

## **APPLICATION OF MARKOV STATE MODEL TO DISCOVERY OF POTENTIAL ALLOSTERIC SITES ON THE SURFACE OF RAS PROTEIN**

**Kots E.D., Kulakova A.M., Brekhov A.T.**

Lomonosov Moscow State University, Chemistry department Russia, 11991, Moscow, Leninsky Gory, 1-3. Tel.:+7(495)939-48-40, E-mail: kots.katya@gmail.com

Activated small GTPase RAS acts as a switcher of signal transduction in cells. RAS protein is active when bound to guanosine triphosphate (GTP). RAS is switched off when GTP is hydrolyzed to guanosine diphosphate (GDP). Several active site mutations hinder RAS from binding to GTPase activating protein (GAP). As a result, permanently activated RAS proteins cause overactive signaling inside cell. Thus, searching of allosteric sites on the surface of RAS is essential for identification of antineoplastic drug target.

Discovery of allosteric regulators for RAS deactivation is complicated by the landscape of RAS surface, which has no visible cavities, available for drug binding. One of the major disadvantages of the pocket detection tools applied up to date is that they usually operate with static protein structures. Surface analysis of a unique protein structure leaves out of consideration the possibility of cavity formation in a different protein conformation.

Current work focuses on development of a new hybrid technique for allosteric sites detection. The method includes large-scale molecular dynamics simulations (up to 1 millisecond) followed by Markov state kinetic model calculation and determination of allosteric paths leading to the active site residues responsible for GAP binding (switch I and switch II).

Markov state model enabled us to allocate the slowest transition in RAS system that corresponds to transformation between active and inactive forms. For two regions on RAS surface solvent accessible area increases in ensemble of calculated active state structures of RAS as compared to inactive state. The length of allosteric paths in active RAS system is longer, and their amount is considerably smaller than in inactive RAS. The result confirms the possibility of allosteric binding of a drug-like molecule in proposed sites.

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