NPCoronaPredict: Multiscale modelling of the nanoparticle biomolecular corona

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1. Introduction

The layers of proteins and other biomolecules surrounding a nanoparticle (NP) in a biological environment – the nanoparticle corona – plays a vital role in determining the effective biological identity of the NP, its potential for adverse outcomes, and its eventual fate in the body [1]. The corona is a dynamic, mesoscopic entity formed over the course of hours, yet is highly dependent on fast, atomic-scale interactions between the surface of the NP and potential ligands. Consequently, it is extremely challenging to model the corona using conventional molecular dynamics. To overcome this issue, we have developed the NPCoronaPredict software package, which enables prediction of the contents of the nanoparticle corona via a multiscale modelling approach, employing a systematic scaling up of the system from the atomistic level of small molecules to nanomaterial surfaces, to coarse-grained modelling of the adsorption of proteins and other biomolecules, and finally to the evolution of the corona of an NP immersed in a mixture of these adsorbates [2,3].

2. Biomolecular adsorption

Although atomistic modelling of the adsorption of a protein or other large biomolecule is feasible via molecular dynamics simulations, the required time and computational resources render this unfeasible to carry out for the wide range of potential adsorbates present in realistic models of biological media. Thus, coarse-grained approaches are necessary to ensure that adsorption energies can be computed within an acceptable amount of time. We have previously developed the UnitedAtom methodology for protein adsorption, which precomputes the interactions between amino acids and NP surfaces and uses these to predict the adsorption of an entire protein by summation over all AA beads, taking into account their location in the protein relative to the NP in different orientations [4]. Recently, we have adapted this methodology to allow for modelling of the adsorption of essentially arbitrary biomolecules comprised of smaller organic molecular fragments to multi-component NPs consisting of well-defined single NPs, greatly expanding the range of systems which can be explored. The required input is a set of potentials representing the interaction between an organic fragment and a given nanomaterial, with over one hundred fragments parameterised to over fifty chemically distinct nanomaterials with multiple variants of these.

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3. Corona formation

The initial corona, primarily small biomolecules with a high concentration in the medium, forms within milliseconds, while the final corona evolves over the course of several hours. To capture these dynamic processes over this extended time period we employ a kinetic Monte Carlo method, which treats adsorbates as hard spheres and simulates their random sequential adsorption and desorption for a pre-defined length of time [5]. This methodology uses the adsorption energies output from UnitedAtom together with collision rates computed from kinetic theory to produce a set of adsorption and desorption rate constants for each possible orientation of each biomolecule relative to the surface of the NP, accounting for proteins with multiple binding sites or elongated structures. Using these rate constants, the steady-state corona is obtained, and quantities of each adsorbed biomolecule provided. These are of direct interest in terms of mass abundance, and we provide further post-processing tools to produce corona-averaged descriptors, e.g., the total charge of adsorbed molecules normalised by the surface area of the NP or the total number of residues of a certain type present in the corona. These descriptors provide further insight into the nature of the corona and the identity presented by the NP to its biological environment for use as input to QSAR and other machine-learning methods as they provide a convenient and biologically meaningful representation of the NP.

4. The NPCoronaPredict package

To streamline the use of our models, we have developed the NPCoronaPredict package which contains both UnitedAtom and CoronaKMC, while supplying a set of tools and interfaces to enable corona prediction with minimal user effort, and is freely available open-source [2,3]. This package contains a set of input potentials generated via metadynamics and augmented with additional potentials produced using machine-learning methods. A Python script, NPCoronaPredict.py, is supplied which automates running UnitedAtom for a selected NP and set of biomolecules, converts the output into rate constants, and runs the CoronaKMC script for final corona prediction. We also provide a simplified GUI to perform some of the most common tasks: downloading requested structures from either the Protein DataBank or AlphaFold DB as required, running UnitedAtom calculations for selected biomolecules and nanoparticles, and visualising the results as shown in Figure 1. To assist in designing complex multi-component nanoparticles we also provide the graphical tool NPDesigner for step-by-step construction of these composite NPs for use in UnitedAtom.

5. Conclusions

We have developed a multiscale methodology for predicting the contents of the biomolecular corona surrounding a nanoparticle, enabling rapid scanning of a wide range of NPs and biological media. This methodology is implemented in the open source NPCoronaPredict software package, which provides both a simplified graphical interface and a suite of command-line tools for the prediction of biomolecule adsorption affinities and the resulting corona. The output from this software package is immediately useful in characterising the nature of the nanoparticle corona and is of use in bioinformatics and predictive modelling of nanoparticle toxicology due to providing convenient numerical descriptors quantifying the biological identity of a given nanoparticle in a target organism.

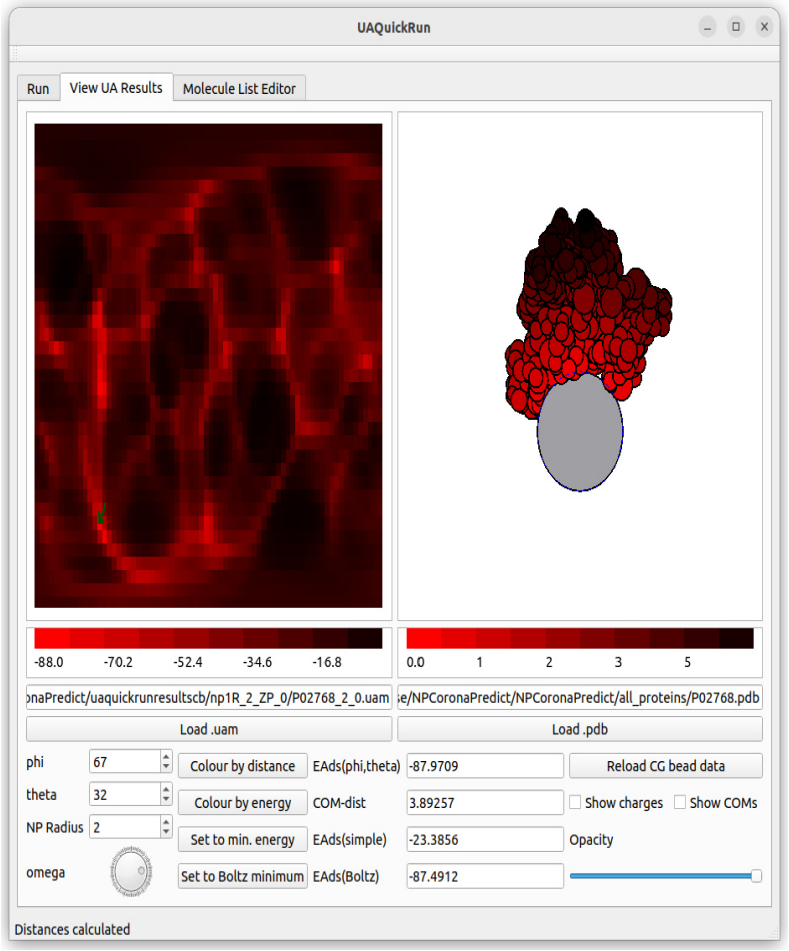

Figure 1: A snapshot of the graphical interface provided to compute biomolecule – nanoparticle adsorption energies, shown here for human serum albumin on a 2nm carbon black NP. The graphic on the left-hand side shows a computed adsorption heatmap, with red indicating strongly adsorbing orientations. The right-hand figure shows a schematic of the selected conformation of the protein, here chosen to be the most favourable binding conformation.

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7. References

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