

Roadmap for Computer-Aided Modeling of Theranostics and Related Nanosystems

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Abstract. Detailed understanding of the interactions of novel metal-containing nanoparticles with biological membranes, macromolecules and other molecular targets of the living cell is crucial for the elucidation of the biological actions of such functionalized nanosystems. We present here the construction and modeling of thiolate-protected gold clusters and the prediction of their static and dynamic properties.

1 Introduction

Nanotechnologies have significant influence on the recent research and development in many application areas. The biomedicine belongs to the most influenced fields. Thanks to the introduction of a new kind of nanoparticles (NPs) entitled theranostics (NP systems designed for combined diagnostics and therapeutic use), a new horizon was opened in imaging and treatment. Theranostic systems can be constructed from metallic core NPs functionalized with monolayer-covered bio-active molecules. Despite the recent “state of the art” level of molecular modeling methodologies and the number of articles published annually on noble-metal nanostructures, this particular field is still in the discovery phase [1]. In addition, the detailed understanding of the interactions of functionalized NPs with biological membranes, macromolecules and other entities of the living cells has crucial importance for the elucidation of the mechanisms governing the biological actions of such nanosystems. Insights into molecular details as to how these nanomaterials interact with subcellular nano-machinery of the cells can facilitate the design and engineering of a new generation of NPs [2]. We were interested in building and modeling thiolate-protected gold clusters and gold clusters functionalized with other biomolecules. We have computed their static and dynamic properties. Due to the system size and the inherent difficulties of the metallic NP modeling, such a task is a formidable challenge. As a part of our modeling roadmap, we aim to build models for NP – chromatin fragments, resembling interactions of such particles with higher-order DNA structures of living cells. Reliable computer modeling of intra- and intermolecular interactions in NP-chromatin models is a very complex task due to the size of such systems. Accordingly, we proceeded in several modeling steps which are described below.

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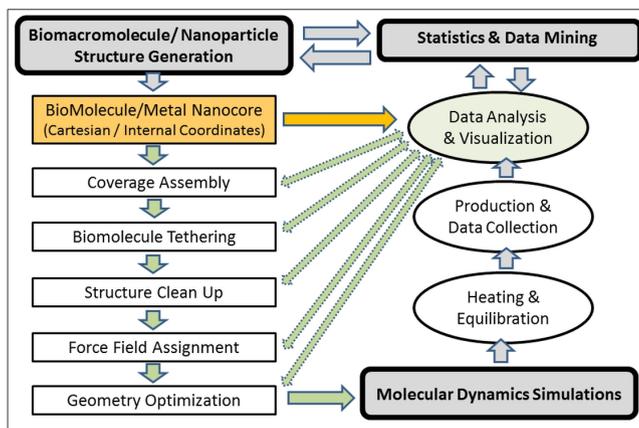


Figure 1. Schematic roadmap starting from structure generation. Due to the number of atoms and the complexity of the systems, the permanent data analysis and visualization are of key importance to the derivation of solutions

2 Computational methodology

Several different computational protocols were needed to build, compute, and analyse the nanosystems under study. Figure 1 represents the roadmap – interconnections between different tasks starting from structure generation (upper left box). Understanding the structural complexity of the studied systems (starting from gold-containing NPs to model theranostics up to building DNA-related biomacromolecular systems) required very different approaches (all-atom (AA) versus coarse-grained (CG) modeling). Accordingly, different programs (running on Windows, Linux, MacOS) and web services were used in order to fill the boxes shown in Figure 1. Table 1 summarizes the most important programs used in the presented study. Taking into account our former experience with GPGU computing [3], we preferred the GPGU versions of the listed programs where available.

3 Results and discussion

We were interested in functionalization of differently sized gold-core NPs (from 25 to more than 100 Au atoms). Based on the experimental availability of Au-related structural data the data of Murray et al [4] were used for the construction of Au-25 clusters and the data of Kornberg et al [5] for the Au-102 clusters. The results of geometry optimization (carried out by the Forcite program of Materials Studio, see Table 1) of two differently functionalized Au₂₅S₁₈ clusters are presented in Figure 2.

MD simulations (Forcite program of Materials Studio) of these nanoclusters confirmed the conformational stability of the systems. In addition to molecules shown in Fig. 2, we built and calculated several other NPs in two ways: by enlarging the number of core Au atoms and, changing the functionalizing coverage as well. Even more, we have included doxorubicin into the NP [6] as a known way of facilitating drug delivery.

In the next step, we were interested in the development of advanced models for biomacromolecular systems where we predict possible bindings of the generated NPs. For detailed atomistic modeling of functionalized gold NP-nucleosome interactions, we downloaded the structure of nucleosome core particle (NCP) resolved at 2.5 Å resolution [7]. In accordance with our roadmap-scheme (Fig. 1), we ended up with minimized structure of NCP to which the gold-core NPs were docked. Figure 3 represents the lowest-energy structure obtained in this way.

Table 1. Summary of computational tools used in presented study

PROGRAM or WEB SERVICE:	Reference or provider:
Discovery Studio (a) Materials Studio (b)	(a) BIOVIA, Discovery Studio Modeling Environment (2015) (b) Accelrys/BIOVIA Materials Studio v7.0, 2013 Dassault Systèmes, San Diego, USA
HEX	D.W. Ritchie, <i>Evaluation of protein docking predictions using Hex 3.1 in CAPRI rounds 1 and 2</i> , <i>Proteins</i> 52 (1) 98–106 (2003)
ICM	R.C. Stolz and T.C. Bishop, <i>ICM Web: the interactive chromatin modeling web server</i> , <i>Nucleic Acids Res.</i> 38 (Web Server issue) W254–61 (2010)
MAESTRO	<i>Maestro</i> , version 10.1.012, in Schrödinger Release 2015-12015, Schrödinger, LLC: New York, NY., USA
NAMD (c) VMD (d)	(c) L. Kale et al., <i>NAMD2: Greater scalability for parallel molecular dynamics</i> , <i>Journal of Computational Physics</i> 151 (1) 283–312 (1999) (d) W. Humphrey, A. Dalke, and K. Schulten, <i>VMD: visual molecular dynamics</i> , <i>Journal of Molecular Graphics</i> 14 (1) 27–28, 33–38 (1996)
PACKMOL	L. Martinez et al., <i>PACKMOL: a package for building initial configurations for molecular dynamics simulations</i> , <i>Journal of Computational Chemistry</i> 30 (13) 2157–2164 (2009)
VDNA	T.C. Bishop, <i>VDNA: the virtual DNA plug-in for VMD</i> , <i>Bioinformatics</i> 25 (23) 3187–3188 (2009)

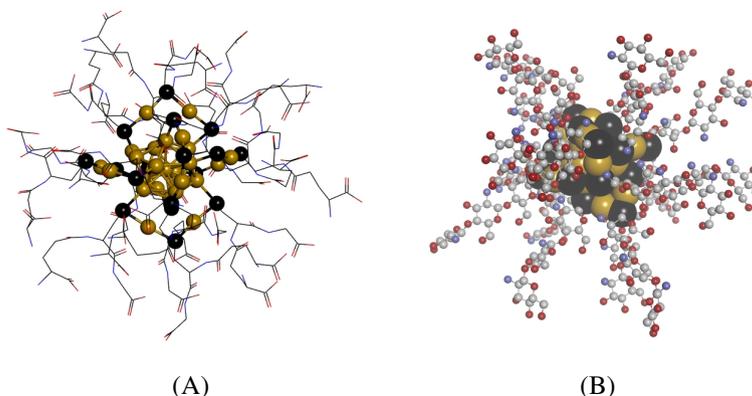


Figure 2. Glutathion and chitotriose functionalized NPs: (A) Au₂₅Glut₁₈ with the Au-S core shown in ball&stick and glutathions in line representation; (B) Au₂₅Chito₁₈ with the Au-S shown as CPK models and S-linked chitotriose molecules shown in ball&stick representation. The S atoms are colored black.

The computer-aided modeling of chromosome fragments is a complex task due the size and related number of atoms of these systems. There are several computational resources helping the task, and we ended up with plenty of interesting coarse-grained structures. One of these structures is shown in Figure 3. Part of the molecule was updated by atomistic representation of histone in order to have better option to realistically dock the functionalized NP and get deeper insight into atomistic details of the intermolecular interactions. Due to the complexity/size of the system this modeling and the corresponding computations are not finalized yet.

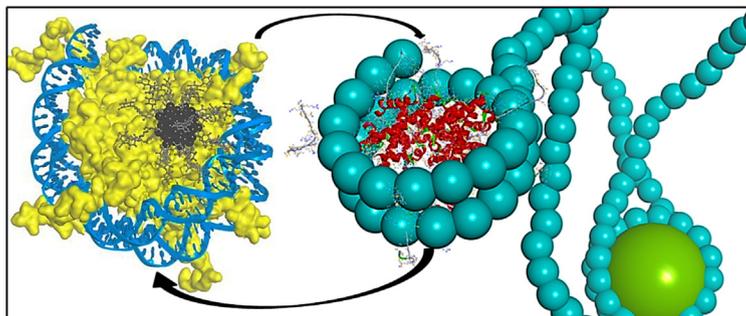


Figure 3. NCP in interaction with chitriose functionalized gold NP (left; the NP is shown in black) and coarse-grained chromatin model with embedded all-atom histone (right). The arrows indicate the corresponding structural parts of NCP/chromatin. In coarse-grained model the medium size circles correspond to nucleotides. The largest circle corresponds to the second histone. Real molecular surface is shown for histone proteins (left).

4 Conclusion

Based on hardware and software availability, together with the gained experience in the generation of complex supramolecular assemblies, we were able to construct functionalized gold-NPs and calculate their static and dynamic properties. We proceeded to the modeling of their interactions with more complex macromolecular entities present in living cells like nucleosome particles. Such approaches will be of key importance for computer-aided modeling of biomarkers, as well as the interpretation of data for upcoming use in free-electron X-ray experiments.

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