Possibilities and current limitations of joining MD simulations and experiments: the cases of amyloid aggregation and membrane binding proteins

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Abstract

In this talk I will show for two different examples how the combination of molecular dynamics (MD) simulations and experiments enrich each other, thereby providing a more complete picture of the dynamics and interactions of proteins than the sole application of each of the individual methods would reveal. The first example is concerned with protein aggregation, which is the main area of interest in our group. The aim of our work is to understand the physicochemical principles that govern the highly complex process, which may lead to fatal diseases, as in the case of Alzheimer's disease. All-atom molecular dynamics (MD) simulations of protein aggregation in explicit solvent have been performed for over a decade, revealing valuable information about this phenomenon. However, these simulations are challenged by three main problems: (1) The accuracy of current all-atom force fields in modeling protein aggregation is insufficient.1 We currently work on first identifying why the force fields fail to reproduce the aggregation kinetics and then resolving these problems. (2) The second problem is that all-atom MD simulations of protein aggregation are generally performed at protein concentrations orders of magnitude higher than the comparable in vitro and in vivo situations, limiting structural rearrangements between aggregate growth events.2 In order to overcome this limitation much longer simulations of the individual aggregation states are needed than was done in the past, as we showed in our recent work.3 (3) The third problem is the well-known length- and time-scale problem. Even when we manage to simulate the aggregation process for tens or even hundreds of mircoseconds, this is not enough to meet the corresponding scales usually tested in experiments of protein aggregation, which report on nm-to-μm long aggregates that form on the time scale of minutes and beyond. This limitation can only be solved by designing experiments that also report on the early aggregation events, and by developing multiscale simulation approaches that will allow to extend the length- and time-scales to be simulated. Similar problems are also faced in the second example that I will discuss in my talk, which is about the aggregation and lipid-membrane binding of guanylate binding proteins. [1] M. Carballo-Pacheco, A. E. Ismail, B. Strodel. On the Applicability of Force Fields to Study the Aggregation of Amyloidogenic Peptides Using Molecular Dynamics Simulations. J. Chem. Theory Comput. 14:6063-6075 (2018)

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