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Magnetic molecular dynamics simulations of A2A receptor in solution

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Abstract

In this paper, we present the results of the application of an external static magnetic field with the Velocity Verlet algorithm within Molecular Dynamics simulations of the A_{2A} adenosine receptor protein in solution. Molecular Dynamics simulations allow to understand at molecular level the interaction mechanisms between atoms under specific conditions. Here, for the first time, MD simulations of a receptor protein have been performed in presence of an external magnetic field in order to try to elucidate specific endpoints of interaction with the field.

1. Introduction

Several studies have shown how the use of low frequency magnetic fields may have biological effects on different cells functions. It has been reported that the use of pulsed magnetic fields increases the anti-inflammatory effect of different types of cells such as neutrophils, synoviocytes, chondrocytes and osteoblasts, with significant reduction in some of the most important inflammatory cytokines [1-3]. Much research activity has focused on the mechanisms of interaction underlying such effects, pointing out an involvement of adenosine receptors (ARs) and in particular, showing that pulsed magnetic exposure mediates a significant upregulation of A_{2A} adenosine receptor. Nevertheless, since direct experiments on the action of magnetic fields on transmembrane proteins, as the A_{2A} adenosine receptor, are not easily to be performed, it still remains to be elucidated which is the final endpoint of the exposure.
To this regard, simulations based on Molecular Dynamics (MD) to study molecules behavior, under different physical conditions, may become a strategic tool. MD simulations are usually used to analyze organic compunds, protein structures, membrane patches or ionic solutions subjected to the action of external agents such as thermal or electromagnetic signals [4 - 8].
Recently authors have implemented a procedure to introduce a static homogeneous magnetic field in the Gromacs software, one of the most used environments for MD. The procedure has been tested for very simple targets as charged ions in vacuum and in water solution [9].

In this paper, we want to show the effects of magnetic fields on the behavior of A_{2A} adenosine receptor protein in typical buffer solution, using MD simulations. The core of the numerical solution solved by Gromacs has been modified to take into account the magnetic force acting on single charged particle as reported in [7]. Simulations have been performed either in no field condition or with the application of the field and either for the buffer solution alone or with the A_{2A} adenosine receptor in the buffer solution.

2. Materials and Methods

Gromacs [10] is a versatile software, used in MD simulations, to study molecules behavior under different physical conditions.
To implement the magnetic field, we employed the Velocity Verlet (VV) algorithm firstly proposed in [9], in which the Lorentz force acts on the charged particles, which perform Larmor oscillations at the Larmor frequency when an external magnetic field is applied. In [11] three different methods are reported to solve the motion equations when a static homogeneous external magnetic field is applied. Since we used in our simulations a time step sufficiently small, we adopted the inversion algorithm to solve the equations of positions and velocities, in which the strength of the magnetic field is dependent on the value of the time step, as reported in [9].
For the simulations of the NaCl buffer solutions we have chosen the ionic concentration from experiments (DMEM concentration [1]). MD simulations have been performed in NVT (number of particles, volume and temperature constants) ensemble at a temperature of 300 K using the Nose-Hoover thermostat in a box of 12 x 12 x 12 nm^3 of dimension and with an integration step of 1 fs (Fig. 1a). The gromos45 force field has been used simulating 114 Na^+ and Cl^- ions (reproducing the DMEM concentration of 110mM) and 57577 water molecules. For the adenosine receptor A_{2A} molecular model, the 3PWH PDB structure has been chosen, but in the unbound configuration in order to firstly analyze the protein behavior with no ligand (see Fig. 1b). The adenosine receptor A_{2A} molecule was immersed in the NaCl buffer solution and because of its positive charge (+6e) 6 more Cl- ions were added to the simulations box to neutralize the system.

A total number of 4 simulations of t = 20 ns each have been carried out, two without any external field (only buffer solution (Fig. 1a) and A_{2A} receptor in solution (Fig. 1b) and two with an external value of magnetic induction B = 1T.

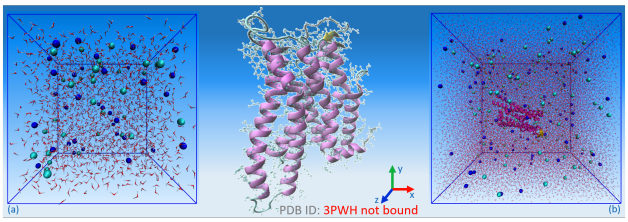

Figure 1: (a) Molecular dynamics model of the Buffer solutions with 114 Na^+ and Cl^- ions and 57577 H_20 molecules. (b) the adenosine A_{2A} receptor (7 transmembrane alpha-helices) on the left and immersed in the buffer solution on the right. The dimension of the box is 12 x 12 x 12 nm^3.

3. Results

Overall results have been examined looking at the diffusion coefficient of the different chemical species within the simulation box. The mobility of water molecules is indicated by the value of the self-diffusion coefficient, which depends on the environment parameters as temperature, pressure or the structure [12]. The values of the self-diffusion coefficients have been obtained following the Einstein relation based on the mean-square displacement function.

Figure 2 reports results of self-diffusivity in the case of ionic solution alone. For water molecules, no changes occurred (see Fig. 2, blue label). Looking at ions diffusivities, when no B field is applied a value of 2.5 and 2.1 is reached for the Cl^- and Na^+ ions respectively. In presence of the B field, a decrease of 10% is appreciated for the Na^+ ions and an increase of 18% is reported for the Cl^- particles diffusivity (Fig. 2, yellow and green respectively). This result suggests an interaction between the applied B field and the free charged molecules.

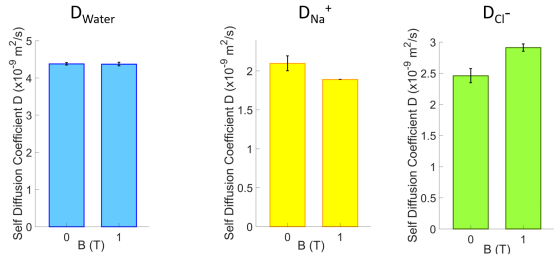

Figure 2. Self-diffusion coefficient D, for water (blue), Na+ (yellow) and Cl- particles.

Afterwards the adenosine A_{2A} receptor has been included in the buffer solution, adding to the simulation box six more Cl^- ions to neutralize the environment, and MD simulations have been done with 0 and 1 T of B field. Preliminary results are reported in Fig. 3 for a total duration t=20 ns. Protein diffusivity has a value of about $2x10^{-9}$ m^2/s slightly higher than the diffusivity values measured experimentally for other protein structures (myoglobin, lysozime) in a work of Nesmelova et al. [13], in the absence of magnetic field. When the B field is applied, the protein was subjected to a decrease of 80% in its mobility showing a direct effect of the B field on the charged residues of the A_{2A} receptor protein.

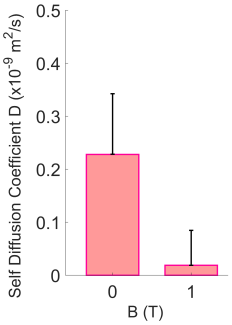

Figure 3. Self-diffusion coefficient for A_{2A} receptor

4. Conclusions

In this paper, for the first time, we used the implementation of a static external magnetic field based on the introduction of the Lorentz force into the VV algorithm, inside the Gromacs software, in order to explore the effects of a magnetic field on the A2A receptor molecular model. First results of 20 ns simulations show an effect of the B field on the self-diffusivity of the protein.

5. References

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