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# Self-Assembly of Amyloid-Beta and Its Piezoelectric Properties

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## Abstract

Investigating amyloid nanofibril self-assembly, with an emphasis on the electromechanical property of amyloid peptides, namely, piezoelectricity, may have several important implications: 1) the self-assembly process can hinder the biological stability and give rise to the formation of amyloid structures associated with neurodegenerative diseases; 2) investigations in this field may lead to an improved understanding of high-performance, functional biological nanomaterials, 3) new technologies could be established based on peptide self-assembly and the resultant functional properties, e.g., in the creation of a piezoelectric device formed with vertical diphenylalanine peptide tubes as a piezoelectric biosensor, and 4) new knowledge can be generated about neurodegenerative disorders, potentially yielding new therapies. Therefore, in this review, we will present the current investigations associated with self-assembly of amyloid-beta, the mechanisms that generate new structures, as well as theoretical calculations exploring the functionality of the structures under physiological pressure and electric field.

## Keywords

Amyloid, Neurodegenerative Disorders, Self-Assembly, Piezoelectricity

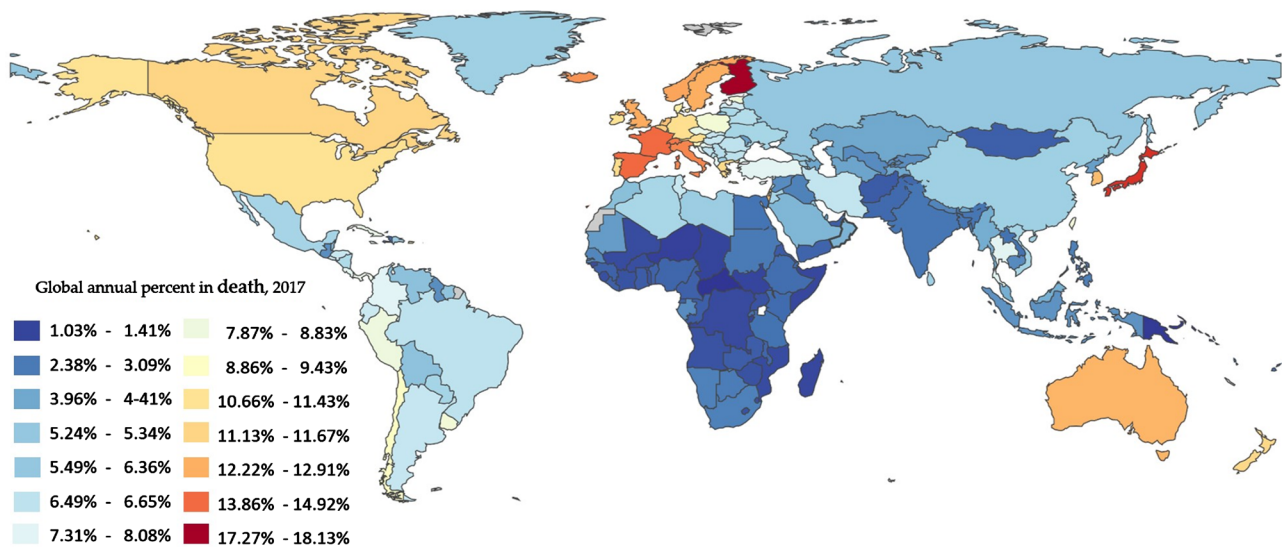
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## 1. Introduction

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease,

Huntington disease, and others [1] [2] are diseases with worldwide prevalence associated with the disruption of signaling pathways at the neuronal level and linked to the elderly population of countries with high longevity, **Figure 1**. The interaction of amyloid fibril deposits with cellular components is said to be responsible for these disorders; since amyloids have an essential physiological role in lipid homeostasis. Modifications to the self-assembly properties or molecular stability of amyloids [3] can result in the formation of amyloid fibrils that completes the self-assembly process in the cell membrane [3] [4]. In the study of the cause of neurodegenerative disorders, several approaches can be established, such as assembling the amyloids with lipids, since other neuronal factors change with the presence of amyloids, as has been discovered for soluble fractions of lipids or potassium voltage-gated channels [5]; additional experiments showed a change in the aggregation of the amyloid molecules when interacting with other biomacromolecules. These observations, for instance, indirectly show that lipids and voltage-sensitive peptides modify the structural and aggregation properties of the amyloids. These prior studies required molecular biology methods, followed by complex physiology measurements. From our perspective, the formation and properties of those complex molecules might be controlled by the interaction with lipids and voltage-dependent peptides. Such assemblies may have some biofunctional role, especially if the possible interactions between voltage-gated channels and voltage-sensitive peptides are taken into account [6].

The presence of phenylalanine fragments is of vital importance for the self-assembly [7] since according to molecular modeling, dipole moments are detected in amyloid derivatives as diphenylalanine (FF) [8] suggesting that the three-dimensional ordering (self-assembly) might produce an electromechanical response as reported by Kholkin *et al.*, [9] in nanotube-type auto-assemblies



**Figure 1.** Distribution of annual percent of neurodegenerative diseases at the global level available until the year 2017, according to the Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2018. Available from <http://vizhub.healthdata.org/gbd-compare> (Accessed: December 9, 2019).

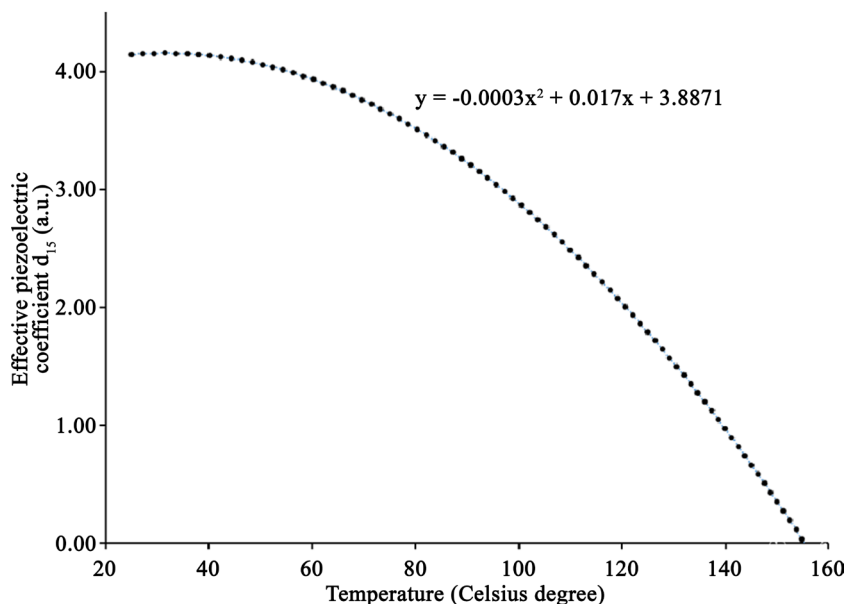
with a high effective piezoelectric coefficient of at least 60 pm/V. These electromechanical properties of macromolecular self-assemblies are of primary importance, for instance, in the synthesis of new organic ferroelectric, piezoelectric nanostructures fundamental to the creation of a new class of materials from biomedical up to electronic biocompatible “green” or “ecological” memory devices [10] [11], the understanding of which can serve as the basis to produce organic and organic-inorganic self-assembled micro and nanomaterials. In order to define the role of the external factors on the assembly of amyloids, it is necessary to study the electromechanical properties as tunable features in the amyloids.

## 2. Self-Assembly

Self-assembly is a common molecular-scale phenomenon found in the organic, inorganic, and hybrid matter, and is ubiquitous where the interplay of polar and non-polar local interactions coexists [12]. Piezoelectric properties in the self-assembly of organic molecules [9] is a fascinating process that has inspired recent molecular approaches to micro- and nanodevice design [13] as well as biomimetic approaches [14] to the design of drugs to target the formation of plaques associated with diseases like Alzheimer’s [15] [16]. Self-assembly of peptides and greater control of functional morphogenesis is a complex process and likely self-assembly processes are strongly governed by biological and physico-chemical factors [17]; therefore, understanding intrinsic and extrinsic factors on amyloid self-assembly is a vital step towards a promising route of exploiting self-assembled structures in nanotechnologies [18]. For example, the biological stability of some peptide domains under different thermal conditions and environments (*i.e.*, vacuum) might also be found in amyloids.

At the present time, determining the exact role of each factor and the degree of integration of the different processes is difficult to achieve [19], but various targeted studies have suggested their importance. With the identification of active regions for self-assembly in the amyloid peptide (diphenylalanine “FF” region), new tubular organic structures have been successfully synthesized [17] [20] [21].

It should be noted that the role of the active regions was determined by *in vitro* experiments as one of the possible mechanisms responsible for the formation of amyloid in tissues, which leads to disease formation. On the other hand, based on chemical and computational studies [8], it was determined that an important part of the stability of the self-assemblies originates in the pi-pi stacking of the hydrophobic FF regions [16] [22] and whose piezoelectric properties decrease according to a second-order polynomial function with temperature, accompanied by an irreversible phase transition towards another crystalline phase as reported by Heredia *et al.* [8] (**Figure 2**). Self-assembly processes may lead to the formation of the well-known hierarchical structure of beta amyloids [23] and similar complex macromolecules [4]. Studying the self-assembly process is crucial to understand its mechanism since it may become possible to hinder



**Figure 2.** Behavior of effective piezoelectric coefficient  $d_{15}$  of diphenylalanine peptide nanotubes with respect to the temperature, according to the results reported by Heredia *et al.* in “Temperature driven phase transformation in self-assembled diphenylalanine peptide nanotubes”.

the development of amyloid structures associated with diseases and to exploit the design of new technologies based on peptide self-assembly and the resultant functional properties, e.g., a piezoelectric device formed with vertical FF peptide tubes as a piezoelectric biosensor [13] [24], for this reason, the stability of the self-assemblies is discussed below.

The feasibility of self-assembly of some amyloid domains is of importance [17] [19] [25] [26] since the synthesis of a piezoelectric peptide-based device is plausible [9]. One of the most used domains is the  $A\beta$ (1 - 40) region because it represents the most abundant  $A\beta$  isoform in the brain [27] and the topographical features of  $A\beta$ (1 - 40) fibrils are thought to play an important role in neurodegenerative disorders and other diseases [28] [29]; works about it have shown that the production rates of  $A\beta$ (1 - 40) and  $A\beta$ (1 - 42) isomorphs are the same or in a higher proportion, and that  $A\beta$ (1 - 42) fragment in neurodegenerative disorders is much more prone to form fibrils [2] [30]. Although initially, the preference for amyloid regions in self-assembly has been chosen based on the ease of self-assembly, in some works based on the optimization of piezoelectric organic structures, revealed a clear effect on the macroscopic amyloids when mixed with other molecules [29] [31] [32].

### 3. Self-Assembly in Water

In the past century, tubular  $A\beta$  structures were studied by Max Perutz [29] who established that encased water molecules should be of main importance for their biological activity. Indeed, water molecules are responsible for the electromechanical behavior in some amyloid structures [33] [34]. Initial experiments using atomic

force microscopy (AFM) of different biostructures in liquid [35] and air [36] environments on different substrates [37] described the different self-assemblies observed, including peptides. Solutions of the amyloid peptide are commonly dissolved in fluorinated alcohol (1,1,1,3,3,3-hexafluoro-2-propanol) and then self-assembled in another solvent [38] [39] to form fibers with around 10 nm diameter depending on the pH, *v. gr.*, distilled water (Milli-Q) to obtain fibrils (PBS, pH 7.4, 37°C) [40].

Organic molecular self-assembly in water or at solid surfaces is a well-known phenomenon governed by the interplay between molecule–molecule and molecule–substrate interactions, which can be tailored by varying molecular building blocks, ion strengths, surface chemistry, and structure, as well as substrate temperature [12] [14] [38]. Indeed, one of the questions in the study of self-assembled organics is the role that water molecules play at the surface or inside self-assembled structures [29], being a precedent in these studies is the identification of electromechanical properties in diphenylalanine nanotubes [9].

The self-assembly of amyloid nanofibril in aqueous solutions has been investigated in detail as a function of ion concentration, temperature, and lipid and amino acid incorporation to determine the mechanism of electromechanical coupling in organic macromolecular assemblies [41] [42] and the pathway to optimize and exploit this functional property of inherently biocompatible materials, like in collagen-apatite at the nanoscale [43]. Organic supramolecular structures are easily fibrillated from water solutions to produce self-assembled organic piezoelectric nanostructures. Controlled self-assembly conditions *e.g.*, temperature, pH [26], have been previously used to describe the physicochemical effect on the fibril nanostructure by mean infrared spectroscopy (FTIR) [44]. That is important since in the modality of Attenuated Total Reflectance (ATR-FTIR) FTIR is applied to know the evolution in the secondary structure of the molecules as a method described by Dave *et al.*, using the amide I band position [45]. The presence of amide II and I FTIR might substantiate an oligomerization process of prebiotic relevance. However, it also is important to consider structural factors in the role of the origins of piezo- and ferroelectricity. These electromechanical and electrical properties studied through nanoscale measurements are required to develop an accurate biophysical description, that can be achieved by a high resolution technique as piezoresponse force microscopy, PFM, in which a conducting probe scan the sample surface that allows to determine the morphology and nanostructure of the self-assemblies. PFM is a powerful tool for studying piezoelectric and ferroelectric phenomena at the micro- and nanoscale levels. In this method, a sharp conductive scanning probe microscopy tip in contact with the surface is periodically biased, and bias-induced surface displacements are translated into the mechanical motion of the tip, which is measured using the AFM electronics and an external lock-in amplifier. In PFM imaging, both out-of-plane (OOP) and in-plane (IP) displacements can thus be monitored to get insight into the nanoscale piezoelectric

and ferroelectric properties of piezoelectric materials [46].

Experimental investigations provide clues that explain the importance of the physicochemical aspects involved in the observed piezoelectric activity in organic materials, elucidate how these are integrated into biological processes, and provide a route for exploiting such materials in applications. Analysis by AFM-PFM has been applied to self-assembled amyloid peptide structures, complementing other techniques, to characterize at the nanoscale the molecular building blocks ( $A\beta$ , the amyloid peptide) and the formation and characterization of the fibril and further macromolecular assemblies.

#### 4. Electromechanical Properties

Electromechanical activity has been observed in FF peptide structures [8] [9]; however, it is necessary to understand the role of the molecular building blocks themselves on the existence of said activity, in order to i) determine possible peptide-peptide interactions, ii) investigate the use of other organic surfactants for further self-assembly in tubular structures, and iii) quantify the electromechanical response at the nanoscale. For this purpose, it is not only necessary to evaluate the role of ionic strength or thermal changes on self-assembly, but the addition of other molecules such as lipids, amphipathic molecules in the cell membrane, and amino acids must be assessed [47].

In our view, the interactions between amyloid structures and membrane-related molecules such as lipids and voltage-gated channels might elucidate a biofunctional/structural role of the piezoelectric amyloid structures [28]. The observation of multiple conformational states of amyloid fibrils in tubes and wires from the same polypeptide sequence depending on the environmental features (e.g., pH) makes this hypothesis feasible. Furthermore, recent electrophysiology data has measured amyloid-beta toxicity in neurons, inferring an *in vivo* electrical sensitivity of amyloid structures [48].

#### 5. Theoretical Calculations

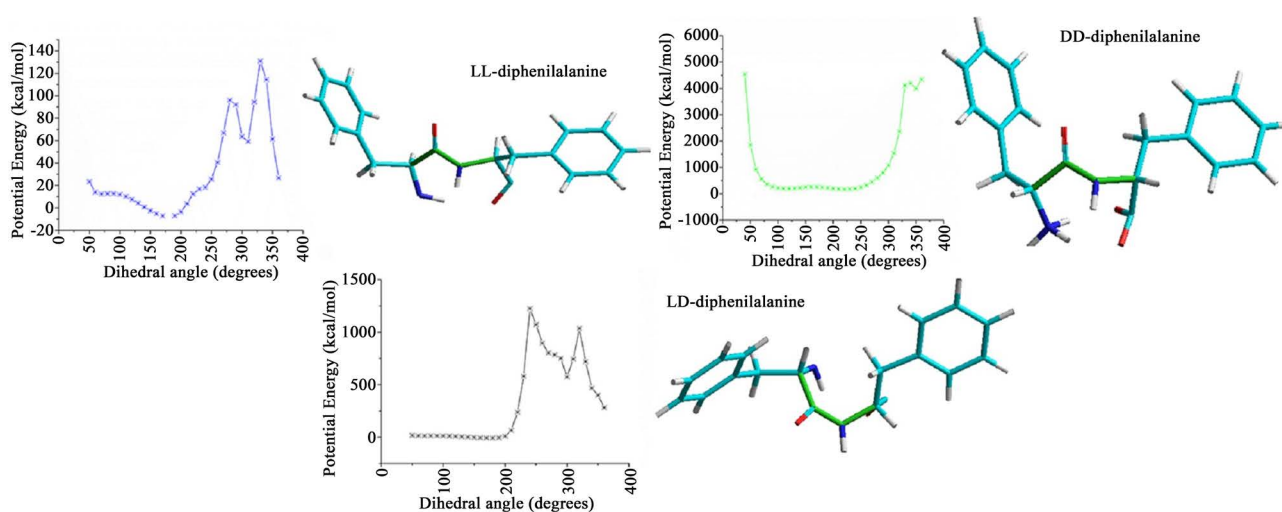
In order to determine that organic piezoelectricity is produced when amyloid biomolecules assemble and that its stability under electric fields change, molecular simulations were performed, similar to those carried by Kell, Brünger, Gupta and Bystrov [22] [49] [50] [51]. Differences in molecular arrangements in the amyloid biomolecules in tubular structures [20] and crystalline packing were considered. In this approach, molecular dynamics simulations were performed with a possible crystal considering the most stable conformations of the dipeptides in chiral LL, LD, and DD conformations. For this analysis, different physicochemical conditions of pressure and electric field were employed (Table 1). Since self-assemblies of FF strongly depend on crystal nucleation, an additional study was performed to find the most stable structural conformation. For this purpose, an OPLS Force Field was used in the Hyperchem software [52] to determine the potential energy of the dihedral angle ( $\omega$ ) that forms the pep-

tide bond from  $0^\circ$  up to  $180^\circ$  (**Figure 3**). The potential energy minima of the dihedral symmetry reached  $-382 \text{ kcal}\cdot\text{mol}^{-1}$ ,  $148 \text{ kcal}\cdot\text{mol}^{-1}$ , and  $386 \text{ kcal}\cdot\text{mol}^{-1}$  for LL, LD, and DD diphenylalanine values, respectively, being the LL chiral dimer is the most stable conformation. Once the most stable molecular configuration was determined (using an ab-initio method on the Polypargen platform [53] [54] [55] [56] [57]), the molecule parameters obtained were introduced in the GROMACS software [58] [59] [60] (OPLS-AA [61] [62]), while molecular dynamics was performed in NTP during 5 nanoseconds with and without pulsed electric fields (**Figure 3**). Then, with this information, it is possible to gain insight into the molecular stability.

More precisely, these results show that the most stable omega dihedral angles are the ones from the LL and DD enantiomers (corresponding to  $120^\circ$ ) whereas the LD-diphenylalanine has an omega dihedral angle of about  $60^\circ$ . With the structural restrictions of these angles, the dipeptides were geometrically optimized

**Table 1.** Calculation of dipole moments and dielectric constants of diphenylalanine crystals, calculated by NPT molecular dynamics of LL and LD dipeptide using the dihedral angle from  $60^\circ$ .

Pressure/Electric field pulsed Z		3 × 3 crystal	5 × 5 crystal	7 × 7 crystal	9 × 9 crystal
760 mm Hg	epsilon	3.74607 <sub>LL</sub>	4.38325 <sub>LL</sub>	13.3933 <sub>LL</sub>	23.3795 <sub>LL</sub>
		2.78112 <sub>LD</sub>	3.00154 <sub>LD</sub>	6.94678 <sub>LD</sub>	1.29688 <sub>LD</sub>
	dipole moment <sup>1</sup>	20.4390 <sub>LL</sub>	20.0439 <sub>LL</sub>	19.8710 <sub>LL</sub>	19.9385 <sub>LL</sub>
		8.27050 <sub>LD</sub>	8.08310 <sub>LD</sub>	8.03820 <sub>LD</sub>	8.20280 <sub>LD</sub>
5 V·nm <sup>-1</sup>	epsilon	5.000985 <sub>LL</sub>	2.47747 <sub>LL</sub>	2.79798 <sub>LL</sub>	4.00701 <sub>LL</sub>
		2.49856 <sub>LD</sub>	2.05219 <sub>LD</sub>	7.88489 <sub>LD</sub>	25.5841 <sub>LD</sub>
	dipole moment <sup>1</sup>	20.8982 <sub>LL</sub>	19.8585 <sub>LL</sub>	19.8533 <sub>LL</sub>	20.0747 <sub>LL</sub>
		8.42840 <sub>LD</sub>	8.0507 <sub>LD</sub>	8.15980 <sub>LD</sub>	8.2554 <sub>LD</sub>

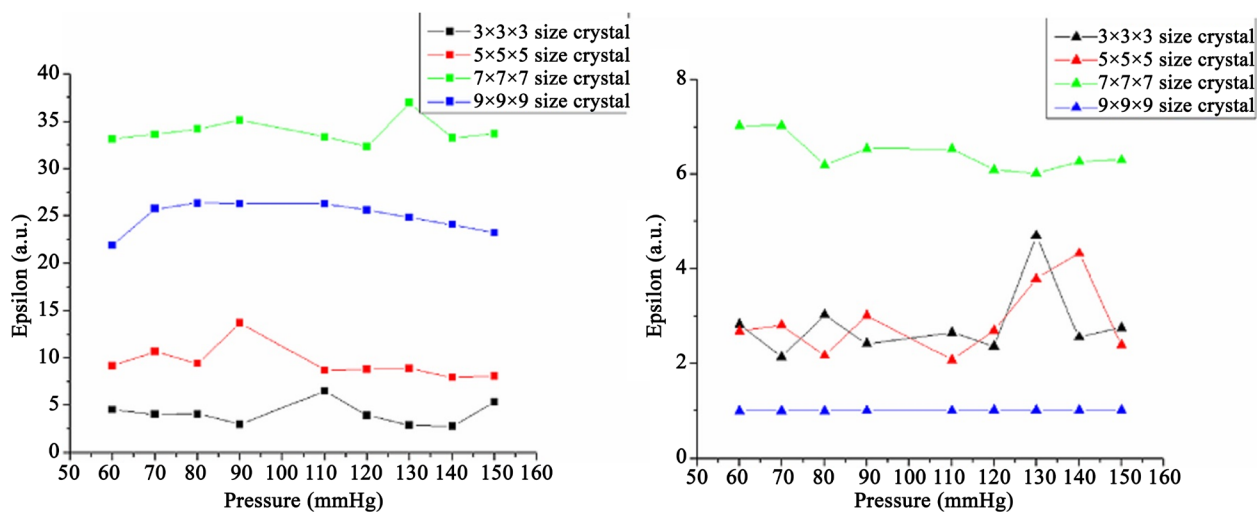


**Figure 3.** Calculation from potential energy twisting omega dihedral angle considering the most stable conformation for the diphenylalanine (FF) dipeptides. Left, LL-diphenylalanine, center, LD-diphenylalanine and right, DD-diphenylalanine.

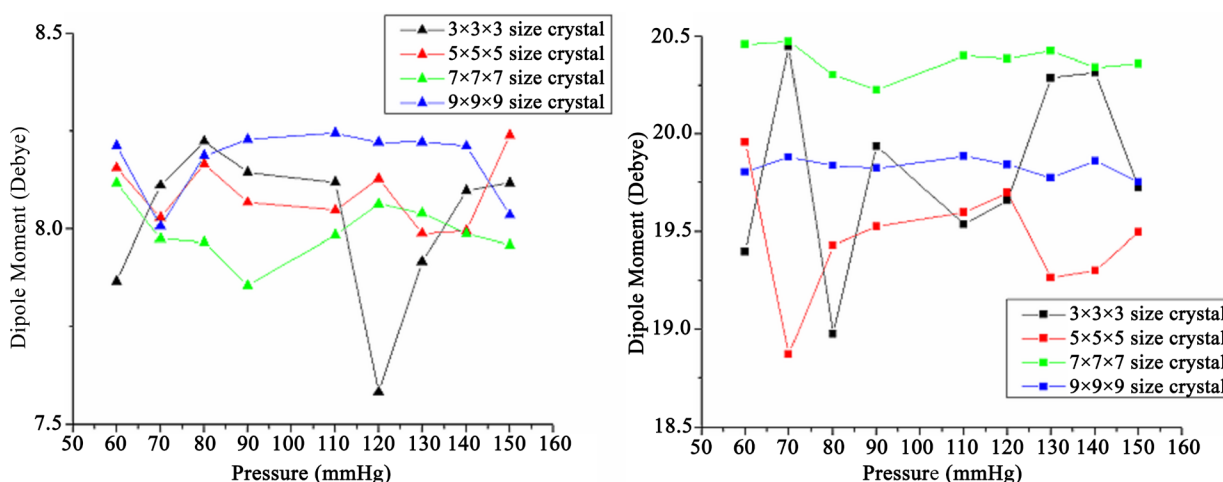
through the Leapfrog integration method (step integrator up to an RMS of 0.01, 2500 steps of 0.001 ps). Moreover, with the purpose to determine the possible piezoelectric properties at isobaric and isochoric conditions, the molecular dynamics simulations were performed in the dipeptide crystal and with no pulsed electric field. Both simulations were compared to determine the possible molecular displacement of the crystals via electric field; these results are displayed in **Table 1**).

In the case of LL-diphenylalanine, it is noticeable that the data distribution function (epsilon value) decreases in the presence of a pulsed electric field, *i.e.* the dipole-dipole interaction is weaker, suggesting a dissociation between the dipoles of the peptides. It is caused by a change in the dimensions by expansion of the crystal slab when an electric field of  $5 \text{ V}\cdot\text{nm}^{-1}$  is applied. On the other hand, in the case of LD-diphenylalanine, since it presents a dihedral angle of less than  $60^\circ$  (**Figure 3**), the aromatic rings separate the neighboring molecules, and therefore the value of epsilon is 5 times smaller than that of the LL molecules (**Table 1**). This fact is also reflected in the dipole moment of the LD crystal since the random interactions in their positions in the dynamics decrease this value drastically compared to those calculated from the LL crystal. The electric field does not significantly modify the parameters epsilon and dipole moment. Additionally, with the minimized energy conformation of crystals, 5 ns NPT dynamics were performed with the OPLS-AA force system for pressures that exist in a human body with pressure around 60 - 100 mmHg and 110 - 150 mmHg, resulting in variations of the average dipole moment values of the crystal and in the epsilon with respect to the pressure, whose results are shown below for the dipeptides.

Considering the simulations in the LL and LD crystals, the molecular dynamics rendered relevant results when the models were subjected to the mentioned pressures (**Figure 4**). The variation in pressure (**Figure 4**) refers to the interaction of a dipole with its neighboring dipole, presenting a tendency to align itself



**Figure 4.** Epsilon behavior of (left) LL and (right) LD dipeptide crystals as a function of pressure.



**Figure 5.** Dipole moments from the simulations (left) LD and (right) LL crystal as a function of pressure.

by increasing the initial crystal size from 5 nm per edge to 7 nm per edge. Moreover, if the edge size continues to increase up to 9 nm, the parameter epsilon presents a decrease; therefore, there is a maximum for which these dipole-dipole interactions are relevant in the crystal behavior. Pressure variations increase the dipolar moment average in LD crystals of  $5 \times 5 \times 5$  and  $7 \times 7 \times 7$  nm of edge, at a pressure of 120 mm Hg corroborate that in these conditions there is a high dipolar moment average due to the alignment of most dipoles in one direction. For LL crystals the piezoelectric behavior presents variations in pressure of 130 mm Hg in the crystals of  $3 \times 3 \times 3$  to  $9 \times 9 \times 9$  nm of edge, **Figure 5**.

## 6. Conclusion

The success of the electromechanical studies allows identifying inhibitors or controllers of the amyloid self-assembly process. Therefore, for the purpose of improving the electromechanical properties, it is necessary to: study the solvent-peptide interactions by tuning the ion strength and thermal conditions during assembly; quantify the electromechanical activity in self-assembled structures; and determine the role of intramolecular forces (arising from the presence of water) on piezoelectricity and mechanism of piezoelectricity and its possible role in amyloid stability as well as the nanoscale structure in different directions (*i.e.*, cross-section, surface) of the amyloid structures; and develop the framework to exploit electromechanical coupling in amyloid-based structures for nano-bio technologies, such as piezoelectric biosensors.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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