Protection and Cure in the Face of Nerve Agent Exposure

By Gary Sivak and Dinah Luneke

This Challenge project, "Defense Against Chemical Warfare Agents (CWAs) and Toxic Industrial Chemicals (TICs): Filtration, Prophylaxis and Therapeutics," was run at the ASC MSRC by Dr. Margaret Hurley, Army Research Laboratory (ARL), Aberdeen, Maryland, and collaborators Dr. Gerald Lushington and Dr. Jianxin Guo of the University of Kansas. ASC MSRC HPC System Utilization: 590,698 total hours

Dateline March 20, 1995, Tokyo, Japan. In an act of domestic terrorism, members of an obscure religious group, Aum Shinrikyo, perpetrated a Sarin gas attack on the Tokyo subway system, injuring thousands, and killing 12.

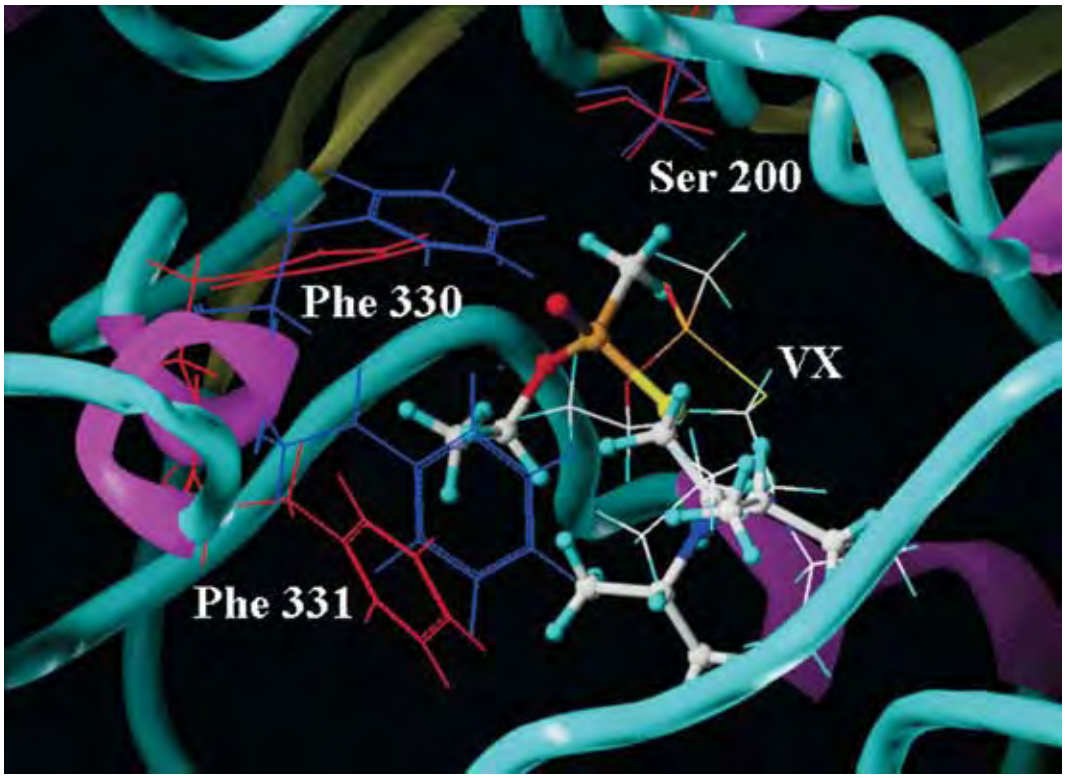
What if a similar attack were to occur against a group of our warfighters in the mountains of Afghanistan today? The goal of this project is to facilitate the development of compounds that can be administered to our warfighters for their protection and cure. While the primary emphasis of this research focuses on military applications, there are very far-reaching connections; as Dr. Hurley pointed out, "As this could be of interest for anyone from emergency first-response teams to agricultural workers exposed to chemically similar pesticides."

Research Goals

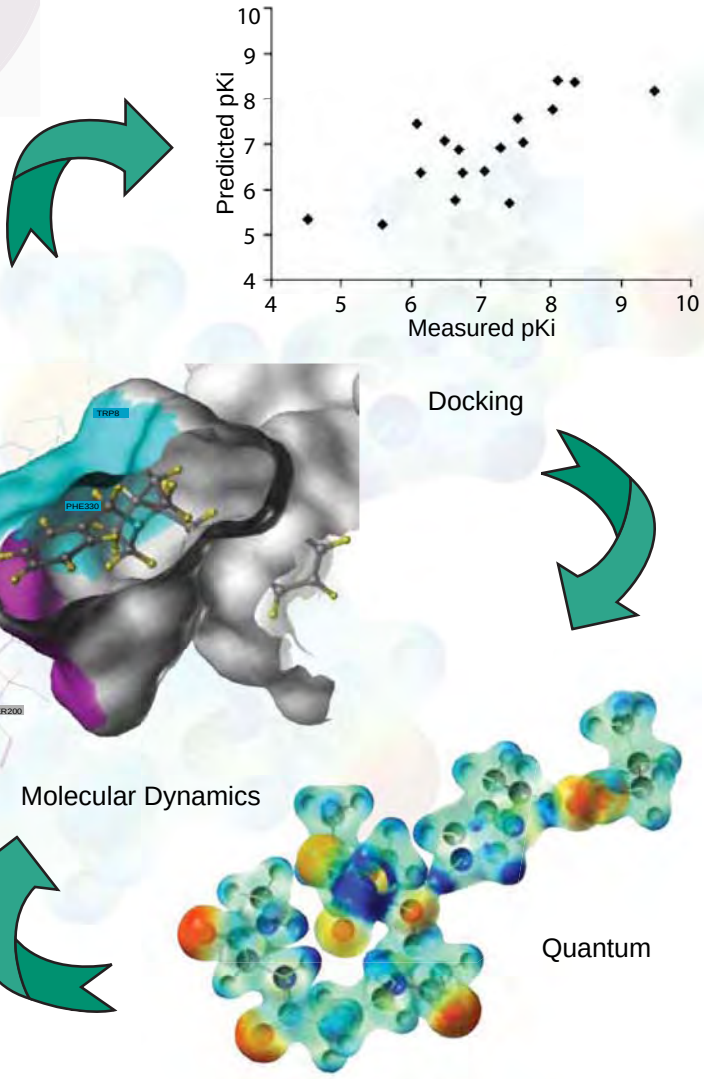
Through their computational chemistry studies at the ASC MSRC, Dr. Hurley and co-workers are investigating the many complex reactions by which nerve agents and other compounds bind with the enzyme acetylcholinesterase (AChE) within living systems. This project keeps progressing as new developments, refinements and discoveries are made. One goal is to analyze and help develop improved scavenger compounds, also called bioscavengers, to sweep up nerve agents from the body's systems over time. According to Dr. Hurley, "[the team] wants to develop a soup-to-nuts model of this enzyme in order to understand binding to and unbinding from cholinesterases, how to flush nerve agents out of the human body's systems, and what compounds to administer to protect soldiers."

Technical Details

Acetylcholine (ACh) is a neurotransmitter that transmits impulses from the human body's nerves to the muscles. After the muscle contracts, the body uses AChE to break down ACh, thereby instructing the muscle to stop contracting and to relax. When nerve agents bind to and irreversibly inhibit the action of the enzyme, the concentration of this neurotransmitter builds up, the nerves remain polarized, the muscles contract fiercely, and usually suffocate the victim by preventing breathing and heart action.



Molecular dynamics simulations show sympathetic side chain flexion assisting nerve agent transport to the active site.



Data at multiple time/length scales from theoretical modeling (docking, molecular dynamics, quantum mechanics) are used to study all aspects of transport and binding in cholinesterase systems.

Definitions

Acetylcholine (ACh) - a neurotransmitter that mediates between nerves and muscles. It allows electrical impulses to transmit along the nerves to the muscles. ACh is in the group of compounds called organic acid esters.

Acetylcholinesterase (AChE) - an enzyme produced in the body that breaks down the neurotransmitter acetylcholine after it instructs the muscle to contract.

Conformation - the allowed motions within the pieces of a molecule, as well as the shape and orientations the pieces can assume, as constrained by the bonds within the structure of a molecule.

Nerve Agent - a lethal chemical (organophosphate, liquid or gas) that binds to the AChE enzyme, preventing it from breaking down a build-up of ACh. Nerve agents disrupt the mechanism by which nerves transfer impulse messages to both organs and muscles.
Reference: http://en.wikipedia.org/wiki/Nerve_gas

QSAR - Quantitative Structure-Activity Relationship. A chemical statistical analysis technique.

Scavenger Compounds (also known as Bioscavengers) - function in the blood, like a sponge, to absorb the nerve agent before it can do its damage. They sweep up nerve agents because they bind to the nerve agents more strongly than the nerve agents bind to AChE. Reference: http://Nexiabiotech.com

Although this research is predominately applied science/chemistry, there is also a great deal of basic chemistry used. “The molecular interactions that hold the enzyme in its optimal conformation (shape) and promote catalysis have never been elucidated,” Dr. Hurley explained. “Therefore, toxicity prediction of nerve agents and antidote effectiveness can only be hypothesized by extrapolation from the behavior of familiar chemicals. A sound theoretical basis would allow reasonable predictions on compounds unrelated to those already studied.”

DoD HPC resources enable the team to extend their study of AChE inhibition to three increasingly intensive levels of chemistry theory:

- Virtual screening of inhibitor formulation (molecular docking) utilizes a Quantitative Structure-Activity Relationship (QSAR) database search. Pharmaceutical companies use this technique to screen candidates, and zero-in on likely active compounds for new drugs.
- Analysis of competitive transport kinetics (rate equations) involves nerve agents and therapies reacting with AChE. This deals with transport to the active site on the enzyme, i.e., the molecular movement, rather than typical chemical reactions or bonds.
- Prediction of reaction kinetics, thermodynamics and physical properties consists of fundamental modern chemistry using HPC and the equations of quantum mechanics. It predicts the geometries and energies (strengths) of the chemical bonds between AChE, nerve agents, and therapeutic agents.

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"In this research there exists so much activity occurring among the chemical constituents that you must study the effects on different time and length (distance or size) scales. The scales differ by many orders of magnitude," according to Dr. Hurley. "This is a multiscale study, and one code cannot compute it all. This research is not an idiot-proof black box approach, results are emerging simultaneously from quantum chemistry, molecular dynamics, and molecular docking, and results from each scale help provide a reality check for what's going on at the other scales."

Advancing the Front at ASC

Dr. Hurley primarily uses the Commercial Off-The-Shelf (COTS) codes Gaussian and Amber on the SGI Origin 3900 system at the ASC MSRC. "I like running at the ASC as their user services are great, and they do a great job with a completely seamless process," Dr. Hurley remarked. "The ASC MSRC HPC systems are stable and provide the reasonable throughput that I need. Running on these HPC systems affords me a higher fidelity for my research. In computing using quantum mechanics, it is impossible to achieve this caliber of result without HPC. In the future, I expect more of the same level of quality service that I currently receive."

Value to the DoD

Dr. Hurley says that the beauty of this research involves saving money on lab experiments and tests. For example, her QSAR methods have demonstrated a high level of predictivity, yielding a high correlation value of 0.69 between the calculated results and experimental values, for a 16 molecule test set. [1] "With other methods, you're lucky to get a correlation value of 0.13," according to Dr. Hurley.

Additionally, a sound working model of AChE inhibition would also help speed the scavenger development process, thereby better protecting our warfighters.

For more information, contact the ASC MSRC at asc.hp.outreach@wpafb.af.mil.

References

[1] Multiscale Computational Studies of Cholinesterase Inhibition for Improved Therapy and Protection Against Nerve Agent Exposure

User Tip!

Debug Queue
Check for errors in these areas:

- Syntax errors
- Environment variables
- Successful copying of files
- Changing to the right directories
- Ensure mail messages are sent

More info: www.asc.hpc.mil/customer/userdocs

User Tip!

Quick Reference Guides are readily available on our website. Gain the most from our HPC resources by accessing this documentation designed to help you better understand how to use the resources of the ASC MSRC.

www.asc.hpc.mil/customer