Bright Ideas

"The optical surgical guidance system has

Several times our techniques

Declaring War on Side Effects

1. Collateral damage, in military jargon, refers to unintended carnage that is a consequence of waging war. At Vanderbilt biomedical engineers are attacking the problem of "collateral damage" that results from battling disease. Their goal is to make medical procedures free of side effects. New technology-guided therapy, the result of collaborations between biomedical engineers and surgeons, is helping medical practitioners wage war on diseased tissue while leaving healthy tissue and organs intact.

In brain surgery a small error can cause a lot of unintended damage. CAT scans reveal the blueprint of the brain, but surgeons may have difficulty locating *exactly*—the operative word—how the specific site in the brain relates to the scan. Robert Galloway, professor of biomedical engineering, surgery and neurosurgery, has perfected a device that helps neurosurgeons "see" what they are doing, using optical techniques to track the position of surgical tools on the CAT scan or MRI.

On the operating room wall, an optical device "finds" the tool in space and then relates the tool to images of the patient's brain. The brain is located using four inserts in the patient's skull, placed by the surgeon. Using those four points, software developed by Galloway's team rotates the CAT scan on the screen and shows its relationship—within millimeters—to the surgeon's tool. Surgeons guide themselves by looking on the screen, at the patient or both.

A cancerous tumor looks very similar to brain tissue, so the scan is used to define the edges of the tumor. Many other cerebral procedures require great precision, as in treatment for Parkinson's disease in which a neurostimulator is placed at a specific node in the brain.

"The human eye can see in maybe two and a quarter dimensions—length, width, and a little bit of depth," says Galloway. "But it can't see [through tissue to] the back of someone's head, and brain tissue is opaque. This device lets the surgeon know what's underneath."

Anita Mahadevan-Jansen, assistant professor of biomedical engineering, is also advancing the tools available to aid cancer surgery. She has developed a probe that will perform a tissue biopsy on the fly. Her device uses two light sources, each delivered to the area under study by a slender fiber-optic probe. The first uses broadband white light reflected out of the tissue in a scatter pattern that is read by an optical device. The second uses a nitrogen laser, which causes certain molecules in the body to fluoresce. "We use the reflectance data from the white light to account for blood and the fluorescence data to give us a sense of the biochemistry and morphology of the tissue," she says.

Anita Mahadevan-Jansen

DANIEL DUBOIS

The tissues are analyzed by comparing the reflection/scattering pattern of a given tissue with known patterns of normal and cancerous tissue. "The optical surgical guidance system we've developed has achieved nearly 100 percent accuracy in identifying the margins of brain tumors," says Mahadevan-Jansen. "Several times our techniques indicated that the surgeon had not quite gotten the entire tumor, and the histological results of the laboratory proved that the optical data were correct."

Unlike brain tumors, the cervix and ovaries have healthy tissue, cancerous tissue, and tissue that is in-between. Mahadevan-Jansen uses a different optical technique to diagnose

achieved nearly 100 percent accuracy.

indicated that the surgeon had not quite gotten the entire tumor. —ANITA MAHADEVAN-JANSEN

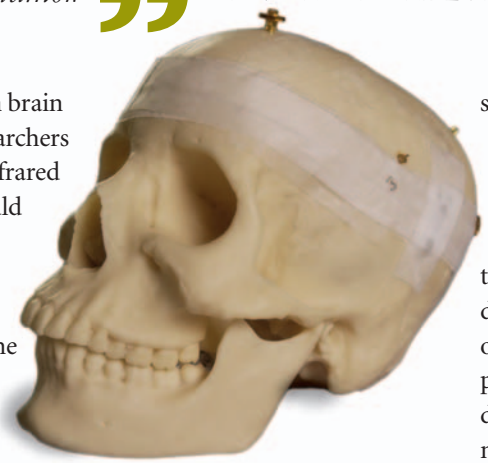
cancers of the ovaries and cervix. "We found that using fluorescence produced too many false positives," she says.

Instead, Mahadevan-Jansen uses a form of spectroscopy called Raman Scattering. The technique measures vibrational energies of the tissue's molecules. "Most photons enter and exit material at the same wavelength or energy level," she says. "But a small fraction of light emerges in directions other than the incoming beam, with greater or lesser energy than the initial light. We measure those frequency shifts and produce a pattern that is characteristic of particular molecular species."

Like the equipment used in the brain research, Raman Scattering equipment uses a laser light source, fiber to deliver the light and return data through a probe, a spectrograph to measure the data, a charge-coupled device camera to digitally record the data, and a computer to control the process and graphically present the results.

In neurosurgery a fraction of a millimeter can spell the difference between success and failure. Researchers have tried to use conventional lasers for brain surgery in the past but largely abandoned the effort because collateral damage to surrounding tissue was too great.

The goal is to find a wavelength that destroys a tumor without harming the rest of the brain. Using non-human brain material, Vanderbilt researchers first tried a part of the infrared spectrum that water would absorb. But the water became superheated and created mini-steam explosions throughout the material. They next tried an infrared wavelength of 6.45 microns, a length that both proteins and water would absorb. It worked very well, ablating (vaporizing) the tumor without harming surrounding brain matter, all at a level of precision sharper than a surgeon's scalpel. And ablation is less invasive than removal would be.



E. Duco Jansen, an assistant professor of biomedical engineering, has a special interest in the relationship between lasers and human tissue. The problem facing Jansen was to deliver the laser in a tool that surgeons would find workable. The intensity of the laser pulse melted the fiber-optic cables, so instead Jansen used small, lightweight, flexible, hollow-core tubes called "waveguides," which have a mirror coating on the interior. The reflecting quality of these tubes "bent" the light at the behest of the surgeon. Jansen designed a comfortable handpiece, together with a lens that would focus the beam down to 0.2 millimeters, the degree of precision needed in this type of surgery.

Ultimately, Vanderbilt neurosurgeons hope to use the University's free-electron laser, together with a computer-assisted guidance system, to remove tiny brain tumors near vital nerves and arteries that are too risky to excise with conventional medical lasers or by traditional brain surgery. Some of these applications will be based on the clean cutting of soft tissue. Other uses may include welding tissue to assist in wound healing, repairing nerves, reattaching retinas or monitoring neurological activity—applications where infrared light proves superior to other wavelengths.

Probably no medical therapy is more notorious for side effects—and riper for better therapeutic tools—than cancer treatment. Ales Prokop, research professor of chemical engineering, works on drug delivery systems, using techniques of nanotechnology—that is, he designs a molecule that will perform a particular function.

"Drugs are a medical problem," he says, "but drug delivery systems are an engineering problem." A drug exists that will cut off growth of blood capillaries in a cancerous tumor, effectively killing it, but the problem is to deliver the drug without affecting the rest of the body. Prokop constructs protein molecules specifically designed to bind to the tumor, molecules that are large enough to carry the drug. Because the drug is delivered directly to the tumor site, it can be stronger than currently used chemotherapy potions, which course more or less randomly through the bloodstream, causing the catastrophic side effects associated with chemotherapy today.

Throughout the stories of these breakthroughs, the theme is cooperation between engineering and medical faculty. In both fields, the goal is to cure the problem without creating new ones. No more collateral damage.

Genetics, Fiction and Public Debate

2. Ever since Mary Shelley first brought *Frankenstein* to literary life nearly 200 years ago, readers have been both fascinated by and fearful about the ways science affects our lives. From masterpieces like Aldous Huxley's *Brave New World* to camp movies like "Attack of the Killer

Tomatoes," works of literature and film can affect our thinking on issues like cloning and genetic coding.

Jay Clayton, chair of the English department at Vanderbilt, thinks such works of popular culture deserve closer scrutiny. He's made the case for serious study of genetics in popular culture so compelling that he recently won the first National Institutes of Health (NIH) grant ever awarded to a literature professor.

Clayton was awarded the $100,000 grant in September by the National Human Genome Research Institute of the NIH. In collaboration with Professor Priscilla Wald of Duke University, he will lead a 12-member team to study and catalog the topic of genetics in literature, film and popular culture.


NEIL BRAKE

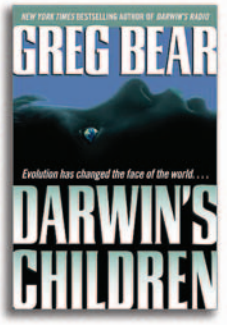
Clayton

"I think the NIH was persuaded by our argument that the way in which the public learns about genetics is a great source of misinformation and that somebody needs to be thinking about the kind of view our public is getting," says Clayton. "That includes a whole spectrum of cultural artifacts—movies and comic books, serious works of literature and provocative science-fiction novels that are not, perhaps, written with a great deal of literary grace or complexity but nonetheless raise really smart, probing issues."

In the debate about cloning, he says arguments are skewed by false assumptions springing from pop culture. "A film like 'Jurassic Park' completely mangles the entire notion of cloning in very damaging ways, creating fears that are groundless," Clayton says. "Certainly, there are legitimate concerns about cloning. But the fears that you'll get a Xerox copy of an animal are utterly groundless. That's not how cloning works."

In the film "Multiplicity," the character played by Michael Keaton is cloned, and then the clones are cloned. The process results in less-and-less intelligent versions of the original. "That taps into the whole 19th-century eugenicists' notion of degenerate populations—of populations getting worse and worse," says Clayton. "First of all, it misunderstands the science behind cloning. But there's also a deeper subtext of the production of defective humans—idiots—that ties in with eugenics notions that need to be rigorously guarded against.

"Common notions of science out of control are encapsulated and given their greatest power in *Frankenstein*," Clayton adds. "The FDA recently said it was safe to eat cloned beef. But in Europe the public refers to any kind of genetically engineered food as 'Frankenfood.' Everyone still uses Mary Shelley's *Frankenstein* as a touchstone."



The research team will also look into ideas about genetics raised both in pulp works and in serious novels like Jeffrey Eugenides' Pulitzer Prize-winning *Middlesex: A Novel* and Richard Powers' *Gold Bug Variations*, which Clayton describes as "on a par with James Joyce's *Ulysses* in terms of difficulty."

In a way, Clayton has been preparing for this project all his life. An avid reader since childhood, he was drawn to both literary masterpieces and science fiction. "I was never a snob about reading," he says. "And now all those hours I spent under the bed sheet with a flashlight reading Arthur C. Clarke and H.G. Wells and Isaac Asimov when I was supposed to be sleeping are paying off."

His wife, Ellen Wright Clayton, is a physician and law professor at Vanderbilt who studies the ethical, social and legal implications of genetics advances. "After 20 years of discussion around the dinner table, I realized that I had learned a lot about the social implications of advances in genetics," he says.

The research project will produce a book of essays designed to set the future course for scholars on the subject, a list of relevant books and films and a Web site to serve as a central source of information.

"We're going to get this important topic into the literature classroom," says Clayton. "Every student in high school in America takes English literature courses. This is a chance to raise these issues—the future of science, its consequences in society—in classrooms where it's never appeared before."

As the first literature professor of an NIH grant, Clayton says he feels a "huge responsibility to prove the value of funding interdisciplinary research in the humanities through the NIH and other national organizations. The future of education is interdisciplinary teams getting together to study an important issue, and the humanities should not be left behind."

Inside the Brain of Don Juan

When it comes to sex, more is not always better. High-profile cases in recent years have detailed problems of the rich and famous whose personal relationships have been wrecked by a seeming obsession with sex. And letters from women and men whose

spouses are consumed by Internet porn have become standard "Dear Abby" fare.

A group of Vanderbilt addiction researchers is interested in finding out what's going on in the brains of people with problematic hypersexuality, and how their brain mechanisms compare with those of typical individuals.

"No one in the past has stopped to examine the motivation of people like Don Juan," says Dr. Peter Martin, director of the Division of Addiction Medicine at Vanderbilt. "He was viewed as a highly successful man rather than someone suffering from an inability to sustain relationships. That is kind of an empty life, and it takes time away from being able to do other things that are joyful and constructive."

Martin, who is also a professor of psychiatry and pharmacology at Vanderbilt, along with colleagues Dr. Reid Finlayson, assistant professor of psychiatry, and Dr. Mitchell Parks, research fellow in psychiatry, want to determine if such behavior is a true addiction and, if so, how it compares with other types of addiction.

"I do not like to use the term 'sexual addiction' because we do not yet know whether it is in fact an addiction," says Martin. "It could be an obsession or a compulsion. All three involve models of repeated behavior that's dysfunctional, but the brain mechanisms involved are quite different." In a nutshell, addiction is something that involves preoccupation with the pursuit of something that is not necessarily beneficial and may, in fact, be very harmful.

To aid them in their studies, Martin and his colleagues are using functional magnetic resonance imaging (fMRI), a technique that allows them to identify which brain regions become active during the performance of specific tasks.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Martin

"We have identified activation of parts of the brain that are involved in attention, motor imagery, preparation and planning," says Martin. With heterosexual males as their subjects, the researchers have compared what happens in the brain when the subject views a nude woman alone with what happens when the subject views a more graphic depiction of a heterosexual sex act.

"The part of the brain that seems to be brought into play early on is the region called the anterior cingulate," Martin explains, "which is the same region that other researchers have shown is activated during cocaine exposure." When typical subjects view the more graphic material, Martin says, there is also activation of the motor imaging and motor planning regions of the brain.

Now the Vanderbilt researchers want to explore what happens in the brain of subjects with problematic hypersexuality when those persons view the same material. "We have found that in the few patients we've studied who have problematic hypersexuality, they are actually shutting down this anterior cingulate region of the brain. It is very similar to what cocaine addicts do when they see cocaine stimuli," Martin says. "They are trying to inhibit this sort of pleasure emotion, suggesting that it's uncomfortable for them."

Persons with problematic hypersexuality also seem to have comparatively less activation of the motor imaging and motor planning regions of the brain. "It is almost as if the patients are subconsciously inhibiting it," says Martin. "Or it could be that they have seen such images so often that for them it does not mean as much as for the normal volunteers. The interpretation at this point is not clear."

The patients with problematic hypersexuality "may never attain pleasure no matter what they do," Martin suggests. "They are taking part in this activity seeking something they are never going to find until they get treatment, either talk therapy or medication."

One obvious challenge Martin and colleagues face is recruiting research subjects, particularly those with problematic hypersexuality. "There is a tremendous stigma associated with problems in sexual functioning," he says. But that may soon change: Their work has caught the attention of "Dateline NBC" producers, who have interviewed Martin for a segment tentatively planned for airing early this year.

Although their research to date has focused on men, Martin says problematic hypersexuality is a significant problem for women, too. "It is profoundly affecting lives. People come to work sleepy because they were looking at the Internet all night. They become alienated from their families."

Martin also worries about what's happening to society at large. "The landscape of sexual development, sexual relationships, and other kinds of personal relationships is being changed by the plethora of things we weren't exposed to 20 or 10 or perhaps even five years ago."