Antibiotics made of toxins

Transport of albicidin through the bacterial TSX channel

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In Short

- Antibiotics
- Cell transport
- Molecular dynamics
- Enhanced sampling
- Replica Exchange Umbrella Sampling

The worldwide emerging resistance of bacteria against antibiotics, also knows as antibiotic resistance crisis, is a severe threat for human health and annually results in millions of death [1]. Consequently, the identification of new antibiotics is one of the most urgent topics in health care. Although a lot of effort has been done in the last decade, the search for new potent antibiotics remains very challenging.
Many new antibiotics show a high potential at their biological targets but are inactive in cells which avoids therapeutic application. This drawback is often a consequence of low of no transport into the host cell. This problem is *inter alia* addressed by knock-out experiments but insights on the molecular level are extremely difficult to gain. Thus, the transport mechanism of most antibiotics remains elusive.

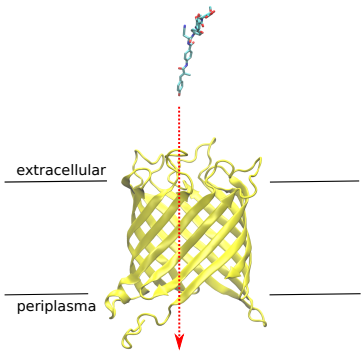

Figure 1: *Schematic illustration of the albicidin (sticks) transport through the bacterial TSX channel (yellow cartoon). The red arrow indicates the pulling direction in SMD simulations.*

In this project, we aim to shed light into the transport mechanism 1 by using classical molecular dynamics (MD) simulations. We plan to investigate the transport of albicidin, a new potential antibiotic from the bacterium *Xanthomonas albilineans*, through the TSX channel located at the outer membrane of gram-negative bacteria. Albicidin is toxic for the sugar cane and has the intersting property to kill gram-negative bacteria. However, for the investigation of the transport classical MD simulations are not sufficient, since the passive transport of large molecules like albicidin across membranes is out of reach this technique[2].
Therefore, we will approach the task by extending MD simulations with enhanced sampling techniques, namely steered and replica exchange umbrella sampling simulations. The cheap constant velocity pulling or steered MD simulations will be used to generate conformations of albicidin in the TSX channel which will subsequently be used for the expensive highly parallelized replica exchange umbrella sampling. The basic idea in this method is to simulate many copies of albicidin along the reaction coordinate, the TSX pore, which are allowed to exchange their Hamiltonian during time. In this way, the sampling of the phase space is strongly enhanced which is a prerequisite for understanding the transport. We will use 120 windows, parallel simulations, to reach a sufficient sampling of the phase space. These settings are in good agreement with recent benchmarking tests reported in literature [3].

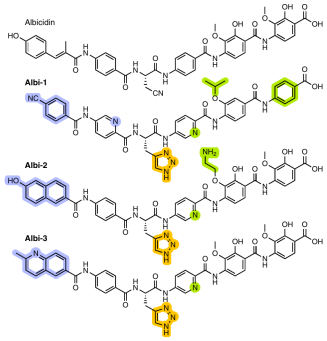

Figure 2: *Structure of albicidin and already published derivatives. The figure is adopted from Michalczyk et al. [4].*

With this setup free energy profiles will be calculated which illustrate energy barriers of the albicidin transport through the TSX pore. With energy profiles of different albicidin derivatives at hand, a quantitatively comparison of the transport becomes possible and allows us to predict albicidin derivatives

with optimized transport properties. This knowledge will serve our collaborators, who already produced many derivatives[4], to synthesize and test these new molecules.
Another task is to investigate the effect of variations in the TSX channel on the transport of albicidin. This might become very relevant as soon as resistances induced by point mutations in TSX occur making the channel impassable for wild type albicidin. In this scenario, optimized albicidin derivatatives with altered trasport properties might become of high interest because they still might diffuse through mutated TSX.

WWW

https://leibniz-fmp.de/de/research/research-areas/chemical-biology/han-sun

More Information

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Project Partners

Suessmuth lab at TU Berlin

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