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# TOWARDS MECHANISMS OF NANOTOXICITY – INTERACTION OF GOLD NANOPARTICLES WITH PROTEINS AND DNA

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**Abstract:** Even though most of the existing studies of gold nanoparticles indicate that they are safe to use, some researchers show that specific forms of nanoparticles (e.g. nanorods) are able to destroy the cell membrane and very small nanoparticles (below 37 nm in diameter) in high concentration have been deadly for mice.

We used the Amber12 package to perform a series of molecular dynamics (MD) simulations of gold nanoparticles with various small proteins important for the human body and a DNA molecule to determine the interactions and consequently the possible toxicity of gold clusters. Lennard-Jones interactions were used to simulate the behavior of gold nanoparticles with biomacromolecules in water with an optimal set of parameters (selected based on a comparison of MD structures and structures computed by DFT). Gold nanoparticle structures were obtained as a result of MD simulations from an initial structure, where gold atoms were at a distance of 10 Å from one another. A predicted BDNA structure of a palindromic sequence 'CGCATGAGTACGC' and a 2JYK molecule were used as representatives of the DNA molecule. The preliminary results show that, in particular small gold nanoparticles, interact strongly with proteins and DNA by creating stable complexes, which can then cause harmful reactions to the human body when present in high concentration.

**Keywords:** gold nanoparticles, proteins, DNA, molecular dynamics

## 1. Introduction

Nanoparticles are nowadays widely used as microchip elements in cancer therapy, sensors of food quality or in antibacterial layers. Although gold is treated

by the WHO as safe to use in food coloring or as another food ingredient, the commission's report [1] does not consider a possibility of using gold in the form of nanoparticles. The existing studies of gold nanoparticles indicate that they are safe to use, however, some researchers show that specific forms of nanoparticles, such as nanorods, are able to destroy the cell membrane. Moreover, very small nanoparticles (below 37 nm in diameter) in high concentrations have been shown to be deadly for mice [2].

## 2. Methods

We used the Amber12 package with an ff12SB force field to perform a series of molecular dynamics (MD) simulations of gold nanoparticles with various small proteins important to the human body and DNA molecules. Since gold atoms in nanoparticles do not create any chemical bonds and their charge in non-polarizable force field is equal to 0, the Lennard-Jones potential (Equation (1)) was used to simulate gold nanoparticles with a most current set of parameters (mass = 196.967, $r_0 = 2.951$ Å, $\varepsilon_0 = 5.29$ kcal/mol), where $r_0$ stands for the equilibrium non-bond distance between two gold atoms and $\varepsilon_0$ represents the equilibrium non-bond energy [3].

$$E = \varepsilon_0 \left[ \left( \frac{r_0}{r} \right)^{12} - 2 \left( \frac{r_0}{r} \right)^{6} \right] \tag{1}$$

Our preliminary tests revealed that, from many of the available sets of Lennard-Jones potentials, this one was not only the most current and well tested, but also performed well in tests, in which the starting structures were those of gold clusters obtained from DFT simulations [4, 5].

All the performed MD simulations used the explicit water model (TIP3P), which is an optimal combination of accuracy and computational effort. Periodic conditions with constant pressure were used in equilibration runs (1 ns) and with a constant volume in productive runs (99–199 ns). The Berendsen thermostat was used to maintain the temperature of 300 K during the simulation. We decided to run one long trajectory instead of multiple shorter ones, due to the long time needed to equilibrate the system, which would not be achieved in shorter simulations.

Gold nanoparticle structures were obtained as a result of MD simulations from initial structures where all the gold atoms were at a distance of 10 Å from one another, and with the use of a cutoff value equal to 9 Å as gold atoms in the initial structure were not interacting with one another directly. Final structures of gold nanoparticles were obtained after 50 ns for 64 Au atoms, 100 ns for 184 Au atoms and 500 ns for 512 Au atoms.

A set of "important small proteins" existing in human bodies was taken with the following PDB codes: 1GZW, 1MGS, 1LV9, 2D58. The BDNA structure with the 'CGCATGAGTACGC' palindromic sequence, which was generated by molecular modeling, and a bigger 23 bp DNA molecule with PDB code 2JYK were taken as a representative DNA molecules. Each simulation of biomacromolecules

with gold clusters was started from an initial structure in which both molecules were at a distance of at least 20 Å.

## 3. Results

The performed simulations revealed that the timescale of 200 ns was not long enough to observe the whole set of motions between gold nanoparticles and biomacromolecules, but nevertheless, gave some substantial knowledge about the system's behavior. For the two test proteins (1GZW and 2D58) simulated with a gold cluster of 64 atoms, the structures were very similar before and after simulation and any major disturbance could not be observed (Figure 1). The simulation of 1MGS with the same gold cluster ended in a complex structure, in which unstructured fragments and loops of the protein dimer were "hugging" the gold nanoparticle (Figure 2). The biggest difference of the protein structure was observed for 1LV9, which was almost completely destroyed after the simulation. However in a preliminary test with a bigger gold cluster (180 atoms), the structures of all proteins were closer to the native structures (Figure 3). Larger influence of smaller gold nanoparticles on the structure of proteins was in full agreement with the experimental results [2]. However, this assumption has to be proved on a larger timescale of simulations with more trajectories.

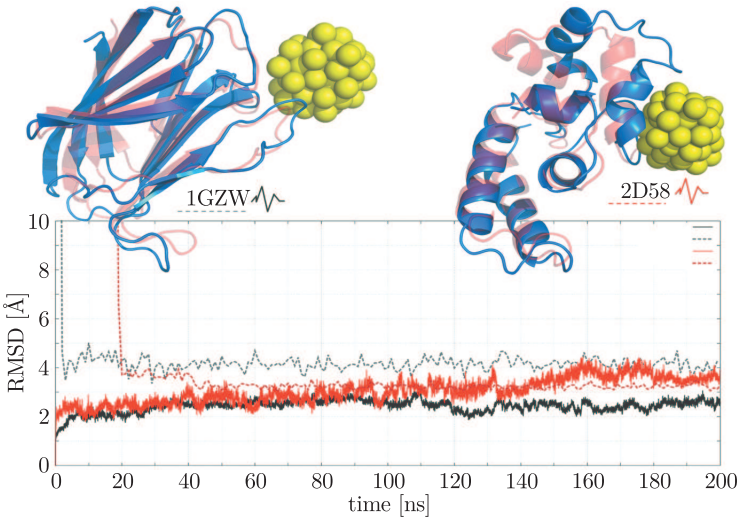


**Figure 1.** Structures of 1GZW and 2D58 proteins after 200 ns of MD simulation (blue) superimposed on experimental structures (red) with plots of RMSD (solid lines) and minimal distances between gold cluster and protein (dashed lines)

Simulations of a small gold cluster (64 gold atoms) with DNA showed that small gold nanoparticles have the ability to get inside DNA strands and break the Watson-Crick interactions between base pairs (Figure 4). Such behavior was observed when a gold nanoparticle managed to attach to the end of the DNA.

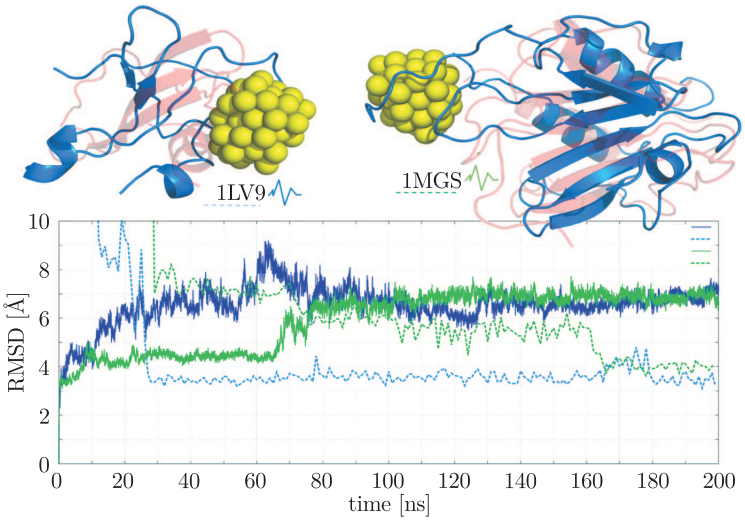


**Figure 2.** Structures of 1LV9 and 1MGS proteins after 200 ns of MD simulation (blue) superimposed on experimental structures (red) with plots of RMSD (solid lines) and minimal distances between gold cluster and protein (dashed lines)

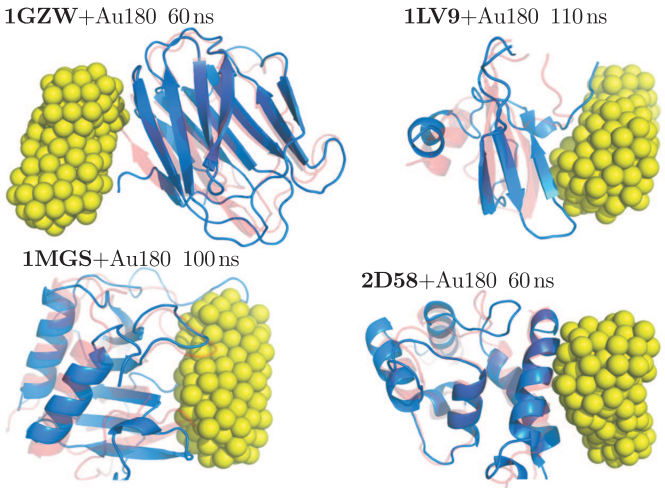


**Figure 3.** Structures of four test proteins after initial MD simulation (blue) superimposed on experimental structures (red)

We are currently performing simulations to verify if the same situation could be observed for a gold cluster binding through major and minor grooves.

## 4. Conclusions

The preliminary results show that very small gold nanoparticles can have negative impact on some biomacromolecules, as is in case of the 1LV9 protein interacting with a 64 gold atoms cluster, where such interactions can highly disturb the native structure of the protein.

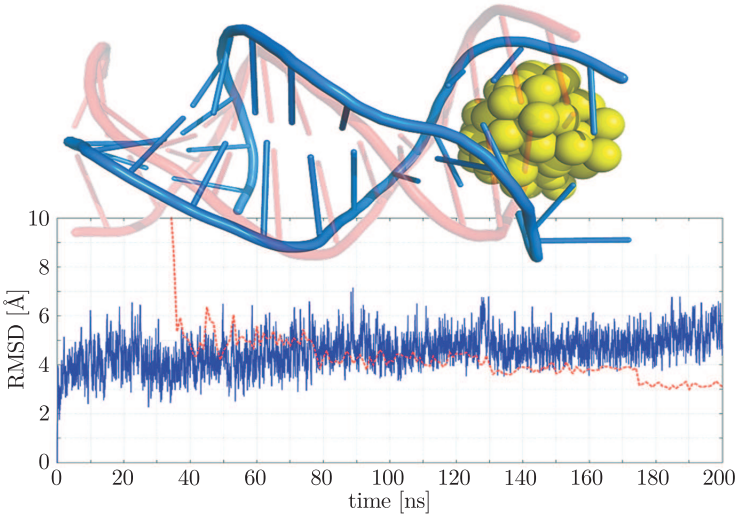


**Figure 4.** Structure of palindromic DNA (CGCATGAGTACGC) after 200 ns of MD simulation (blue) superimposed on initial structure (red) with plots of RMSD (solid lines) and minimal distances between gold cluster and DNA (dashed lines)

Encouraged by the preliminary results we have decided to perform even longer MD simulations with more trajectories to fully observe the behavior of biomacromolecules with gold nanoparticles and extend the investigated system to include larger gold clusters (512 atoms).

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