

Pathway for free energy steepest descent

A usually adopted approximate method for determining the native aggregation pathway of fibrils is the steepest descent principle of free energy. It assumes fibrillation proceeds along the path in which the free energy of the system declines fastest. To be explicit, we first discretize the whole free energy surface and the minimal step along each direction is set as $\{\Delta C\}$. Then starting from the initial denatured state $\{C = 0\}$, for each time we choose the steepest descent direction of the free energy of the system from all possible choices (the forwarding step size is $\{\Delta C\}$). Based on the optimization of each step, we can construct the whole aggregation pathway. Therefore the pathway for free energy steepest descent is a local optimization method, which may not grantee the finding of global minimum.

Based on the method of free energy steepest descent, we can also determine that the critical nucleus size for homogeneous nucleation process is 3 peptides. Here we set the minimal step size $\{\Delta C = 0.2\}$ and the total calculation steps as $n = 50$. Comparing the different aggregation pathways for nucleus composed by 2-6 peptides (see Table. S1), we can see that for nucleus size 2-3, the pathway for free energy steepest descent proceeds along the directions in which only a part of constraint parameters can be increased (C_2 or C_1C_3). So that there is always some peptide cannot easily aggregate in the system (corresponding to the one with small constraint parameter), which means the formation of fiber nucleus must cross a very high free energy barrier. While for nucleus size 4-6, all constraint parameters increase simultaneously along the pathway for free energy steepest descent, which means all peptides can aggregate easily in the system. In conclusion, we can make a judgment that trimer serves as the critical nucleus size for homogeneous nucleation of amyloid fiber. Similar conclusions could also be arrived for the cases with smaller minimal step size ($\{\Delta C = 0.05\}$) and much longer total calculation steps ($n = 500$) (data not shown).

Another example comes from the study of the attachment of single free peptide onto existing pentamer. From the data shown in Table. S2, we can see the residue attachment starts with Gln-4, while the attachment of Asn-6 is much tighter. Since the side-chain of Gly-1 is the smallest, its corresponding energy barrier is very low and the attachment is easy too. These three residues exactly coincide with the folding core identified in the main text based on the on-or-off mechanism. However the aggregation order of another four residues cannot be identified by current method.

Since according to the data plot shown in Fig.8 in the main text, an unfavorable free energy barrier must be crossed before the peptide attachment is finished. This cannot be well captured by the method of free energy steepest descent.

Table. S1. The pathway for free energy fastest decaying when nucleus size n=2, 3, 4, 5, 6 respectively.

Step	C_1	C_2	blank	Step	C_1	C_2	C_3	blank	Step	C_1	C_2	C_3	C_4
1	0	0		1	0	0	0		1	0	0	0	0
2	0	0.2		2	0	0	0.2		2	0	0	0.2	0
3	0.2	0.2		3	0	0.2	0.2		3	0	0	0.2	0.2
4	0.4	0.2		4	0.2	0.2	0.2		4	0	0.2	0.2	0.2
5	0.4	0.4		5	0.2	0.4	0.2		5	0.2	0.2	0.2	0.2
6	0.6	0.4		6	0.4	0.4	0.2		6	0.2	0.4	0.2	0.2
7	0.6	0.6		7	0.4	0.4	0.4		7	0.2	0.4	0.4	0.2
8	0.6	0.8		8	0.6	0.4	0.4		8	0.4	0.4	0.4	0.2
9	0.6	1.0		9	0.6	0.4	0.6		9	0.4	0.4	0.4	0.4
10	0.6	1.2		10	0.8	0.4	0.6		10	0.4	0.6	0.4	0.4
11	0.6	1.4		11	0.8	0.4	0.8		11	0.4	0.6	0.6	0.4
12	0.6	1.6		12	1.0	0.4	0.8		12	0.6	0.6	0.6	0.4
13	0.6	1.8		13	1.0	0.4	1.0		13	0.6	0.6	0.6	0.6
14	0.6	2.0		14	1.2	0.4	1.0		14	0.6	0.8	0.6	0.6
15	0.6	2.2		15	1.2	0.4	1.2		15	0.6	0.8	0.8	0.6
16	0.6	2.4		16	1.4	0.4	1.2		16	0.8	0.8	0.8	0.6
17	0.6	2.6		17	1.4	0.4	1.4		17	0.8	0.8	0.8	0.8
18	0.6	2.8		18	1.6	0.4	1.4		18	0.8	1.0	0.8	0.8
19	0.6	3.0		19	1.6	0.4	1.6		19	1.0	1.0	0.8	0.8
20	0.6	3.2		20	1.8	0.4	1.6		20	1.0	1.0	1.0	0.8
21	0.6	3.4		21	1.8	0.4	1.8		21	1.0	1.0	1.0	1.0
22	0.6	3.6		22	2.0	0.4	1.8		22	1.0	1.2	1.0	1.0
23	0.6	3.8		23	2.0	0.4	2.0		23	1.2	1.2	1.0	1.0
24	0.6	4.0		24	2.2	0.4	2.0		24	1.2	1.2	1.2	1.0
25	0.6	4.2		25	2.2	0.4	2.2		25	1.2	1.2	1.2	1.2
26	0.6	4.4		26	2.4	0.4	2.2		26	1.2	1.4	1.2	1.2
27	0.6	4.6		27	2.4	0.4	2.4		27	1.4	1.4	1.2	1.2
28	0.6	4.8		28	2.6	0.4	2.4		28	1.4	1.4	1.4	1.2
29	0.6	5.0		29	2.6	0.6	2.4		29	1.4	1.4	1.4	1.4
30	0.6	5.2		30	2.6	0.6	2.6		30	1.4	1.6	1.4	1.4
31	0.6	5.4		31	2.8	0.6	2.6		31	1.6	1.6	1.4	1.4
32	0.6	5.6		32	3.0	0.6	2.6		32	1.6	1.6	1.6	1.4
33	0.6	5.8		33	3.0	0.6	2.8		33	1.6	1.6	1.6	1.6
34	0.6	6		34	3.2	0.6	2.8		34	1.6	1.8	1.6	1.6
35	0.6	6.2		35	3.2	0.6	3.0		35	1.8	1.8	1.6	1.6

36	0.6	6.4		36	3.4	0.6	3.0		36	1.8	1.8	1.8	1.6
37	0.6	6.6		37	3.4	0.6	3.2		37	1.8	1.8	1.8	1.8
38	0.6	6.8		38	3.6	0.6	3.2		38	1.8	2.0	1.8	1.8
39	0.6	7.0		39	3.6	0.6	3.4		39	2.0	2.0	1.8	1.8
40	0.6	7.2		40	3.8	0.6	3.4		40	2.0	2.0	2.0	1.8
41	0.6	7.4		41	3.8	0.6	3.6		41	2.0	2.0	2.0	2.0
42	0.6	7.6		42	4.0	0.6	3.6		42	2.0	2.2	2.0	2.0
43	0.6	7.8		43	4.2	0.6	3.6		43	2.2	2.2	2.0	2.0
44	0.6	8.0		44	4.2	0.6	3.8		44	2.2	2.2	2.0	2.2
45	0.6	8.2		45	4.4	0.6	3.8		45	2.2	2.4	2.0	2.2
46	0.6	8.4		46	4.4	0.6	4.0		46	2.2	2.4	2.2	2.2
47	0.6	8.6		47	4.6	0.6	4.0		47	2.4	2.4	2.2	2.2
48	0.6	8.8		48	4.6	0.6	4.2		48	2.4	2.4	2.2	2.4
49	0.6	9.0		49	4.8	0.6	4.2		49	2.4	2.6	2.2	2.4
50	0.6	9.2		50	5.0	0.6	4.2		50	2.4	2.6	2.4	2.4

Step	C_1	C_2	C_3	C_4	C_5	blank	Step	C_1	C_2	C_3	C_4	C_5	C_6
1	0	0	0	0	0		1	0	0	0	0	0	0
2	0	0	0.2	0	0		2	0	0	0.2	0	0	0
3	0	0	0.2	0.2	0		3	0	0	0.2	0.2	0	0
4	0	0.2	0.2	0.2	0		4	0	0.2	0.2	0.2	0	0
5	0	0.2	0.2	0.2	0.2		5	0	0.2	0.2	0.2	0.2	0
6	0.2	0.2	0.2	0.2	0.2		6	0.2	0.2	0.2	0.2	0.2	0
7	0.2	0.2	0.4	0.2	0.2		7	0.2	0.2	0.2	0.2	0.2	0.2
8	0.2	0.4	0.4	0.2	0.2		8	0.2	0.2	0.2	0.4	0.2	0.2
9	0.2	0.4	0.4	0.4	0.2		9	0.2	0.2	0.4	0.4	0.2	0.2
10	0.4	0.4	0.4	0.4	0.2		10	0.2	0.4	0.4	0.4	0.2	0.2
11	0.4	0.4	0.4	0.4	0.4		11	0.2	0.4	0.4	0.4	0.4	0.2
12	0.4	0.4	0.6	0.4	0.4		12	0.4	0.4	0.4	0.4	0.4	0.2
13	0.4	0.6	0.6	0.4	0.4		13	0.4	0.4	0.4	0.4	0.4	0.4
14	0.4	0.6	0.6	0.6	0.4		14	0.4	0.4	0.4	0.6	0.4	0.4
15	0.4	0.6	0.8	0.6	0.4		15	0.4	0.4	0.6	0.6	0.4	0.4
16	0.6	0.6	0.8	0.6	0.4		16	0.4	0.6	0.6	0.6	0.4	0.4
17	0.6	0.6	0.8	0.6	0.6		17	0.4	0.6	0.6	0.6	0.6	0.4
18	0.6	0.6	1.0	0.6	0.6		18	0.4	0.6	0.6	0.8	0.6	0.4
19	0.8	0.6	1.0	0.6	0.6		19	0.4	0.6	0.8	0.8	0.6	0.4
20	0.8	0.6	1.2	0.6	0.6		20	0.6	0.6	0.8	0.8	0.6	0.4
21	0.8	0.6	1.2	0.6	0.8		21	0.6	0.6	0.8	0.8	0.6	0.6
22	0.8	0.8	1.2	0.6	0.8		22	0.6	0.6	0.8	1.0	0.6	0.6
23	0.8	0.8	1.2	0.8	0.8		23	0.6	0.8	0.8	1.0	0.6	0.6
24	0.8	0.8	1.4	0.8	0.8		24	0.6	0.8	1.0	1.0	0.6	0.6
25	1.0	0.8	1.4	0.8	0.8		25	0.6	0.8	1.0	1.0	0.8	0.6

26	1.0	0.8	1.6	0.8	0.8		26	0.8	0.8	1.0	1.0	0.8	0.6
27	1.0	0.8	1.6	0.8	1.0		27	0.8	0.8	1.2	1.0	0.8	0.6
28	1.0	1.0	1.6	0.8	1.0		28	0.8	0.8	1.2	1.2	0.8	0.6
29	1.2	1.0	1.6	0.8	1.0		29	0.8	0.8	1.2	1.2	0.8	0.8
30	1.2	1.0	1.8	0.8	1.0		30	0.8	1.0	1.2	1.2	0.8	0.8
31	1.2	1.0	1.8	1.0	1.0		31	0.8	1.0	1.2	1.4	0.8	0.8
32	1.2	1.0	1.8	1.0	1.2		32	0.8	1.0	1.4	1.4	0.8	0.8
33	1.2	1.0	2.0	1.0	1.2		33	1.0	1.0	1.4	1.4	0.8	0.8
34	1.4	1.0	2.0	1.0	1.2		34	1.0	1.0	1.4	1.4	1.0	0.8
35	1.4	1.0	2.2	1.0	1.2		35	1.0	1.0	1.6	1.4	1.0	0.8
36	1.4	1.2	2.2	1.0	1.2		36	1.0	1.0	1.6	1.6	1.0	0.8
37	1.4	1.2	2.2	1.0	1.4		37	1.0	1.0	1.6	1.6	1.0	1.0
38	1.4	1.2	2.2	1.2	1.4		38	1.0	1.2	1.6	1.6	1.0	1.0
39	1.4	1.2	2.4	1.2	1.4		39	1.0	1.2	1.6	1.8	1.0	1.0
40	1.6	1.2	2.4	1.2	1.4		40	1.2	1.2	1.6	1.8	1.0	1.0
41	1.6	1.4	2.4	1.2	1.4		41	1.2	1.2	1.8	1.8	1.0	1.0
42	1.6	1.4	2.6	1.2	1.4		42	1.2	1.2	1.8	1.8	1.2	1.0
43	1.6	1.4	2.6	1.2	1.6		43	1.2	1.2	1.8	1.8	1.2	1.2
44	1.6	1.4	2.6	1.4	1.6		44	1.2	1,2	1.8	2.0	1.2	1.2
45	1.6	1.4	2.8	1.4	1.6		45	1.2	1,2	2.0	2.0	1.2	1.2
46	1.8	1.4	2.8	1.4	1.6		46	1,2	1.4	2.0	2.0	1.2	1.2
47	1.8	1.6	2.8	1.4	1.6		47	1.4	1.4	2.0	2.0	1.2	1.2
48	1.8	1.6	3.0	1.4	1.6		48	1.4	1.4	2.0	2.2	1.2	1.2
49	1.8	1.6	3.0	1.4	1.8		49	1.4	1.4	2.2	2.2	1.2	1.2
50	1.8	1.6	3.0	1.6	1.8		50	1.4	1.4	2.2	2.2	1.4	1.2

Table. S2. The pathway for free energy fastest decaying for single free monomer attaching onto an existing pentamer. Here we set the minimal step size $\{\Delta C = 0.1\}$ and the total calculation steps as $n = 50$

Step	C_1	C_2	C_3	C_4	C_5	C_6	C_7
1	0	0	0	0	0	0	0
2	0	0	0	0.1	0	0	0
3	0	0	0	0.1	0.1	0	0
4	0.1	0	0	0.1	0.1	0	0
5	0.1	0	0	0.1	0.2	0	0
6	0.2	0	0	0.1	0.2	0	0
7	0.2	0	0	0.1	0.2	0.1	0
8	0.3	0	0	0.1	0.2	0.1	0
9	0.3	0	0	0.1	0.2	0.2	0
10	0.3	0	0	0.1	0.2	0.3	0
11	0.4	0	0	0.1	0.2	0.3	0

12	0.4	0	0	0.1	0.2	0.4	0
13	0.4	0	0	0.1	0.2	0.5	0
14	0.4	0	0	0.1	0.2	0.6	0
15	0.5	0	0	0.1	0.2	0.6	0
16	0.5	0	0	0.1	0.2	0.7	0
17	0.5	0	0	0.1	0.2	0.8	0
18	0.5	0	0	0.2	0.2	0.8	0
19	0.5	0	0	0.2	0.2	0.9	0
20	0.5	0	0	0.3	0.2	0.9	0
21	0.5	0	0	0.3	0.2	1.0	0
22	0.5	0	0	0.4	0.2	1.0	0
23	0.6	0	0	0.4	0.2	1.0	0
24	0.6	0	0	0.4	0.2	1.1	0
25	0.6	0	0	0.5	0.2	1.1	0
26	0.6	0	0	0.5	0.2	1.2	0
27	0.6	0	0	0.5	0.2	1.3	0
28	0.6	0	0	0.6	0.2	1.3	0
29	0.6	0	0	0.6	0.2	1.4	0
30	0.6	0	0	0.7	0.2	1.4	0
31	0.6	0	0	0.7	0.2	1.5	0
32	0.7	0	0	0.7	0.2	1.5	0
33	0.7	0	0	0.8	0.2	1.5	0
34	0.7	0	0	0.8	0.2	1.6	0
35	0.7	0	0	0.9	0.2	1.6	0
36	0.7	0	0	0.9	0.2	1.7	0
37	0.7	0	0	0.9	0.2	1.8	0
38	0.7	0	0	1.0	0.2	1.8	0
39	0.7	0	0	1.0	0.2	1.9	0
40	0.7	0	0	1.1	0.2	1.9	0
41	0.8	0	0	1.1	0.2	1.9	0
42	0.8	0	0	1.1	0.2	2.0	0
43	0.8	0	0	1.2	0.2	2.0	0
44	0.8	0	0	1.2	0.2	2.1	0
45	0.8	0	0	1.3	0.2	2.1	0
46	0.8	0	0	1.3	0.2	2.2	0
47	0.8	0	0	1.3	0.2	2.3	0
48	0.8	0	0	1.4	0.2	2.3	0
49	0.9	0	0	1.4	0.2	2.3	0
50	0.9	0	0	1.4	0.2	2.4	0