Avian Flu Grid: International Collaborative Environment for Team Science on Avian Influenza

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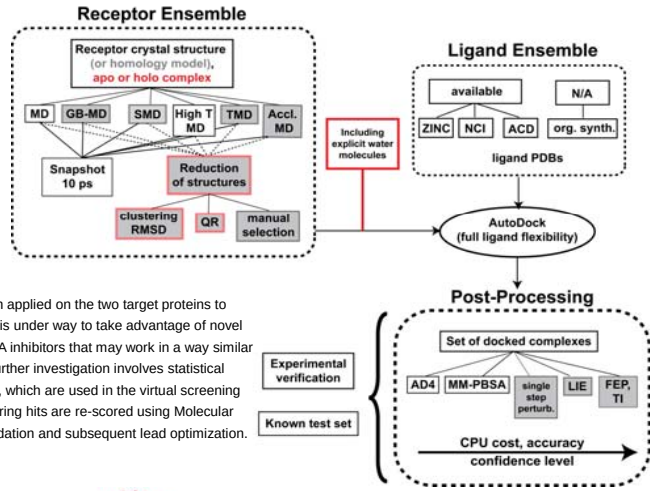
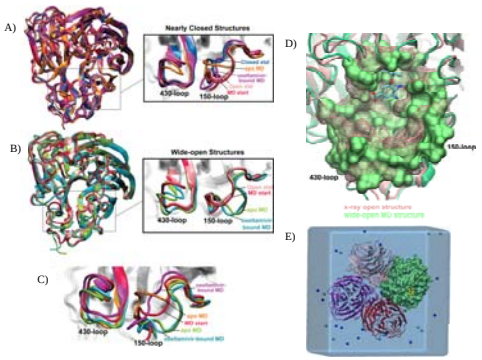
Abstract

The avian influenza virus type A, especially subtype H5N1, is becoming the world's largest pandemic threat due to its high virulence and lethality rate in birds, quickly expanding host reservoir, and high rate of mutations. The two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA) of influenza virus play important roles in the interactions with cellular receptors containing terminal N-acetylneuraminic acid (Neu5Ac, or NANA) moieties, aka, sialic acids. The approved anti-influenza drugs, oseltamivir and zanamivir, inhibit H5N1 infection by targeting the NA active site, thereby blocking the release of newly formed viral particles. However, research has shown that antigenic drift may give rise to new strains that are resistant to existing NA inhibitors and antigenic shift could give rise to new virulent subtypes of the flu virus. Thus, it is crucial to design novel HA- and NA-targeted inhibitors, which can be used in combination for optimal prophylaxis and treatment.

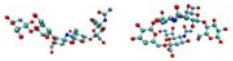
The Relaxed Complex (RC) scheme and Molecular Dynamics (MD) simulations have been applied on the two target proteins to capture key protein dynamics information and accounting for receptor flexibility. Research is under way to take advantage of novel loop flexibilities and changing cavity shapes adjacent to NA active site to discover novel NA inhibitors that may work in a way similar to the HIV integrase inhibitor, raltegravir, inspired by the RC/MD simulation procedures. Further investigation involves statistical cluster analysis for rational selection of representative HA/NA protein structure snapshots, which are used in the virtual screening with synthetic and natural compound libraries. Finally, the binding energies of the high scoring hits are re-scored using Molecular Mechanics-Poisson Bolzmann Surface Area (MM-PBSA) method before experimental validation and subsequent lead optimization.

Computational Methods

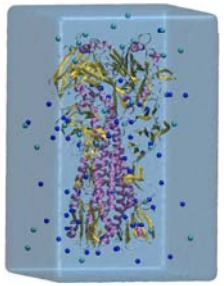




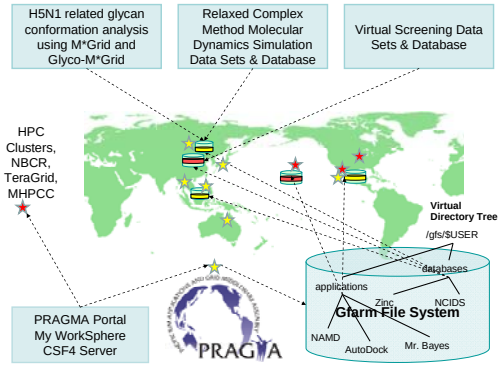
A-C) Structural alignment of the crystal structures and MD snapshots shows the wide range of motion available to the 150- and 430-loops. D) Alignment of the open x-ray structure (pink cartoon and wireframe) and the wide-open MD snapshot (green, MSMS surface) illustrates the significant cavity expansion during the apo simulation. E) The N1 tetramer system, with oseltamivir bound in the active sites has ~112,000 atoms. One of the chains is shown in MSMS surface representation (green).



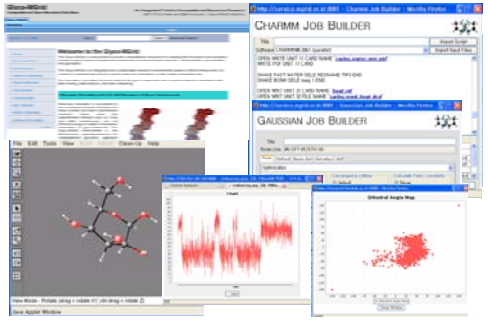
Avian LSTa α2, 3 linkage; Human LSTc α2, 6 linkage



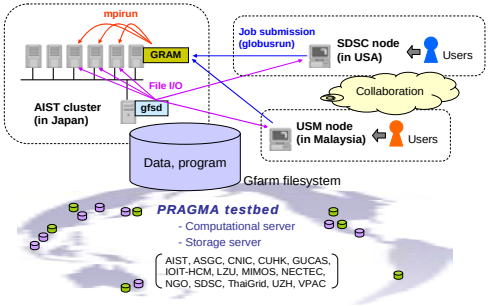
The HA system, with ions, is shown in side view.



Integrative Effort: Avian Flu Grid



Glyco-M*Grid
http://www.mgrid.or.kr
A grid portal-based integrated environment for e-Glycomics, provides a powerful tool for tackling the glycobiology in the avian flu systems



PRAGMA Data Infrastructure
http://datafarm.apgrid.org
2.58 TB disk space is provided by 45 Gfarm filesystem nodes from 14 organizations in the Asia-Pacific region.

CSF4 meta-scheduler (**http://gcsf.sourceforge.net**)
PRAGMA portal environment (**https://portal.pragmagrid. net:9443**)
Opal-based application specific web services (**http://nbcr.net/serivces**)
Scientific Data Grid (**http://pragma.sdg.ac.cn**)
NaPIMM portal (**http://www.usm.my**)
TeraGrid (**http://www.teragrid.org**)
National Biomedical Computation Resource (**http://nbcr.net**)
Maui High Performance Computing Center (**http://www.mhpcc.edu**)
Vision workflow management tools (**http://mgltools.scripps.edu**)
For more information, please visit the project website at **http://avianflugrid.pragma-grid.net**

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