Title: Computer modeling of ion protein interactions: Allosteric effects of phenolic ligands and ions on insulin hexamer structure

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Abstract: Insulin hexamer is an allosteric protein capable of undergoing conformational changes between three states: T6, T3R3, and R6. Transitions between them, as well as the formation of insulin hexamers, are mediated through binding of phenolic ligands or ions. This thesis presents a molecular dynamics study of allosteric behavior of insulin using empirical force fields. Two effects are closely inspected – cation ($Zn^{2+}$, $Ca^{2+}$, $K^+$, and $Na^+$) binding to the insulin hexamers and a possible binding of two neurotransmitters – dopamine and serotonin to the phenolic pocket. The results show that high charge density cations ($Zn^{2+}$ and $Ca^{2+}$) are mostly localized in the B13 glutamate cavity, slow-down diffusion, while preventing other cations from entering. In contrast, low charge density cations ($Na^+$ and $K^+$) do not have this effect. Concerning neurotransmitters, dopamine does not bind to the phenolic pocket whereas serotonin binds in a similar way like phenol. During an investigation of the phenolic pocket, previously unknown binding pockets for neurotransmitters were found on the surface of hexamer. These pockets were closely inspected and it was found that among the investigated species, dopamine binds the strongest. The present computational results are supported by experimental evidence based on protein crystallography and biochemical essays (collaborators J. Jiracek et al. and M. Brzozowski et al.).

Keywords: molecular dynamics, empirical potentials, insulin hexamer, phenolic ligand, phenol, neurotransmitters, dopamine, serotonin, ions, zinc, calcium