Project title: Probing mechanisms of bacterial infection through computer simulations

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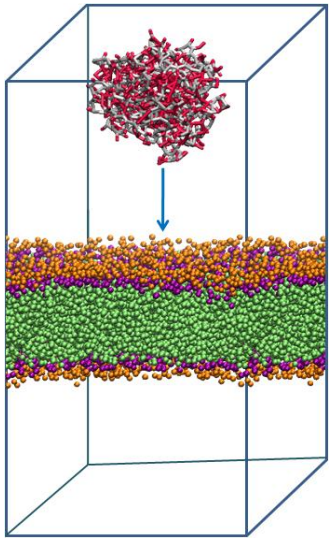
Project description:

Motivation: A major cause of infection in living cells is the development of a bacterial biofilm in the host tissue. Biofilms are aggregates of bacteria surrounded by a polymeric matrix that can adhere to almost any surface including blood vessels, medical implants, and surgical devices. Once inside the living tissue, the bacterial biofilms interact with the host cells through chemicals known as signaling factors. The signaling factors are typically relatively small polypeptides that have profound effects on the cellular activities of the host. The signaling process is quite complex. Our present understanding of the interactions between the signaling factors and the host cell is far from complete. A better understanding of the physical and chemical mechanisms underlying the signaling process could provide alternative ways to prevent infections.

We use computer simulations to identify the key interactions between the signaling factors and the cell membrane of the host cell. We aim to develop a capability to predict how the structure and composition of the polymeric matrix of the biofilm and chemical structure of the signaling factor affect signal translocation through the biofilm and across host cell interface. Insights from the simulations will be critical in developing prototypes for antibacterial agents.

Research work: In this project, molecular dynamics simulations are currently being used to study the interactions between model cell-membranes and α-tumor necrosis factor (α-TNF), a common signaling factor. To keep the computational cost low, the molecular dynamics simulations are carried out in a coarse-grained representation, which is benchmarked against more detailed atomistic ones. In order to identify the energy barrier associated with the translocation of the α-TNF through the cell-membrane, we perform potential of mean force calculations. Similar calculations are being performed from the α-TNF in a model biofilm matrix.



Initial MD simulation setup for α-TNF and cell membrane interactions. Water molecules are not shown for clarity.

In continuation of the this *computational project*, the IGERT fellow will extend our methodology to (1) other signaling factors, such as- G-CSF, GM-CSF, MCP-1, IL-6, and IL-8, (2) calculate potential of mean force of the binary interactions, and (3) identify similarities in structures and trends in the amino-acid sequence of the signaling factors that enhance the interactions with the host cell.

This computational approach could provide unprecedented molecular level insight into the signaling process between the bacterial biofilm-cell membrane interfaces. This project is a good fit for the *Biomaterial Interfaces* division of the IGERT program.