PhD thesis title:

An interdisciplinary approach to the design of effective nanoparticle-based antimicrobials

Supervisors:

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Scientific context and objectives:

Antimicrobial resistant microorganisms are a major threat to public health. The World Health Organization (WHO) considers this societal risk to be a priority, as such resistant pathogens are estimated to cause the death of 700,000 people a year through the world, and health agencies predict about 10 million deaths a year by 2050, attributable to resistant microorganisms, if tremendous research efforts are not made to develop new antimicrobials. In this framework, gold nanoparticles (NPs) functionalized with active molecules have been found to present remarkable antimicrobial effects against resistant bacteria and fungi [1-5], and a significant delay in resistance development [2-4,6,7]. However, these hybrid antimicrobials need to be optimized in terms of stability/efficiency, as a successful therapy is conditioned by an efficient drug with extended lifetime and as low as possible administered doses [8-10], the combination of these qualities allowing a drastic reduction of side effects and giving the microorganism less time to develop resistance. To design and develop optimal hybrid antimicrobials, it is crucial to master their structure at the atomic scale [11, 12].

The structural exploration of these systems at the atomic scale requires both high-performance algorithms for the global exploration of the molecules adsorption modes on the NPs, and also the implementation of quantum chemistry methods, in which the electronic level description allows for evaluating charge transfers, crucial with regard to ligands adsorption and interaction. Obtaining this information therefore requires a multi-level approach i.e. a coupling of models and methods at the intersection of physics, theoretical chemistry, computer science and applied mathematics [13]. In recent years, robotics-inspired algorithms have emerged as a new approach to explore the energy landscape of molecular systems in order to identify stable conformations and the most likely conformational transitions [14, 15]. Current versions of these algorithms are able to efficiently deal with problems in relatively large dimensions, but are still limited to moderate-sized molecular systems.

The main objective of this thesis will be to carry out the algorithmic developments to treat complex systems containing a gold NP and the grafted molecules, in the presence of the surrounding solvent. We will build on recent work on molecule-surface systems conducted by Juan Cortés (LAAS-CNRS) and Nathalie Tarrat (CEMES-CNRS) in collaboration with researchers at the Max Planck Institute (MPI) in Stuttgart [16, 17]. The proof-of-concept algorithmic approach developed in this interdisciplinary collaborative context will be the basis for this thesis. It is based on a synergistic combination of sampling, optimization and clustering methods. With the participation of Cathy Maugis-Rabusseau (IMT-INSA), we will develop more sophisticated and efficient versions of the algorithm, able to treat the complexity of the problems addressed in this project. The reliability of our results will be tested by comparison with experimental data (STM images) related to the self-organization of molecules on extended gold surfaces (collaboration with the MPI-Stuttgart). Subsequently, global explorations will be carried out for different sizes/morphologies of the gold NPs, and for different coverages for a given antimicrobial molecule. Once the most probable structures will be located, quantum chemistry calculations (DFT and DFTB) will provide a precise description of the atomic and electronic structures of these nanoconjugates and their stability.

In parallel to this theoretical/algorithmic work, experiments will be carried out in the framework of a collaborative project. The size/morphology-controlled synthesis and structural characterization of selected systems will be carried out at CEMES-CNRS and the functional investigation of the synthetized hybrid NPs will be carried out at the TBI institute (PHYGE team, headed by Jean M. François). Feedback from these experiments combined with the computational data obtained in the framework of this thesis will be used to design optimized hybrid nano-antimicrobials.

References:

[1] Int J Nanomed. 2019, 14, 5323–5338. [2] Pharmaceutics 2018, 10, 11. [3] Nano Futures 2017, 1, 015004. [4] ACS Nano 2014, 8, 10682–10686. [5] Appl. Environ. Microbiol. 2012, 78, 2768. [6] JACS 2014, 136, 5295–5300. [7] Nanoscale 2013, 5, 8340–8350. [8] Nanoscale Res. Let. 2007, 2, 614. [9] Nanoscale Res. Let. 2009, 4, 794. [10] Nanoscience and Nanotechnology 2012, 2, 14. [11] Nanoscale 2015, 7, 14515–14524. [12] Materialia 2018, 4, 297 –309. [13] Z. Naturforsch B 2016, 71, 351–374. [14] J. Comput. Chem. 2011, 32, 3464–3474. [15] IEEE Transactions on Nanobioscience 2015, 14, 545–552. [16] Angew. Chem. 2019, 131, 8424–8428. [17] RSC Advances 2019, 9, 35813–35819.

Expected skills:

- Strong background in algorithms and applied mathematics (mainly in optimization, notions of statistics would be appreciated).
- Good programming skills, mainly C++.
- Background in chemical physics, molecular modeling or material sciences is not mandatory, but would be a plus.
- Teamwork skills are also very important for the achievement of the project.

Applications:

Please send an email containing your CV to Juan Cortés (juan.cortes@laas.fr), Cathy Maugis-Rabusseau (cathy.maugis@insa-toulouse.fr) and Nathalie Tarrat (nathalie.tarrat@cemes.fr), indicating in the subject **"PhD candidate nano-antimicrobials"**.