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

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ABSTRACT

Peptide self-assembly into nano-scale architectures provides numerous advantages for biomaterial applications. Screening sequence space via experiment to discover peptides that self-assemble into amyloid fibrils is challenging. A *pep*tide *a*ssembly *d*esign (**PepAD**) algorithm is developed in this work to help us identify the sequence signatures of fibril-forming peptides in a fast and efficient manner.

BACKGROUND

Peptide β-sheet assemblies and opportunities for new designs

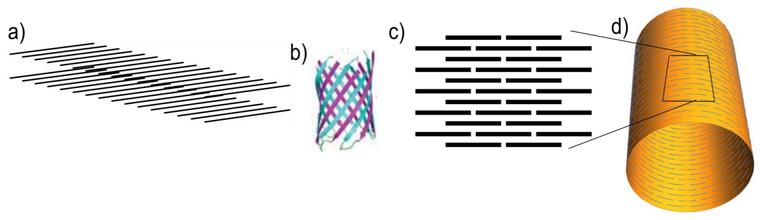

Figure. Schematics of (a) β-sheet nanofiber, (b) β-sheet nanoparticle, (c) β-sheet brickwork nanosheet, and (d) nanosheet curved to form a nanotube.

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

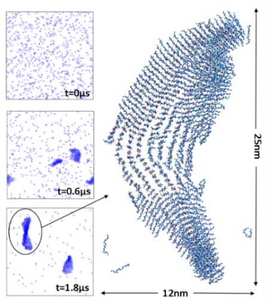

Figure. Snapshot from DMD/PRIME20 simulation of 768 Aβ(16-22) peptides aggregating at T = 326 K, C = 5 mM.

Experimental measurements of peptide assembly and structure

Solid-state NMR spectroscopy has the unique ability to probe molecular structure of peptide assemblies.

OBJECTIVE 1: 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).

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

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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.

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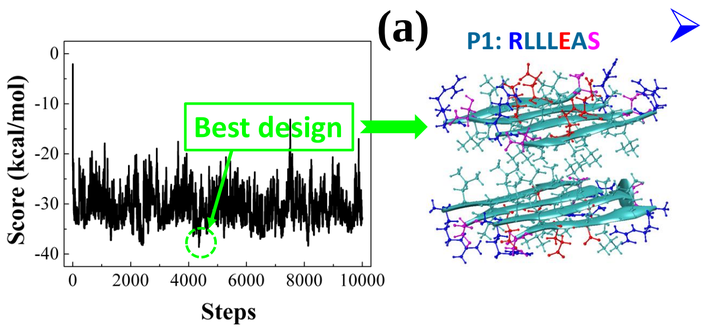
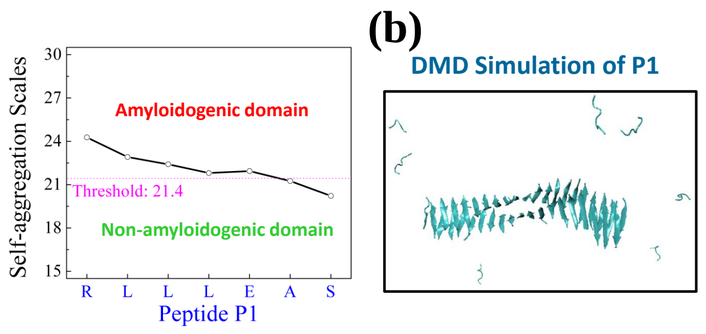
The design is accepted or rejected based on Monte Carlo Metropolis sampling.

➢ **Progress:** We developed a PepAD algorithm that is used to discover peptides that self-assemble into the desired supramolecular structure.

OBJECTIVE 2: To use bioinformatic method and DMD simulation to evaluate the self-assembled behavior of the in-silico discovered peptides





➢ **Progress:** (a) Used the PepAD algorithm to discover a 7-mer peptide P1 (sequence: RLLLEAS). (b) The self-aggregation propensities of P1 were evaluated using the FoldAmyloid tool, and the self-aggregated structure of P1 was examined by DMD simulation.

Note:

1. Residues along the chain below the self-aggregation threshold of 21.4, defined in the FoldAmyloid tool are in amyloidogenic domain; otherwise they are in non-amyloidogenic domain.
2. PepAD–generated peptides with no more than 2 residues below 21.4, were found via DMD/PRIME20 to spontaneously self-assemble into amyloid fibrils.

OBJECTIVE 3: To extract sequence patterns and signatures of predicted 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)

➢ **Progress:** Based on the objective 2 results, we examined the 300 top-scoring peptides discovered from the PepAD algorithm and characterized their sequence patterns and signatures. For example: sequence RAVLEIS has the pattern CHHHCHP.

OBJECTIVE 4: Use biophysical characterization techniques to see if the structures designed in Objectives 1-3 self-assemble as predicted

➢ **Plan of work:** The in-silico discovered peptides that can form amyloid fibrils in the DMD simulations have been sent to our collaborator Prof. Paravastu's lab for further experimental verification by using the ssNMR technique. The results will be fed back to improve our computational algorithm's design capability.