UC Irvine Study Points to New Approach to Influenza's Antiviral Resistance

SDSC Supercomputer Assists in Developing Molecular Simulations

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Researchers from the University of California, Irvine, with assistance from the San Diego Supercomputer Center at UC San Diego, have found a new approach to the creation of customized therapies for virulent flu strains that resist current antiviral drugs.

The findings, published online this week in *Nature Communications*, could aid development of new drugs that exploit so-called flu protein 'pockets.'

Using powerful computer simulations on SDSC's new *Trestles* system, launched earlier this year under a $2.8 million National Science Foundation (NSF) award, UCI's Rommie Amaro and Robin Bush together with SDSC's Ross Walker created a method to predict how pocket structures on the surface of influenza proteins promoting viral replication can be identified as these proteins evolve, allowing for possible pharmaceutical exploitation.

"Our results can influence the development of new drugs taking advantage of this unique feature," said Amaro, an assistant professor of pharmaceutical sciences and computer science at UCI. Prior to joining UCI in 2009, Amaro was a postdoctoral fellow in chemistry at UC San Diego.

The search for effective flu drugs has always been hampered by the influenza virus itself, which mutates from strain to strain, making it difficult to target with a specific pharmaceutical approach. The most common clinical flu treatments are broad-based and only partially effective. They work by interrupting the action of an enzyme in the virus called neuraminidase, which plays a critical role in viral replication.

In 2006, scientists discovered that avian influenza neuraminidase (N1) exhibited a distinctive, pocket-shaped feature in the area pinpointed by clinically used drugs. They named it the 150-cavity.

Amaro and Bush, associate professor of ecology and evolutionary biology, conducted research using resources at the San Diego Supercomputer Center, as well as the National Institute for Computational Sciences (NICS) to learn the conditions under which the pockets form. They created molecular simulations of flu proteins to predict how these dynamic structures move and change, as well as and where and when the 150-cavity pockets will appear on the protein surface.

This sequence analysis method could be utilized on evolving flu strains, providing vital information for drug design, Amaro said. "Having additional antivirals in our treatment arsenal would be advantageous and potentially critical if a highly virulent strain, for example, H5N1, evolved to undergo rapid transmission among humans or if the already highly transmissible H1N1 pandemic virus was to develop resistance to existing antiviral drugs," she added.

Walker, an assistant research professor who runs the Walker Molecular Dynamics Lab at SDSC, developed a customized version of the AMBER software, a widely used package of molecular simulation codes, to run these

specific simulations on *Trestles* under the NSF's TeraGrid Advanced User Support System. That included detailed performance tuning including hard-coding atom counts, atom types and parameters, and being able to use *Trestles* for uninterrupted two-week runs that together consumed more than one million SUs (single processor hours).

"We initially used the *Athena* supercomputer at NICS, which provided us with all the initial comparison data before Trestles came online earlier this year," said Walker, who is also an adjunct assistant professor in UC San Diego's Department of Chemistry and Biochemistry. "We had *Trestles* all ready to go as soon as the first H1N1 protein structure was available, and using the earlier work we did on *Athena*, we were able to put *Trestles* immediately to work to conduct simulations of the structure as part of this research."

Robert Swift and Lane Votapka of UCI, as well as Wilfred Li of UC San Diego, also contributed to the study, which received support from the National Institutes of Health and the NSF.

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