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Biophysics and data science approaches towards Central Nervous System translational medicine

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By merging structural macromolecular data with systems biology simulations, we developed a framework to simulate the signal-transduction kinetics induced by ligand-neuronal GPCR interactions, as well as, the consequent change of concentration of signaling molecular species, as a function of time and ligand concentration. Therefore, this tool brings to the light the possibility to investigate the subneuronal effects of ligand binding upon receptor activation, deepening the understanding of the relationship between the molecular level of ligand-target interactions and higher-level cellular and physiologic or pathological response mechanisms. We show here the application to the adenosine receptor A2a, where we combined structural data from drug-target interactions filtered by a random forest classifier with the above-mentioned signal-transduction kinetic model to identify new antagonists of adenosine receptor A2a. The latter has emerged as an attractive approach for treating Parkinson's disease and other pathologies. Among the tested compounds in a radioligand binding assay, we found a promising drug candidate, which differs significantly from previously discovered ligands.

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