

IMPACT STATEMENT

Relevance to FY23 PRMRP Topic Area: The proposed research project is highly relevant to the proteomics topic area, specifically as it applies to infectious diseases caused by zoonotic emergence. The Emergenet algorithm can distill the emergent rules of organization of key viral proteins, uncovering how proteins respond to dynamic fitness landscapes and adapt to new hosts while evading host immune defenses. These investigations can provide key insights into protein evolution and reveal novel patterns that can aid in the discovery of vaccines and prevent the emergence of new virus strains.

Relevance to FY23 PRMRP Strategic Goal: The proposed research project addresses the strategic goal of epidemiology, with a focus on identifying strategies for surveillance or developing modeling tools and/or biomarkers to predict outbreaks or epidemics. The BioNORAD platform provides a theory-backed, experimentally validated, and scalable solution to emergence prediction, preempting strains expected in future human circulation and approximating Influenza Risk Assessment Tool (IRAT) scores of non-human strains without experimental assays or subject matter expert scoring a million times faster. As a comparison, while 22 strains have been scored by the IRAT since 2013, we can analyze and score the entire GISAID and NCBI database in under a week with a moderately powerful computing cluster. This represents a significant improvement in our ability to predict pandemics caused by Influenza A viruses.

Potential impact, either short-term or long-term on the field of study and/or patient care:

The potential impact of the proposed research on the field of study and patient care is immense. Currently, pandemic preparedness and response is reactive and slow, often leading to significant loss of life and economic damage. The ability to accurately predict the emergence of high-risk pandemic strains before they have the opportunity to trigger a pandemic would revolutionize our approach to pandemic preparedness and response, allowing us to rapidly develop and produce vaccines tailored to the specific strain before the pandemic even begins, potentially saving countless lives.

Furthermore, by understanding the evolutionary constraints and cross-dependencies that give rise to high-risk strains, we can begin to develop targeted interventions to prevent these strains from emerging in the first place. This could involve inoculating animal reservoirs with vaccines tailored to these high-risk strains or developing targeted surveillance efforts in animals before they have the opportunity to jump to humans.

The potential impact of this work is not limited to pandemic preparedness, and can foster a more nuanced understanding of how viruses evolve and adapt over time. This could lead to the development of new therapeutic strategies that specifically target the evolutionary pathways of viruses, potentially revolutionizing the treatment of viral infections. In addition, the development of the BioNORAD platform has implications beyond Influenza A viruses. The methods developed as part of this work can be applied to other viruses with pandemic potential, such as coronaviruses and other respiratory viruses.

Overall, the potential impact of this work is significant, both in the short-term and long-term. By developing a better understanding of the evolutionary forces that give rise to high-risk pandemic strains and by providing an early warning system to identify emerging strains before they have the opportunity to trigger a pandemic, we can revolutionize our approach to pandemic preparedness and response, making this research project a critical investment in the future of our society.

Potential to generate preliminary data that can be used as a foundation for future research projects: The BioNORAD platform's ability to predict the emergence of novel Influenza A strains with high pandemic potential, as well as estimate their evolutionary trajectories, will generate a wealth of data that can be used as a foundation for future research projects. The knowledge and insights gained from this research will facilitate the development of more effective and efficient biosurveillance methods and tools, as well as the design of new therapeutics and vaccines that target specific viral strains. Furthermore, this work will provide a framework for future studies aimed at predicting the emergence of other infectious diseases with pandemic potential.

In addition, the Emergenet algorithm's ability to learn an appropriate biologically meaningful comparison metric from data, without assuming any model of DNA or AA substitution or a genealogical tree a priori, represents a significant advance in the field of machine learning. This has the potential to impact a wide range of research areas beyond infectious disease epidemiology, such as protein structure prediction and drug design. The proposed research will not only advance our understanding of Influenza A evolution and pandemic risk assessment but also contribute to the broader scientific community's knowledge of machine learning and artificial intelligence.