In silico study of protein-nanoparticle assembly and protein aggregation in crowded environments

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A pristine nanoparticle (NP) in a biological fluid is covered spontaneously by absorbed biomolecules forming a corona. Proteins, in particular, are one of the main components of it and can be part of the 'hard' or the 'soft corona', remaining for a relevant time on the NP or dynamically exchanging with those in solution, respectively [1]. Experiments debate if the irreversible protein adsorption can cause loss of specificity in targeting of pre-functionalized NPs [2] or not [3]. Other data show that a minority of the protein's epitopes are appropriately arranged for receptor binding, consistent with a stochastic and irreversible adsorption process in which proteins are, at least partially folded in their native state even when adsorbed in the hard corona [4]. Therefore, the details of the protein-NP assembly are essential to understand the possible nanoMedical applications [5]. Here we perform *in silico* studies to understand how the presence of interfaces or crowding affect the stability of the native state of a protein and its aggregation rate.

We consider several cases of proteins, from those with a unique native state to those intrinsically disordered, by means of a coarse-grain protein model in explicit solvent [6-9]. By Monte Carlo calculations, we show how relevant is the water contribution to protein denaturation and folding [10, 11] and to protein design [12]. We reveal that the hydropathy profile of proteins is a consequence of evolutionary pressure exerted by water in simplified geometries [12] and in bulk [13]. We find that a hydrophobic interface destabilizes the protein native state but can allow it to fold even if adsorbed onto a surface [14].

Furthermore, we study the proteins in a crowded environment, where the aggregation is tuned in a way that enable them to be functional at the concentrations required for optimally efficient performance [15]. We show how the increase of the concentration of individual protein species can induce a partial unfolding of the native conformation without the occurrence of aggregates. A further increment of the protein concentration results in the complete loss of the folded structures and induces the formation of protein aggregates (Fig. 1). We discuss the effect of the protein interface on the water fluctuations in the protein hydration shell and their relevance in the protein-protein interaction [16]. These results can lead the way for engineering proteins and drugs that would be functional at extreme conditions and it is potentially relevant in protein-NP assembly for nano-Medicine applications [17, 18].

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Figures

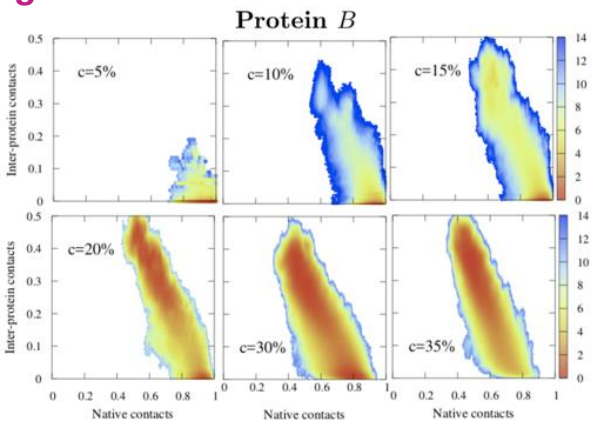

Figure 1. Protein unfolding vs aggregation. Color map of the free energy profile of a selected protein, as function of the native contacts and inter-protein contacts, for different protein concentration *c*. Native contacts and inter-protein contacts have been normalized to 1. Adapted from [16].