"I like to move it, move it" – molecular dynamics-driven optimization of ligand residence time as an opportunity to improve pharmacological efficacy

The diverse set of compound parameters is optimized during the process of the potential transformation of a ligand into a future drug. They are related to either the provision of a proper pharmacological activity or safety of its use. In the Project, we focus on the compound feature, which is often neglected at the stage of *in silico* design and initial examination of biological potency *in vitro*: **residence time**. It is defined as a period for which a receptor is occupied by a ligand. The Project is a response to many recent reports, which stress the importance of this parameter for the pharmacological action of chemical compounds and indicate that the **lengthening of the duration of ligand-receptor complex can result in more efficacious drugs**, larger therapeutic windows and extended dose intervals. The concept of the correlation of the duration of compound action with the endurance of its complex with the protein is not new, as it reflects the Paul Ehrlich's doctrine *Corpora non agunt nisi fixate* from the 19th century. Nevertheless, the focus on its importance has significantly intensified in recent years.

In the Project, we will comprehensively **examine the molecular determinants of compound residence time for ligands of three important therapeutic targets: selected subtypes of serotonin receptors (5-HT$_{2A}$ and 5-HT$_7$) and μ-opioid receptor**. All these proteins are representatives of the G protein-coupled receptors (GPCRs), which are the most diverse group of receptors in the human genome, involved in the majority of physiological processes occurring in living organisms. Due to their biological role, GPCRs constitute mainstay of drug design campaigns (it is estimated that the 30-40% of drug introduced to the market targets GPCRs). Most attention on serotonin receptors is focused on their role in the central nervous system, and the malfunctioning of the serotonergic system is related to the number of mental disorders. Serotonin receptor ligands are also examined in terms of their role in the modulation of pain response and in the Project we will focus on 5-HT$_{2A}$R and 5-HT$_7$R ligands with proven analgesic properties and possessing ability to overcome side effects related to the use of opioids. On the other hand, μ-opioid receptor is the therapeutic target for most clinically used opioids, commonly used for pain management. Currently used opioids are unfortunately connected with the risk of a wide range of side effects, such as respiratory depression, gastrointestinal dysfunctions, and development of tolerance, dependence, and addiction. As pain is a condition that affects (to various extents) the great majority of the world's population, the search for novel compounds with analgesic properties is highly desirable.

The Project involves the **application of the state-of the-art *in silico* (molecular dynamics) and *in vitro* (radioligand-based and surface plasmon resonance) methods to the carefully selected series of compounds (5-HT$_{2A}$R, 5-HT$_7$R, μ-opioid receptor ligands**) with varying pharmacological activity. **Identification of molecular determinants for prolonged residence time** will be supported by the **machine-learning-based tools developed within the Project to handle output of the molecular dynamics simulations, post-process it, and predict residence time on its basis**. The knowledge gained during the Project will be used to **introduce specific modifications to selected lead structures and perform compound optimization in terms of the time of the receptor occupancy**. In addition, it will be applied to the **enumeration and screening of the focused virtual library of derivatives of existing ligands** of considered receptors in order **to identify ligands with the ability to form long-lasting complexes with the respective target**. Moreover, all gathered computational **data will become part of the GPCRmd**, a comprehensive repository of molecular dynamics simulation data on GPCRs.