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Study for the Development of a Biosensor Aimed at the Interaction-Response of Chemical War Agents and Ionizing Radiation

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Abstract: It has long been known that the nuclear sector is a potential branch capable of solving major obstacles relevant to modern society with regard to energy demands. The technology in this sphere is associated with various possibilities, including areas that require multidisciplinary expertise for their respective advancements, such as medical sciences, security and defense, national autonomy and sovereignty, energy generation, food technology, among others. With the development of nanostructured technologies, highly sensitive, accessible, and easy to handle, it is possible to introduce new alternatives to reduce the "gap" between these possibilities within the sector, making the nuclear area more visible to new researchers due to the potential for new research to be developed. With the prospect of innovation for the sector and with increasing technological input, a special look at instrumental and measurement issues is necessary, since it is also necessary to ensure the quality of nuclear technology for the development of any system focused on this theme. This research presents a combination of different areas, highlighting the multidisciplinarity of construction, aiming to obtain the necessary support for the creation of a device capable of interacting with systems that represent chemical and radiological-nuclear threats. As it is a biosensor, it presents a biological interface sensitive to chemical warfare agents (organophosphates), neurotoxins and undergoes a process analogous to radiolysis, it is the means by which it is possible to associate electronics to the system, being capable of transducing information from one form of energy to another, making it possible to quantify and obtain relevant and proportional information about the exposure of this system created. For the *in silico* study carried out, the energy fluctuations for both the chemical simulations and the MCNP simulations were guiding the verification process, since the lower the energy value, the stronger the chemical interaction between ligands and enzymes.

Keywords: Innovation; Biotechnology; Radiations; Chemical Warfare; Biosensor.

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Estudo para Desenvolvimento de Biossensor Voltado à Interação-Resposta de Agentes Químicos de Guerra e Radiações Ionizantes

Resumo: É conhecido há muito tempo que o setor nuclear é um ramo potencial capaz de solucionar grandes entraves pertinentes à sociedade moderna no que diz respeito às demandas energéticas. A tecnologia dessa esfera está associada às diversas possibilidades, incluindo áreas que precisam da multiprofissionalidade para seus respectivos avanços, como nas ciências médicas, segurança e defesa, autonomia e soberania nacional, geração de energia, tecnologia de alimentos, entre outros. Com desenvolvimento de tecnologias nanoestruturadas, altamente sensíveis, acessíveis, de fácil manuseio é possível inserir novas alternativas para que diminua o "gap" entre essas possibilidades dentro do setor, fazendo com que a área nuclear esteja mais visível a novos pesquisadores devido também a potencialidades de novas pesquisas a serem desenvolvidas. Com a perspectiva de inovação para o setor e com aporte tecnológico em ascensão, é necessário um olhar especial para questões instrumentais e de medidas, uma vez que é necessário também assegurar a qualidade da tecnologia nuclear para o desenvolvimento de qualquer sistema voltado a essa temática. Essa pesquisa apresenta uma combinação de diferentes áreas, evidenciando a multidisciplinaridade da construção, visando obter aporte necessário para criação de um dispositivo com capacidade de interagir com sistemas que representem ameaças químicas e radiológicas-nucleares. Por se tratar de um biossensor, apresenta uma interface biológica sensível a agentes químicos de guerra (organofosforados), neurotoxinas e a sofrer um processo análogo à radiólise, é o meio pelo qual é possível associar uma eletrônica ao sistema sendo capaz de transdução de informação numa forma de energia em outra, sendo possível quantificar e obter informações relevantes e proporcionais sobre a exposição desse sistema criado. Para o estudo *in silico* realizado as flutuações de energia tanto para as simulações químicas quanto para as simulações em MCNP foram norteadores no processo de verificação, uma vez que, menor o valor de energia, mais forte a interação química entre ligantes e enzimas.

Palavras-chave: Inovação; Biotecnologia; Radiações; Guerra Química; Biossensor.

1. INTRODUCTION

The development of technologies has always been gaining prominence due to its great potential to meet demands closely linked to exposed weaknesses. These needs may be related to applications in energy, medicine, radiopharmaceuticals and curative, interventional and diagnostic health, applications in the areas of security and defense, food technologies, academic development, among others. The use of applied nuclear physics and nuclear chemistry opens up a set of great possibilities due to the capacity for interaction between the development of new instrumentation and countless other possibilities. The combination of applied nuclear physics and integrated biological systems allows us to convert one form of energy into another, based on the reading of a transduced biological signal, for example, an initial purely chemical signal into an electrical signal [1].

The ability to detect or sense chemical warfare agents and ionizing radiation in the same device is something new; there are no records of a device or tool with such descriptions. In addition to increasing national autonomy on the subject, in view of minimizing costs as an essential engineering parameter, it corroborates ideas on nuclear safety, microstructure applications, nuclear engineering applications, efficiency, quality (sensitivities), response capacity in incident scenarios, and others. The development of new biosensors with versatile applications shows new possibilities, being able to act in the characterization of chemical warfare agents (such as organophosphate detection), neurotoxic toxins, and ionizing radiation.

Acetylcholinesterase is an enzyme involved in the degradation of the neurotransmitter acetylcholine, and is widely distributed in living organisms [2] and is responsible for the transmission of neural impulses.

In view of this, the idea behind this research is the possibility of combining knowledge from different areas, such as nuclear physics, nuclear chemistry, physical chemistry, biochemistry, biotechnology, electronics and other possibilities, with the aim of developing

materials necessary for the creation of a new biosensor. The aim is to carry out *in silico* molecular modeling studies to create a solid perspective, shortening the path to laboratory experimentation.

2. MATERIALS AND METHODS

In this work, the biosensor with potential application for detecting organophosphate compounds and ionizing radiation will be developed in three stages: the first stage by theoretical studies, the second stage by molecular modeling studies (docking) between a biological receptor (molecular target) and the compounds of interest, using molecular mechanics, in the case of chemical warfare agents, and quantum calculations, in the case of ionizing radiation using computational simulation with the MCNPX code (general-purpose Monte Carlo radiation transport code, continuous energy, generalized geometry, time-dependent) and Vised software, which is a visual editor for MCNPX. The results of the in silico studies will serve as a starting point for the construction of the biosensor (which is the third stage of this study). (a) The first stage consists of molecular docking studies between the enzyme acetylcholinesterase with the main QFAs and two Aflatoxins (B1 and M1). These agents are organophosphate compounds and aflatoxins capable of inhibiting the molecular targets in question and causing cholinergic syndrome in humans and animals. For this purpose, the receptor model was constructed and validated from crystallographic structures deposited in the Protein Data Bank (Computational Structural Models (CSM))[3]. The three-dimensional structure of the organophosphates and toxins were constructed and the partial atomic charges were calculated using the Spartan'08 program (Version 08 ®, Wavefunction, Irvine, CA, USA, collaboration with Q-Chem, 2009)[4]. Figures 01, 02 and 03 (present in the next chapter) represent the three-dimensional structural formulas of the organophosphates Ciclosarin and Tabun constructed in Spartan'08. Then, docking studies were performed using the Molegro Virtual Docker (MVD) ® program (version 6.0, CLC bio, Aarhus, Denmark, 2013)[5], and the results were evaluated according to the interaction energy and residues interacting with the enzyme. This modeling stage was carried out in the Laboratory

of Molecular Modeling applied to Chemical and Biological Defense (LMDQB) of the Chemical Engineering Section of IME; - (b) second stage, was carried out for the purpose of detecting ionizing radiation. Computer simulations were performed using the MCNPX code (general-purpose Monte Carlo radiation transport code, continuous energy, generalized geometry, time-dependent) (MCNPX EXTENSIONS VERSION 2.6.0, Los Alamos National Laboratory, 2008)[6]. The code generated in MCNPX had its geometry evaluated using the Vised software (which is an extension of the MCNPX code). This simulation step was performed at the Nuclear Simulation Laboratory (LSN) of the Nuclear Engineering Section of IME; (c) the third step will be the construction of the biosensor, using the previous results as a starting point.

For signal interpretation, the mathematical correlation that can be used directly, correlating [Cal] and [eV] in the form:

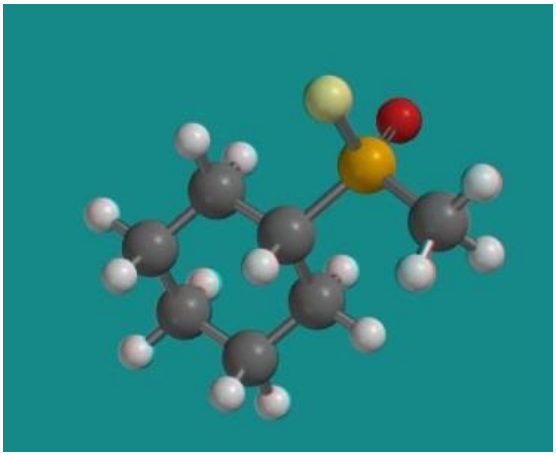
$$\frac{4{,}18\ [\mathrm{J}]}{1\ [\mathrm{Cal}]} * \frac{1\ [\mathrm{C}]}{34\ [\mathrm{J}]} * \frac{1\ [\mathrm{íon}]}{1{,}6 \cdot 10^{-19}\ [\mathrm{C}]} * \frac{34\ [\mathrm{eV}]}{1\ [\mathrm{íon}]} \quad (1)$$

3. RESULTS AND DISCUSSIONS

It is possible to address the agreement of the results obtained through computer simulations, from the creation of organophosphate molecules and toxins, such as chemical warfare agents (CWA), in addition to simulations via MCNPX resulting in information that characterizes a representative model.

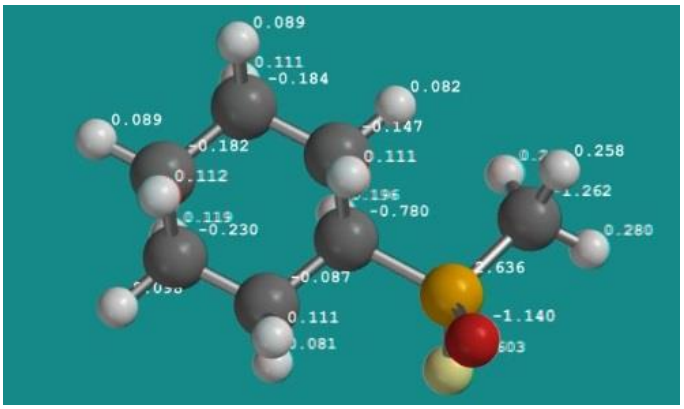
To visualize the creation of systems: Figures 01, 02 and 03 related to some organophosphates created for molecular modeling and Figures 04, 05 and 06 visual geometries for simulation in MCNPX.

Figure 01: Cyclo-Sarin.



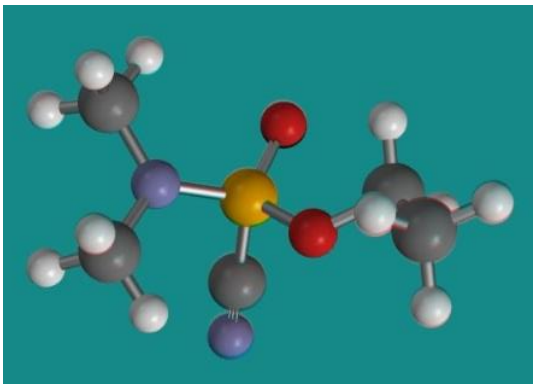
Source: Prepared by the author.

Figure 02: Cyclo-Sarin with charges.



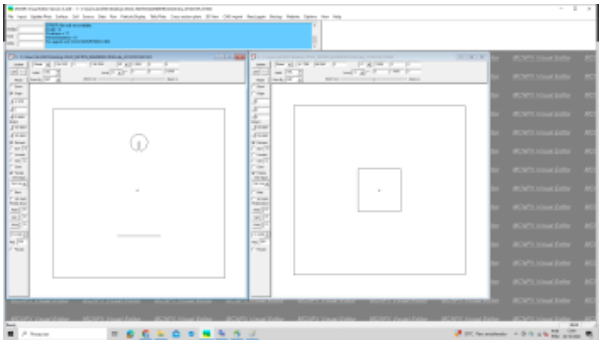
Source: Prepared by the author.

Figure 03: Tabun.



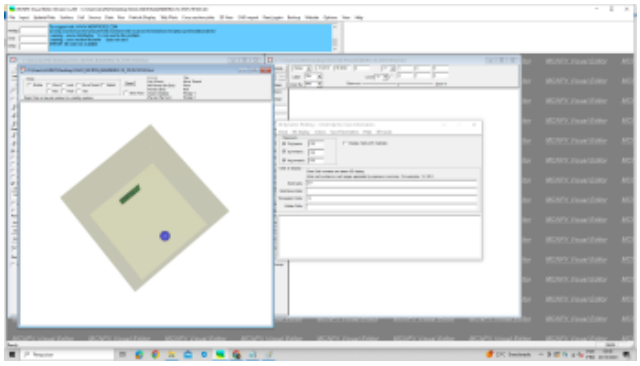
Source: Prepared by the author.

Figure 04: 2D VISED System.



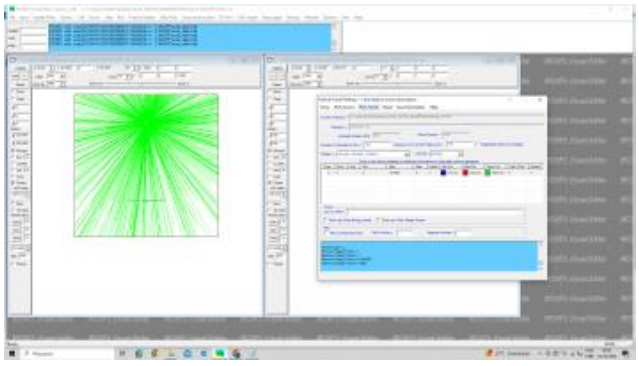
Source: Prepared by the author.

Figure 05: 3D VISED System.



Source: Prepared by the author.

Figure 06: 3D VISED System Simulation.



Source: Prepared by the author.

By focusing on the schematic representation, it is possible to verify a certain trend among the resulting data, from the dispersion of energy around a given target, the absorbed

energy, the energy by the Compton effect, scattering and other properties. Table 01 presents the results of the interaction energy between the compounds studied with the enzyme acetylcholinesterase and with the main hydrogen bond residues. The distance between the compounds and the residues of the catalytic triad of the enzyme was also evaluated.

Table 01: Better Results of Interactions between Ligands and AChE.

Molecule	Score [kCal/mol]	Distance [Å]	Residue
Ciclosarin	-64,23	3,24	Ser - 203 / Gly - 122
Sarin	-57,82	3,55	Ser - 203 / Gly - 122
Soman	-61,03	3,31	Ser - 203 / Gly - 122
Tabun	-58,84	3,97	Ser - 203 / Gly - 122 / Ser - 125 / Tyr - 124
VR	-100,21	3,10	Ser - 203 / Gly - 122
VX	-94,73	3,41	Ser - 203 / Gly - 122
Novichok - A230	-81,18	3,15	Ser - 203 / Gly - 122
Novichok - A232	-78,44	3,12	Ser - 203 / Gly - 122
Novichok - A234	-85,50	3,31	Gly - 122
Novichok - A242	-99,24	3,28	Tyr - 124 / Gly - 122
Novichok - A262	-109,24	3,22	Ser - 203 / Gly - 122
Aflatoxina B1	-138,79	XX	Tyr - 124 / Tyr - 337
Aflatoxina M1	-139,06	XX	Tyr - 124 / Ser - 125 / Tyr - 337

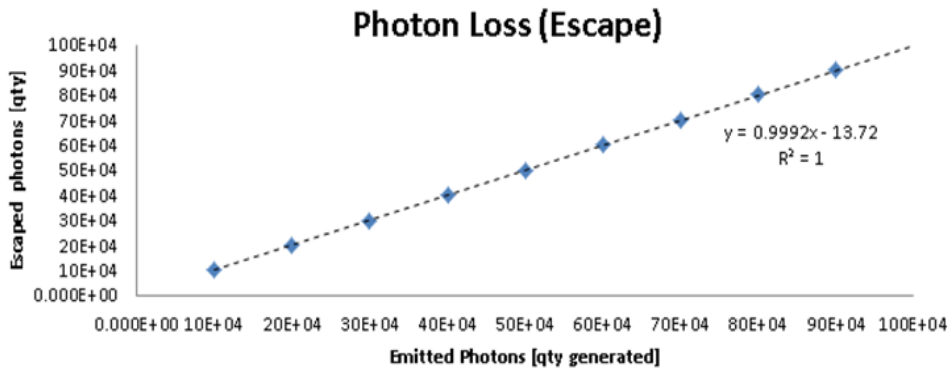
Source: Prepared by the author.

It is possible to verify from table 01 that the results suggest a strong inhibition of the AChE enzyme due to the proximity of organophosphates and aflatoxins in its active site, since the fluctuation in energy presented in Kcal/mol is extremely relevant, causing the inactivation of the enzyme. By selecting the most promising results (organophosphates VR and Novichok-A232 and Aflatoxin M1 toxin) we can infer that when there is a phosphate group in the composition of the ligand, the interaction residue becomes the molecular target which is responsible for the hydrolysis of acetylcholine, undergoing a rearrangement and preventing this hydrolysis process from happening, resulting in an increase in acetylcholine in the system, impairing the propagation of nerve impulses.

Figures 07 and 08, below, show the amount of particles generated, the amount of particles that escape (do not collide with the target) and those that are captured, for ERN

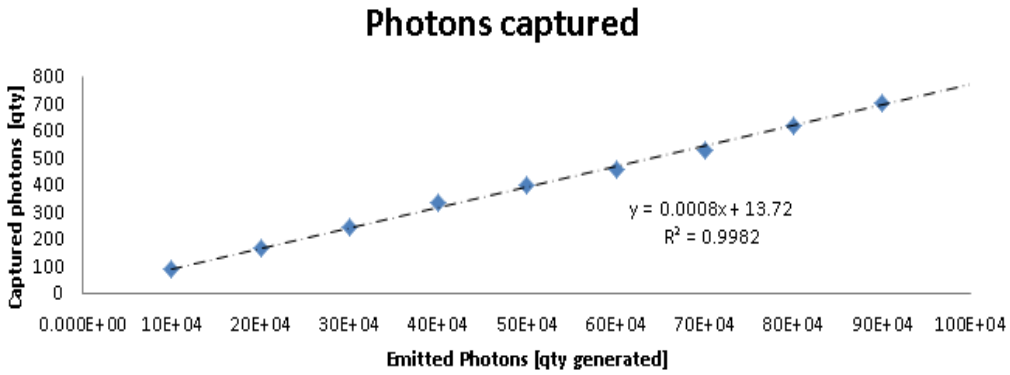
evaluation, the figures (07 and 08) show this information, created with the MCNPX code for simulated study as well.

Figure 07: Photon tracking (lost).



Source: Prepared by the author.

Figure 08: Photon tracking (captured).



Source: Prepared by the author.

Figures 07 and 08 present the results obtained in simulations with the MCNPX code, making evident a linear distribution of simulation data [7], highlighting the low probability of interaction between photons and the biosensor under development. This linearity suggests that the rate of photons detected by the biosensor is proportional to the intensity of the incident radiation, and the low probability of interaction indicates that the majority of photons generated are not absorbed by the control volume. Considering that photons that do not interact with the biosensor are not absorbed, it is plausible to infer that they remain

in the environment and may be subject to other effects of ionizing radiation. This finding raises questions about the sensitivity and specificity of the biosensor, in addition to the implications of the presence of undetected photons.

In this way, when working with radiation, which are statistical phenomena, it is possible to relate the behavior of the system in relation to the amount of energy deposited on the study plate (target) that represents the biosensor interface, if with this energy deposited in the medium It will be possible to quantify how this interaction will emit a response signal and the proportionality of the signal. These variables are tools for an empirical evaluation, but are partially predictable with a well-modeled and representative study system, once the amount of energy of the particles is known, the other variables corroborate to delineate the entire system.

4. CONCLUSIONS

The research and data point towards the formalization and materialization of the prototype, since a subtle variation in the electrical potential can be measured, and conclusions and inferences can be made. This can generate significant impacts, both due to its innovative potential and as a resource to be used in the field in relation to systems that use radionuclides for other studies. The results obtained so far indicate that the proposed equipment has the potential to perform detection quickly, accurately and at a lower cost due to its high sensitivity, contributing to the development of national technology.

For this observed data set, the results obtained regarding the interactions of the models of interest, selecting the most prominent poses being organophosphates VR and Novichok-A232 and Aflatoxin M1 toxin for AChE (Acetylcholinesterase), with Pi - Ser203 distances respectively 3.10 Å and 3.12 Å with energy fluctuations of -100.21 [Kcal/mol], -78.44 [Kcal/mol] and -139.06 [Kcal/mol], shows that the presence of the phosphate group in the ligand composition makes it an excellent nucleophile, promoting a stronger interaction with

Ser203 and the fact that it presents a negative sign as shown in Table 01 reinforces the idea of attraction, making enzymatic inhibition by the interaction of the organophosphate favorable.

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