Aggregation Rate of Amyloid Beta Peptides is Controlled by Beta-Content in Monomeric State and Mechanical Stability of Fibrillar Structure

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Introduction

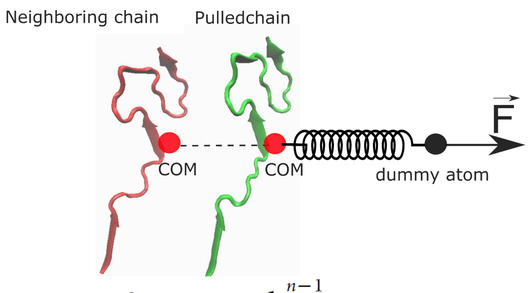
Recently, evidence has been found that the rate of protein aggregation is related to the mechanical stability of the fibrillar structure and the content of beta in the monomeric state in such a way that the higher the mechanical stability or the beta content, the faster the formation of fibrils. However, this conclusion was supported by limited data. In this report, we quantify the relation ship of beta content and mechanical stability with experiment aggregation rate for a data set of Aβ42 in wild type and its 20 mutants, whose aggregation rate was measured experimentally. Using all-atom steered molecular dynamics (SMD) and conventional molecular dynamics (CMD) simulations, we can access the mechanical stability of the fibril structure and the beta content in the monomeric state. Our result supports the hypothesis that mechanical stability and beta content are related to the aggregation rate. Since estimation of the aggregation rate using all-atom simulations is nearly forbidden by current computational capabilities, our result is useful for predicting it based on information obtained from CMD for monomers and SMD simulations for fibrils, which are computationally feasible.

Materials and Methods

Molecular Dynamics Simulation

- Implicit solvent
- Gromacs version 4.5.5
- Force field: OPLS/AA
- 12 replicas each peptide, 500 ns/each replica
- Temperature range: 290.2K. … 490.2K
- Secondary structure analysis: Stride

Steer Molecular Dynamics Simulation



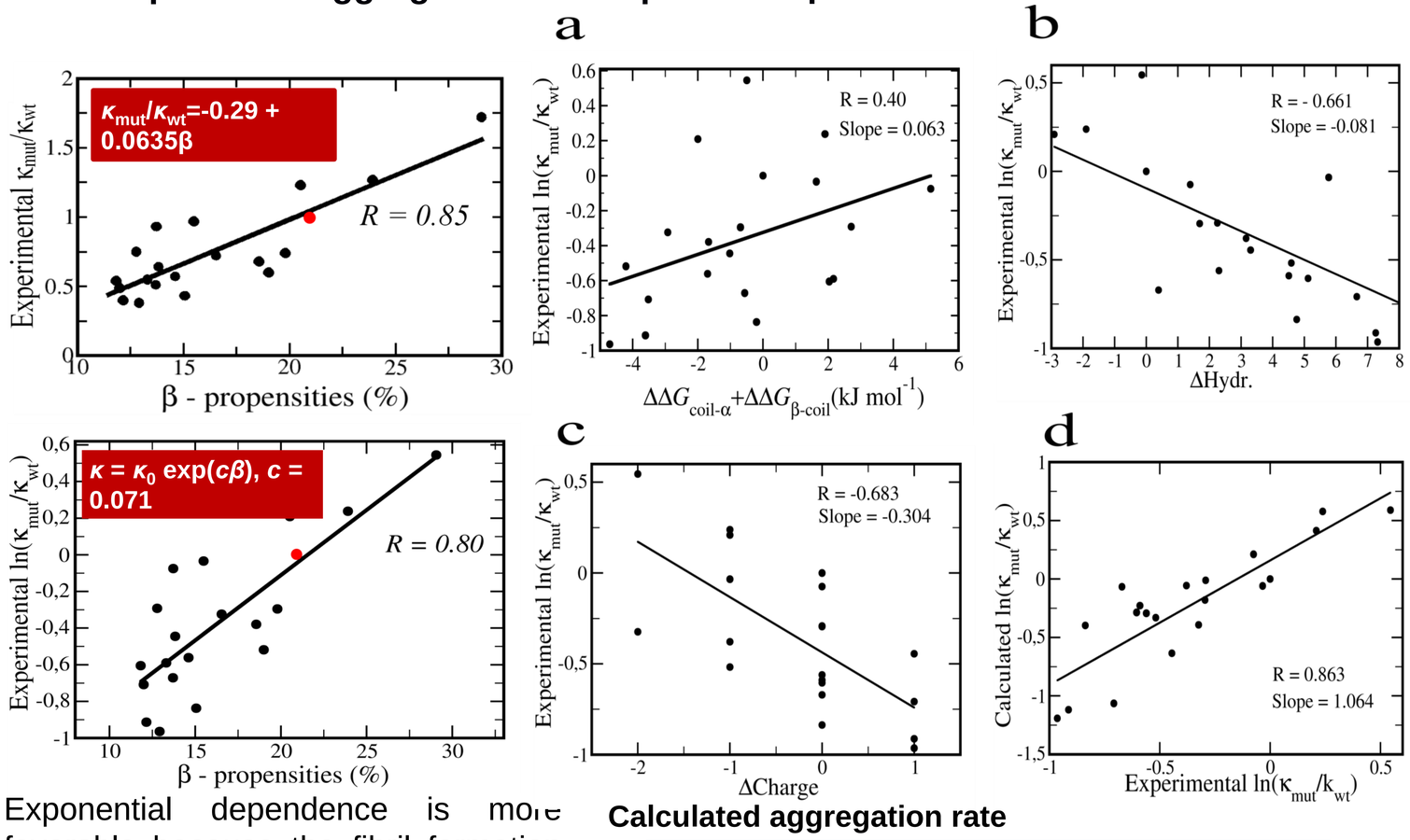
$$W_{\text{pull}} = \int F(x)\mathrm{d}x = \frac{1}{2}\sum_{i=1}^{n-1}(f_{i+1} + f)(x_{i+1} - x_i)$$

- Explicit solvent: water model TIP3P
- Gromacs version 5.1.2
- Force field: CHARMM36m
- Spring constant k = 1000 (kJ/mol/nm2)
- Pulling speed v = 1 nm/ns

No	Mutations	Simulation				Experimental aggregation rate
		Fmax (pN)	Work (kcal/mol)	$\Delta G^{\ddagger}_{\text{unbind}}$ (kcal/mol)	β-content (%)	$\log(\kappa_{mut}/\kappa_{wt})$
1	2NAO	1922.9±137.9	473.2±48.2	75.3±12.7	20.94±1.91	0
2	I41D-A42Q	1550.4±178.6	392.5±33.8	52.5±14.4	12.92±2.37	-0.964
3	I41D-A42S	1424.5±89.7	337.3±67.5	40.4±3.9	12.15±1.93	-0.913
4	I41H-A42D	2153.6±228.8	485.4±43.4	95.6±27.5	11.99±2.38	-0.708
5	I41E-A42L	2117.8±203.4	433.5±66.4	88.6±28.9	13.83±2.32	-0.445
6	I41H-A42N	1632.1±256.8	437.0±55.0	52.0±20.8	15.06±2.85	-0.837
7	A21G	1648.1±114.6	362.2±17.9	51.7±12.7	13.7±2.02	-0.671
8	I41T-A42N	1923.6±155.1	447.2±32.1	77.4±20.7	11.82±1.74	-0.605
9	I41T-A42Q	1757.1±141.4	462.9±36.8	55.4±17.2	13.31±1.82	-0.59
10	I41Q-A42Y	1876.7±294.6	434.9±39.3	81.2±32.9		-0.382
11	I41L-A42N	1666.9±171.9	399.0±35.7	71.0±22.3	14.61±2.66	-0.561
12	I41Q- A42L	1842.7±198.1	410.7±32.8	65.8±24.8	19.79±3.17	-0.295
13	I41T-A42M	1635.9±316.3	419.2±64.1	85.4±33.4	12.78±1.8	-0.292
14	I41T- A42I	1792.5±201.3	454.5±44.3	82.9±16.3	13.72±1.96	-0.075
15	I41K	1821.7±247.9	461.4±35.0	69.9±26.7	19.00±4.12	-0.518
16	I41K-A42L	2126.6±237.4	443.0±59.1	85.8±29.6	18.56±3.46	-0.379
17	I41R-A42R	1543.8±204.0	437.6±54.1	63.3±19.1	16.54±2.07	-0.324
18	A42R	1972.3±337.0	470.1±43.4	68.1±18.4	15.49±1.9	-0.034
19	E22G	2240.1±323.3	519.0±47.0	119.9±35.3	20.52±2.43	0.209
20	D23N	2376.2±208.9	534.9±38.0	153.4±29.8	23.91±2.39	0.238
21	E22K	2641.4±312.7	574.0±51.2	173.2±43.0	29.06±3.53	0.545

Results

Experiment Aggregation rate depends on β-content in monomeric state



Exponential dependence is more favorable because the fibril formation is a barrier-crossing process.

Calculated aggregation rate

$$\ln(\kappa_{mut}/\kappa_{wt}) = A.\Delta\Delta G + B.\Delta\text{Hydr} + C.\Delta\text{charge}$$

A, B and *C* are the slopes from Figures a, b and c below

Conclusions

We have found a strong correlation between the experimental aggregation rate and β-propensity in the monomeric state and the mechanical stability in the fibrillar structure. The dependence of κ on *β, Fmax, W, and* ΔG are expressed by an exponential function in such a way that the higher the β-propensity, the faster formation of fibril. But linear dependence is not excluded, probably due to the fact that the data set is not large enough. Nevertheless, our result sheds light on our understanding of major principles that regulate the self-aggregation propensity of proteins, in particular, intrinsically disordered proteins.

References

Thu, T. T. M et al, , J. Chem. Phys, 150, 225101, 2019.
Thu, T.T.M and Li, M.S., J. Chem. Phys. 157, 055101 2022.

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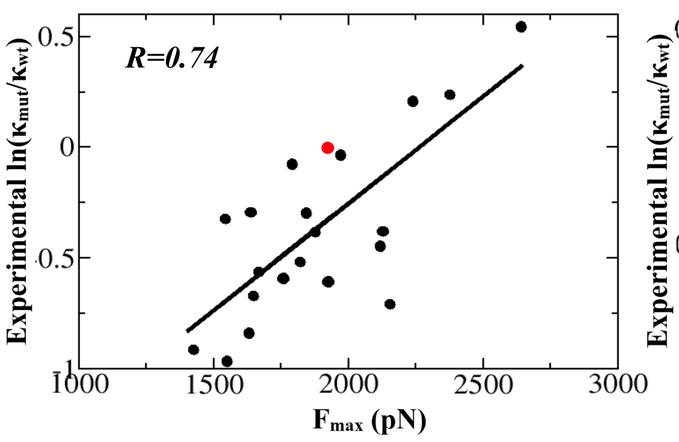
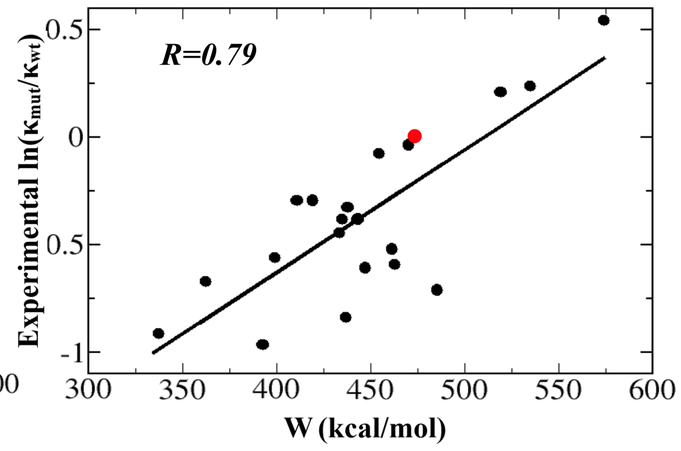
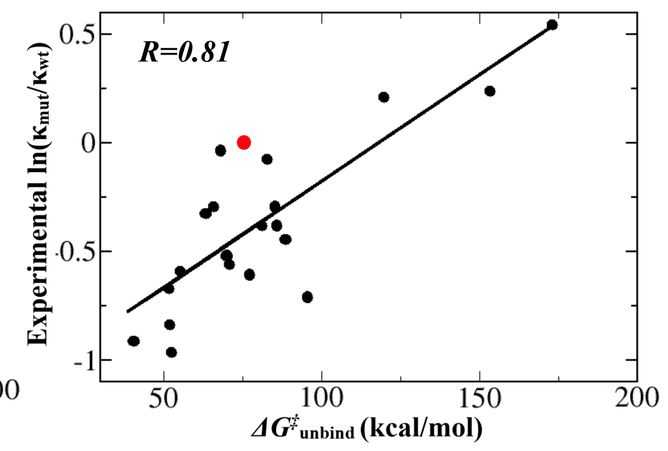
Aggregation rate depends on mechanical stability of fibrillar structure: Evidence from a dataset of 21 sequences



Dependence of the logarithm of relative aggregation rate on rupture force. The red circle refers to WT. Linear fits are y = -2.185 + 0.00096514 * x .

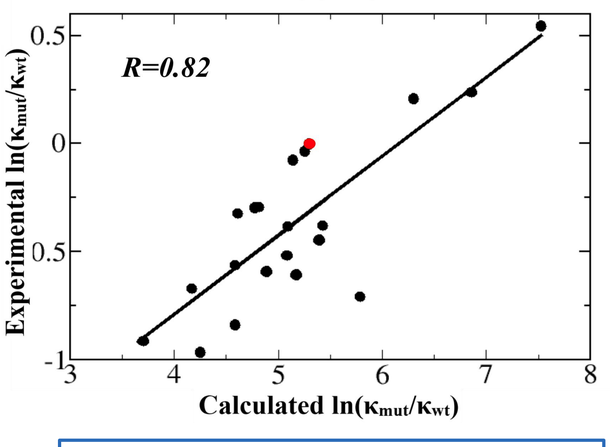


Dependence of the logarithm of the relative aggregation rate on pulling rate. The red circle refers to WT. Linear fits are y = -2.9188 + 0.0057183 * x



Dependence of the logarithm of the relative aggregation rate on unbinding free energy barrier. The red circle refers to WT. Linear fits are y = -1.159 + 0.0097954 * x

Calculated aggregation rate



$$\ln(\kappa_{mut}/\kappa_{wt}) = A.F_{max} + B.W + C.\Delta G^{\ddagger}_{unbind}$$

A, B and *C* are the slopes obtained from the linear fit between the exponential aggregation rate and the rupture force, work and unbinding free energy barriers, respectively