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Predicting Fixation Tendencies of the H3N2 Influenza Virus by Free Energy Calculation

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(Submitted on 26 Apr 2012)

Influenza virus evolves to escape from immune system antibodies that bind to it. We used free energy calculations with Einstein crystals as reference states to calculate the difference of antibody binding free energy ($\Delta\Delta G$) induced by amino acid substitution at each position in epitope B of the H3N2 influenza hemagglutinin, the key target for antibody. A substitution with positive $\Delta\Delta G$ value decreases the antibody binding constant. On average an uncharged to charged amino acid substitution generates the highest $\Delta\Delta G$ values. Also on average, substitutions between small amino acids generate $\Delta\Delta G$ values near to zero. The 21 sites in epitope B have varying expected free energy differences for a random substitution. Historical amino acid substitutions in epitope B for the A/Aichi/2/1968 strain of influenza A show that most fixed and temporarily circulating substitutions generate positive $\Delta\Delta G$ values. We propose that the observed pattern of H3N2 virus evolution is affected by the free energy landscape, the mapping from the free energy landscape to virus fitness landscape, and random genetic drift of the virus. Monte Carlo simulations of virus evolution are presented to support this view.

Comments:	5 tables and 4 figures
Subjects:	**Biomolecules (q-bio.BM)**
Journal reference:	J. Chem. Theory Comput. 7 (2011) 1259-1272
Cite as:	**arXiv:1204.6060v1** [q-bio.BM]

Submission history

From: Michael Deem [view email]

[v1] Thu, 26 Apr 2012 20:57:58 GMT (1577kb)

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