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pKa Calculations of Key Ionizable Protein Residues in Acetylcholinesterase

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One of the most abundant quantities characterising proteins is its isoelectric point, which is directly dependent on the number of charged ionizable residues, on the pKa of all ionizable residues more exactly. In this work, the pKa of buried protein aminoacids are estimated using method based on molecular dynamics called thermodynamic integration. The main scope is to compute pKa in acetylcholinesterase, but the computations on a small protein, thioredoxin, will be also presented as benchmark calculations.

Detailed analysis

The pKa computations will be performed as a thermodynamic integration by Sander program from the Amber program suite. The thermodynamic integration method runs molecular dynamics with a mixed potential in different integration points with variable value of a mixing parameter. The mixed potential is combined from the potentials of two distinct states of the molecule differing by van der Waals or electrostatic properties of a few of its atoms. The result of thermodynamic integration is a deprotonation free energy difference between deprotonation in the solution and in the protein. The planned simulation length is about 10ns with 1fs timestep for each of the selected protein ionizable residues, which constitutes, even these days, considerable amount of computational time. In order to perform a thermodynamic integration calculation, Sander has to run in parallel on at least two processors. The whole run will divided into small pieces computed separately in the grid environment.

Conclusions and Future Work

Even such sophisticated and computationally expensive methods as thermodynamic integration using force fields still provide only rough and qualitative results in the field of pKa computation. The future work will include further attempts to compute more precise free energy values using polarizable force fields.

Impact

There are no reported computational studies on the pKa computations on acetylcholinesterase. The results will provide better picture of electrostatic interactions in the enzyme and valuable input for setting up the ionizable residues for force field molecular dynamics simulations. So far, the benchmark computations on thioredoxin are nearly finished, acetylcholinesterase will be computed in the grid environment. The main purpose of the benchmark was to reproduce thioredoxin pKa results already reported (Simonson et al., J.Am.Chem.Soc.,2004,126,4167.) and evaluate following: our model for the electrostatic change connected with deprotonation, alternative usage of new Amber force field 03, Self-Guided Langevin dynamics used to encrease sampling. We found the Amber force field 03 less suitable for this task giving even higher overestimation of the free energy values than Amber force field 99. We were also able to successfully reproduce the reported free energy value for thioredoxin, 9.1 using Amber force field 99, 10.5. Our value is within the error estimated in the original work. The other evaluations and acetylcholinesterase computations are under way.

Keywords

thermodynamic integration, acetylcholinesterase, thioredoxin, ionizable residues, pKa, ff03, ff99

URL for further information

http://www.ncbr.chemi.muni.cz/group/lcc/acetylcholinesterase.html

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