Molecular dynamic study of the ligand binding domain of estrogen receptor alfa and beta

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Motivation

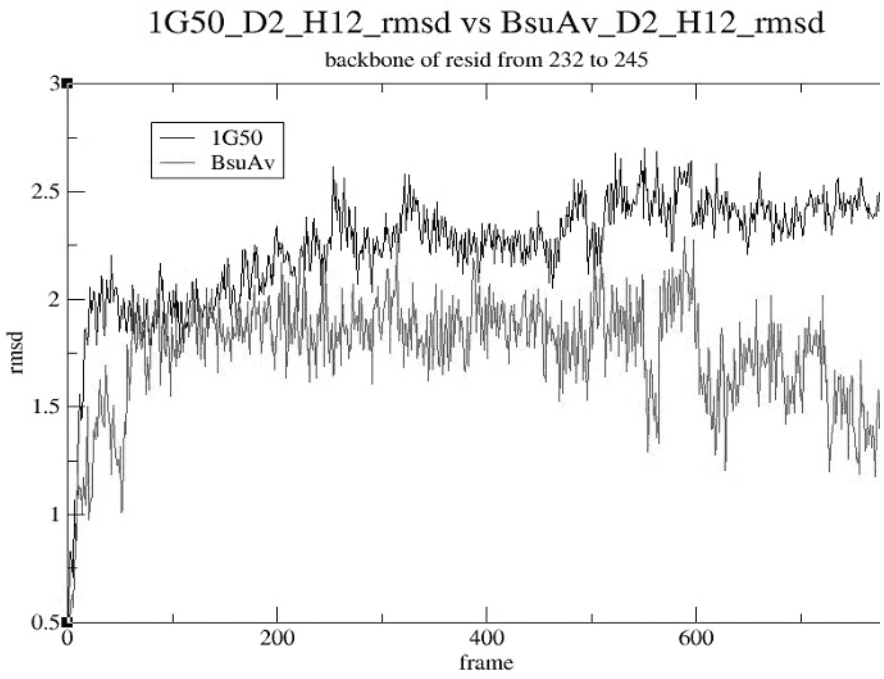
Estrogen Receptor belongs to the Nuclear receptor family, there are two different currently known subtypes Era and Erb. Levels and proportion of the two subtypes differs in different target cells. We can hypotheses a different pharmacological activity upon ligand binding. The aim of this work is the investigation through molecular dynamics simulations, on both the subtypes a and b of the estrogen receptor, of possible differences among them and for the study of their dynamical behaviour.

Methods

The Era apo protein was downloaded from Protein Data Bank (code 1G50). The corresponding structure of Erb apo protein is completely missing, so it was reconstructed by homology modelling techniques using structure of Era as a template. Molecular mechanic (MM) and dynamic (MD) simulations where carried out in explicit solvent with NAMD suite of programs based on AMBER force field, applying PME algorithm and periodic boundary conditions for the non-bonded terms of the potential. The protocol followed in the structure refinement is: minimization of the protein in vacuo with conjugate gradient algorithm, minimization of the solvent with the protein constrained, minimization of the protein and the solvent. After optimization, the system was heated gradually, starting from an initial temperature of 50 K to 300 K for 5ps for a total of 30ps. The total simulation time (with a time step of 1fs) is of 3ns, at a t temperature of 300 K kept constant by a bath coupling.

Results

By means of these simulations we analysed and compared the trajectories of the two receptors in energetic and structural terms. The core structure of both receptors is conserved during the 3ns time, but also some differences I the two isoforms appears. In analysing the potential energy during the simulation we can assume that Era is energetically more stable than Erb, but it undergoes more structural rearrangements. The deviation from the starting structure was monitored by calculating the root mean square deviation as a function of time on all the atoms of the protein, backbone atoms, active site atoms and helix 12. It seems that the structure of Era is more flexible in particular in the active site and in the helix 12 than ERb as it can be seeing in graphs (figure1).



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