EML WEBINAR

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7 AM CALIFORNIA, 10 AM BOSTON
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SIMULATION-ASSISTED DISCOVERY OF MEMBRANE TARGETING NANOMEDICINE

The COVID-19 pandemic has brought infectious diseases again to the forefront of global public health concerns. Here, we discuss some recent work on simulation-assisted discovery of membrane targeting nanomedine to counter increasing antimicrobial resistance and potential application of similar ideas to the current pandemic. A recent report by the world health organization (WHO) warned that 10 million people worldwide could die of bacterial infections each year by 2050. To avert the crisis, membrane targeting antibiotics are drawing increasing attention due to their intrinsic advantage of low resistance development. In collaboration with a number of experimental groups, we show examples of simulation-assisted discovery of molecular agents capable of selectively penetrating and aggregating in bacterial lipid membranes, causing membrane permeability/rupture. Through systematic all-atom molecular dynamics simulations and free energy mapping, we demonstrate that the membrane activity of selected molecular agents correlates with their ability to enter, perturb and permeabilize the lipid bilayers. Further study on different cell membranes demonstrates that the selectivity of these membrane targeting antimicrobials results from the presence of cholesterol in mammalian membranes, as the cholesterol condenses the hydrophobic region of the membrane, preventing them from penetration by the antimicrobial molecules. Following the penetration, we establish a continuum theory of membrane antimicrobials and derive the energetic driving force for the pore growth on bacterial membrane. We show that the energy barrier to membrane pore formation can be significantly lowered through domain aggregation of antimicrobial molecules with intrinsic curvature and a sharp interface. The theory is consistent with experimental observations and validated with coarse-grained molecular dynamics simulations of molecular domain aggregation leading to pore formation in a lipid membrane. The mechanistic modelling and simulation provide some fundamental principles on how molecular antimicrobials interact with bacterial membranes and damage them through domain aggregation and pore formation. This study suggests a general simulation-based platform to accelerate discovery and innovation in nanomedicine against infectious diseases.

Professor Gao has pioneered many areas of research, including dynamic instability of fracture, morphological changes of elastic solids, gradient plasticity, and nanobiomechanics. He was professor at Stanford University and Brown University, and Director at Max Planck Institute for Metals Research. He is Distinguished University Professor at Nanyang Technological University and Scientific Director of Institute of High Performance Computing in Singapore.

Discussion Leader: Professor Markus Buehler, Massachusetts Institute of Technology

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