Bridging Experiments and Molecular Modeling to Decode Cargo-Responsive Nanocarriers

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The rational design of nanocarriers for drug delivery and theragnostic applications requires more than the optimization of loading capacity, average size, or apparent colloidal stability. In many supramolecular and self-assembling systems, the cargo is not a passive guest: it may actively reshape the structural organization, dynamic stability, solvent exposure, and interaction pattern of the carrier. Understanding this cargo-induced remodeling is therefore essential to connect formulation properties with biological performance.

Here, we present an integrated biophysical and molecular-descriptor strategy to characterize cargo-responsive nanocarriers for drug delivery. The approach is conceived to bridge experimental observables and molecular-level interpretation. Experimental characterization provides information on size distribution, colloidal behavior, optical response, and structural perturbation through techniques such as dynamic light scattering, UV-vis and fluorescence spectroscopy, circular dichroism, and complementary nanoscale/morphological analyses when available. These data are then interpreted together with molecular modeling and simulation-derived descriptors that capture the dynamic organization of the loaded nanocarrier. Rather than treating simulations as a stand-alone computational layer, the workflow uses them as an interpretative tool to translate experimental evidence into engineering-relevant descriptors. These include nanocarrier compactness, cargo exposure to the solvent, persistence of cargo-carrier contacts, dynamic stability of the loaded assembly, conformational flexibility, and the emergence of metastable organizational states. In this framework, free-energy landscapes and clustering analyses are not presented as purely theoretical outputs, but as design maps that help identify whether different cargoes stabilize, destabilize, or redirect the accessible conformational space of the carrier.

This strategy is illustrated on representative self-assembling nanocarrier/cargo systems under investigation in our group, with the aim of defining a transferable workflow for comparing different payloads and formulation conditions. The final goal is to support a more rational design of nanocarriers in which cargo loading, structural response, and dynamic stability are treated as coupled variables. Such a description may be particularly useful for the development of delivery and theragnostic platforms where the functional behavior depends not only on what the carrier contains, but also on how the cargo remodels the carrier itself.