Institute for Applied Simulation
Phylogenetics reveals competition of human flu subtypes

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Research project
Predicting the dynamics of seasonal influenza

Lead:
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Research Group Applied Computational Genomics

Using phylodynamic and phylogeographic modeling we analysed molecular sequences from around 3000 influenza strains isolated from patients participating in the global prospective clinical study IRIS. We were able to infer alternating patterns of effective reproductive numbers and migration between influenza subtypes after the 2009 pandemic. For the first time, this demonstrates that cross-protective immunity (i.e., competition between viral subtypes) is an important driver of influenza seasonality.

Influenza is a common viral respiratory infection, which often causes epidemics. Seasonal patterns of influenza infections have been intensely studied. Better understanding of influenza dynamics helps to guide efficient vaccine development, to fight new highly contagious strains spreading through human populations. Yet, the dynamics of flu circulation remains difficult to predict.

Reconstruction of an evolutionary history

In collaboration with scientists from the University of Veterinary Medicine of Hannover and F. Hoffmann-La Roche AG, we have applied computational methods to analyse complete protein-coding influenza sequences, i.e. hemagglutinin (HA) and neuraminidase (NA). Sequences from approx. 3000 influenza A and B strains were collected as part of the Influenza Resistance Information Study (IRIS) over 5 years, starting with the 2009 pandemic, and were extended with public data.

The main expertise of the Applied Computational Genomics Team is the development of computational methods for the reconstruction of evolutionary history (including multiple sequence alignment and phylogeny). This includes modeling sequence evolution over time, for example to evaluate the impact of natural selection and other evolutionary forces that shape genomics sequences and drive changes in fitness. In this project, the teams own software was first used to construct multiple sequence alignments and viral phylogenies. These were subsequently used to perform further inferences of viral phylodynamics based on modelling of underlying population dynamics and discrete trait migrations between geographical locations (Figure).

Quantifying global virus migration pattern

As a result we quantified global virus migration patterns with high spatio-temporal resolution, while estimates of global effective reproductive number (R) was used to evaluate herd immunity. Considering that some individuals are immune (e.g., due to prior infection or immunisation), not all contacts can lead to new infections. This decreases the numbers of secondary infections in partially susceptible population. The host-pathogen dynamics are summarized by R, computed as the ratio between secondary infections and recovered individuals. The herd immunity threshold can be described as the fraction of a population that has to be immune to stabilise the disease spreading (R=1).

New insights contribute to a better understanding

Two influenza A subtypes H1N1 and H3N2 showed alternate phases of growing and declining R estimates, suggesting a global pattern oscillating around R=1 (Figure). Similarly, we observed alternation of the numbers of migration events of influenza A indicating that herd cross-immunity is an important determinant of global circulation of the flu virus. Alternation patterns for influenza B subtypes were less pronounced. These new insights contribute to a better understanding of influenza seasonality. The follow-up study involves using Markov models of codon substitution to evaluate changes of natural selection over time and at different sites of the viral proteins. This approach will help to identify hotspots of diversifying selection that favour viral escape from host's immune system, which will facilitate the prediction of future «escape routes».

Reference: «Global phylodynamics reveals competition between co-existing influenza A subtypes». Gatti, Zhang, Anismova, Schutten, Osterhaus, van der Vries (manuscript under review).

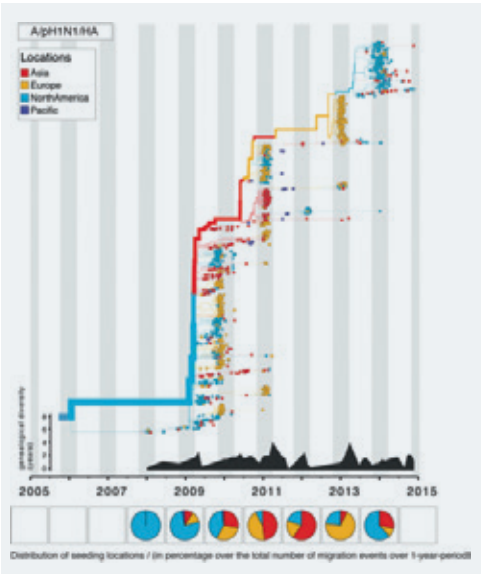

Figure: The inferred spatio-temporal phylogeny with migrations shows evolutionary dynamics of flu; extract from Gatti et al. (under review).