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14-3-3 Proteins and neurodegenerative diseases: A computer simulation perspective

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— Abstract—

Neurodegenerative diseases are defined as the set of ailments that affect the neurons of the nervous system. Examples of these neurodegenerative diseases are Parkinson's Disease, Alzheimer's, and Amyotrophic Lateral Sclerosis (ALS). These diseases cause mental functionality and movement problems, which are weakening and incurable.

You have heard about these ailments, which are commonly studied in a clinical-experimental way. The health sector is making several efforts to find a treatment for such diseases. These efforts are focused on both experimental and theoretical research. But neurodegenerative diseases can also be studied by using computational tools.

Nowadays, computers are an essential ally in searching for solutions to many of the issues affecting our society, specifically, problems related to public health. To take advantage of this tool, a vast range of computer algorithms have been developed. These algorithms are the way we want the computer to do the tasks to solve a problem.

To study neurodegenerative disease's molecular origin, tools, such as molecular dynamics simulation, have been developed from a computational perspective. Molecular dynamics simulation aims to mimic a system's behavior on a computer; in this case, the system would be biological, for instance, a protein in a lipidic brain membrane environment.

Keywords:

Neurodegenerative Diseases; Molecular Dynamics; Proteins.

Neurodegenerative disease is one in which there is cell death, which causes wear and tear of nerve tissue. Neuronal death can be caused by small lesions caused anywhere in the nervous system (Williams, 2002). Some examples of the most common neurodegenerative diseases are amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Crutzfeld-Jakob disease, and Parkinson's disease.

Neurodegenerative diseases cause problems with movement and mental functioning; they are debilitating and incurable. In addition, they share characteristics such as unknown cause, multifactorial origin, non-specific initial symptoms with multiple forms of presentation, and different degrees of disability, affecting the person's quality of life (Amor, Puentes, Baker, & Van der Valk, 2010).

Currently, there is no cure for neurodegenerative diseases, but there are pharmacological treatments that help stop the progression of the disease and control symptoms. In addition, another key point is rehabilitation with physical and occupational therapy. In this way, a better quality of life for the patient can be ensured (Research, 2019). In these diseases, many times certain proteins are involved. You may have heard about proteins since high school, which are macromolecules formed by linear chains of amino acids and are particularly important in different biological processes (Figure 1, representation of an amino acid chain).

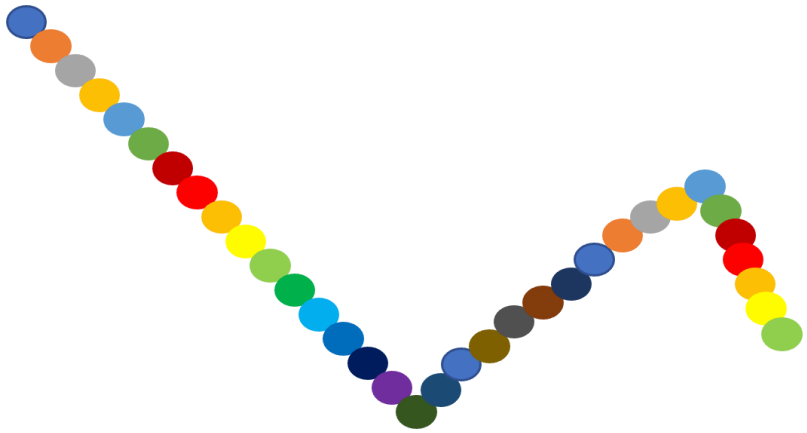

Figure 1. Representation of an amino acid chain. Source: Own elaboration

Efforts have been made in *postmortem* studies to improve diagnoses and detect biochemical markers related to these diseases. A biochemical marker can be defined as any protein, hormone, or substance that is detected in body fluids or tissues. Inside the biochemical markers, 14-3-3 proteins and the amyloid-beta protein were found, to name a few (Foote & Zhou, 2012).

So, some of the proteins mostly related to neurodegenerative diseases are 14-3-3 proteins, which are a family that is mostly expressed in the brain and have seven isoforms (this word refers to different forms of a protein) which are: β, γ, ε, η, ζ, σ and τ/θ. 14-3-3 proteins are involved in biological processes such as signal transduction, apoptosis, neuronal development, and the cell cycle, and have been linked to some neurodegenerative diseases (Foote & Zhou, 2012).

A COMPUTATIONAL APPROACH TO THE STUDY OF NEURODEGENERATIVE DISEASES

As we have mentioned before, there are several ways to study neurodegenerative diseases. One of them is from the experimental point of view and another can be from the computational point of view, for example, through the computational simulation method known as molecular dynamics. The computational simulation aims to reproduce on a computer the behavior of a system, in this case, the biological system. For example, the behavior of a certain protein related to neurodegenerative disease. Figure 2 illustrates that computational simulation occupies an intermediate place between theory and experiment and, therefore, is very often also known as a computational experiment with which conditions can be achieved easily that, in the experiment, would be exceedingly difficult or expensive.

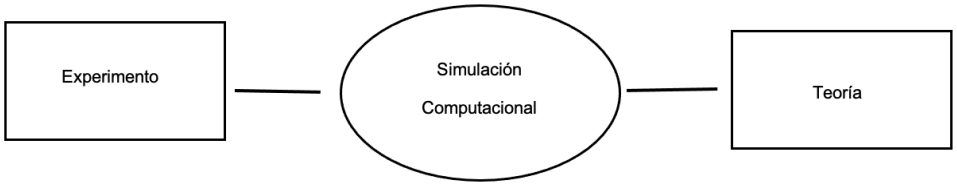

Figure 2. Computational simulation lies between experiment and theory. Source: Own elaboration

Molecular dynamics is a technique in which molecules are described as linked point objects that can have electric charge, and magnetic dipole moment, among other physical properties. This technique describes the temporal evaluation of bonds, bond angles, torsions, and interactions modeled by a force field, which is represented by equations that characterize an interaction potential (Maldonado Arce, *et al.*, 2016).

Although there are computational tools for the study of neurodegenerative diseases and corresponding biological systems, such as a model brain membrane, a computational simulation study has not yet been carried

out using the method of molecular dynamics of a model brain membrane and its interaction with a 14-3-3 protein.

Now we will briefly describe some of the best-known neurodegenerative diseases, some studies using molecular dynamics of these diseases, and the potential role of 14-3-3 proteins in the pathogenesis of these diseases.

Alzheimer's disease accounts for one of the most common neurodegenerative diseases (WHO, 2020). Alzheimer's disease is the most usual form of senile dementia. As reported in the United States, 5 million people were affected by this disease, and globally, the figure was 25 million people (WHO, 2020). While, for the specific case of Mexico, according to data from Gutiérrez Robledo *et al*., 800,000 people suffered from Alzheimer's in 2014 (Government of Mexico, 2017).

The affected areas of the brain observed in Alzheimer's disease can be the hippocampus and areas related to olfactory and visual pathways. The main symptoms of this disease include memory loss, poor learning in general, and dementia (Cummings & Cole, 2002). This disease is characterized by two important pathological aspects: amyloid plaques, which are those formations between the interneuron spaces of the brain's gray matter that serve as a deposit of l peptide amyloid-beta, and neurofibrillary tangles, composed of fibrils intertwined in neurons, which in the case of Alzheimer's are proteins formed of small fibers between neurons. It has been reported that 14-3-3 proteins are related to Alzheimer's disease, based on their location near the neurofibrillary tangles, and thus the interaction of proteins related to the development of the disease occurs (Foote & Zhou, 2012).

However, the causes of Alzheimer's disease are not yet known, but there are several hypotheses such as metabolic disorders, acetylcholine deficiency, and the accumulation of amyloid β-proteins, 14-3-3 proteins, and neurofibrillary tangles (Foote & Zhou, 2012). The first hypothesis relates the development of the disease to metabolic disorders such as hyperglycemia (high blood sugar) and insulin resistance (Gualdrón & Ávila, 2007). The second hypothesis, the deficit of acetylcholine, is the oldest in the development of Alzheimer's disease; many of the current treatments are based on this hypothesis. This hypothesis suggests that Alzheimer's is caused by the reduction of acetylcholine, a neurotransmitter (Ferreira-Vieira, Guimaraes, Silva, & Ribeiro, 2016). Finally, hypotheses arose linking the accumulation of amyloid β-proteins, 14-3-3 proteins, and neurofibrillary tangles in the brain.

To study the composition of the brain, how it is related to neurodegenerative diseases, and the proteins related to these diseases, there are both experimental and computational methods.

The molecular dynamics can be accompanied by different models depending on the spatial or temporal scale that interests us. To study bio-

logically relevant systems without losing structural details, coarse-grained models represent a suitable alternative. These models reduce the number of atoms and, therefore, the computational cost of the system. What is done in a coarse-grained model is to represent a certain number of atoms with a pseudo-particle.

Thus, for example, we can cite the study conducted in 2017 by Ingólfsson *et al.*, where they used the coarse-grained model known as Martini, to develop and examine a model of a lipid brain membrane such as the one illustrated in Figure 3, and this was compared with a mammalian plasma membrane. Compositional differences between the membranes showed complementary influence on many of the bilayer's properties.

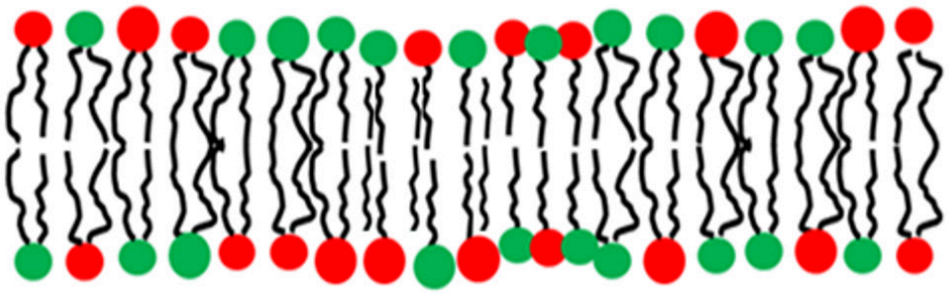

Figure 3. Representation of a biological membrane. The hydrophilic heads are red and green, while the hydrophobic tails are black. Source: Own elaboration

Now, continuing with the most common neurodegenerative disease is Parkinson's disease, which is progressive and one of its symptoms is tremors, which begin imperceptibly, but later cause damage such as:

- Stiffness
- Balance Problems
- Impairments in speech and writing
- Decrease in the movement of the affected person

This disease is characterized by dementia caused by Lewy bodies, which are abnormal aggregations of proteins that contribute to the development of the disease and the loss of the neurotransmitter dopamine. 14-3-3 proteins are related to the disease due to their localization concerning other proteins that also are related to their development and the binding with these proteins. It has been observed that this disease is caused by the gradual death of neurons that produce dopamine. The latter is a chemical messenger, which when decreased causes an abnormality in the activity of the brain, which leads to the development of Parkinson's disease (Foote & Zhou, 2012).

It has also been reported that amyloid β- and α-synuclein, both of which are intrinsically disordered proteins, are closely related to Alzheimer's and Parkinson's diseases. For the study of these proteins and diseases, both experimental and computational techniques have been used; for example, Coskuner-Weber & Uversky (2018) reported that nonsense mutations can be used in computer simulations to better study the relationship between Parkinson's disease and the amyloid β and α-synuclein proteins.

In another study, Herrera (2008) reported by computer simulation, the relationship between the interaction of α-synuclein and dopamine. Which, as mentioned above, are related to Parkinson's disease. In this work, we used the technique of molecular dynamics with the force field known as Amber99. Within the results of the study, it is suggested that dopamine ligands bind at a c-terminal end of the protein α-synuclein.

Another of the most common neurodegenerative diseases is Crutzfeldt-Jakob disease, which causes decreased movement and loss of mental function. The types of this disease are 3 and are mentioned below:

- Sporadic type that occurs in unknown situations
- Familiar type
- And finally, the acquired form

Crutzfeldt-Jakob disease may be related to other diseases such as rare human hereditary diseases (such as fatal familial insomnia). In an article, reported by Shamsir & Darby (2005), it is mentioned that these diseases are related to a mutation in codon 178 (sequence of 3 nucleotides of DNA or RNA), but that they differentiate from each other by a polymorphism in codon 129. Using molecular dynamics, these authors investigated the effect of mutation on codon 178 and polymorphism on codon 129.

Regarding the same disease, it may be related to other exceedingly rare human hereditary diseases, such as kuru and fatal familial insomnia. Finally, it has been observed that there is a variant of Crutzfeldt-Jakob disease that triggers mad cow disease (Will *et al*., 1996).

CONCLUSION

Among the different studies that have been carried out on neurodegenerative diseases, some have been through experimental techniques and some others with computational techniques, such as the simulation of molecular dynamics or Monte Carlo. For example, through computational simulations, proteins and ligands related to neurodegenerative diseases have been studied.

Despite the aforementioned studies, a computational simulation study has not yet been carried out using the molecular dynamics method of a model brain membrane and its interaction, for example, with 14-3-3 proteins related to neurodegenerative diseases. The current availability of both theoretical and computational resources allows us to carry out studies of, for example, the interaction of the isoform 14-3-3 tau with a model brain membrane. We are currently developing this type of study.

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