Painkiller Snails

University of Utah scientist Tom Cheatham is gaining new insight into snail toxins that can treat human pain.

Although they come in pretty shells shaped like ice-cream cones and are popular for jewelry, cone snails are carnivorous hunters, and some of the larger species can be deadly to humans. They are equipped with a barbed, hollow tooth that launches like a harpoon. A neurotoxic venom paralyzes small fish almost instantly.

The good news is that these cone-snail venoms, known as conotoxins, show promise in humans as potent painkillers. One conotoxin-derived drug, Ziconotide, received FDA approval in 2004, and others are being tested as possible treatments for Alzheimer’s disease, Parkinson’s disease and epilepsy.

University of Utah pharmaceutical chemist Tom Cheatham and visiting student Pawel Gruszczynski from the University of Gdansk in Poland are using Pople, PSC’s shared-memory SGI Altix, to investigate a family of conotoxins called Mu-conotoxins. “These toxins,” says Cheatham, “are tissue specific and act by binding to voltage-sensitive sodium channels.” Using long-timescale molecular dynamics (MD), with software called AMBER, Cheatham’s group is working to predict and refine the structure of these conotoxins. With Pople, says Cheatham, the aggregate throughput was excellent. “We benefit from the fastest and most balanced machines.”

Their results, analyzed in collaboration with University of Utah experimentalists Greg Bulaj and Toto Olivera, make it possible to map the pharmacophore—the essential molecular features responsible for the drug’s biological activity. This work aims toward identifying the precise atom-by-atom details of how conotoxin molecules—short amino-acid chains called peptides—have their potential pain-killing effect.

Like many games, poker can be formulated mathematically, but the formulations are huge. Two-player poker has a game-tree of a billion—billion (10^18) nodes, notes Gilpin. “To solve that requires massive computational resources. Our research is on scaling up game-theory solution techniques to those large games, and new algorithmic design.” The most computationally intensive portions of their algorithm are a matrix-vector product where the matrix is the payoff matrix and the vector is a strategy for one of the players. This operation accounts for more than 95 percent of the computation, and is a bottleneck to applying game-theory to many problems of practical importance.

To drastically increase the size of problems the algorithm can handle, Gilpin and Sandholm devised an approach that can potentially exploit massively parallel systems of non-uniform memory-access architectures, such as Pople, PSC’s SGI Altix. By making all data addressable from a single processor, shared memory simplifies a central, non-parallelizable operation performed in conjunction with the matrix-vector product. Sandholm and Gilpin have revised their code to run on Pople, and are doing experiments to learn how much parallelism can help, and possibly point to areas for further algorithmic improvement.
To Stop the Pandemic

Modeling with PSC shared-memory resources will improve decision-making in deploying vaccines to stop disease outbreaks

With support of a $10-million grant from the Bill & Melinda Gates Foundation, a team of researchers, including PSC scientist Shawn Brown, is using PSC resources to explore computational models that simulate the spread of infectious disease. The grant funds computer simulations of epidemics to show worst-case and best-case outbreak scenarios. Findings will be used to evaluate new vaccine technologies and modes of vaccine delivery. The goal is more informed decision-making in deploying vaccines in pandemic outbreaks and, in general, to support World Health Organization Communicable Disease Control programs.

The work is coordinated through the Vaccine Modelling Initiative (VMI), headquartered at Pitt’s Graduate School of Public Health (GSPH). VMI is a research partnership among infectious disease experts and public health officials at Johns Hopkins University, Médecins Sans Frontières Epicerite, University of Georgia, Resources for the Future and the World Health Organization. The project will exploit the shared-memory environment of PSC’s SGI Altix to build extensive agent-based models of disease spread in a number of third-world populations. The group expects that a large shared-memory system will improve their ability to complete full studies in a timely fashion.

“Infecious diseases create an enormous burden on the world’s population, from both a human suffering and an economic development perspective,” says Donald S. Burke, M.D., principal investigator of the grant and dean of GSPH. “One of the major challenges we face in stopping infectious disease outbreaks is predicting how control strategies, such as vaccines, will work. By using computer models to conduct epidemiology in silico, we will be able to test the impact of new candidate vaccine technologies and select the most effective strategies.”

Initially, the project will focus on evaluation of new vaccine technologies for influenza, measles and Dengue, a mosquito-borne infection, diseases that affect millions of people globally. Later, the project will develop vaccine models of epidemic pertussis, typhoid, polio, pneumococcus, malaria and tuberculosis.

Day 35 of an influenza outbreak in the United States is visualized with an agent-based model written by Neil Ferguson, Imperial College, London, on PSC’s SGI Altix. The image shows the infected population (red) and population segments at risk (purple). PSC scientist Shawn Brown created this visualization with a PSC-developed interface to Google Earth.
Attracting Future Scientists

An innovative science-learning program called CMIST is helping teachers bring science to life for high-school students.

“The visualizations allow them to understand the concepts as they actually occur,” says Rebecca Day, who teaches high-school biology near Pittsburgh. “It’s one thing to read about it, another thing entirely to see it happening,” says Marian Opest, who teaches science in the Pittsburgh suburb of Penn Hills. They’re talking about CMIST (Computational Modules In Science Teaching), an innovative science-learning program for high-school students developed by a team at PSC.

“CMIST addresses the challenge of science learning for the video-gamed, TV-nation, multitasking population of students,” says Pallavi Ishwad, education outreach specialist for PSC’s National Resource for Biomedical Supercomputing (NRBSC). Ishwad, NRBSC director Joel Stiles, scientific e-learning specialist Jenda Domaracki (NRBSC), and visualization specialist Jacob Czech created and developed CMIST as a learning tool that could reach the majority of students, not just the self-motivated few. The hook is appealing content in an easily usable form.

In contrast to many other teaching tools, CMIST modules are produced with realistic modeling and simulation software, such as developed and used in research at PSC. The pilot module, "Molecular Transport in Cells," produced with software called MCell and DreAMM (co-authored by Stiles and used in research centers around the world) presents important principles of osmosis and diffusion with 3D examples. Recent new modules include "Brownian Motion" and "Enzyme Structure and Function." CMIST is distributed as ready-to-use DVDs that include complete lecture slides, animations, a lesson plan aligned to national and state standards, and worksheets with answer keys.

Packed in large part by NIH, the CMIST team has presented the program to regional high-school science teachers in half-day workshops at which teachers have given enthusiastic, positive feedback. PSC has also presented CMIST to teachers and administrators at state and national meetings, and is introducing web-based plans aligned to national and state standards, complete lecture slides, animations, a lesson plan aligned to national and state standards, and worksheets with answer keys.

PSC’s Pittsburgh Supercomputing Center is adapting the Linux-based program to run on desktop platforms, and is developing a curriculum to go with it. Marylou Kunkle, like Soyke an undergrad at the University of Illinois Urbana-Champaign, is adapting the Linux-based program to run on desktop platforms, and is developing a curriculum to go with it. Marylou Kunkle, like Soyke an undergrad at the University of Illinois Urbana-Champaign, is adapting the Linux-based program to run on desktop platforms, and is developing a curriculum to go with it. Marylou Kunkle, like Soyke an undergrad at the University of Illinois Urbana-Champaign, is adapting the Linux-based program to run on desktop platforms, and is developing a curriculum to go with it. Marylou Kunkle, like Soyke an undergrad at the University of Illinois Urbana-Champaign, is adapting the Linux-based program to run on desktop platforms, and is developing a curriculum to go with it. 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