

vRNAsite: Prediction and evaluation of viral RNA-RNA interaction sites between influenza A wild type and mutant vRNAs

Content

Seasonal influenza A virus (IAV) epidemics are difficult to counter with vaccination. This is due to the unique packaging of the eight viral RNA (vRNA) segments and the ability to create reassortants between different strains. One theory about packaging involves vRNA-vRNA interactions (RRI) between different segments [1,2], however to our knowledge there has been no attempt to computationally analyze the involved mechanisms. Here, we present vRNAsite which predicts possible RRIs between all IAV vRNAs.

vRNAsite takes the original and mutated segments as input and a sliding window between any two vRNAs calculates minimum free energy (MFE) dependent scores for each single nucleotide pairing via RNAcofold [3]. Resulting scores are used to evaluate possible interaction sites as well as differences between WT and mutant RRIs. Our first results show multiple sites with promising scores hinting at possible RRIs. We validated one of these sites with an *in vitro* experiment involving the avian H5N2 virus [2]. Here, only four compensatory point mutations between segment 2 (PB1) and 8 (M) led to a significantly attenuated viral reproduction when one of the two mutants was present. An introduction of both mutant vRNAs restored the viral reproduction to WT levels.

With this work we demonstrate that a computational approach for the packaging of IAV is essential. We will further develop vRNAsite with the goal of predicting complete packaging networks for IAV. This might yield the ability to predict the pathogenic potential and reproductive capacity of reassortant IAVs, which would lead to an improvement in IAV vaccination development.

References

- [1] Fournier E, et al. (2012). *A supramolecular assembly formed by influenza a virus genomic RNA segments*. Nucleic Acids Res., 40:2197–2209.
- [2] Gavazzi C, et al. (2013). *A functional sequence-specific interaction between influenza a virus genomic RNA segments*. Proc. Natl. Acad. Sci. U.S.A., 110:16604–16609.
- [3] Lorenz R, et al. (2011). *ViennaRNA package 2.0*. Algorithms for molecular biology : AMB, 6:26.

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