

Texas Advanced Computing Center - Inside the Swine Flu Virus

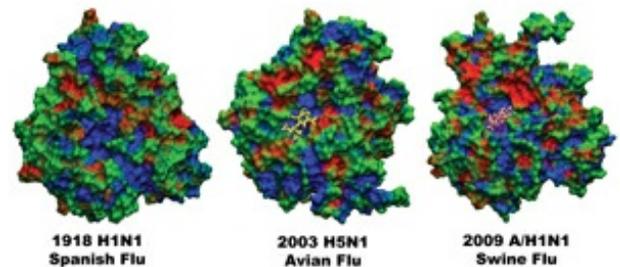
Inside the Swine Flu Virus

Researchers use Ranger supercomputer to discover how mutations in viral protein lead to drug resistance

Swine flu, also known as the A/H1N1 virus, first surfaced in Veracruz, Mexico in April 2009. A deadly form of Influenza A that combines the DNA of swine, avian and human flu viruses, it awakened a lingering dread of a pandemic as it spread throughout the United States, Canada, and around the world.

With more than 11,000 cases reported and 85 fatalities to date, A/H1N1 has not yet erupted into the "plague" that some feared, but it has questioned our readiness to confront more virulent forms of the disease that may come in the future.

Computational models show Spanish H1N1 with no drugs bound, Avian H5N1 with Tamiflu bound, and Swine A/H1N1 with Relenza bound.



To forestall the dangers of avian flu and other diseases, a team of researchers led by Klaus Schulten (from the Department of Physics, U. of Illinois at Urbana-Champaign) and Thanh Truong (Department of Chemistry, U. of Utah) involving their coworkers Eric Lee and Ly Le, respectively, have been using high performance computers to look inside the flu virus and study how antiviral medications interact with its proteins.

The project "turned very hot due to the world-wide health threat from swine flu," said Klaus Schulten, director of the Theoretical and Computational Biophysics Group at the Beckman Institute of his university. At the forefront of flu physics, the researchers found themselves in the midst of an emergency situation where their scientific insights would play a crucial role. When evidence emerged that the A/ H1N1 virus that led to deaths in Mexico was resistant against Tamiflu, one of the most prescribed anti-flu drugs, the stakes rose higher. Resistance to front line drug defenses could make swine flu a very dangerous virus.

The researchers faced some vital questions: How do drugs bind to the flu viruses? What made some forms of the virus resistant to previously-effective drugs? And was it possible to find a new weak spot on the virus by which a drug could permanently disable the whole suite of influenza viruses? These questions could only be answered, and answered quickly, by computational simulation.

"Simulations are the only way that one can visualize what is actually happening when a drug binds to a flu protein," said Lee. "They let us to peek into the molecule so we can see the atomic interactions that are responsible for the protein and drug binding events. This is important, because drugs are designed with these specific atomic interactions in mind."

The group had models of the Spanish and Avian flu viruses, but to understand the current outbreak, they needed to determine the three-dimensional structure of the new A/H1N1 virus, or more specifically the virus' neuraminidase protein: a mushroomshaped projection on the surface of the influenza virus that plays a crucial role in the virus' reproductive cycle.

Neuraminidase is the main target for commercial antiviral drugs, but it is also the most quickly evolving part of the virus, playing cat and mouse with drugs and necessitating new flu medications each year.

(clockwise) Thanh Truong, Department of Chemistry, University of Utah; Ly Le, Department of Chemistry, University of Utah; Eric Lee, research scientist at the Beckman Institute, University of Illinois; and Klaus Schulten, director of the Theoretical and Computational Biophysics Group and a faculty member at the Beckman Institute, University of Illinois



Combining genetic sequence data from swine flu samples with information from homology, or common ancestral characteristics (Swine flu is 91% identical to Avian flu), the researchers created the first atomistic model of A/H1N1 neuraminidase.

Then, using NAMD (NANoscale Molecular Dynamics), a powerful atomic-level 3D modeling program developed by the Schulten group, the scientists prepared simulations to show how the three virus neuraminidases (Spanish, Avian and Swine flu) interact with: the two mostprescribed flu-fighting medicines (Tamiflu and Relenza), two phase III trial drugs candidates (Peramivir and A-315675), and Sialic acid, their natural target on the human cell.

If they pushed the pace of their simulations, the research could provide useful insights in real time. The study could be crucial to stockpiling the right medicines and accelerating the design of new drugs to fight mutating viruses. But the researchers would need access to a supercomputer to develop a rapid prognosis of the swine flu virus' evasion

mechanism.

On April 30, Schulten called the Texas Advanced Computing Center (TACC) and received a special allocation on Ranger, one of the world's most powerful supercomputers, to execute emergency simulations.

"This is a perfect example of cooperation among TeraGrid staff to provide a research team with time-critical access to the petascale resources funded by the National Science Foundation," said Chris Hempel, TACC associate director of User Services. With priority access to Ranger through a special queue, the group employed between 2,000 and 3,000 processors continuously over two weeks, and produced simulations that revealed how drugs normally bind to the neuraminidase and how changes to the A/H1N1 protein could cause drug resistance.

Antiviral drugs work by binding in a deep pocket — a receptor — on the surface of the neuraminidase. "If that receptor is occupied by drugs, like Tamiflu or Relenza, then production of the virus is stopped," Schulten said. "The drug is like an off button."

The current strain of A/H1N1 swine flu does not appear to be drug resistant yet, but the high rate of mutations among normal seasonal strains of the flu may transfer their Tamiflu drug-resistance genes to the swine flu. Relenza and the phase III trial drugs are effective against Tamiflu-resistant strains. However, according to researchers, resistance to these new drugs is likely not far behind, underscoring the need to understand precisely how mutations make the flu immune to antiviral therapy.

By anticipating the likely atomic-level mutations in the virus' structure, they believe it will be possible to intelligently design a drug or vaccine that can't be resisted.

"We're in a race against nature," said Lee. "Mutations happen naturally and we have to predict what might happen and stay one step ahead."

The project represents a computational, as well as a scientific, breakthrough, according to Schulten. "We were able to learn something in a few weeks that usually would take many months," he said. "We investigated the site of the reactions and made sense of the interactions, and we think that our computational view can help create drugs that are optimally attuned to avoid resistance."

The group is preparing the initial results of their virtual drug trials for publication. They will continue to analyze their data in the coming months, while simulating potential mutant varieties of the flu viruses.

Supercomputers routinely assist in emergency weather forecasting, earthquake predictions, and epidemiological research. Now, says Schulten, they are proving their usefulness in biomedical crises.

"It's a historic moment," he said. "For the first time these supercomputers are being used for emergency situations that require a close look with a computational tool in order to shape our strategy."

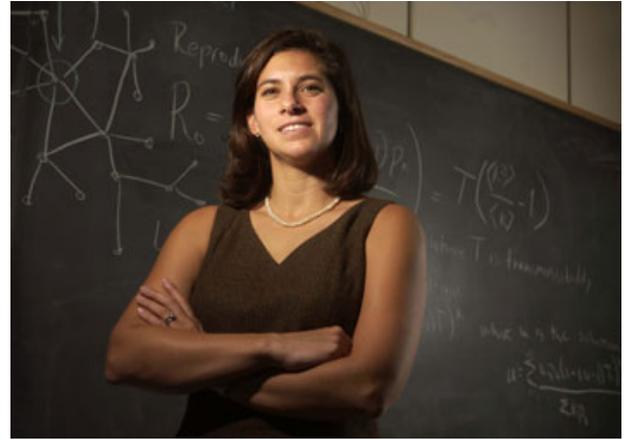
UT Austin researchers predict best intervention strategies for H1N1 virus

At The University of Texas at Austin, Lauren Ancel Meyers is using TACC's Lonestar supercomputer to predict how the new strain of H1N1 flu is spreading throughout North America and to determine the best intervention strategies.

"Our goal is to develop powerful and flexible software so that public health agencies like the Center for Disease Control (CDC) and British Columbia CDC can come to us with candidate intervention strategies and we can use our model to predict their effectiveness, and improve them," Meyers said.

For example, the United States has roughly 80 million doses of antiviral drugs in a stockpile. The important public health questions are: Given that a stockpile of anti-virals exists, which communities should get the first limited doses and in what quantity? What cities are the targets and what is the best timing for the other releases? Should the CDC

**Lauren Ancel Meyers, Associate Professor,
College of Natural Sciences, The University of
Texas at Austin and Associate Director of Division
of Statistics and Scientific Computation**



release the drugs to cities in proportion to population size? Would it be better to target releases to areas where swine flu cases already exist?

Meyers and her team are addressing these questions with their models. They have incorporated the latest information about H1N1 flu and are using their optimization software to determine the best timing and targets for vaccine, antiviral and other intervention resources. At this point, the results are for demonstration purposes only, but they illustrate the potential utility of these important computational tools.

According to Meyers, infectious disease epidemiology, especially on the modeling side, has advanced tremendously in the last decade.

"In the past, we've taken methods from statistical physics for modeling the spread of a liquid through a network and applied them to modeling the spread of disease through contact patterns in human populations," Meyers said. "In this case, we're taking methods developed for operations research and applying them to epidemiology to optimize intervention strategies. Multidisciplinary research is fueling great advances in our ability to predict and control infectious disease like North American H1N1 flu."

Klaus Schulten's work is supported by the grant from the National Institutes of Health P41-RR005969.

May 27, 2009

The Texas Advanced Computing Center (TACC) at The University of Texas at Austin is one of the leading centers of computational excellence in the United States. The center's mission is to enable discoveries that advance science and society through the application of advanced computing technologies. To fulfill this mission, TACC identifies, evaluates, deploys, and supports powerful computing, visualization, and storage systems and software. TACC's staff experts help researchers and educators use these technologies effectively, and conduct research and development to make these technologies more powerful, more reliable, and easier to use. TACC staff also help encourage, educate, and train the next generation of researchers, empowering them to make discoveries that change the world.