Energized Enzymes

Voltage-dependent activation of enzymes

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In Short

- Voltage-activation
- Enzymes
- Transmembrane potential
- Molecular dynamics
- Molecular modelling

The activation of proteins by changes in the transmembrane potential (TMP) is an ubiquitous process in nature. The detection of these processes, however, is still challenging since todays experimental methods are not sensitive enough to detect structural changes on the atomic level during these fast dynamics. Therefore, computer simulations are a helpful tool for identifying these fast dynamics in complex biological systems. Together with experimental data they offer a better understanding and help to improve the experimental setup.

This project addresses the voltage-activation of proteins which either are embedded in a biological membrane or are binding to it. For this, different approaches for generating the transmembrane potential will be evaluated with molecular dynamics simulations. With these approaches, the dynamics of the activation process of different voltage-sensitive proteins will be analysed in dependence of the strength of the transmembrane potential and the lipid composition of the bilayer. In order to reach processes on the micro- or even millisecond the enhanced sampling technique accelerated molecular dynamics simulations will be applied.

First, two main approaches for simulating the TMP in molecular dynamics (MD) simulations will be evaluated in detail. On the one hand, the TMP will be generated by using a homogenous electric field perpendicular to the membrane plane [1], and on the other hand, an explicit ion gradient will be applied in a dual-membrane system [2] (Figure 1). While the implicit modelling is a computational fast approach, the use of the explicit ion gradient is a more accurate, since it generated an inhomogenous electric field across the membrane, but computational more expensive way to model the TMP.

Fundamental tests of the TMP modelled by both approaches will also include biomembranes with different lipid compositions which might also effect the

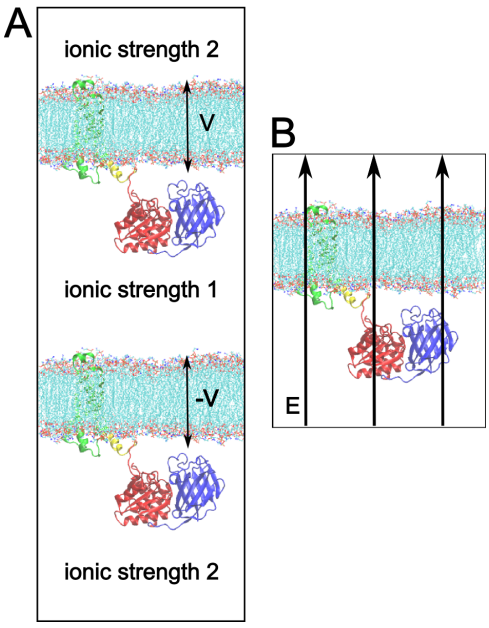

***Figure 1:** Modelling of the TMP by an explicit ion gradient in a dual-membrane system.*

behaviour of the bilayer. The difference of charged and uncharged lipids will be in the main focus since they could strongly influence the dynamics of embedded or attached enzymes.

Second, the molecular systems will be extended by membrane proteins and soluble proteins binding to the membrane upon activation. For these working packages, the fundamental results obtained in membrane-only systems are of essential significance since the voltage response in protein-membrane systems is expected to be slower.

As example for membrane proteins, Quasars will be simulated. These proteins are related to archaerhodopsins but show manifold higher fluorescence quantum yields which makes them potential tools in optogenetics [3]. Here, their dynamics upon changes in the TMP will be investigated. As a model system for soluble proteins binding to the membrane, the voltage-dependent dynamics of PTEN will be investigated. PTEN is a well-charcterized tumour supressor in human [4]. Its transient interaction with the membrane is essential to specifically dephosphorylate phosphatidylinositols (PIPs) which act as second messengers and imbalances in the cell's PIP pool could result to tumour genesis. In this case, two points, the voltage-dependent membrane recruitment and possible voltage-induced structural changes, are of relevance. Furher, the lipid composition for the protein activation will be analysed.

Since the time scales of the voltage-activation processes of these proteins are not exactly clear, conventional MD might not be sufficiant to completely describe these dynamics. In particular, larger structural changes might not be observed in high nanosecond time scales. Therefore, the enhanced sampling technique accelerated MD simulations [5] will be applied to capture dynamics on the micro- to milli-second time scale. The basic idea of this technique is flatten the potential energy landscape by raising energy wells. In this way, energy barriers separating energy minima are descreased and transitions from one well to the other are allowed.

WWW

http://www.biomodeling.tu-berlin.de

More Information

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