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Simulations delineating the cross interaction between Aβ and IAPP

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Article

Amyloid Cross-Interactions through the Lens of Simulations: The Case of Aβ–IAPP

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Xenophon Xenophontos, Anastasia Vlachou, Ryleigh K. Hunt, and Phanourios Tamamis*

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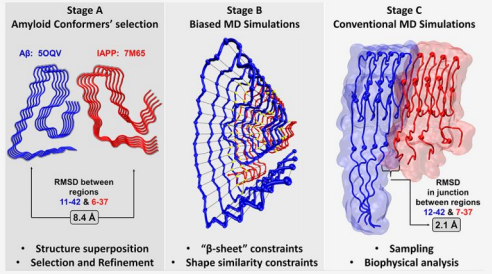
ABSTRACT: While significant progress has been made in developing approaches to study amyloid self-assembly leading to homomeric fibril formation by identical proteins, our understanding of heteromeric cross-interactions formed by different proteins is limited. Understanding such cross-interactions, resulting from cross-seeding and/or coaggregation, is undeniably key due to their occurrence in biology and their implication in diseases. We have developed a new computational approach for the study of heteromeric amyloid cross-interactions in axial stacking, biased molecular dynamics (MD) simulations, followed by conventional MD simulations. The biased MD can mimic, facilitate, and accelerate the cross-interaction process, allowing the cross-interacting entities to adapt their conformations and interactions with each other. Our approach has been applied to delineate the amyloid cross-interactions that can be formed by Aβ and IAPP in axial stacking. The computationally derived conformers demonstrate a high degree of compatibility in β-sheet interactions and side chain contacts in the Aβ–IAPP cross-interaction and beyond, forming an amyloid steric zipper nearly throughout the structure. Our results depict that IAPP in the junction can cross-interact intermolecularly with an Aβ fibril nearly as favorably as with an IAPP fibril. At least for the polymorphs examined, while both Aβ and IAPP can adapt to each other in the junction, IAPP has a higher propensity to adopt a polymorph that is formed by homomeric Aβ. This is in line with the notion that an Aβ fibril can be a seed for IAPP. We suggest that the capacity of amyloids to adopt different polymorphs and the types of polymorphs they can adopt determine and drive their cross-interacting capacities; this is valid at least for the cross-interaction investigated here and could hold for other amyloid cross-interactions in general.



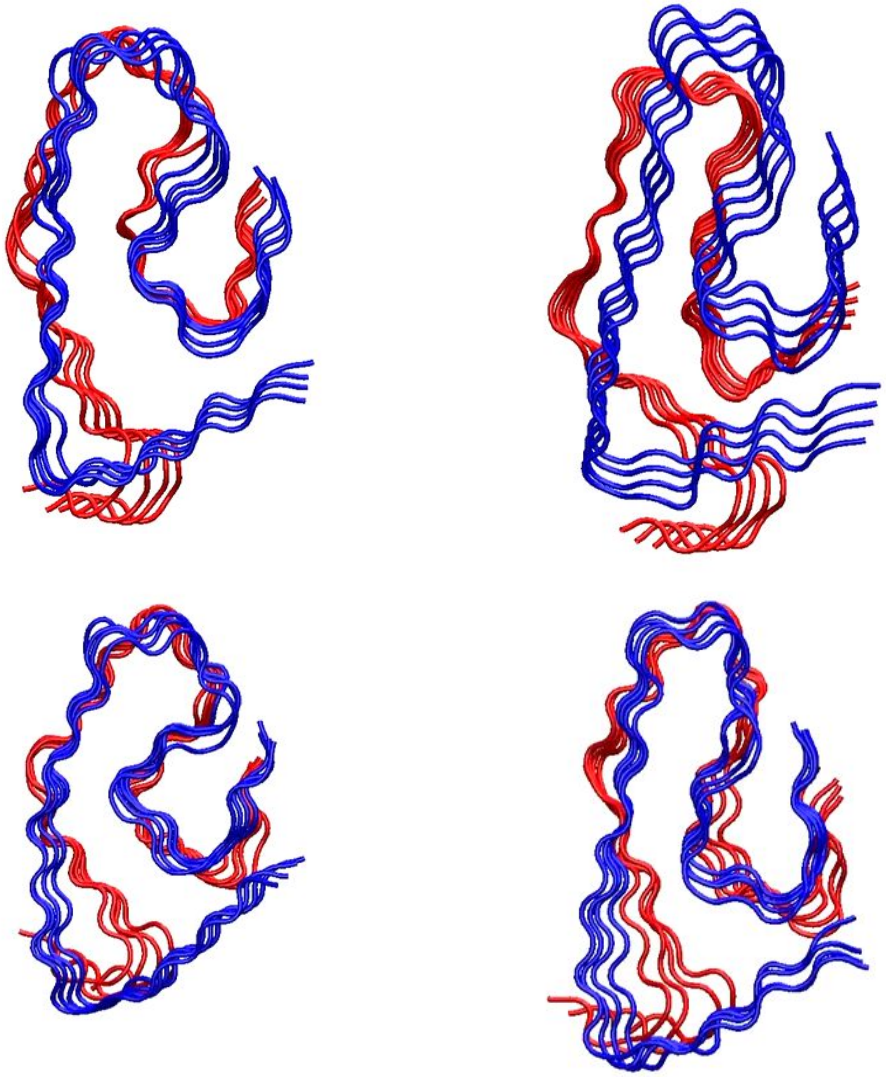
- **TAMU HPRC:** Grace cluster
- **Setup:** CHARMM/CHARMM-GUI
- **Simulations:** OpenMM/CHARMM-GUI
- **Nodes:** GPUs (a100)
- **Max Memory Requested:** 7.5 GB
- **Runtime:** 23 hours (1380 hours in total)

open heteromeric conformer

closed heteromeric conformer

Biased MD Simulations

Conventional MD Simulations



Simulations of Cross-Interacting fibrils between Aβ and IAPP

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Simulations designing amendments to clays for PFAS sorption

Contents lists available at ScienceDirect

Computers and Chemical Engineering

journal homepage: www.elsevier.com/locate/compchemeng

Caffeine, riboflavin and curcumin amended clays for PFAS binding

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ARTICLE INFO

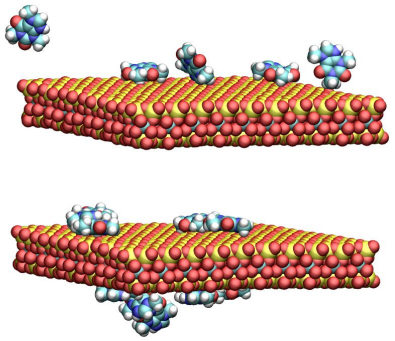
Keywords:
Montmorillonite clay
Caffeine
Curcumin
Riboflavin
PFAS
Molecular dynamics simulations

ABSTRACT

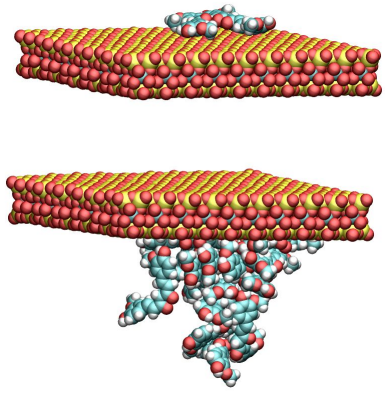
Per- and polyfluoroalkyl substances (PFAS) are usually found in mixtures with other toxic compounds. Therefore, the study and design of broad acting sorbents, such as clays, is an attractive sorption solution. We previously demonstrated that clays amended with choline and carnitine could enhance PFAS sorption properties. Here, we used computations to screen from a pool of chemical compounds, which are either supplements or generally recognized as safe, and identified particular supplements that can be amended to clay and potentially improve its sorbing capacity for PFAS in acidic conditions. Simulations were initially used as a tool to identify promising amendments to the clay, while subsequently, simulations evaluated which selected amendments could potentially bind PFAS. Our results showed that caffeine-, riboflavin- and curcumin-amended clays can, in particular instances, enhance the binding of different PFAS compared to parent clays. Experiments investigated the sorption properties of the designed systems. Notably, caffeine-amended clay significantly enhanced GenX binding when compared to parent clay, with its binding capacity being increased from 0.15 mol/kg to 1.17 mol/kg. Caffeine-amended clay also enhanced binding for PFOS by 125%, compared to the parent clay, and for PFOA to a lesser extent. Additionally, riboflavin-amended clay enhanced binding for GenX, PFOA and PFOS by 120%, 23%, and 70%, respectively, compared to the parent clay. Our studies provide atomistic details into their mechanisms of action. Both the novel computational library of chemical compound-amended clays and the approach utilized, combining computations and experiments, could enhance the future design of novel amended clays for other toxins.

Consensus Best amended-clays for enhanced PFAS binding

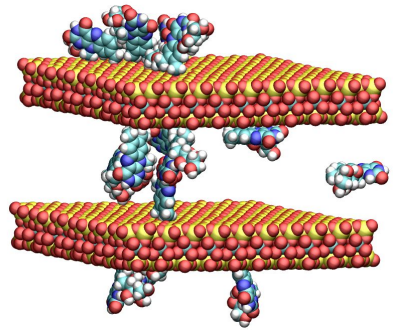
Caffeine-amended clay



Curcumin-amended clay

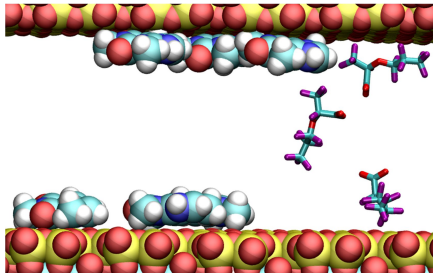


Riboflavin-amended clay

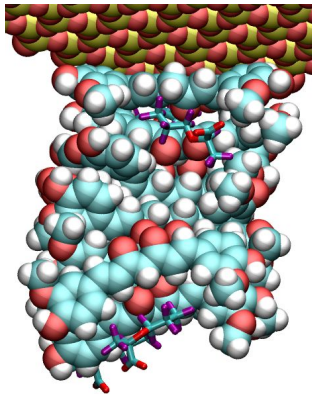


Caffeine predominantly lays flat on clay surface, curcumin forms large aggregates on the exterior clay surface, and riboflavin binds to clay either individually or by forming small clumps.

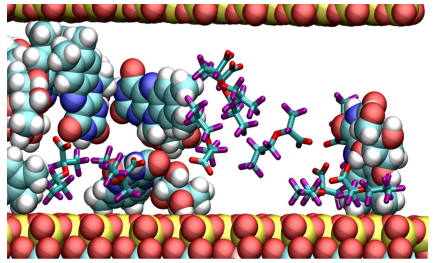
GenX binds to Caffeine-amended clay



GenX binds to Curcumin-amended clay



GenX binds to Riboflavin-amended clay



- **TAMU HPRC:** Grace cluster
- **Setup:** CHARMM/CHARMM-GUI
- **Simulations:** OpenMM/CHARMM-GUI
- **Nodes:** GPUs (rtx)
- **Max Memory Requested:** 2.5 GB
- **Runtime:** 32 hours (2464 hours in total)

- GenX interacts with caffeine-amended clay with its perfluoroalkyl tail while it simultaneously interacts with the clay surface
- GenX interacts with curcumin clump with its perfluoroalkyl away from the clay surface
- GenX interacts with riboflavin-amended clay with its tail and the clay surface (can form hydrogen bonds with riboflavin)

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Simulations of chlorophyll-amended clays aiding aflatoxin-B1 sorption

toxins MDPI

Article

Green-Engineered Montmorillonite Clays for the Adsorption, Detoxification, and Mitigation of Aflatoxin B1 Toxicity

Johnson O. Oladele [1,2], Xenophon Xenophontos [3], Gustavo M. Elizondo III [1,4], Yash Daasari [2], Meichen Wang [5], Phanourios Tamamis [3,6], Natalie M. Johnson [1,4] and Timothy D. Phillips [1,2,*]

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[4] Department of Environmental & Occupational Health, Texas A&M University, College Station, TX 77843, USA
[5] Department of Environmental Health Sciences, University of Massachusetts Amherst, Amherst, MA 01003, USA; meichenwang@umass.edu
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Abstract: Dietary and environmental exposure to aflatoxins via contaminated food items can pose major health challenges to both humans and animals. Studies have reported the coexistence of aflatoxins and other environmental toxins. This emphasizes the urgent need for efficient and effective mitigation strategies for aflatoxins. Previous reports from our laboratory have demonstrated the potency of the green-engineered clays (GECs) on ochratoxin and other toxic chemicals. Therefore, this study sought to investigate the binding and detoxification potential of chlorophyll (CMCH and SMCH) and chlorophyllin (CMCHin and SMCHin)-amended montmorillonite clays for aflatoxin B1 (AFB1). In addition to analyzing binding metrics including affinity, capacity, free energy, and enthalpy, the sorption mechanisms of AFB1 onto the surfaces of engineered clays were also investigated. Computational and experimental studies were performed to validate the efficacy and safety of the clays. CMCH showed the highest binding capacity (Qmax) of 0.43 mol/kg compared to the parent clays CM (0.34 mol/kg) and SM (0.32 mol/kg). Interestingly, there were no significant changes in the binding capacity of the clays at pH2 and pH6, suggesting that the clays can bind to AFB1 throughout the gastrointestinal track. In silico investigations employing molecular dynamics simulations also demonstrated that CMCH enhanced AFB1 binding as compared to parent clay and predicted hydrophobic interactions as the main mode of interaction between the AFB1 and CMCH. This was corroborated by the kinetic results which indicated that the interaction was best defined by chemosorption with favorable thermodynamics and Gibbs free energy (ΔG) being negative. In vitro experiments in Hep G2 cells showed that clay treatment mitigated AFB1-induced cytotoxicity, with the exception of 0.5% (*w*/*v*) SMCH. Finally, the in vivo results validated the protection of all the clays against AFB1-induced toxicities in Hydra vulgaris. This study showed that these clays significantly detoxified AFB1 (86% to 100%) and provided complete protection at levels as low as 0.1%, suggesting that they may be used as AFB1 binders in feed and food.

Keywords: aflatoxin; food safety; mycotoxin; enterosorbent; NovaSil; Alphasil; clay; molecular dynamics; isotherms; kinetics

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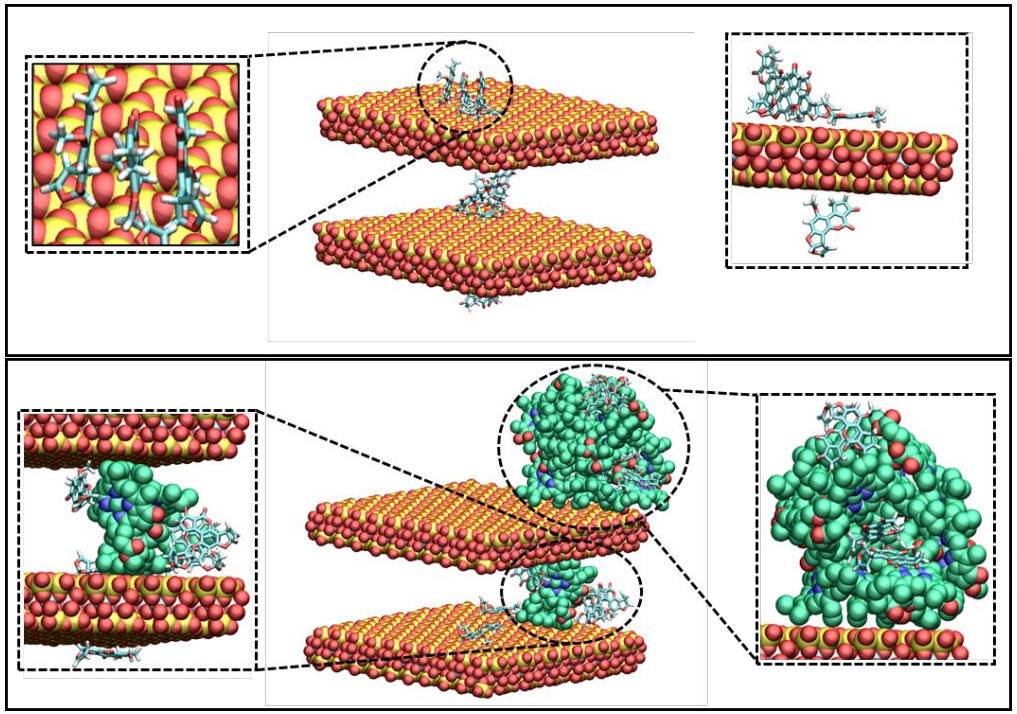
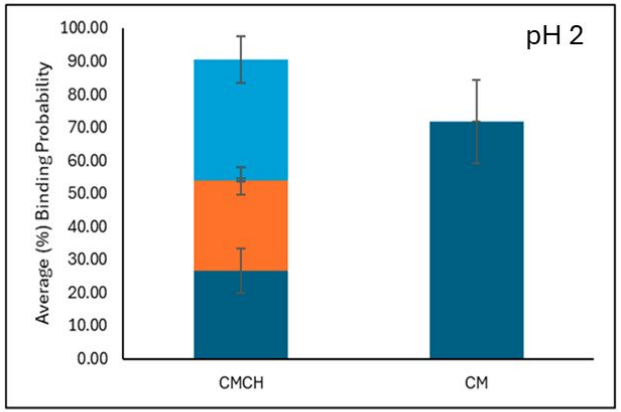
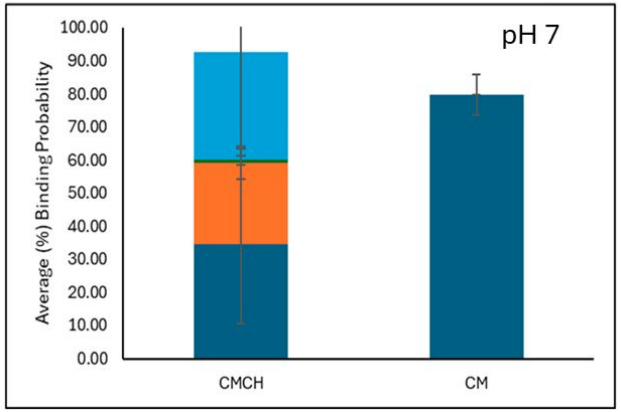


- Aflatoxin B1 has a high binding propensity to parent clay at both acidic and neutral conditions.
- Chlorophyll slightly enhances the binding of Aflatoxin B1
- Aflatoxin B1 aggregates and interacts with chlorophyll amendments
- No preference of Aflatoxin B1 to interact with head or tail of Chlorophyll





- **TAMU HPRC:** Grace cluster
- **Setup:** CHARMM/CHARMM-GUI
- **Simulations:** OpenMM/CHARMM-GUI
- **Nodes:** GPUs (rtx)
- **Max Memory Requested:** 2.5 GB
- **Runtime:** 27 hours (324 hours in total)

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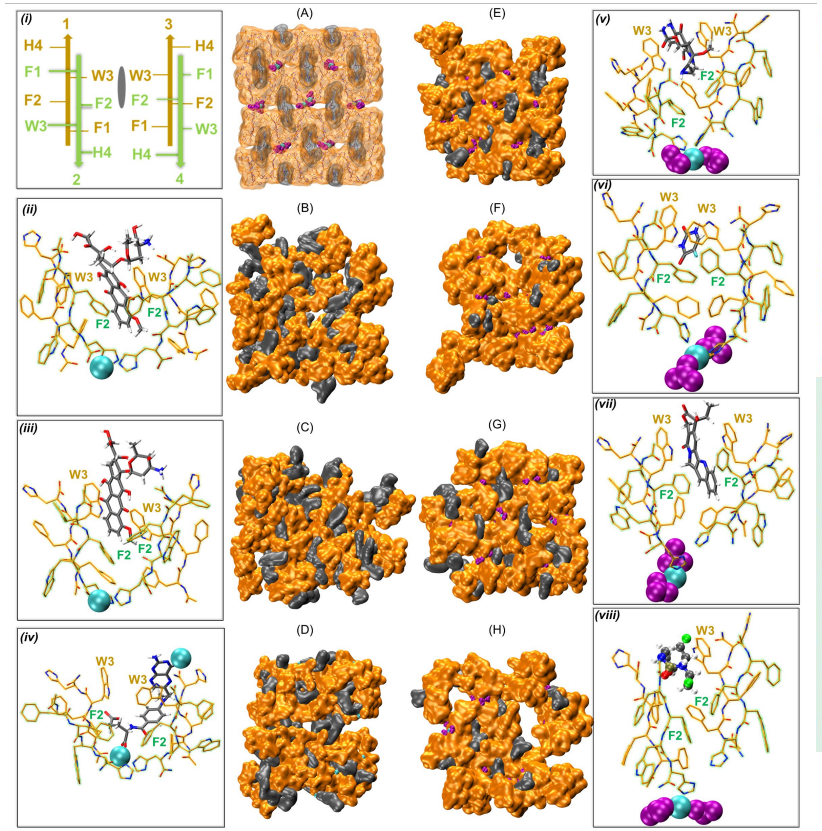
Computational Design of Minimalistic Peptide Carriers for Cancer Drugs



Representation of the modeled ordered assemblies prior to simulations for a representative drug (CPT) along with (i) a panel showing a 2D graphical representation of the structural unit comprising one drug and two pairs of peptides in antiparallel β-sheets (peptide 1–peptide 2 and peptide 3–peptide 4) with the two opposite pairs parallel orientated to each other (peptides 1 and 3 (orange) in back, peptides 2 and 4 (green) in front). Representation of the ordered assemblies of different systems with different drugs (B) EPI, (C) DOX, (D) MTX, (E) MIT, (F) 5FU, (G) CPT, and (H) CP. Panels (ii–viii) show a representative structural unit extracted from the simulations of ordered assemblies from (B–G), respectively. In (ii–viii), peptides are shown with orange licorice and drugs with gray licorice, while additionally, to discriminate between peptides on the front and peptides on the back, peptides on the front layer are shown with a green outline, while the peptides on the back layer are shown with a yellow outline.

ACS APPLIED BIO MATERIALS

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Article

Minimalistic Peptide Nanocarriers for Multiple Cancer Drugs

Anastasia Vlachou,[#] Om Shanker Tiwari,[#] Sonika Chibh, Jake R. Remmert, Ehud Gazit,[*] and Phanourios Tamamis[*]

Cite This: https://doi.org/10.1021/acsabm.5c01234

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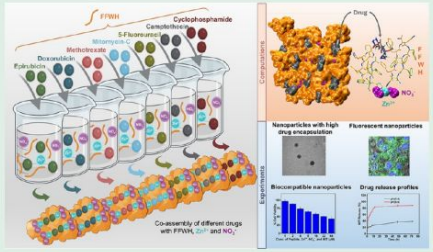
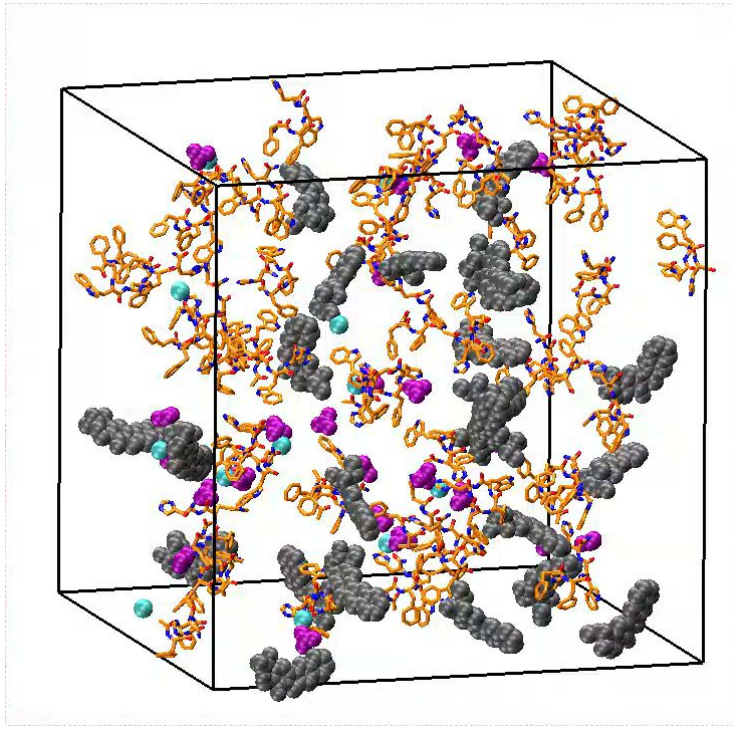
ABSTRACT: The co-assembly of minimalistic peptides with cancer drugs, leading to the formation of nanocarriers for drug delivery, comprises a promising direction in chemotherapeutics. We computationally designed fluorescent minimalistic four-residue peptide nanocarriers for multiple cancer drugs: Epirubicin, Doxorubicin, Methotrexate, Mitomycin-C, 5-Fluorouracil, Camptothecin, and Cyclophosphamide. The optimally designed resulting nanocarriers formed by FFWH have notable drug encapsulation properties for the drugs investigated, according to both computational and experimental studies. Additionally, the nanocarriers possess biocompatibility, enhanced fluorescence, and uptake into HeLa cells using live cell confocal microscopic images. Our simulations demonstrate how the same peptide can efficiently be used to encapsulate these drugs as well as provide structural and biophysical understanding of their properties. We suggest that the designed nanocarriers can serve as programmable nanostructures for the future design of new generations of advanced nanocarriers with potential cancer- and patient-specific targeting properties.

KEYWORDS: *minimalism, short peptides, cancer drugs, co-assembly, nanocarriers*



Peptide: orange **Drug: gray**

Zn^{2+}: cyan **NO_3^- : purple**



Simulations showing an example early co-assembly stage of peptides, drugs and ions

- **TAMU HPRC:** Grace cluster
- **Setup:** CHARMM/CHARMM-GUI
- **Simulations:** OpenMM/CHARMM-GUI
- **Nodes:** GPUs (a100)
- **Max Memory Requested:** 5 GB
- **Runtime:** 11 hours (8400 hours in total)

Simulations performed on GRACE, using GPUs