A pathologist peers into her microscope, studying cells from a prostate tumor, slender stems forming serpentine curves. She examines the amount of tissue between tumor cells, the size of the nuclei, and many other aspects of the cells, which have been stained with special dyes to make their features more visible. She looks at several different slides of the same tumor. She then grades the tumor, assigning it a number from one to five that ranks its severity. She thereby plays a key role in determining how that tumor will be treated.

It’s not at all unlikely that the grade she assigns would be assigned differently by another pathologist.

“Grading is one of the most critical parts in the classification of cancer, but it’s also one of the most subjective,” says Michael Becich, associate professor of pathology at the University of Pittsburgh School of Medicine. He believes survival rates for those with prostate cancer would improve if tumor grading were more objective, so he taught a machine with superhuman capabilities to help pathologists with their jobs.
Pitt Med

PSC's system is hundreds of times faster than a desktop computer, and it's about to get faster. PSC just got a turbocharge from the National Science Foundation (NSF). After intense lobbying from scientists throughout the country who made the case that an even more powerful supercomputer was needed to advance nonmilitary research, the agency chose PSC as the site for a $45 million terascale Compaq system capable of six-teraflop processing; the system should be completed this fall. In case you haven't been keeping up with your latest issues of *Supercomputing Today*, a teraflop is a trillion calculations per second. In other words, PSC's new system will be able to perform 1,000 calculations for every person on the planet in just one second. With 2,728 processors, each four times faster than today's best desktop processors, the terascale supercomputer will have a peak speed 13 times faster than PSC's current machine. It will be 10,000 times more powerful than a desktop computer. PSC's existing system is fast, no doubt. Its new terascale system will be what scientists refer to as really fast. It will give them the capability to do what, until now, they have only imagined.

"You attack a totally different set of problems if you have that speed at your fingertips," says Ralph Roskies, Pitt professor of physics and coscientific director of PSC, which is a collaboration between Pitt, Carnegie Mellon University, and Westinghouse Electric Company.

Roskies likes to compare supercomputers to cars. A car does little beyond moving you faster than you would otherwise, yet cars have totally transformed society. Likewise, a supercomputer's primary asset is speed. And likewise, the supercomputer's speed is transformative—allowing scientists and engineers to shed new light on old problems. Using PSC, astrophysicists are simulating black holes, meteorologists are developing more precise weather forecasts, and engineers are designing more efficient power-generating turbines. In the biomedical arena, all that computational power has gone straight to some researchers' heads, in the very best sense. It has given some creative minds a powerful tool in their examination of wellness and disease, and in their approaches to diagnosis and treatment.

Becich's supercomputing access meant he could be more inventive as he thought about how to improve the lot of the some 180,000 American men diagnosed each year with prostate cancer (nearly 32,000 of whom die).
What he came up with is a quality-assurance tool to aid pathologists in grading prostate tumors.

To create this tool, Becich gave the supercomputer the oncological equivalent of a handwriting-analysis lesson. This is how his system works: Becich gives the supercomputer a slide that has been converted into a numerical format a computer can recognize. The computer studies the tumor and calculates its “digital signature.” The signature is like a list of vital statistics. It describes those features of the tumor that have proven most useful in enabling the computer to distinguish among the five grades. For example, the signature includes stats based on the tumor’s “spanning tree”—a branching, angled line that connects all of the cell nuclei in the shortest possible route. In the higher grades of cancer, the spanning trees have longer line segments and sharper angles between line segments, which means a tumor is more severe. Likewise, shorter line segments and softer angles signal less-advanced tumors.

The supercomputer then compares that digital signature to what is in its storehouse—a computerized gallery of prostate tumor images. The computer has already calculated the signature for each image in its storehouse, which also has been graded by an expert pathologist. The computer hunts through the storehouse to find images that most closely resemble the unknown tumor and gives the pathologist a ranked list of likely matches. The pathologist can then view the matching tumors and the grades assigned to them.

Pathologists won’t need supercomputers to use Becich’s diagnostic tool. Becich is applying what he is learning from his PSC work to build a diagnostic aid that pathologists can run on a desktop computer using a CD-ROM.

Becich’s work could help pathologists throughout the world with their diagnoses. He has grander plans, too. A while back, he started to wonder if the supercomputer could actually teach humans new ways of looking at tumors.

Becich has found a way to get the supercomputer thinking for us: In research he’s planning, the supercomputer will analyze data from 600 prostate cancer patients. The data include slides of the patients’ tumors, along with details about what happened to each patient over a 10-year period. The computer will then group together those patients whose disease followed the same course, regardless of the grade assigned to their tumor. For example, it will group those who developed metastatic disease. The computer will look at all the slides from these patients and ask, What features do these tumors share that are not present in the tumors that proved to be less aggressive? How might we predict from the slides which tumors will progress to metastatic disease?

“The fun part is letting the computer go free and saying, find me all the features that predict these bad ones,” says Becich.

The work of assistant professor of anesthesiology Pei Tang is, in supercomputing jargon, computationally intense. In other words, it requires a lot of effort on the part of the supercomputer—billions and billions of calculations. When Tang submits a project to PSC, the center usually dedicates 128 processors to it, and each processor works for 240 hours—10 days—to finish the job.

Tang’s goal is to understand how general anesthesia works its magic, rendering people unconscious, ensuring they feel no pain during surgery, and leaving them with no memory of the operation. Though general anesthesia has been used for more than a century, no one understands why or how it works. In her attempt to lay bare the mystery, Tang decided superhuman, or at least supercomputational, methods were in order.

Like any investigator who wants access to PSC’s behemoth system, Tang submitted a proposal for supercomputing time—competing with scientists from across the country. Because of the computational intensity of Tang’s project, a panel appointed by NSF reviewed her proposal. (Smaller runs can be approved internally at PSC.) As a noncommercial researcher, Tang was awarded time on the machine for free.

Tang, who is a PhD and chemical physicist, is determined to unveil what’s happening at the molecular level when someone is anesthetized. Although laboratory techniques such as crystallography can provide still representations of molecules, computational modeling allows Tang to see how molecules move individually and at split-second intervals. Before the computer can determine how the molecules will move, Tang must first describe all the atoms involved. No simple task. She starts with a general physiological situation she wants to model and then creates a lineup and stats for every single atomic player.

From her laboratory experiments, Tang knew that anesthetics affect cell membranes, particularly the ion channels through which ion particles pass in and out of the cell. Cell membranes are complex, so Tang created a simplified model of a membrane and an ion channel traversing it.

Tang describes her model as a sandwich. Imagine a double hamburger—bun, meat patty, meat patty, bun. The two inner layers—the meat patties—are the lipid bilayers. Semipermeable, water-repellent, and made of fats, these lipid bilayers are basic ingredients in cell membranes. The two outer layers—the buns—are the water molecules that surround cells in abundance. Imagine a straw going all the way through the sandwich from top to bottom. This is the ion channel. In her model, molecules of halothane—the anesthetic Tang chose for her model—interact with this simplified representation of a membrane.

Her next step was to specify exactly how many molecules would be part of the model—5,538 water molecules, 182 lipid molecules, 10 molecules of the anesthetic halothane, and one macromolecule of the protein gramicidin, which single-handedly forms the ion channel. She next broke each molecule down into its constituent atoms—16,614 atoms from water, 21,476 from the lipids, 80 from halothane, and 552 from gramicidin. One measuring stick for a simulation is the number of atoms it contains. At 38,724 atoms, Tang’s system is considered huge.

Tang’s next job was to describe the features of every single atom, including its relationship to each of the other 38,723 atoms, in the only terms the computer understands—numbers. Her numerical portrait of each atom delineated characteristics such as the attractions and repulsions among atoms. She compiled a host of descriptive details for every single atom.

Then it was time to let the supercomputer stew. She gave it the information about all the atoms. She gave it the laws of physics that allow her to calculate the atoms’ activity.

The supercomputer’s job was to track the atoms for two nanoseconds (a nanosecond is 10⁻⁹ or .000000001 second). That couldn’t take much time, right? Wrong. Remember,
Tang’s work is computationally intense—one run takes 10 days. Here’s how the supercomputer spends those days:

To get a slow-motion picture of those two nanoseconds, the computer breaks time into femtoseconds (femto is $10^{-15}$ or 0.000000000000001 second), and takes a numerical snapshot at each femto-interval. It captures the atoms at a given instant by calculating all the physics equations for the set of nearly 40,000 atoms—which takes a single processor about a minute. Then it moves forward another femtosecond and churns through the equations again. And again. And again. There are a million femtoseconds in a nanosecond, so the computer must run through the calculations two million times. Simulating what happens to the atoms during two nanoseconds ends up taking 30,720 processor hours. (A processor hour is an hour on one of the supercomputer’s many processors.)

What the supercomputer finally spits out at the end is a bunch of numbers—an account of the atoms at each femtosecond slice of time. Software converts the numbers into an animated movie, stretching the two nanoseconds into several seconds so that human eyes can watch the molecules in action.

Tang’s simulation shows that the halothane molecules tend to go to the region where the lipid and water molecules meet. They are drawn to a particular segment of the gramicidin found on each side of the entry to the ion channel.

Her persistence is paying off: A revealing picture of halothane is emerging.

James Antaki got tired of taking stabs in the dark—that’s why he has turned to PSC.

Throughout the past 50 years, researchers like Antaki have tried to find a safe way to pump blood artificially in patients whose hearts are failing. Initially, they removed the
diseased heart and replaced it with an artificial one, but that increased blood clotting. Later, they found that, instead of removing the heart, they could implant a booster pump to supplement or take over its function. The booster pumps, however, also have blood-clotting problems and are not considered safe for long-term use. They are used only as a stopgap measure to hold off death in the hope that a donor organ can be found for a heart transplant. If, however, these pumps were safe enough to be implanted for years rather than just months, they might serve as an alternative to heart transplants. Today, some cardio researchers see the design of a safer pump as the brass ring.

Their efforts are hit-or-miss. They speculate that a particular alteration will have a desired effect and then build a model to test their theory. There’s a smarter way to approach redesign, believes Antaki, who is an associate professor of surgery and mechanical engineering at Pitt. He contrasts the design of heart pumps to that of aircraft. Today, the airline industry would never develop an aircraft propeller design through guesswork. It would never evaluate the design by building the propeller, installing it on a plane, and taking the plane for a test flight.

“The aircraft industry has sophisticated mathematical and numerical models that facilitate the design of safe, economical aircraft, while the analogous models for artificial organs are still in an embryonic stage,” wrote Antaki in a recent proposal to NSF. He wants to bring pump design into the jet age.

The proposal submitted by Antaki and his collaborators, including Omar Ghattas of Carnegie Mellon University, who is the principal investigator, was one of only 63 funded out of 1,400 submitted to an NSF program supporting information technology research. They were awarded $4.9 million to create blood flow models that will expedite the design of a better heart pump. By the time they’ve finished the project, they hope to have modeled tens of thousands of red blood cells suspended in fluid. They’ll use the supercomputer to track the activity of the cells—how they clump, alter their shape, rupture, bounce off one another, flow in a variety of conditions, and become damaged by the pump.

The task will not be easy. Currently, no techniques exist to model the flow of bodies that interact and collide. NSF has given Antaki and his collaborators five years to develop computational methods to harness the supercomputer’s power. If they succeed, they will have built the most detailed, realistic model of blood flow ever made.

Then they can make a calculated and well-rehearsed lunge for that brass ring—a truly safe and effective heart pump.

Given the track record of the hardware industry, it may be that one day we’ll all have terascale computers on our desks. That’s when Ralph Roskies and his colleagues at PSC will be off building a computer some-multiple-of-a-trillion-scale, a system so powerful we’ll have to make up new prefixes, expand our language. And all those processors chugging away, churning out a godzillion calculations every Zen-second—they’ll just be working harder and harder to keep up with the human imagination.