

# Molecular mechanisms involved in the destabilization of two types of R3-R4 tau fibrils associated with chronic traumatic encephalopathy

by Fisetin

Jiaxing Tang<sup>a</sup>, Ruiqing Sun<sup>a</sup>, Jiaqian Wan<sup>a</sup>, Yu Zou<sup>b\*</sup>, Qingwen Zhang<sup>a\*</sup>

<sup>a</sup> School of Physical Education, Shanghai University of Sport, 399 Changhai Road, Shanghai 200438, People's Republic of China

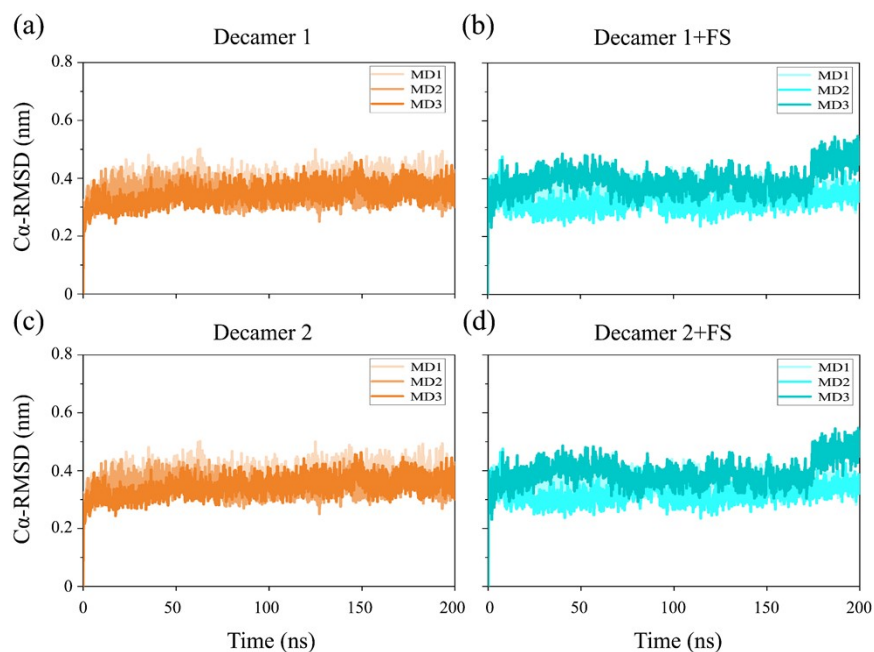
<sup>b</sup> Department of Sport and Exercise Science, College of Education, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, Zhejiang, People's Republic of China

### Corresponding authors:

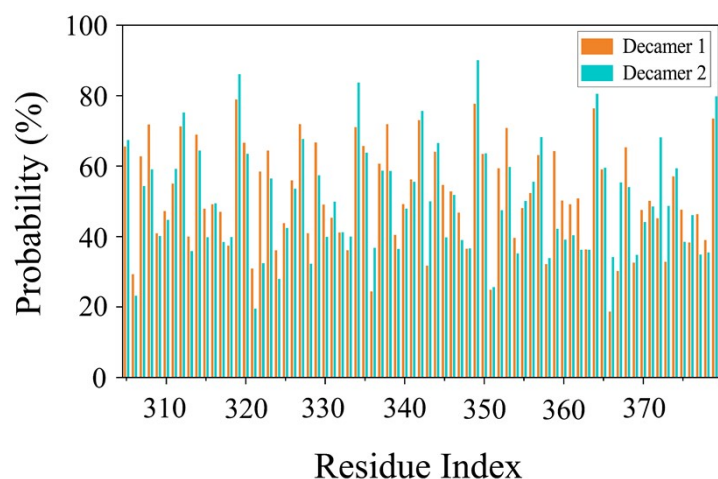
\* E-mail: zouyuzy@zju.edu.cn (Yu Zou)

\* E-mail: zqw@sus.edu.cn (Qingwen Zhang)

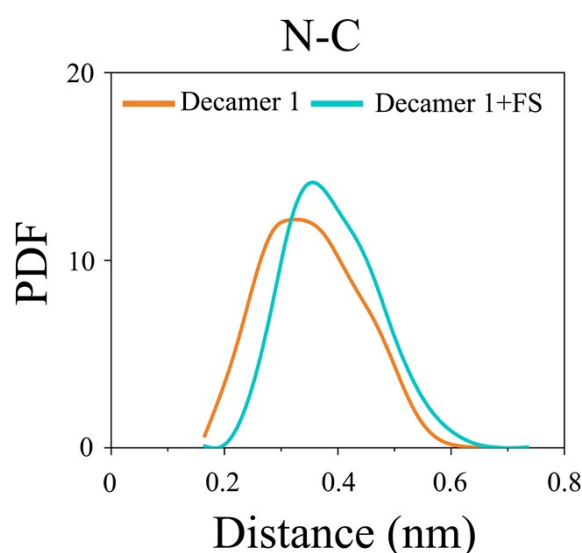
**This supporting material contains eight figures and two tables.**



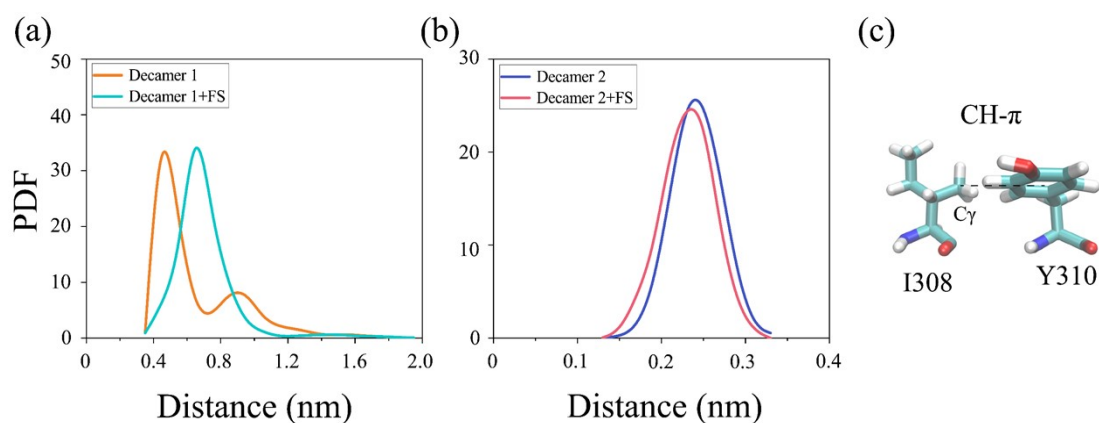
**Figure S1.** Time evolution of C $\alpha$ -RMSD values of each three MD trajectories for the fibrils in Decamer 1 (a), Decamer 1 + FS (b), Decamer 2 (c), and Decamer 2 + FS systems (d).



**Figure S2.** Residue-based  $\beta$ -sheet of the two types of fibrils in Decamer 1 and Decamer 2 systems.

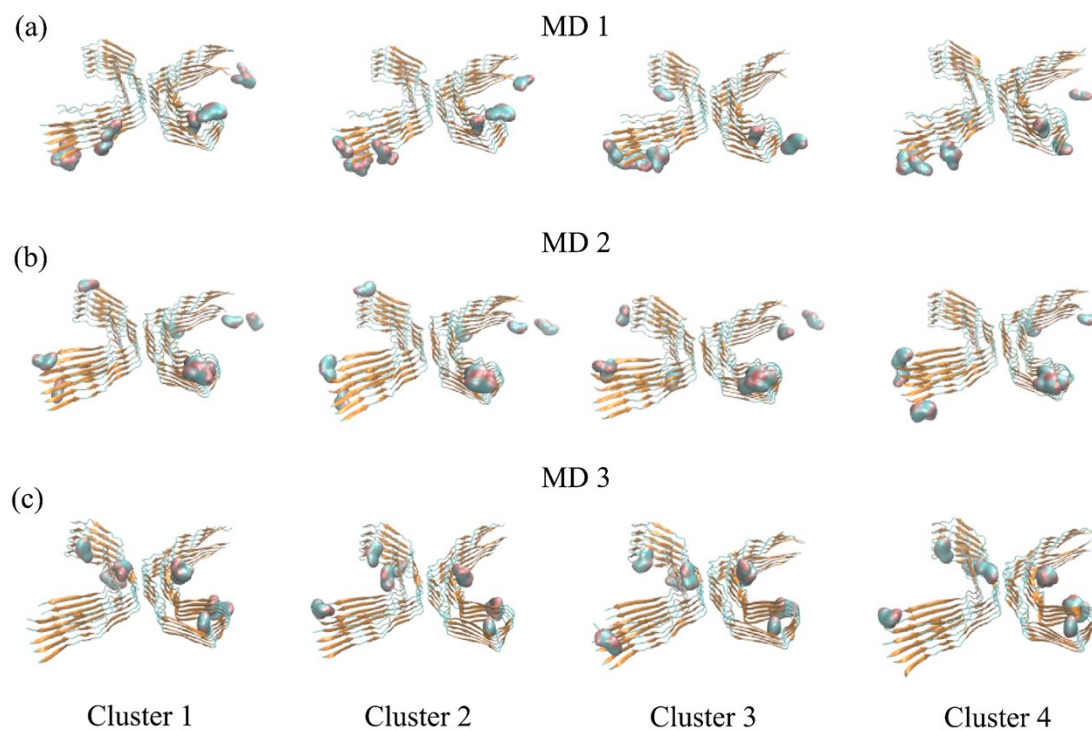


**Figure S3.** PDF of the distance between the N-terminal and C-terminal of the type 1 fibril in Decamer 1 and Decamer 1 + FS systems.

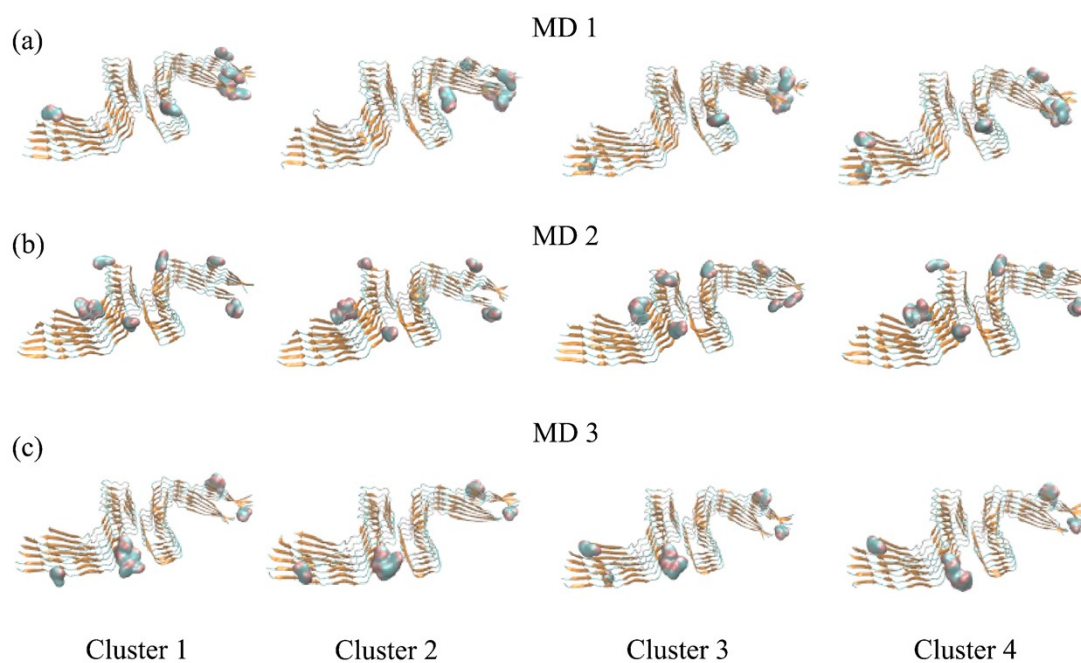


**Figure S4.** PDF of distance between the centroid of aromatic ring of Y310 and the  $C_\gamma$  atom of I308 of the two types fibrils in Decamer 1/Decamer 1 + FS systems (a), and

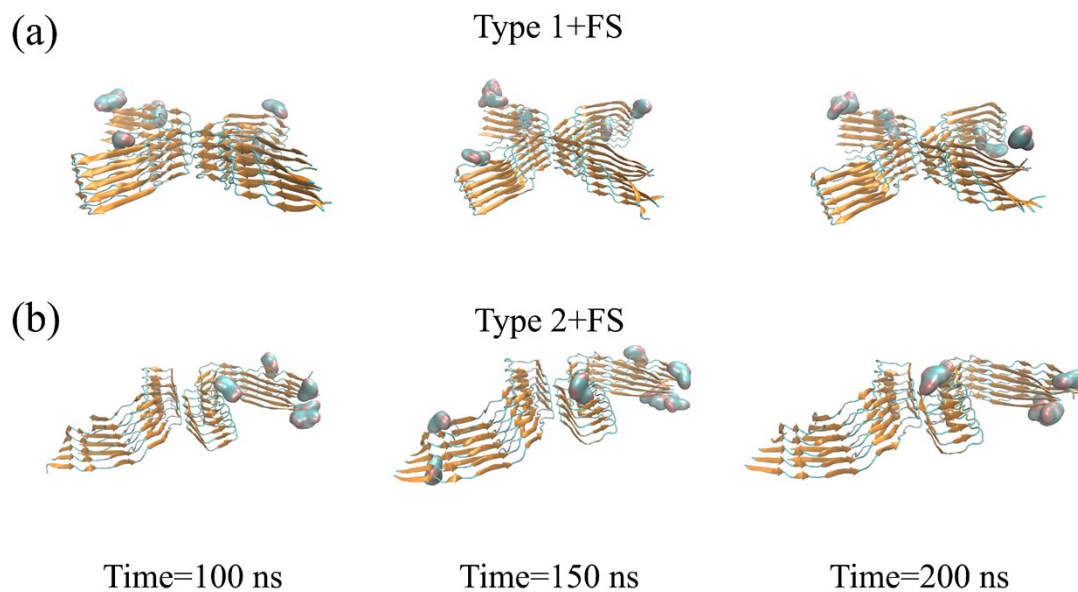
Decamer 2/Decamer 2 + FS systems (b). Representative snapshot of the CH- $\pi$  interaction formed between residue I308 and Y310.



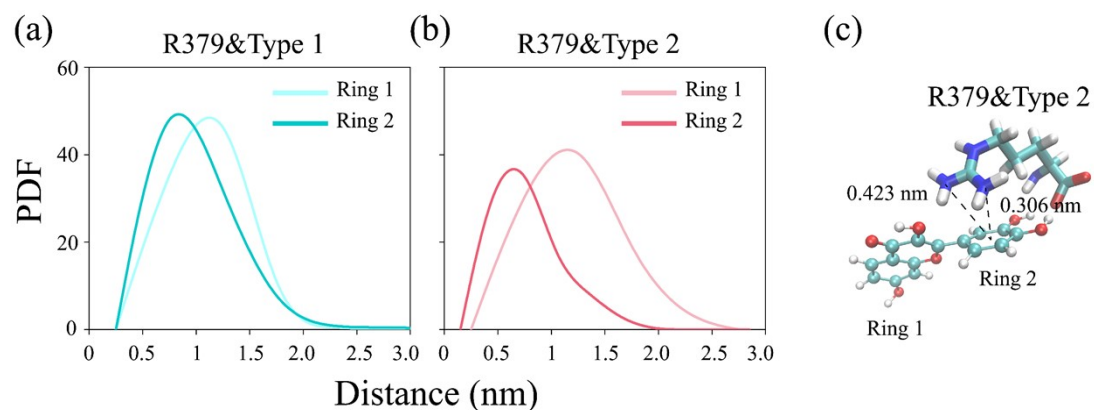
**Figure S5.** The most populated four conformational clusters of FS binding on the type 1 fibril for the three trajectories.



**Figure S6.** The most populated four conformational clusters of FS binding on the type 2 fibril for the three trajectories.



**Figure S7.** Representative snapshots of FS molecules binding on the elongation sides of the type 1 fibril (a) and type 2 fibril (b) in the moments of 100 ns, 150 ns and 200 ns.



**Figure S8.** PDF of distance between the centroid of aromatic rings of FS and positively charged groups of the residue R379 of the two types of fibrils (a, b). Representative snapshot of the cation- $\pi$  interaction formed between Ring 2 of FS and R379 of the type 2 fibril (c).

**Table S1.** Secondary structure statistics of the type 1 fibril in the two systems.

Systems	Coil (%)	$\beta$ -sheet (%)	$\beta$ -bridge (%)	Bend (%)	Turn (%)
Decamer 1	36.20 $\pm$ 0.16	51.42 $\pm$ 0.39	2.93 $\pm$ 0.27	9.26 $\pm$ 0.09	0.17 $\pm$ 0.02
Decamer 1 + FS	39.32 $\pm$ 2.64	48.43 $\pm$ 2.75	3.00 $\pm$ 0.33	9.11 $\pm$ 0.58	0.13 $\pm$ 0.02

\*The values are marked as mean  $\pm$  standard deviation.

**Table S2.** Secondary structure statistics of the type 2 fibril in the two systems.

Systems	Coil (%)	$\beta$ -sheet (%)	$\beta$ -bridge (%)	Bend (%)	Turn (%)
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Decamer 2	$36.56 \pm 0.09$	$50.11 \pm 0.15$	$2.82 \pm 0.12$	$10.00 \pm 0.04$	$0.52 \pm 0.06$
Decamer 2 + FS	$38.04 \pm 1.30$	$48.30 \pm 1.24$	$2.98 \pm 0.02$	$10.18 \pm 0.12$	$0.51 \pm 0.08$

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\*The values are marked as mean  $\pm$  standard deviation.