CSSI Element: Computational Toolkit to Discover Peptides that Self-assemble into User-selected Structures

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BACKGROUND

Peptide β-sheet assemblies pose opportunities for new designs

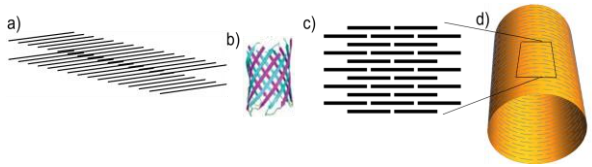
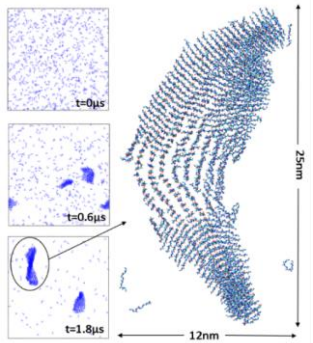


Figure. Schematics of (a) β-sheet nanofiber, (b) β-sheet nanoparticle, (c) β-sheet brickwork nanosheet, and (d) nanosheet curved to form a nanotube.

Discontinuous molecular dynamics (DMD)/PRIME20 simulation of spontaneous peptide self-assembly

Figure. Snapshot from DMD/PRIME20 simulation of 768 Aβ(16-22) peptides aggregating at T = 326 K, C = 5 mM.



OBJECTIVE : To develop an open software toolkit , "PepAD" that enables the identification of fibril-forming peptides

A **random sequence** is generated to drape on a user specified peptide scaffold (here referred to 2-layer β–sheet structure).

The **sequence is changed** through mutating amino acid or exchanging amino acids along the peptide chain. Side-chain configuration is subjected to energy minimization.

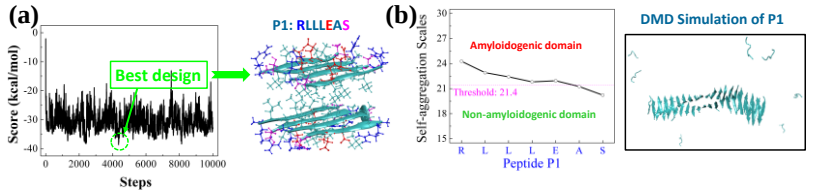
The score is evaluated according to the equation

$$\Gamma_{score} = \Delta G_{binding} - \lambda \times P_{aggregation}$$

where $\Delta G_{binding}$ is the binding free energy, λ is a weighting factor, and $P_{aggregation}$ accounts for the intrinsic aggregation propensity of peptides.

The design is accepted or rejected based on Monte Carlo Metropolis sampling.

OBJECTIVE : To use PepAD & bioinformatics & DMD simulation to evaluate the assembled behaviors of the in-silico discovered peptides



OBJECTIVE : To characterize the sequence patterns/signatures of fibril-forming peptides

Pattern	C	H	H	H	C	H	P
Signature	R	X_1	X_1	X_1	E/D	X_1	S
Pattern	**H**	**H**	**C**	**H**	**P**	**H**	**C**
Signature	A	L	R	L	S	L	E/D
Pattern	**C**	**H**	**H**	**H**	**P**	**H**	**C**
Signatures	R	X_1	X_1	X_1	S	X_1	E/D
	R	W/F	X_1	X_1	Q	X_1	E/D

The symbols **C**, **H**, **P** in pattern indicate **c**harged, **h**ydrophobic, **p**olar amino acids

(X_1 could be any one of the amino acids A, V, L, I)

Conclusion: A *pep*tide *a*ssembly *d*esign (PepAD) algorithm was developed and combined with the DMD simulation to discover peptide sequences that can self-assemble into β–sheet structures.