

# In Silico Docking Studies of Ag Nanoparticles and Its Derivatives Against NS5B Protein of Hepatitis-C Virus

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## Research Article

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# Abstract

Nanotechnology refers to the synthesis of nanomaterials (1-100nm) and their applications. Nanoscience can deal with individual atoms and molecules. In recent times, an agreement has started to rise about the informatics foundation expected to accumulate, curate, and share data among every one of the fields in nanotechnology. Nanoinformatics is fulfilling this demand. It is the science about figuring out which data is important to the nanoscale science and after that creating and implementing viable systems for gathering, approving, sharing, analyzing, modeling, and applying that information. Nanoinformatics is essential for efficient production and relative description of nanomaterials. The present study focused on the prediction of interactions of three ligands i.e. silver nanoparticles, tyrosine capped silver nanoparticles, and silver oxide nanoparticles with NS5B protein of HCV. AutoDock 4, Discovery Studio, ChemDraw Ultra, OpenBabel, and Chimera software were used. Computational docking helps to evaluate conformations of small ligands attached to macromolecular proteins. NS5B plays a crucial role in HCV replication. It weighs about 66-KDa. It is an RNA-dependent RNA membrane-associated polymerase. The results were obtained from AutoDock 4 and visualized in Discovery Studio and Chimera. Silver nanoparticles showed interactions with LYS81, LYS172, LYS173, TYR176, and ASP177. Tyrosine capped silver nanoparticles formed bonds with SER218, ASP220, GLU357, and LEU362 in the palm region. Silver oxide nanoparticles interacted with LEU260, TYR261, ARG280, and ALA281 in the finger domain. All these three ligands showed promising results to inhibit the NS5B enzyme halting HCV replication.

## Introduction

### Nanotechnology

Nanotechnology refers to the synthesis of nanomaterials (1-100 nm) and their application. Indeed, even well before the beginning of the "nano-era", individuals were subconsciously running over different nanosized objects and the related nanolevel procedures and utilizing them practically. For instance, since the time before BC, people utilize characteristic fabrics such as cotton, silk, wool, flax. They could produce them and process them into items. These textures were having pores of about 1-20 nm. Owing to the presence of nanopores, they were having some good properties like well sweat absorbing, rapid swelling, and drying making them suitable for wearing.

In 1959, first of all, Richard P. Feynman gave the concept of nanotechnology in his renowned address "There's Plenty of Room at the Bottom." This address is considered as the beginning of the nanotechnology prototype. In 1974, N.Taniguchi was the first person who introduced the word "Nanotechnology" at the international conference on industrial production in Tokyo. Metal nanoparticles like gold, silver, and platinum have achieved extensive consideration in few years because of their crucial and mechanical intrigue. Currently, chemical, physical, and most preferably biological synthesis of nanoparticles are being carried out.

Nanotechnology plays important role in agriculture, electronics, textiles, pharmaceuticals, etc. [1] because of the remarkable properties of nanomaterials. Small particles of different substances had properties different from those of similar substances with the bigger molecule. The characteristics of small particles resemble atomic properties beneath 1 nm. On the other hand, their properties resemble that of material at the macro level when greater than 100 nm [2]. From 1nm to 100 nm, a particle exhibits new and different behavior due to quantum effects. In this era of the pandemic, it is a nanotechnology that is creating hope to defeat COVID-19 because a vaccine against SARS-CoV-2 based on mRNA was designed and delivered through a nano-liposomal entity. This vaccine is in clinical trials right now [3].

## Metal Nanoparticles

Metal nanoparticles have been used in different applications. They are gaining interest in the scientific and commercial fields [4]. They can impressively change biological and physicochemical characteristics as they have high electrical properties, increased tolerance to mechanical and thermal pressure, high surface area, and high optical and magnetic properties [5, 6]. These unique characteristics have enabled nanomaterials to be used in different fields including electrical, magnetic, optical, and electronic devices. Because of these unique characteristics, nanomaterials can be used in different products including electrical, magnetic, optical, and electronic devices. Some nanoparticles are modified to increase their efficiency and usage. Silver oxide, titanium oxide, and copper oxide are few prominent examples of engineered nanoparticles. Some nanomaterials are also used in different production industries, for example, the production of sunscreens and stain-repellent clothes. Investigations and diagnosis are also facilitated by the use of simple and engineered nanomaterials in medical equipment and procedures such as diagnostic kits, imaging, magnetic resonance imaging (MRI), and drug delivery [7]. The biomedical industry is also blessed with metal nanoparticles. In the light of nanotechnology, the field of nanomedicine has been a point of intense consideration for efficient and quick diagnosis and creating various methods of therapies utilizing nanoparticles in various diagnostic gadgets [8]. Ag, Pt, and Au nanoparticles are considered noble nanoparticles [6]. These nanoparticles exhibited nontoxic positive effects in biological systems revealing a new dimension of exploration in biological research [9]. Some engineered nanoparticles, such as titanium dioxide ( $\text{TiO}_2$ ), zinc oxide ( $\text{ZnO}$ ), ferrous oxide ( $\text{FeO}$ ), cupric oxide ( $\text{CuO}$ ), silver oxide ( $\text{Ag}_2\text{O}$ ), aluminium oxide ( $\text{Al}_2\text{O}_3$ ), also have antimicrobial properties and perform noteworthy activities in numerous medical applications.  $\text{TiO}_2$ , for instance, is used to inhibit the spread of various diseases [10]. In addition, aluminum oxide nanoparticles have many applications and demonstrated antimicrobial characteristics [11]. The zinc-doped titania nanoparticles have uncovered improved pro-angiogenic properties, which may be helpful in various applications [12]. Silver nanoparticles have tremendous antimicrobial activity. While drug delivery mechanism is made efficient by using gold nanoparticles to cure many illnesses such as cancer [13].

## Silver Nanoparticles

Because of their exceptional properties, silver nanoparticles have been utilized for many applications counting as anti-viral and anti-bacterial agents. They are being used in healthcare products, beauty care products, the food industry, pharmaceutical industries, and medical and electronic devices [14]. The biological characteristics of silver nanoparticles depend on various parameters [15]. In systematic and local administration, bioavailability of therapeutic agents get improved because of the physiochemical properties of the nanoparticles [16]. Silver nanoparticles produce by using the berry extract of *Sea Buckthor*, display a broad range of antioxidant, anti-inflammatory and anticancer activities [17]. AgNPs are proven to be safe antibacterial and antibiofilm compounds against MDR *K. pneumonia* [18]. Silver nanoparticles produced by *Sphingobium* sp. MAH-11 may act as an intense antimicrobial agent in many treatments [19]. Hence, the synthesis of silver nanoparticles in a controlled manner is useful in several biomedical applications [20].

Currently, medication and immunization advancement for the evacuation of different viral ailments are under critical consideration, various viral strains have been developed that are no more sensitive to drugs and vaccines. So it is imperative to present the multidisciplinary approaches with the established epidemiology, alongside the clinical phases to present a new drug or vaccine which possesses great effectiveness against the resistant strain. Nanotechnology has revolutionized the field of medicine. Nanoparticles, especially silver, have antiviral activities against the many viruses that are ruining lives worldwide.

## Nanoinformatics

Biological data are being produced at an extraordinary rate [21]. Because of this exponential growth of information, computers have turned out to be irreplaceable for biological research. Such an approach is perfect due to the simplicity with which computers can deal with a huge amount of information [22]. The utilization of computational systems to comprehend and sort out the data related to biological macromolecules is known as bioinformatics. In recent times, an agreement has started to rise about the informatics foundation expected to accumulate, curate, and share data among every one of the partners in nanotechnology [23]. The inconstancy of nanomaterials made risk assessment unrealistic. Easily accessible data and artificial intelligence approaches are necessary to guarantee consumer wellbeing [24]. A more effective way is required by utilizing nanoinformatics for efficient and broad sharing of data related to nanotechnology. Nanoinformatics is depicted as "the science regarding figure out which data is important to the nanoscale science and after that creating and implementing systems for gathering, approving, sharing, analyzing, modeling and applying that information".

## Molecular Docking

Nanoinformatics is an emerging science. It contains databases and tools. Some of them are Nanomaterial Biological Interactions Knowledgebase, InterNano, Nanoparticle Information Library, etc. Nowadays, as nanomedicines are being used and found to have high efficiency, molecular docking of

nanomaterials is in trend. In drug discovery, docking is a critical computational technique predicting protein-ligand interactions. The two fundamental characteristics of docking programs are docking precision and scoring reliability [25]. Docking accuracy demonstrates how similar the predicted ligand to the experimental data, whereas scoring reliability positions ligands because of their affinities. Docking accuracy evaluates searching algorithm and scoring reliability assesses scoring functions. In the docking program, the numerous searching algorithms work differently as for randomness, speed, and the area covered. Many searching algorithms show good performance when used against the known structure. Presently, numerous sorts of docking programs are easily accessible, among which, AutoDock is frequently used and openly accessible [26]. As protein-nanoparticle interactions are not easy to examine utilizing experimental techniques, molecular docking tools facilitate to ease this difficulty.

## NS5B Protein

*Hepatitis C virus* is included in the family *Flaviviridae*. It has a +RNA single strand (Choo 1989). The HCV genome contains roughly 9,600 nucleotides, which encode for 3,000 amino acid residues for polyprotein precursor. About 170 million people are carriers of HCV around the world. A significant number of these people are awaited to be suffered from critical HCV-related liver diseases. NS5B stands for nonstructural 5B protein present in HCV. It weighs about 66-KDa. It is an RNA-dependent RNA membrane-associated polymerase [27]. It takes part in RNA replication, however, the exact molecular mechanism is not completely known yet.

The RNA replication is comprised of two phases. In the first phase, the formation of a new RNA strand starts at the 3' end of the RNA template. This initiation phase does not need a primer to start, therefore can be called a primer independent or de novo mechanism. Hydroxyl group at 3' position of first NTP makes a bond with new coming NTPs. In the second phase, elongation occurs by adding more complementary NTPs.

NS5B has three structural domains denoted as fingers (residues 1 to 187 and 228 to 286), palm (residues 188 to 227 and 287 to 370), and thumb (residues 371 to 563). Its catalytic site contains residues from 214 to 332. At the enzymatic molecular surface, there is a site in a pocket specific for the binding of rGTP molecule. This specific site is at a distance of 30 Å from the catalytic site. It is situated at the junction of fingers and thumb domains regulating the enzymatic activity allosterically.

The repetitive cases of Hepatitis C virus (HCV) infection causes more than 71 million people to face chronic stage that results in different liver diseases [28]. A deeper understanding of HCV revealed vital proteins that are important for HCV survival and enabled the scientists to target them to make HCV therapy more efficient [28, 29]. Antiviral drugs are designed to directly act on 3 important HCV functional proteins i.e. NS5B polymerase, NS5A, and NS3 [30]. The present HCV therapy using ledipasvir, ombitasvir, and sofosbuvir has some adverse effects like anemia, rash, bilirubin, nausea, pruritus, and photosensitivity [31]. The need for reduction in these adverse effects and increment in liver diseases

demand improved treatment. This article focuses on the docking of different derivatives of silver nanoparticles to look into alternative, safe, and highly efficient HCV therapy methods.

## Material & Methods

### Retrieval of NS5B 3D Structure from Protein Data Bank

Protein Data Bank (PDB) was built up as the first freely available repository for biological molecules in 1971. It was a single worldwide library for 3-dimensional structures of bio-molecules and their complexes with other small molecules. Presently, the PDB archive contains ~167518 entries (August 2020). The PDB repository contains data obtained through three techniques: X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), and electron microscopy [32]. 3D structure of HCV encoded nonstructural 5B (NS5B) protein with 2HWH identity number was taken from PDB website.

### Deleting Water Molecules

Water molecules present in NS5B structure were deleted using AutoDock tools because many of the water molecules present in protein structure are either loosely bound and easily displaced by a ligand or not necessarily quite in the positions they appear to be-fitting water molecules to the residual electron density after the protein structure is fitted, is an inexact science. In most cases, water molecules are not involved in the binding. That's why they are preferably removed to ease computations and clear water molecules present in a catalytic pocket so that the pose searching process would not be disturbed. In docking, there is a search for molecules that can create multiple favorable contacts to the protein, water molecules might confound this procedure. As a result, wrong conformation pose is obtained as the ligand forms more solvent assisted salt bridge interactions.

### Adding Hydrogen Atoms

Protein-ligand or protein-protein complexes are virtually observed in molecular docking simulation. Macromolecules are present in a charged form with no atom missing in the human/animal body. So, it is necessary and sensible to add charges and missing atoms (hydrogen and in some cases non-hydrogen) to protein before proceeding with a docking experiment.

Most macromolecular structure data do not contain hydrogen atoms in their corresponding PDB files and docking software requires the hydrogen atoms to be in place to compute algorithmic calculations. So, the addition of hydrogen atoms is necessary for docking. The polar hydrogen atoms allow the establishment of hydrogen bonds that may be present between the macromolecule and the ligands tested. Hence, missing hydrogen atoms were added to the NS5B protein.

## Compute Gasteiger Charge

To get important and useful outcomes from any electrostatic calculations, designating suitable atomic partial charges to ligand and macromolecule is necessary. Marsili-Gasteiger partial charges are appointed employing a two-phase algorithm. First, each atom in a molecule is designated with seed charges. Then, some amount of these initial charges are transferred from one atom to the other bonded atom. The direction of movement of partial charges depends on the electronegativity difference between two bonded atoms. With each cycle of repeating algorithm, attenuation of charges occurs. Gasteiger partial charges of 17.0062 were added to the NS5B protein in the AutoDock tool.

## Energy Minimization

Computational chemistry depicts energy minimization as the process of searching a pattern in space where atoms are gathered, the total inter-atomic force on every atom is near to zero and the potential energy surface (PES) is a static point. This searching mechanism during the energy minimization process is based on some computational model of chemical bonding. Energy minimization is essentially about "settling" the model into a relatively energetically favorable state. Protein structures often have errors of various magnitude such as atoms partially overlapping, side chains in the wrong positions, etc. Energy minimization looks for the pathway that gives the most reduction in the overall energy of the system, relaxing bond lengths, angles, non-bonded interactions, etc. into more favorable states.

## Retrieval of Ligand 3D Structures

Silver nanoparticles, tyrosine capped silver nanoparticles and silver oxide nanoparticles were used as ligands in molecular docking. The structure of silver, tyrosine capped silver, and silver oxide nanoparticles were drawn in Chemdraw Ultra 12.0 software. Chemdraw Ultra software is used to draw a nearly unlimited variety of biological and chemical drawings.

## Preparing Grid Parameter File (GPF)

The Grid box center was assigned on active site cavity in NS5B protein with 1 angstrom spacing of each grid point. While x,y, and z coordinates for grid points were 1.874, -0.603, and 27.509 respectively. In this way, the whole protein molecule was covered within a grid box to allow free rotation of the ligand molecule within the protein. All the grid-related information was saved as a grid parameter file (gpf). The gpf determines the search space in the receptor.

## Running Autogrid4

The autogrid was run by using a grid parameter file (gpf). Autogrid4 gets information about the receptor around which potential is to be computed, map types to be figured out, and the extent and location of those maps from the grid parameter file [33]. The probe atom is employed in 3D space at regular points to pre-calculate the energy in the receptor. These pre-calculated energies get stored as grid maps. Each type of atom contains its grid map. Besides, electrostatic and desolvation maps are also generated. In this way, in ligand molecule, every type of atom is subjected to a rapid evaluation of energy to precalculate its affinity potentials [34].

## Preparing Docking Parameter File (DPF)

In docking parameters, a genetic algorithm with default settings was selected to be used during the docking process. The docking parameter file reveals AutoDock about the utilization of map files, movement of the ligand molecule, center, torsions, beginning of the ligand, movement of the flexible residues in the receptor if modeling of the side chain motion is required, type of algorithm to employ and its iteration. It contains file extension as ".dpf" [33].

## Running AutoDock4

AutoDock runs search algorithms using grid maps to determine ligand-protein binding at each point to find the suitable conformations. Subsequently, numerous docked conformations are acquired. AutoDock needs grid maps for each type of ligand atom evaluated by AutoGrid, a ligand PDBQT file, and a docking parameter file which determines the parameters for the docking [34].

Presently, AutoDock contains four distinct algorithms i.e. the original Monte Carlo simulated annealing (SA), a traditional Darwinian genetic algorithm (GA), local search (LS) and hybrid genetic algorithm with local search (GALS). The Lamarckian Genetic Algorithm performs a highly effective search [33].

## Result Analysis

The results obtained from AutoDock were observed and analyzed in Chimera and Discovery Studio Visualizer version 17.2.0.16349.

## Results & Discussion

NS5B contains three domains named palm, fingers, and thumb (figure 1). Palm includes the residues from 188 to 227 and 287 to 370, fingers residues from 1 to 187 and 228 to 286, and thumb contains residues from 371 to 563 [35].

# Ag NP-NS5B Protein Interaction

Silver nanoparticles interacted with the finger domain of NS5B protein. Five amino acid residues i.e LYS81, LYS172, LYS173, TYR176, and ASP177 showed interaction with Ag nanoparticles. LYS81 is involved in metallic bonding with Ag nanoparticles. LYS81 is one of the amino acids to which RNA binds. Hence Ag nanoparticle can cause hindrance in the attachment of RNA to LYS81. Amino acid residues from 168-183 in the finger domain also help to bind template RNA [35]. Interaction of Ag nanoparticle with LYS172, MET173, TYR176, and ASP177 can inhibit the template RNA to bind with the finger domain.

# Tyrosine Capped Ag NP-NS5B Protein Interaction

Tyrosine capped silver nanoparticles were found to have hydrogen bonding with SER218, ASP220, GLU357, and LEU362. The ligand molecule is having three hydrogen bonds (green color) with SER218 with bond lengths of 2.14 Å, 2.36 Å, and 2.51 Å. While ASP220 and GLU357 are interacting with the ligand through a single hydrogen bond with 2.23 Å and 1.80 Å distances respectively. Furthermore, there is a metallic interaction of 3.06 Å with LEU362.

Tyrosine capped silver nanoparticle interacted with the palm region of NS5B protein. The site where the ligand attached with four amino acid residues is a catalytic site. ASP220 and SER218 are part of motif A and GLU357 and LEU362 are included in the motif E region [35]. ASP220 plays a role to coordinate magnesium ions to assist in nucleotide addition during the RNA elongation process. While motif E helps to maintain relative positioning of thumb and palm domains [36]. The ligand molecule can inhibit the ASP220 to bind with magnesium ion to stop the addition of new nucleotides during RNA synthesis. It may also distort the ability of motif A to select the type of nucleic acid which needs to be gone under the polymerization process. Furthermore, it may deform the motif E and hence the spatial arrangement of the thumb and palm domain can be disturbed. As the ligand molecule is present within the catalytic pocket, it may cause hindrance for the RNA molecule that is being synthesized. In this way tyrosine capped silver nanoparticles can act as an inhibitor for NS5B protein to stop the replication of HCV.

# Silver Oxide NP-NS5B Protein Interaction

The oxygen atom of the ligand molecule showed three hydrogen bonds with TYR261, ARG280, and ALA281 with distances of 3.15 Å, 3.64 Å, and 1.98 Å respectively. Additionally, one silver atom of the ligand molecule was involved in charge repulsion with ARG280 with 2.33 Å distance and the other silver atom is making metallic interaction with LEU260 with 3.33 Å distance.

NS5B encircles the active site due to the extensive interaction between finger and thumb domains and that's why is not allowed to change their spatial arrangement freely of each other. Because fingers and thumb are associated through two flexible finger loops (ϕ1 and ϕ2), a conformational disturbance in one domain causes the change in the other domain [37]. Subdomains of fingers and thumb determine the

shape of the binding channel of the enzyme which binds the nucleic acid [38, 39]. At the front and back of the enzyme, fingertips are involved in the formation of template and NTP channels respectively [40]. NS5B protein in complex with GTP has been crystallized. The crystallized structure of NS5b complexed with GTP molecule shows that GTP not only binds to the active site but also to the thumb domain near to the delta-1 loop of fingertip which lies between the thumb and finger domains. Even though this GTP binding site is situated 30 Å far from the active site, it has a regulatory role in dynamic interactions of subdomains of fingers and thumb [38].

Silver oxide nanoparticle Binds with four amino acid residues in the finger domain. It can induce a structural change in the finger region distorting the spatial arrangement of the domain. As the finger domain is linked with the thumb domain so a change can occur in the positioning of the thumb domain as well. Disturbed positioning and structure of thumb and finger domains result in the deforming of the template and nucleic acid binding channel. The attached ligand can also act as a blocker for newly coming rNTPs. Furthermore, the regulatory mechanism of NS5B through the GTP molecule can be breached and damaged by the ligand through disfiguring the GTP binding site resulting in allosteric inhibition.

Binding energy is emitted as a result of ligand-target binding causing a decrease in overall complex potential energy. The release in binding energy facilitates the ligand to transform its conformation from its maximum energy state to bound conformation having minimum energy. Hence, the greater the released binding energy, the greater will be the binding affinity of the ligand to the protein. The ligand-binding process will be spontaneous if the binding energy is in a negative value. While the binding process will be nonspontaneous and require energy if the binding energy is in positive value.

The binding energy of silver nanoparticles is -0.17 kcal/mol indicating its low affinity with the protein. Hydrogen bonding dramatically affects the binding energies. Tyrosine capped Ag NP comparatively showed the highest binding energy i.e. -5.29 Kcal/mol due to the presence of multiple atoms in it forming multiple H-bonds, hence increasing binding energy.

## Conclusion

All the results obtained from computational docking of the four ligands individually to NS5B protein show promising effects to inhibit the protein activity. NS5B protein is an RNA polymerase and plays a key role in HCV replication. HCV becomes extinct without this protein molecule. There are three domains of the protein i.e. palm, fingers, and thumb which collectively form the active site. All the ligands were docked near to active site inhibiting the RNA replication process. The most effective ligand was tyrosine capped silver nanoparticles Its relative highest binding energy i.e. -5.29 kcal/mol showed its intensive binding with the protein molecule causing more damage to the integral residues forming the active site.

## Declarations

## Funding

Not applicable.

## Conflicts of interest

There is no conflict of interest among the authors.

## Ethics approval

Ethical Review Committee permission was undertaken.

## Consent to participate

Consent to participate was taken from the research supervisor.

## Consent for publication

Before submission of the study, consent was taken from the research supervisor.

## Availability of data and material

Data gathered was original, transparent and reliable.

## Code availability

Not applicable.

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## Tables

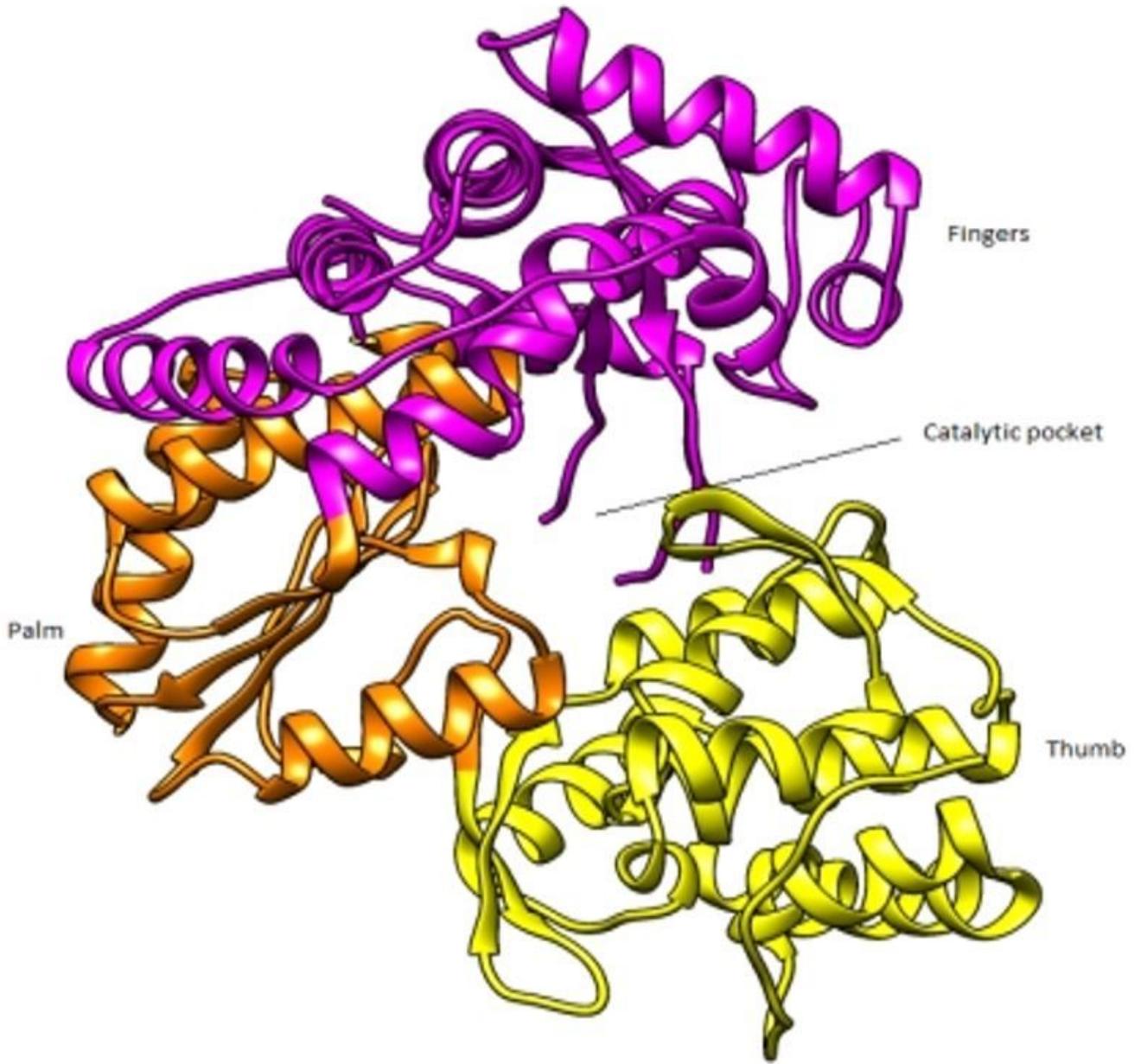
**Table 1:** Motifs and Functional regions of NS5B proteins.

Conserved Elements	Residues	Location	Function
	A 216-227	Palm	Binds Magnesium and choose nucleic acid type.
	B 287-306		Differentiate between rNTP or dNTP
	C 312-325		Coordinates Magnesium
<b>Motifs</b>	D 332-353		Helps accommodate active site NTPs
	E 354-372		Retains rigidness of secondary structure important for spatial arrangement of thumb and palm domains
	F 132-162		Binds incoming NTPs and RNA
	G 95-99	Fingers	Binds primer and template
<b>Functional Regions</b>	I 91-94		Binds template
	II 168-183		Binds template
	III 401-414	Thumb	Binds nascent RNA duplex

**Table 2:** Parameters obtained as a result of computational docking.

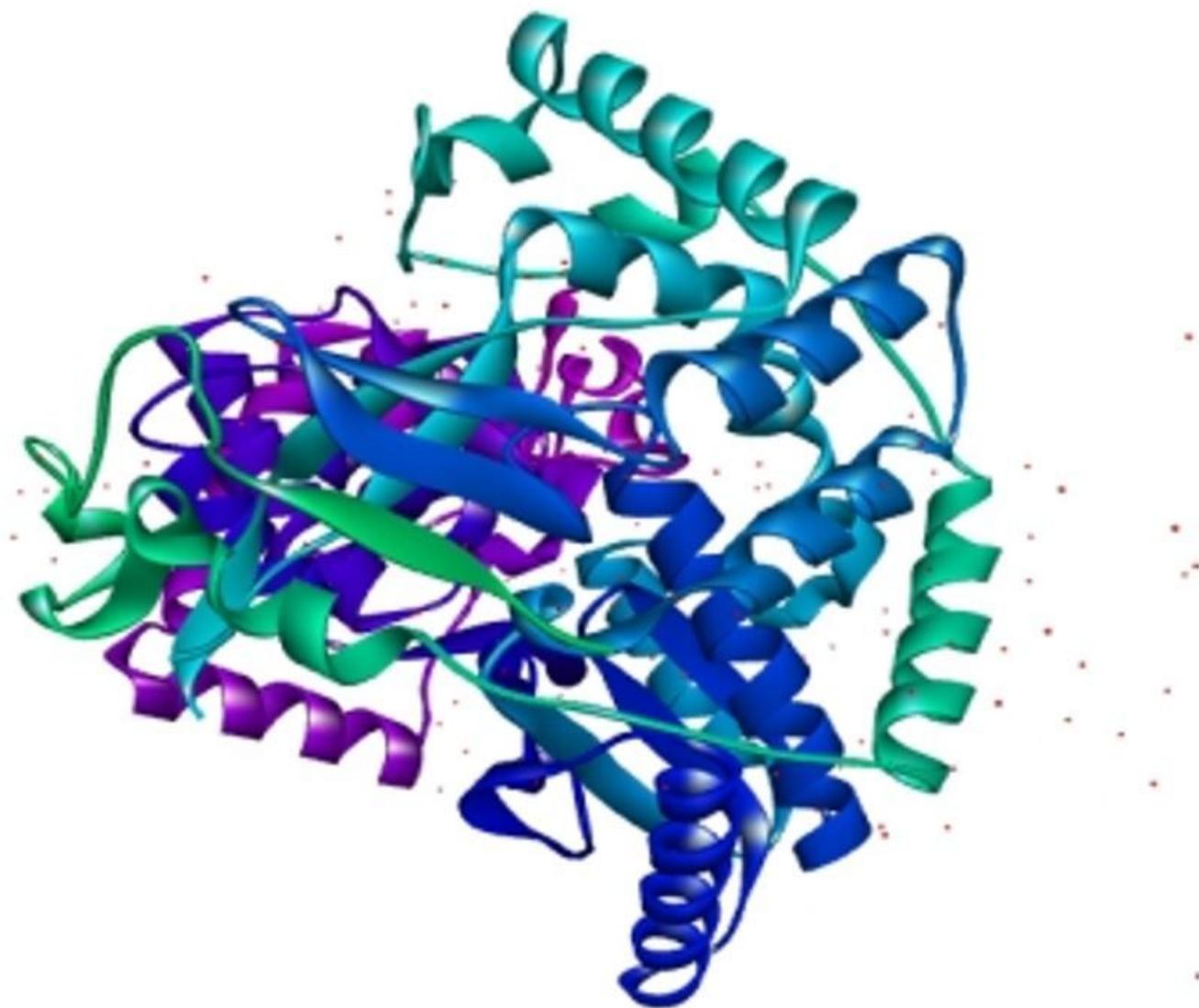
Ligands	Ag Nanoparticles	Tyrosine capped Ag nanoparticles	Silver oxide nanoparticle
Binding energies (Kcal/mol)	-0.17	-5.29	-2.06
Ligand efficiency	-0.17	-0.38	-0.69
Inhibition constant ( $\mu\text{M}$ )	744.78	133.42	31.07
Intermol. Energy	-0.45	-6.93	-2.06
Vdw_hb_desolv_energy	-0.45	-5.38	-2.06
Electrostatic energy	0.00	-1.55	0.00
Torsional energy	0.27	1.65	0.00
Ref RMS	43.48	35.43	37.54

## Figures



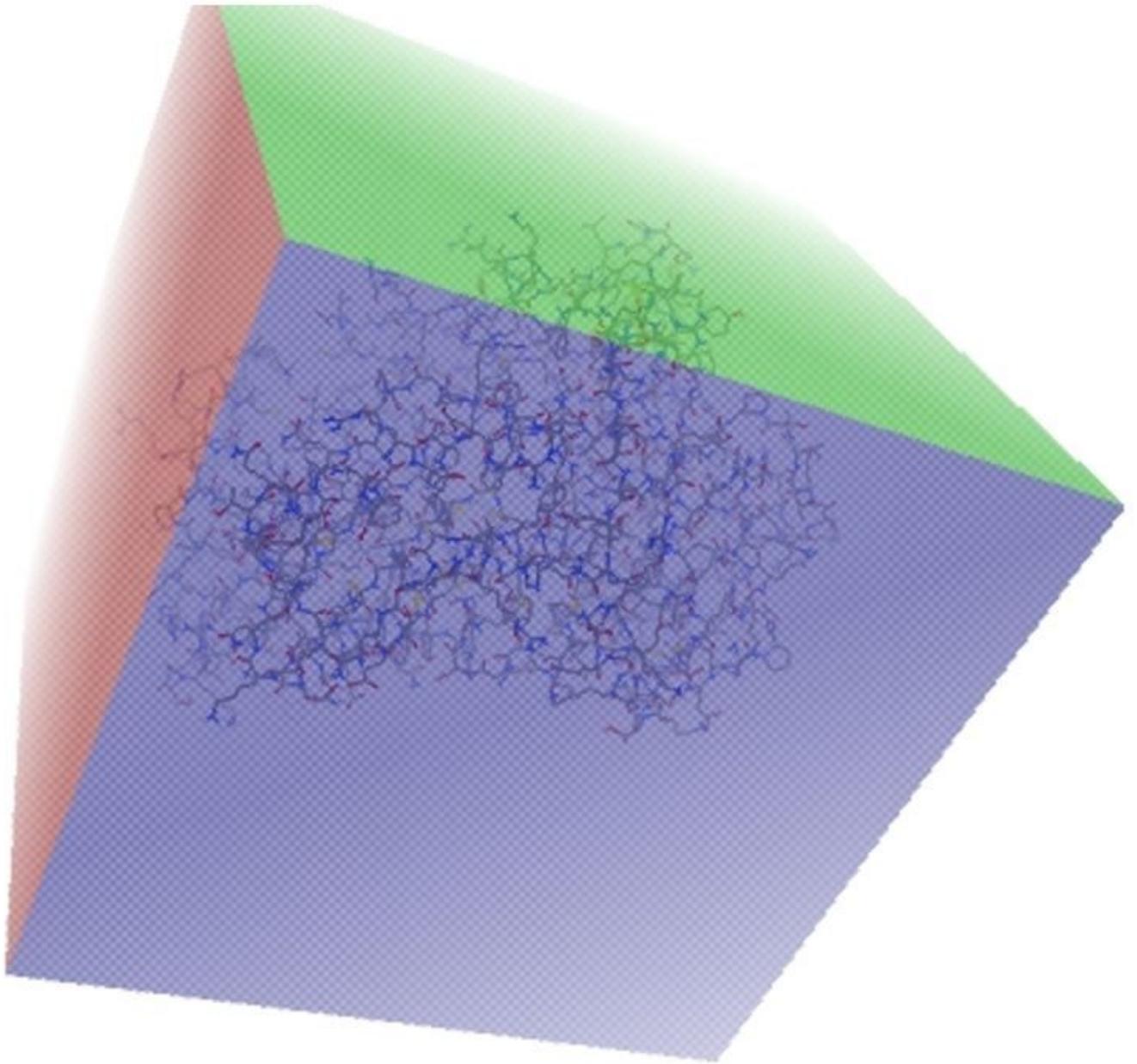
**Figure 1**

Presentation in ribbon form of NS5B protein of HCV.



**Figure 2**

Water molecules are represented as red dots.



**Figure 3**

Protein embedded in the Grid box.

```
parameter_file AD4_parameters.dat
npts 94 88 74 # num.grid points in xyz
gridfld ns5bAmini.maps.fld # grid_data_file
spacing 1.0 # spacing(A)
receptor_types A C HD N NA OA SA # receptor atom types
ligand_types OA Ag # ligand atom types
receptor ns5bAmini.pdbqt # macromolecule
gridcenter 1.874 -0.603 27.509 # xyz-coordinates or auto
smooth 0.5 # store minimum energy w/in rad(A)
map ns5bAmini.OA.map # atom-specific affinity map
map ns5bAmini.Ag.map # atom-specific affinity map
elecmap ns5bAmini.e.map # electrostatic potential map
dsolvmap ns5bAmini.d.map # desolvation potential map
dielectric -0.1465 # <0, AD4 distance-dep.diel;>0, constant
```

**Figure 4**

Grid parameter file.

```

parameter_file AD4_parameters.dat
autodock_parameter_version 4.2      # used by autodock to validate parameter set
outlev 1                             # diagnostic output level
intelec                             # calculate internal electrostatics
seed pid time                        # seeds for random generator
ligand_types OA Ag                  # atoms types in ligand
fld ns5bAmini.maps.fld             # grid_data_file
map ns5bAmini.OA.map               # atom-specific affinity map
map ns5bAmini.Ag.map               # atom-specific affinity map
elecmap ns5bAmini.e.map            # electrostatics map
desolvmap ns5bAmini.d.map          # desolvation map
move sodsv.pdbqt                   # small molecule
about -3.6527 1.5847 -0.0003        # small molecule center
tran0 random                        # initial coordinates/A or random
quaternion0 random                 # initial orientation
dihe0 random                        # initial dihedrals (relative) or random
torsdof 0                           # torsional degrees of freedom
rmstol 2.0                          # cluster_tolerance/A
extnrg 1000.0                       # external grid energy
e0max 0.0 10000                     # max initial energy; max number of retries
ga_pop_size 150                     # number of individuals in population
ga_num_evals 2500000                # maximum number of energy evaluations
ga_num_generations 27000            # maximum number of generations
ga_elitism 1                         # number of top individuals to survive to next generation
ga_mutation_rate 0.02               # rate of gene mutation
ga_crossover_rate 0.8               # rate of crossover
ga_window_size 10                   #
ga_cauchy_alpha 0.0                 # Alpha parameter of Cauchy distribution
ga_cauchy_beta 1.0                  # Beta parameter Cauchy distribution
set_ga                              # set the above parameters for GA or LGA
sw_max_its 300                      # iterations of Solis & Wets local search
sw_max_succ 4                       # consecutive successes before changing rho
sw_max_fail 4                       # consecutive failures before changing rho
sw_rho 1.0                          # size of local search space to sample
sw_lb_rho 0.01                      # lower bound on rho
ls_search_freq 0.06                 # probability of performing local search on individual
set_psw1                             # set the above pseudo-Solis & Wets parameters
unbound_model bound                 # state of unbound ligand
ga_run 10                           # do this many hybrid GA-LS runs
analysis                             # perform a ranked cluster analysis

```

Figure 5

Docking parameter file.

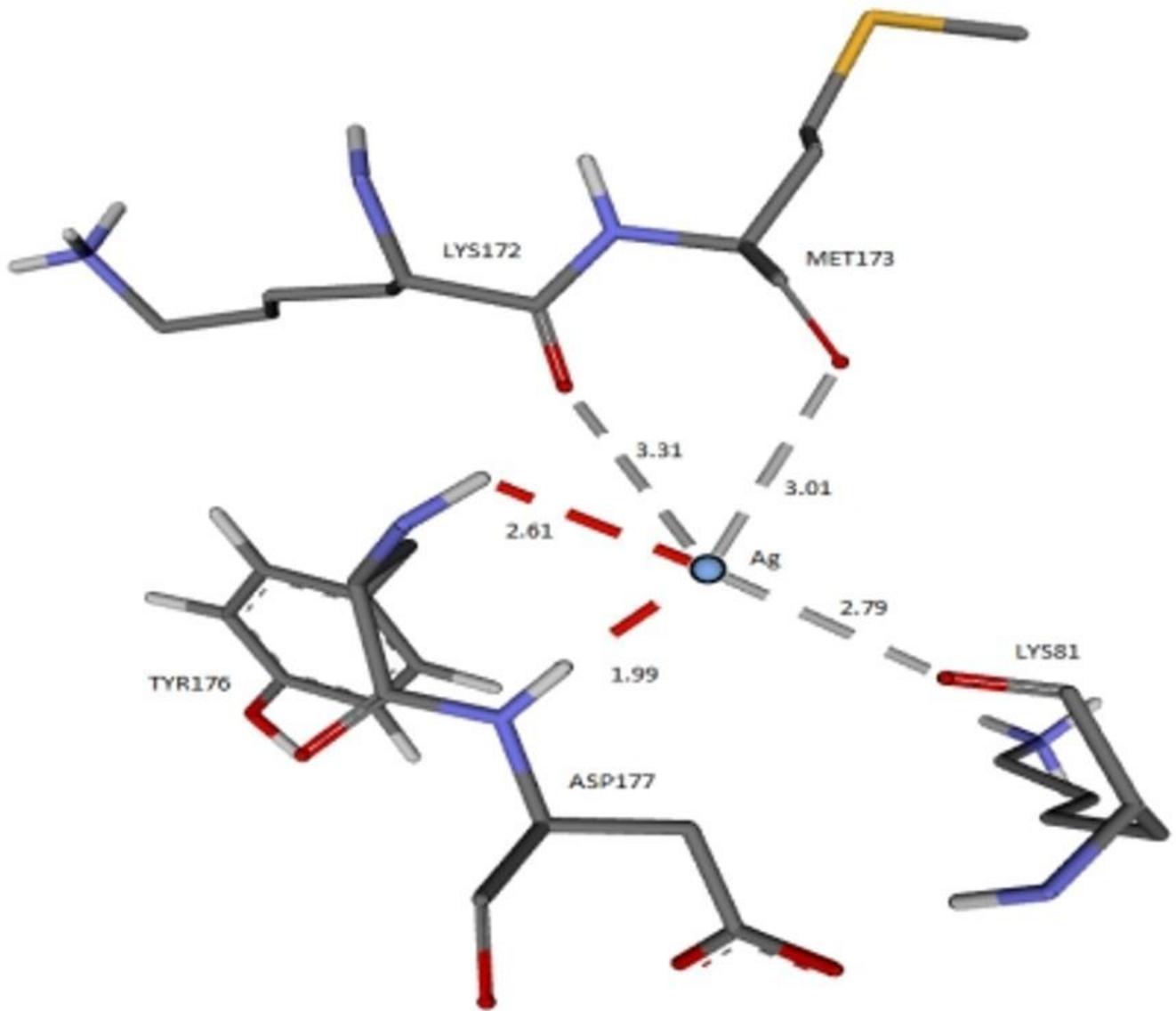
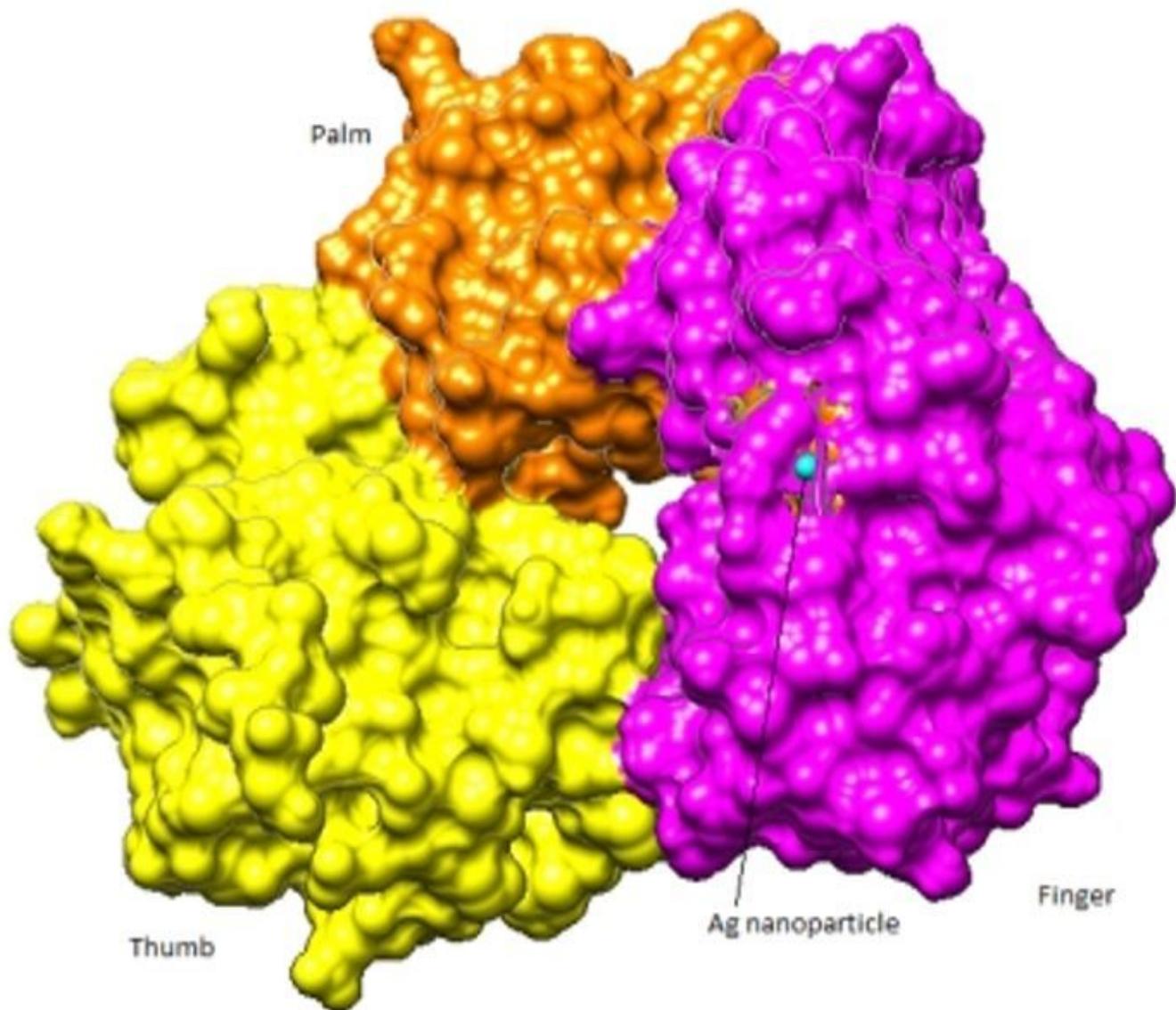


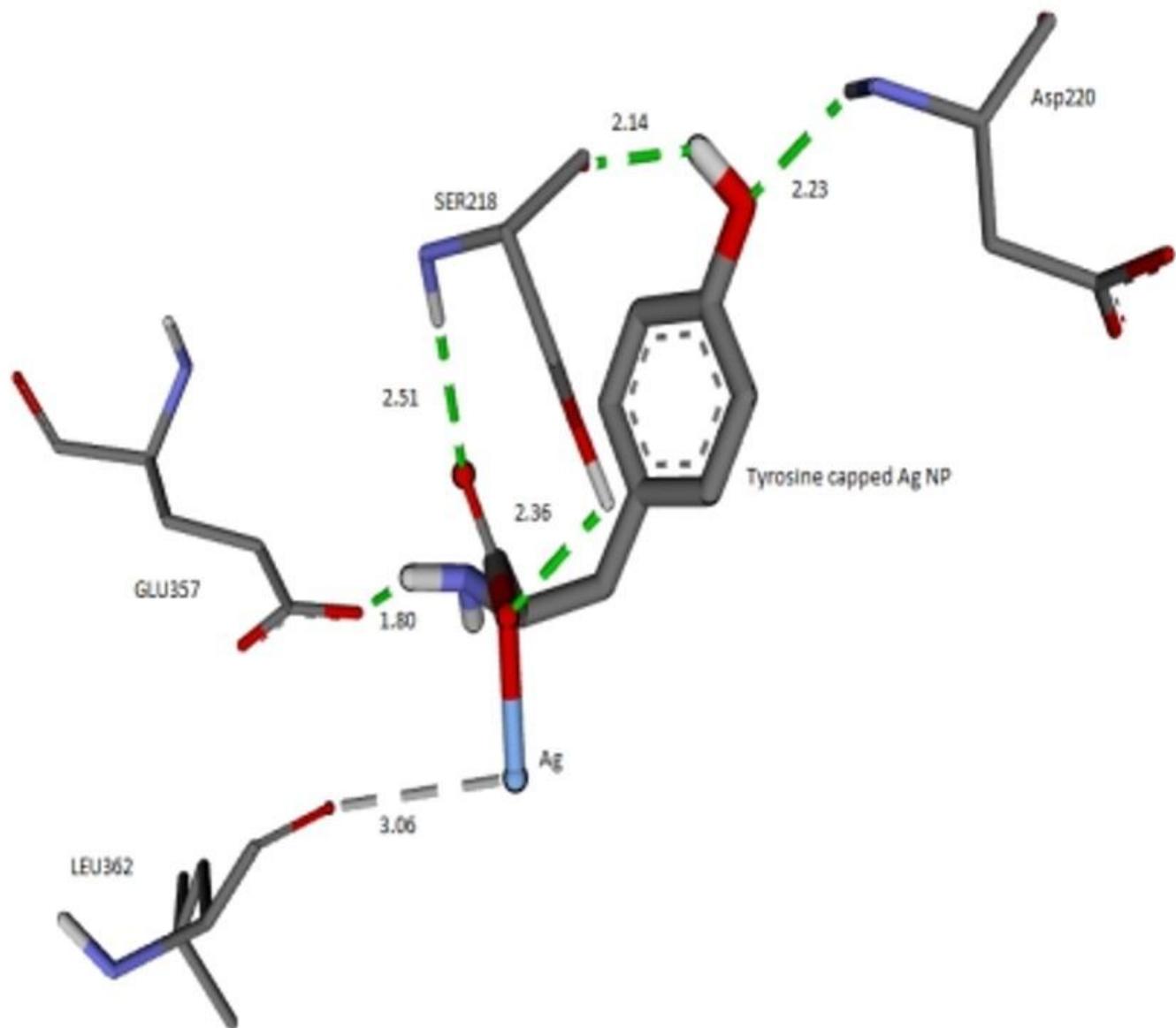
Figure 6

Ag nanoparticle interaction with NS5B residues.



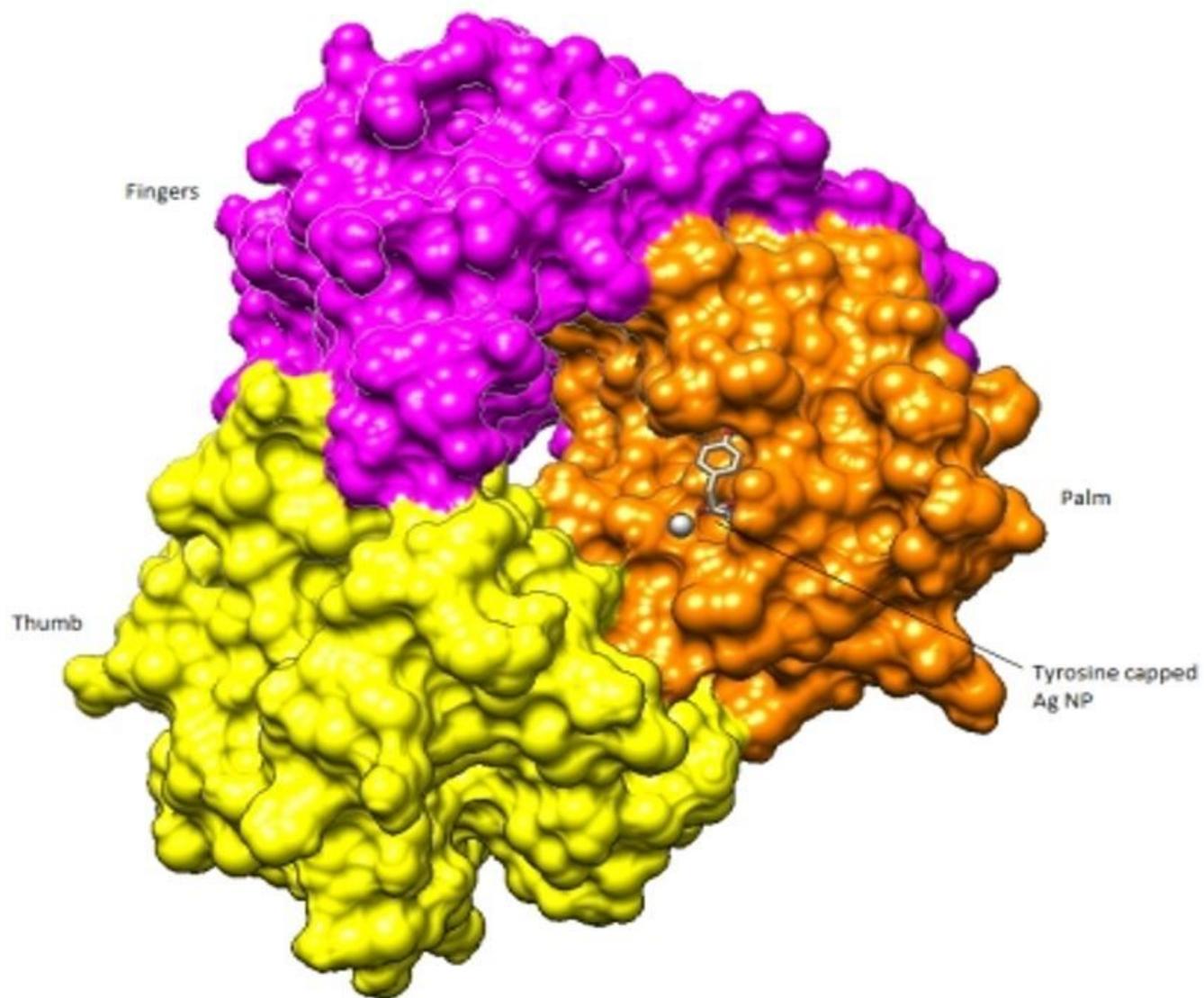
**Figure 7**

Silver nanoparticle is embedded in the finger domain.



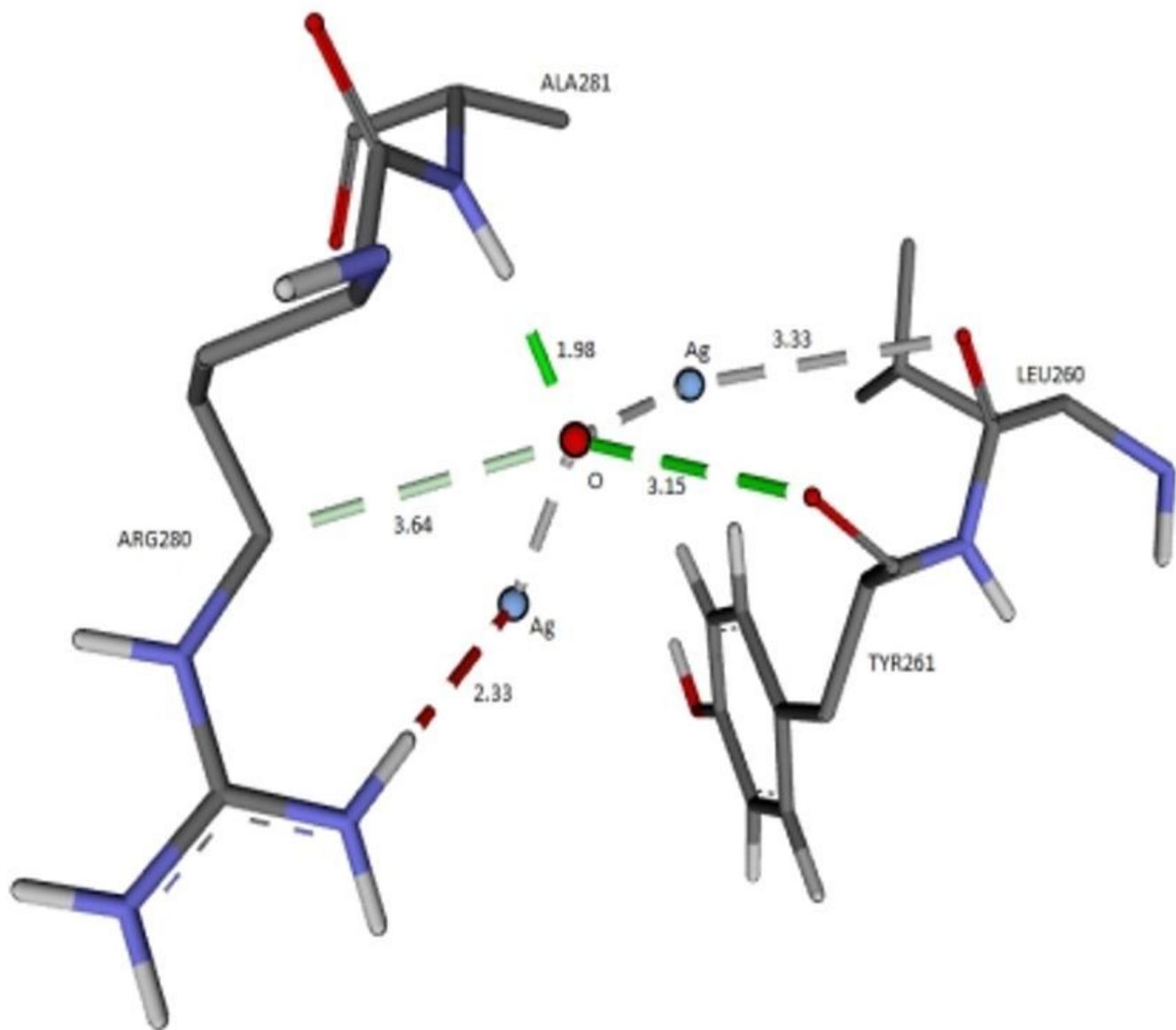
**Figure 8**

Residual interaction of NS5B protein with Tyrosine capped Ag NP.



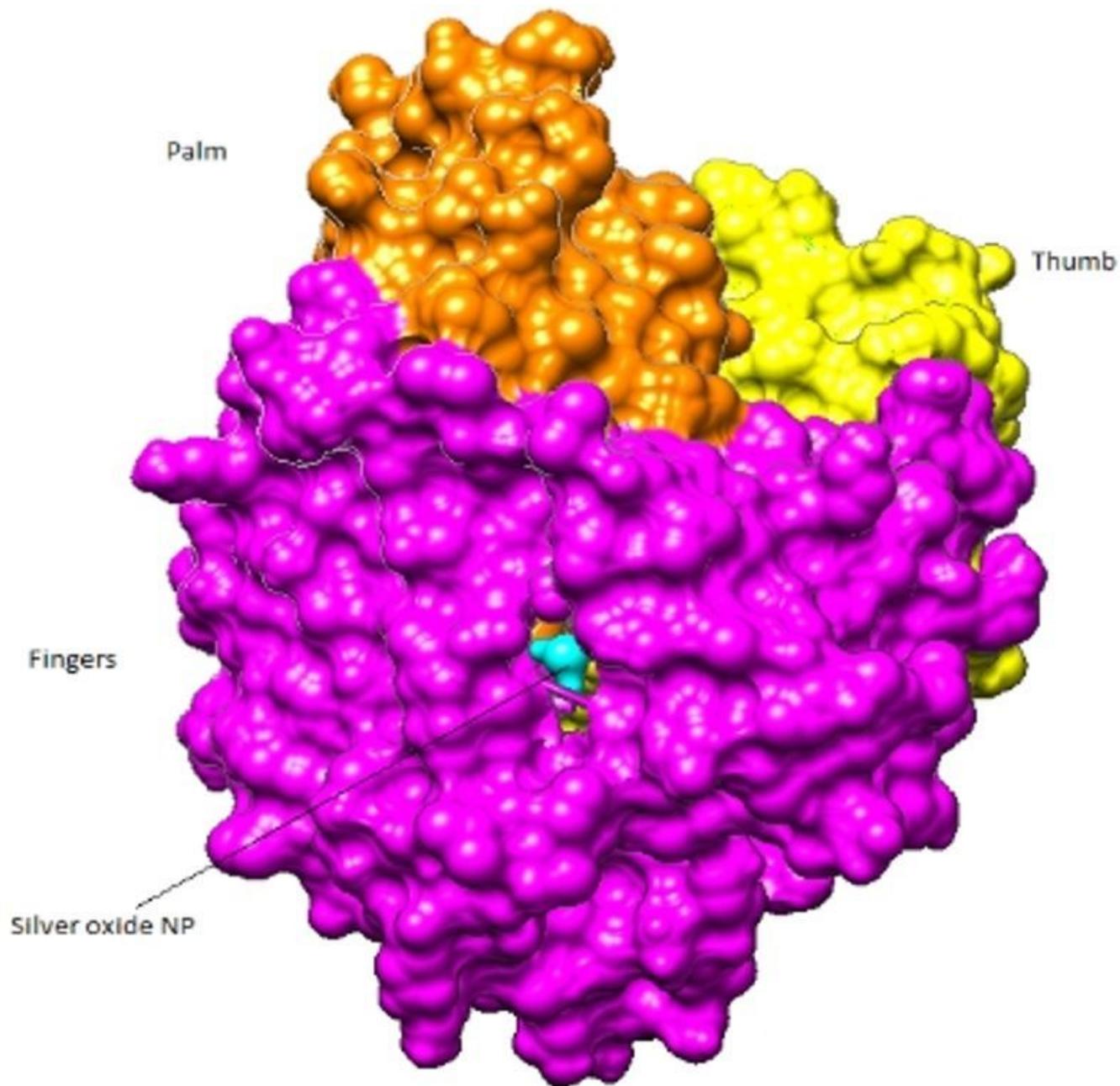
**Figure 9**

Molecular docking of Tyrosine capped Ag NP to palm domain of NS5B protein.



**Figure 10**

Residual interaction of NS5B protein with silver oxide NP.



**Figure 11**

Molecular docking of Ag<sub>02</sub> NP to the Finger domain of NS5B protein.