NICOLAUS COPERNICUS
UNIVERSITY
IN TORUŃ
Faculty of Physics, Astronomy
and Informatics

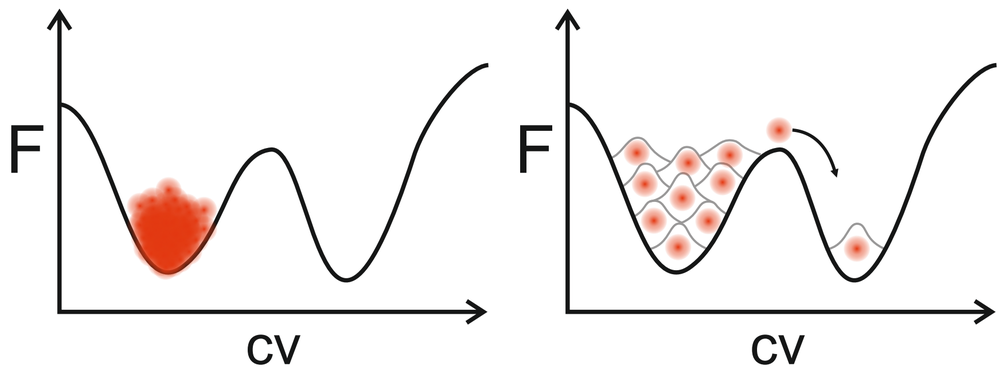
Metadynamics as a tool for a local perturbation in diabetes related large protein complexes

Katarzyna Walczewska-Szewc, Wiesław Nowak

Institute of Physics, Department of Biophysics and Medical Physics
Interdisciplinary Centre for Modern Technologies
Nicolaus Copernicus University in Toruń, Poland

Metadynamics

Metadynamics is the approach of the sampling improvement based on the local modification of the potential energy landscape [1]. Motion of the system along the configurational space of relevant collective variables (CV) can be sped up by adding an artificial Gaussian-shaped bias potential to the energy (F) in each step, to discourage the system from visiting previously visited states.



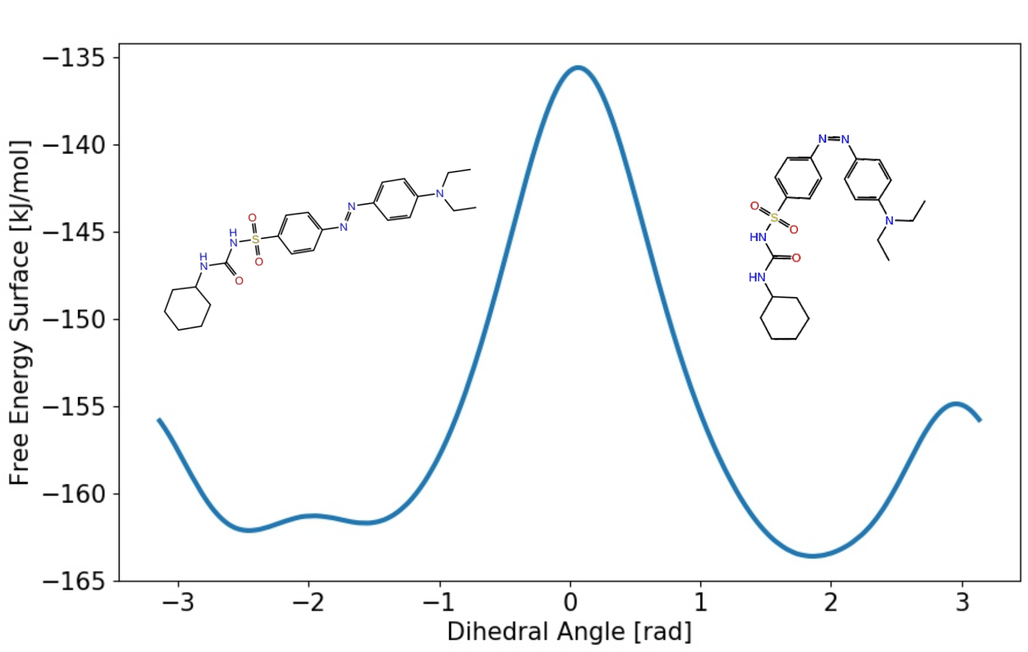
The key to metadynamic simulations is the choice of a proper set of collective variables. These should be sufficient to describe the process we want to study, but may be difficult to sample due to the existence of potential energy barriers or just too slow dynamics along the CV during a simulation.

The local perturbation perturbation

Sulfonylurea drugs are often used to control the blood glucose level in type 2 diabetes (T2D) patients. The role of such drugs is to inhibit the action of ATP-sensitive potassium channels (KATP) which triggers the signalling pathway leading to the insulin release. The usual, oral administration of the sulfonylurea drugs is not always effective, since it is based on the prediction, not on the actual level of the blood glucose.

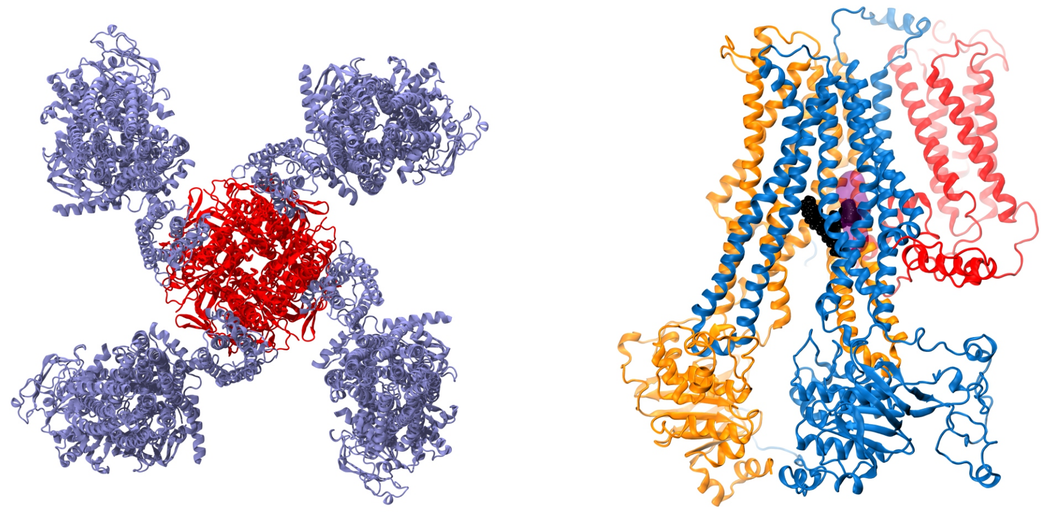
So called photoswitchable drugs, which change their conformation upon light absorption has been showed to efficiently control the insulin release in mice [3]. This ability to 'turn on' or 'turn off' the drug action would allow insulin secretion to be tailored to peak demand. Therefore, it could potentially open up new ways for the treatment of T2DM.

To understand the mechanism of such process we modeled computationally the system of SUR1 (the regulatory unit of KATP) with the photoswitchable sulfonylurea derivative docked to its pocket. Metadynamics simulations drive the trajectory throught all possible dihedral value of the drug swithing between trans (left) and cis (right) conformation, which normally are only obtainable through the photon excitation. As a result we obtained the free energy surface of such transition.



The KATP protein complex

ATP-sensitive potassium channels (KATP) in human pancreatic beta cells close in response to the blood sugar level increase, leading to the insulin release. The channel is made from two different types of protein subunits: Kir6.2 (inward rectifier potassium channel) and SUR1 (sulfonylurea receptor). Four Kir6.2 (red) form the pore through which only potassium ions can move. Each of them is associated which much larger regulatory subunit (blue, right). All eight proteins are needed to make a functional channel [2]. The drug binding site (black) is compared with the standard sulfonylurea binding site (pink) in SUR1.

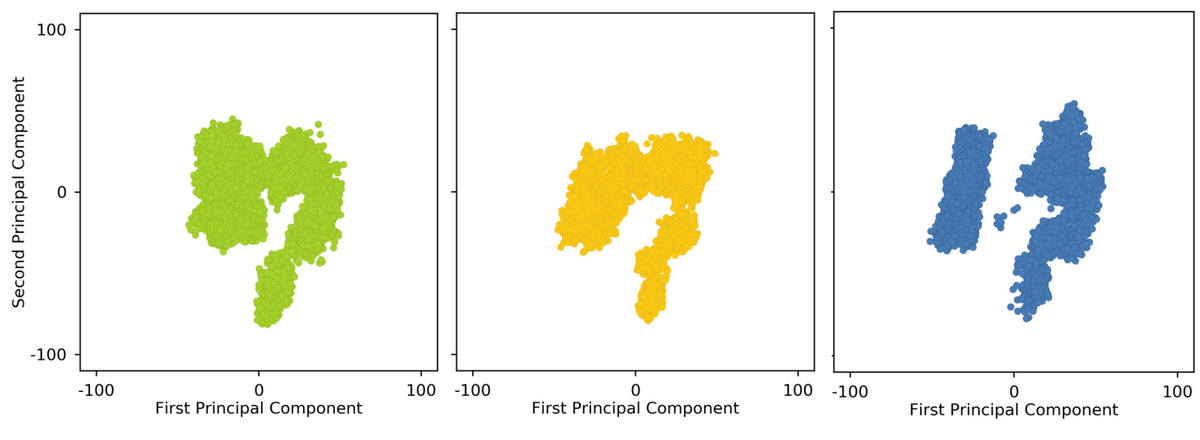


Principal Components Analysis

Principal component analysis (PCA) is a technique for features extraction from the system. It allows to reduce the number of variables which need to be taken into account during analysis of the dynamics of the molecular system. Nevertheless, such projection of the data into a smaller space makes the independent variables less interpretable . The PCA calculations were performed with locally written Python scripts, with the use of the MDAnalysis toolkit[4,5].

Results

The changes in the drug conformation lead to the structural rearrangements of the molecular system. Such rearangement can mimic changes induced by light which can potentially lead to the on/off signaling of KATP system. PCA was calculated for trans (green), intermediate (yellow) and cis (blue) drug conformations using the position of residues in a range of 10 Å around the binding site of the ligand. The figures show slight differences following the perturbation, which in more detailed structural analysis could be associated with a movement of particular residues. Such residues, susceptible for the drug state, may trigger the conformational change of the molecular system.



The authors acknowledge funding from National Science Centre, Poland (grant 2016/23/B/ST4/01770). The computational results used in this review were obtained using resources of Interdisciplinary Centre for Modern Technologies, NCU. This research was carried out with the support of the Interdisciplinary Centre for Mathematical and ComputationalModelling (ICM) University of Warsaw under grant no GA76-10.

1. Laio, A., Gervasio F.L., Rep. on prog. in Phys. **71**(12)
2. Lee, K.P.K., J. Chen, and R. MacKinnon, Elife, 2017. **6**: p. e32481.
3. Broichhagen, J. et al., Nature Comm., 2014. **5**:5116.
4. David, C.C. and D.J. Jacobs, Methods Mol Biol, 2014. **1084**: p. 193-226.
5. Michaud-Agrawal, N., et al., J. of Comp. Chem., 2011. **32**(10): p. 2319-2327.