

Towards the Ionizing Radiation Induced Bond Dissociation Mechanism in Oxygen, Water, Guanine and DNA Fragmentation: A Density Functional Theory Simulation

Santosh KC

San José State University

Ramin Abolfath (✉ ramin1.abolfath@gmail.com)

MD Anderson Cancer Center

Article

Keywords:

Posted Date: May 26th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1666450/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

24 I. INTRODUCTION

25 Deoxyribonucleic acid (DNA), is one of the key components of life which is responsible
26 for the storage and transmission of genetic information [1, 2]. It comprises a phosphate
27 backbone and four nitrogen-containing bases, which are named adenine (A), cytosine (C),
28 guanine (G), and thymine (T). It is found that A base pairs only with the T base, and the G
29 base pairs with the C base [1, 2]. DNA is an important part of life, but, it is very sensitive
30 to the environment.

31 In radiotherapy, the interaction of Mega-voltage ionizing radiation with biological systems
32 causes ionization processes in biomolecules such as DNA, proteins, and their surrounding
33 environment in cell nuclei. Among all of these ionization processes, DNA damage is critical
34 to the clinical outcome of radiotherapy. After initial induction of DNA damage, a dynami-
35 cal cascade of stochastic microscopic events and complex biochemical pathways, including,
36 enzymatic homologous and non-homologous repair and misrepair end-joining determine the
37 lethality of the irradiated cells.

38 Empirical studies in radio-biology and radio-chemistry have suggested induction of ap-
39 proximately 1000 single-strand breaks (SSBs) and 40 double-strand breaks (DSBs) per one
40 gray ($1\text{Gy} = 1 \text{ J/kg}$) of low linear energy transfer (LET) of ionizing radiation such as X-
41 or γ -rays in typical mammalian cells [3-6].

42 Accordingly, the level of DNA molecular base damage has been estimated to be around
43 2,500 to 25,000 per gray in a cell, which is about 2.5-25 times the yield of sugar-phosphate-
44 induced damage in the DNA backbone.

45 The occurrence of initial DNA damage has been classified into direct and indirect pro-
46 cesses. In direct mechanism, ionization takes place via direct electro-dynamical coupling
47 between the source of radiation and DNA molecule. For X- or γ -rays, depends on the en-
48 ergy of the incident photon, the coupling varies among photoelectric and Compton effects
49 where shell electrons are ejected directly. In addition, high enough energy photons may
50 interact with the nuclei of atoms and generate pair of electrons and positrons. Another
51 source of uncharged particles such as neutrons may undergo nuclear interaction and make
52 nuclear fragmentation and produce secondary charged particles as well as photons. The
53 charged particles, either primary or secondary, interact with shell electrons through long-
54 range Coulomb interaction. Under enough energy and momentum transfer, these charged

55 particles eject shell electrons. Thus a “direct damage” originates from the direct ioniza-
56 tion of a molecule, i.e., an isolated molecule (in vacuum) loses a number of shell electrons
57 within atto-second (electromagnetic) time-scales and undergoes structural instability be-
58 cause of electrostatic charge imbalance and the repulsive forces among positively charged
59 nuclei. The threshold of such instabilities requires a minimum number of ionizations and
60 energy on a specific site of DNA.

61 In the indirect mechanism of radiation interactions, the radiation dominantly ionizes
62 water molecules and creates neutral $\cdot\text{OH}$ free radicals [3]. The DNA damage process involves
63 the generation and diffusion of $\cdot\text{OH}$ radicals in cell nuclei and/or aqueous environments
64 followed by chemical reactions that allow the removal of hydrogen atoms from the DNA.
65 This process is energetically favorable for $\cdot\text{OH}$ radicals as it forms a water molecule and fills
66 the electronic shell by neutralizing its magnetic moment.

67 On the other fronts, there is a tremendous concern about the risk of radiation in the
68 human body while going into outer-space [23]. Outer-space consists of an ionizing radiation
69 environment dominated by energetic and penetrating ions and nuclei. Thus, there is a
70 risk of DNA damage due to ionizing radiation and a chance of radiation-induced cancer in
71 manned space exploration [23, 24]. Like in radiotherapy and radiobiology, there is a need
72 for atomic-level understanding of biomolecules in radiation exposed in space. A large-scale
73 computational model, relying on quantum dataset, will provide more realistic computational
74 tools in assessing the biological risks due to space radiation, in particular for astronauts who
75 are planning for the long-term exploration of other planets such as Mars. This is in alignment
76 with NASA’s space radiobiology research that aims to mitigate the detrimental effects of the
77 space radiation environment on the human body, a project focusing on the human presence
78 outside of the relative protective Van Allen belt. Although the spacecraft itself somewhat
79 reduces radiation exposure, it does not completely shield astronauts from galactic cosmic
80 rays, which are highly energetic heavy ions, or from solar energetic particles, which primarily
81 are energetic protons. By one NASA estimate, for each year that astronauts spend in deep
82 space, about one-third of their DNA will be hit directly by heavy ions [26, 27] from Galactic
83 Cosmic Radiation (GCR).

84 We note that because of the aquatic environment in cells, approximately 70 to 80% of
85 interactions take place through indirect damage and the rest are associated with the direct
86 damage. In recent years, various types of molecular simulations were devoted to studying

87 DNA damage by either free radicals, or direct damage [7–12]. This is in particular important
88 to analysis of the recent experiments based on FLASH ultra high dose radiotherapy [12].

89 Here we combine these two events to study their mutual effects. Moreover, many current
90 computational platforms designed for the large-scale simulations of the DNA-damage at the
91 nanoscopic scales [29–35] lack accurate details from the first-principle direct and in-direct
92 processes. We aim to cover the gap in the details of the input parameters and allow the
93 developers to update the tables used for MC simulation of DNA damage.

94 In this study, we focus on the simulation of combined direct and indirect damage to DNA
95 molecules including base and backbone. As a representative of DNA-base, and without
96 loss of generality, we focus on Guanine. We find as a combined function of ionization and
97 hydrogen loss in indirect mechanism, electrostatic repulsion of atomic nuclei dominates the
98 electronic chemical bonds and molecular fragmentation takes place. Thus we quantify DNA
99 fragmentation as a function of ionization and hydrogen abstraction. We show that at least
100 four to five ionization must take place till the molecule undergo mechanical instability and
101 fall apart. Because in energy transfer by a high-energy photon or a charged particle adequate
102 energy may transfer locally to DNA base or backbone, the such number of ionization can
103 be scored.

104 The remainder of the paper is organized as follows. Section II introduces the calculation
105 methods. The results and discussion of the results are described in Sec. III. Section IV
106 provides the conclusion of the research.

107 II. COMPUTATIONAL METHODS

108 First-principles calculations based on Density Functional Theory (DFT)[15, 16] are per-
109 formed to investigate the charged defects in O₂, guanine, and DNA. The core and valence
110 electrons interactions were described within projector-augmented plane-wave (PAW) po-
111 tentials as implemented in the Vienna *Ab-initio* Simulation Package (VASP)[17–19]. The
112 exchange potential with the generalized gradient approximation of Perdew, Burke, and Ernzerhof (PBE) [20]. An energy cutoff of 500 eV is used for the plane-wave basis set in all the
113 calculations. Spin polarization was used in all the calculations. In the PAW potentials used
114 the 2s² 2p⁴, 3s² 3p³, 2s² 2p², 1s¹ and 2s² 2p³ electrons were explicitly treated as the valence
115 electrons for O, P, C, H, and N, respectively. First, the Oxygen and water molecule in a
116

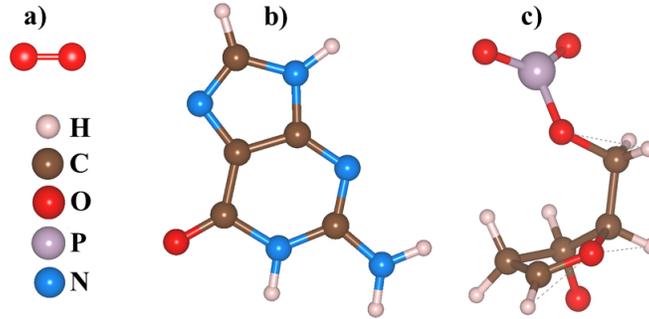


FIG. 1. Optimized atomic structures of the Oxygen, Guanine ($C_5H_5N_5O$), and fragment of Deoxyribonucleic acid (DNA). a) Oxygen b) Guanine and c) fragment of DNA

117 simulation box of size $15\text{\AA} \times 15\text{\AA} \times 15\text{\AA}$ was optimized. Electrons are gradually removed
 118 from the system to observe the oxygen and water bond dissociation. Similarly, we have
 119 investigated the effect of electron extraction in Guanine and DNA molecules. The charged
 120 molecules were relaxed until the Hellman-Feynman forces were less than 0.01 eV/\AA . There
 121 have been successful reports of using DFT-based computational approach with plane-wave
 122 basis set on Guanine and DNA [21, 22].

123 III. RESULTS AND DISCUSSION

124 Our DNA backbone model is similar to the deoxyribose residue used in other *ab-initio*
 125 calculations such as Ref. [14] where the system of interest consists of a DNA nucleobase
 126 modeled by an amino group attached to the deoxyribose as shown in Figure 1(a, b, and c).
 127 The deoxyribose sugar ring is an important component of nucleotides and plays a role in
 128 the stability of DNA double-helix structure. Any damage to the sugar ring causes breakage
 129 of strands and the formation of single-strand break (SSB). The formation of a pair of SSBs
 130 in opposite strands, within ten base pairs, leads to a single double-strand break (DSB).

131 To study the effect of ionizing radiation on the molecules, we systematically perform the
 132 DFT calculation of molecules in various charge states. For a representative of DNA-base,
 133 we consider Guanine in addition to the oxygen and water molecules in our simulations.

TABLE I. The effect of electron removal in the bond length (d) of O_2 molecule. The charge state (q) refers to the number of electron removed from the neutral system. Thus, $q=1$ refers to $1.60217662 \times 10^{-19}$ coulombs per molecule.

Charge (q)	Bond Length d (\AA)	Δd (\AA)
0	1.233	0
+1	1.146	-0.087
+2	1.085	-0.148
+3	1.387	+0.154
+4	7.491	+6.258
+5	7.500	+6.267

A. Effect of electron extraction on oxygen molecules

It is known that oxygen species play important roles in both tumor and normal cells. Typically, tumor cells contain less oxygen with a complex environment known as hypoxic, so they are more radio-resistant than normal tissues. Also, there are specific transitions in oxygen that make the molecular oxygen toxic, such as singlet oxygen. Thus, it is critical to understand how the charge induced radiation environment facilitates the dissociation of oxygen molecule.

First, the oxygen (O_2) molecule was optimized and bond distance and equilibrium energy were obtained. The O-O bond length was found to be 1.233 \AA , which is consistent with experimental and previously reported computational values. In O_2 molecule, we notice that gradual electron extraction shows initially the bond length contracts slightly then expands for when a large number of electrons are removed (See Figure 2). The bond length variation as a function of the charge state of an oxygen molecule is presented in table I. The removal of electrons weakens the bond strength and hence the bond-dissociation energy is reduced. In a pure oxygen molecule, the bond-dissociation energy is stronger due to the formation of double bonds (119 kcal/mole or 5.15 eV/bond).

The figure (2) shows the bond length as a function of the charge state (q). The x-axis label 1 refers to the +1 charge state with removing one electron, resulting in a positive charge in the molecule. We observed that with $q=+4$ (4 electrons are removed) demonstrates the dissociation of the bonds. The distance ($d=7.5 \text{\AA}$) is due to chosen box size of 15 \AA ,

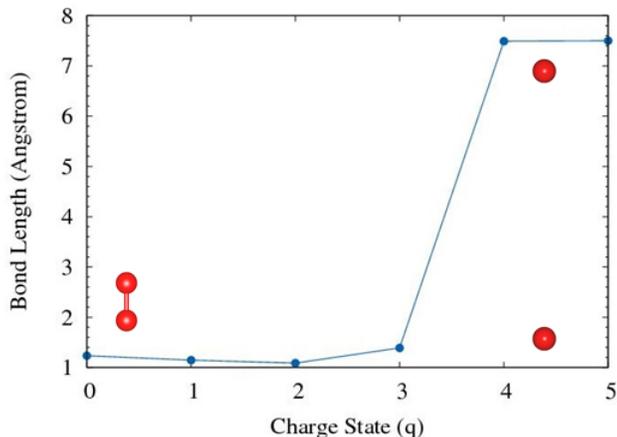


FIG. 2. The effect of electron removal in oxygen molecule. The dots represents the O-O bond, the relative bond distance is indicated by O atoms.

154 indicating that they are isolated from each other.

155 It is found that oxygen depletion leads to lower normal-tissue toxicity at FLASH dose
 156 rates that take place within femto-to nanoseconds of irradiation. The biomolecular damage
 157 would be reduced in an environment with physoxic oxygen levels [12].

158 B. Effect of electron extraction in water molecules

159 Water molecules (H_2O) which are ubiquitous and are a significant part of life pro-
 160 cesses, stabilized as a tri-atomic molecule with C_{2v} molecular symmetry and bond angle
 161 of 104.5° between the oxygen atom and the two hydrogen atoms. The H-O bond length is
 162 close to the bond (O-H) length of 0.9572 \AA and the bond angle (H-O-H) of 104.5° . Our
 163 calculated data are in very good agreement with the experimental reports [See Table II.
 164 We observed that upon extraction of electrons from the water molecule, both the bond
 165 lengths (H-OH) and the bond angle (H-O-H) change significantly as shown in Fig. 3 and
 166 4. Moreover, we would like to mention that these calculations are performed in a vacuum.
 167 For example, the pathway of dissociation of the water molecule, surrounded by other wa-
 168 ter molecules would be significantly different. It stabilizes OH-radical. In Fig. 3, none of
 169 these scenarios correspond to the formation of OH-radical, simply because of symmetry and
 170 periodic boundary condition.

171 The dissociation of the HO-H bond in a water molecule needs approximately 118.8

TABLE II. The effect of electron removal in the bond length of H₂O molecule. The charge state (q) refers to the number of electron removed from the neutral system. Charge q=1 refers to 1.60217662 $\times 10^{-19}$ coulombs per molecule. The H-O-H bond angle is also provided.

Charge (q)	Bond Length d (\AA)	$\Delta d(\text{\AA})$	Θ°	$\Delta\Theta^\circ$
0	0.972	0	104.502	0
+1	1.017	+0.045	109.004	+4.502
+2	1.232	+0.260	179.862	+75.360
+3	5.200	+4.228	80.416	-24.086

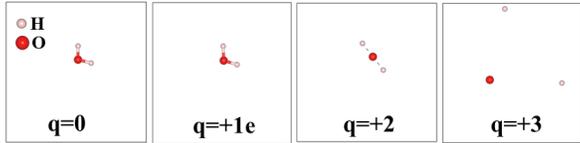


FIG. 3. The effect of electron removal in water molecule.

172 kcal/mol (497.1 kJ/mol) when there is no charge is involved. The bond energy of the covalent O-H bonds of the water molecule is approximately 110.3 kcal/mol (461.5 kJ/mol)[25].
 173
 174 In the case of the ionizing environment, these values will be reduced and hence, this reduction causes the fragmentation of the bonds easily as shown in Fig 3). Figure 4 shows how
 175
 176 the bond length and the angles changes with the application of increasing charge (removal of an electron from the water molecule).
 177

178 For a highly ionizing environment, the bond angles will deviate from the angular to planar before breaking the bonds as shown in the case of charge state (q=2). This indicates that
 179
 180 the 2 electrons extraction per water molecule ($3.20435324 \times 10^{-19}$ coulombs per molecule) is sufficient to drive the fragmentation into ions.
 182

183 C. Effect of electron extraction in guanine and in a fragment of DNA molecules

184 Finally, the impact of the electron extraction in guanine and a fragment of DNA molecule is studied. Guanine, as shown in Fig. (5), is one of the four main nucleobases that exist in DNA. Guanine (2-Amino-1,9-dihydro-6H-purin-6-one: IUPAC) consists of a fused pyrimidine-imidazole ring system with conjugated double bonds and has a planar molecular structure. To avoid spurious interaction due to the periodic boundary condition (PBC)
 185
 186
 187
 188

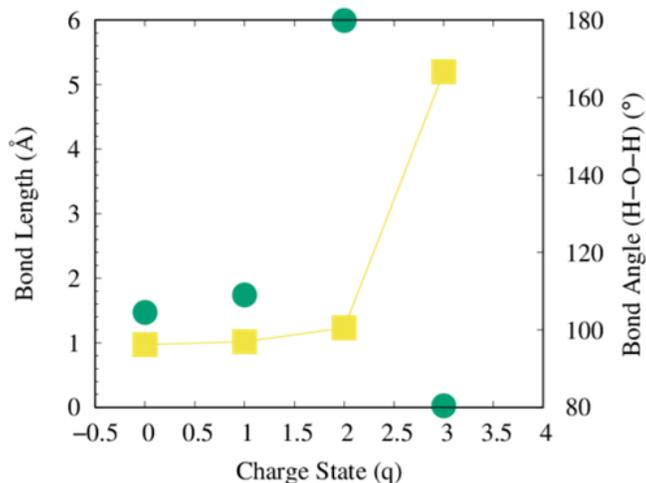


FIG. 4. The effect of electron removal in water molecule. The dots represents the H-O-H bond angles.

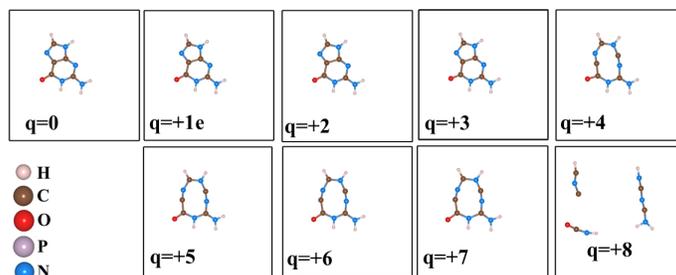


FIG. 5. The effect of electron removal in Guanine molecule.

189 in DFT calculation, a large simulation box was adopted for each molecule. Since, these
 190 molecules have multiple bonds, instead of monitoring individual bond length, we note the
 191 sum of the atomic displacements compared to the initial configurations. The gradual frag-
 192 mentation of the Guanine molecule is observed as shown in Fig. reffig:6. The corresponding
 193 sum of the displacements of the atoms as a function of charge states is shown in Figure 7.
 194 We noticed that when the charge state is 4e, the C-C double bond is broken that will drive
 195 the structural instability.

196 Similarly, upon extraction of electrons from a fragment of DNA as shown in figure 7,
 197 bonds start to change and dissociate when the change is sufficient such as $q=4e$. Eventu-
 198 ally, the molecule starts to collapse into smaller fragments in a sufficiently high ionization
 199 environment. This indicates that these molecules are prone to damage when exposed to an
 200 ionizing radiation environment. In addition, the temperature and pressure might also play a

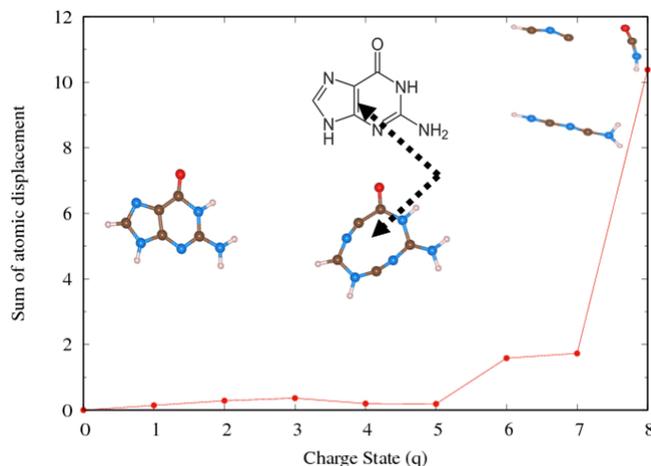


FIG. 6. The sum of the displacement of the atoms as a function of charge (q) in a Guanine. The sum of the displacement is in Å and charge is in terms of number of electrons removed.

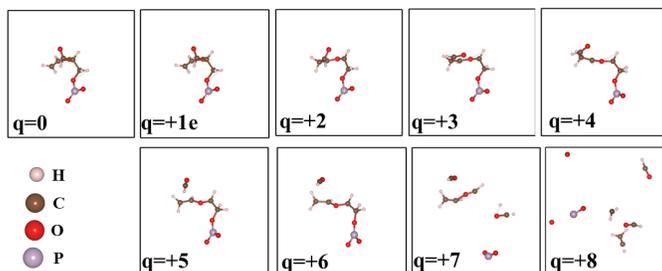


FIG. 7. The effect of electron removal in a fragment of DNA molecule.

201 role in altering this behavior to some extent. Thus, any chances of ionizing radiation-induced
 202 DNA damage should be checked seriously during radiation therapy treatment.

203 Ionizing radiation can extract electrons from these molecules resulting in ions that can
 204 trigger bond dissociation. Our results indicate that radiation directly affects DNA atomic
 205 structure by causing fragmentation. In addition, there might be secondary effects such as
 206 the creation of reactive oxygen species that oxidize proteins and lipids, and cause damages
 207 to DNA, eventually, the overall effect might cause cell death and mitotic catastrophe [28].

208 **D. Effect of hydrogen Contents in the electron extraction and stability of DNA**

209 Moreover, hydrogen deficient molecules were also investigated in order to check their
 210 dependence on the charge-induced dissociation. For illustration, the H atoms were gradually

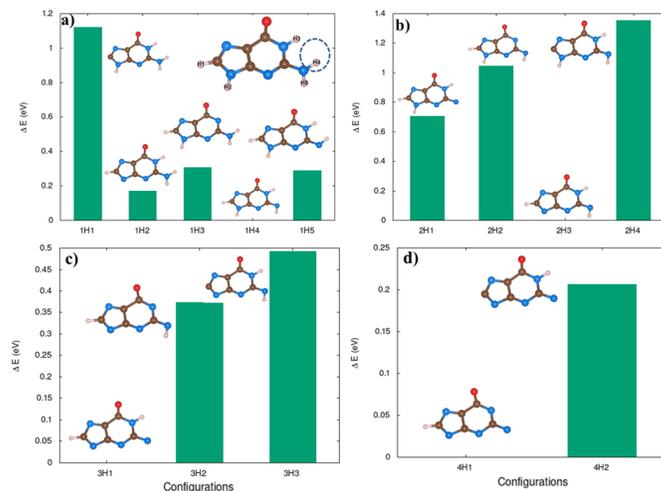


FIG. 8. The effect of hydrogen removal in Guanine molecule. Notation- 1H1 refers to one H removed the first configuration, 1H5 refers to 1H removed and is the fifth configuration. Similarly, 2H1: 2H atom removed and is the first configuration considered and so on. The energy of the configuration is with respect to the energetically most stable configuration in each H contents.

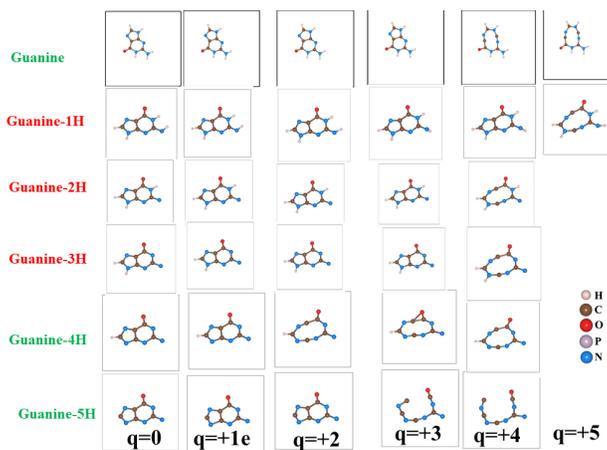


FIG. 9. The effect of electron extraction in hydrogen reduced Guanine molecule.

211 removed from Guanine as shown in Fig. 8. It is observed that even with less electron
 212 removal can trigger the fragmentation of the molecules. Guanine cyclic ring is stable up to
 213 charge state of 3e for when up to 3H atoms are removed. However, they will be significantly
 214 modified when 4 or 5H atoms are removed. In 5H deficient case, the charge state of 3e
 215 completely dissociates the molecule into the molecular chain.

216 In addition, we observed that the fragment of DNA molecule dissociates upon removal of
 217 H atoms. The combined effect of charge and reduced H environment, as illustrated in Fig.

218 9 will lead to the fragmentation of these molecules. This indicates that the charge-induced
219 dissociation of molecules strongly depends on the hydrogen environment.

220 We optimize the geometry after the removal of H atoms, this may end up with a slightly
221 different initial geometry for the removal of electrons. This optimized geometry would be
222 different if we remove the electron first. Therefore, these two operations are not identical.
223 We believe that this may happen in the actual scenario of DNA damage as the H-abstraction
224 is a much slower process compared to direct damage that is electron removal. This is the
225 case of damage induced by a single track of radiation that is responsible for alpha in the
226 linear-quadratic cell survival model. The second scenario that is the removal of H and a
227 subsequent direct ionization is most likely relevant to DNA damage induced by two tracks
228 that is relevant to the beta term in the linear-quadratic cell survival model.

229 The current Monte Carlo (MC) codes utilized in studying the impact of radiation on bio-
230 logical materials lack the details since they use some empirical values for the excitations and
231 DNA damage. This first-principles-based calculation provides important input parameters
232 to take into account in those models.

233 IV. CONCLUSION

234 Using DFT calculations, we systematically investigated the atomic bond dissociation in
235 an ionization environment and the fragmentation behavior of the DNA base pair molecule
236 along with water and oxygen molecules. Our results demonstrate that the bond fragmenta-
237 tion is proportional to the charge of the molecule and there is the limitation of the charge
238 density of the molecule that it can withstand before collapsing into its fragments. This
239 highlights the importance of using the optimal dose of radiation for safe use. Moreover, the
240 bond dissociation behavior strongly depends on the hydrogen contents of the molecule. A
241 hydrogen-reduced environment is detrimental to radiation-induced molecule fragmentation.
242 This research is very applicable in radiation therapy as well as an environment where the
243 human body will be exposed to radiation environments such as nuclear power plants or voy-
244 age to outer space. Thus, this study shed light on the atomic-level details of the mechanism
245 of bond dissociation in the presence of ionizing radiation.

246 **Data availability:** Derived data supporting the findings of this study are available from
247 the corresponding authors upon request.

248 **Acknowledgments:** S. KC acknowledges the faculty start-up grant provided by the
249 Davidson College of Engineering at San José State University. We acknowledge the compu-
250 tational resources provided by the Extreme Science and Engineering Discovery Environment
251 (XSEDE), which is supported by National Science Foundation grant number ACI-1548562
252 and the National Energy Research Scientific Computing Center (NERSC), a U.S. Depart-
253 ment of Energy Office of Science User Facility operated under Contract No. DE-AC02-
254 05CH11231.

255 **Authors contributions:** SK: wrote the main manuscript, prepared figures and performed
256 computational steps RA: proposed scientific problem, wrote the main manuscript and su-
257 pervised the project.

258 **Corresponding Authors:**

259 † santosh.khatrichhetri@gmail.com

260 * ramin1.abolfath@gmail.com

-
- 261 [1] J. D. Watson, F. H. Crick, *Molecular structure of nucleic acids; a structure for deoxyribose*
262 *nucleic acid*, Nature, **171**, 737-738, (1953).
- 263 [2] C. Dekker, M. Ratner, *Electronic properties of DNA*, **14**, 29, (2001).
- 264 [3] J. F. Ward, *DNA Damage Produced by Ionizing Radiation in Mammalian Cells: Identities,*
265 *Mechanisms of Formation, and Reparability* Progress in Nucleic Acid Research and Molecular
266 Biology, **35**, 95-125 (1988).
- 267 [4] D. T. Goodhead, Initial Events in the Cellular Effects of Ionizing Radiations: Clustered
268 Damage in DNA, Int. J. Radiat. Biol. **65**, 7-17 (1994).
- 269 [5] H. Nikjoo, P. O'Neill, D. T. Goodhead, M. Terrissol, *Computational modelling of low-energy*
270 *electron-induced DNA damage by early physical and chemical events*, Int. J. Radiat. Biol. **71**,
271 467-483 (1997).
- 272 [6] Semenenko, V. A.; Stewart, R. D. *A fast Monte Carlo algorithm to simulate the spectrum of*
273 *DNA damages formed by ionizing radiation*, Radiat. Res. **161**, 451-7 (2004).
- 274 [7] Abolfath R. M., *Optical Control of DNA Base Radio Sensitivity*, J. Phys. Chem. B **113**,
275 6938-6941 (2009).
- 276 [8] R. M. Abolfath, T. Brabec, *DNA-backbone radio resistivity induced by spin blockade effect*, J.

- 277 Comput. Chem. **31**, 2601–2606 (2010).
- 278 [9] R. M. Abolfath, A. C. T. van Duin, T. Brabec, it Reactive molecular dynamics study on the
279 first steps of DNA damage by free hydroxyl radicals, J. Phys. Chem. A **115**, 11045 (2011).
280 See the real-time simulations and movies at: <http://qmsimulator.wordpress.com/>
- 281 [10] R. M. Abolfath, P. K. Biswas, R. Rajnarayanam, T. Brabec, R. Kodym, L. Papiez, *Multiscale*
282 *QM/MM molecular dynamics study on the first steps of guanine damage by free hydroxyl*
283 *radicals in solution*, J. Phys. Chem. A 2012, **116**, 3940-3945.
- 284 [11] R. Abolfath, Y. Helo, L. Bronk, A. Carabe, D. Grosshans and R. Mohan *Renormalization*
285 *of radiobiological response functions by energy loss fluctuations and complexities in chromo-*
286 *some aberration induction: deactivation theory for proton therapy from cells to tumor control*,
287 European Physical Journal D **73**, 64 (2019), DOI: 10.1140/epjd/e2019-90263-5
- 288 [12] R. Abolfath, D. Grosshans, R. Mohan, *Oxygen depletion in FLASH ultra-high-dose-rate ra-*
289 *diotherapy: A molecular dynamics simulation*, Med. Phys. **47**, 6551-6561 (2020).
- 290 [13] R. Abolfath, A. Baikalov, S. Bartzsch, N. Afshordi, R. Mohan, *The effect of non-ionizing*
291 *excitations on the diffusion of ion species and inter-track correlations in FLASH ultra-high*
292 *dose rate radiotherapy*, Phys. Med. Biol. 67 105005 (2022). DOI: [https://doi.org/10.1088/1361-](https://doi.org/10.1088/1361-6560/ac69a6)
293 [6560/ac69a6](https://doi.org/10.1088/1361-6560/ac69a6)
- 294 [14] Miaskiewicz, K.; Osman, R. *Theoretical study on the deoxyribose radicals formed by hydrogen*
295 *abstraction*, J Am Chem Soc 1994, 116, 232-238.
- 296 [15] P. Hohenberg and W. Kohn, *P. Hohenberg and W. Kohn*, Phys. Rev. **136**, B864 (1964).
- 297 [16] W. Kohn and L. J. Sham, *Self-consistent equations including exchange and correlation effects*,
298 Phys. Rev. **140**, A1133 (1965).
- 299 [17] G. Kresse and J. Furthmüller, *Efficient iterative schemes for ab initio total-energy calculations*
300 *using a plane-wave basis set*, Phys. Rev. B **54**, 11169 (1996).
- 301 [18] G. Kresse and J. Hafner, *Ab initio molecular dynamics for liquid metals*, Phys. Rev. B **47**,
302 558 (1993).
- 303 [19] G. Kresse and J. Furthmüller, *Efficiency of ab-initio total energy calculations for metals and*
304 *semiconductors using a plane-wave basis set*, Comput. Mat. Sci. **6**, 15-50 (1996).
- 305 [20] J. P. Perdew, K. Burke, and M. Ernzerhof, *Generalized gradient approximation made simple*,
306 Phys. Rev. Lett. **77**, 3865-9 (1996).
- 307 [21] R. Di Felice, A. Calzolari, E. Molinari, and A. Garbesi, *Ab initio study of model guanine*

- 308 *assemblies: The role of $\pi - \pi$ coupling and band transport*, Phys. Rev. B **65**, 045104 (2001).
- 309 [22] E. Shapir, H. Cohen, A. Calzolari, C. Cavazzoni, D. A. Ryndyk, G. Cuniberti, A. Kotlyar,
310 R. Di Felice, D. Porath *Electronic structure of single DNA molecules resolved by transverse*
311 *scanning tunnelling spectroscopy*, Nature Materials **7**, 68-74 (2008).
- 312 [23] C. E. Hellweg, C. Baumstark-Khan, *Getting ready for the manned mission to Mars: the*
313 *astronauts' risk from space radiation*, Naturwissenschaften **94**, 517-526 (2007).
- 314 [24] NCRP, *Operational radiation safety program for astronauts in low-Earth orbit: a basic frame-*
315 *work*, NCRP Report, no. 142 (2002).
- 316 [25] Lehninger, Albert L., et al. *Lehninger principles of biochemistry*. Macmillan, 2005., W. H.
317 Freeman. p. 48.
- 318 [26] L. C. Simonsen, T. C. Slaba, P. Guida, A. Rusek, *NASA's first ground-based Galactic Cosmic*
319 *Ray Simulator: Enabling a new era in space radiobiology research*, PLoS biology **18**, e3000669
320 (2020).
- 321 [27] La Tessa, Chiara, et al. *Overview of the NASA space radiation laboratory*, Life sciences in
322 space research **11**, 18-23 (2016).
- 323 [28] Borrego-Soto, Gissela, Rocío Ortiz-López, and Augusto Rojas-Martínez, *Genetics and molec-*
324 *ular biology* 38 (2015): 420-432.
- 325 [29] S. Agostinelli *et. al.*, *GEANT4—a simulation toolkit*, Nucl. Instrum. Meth. A **506**, 250 (2003).
- 326 [30] Incerti S. *et. al.*, *The GEANT4-DNA project*, Int. J. Modelling Simul. Sci. Comput. **1**, 157-78
327 (2010).
- 328 [31] Schuemann J, McNamara AL, Ramos-Méndez J, Perl J, Held KD, Paganetti H, et al. *TOPAS-*
329 *nBio: An Extension to the TOPAS Simulation Toolkit for Cellular and Sub-cellular Radiobi-*
330 *ology*, Radiat. Res. **191**, 125-38 (2019).
- 331 [32] Faddegon B, Ramos-Méndez J, Schuemann J, McNamara A, Shin J, Perl J, et al. *The TOPAS*
332 *tool for particle simulation, a Monte Carlo simulation tool for physics, biology and clinical*
333 *research*, Phys Medica. **72**, 114-21 (2020).
- 334 [33] Friedland W, Dingfelder M, Kundra P, Jacob P, *Track structures, DNA targets and radiation*
335 *effects in the biophysical Monte Carlo simulation code PARTRAC*, Mutat. Res. 28 711 (2011).
- 336 [34] I. Plante, A. Ponomarev, Z. Patel, T. Slaba, M. Hada, *RITCARD: Radiation-Induced Tracks,*
337 *Chromosome Aberrations, Repair and Damage*, Radiat. Res. **192**, 282-298 (2019).
- 338 [35] Y. Lai, X. Jia, Y. Chi, *Modeling the Effect of Oxygen on the Chemical Stage of Water Radiol-*

339 *ysis using GPU-based Microscopic Monte Carlo Simulations, with an Application in FLASH*
340 *Radiotherapy*, Phys Med Biol. **66** 025004 (2021).