PEREGRINE: Improving Radiation Treatment for Cancer

PEREGRINE "... is a unique system of enormous value to society in terms of improving local control and reducing complications in radiation treatment of cancer."
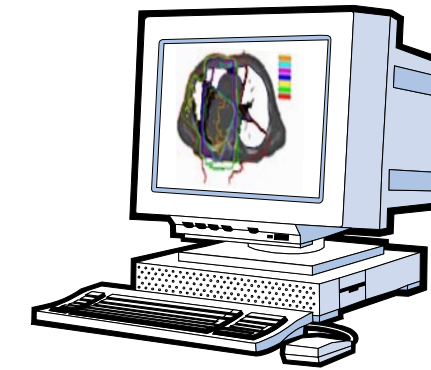
—*Noted medical physicist Dr. Radhe Mohan*

Figure 1. Livermore is using its PEREGRINE radiation therapy planning process to improve major parts of the cancer treatment process, which includes (a) diagnosis using high-resolution CT (computerized tomography) scans, (b) treatment planning, and (c) actual treatment.

EVERY year, about 1.25 million people in the United States are diagnosed with life-threatening forms of cancer. About 60% of these patients are treated with radiation; half of them are considered curable because their tumors are localized and susceptible to radiation. Yet, despite the use of the best radiation therapy methods available, about one-third of these "curable" patients–nearly 120,000 people each year–die with primary tumors still active at the original site.

Why does this occur? Experts in the field have looked at the reasons for these failures and have concluded that radiation therapy planning is often inadequate, providing either too little radiation to the tumor for a cure or too much radiation to nearby healthy tissue, which results in complications and sometimes death.

What can be done to improve this prognosis? Since 1993, Lawrence Livermore National Laboratory has combined its renowned expertise and decades of experience in nuclear science, radiation transport, computer science, and engineering to adapt nuclear weapons Monte Carlo techniques to a better system for radiation dose calculations. Mentored in particle interactions and nuclear data by Lawrence Livermore physicists Bill Chandler and Roger White, and armed with seed money from Livermore's Laboratory Directed Research and Development, medical physicist Christine Siantar began directing a small project to develop PEREGRINE, with the mission of providing better cancer treatment.

What resulted is a radically new dose calculation system that for the first time can model the varying materials and densities in the body as well as the radiation beam delivery system. According to program manager Edward Moses, the PEREGRINE team is moving these unique radiation therapy planning capabilities into the hands of the medical community so that doctors will have the most accurate tool available to plan radiation treatments that cure cancer.

PEREGRINE Breakthrough

PEREGRINE breaks the barriers to accurate dose calculation with the first full-physics model of the radiation treatment process. It uses Monte Carlo calculations, in which statistical sampling techniques are used to obtain a probabilistic approximation of a problem's solution. This enables PEREGRINE to model how trillions of radiation particles interact with the complex tissues and structures in the human body and where they deposit their energy. In the past, Monte Carlo calculations, known to be the best way to model these interactions, would have required days or weeks of supercomputer resources—impractical for radiation treatment planning. The PEREGRINE team has designed and built the Monte Carlo system to plan accurate radiation treatments at a cost and speed practical for widespread medical use. PEREGRINE uses advanced algorithms integrated with off-the-shelf computer hardware configured in sophisticated architectures to bring Monte Carlo–based treatment planning to the desktop.

Better Treatment Strategies

Experts have looked at the diagnosis and treatment planning process to try to explain why current cancer treatments are not more effective.

When a physician suspects malignancy, a computerized tomography (CT) scan is made of the suspected area to determine the exact position and extent of the tumor. If the cancer has not yet metastasized and is susceptible to radiation, the next step is to develop a plan for radiation treatment (Figure 1). Although CT scans provide radiation planners with a three-dimensional (3D) electron-density map of the body, current dose calculation methods model the body as a virtually homogeneous "bucket of water." Inhomogeneities, such as bone and airways, are ignored or highly oversimplified.

Furthermore, interpolated data from dose measurements made in water are used to calculate radiation treatments. These calculations are also based on a variety of simplifications in the way radiation is produced by the source, how radiation travels through the body, and how its energy is deposited.

Some tumors are particularly difficult to treat with radiation because of their proximity to vital organs, the abundance of different tissue types in the area, and the differences in their susceptibility to radiation. Cancers of the head and neck, lungs, and reproductive organs are examples. Radiation planners know that too small a dose to the tumor can result in recurrence of the cancer, while too large a dose to healthy tissue can cause complications or even death. Because of the inaccurate dose provided by today's calculations, doctors trying to avoid damage to healthy tissue sometimes undertreat cancerous tissue (Figure 2).

PEREGRINE is a tool that meets these clinical challenges. It is the only dose calculation system that can be used for all types of radiation therapy, can exactly model the radiation beam delivery system being used for each treatment, and uses each patient's CT scan as a basis for the dose calculations. "Most importantly, the PEREGRINE 3D Monte Carlo algorithms, used with Livermore's atomic and nuclear databases, enable the most accurate dose calculations," Moses says. "These breakthroughs could profoundly impact cancer treatment and the lives of patients who might otherwise die."

When PEREGRINE becomes available for commercial distribution, it will deliver dose calculations economically in today's competitive health-care industry. Because it also can
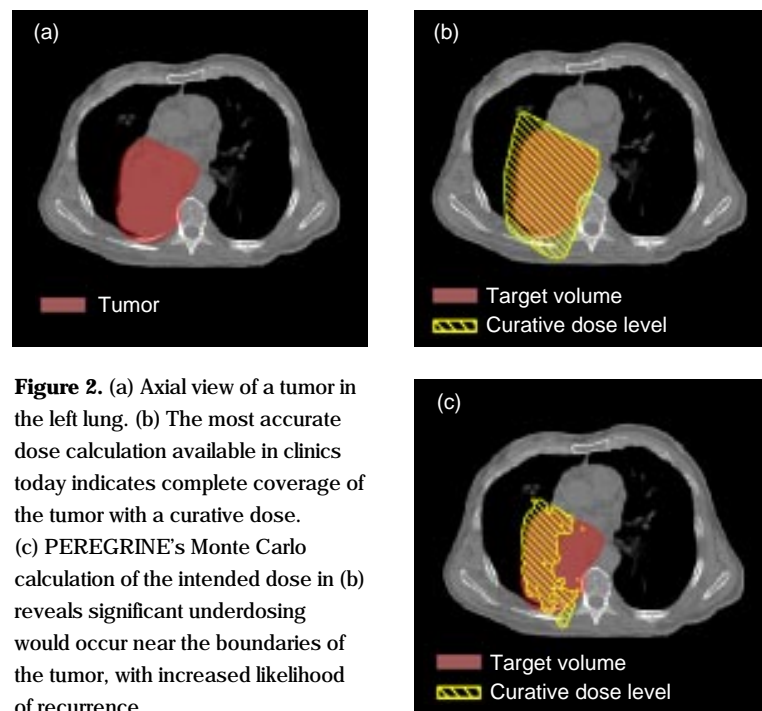
Figure 2. (a) Axial view of a tumor in the left lung. (b) The most accurate dose calculation available in clinics today indicates complete coverage of the tumor with a curative dose. (c) PEREGRINE's Monte Carlo calculation of the intended dose in (b) reveals significant underdosing would occur near the boundaries of the tumor, with increased likelihood of recurrence.

be integrated into existing radiation treatment planning systems through standard network connections, PEREGRINE can be installed in every cancer clinic. With PEREGRINE in the hands of radiation oncologists, patients will have access to an unprecedented level of accuracy in treatment planning. Armed with improved knowledge of predicted dose, physicians will be able to develop aggressive new treatment strategies that minimize the risk to patients. (See the box below for more information on radiation therapy.)

Lawrence Livermore has applied for two patents for key software and hardware elements and intends to submit its first application to the U.S. Food and Drug Administration (FDA) later this year. "Our goal is to make PEREGRINE available for use in cancer treatment centers by late 1998," Siantar says.

Radiation Therapy

Radiation has been used to treat cancer for almost 100 years. However, in most cases, a radiation dose sufficient to kill a tumor may also injure or damage nearby vital tissues or organs. Successful therapy thus depends on choosing the right type of radiation and applying the right amounts to the right places.

Today, tumors usually are treated by beams of particles from a particle accelerator, a process known as teletherapy, which is performed with any of four types of radiation. Photon or electron beams are the most frequently used, while therapies using neutrons or heavy charged particles such as protons are largely experimental. Occasionally, treatment may derive from a radioactive source that is planted inside the body, a treatment known as brachytherapy.

Photon beam energies are high enough for them to be considered x rays. They have moderate to long ranges (tens of centimeters), so they can be used for internal tumors. Photon therapy accounts for about 90% of all radiation treatments in this country.

About 10% of cancer patients receive electron therapy. Electron beams are useful for shallow cancers because electrons have limited penetrating power. Electron treatment spares deeper-lying tissues but is not effective for internal tumors.

High-energy proton beams can be designed to deposit most of their energy at one predictable depth or range. By controlling the beam energy, oncologists can control their range. A planner can tailor a proton beam to deliver most of its radiation dose into the tumor while avoiding healthy surrounding tissue. Unfortunately, proton therapy is very expensive and is available at only two centers in the U.S.

Neutron radiation has the advantage of being more effective than photons for treating some types of radiation-resistant tumors. But neutron treatment is also very damaging to healthy tissue. Experimental treatment is available at just 20 centers worldwide.

New radiation therapies are being developed to treat highly invasive tumors and cancer that has already metastasized. In experimental boron neutron-capture therapy, neutron-absorbing boron is injected into the body where it is absorbed by cancerous cells. When the body is irradiated by neutrons, the neutrons are preferentially absorbed by the boron in the tumors and the tumors are destroyed. Radio-immunotherapy, another approach under study by the research community, uses the chemistry of the body's immune system to target radioactive compounds at metastasized cancerous tumors.

PEREGRINE is now being used in research on photon, electron, proton, and neutron treatment at several leading hospitals across the country. Plans for research with PEREGRINE in the next year include collaborations on boron neutron-capture therapy, brachytherapy, and other advanced methods.

PEREGRINE in Action

The PEREGRINE dose calculation includes two main steps: defining the treatment by describing the radiation source and the patient, and calculating the dose.

Treatment Definition

The treatment-definition generator prepares the data for the specific treatment. As input, the generator requires three data sets for each treatment: the patient transport mesh, the treatment radiation source, and the particle interaction database.

Patient Transport Mesh. The patient's CT scan is composed of a stack of image "slices" (Figure 3a). From these, PEREGRINE creates a 3D map—the patient transport mesh—of the density and composition of all the matter in the vicinity of the radiation beam (Figure 3b). The system creates this map from the CT scan by assigning a material and density value to each volume element (voxel) in the scan. The transport mesh enables PEREGRINE to model details of the patient's body—including irregularities on the body surface, air cavities, and differences in tissue composition—with unprecedented, submillimeter accuracy.

The Radiation Source. Accurate dose calculations also depend on reliable information about the characteristics of the radiation beam delivery system. PEREGRINE is the first dose calculation system to use a complete model for the radiation source of each type of accelerator. The system models the source by dividing the beam delivery system into two parts (Figure 3c). The upper portion of the delivery system is the accelerator itself, with components that do not change from treatment to treatment. The lower portion of the model has components such as collimators, apertures, blocks, and wedges, which are used to customize the beam for each patient's treatment to ensure coverage of the tumor.

PEREGRINE draws from built-in source libraries to model the upper portion of the system and combines that information with the treatment-specific configuration of the lower portion to produce a model of the radiation being delivered. The source model is the first to provide an accurate, comprehensive description of photon, electron, neutron, or proton treatment beams as they enter the body.

Particle Interaction Data. In support of its national security missions, Livermore has developed and maintains the world's most extensive set of atomic and nuclear interaction databases. These huge databases contain information about particle interactions that enable the all-particle tracker to calculate how every

Figure 3. PEREGRINE models both the patient and the radiation source to ensure accurate treatment planning. (a) The CT scan is a stack of image slices less than 1 centimeter (cm) apart. From these, PEREGRINE creates (b) a 3D transport mesh of the patient to model how radiation will interact with the materials in the body. (c) PEREGRINE also models the radiation beam source in two parts: the accelerator itself (above the beam definition plane) and the components that customize the beam for each treatment.
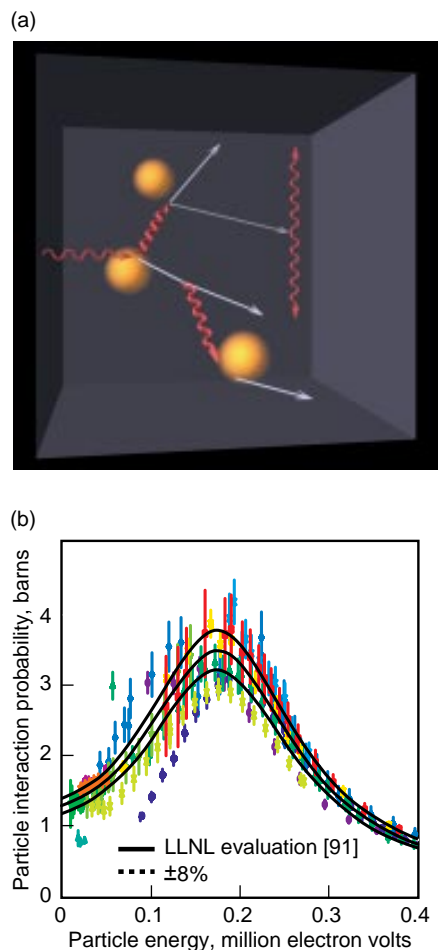
(a) CT-scan stack of patient

(b) Patient transport mesh

(c) Radiation source model

(a)

(b)
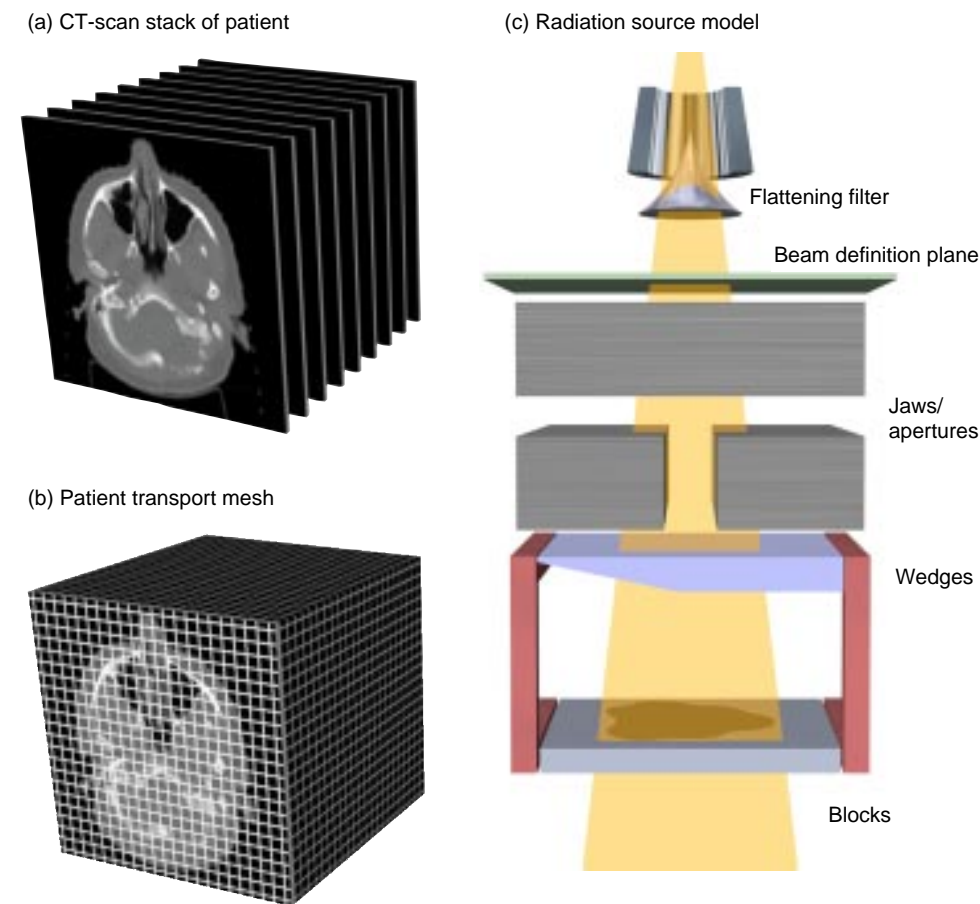
Figure 4. (a) When a particle interacts with the atoms in the body, it creates a shower of secondary (daughter) particles, which in turn move through the body. Lawrence Livermore's all-particle Monte Carlo codes predict these interactions based on the information in the Laboratory's comprehensive atomic and nuclear reaction databases. These databases are derived from the best available measurements and theoretical calculations. (b) The probability of particle interaction depends on the type of particle and the particle's energy.

isotope of every element on the periodic table will interact with any radiation particle. To describe the interaction of radiation particles with the muscle, fat, air, bone, lung, and other tissue in our bodies, PEREGRINE uses interaction data for combinations of these elements (Figure 4). Fatty tissue, for instance, is 12% hydrogen, 64% carbon, 1% nitrogen, and 23% oxygen by weight. Knowing how various radiation particles will behave with these elements enables the system to predict how they will behave in our bodies.

Monte Carlo All-Particle Tracker

The tracker selects a particle from the radiation source and tracks it through the patient transport mesh until it undergoes a collision. PEREGRINE then consults the interaction database and retrieves information on the incident particle and all secondary (daughter) particles resulting from the collision. All the daughter products are tracked as they travel through the transport mesh until they are absorbed in the body or leave the patient. During the simulation, PEREGRINE records the energy deposited at each interaction, building up a map of absorbed dose in the patient transport mesh. By repeating the process for millions of the trillions of particles a patient receives in a treatment, the Monte Carlo algorithm produces a statistically realistic picture of an entire irradiation. Figure 5 illustrates the dose buildup in a radiation treatment. The more particles that are tracked, the more accurate is the simulation of the treatment and the better is the information for the doctor. But tracking particles takes time, and therein lies the challenge—attaining both accuracy and speed.

Supercomputer to Desktop

The historical problem with Monte Carlo has been that the radiation treatment

planning community cannot afford a turnaround time of more than an hour to meet its caseload. Previously, even on a $20-million Cray-1 supercomputer, a single dose calculation took weeks to complete. So Monte Carlo calculations remained in the weapons, reactor, and high-energy-physics research communities where the turnaround time for calculations could stretch over months.

Livermore computer experts have combined state-of-the-art computation techniques and advanced computer architecture to bring Monte Carlo treatment planning to the hospital desktop and office network environment. Taking advantage of recent strides in microcomputer technology, the PEREGRINE dose calculation engine is constructed from economical, off-the-shelf computer components originally developed for file- and Internet-server applications. PEREGRINE can be integrated into any treatment planning system via conventional network connections. Adding it to an existing system will be as easy as adding a file server.

The system design uses multiple processors interconnected by an internal high-speed network. The physics software distributes the calculations for a problem so that the dose is calculated by many microprocessors in parallel. The number of microprocessors can be determined by the user. For example, a big-city clinic that plans many radiation treatments each day would require a larger number of microprocessors to enable the fastest possible turnaround time. A suburban or rural clinic that does fewer radiation treatments might order a smaller, less expensive system. The system design supports hardware upgrades to increase calculational capability and to adapt to future technological changes. Now, a PEREGRINE calculation takes about 30 minutes. As code refinements
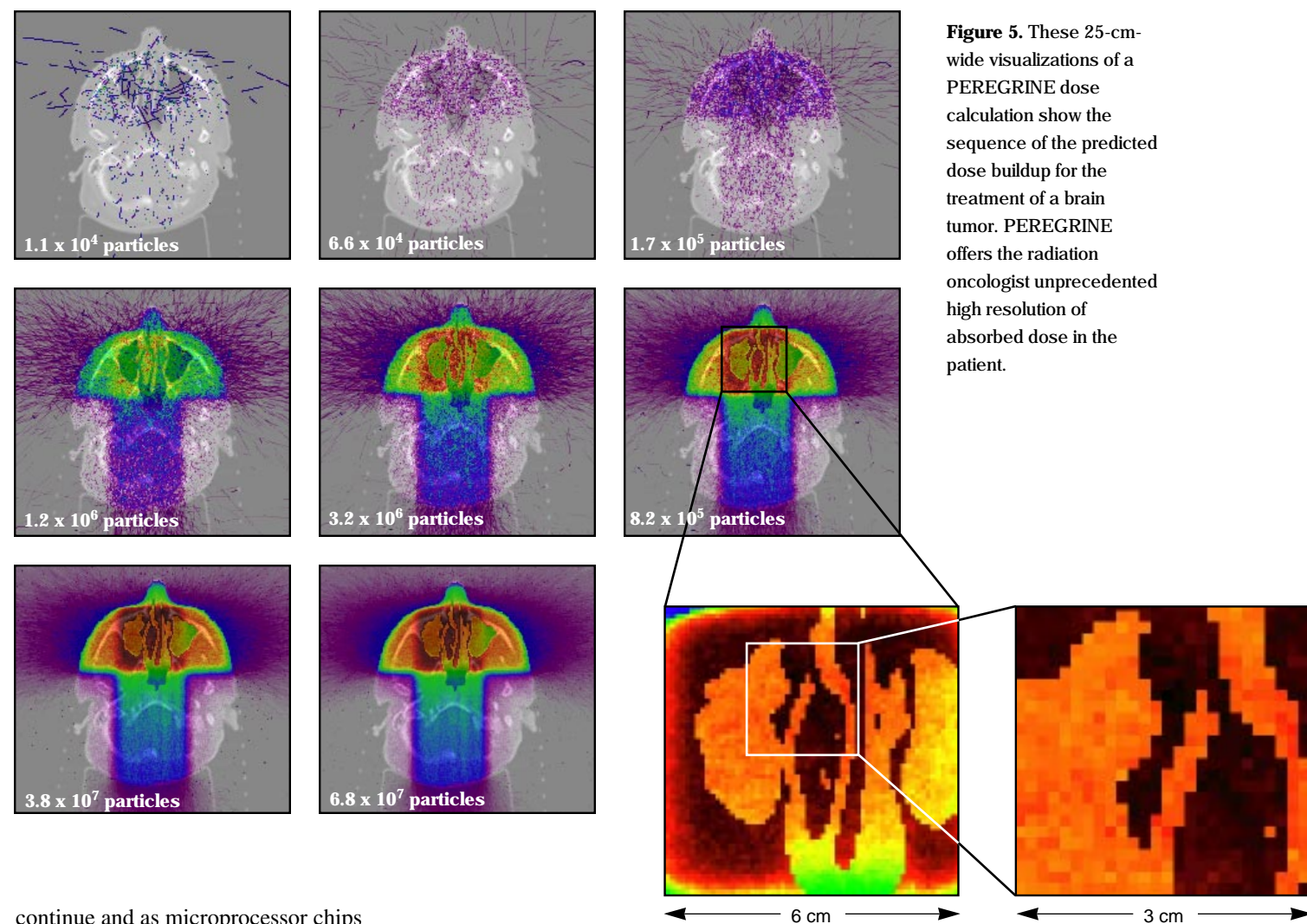

Figure 5. These 25-cm-wide visualizations of a PEREGRINE dose calculation show the sequence of the predicted dose buildup for the treatment of a brain tumor. PEREGRINE offers the radiation oncologist unprecedented high resolution of absorbed dose in the patient.

continue and as microprocessor chips improve, the system will be even faster.

Clinical Verification

Almost since work began on PEREGRINE, the Livermore project team has worked closely with an advisory board of internationally respected medical physicists and physicians in radiation oncology. (See the list of organizations on p. 10.) Dubbed the MEDPAC (Medical Physics Advisory Committee), the group ensures that PEREGRINE incorporates the best physics and that this new technology is relevant in a clinical setting.

The project team is particularly interested in validating the accuracy of PEREGRINE dose calculations against clinical measurements for photon beam (or x-ray) therapy, the most frequently used form of radiation therapy (Figure 6). The University of California, San Francisco (UCSF), has provided over 650 dose distribution measurements in a variety of materials and geometries that simulate conditions in the patient. UCSF and the Medical College of Virginia have provided retrospective cases for dose calculation comparisons for patients with

tumors in the head and neck, spine, lung, and larynx. Livermore has also begun a collaboration with the Radiation Therapy Oncology Group, a team sponsored by the National Cancer Institute, with the goal of using PEREGRINE in their new 3D lung cancer treatment protocol to calculate doses on all their patients.

Through these efforts, Livermore is working to improve the reliability of radiation source characterizations, validate the PEREGRINE dose calculations against clinical measurements, and evaluate the

impact of accurate dose calculations on the patient's outcome. Ultimately, the system should facilitate more accurate standardized clinical trials and more reliable implementation of those results throughout the medical community.

A Look Ahead

Livermore is now working with the radiation treatment-planning community to assure that PEREGRINE integrates easily into existing treatment-planning systems as a simple upgrade. Lawrence Livermore plans to license PEREGRINE to treatment-planning vendors so that it will be widely available.

In the near future, the project team plans to make PEREGRINE fully applicable to electron-beam therapy, stereotactic radiosurgery, and brachytherapy. (See box on p. 6.) Later, the team will study applications for heavy-particle (neutron and proton) therapies, which are used for cancers in and around the salivary glands, spinal cord, and eye.

The team is also pursuing collaborations in the application of the system to cancers of the breast and prostate. PEREGRINE is the only dose calculation algorithm today that can fully model the dose buildup near the surface of the breast, which is very important because of the area's sensitivity to radiation burns. Accurate dose calculations for prostate cancer are critically important because of the sensitivity of nearby structures to radiation injury.

As PEREGRINE becomes more sophisticated, it may change the way radiation treatments are planned. Today, a radiation oncologist studies a patient's CT scans to determine where radiation should and should not be delivered and what the absorbed dose must be to destroy the tumor. The medical physicist and dosimetrist then recommend a plan to deliver the radiation (numbers of beams, angles, etc.) prescribed by the oncologist. The PEREGRINE project team plans to bring "inverse planning" to this process, whereby treatment goals are established by the oncologist and input into PEREGRINE, which then determines how best to deliver the radiation to the patient.

"PEREGRINE may soon help to save thousands of lives," Siantar says. "Its high accuracy, speed, and affordability add up to the likelihood of widespread use at research hospitals and small clinics, which will bring superior radiation dose calculations and better treatment to more patients."
— *Katie Walter*

About the Team

EDWARD MOSES, PEREGRINE program leader since 1994, received a Ph.D. (1977) in electrical engineering from Cornell University, where he specialized in quantum electronics. His earlier Lawrence Livermore experience includes program manager of the AVLIS (Atomic Vapor Laser Isotope Separation) Program from 1986 to 1990.

CHRISTINE SIANTAR, principal investigator of the PEREGRINE program, received her Ph.D. (1991) in medical physics from the University of Wisconsin. Prior to joining Lawrence Livermore in 1994, she gained experience in cancer treatment planning at the Medical College of Wisconsin. Her present duties also include validation and verification of the Monte Carlo calculations for PEREGRINE.

Abstract

PEREGRINE: Improving Radiation Treatment for Cancer

The Lawrence Livermore National Laboratory has developed a radiation dose calculation system that will provide the most accurate and highest resolution treatment planning capability available. PEREGRINE is designed to be fast and affordable and will run on low-cost computer hardware in a hospital network environment. The availability of such accurate dose calculations will improve the effectiveness of radiation therapy by providing quality radiation treatment planning for patients in every clinical environment and facilitating accurate clinical trials. PEREGRINE will provide accurate estimates of required doses for tumor control and normal tissue tolerance and will advance the field of radiation oncology. It can be used for all methods of radiation therapy and could help save thousands of lives each year.

Figure 6. Comparison of PEREGRINE calculations and clinical measurements of radiation dose in water from the University of California, San Francisco, show PEREGRINE's unparalleled accuracy in predicting the delivered dose of radiation