Zusammenfassung:
Defective viral genomes (DVGs) of influenza A (IAV) and B (IBV) viruses, characterized by large internal deletions, can interfere with virus replication and represent promising candidates for antiviral therapy. DVGs are known to induce periodic oscillations in virus concentrations, referred to as the von-Magnus effect in continuously cultured infected cells. Since thousands of different DVGs are present simultaneously in virus populations, experimental identification of potent DVGs that drive antiviral activity remains resource-intensive. To address this, we apply bioinformatics, artificial intelligence and mathematical modeling to prioritize DVGs in silico. To characterize DVGs in more detail, we conducted a comprehensive meta-analysis of various sequencing datasets from in vitro and in vivo IAV and IBV infections. Upon harmonizing raw data using a standardized pipeline, we systematically assessed DVG features such as deletion length, deletion sites, and sequence composition, revealing differences with respect to virus type and host system. Furthermore, we developed a computational method to rank DVGs from seven A/Puerto Rico/8/1934 datasets uncovered 11 highly abundant, previously unnoticed DVGs, which may harbor key features for DVG formation or selection. Moreover, we applied Granger-causality analysis to time-series data from a continuous IAV culture to infer directional dynamics between individual DVGs and the infectious virus concentration. This revealed DVGs with Granger-causing or bi-directional relationships, which indicates their predictive influence on infectious virus concentration. Crucially, the antiviral potential of experimentally validated DVGs reasonably correlates with Granger labels, i.e., potent candidates were classified as Granger-causing, while less effective ones were non-related, confirming the method’s suitability to prioritize DVG candidates. Our vision is to develop integrative approaches, combining meta-analyses and causality modeling, providing a computational framework for pre-selecting high-potential DVGs for next-generation antiviral strategies.