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ORIGINAL ARTICLE

'Molecular Dynamics Simulation of Human Serum Albumin Interaction with Spherical Gold-Nanoparticle'

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Abstract

Nanoparticles (NPs) recently have gained great attention, because of their usage as Drug carriers. Using of NP in drug delivery has succeeded at initial levels. However, the administration of high concentrations at target or unspecified sites inside the human body has adverse effects and gives rise to diseases. Since NP conjugation to the protein affects protein structure and consequently its dynamics. So, it influences their biological function. In our current study, we compute the induced structural effects and dynamics on protein upon gold nanoparticle (AuNP) binding using atomistic level molecular dynamics simulation. A spherical AuNP with a radius of 2 nm was used. Human serum albumin (HSA) is selected as a representative of blood proteins in this study.

To calculate the induced effects of spherical AuNP on the protein structure, the root mean square deviation and the change in the protein's residues secondary structure were calculated. According to our work; the conformational alterations that happened by the NP are referred to the nature of the structural characteristics of Human serum albumin protein as it is an α-rich protein, which makes it less resilient to any external perturbation. These effects are mainly due to the induced nonbonded interactions formed between NP and protein.

Keywords: Gold nanoparticle, Human serum albumin protein, Molecular dynamic, Simulation

1. Introduction

Nanoparticles (NPs) are materials of size ranging from 1 to 100 nm, which gives them completely different characteristics compared with their bulk counterparts. So, they have diverse and exceptional physical, optical, and electronic properties [1]. Consequently, they have a broad range of applications such as biomedical applications as bioimaging [2], diagnosis [3,4], and drug delivery [5].

Two major methods have been applied in drug delivery. The first method is to bind the drug of interest to a suitable NP, then it is targeted to the required action site. The second method is NP capsule contains the drug which released at certain cells. The success of these techniques relies on the nanoparticle type as well as the ligand property, and it has an advantage over traditional drug delivery methods. As a consequence, smaller doses of the drug are required to be interact with tissues which decreases undesirable side effects [6,7].

At the NP contact with any part across the blood stream as proteins, a particular interaction happens. A layer is formed by proteins around nanoparticle which is called the protein corona. The biological reactivity of different nanoparticles is affected by the stability of this corona, but it is associated with conformational changes in the bound proteins [8]. Recently, intensive research was performed to understand the nature of the interaction between nanoparticle and protein [9]. Also, experimental studies have focused on the nanoparticle effect on protein structure in three dimensions as the case of T4-lysozyme [10]. However, experimental research

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supply with investigation at the macroscopic level. Whereas for understanding the interaction at an atomic level, we use computational methods such as molecular dynamics simulations (MDs) and density functional theory and the subatomic, respectively, which helps to have an accurate view and track these changes in a very short time scale (1fs). Tang et al. illustrated the unfolding of collagen triple helices by AuNP using molecular dynamic simulation [11].

Nanoparticles carrying drugs travel through blood circulation to the target tissues and organs, and as a consequence, it interacts with its proteins. Human serum albumin protein (HSA) is abundantly present in blood and constitutes approximately 60 % of plasma proteins. It has an important role in the transport of materials as fatty acids, and drugs, whether they are endogenously and exogenously released [12].

NPs usage in delivery of drugs is achievable if only HSA−NP interaction, does not alter its 3d structure and native conformation and hence will not affect HSA biological function. So, it becomes important to probe AuNPs effect on the HSA structure. We have considered AuNPs, as they are extensively used, where they have an interesting therapeutic, optical, and electrical properties. AuNPs have a great impact in the biomedical field as they act as an antimicrobial agent. They are used in the biomedical fields based on nanogold, such as, orthopedic materials, bandages and drug-delivery mechanism [10]. Some of them have great important in all fields of nanobiotechnology, the other have adverse effects as in previous work [11,13].

Here, we have studied the conformational changes, the flexibility of the structure and the HSA protein dynamics in the existence of AuNP. The AuNP and the HSA protein interaction have explained by using molecular dynamics simulation at the atomistic level.

2. Computational details

The system containing HSA protein and the spherical AuNP was built as follows. The AuNP was created as a sphere with a radius of 2 nm using NP builder CHARMM-GUI program [14]. And the protein 3d structure was taken from the protein data bank (PDB) portal (1n5u). A cubic periodic box containing an all-atom HSA−NP complex, of side 14.0 nm is created, where the complex is centrally inserted. A water solvation layer of thickness 2 nm surrounded the complex. So, it enables us to show explicitly water solvation effect on the HSA−NP complex while keeping the atoms of the system in the periodic box to be convenient, consequently the simulation was extended to 100 ns. NP-free simulation was conducted for 100 ns as a control or reference, to show the effect of AuNP on the protein. Any possible close contact between protein's atoms and the AuNP was avoided by slightly shifting AuNP away from HSA, to avoid repulsive effect of van der waals forces. To neutralize the system, some hydrogen and hydroxide ions are replaced by Na+ and Cl−. So that NaCl salt concentration is set to 0.15 M. The system of the complex contains finally more than 270 000 atoms. Fig. 1 shows the initial configuration of HSA−NP complex. The ions, gold atoms and HSA protein are characterized by the Optimized Potentials for Liquid Simulations All Atoms (OPLS-AA) force field that is developed and modified by Heinz group [15]. This force field describes the properties of AuNP. We use simple point-charge (SPC) water model to describe the water molecules, which is recommended when the OPLS-AA force field is applied [15]. To investigate and compare the structure and the flexibility of HSA protein in the complex and in the bulk solution, atomistic MD simulations were performed. A 100 ns MD simulation with a 2-fs time step is conducted after an energy minimization and system equilibration. Nose−Hoover thermostat was used to maintain the temperature of the system to 300 K [16]. The positions of NP atoms are held fixed during system minimization and MD simulations. The nonbonded interaction energy is expressed as the summation of the short-range van der Waals, which is described using Lennard-Jones 6−12 function with a 1.0 nm cut-off, and long-range electrostatic interactions were described by the Coulombic function and

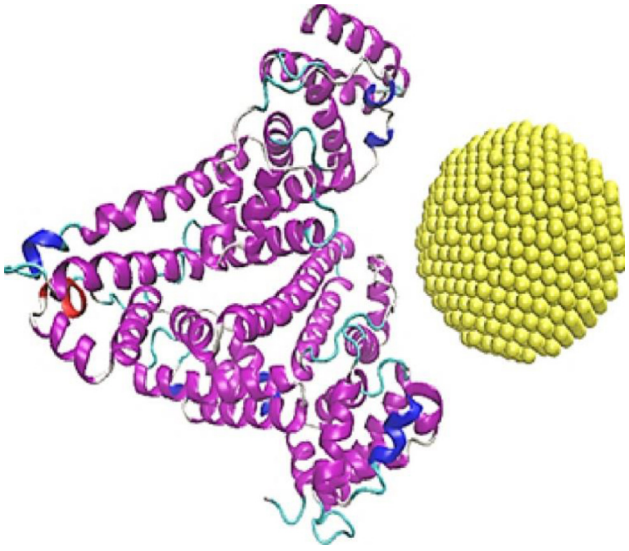

Fig. 1. The starting structure of Human serum albumin-gold nanoparticle complex. The secondary structure is represented by alpha helices (purple), 3_{10} helices (blue) and turns (cyan). The gold nanoparticle is represented by yellow sphere of radius 2 nm.

treated with particle mesh Ewald sum [17]. The nonbonded interaction energy among gold atoms is set to zero during the simulation. Hydrogen bonds are constrained to their equilibrated lengths using the LINCS algorithm [18]. However, the other bonded interactions are described as in the OPLS-AA force field. The atomistic MD simulation was conducted using Gromacs-2018.1 [19].

We have calculated the change in the complex root mean square of deviation as a function of time. The secondary structure content with respect to the reference starting structure over the 100 ns was calculated using DSSP (Dictionary of the protein secondary structure) program implemented in GROMACS [20]. Moreover the electrostatic potential surface was calculated using pdb2pqr [21] and

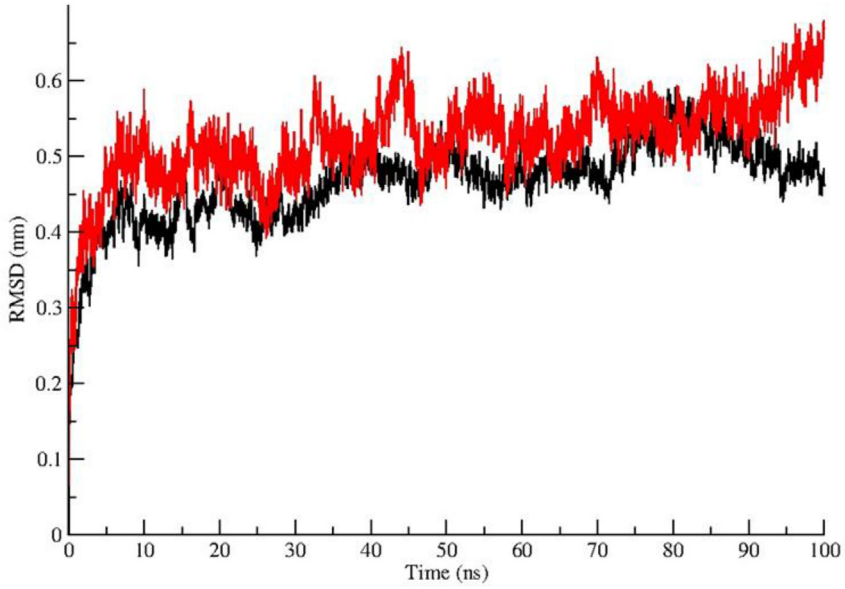

Fig. 2. The root mean square of deviation (RMSD) in nm. of the nanoparticle-bound (red) and free (black) proteins with respect to its crystalline structure.

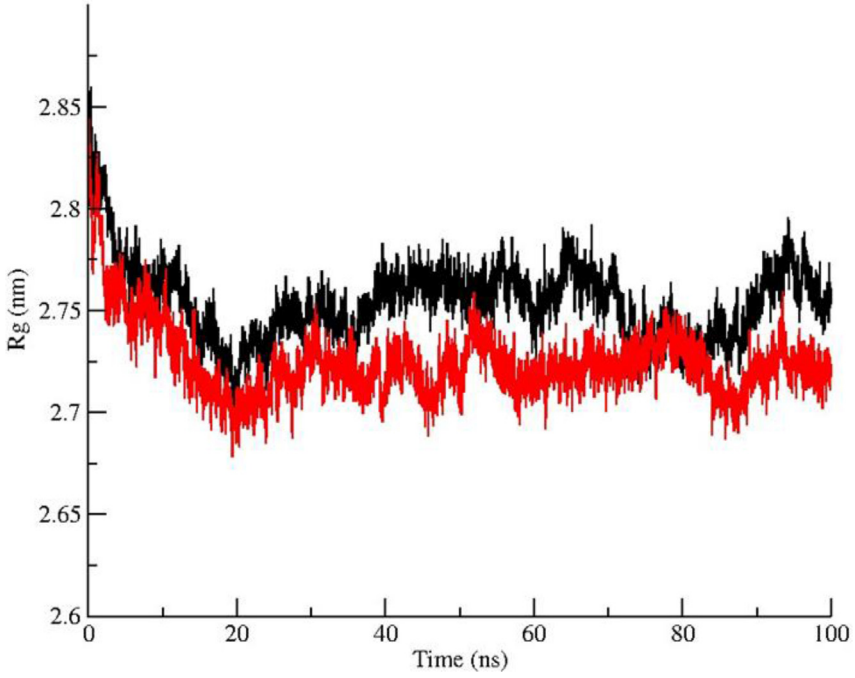

Fig. 3. Radius of gyration (Rg) in nm. of the nanoparticle-bound (red) and free (black) proteins.

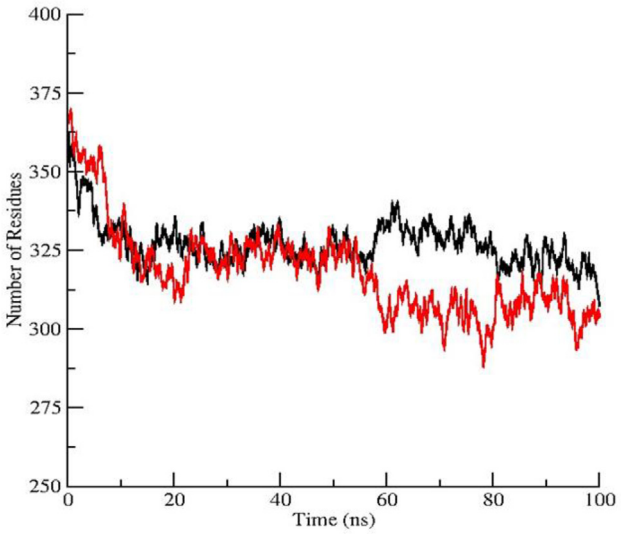

Fig. 4. The number of residues forming the secondary structure as a function of time, of the nanoparticle-bound (red) and free (black) proteins.

APBS [22] programs and then visualized using VMD program [23], for the staring and final protein configurations along with the corresponding total dipole moment vector of the protein.

3. Results and discussions

To investigate the spherical AuNP effect on HSA's structure, we have implemented 100 ns atomistic molecular dynamics simulation. To study the structural conformational changes and the protein stability, the root-mean-square deviations (RMSDs) of atomic positions compared with their reference structure has been calculated as a function of time as illustrated in Fig. 2. From the analysis of the RMSD, it has shown that structural fluctuations of NP-free protein in water has a maximum atomic deviation with respect to its initial position of 0.55 nm. While the NP-bound protein has a higher deviation of 0.68 nm. Thus, the protein shows considerable structural changes in the presence of AuNP.

Radius of gyration which shows the degree of protein structure compactness, was calculated as a function of time for both NP-bound and free proteins as shown in Fig. 3. There is an obvious decrease in the protein radius of gyration as a result of the NP presence compared with that of the free protein. That confirms the results of RMSDs calculation. Accordingly, conformational changes were induced in the presence of AuNP.

To quantify this change more accurately, the secondary structure content of the protein was calculated using DSSP program implemented in GROMACS [20]. As shown in Fig. 4. The secondary structure content represented by the number of residues forming α-helices, β-sheets as a function of crystalline structure. There an obvious decrease in the secondary structure where the minimum number of residues forming the protein helical secondary structure was dropped to 285 compared with that of free protein, which maintains 310 residues. Moreover HSA is an α-helix-rich protein, according to our calculation there is no detectable transitions from α-helix to any other secondary structure forms such as β-sheets during the simulation, this as a consequence of the complete unfolding of the

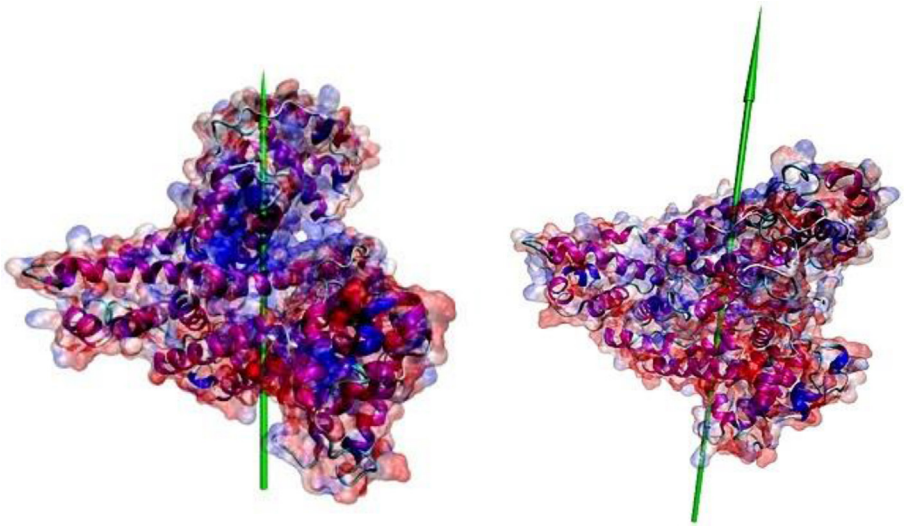

Fig. 5. The starting and final structure of Human serum albumin (HSA) protein. These structures are coloured by electrostatic potential surface of −5 (red) and 5 (blue) K_bT/e. The corresponding secondary structure is also represented by helices (purple), 3_{10} helices (blue), and turns (cyan). The green arrow shows the Total dipole moment vector of the protein.

affected residues. So, it desaturates the protein, which render it unfunctional.

To get a clear view of the charge distribution over the protein surface, the electrostatic potential for the starting and the final structures along with the corresponding secondary structure in addition to the total dipole moment of the protein are shown in Fig. 4. Observable changes in both potential surface and the protien total dipole moment. The total dipole moment is increased from 720 to 1108 Debye. This illustrate the reason for the accompanying changes in the structure, which is mainly due to the nonbonded interactions formed between the NP and the protien, which in turn weaken bonds forming the protein structure itself. Since HSA is helix-rich protein, it shows low resilience against any external perturbation whether mechanical as reported by Markus et al. [24] or electrical as it was reported by Elsheshiny et al. [25] Fig. 5.

4. Conclusion

According to our study, observable changes in the HSA protein structure was detected upon its interaction with spherical gold nanoparticle with radius 2 nm. These structural changes were illustrated through the calculation of RMSDs of protein atomic positions with respect to the starting structure and the secondary structure content as a function of time. This was reflected obviously on the charge distribution over the protein surface, which is expressed as protein potential surface, and reflected accordingly on the total dipole moment of the protein.

This change in the protein structure, consequently, affects its function and hence explained the reason for the induced/inherent toxicity upon the introduction of AuNP into blood. According to our study, the major cause of that effect is helical nature of the protein secondary structure that makes it cooperatively unfolded [26,27]. The application of Spherical AuNP with a radius of 2 nm is not recommended in drug delivery mechanism because it affects adversely Human serum proteins.

Ethics information

None.

Funding

None.

Author contributions

A. A. Els proposed the study methodology, performed calculations, and wrote the first draft. S. S. A revised the methodology, supervised the study, and reviewed/edited the manuscript.

Conflicts of interest

No conflict interest in this study was declared.

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References

[1] Moriarty P. Nanostructured materials. Rep. Prog. Phys. 2001; 64:297–381. https://doi.org/10.1088/0034-4885/64/3/201.
[2] Wolfbeis OS. An overview of nanoparticles commonly used in fluorescent bioimaging. Chem. Soc. Rev. 2015;44. https://doi.org/10.1039/c4cs00392f.
[3] Bejarano J, Navarro-Marquez M, Morales-Zavala F, Morales JO, Garcia-Carvajal I, Araya-Fuentes E, et al. Nanoparticles for diagnosis and therapy of atherosclerosis and myocardial infarction: evolution toward prospective theranostic approaches. Theranostics 2018;8. https://doi.org/10.7150/thno.26284.
[4] Baetke SC, Lammers T, Kiessling F. Applications of nanoparticles for diagnosis and therapy of cancer. Br. J. Radiol. 2015;88. https://doi.org/10.1259/bjr.20150207.
[5] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. J. Contr. Release 2016;235. https://doi.org/10.1016/j.jconrel.2016.05.044.
[6] Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres M del P, Acosta-Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. J. Nanobiotechnol. 2018;16. https://doi.org/10.1186/s12951-018-0392-8.
[7] Calzoni E, Cesaretti A, Polchi A, Di Michele A, Tancini B, Emiliani C. Biocompatible polymer nanoparticles for drug delivery applications in cancer and neurodegenerative disorder therapies. J. Funct. Biomater. 2019;10. https://doi.org/10.3390/jfb10010004.
[8] Mu Q, Jiang G, Chen L, Zhou H, Fourches D, Tropsha A, et al. Chemical basis of interactions between engineered nanoparticles and biological systems. Chem. Rev. 2014;114. https://doi.org/10.1021/cr400295a.
[9] Park SJ. Protein-nanoparticle interaction: corona formation and conformational changes in proteins on nanoparticles. https://doi.org/10.2147/IJN.S254808; 2020.
[10] Yuan J, Guo QQ, He XZ, Liu YP. Researching on the adsorption of protein on gold nanoparticles. Adv. Mater. Res. 2011;194–196:462–6. https://doi.org/10.4028/www.scientific.net/AMR.194-196.462.
[11] Georgieva ER. Protein conformational dynamics upon association with the surfaces of lipid membranes and engineered nanoparticles: insights from electron paramagnetic resonance spectroscopy. Molecules 2020 Nov 18;25(22):5393. https://doi.org/10.3390/molecules25225393.
[12] Tang M, Gandhi NS, Burrage K, Gu Y. Interaction of gold nanosurfaces/nanoparticles with collagen-like peptides. Phys. Chem. Chem. Phys. 2019;21:3701–11. https://doi.org/10.1039/c8cp05191g.
[13] Fanali G, Di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol. Aspect. Med. 2012;33. https://doi.org/10.1016/j.mam.2011.12.002.

[14] Tao C. Antimicrobial activity and toxicity of gold nanoparticles: research progress, challenges and prospects. Lett. Appl. Microbiol. 2018;67. https://doi.org/10.1111/lam.13082.
[15] Schmid G, Kreyling WG, Simon U. Toxic effects and biodistribution of ultrasmall gold nanoparticles. Arch. Toxicol. 2017;91. https://doi.org/10.1007/s00204-017-2016-8.
[16] Fratoddi I, Venditti I, Cametti C, Russo MV. The puzzle of toxicity of gold nanoparticles. The case-study of HeLa cells. Toxicol. Res. 2015;4. https://doi.org/10.1039/c4tx00168k.
[17] Heinz H, Vaia RA, Farmer BL, Naik RR. Accurate simulation of surfaces and interfaces of face-centered cubic metals using 12-6 and 9-6 Lennard-Jones potentials. J. Phys. Chem. C 2008;112. https://doi.org/10.1021/jp801931d.
[18] Evans DJ, Holian BL. The Nose-Hoover thermostat. J. Chem. Phys. 1985;83. https://doi.org/10.1063/1.449071.
[19] Andricioaei I, Karplus M. Particle mesh Ewald: an N·log(N) method for Ewald sums in large systems. Stat. Mech. Fluid Mix. J. Chem. Phys. 2001;115.
[20] Hess B, Bekker H, Berendsen HJC, Fraaije JGEM. LINCS: a linear constraint solver for molecular simulations. J. Comput. Chem. 1997;18. https://doi.org/10.1002/(SICI)1096-987X(199709)18:12<1463::AID-JCC4>3.0.CO;2-H.
[21] Abraham MJ, Murtola T, Schulz R, Páll S, Smith JC, Hess B, et al. Gromacs: high performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX 2015:1−2. https://doi.org/10.1016/j.softx.2015.06.001.
[22] Kabsch W, Sander C. Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical features. Biopolymers 1983;22. https://doi.org/10.1002/bip.360221211.
[23] Dolinsky TJ, Nielsen JE, McCammon JA, Baker NA. PDB2PQR: an automated pipeline for the setup of Poisson-Boltzmann electrostatics calculations. Nucleic Acids Res. 2004;32. https://doi.org/10.1093/nar/gkh381.
[24] Baker NA, Sept D, Joseph S, Holst MJ, McCammon JA. Electrostatics of nanosystems: application to microtubules and the ribosome. Proc. Natl. Acad. Sci. U. S. A. 2001;98. https://doi.org/10.1073/pnas.181342398.
[25] Humphrey W, Dalke A, Schulten K. VMD: visual molecular dynamics. J. Mol. Graph. 1996;14:33−8. https://doi.org/10.1016/0263-7855(96)00018-5.
[26] Buehler MJ, Keten S. Elasticity, strength and resilience: a comparative study on mechanical signatures of α-Helix, β-sheet and tropocollagen domains. Nano Res. 2008;1. https://doi.org/10.1007/s12274-008-8006-7.
[27] Elsheshiny AAA, Ashcroft AE, Harris SA. A comparison of the electromechanical properties of structurally diverse proteins by molecular dynamics simulation. J. Biomol. Struct. Dyn. 2014;32. https://doi.org/10.1080/07391102.2013.833864.