Over the years, mankind has been struggling with antibiotic-resistant bacteria. As a consequence of the widespread overuse of antibiotics, several bacteria strains have developed effective drug resistance. It was recently reported that the newly discovered "New Delhi" superbug Klebsiella pneumoniae is resistant to all known antibiotics, even those called the "last-resort antibiotics". World Health Organization (WHO) reports that each year at least 700,000 people lose their battle against antibiotic-resistant microbes. Unfortunately, WHO's forecasts are not optimistic. Unless new solutions are discovered by 2050, millions of people may die annually. There are many reasons for the immunization of microorganisms, including continuous mutations, i.e. modifications of the genetic material, or acquiring genes of resistance from other organisms. Moreover, the human factor strongly influences the resistance of bacteria, e.g. by frequent uptake of antibiotics. Faulty uptake is also an issue when insufficient doses or too short of drug therapy duration is present. Over time, microbes will escape from the lethal effects of antibiotics, developing their own adaptive mechanism.

In order to reduce this phenomenon, one of the proposed approaches assumes using antibacterial compounds with a broad spectrum of activity against slowly evolving bacterial structures such as membranes. Plenty of widely used antiseptics belong to the special detergents group (cationic surfactants), which have a preferential effect on lipids, being effective against bacteria even at low concentrations. Well-known ones: octenidine (OCT) and chlorhexidine (CHX) are widely used on the market.

Recent scientific reports suggest that the selective action of these compounds may be related to the differences in the mechanical properties of cell membranes in various organisms. This is important information because the mentioned features of biological structures are crucial for the functioning of cells and an essential factor influencing the formation of tissues. Hence, this project aims to model the formation of the appropriate lipid structures of bacterial membranes - so-called microdomains. Those are known for their resistant mechanical properties. This will enable verification of whether the mechanical parameters are the source of the selective activity for these antibacterial compounds. The presence of microdomains in bacterial membranes is well documented. It has been suggested that they are responsible for maintaining the integrity, fluidity, and rigidity of the membrane, as well as facilitating many regulatory and organizational functions of cells. Disruption of this organization may disorder the proper function of the microbe and, ultimately lead to the loss of activity required for the cell's survival.

This project's objective verifies whether the selective activity of antiseptics is caused by specific interaction with domains in the membrane, that can be directly linked to the mechanical properties of the membranes. First, novel numerical models of bacterial membranes enriched with lipid microdomains will be optimized. The computer models will be simulated using molecular dynamics, which will allow to observe the domain formation at the molecular level. This will be further followed by molecular models translation into experimental ones with spherical membrane shapes called liposomes in the laboratory. Afterward, numerical and experimental models of bacterial bilayers enriched with microdomains will be treated with selected antibacterial compounds in various concentrations. This allows to evaluate the hypothesis about the agent’s selective mode of action. In this project, the combination of numerical and experimental techniques will provide a complex and precise description of the domain formation process in bacteria and the destructive effect of antimicrobial substances.

The project also addresses the main objectives of the EU's *One Health* plan against antimicrobial resistance (AMR) action whose major assumptions are to boost the research and provide novel solutions and tools to prevent and control the spread of AMR. Understanding the molecular mode of destruction of lipid microdomains will open a new path for the development of antibacterial substances that are even more effective than before to fight antibiotic-resistant strains of bacteria.