Physical mechanisms in infectious diseases

Influenza virus has had a tremendous impact on human health. In addition to the threat of another severe pandemic from influenza, emerging viruses such as Zika pose a massive global health threat, and highly drug-resistant bacteria are also a global threat. Peter Kasson´s research group studies the mechanistic basis all of these pathogens in order to develop better therapies.

Influenza virus infects cells via a process of membrane fusion. Membrane fusion is the primary means by which large molecular payloads are transported into cells. As such, membrane fusion provides the mechanism for the entry and infection by enveloped viruses such as influenza, Ebola, SARS, and HIV. Peter Kasson´s research group studies membrane biology of virus-host cell interactions, with a focus on influenza as both a common model system and an important human pathogen. Three fundamental questions in influenza infection are addressed: how does influenza recognize cell-surface glycans on the cells it infects, how do fusion proteins catalyze membrane fusion and bring about viral entry, and how does cellular lipid metabolism permit or inhibit viral replication.

”We study several aspects of viral entry: how membrane composition can alter the mechanism and efficiency of entry, and how protein-lipid interactions mediate membrane fusion and release of the viral genome inside the cell. In each of these areas, we use a variety of biophysical, structural, and computational approaches to build an integrated understanding of viral entry”, says Peter Kasson.

A quite recent finding that excites is the finding that cholesterol has a direct effect on the infectivity of the influenza virus being a possible way to interfere with the infections. If you remove cholesterol the virus doesn´t work that well, Peter explains. Other researchers have also seen that people getting anti-cholesterol drugs are less likely to die of influenza, and the Kasson lab findings help explain why.

Using a combination of novel computational methods and targeted experiments the research group generate robust quantitative and mechanistic models for these processes. This will yield important insight into the biochemistry of viral infection. He says that experimental mutagenesis has yielded much data on the functional requirements of the proteins that catalyze fusion, but they have no robust theory that could have predicted these results. The influence of the membrane environment is key: in some viruses, mutations that would normally block fusion can be rescued by adding exogenous lipids.

“We seek to develop better models of protein-lipid interplay in membrane fusion by influenza. The development of robust predictive models for the mechanism of lipid membrane fusion will greatly aid in understanding the underlying physical process and how to effectively target it with antiviral agents”, says Peter Kasson.

They are developing high-performance simulation methods to analyze membrane fusion and use these methods to predict the catalytic mechanism of influenza fusion proteins, and understand how fusion is defective in known mutants of influenza, and understand the mechanism of interaction between fusion peptide mutants and membrane perturbations. Computational predictions will be evaluated against biophysical experiments.

“This is an exciting time for molecular simulation, because within the past few years we have gained the ability to quantitatively predict experimental observables for small biomolecules. Our interest and expertise lies in achieving the next revolution in computational methods: addressing the more complex cellular environments required to analyze problems in cellular biophysics and infectious disease” says Peter Kasson.

Their long-term goal is to leverage synergy between computation and biophysical experimentation for a mechanistic understanding of viral infection and to design new therapeutic strategies.

“Complex problems that are intellectually challenging interest me and also problems where a solution will have huge impact on human health, that is what excites me”, says Peter Kasson.