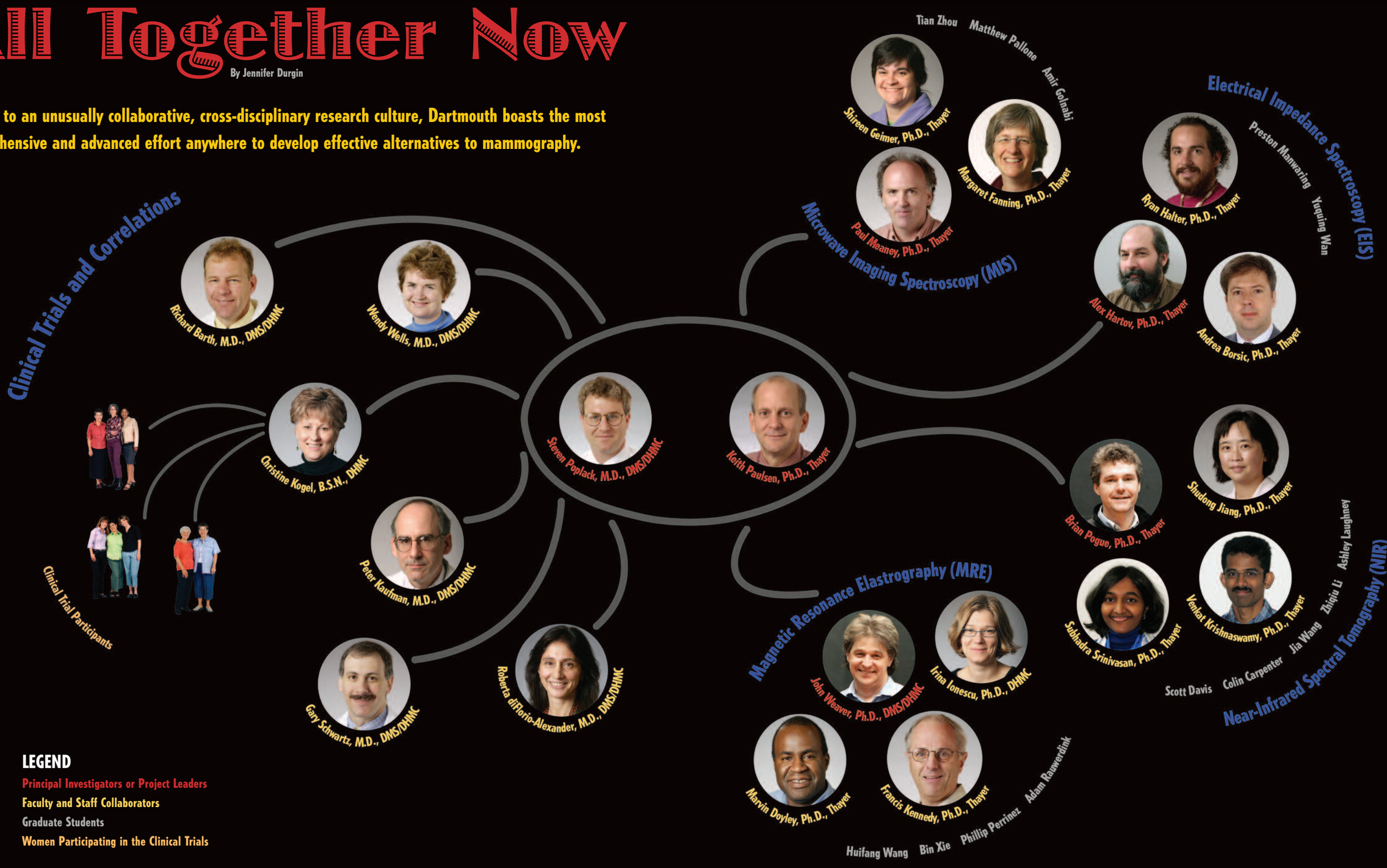
All Together Now

By Jennifer Durgin

Thanks to an unusually collaborative, cross-disciplinary research culture, Dartmouth boasts the most comprehensive and advanced effort anywhere to develop effective alternatives to mammography.



LEGEND

Principal Investigators or Project Leaders

Faculty and Staff Collaborators

Graduate Students

Women Participating in the Clinical Trials

ILLUSTRATION BY JENNIFER DURGIN

Depending on a woman's age, family history, and other risk factors, as well as the skill of her radiologist, the chance of a false positive ranges from less than 1% to 98% on a first mammogram. After nine mammograms, it's estimated that 43% of women will have experienced a false alarm.

Large, medium, small. Conical, round, elongated. Dense, fatty, fibrous. The wide variety of breast sizes, shapes, and compositions is more than just a cosmetic concern for women (or a curiosity for men, for that matter). That variability is part of why detecting cancer in breasts is so difficult and why mammography, for all of its merits, often falls short.

For all the breast cancers that mammography detects, many slip by unnoticed. And for all the abnormalities it identifies, only a small fraction of them turn out to be cancer. That results in a lot of women with undetected breast cancer and a lot more who experience the emotional and physical stress of a false alarm, also known as a false positive. Depending on a woman's age, family history, and other risk factors, as well as the skill of her radiologist, the chance of a false positive ranges from less than 1% to 98% on a first mammogram. After nine mammograms, it's estimated that 43% of women will have experienced a false alarm.

Add in the discomfort for many women of having their breasts compressed between two glass plates, plus the exposure of healthy breast tissue to ionizing radiation, and it's no wonder that some researchers are looking for a better screening method.

"I do mammography every day, and I strongly believe that it helps women," says Dartmouth radiologist Steven Poplack. "Unfortunately, what often gets quoted to the public is that mammography is 90% sensitive and we can find a cancer that is the size of a head of a pin, which is true in certain people." But that's not the whole story, he adds. "If you look at all comers, it's really not that sensitive. . . . Mammography has room for improvement and therefore the need for alternatives."

About 10 years ago, a group of engineers at Dartmouth's Thayer School of Engineering began exploring that need with the help of Poplack and others at Dartmouth Medical School. In 1999, the group secured a multiyear, $7.1-million program project grant from the National Institutes of Health (NIH) and began developing four different breast-imaging technologies. In 2007, the collaboration—which now includes nearly 40 researchers at DMS, DHMC, and Thayer—was awarded a five-year, $7.7-million renewal from the NIH. At the end of this funding cycle, Poplack and his coinvestigator, Thayer engineer Keith Paulsen, hope to be able to move one or more of the imaging technologies into multicenter clinical trials.

The breast-imaging techniques being developed at Thayer and DMS differ from mammography in that they focus on functional rather than structural information. One might say that mammography detects tissue that *looks* like a tumor, whereas the new Dartmouth modalities detect tissue that *acts* like a tumor.

For example, magnetic resonance elastography (MRE) uses an MRI scanner and specialized coils to measure the stiffness of breast tissue. "Almost all cancer is stiff," says John Weaver, Ph.D., a professor of radiology at DMS and the MRE project leader. "There is no other property that is so characteristic of cancer as increased stiffness." If MRE detects an area of the breast that is particularly stiff, or inelastic, that area might be a tumor—or so the hypothesis goes.

The other three alternative modalities exploit the electromagnetic spectrum to measure various tissue properties. (The chart on the facing page details key points on the spectrum.) Two of the three—microwave imaging spectroscopy (MIS) and electrical impedance spectroscopy (EIS)—measure the ability of different regions of the breast to hold or conduct electricity. Part of what defines a tissue as cancerous is its architecture—how the cells and blood vessels are organized. Normal tissue is quite orderly. Cancer, however, is "just a jumble," says Alex Hartov, an engineer at Thayer and the EIS project leader. "A lot of membranes, a lot of vascularity . . . all these things are associated with different electrical properties."

The fourth modality, near-infrared spectral tomography (NIR), uses "a very unique spectral window," says Brian Pogue, a Thayer engineer and the NIR project leader. The near-infrared wavelength range "is where the blood absorption drops way, way down, and the water absorption hasn't really increased very much," he explains. This allows electromagnetic waves to penetrate farther into the tissue and reveal information about its hemoglobin and oxygen saturation levels, both of which can signal the presence of a tumor.

Although the four modalities tackle the problem of breast imaging from different angles, several challenges tie them together. The first and most daunting one is computational complexity.

Mammography uses x-rays to generate a picture of the breast. Because of their frequency and wavelength, x-rays penetrate the body in more or less a straight path. So constructing an image from x-ray data is a linear problem—a relatively easy mathematical equation to solve.

MIS, EIS, NIR, and MRE, however, require much more complicated computations. The electromagnetic waves used in MIS, EIS, and NIR may travel smoothly through some regions of the breast but be deflected, distorted, or absorbed by other regions, depending on the tissue properties in each region. Likewise, the mechanical waves generated during an MRE exam travel through breast tissue in all sorts of complex patterns.

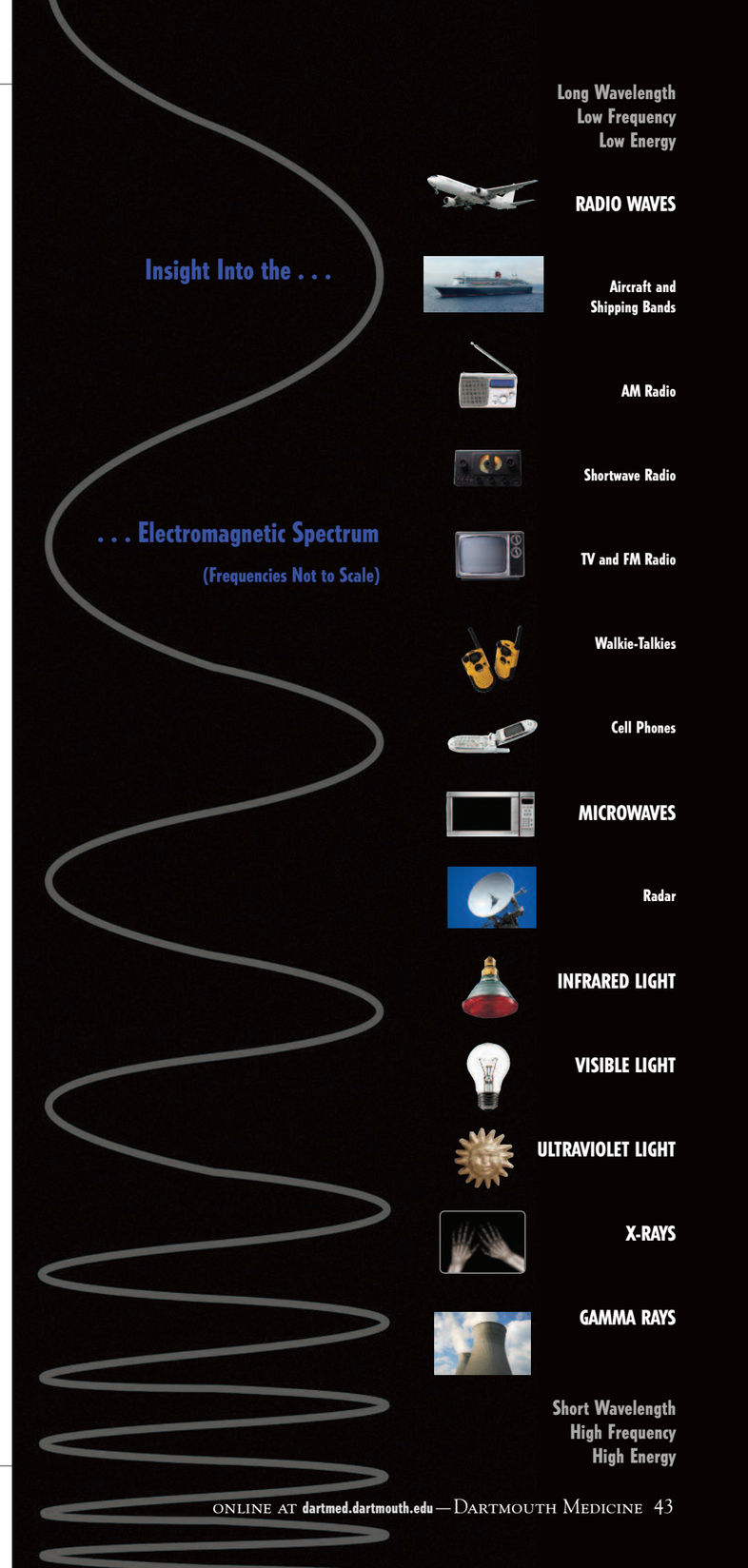
In order to create a picture from the data gathered by each modality, the engineers needed to design software that uses what's called an iterative approach. In each modality, the signals can be measured as they are sent and received. But what happens to the signals in between, as they travel through the breast tissue, is unknown.

"You know what you're getting out, [and] you know what you're putting in," explains Margaret Fanning, an engineer who has been working on the MIS project since it began. But the researchers don't know what's happening to the signal within the tissue. "So you guess," Fanning says, "and then you compare." Or, more precisely, the software guesses and then compares. First it guesses the spatial distribution of the tissue's physical properties; then it calculates the response that would be observed given that estimate; it compares those results to the actual data; then it makes another estimate based on the new information. The software keeps refining its guesses until the real response and the calculated response converge.

The mathematical and engineering problems involved in getting these modalities to work are "huge," says Paul Meaney, the Thayer engineer who heads up the MIS project. Several groups worldwide have tried to develop microwave-imaging techniques, for example, but "then they really fall down," he says, in trying to build an actual imaging system. In contrast, the Thayer group has managed to develop both the software and the hardware—free-standing machines for MIS, EIS, and NIR, plus specialized equipment that's used inside an MRI scanner for MRE and NIR.

But just clearing the mathematical and engineering hurdles still doesn't get the modalities to a patient's bedside. "Once [you've] got an algorithm that works, a piece of hardware that works," explains Meaney, "you start taking these images and you start to say, 'What do these images mean?'"

In other words, if the modalities are to have any future beyond the investigational stage, the engineers have to work closely with medical specialists. There are two Dartmouth clinicians who have been involved with the projects from the beginning—Poplack and pathologist Wendy Wells. More recent additions to the team include surgeon Richard Barth, oncologists Gary Schwartz and Peter Kaufman, and radiologist Roberta diFlorio-Alexander.



Jennifer Durgin is Dartmouth Medicine's *senior writer.*

Mammograms look at architectural distortions in breast tissue. But the new modalities look at totally different things. They look at oxygenation, hemoglobin concentration, elasticity, conductivity, permittivity . . . "all these things that, to be quite honest, I didn't have a clue as to what the underlying tissue correlates might be," admits pathologist Wells.

For a WEB EXTRA audio interview with Wendy Wells, including how her involvement in this project has changed her view of pathology, see dartmed.dartmouth.edu/winter07/html/together_we.php.

"The fun part and the hard part are that we speak different languages," says Poplack. The benefit, he adds, lies in the fact that it "forces you to step outside of your traditional thinking."

Wells, who is associated with Norris Cotton Cancer Center's Comprehensive Breast Program, agrees whole-heartedly. Her role in the research has been to try to correlate the pictures generated by each of the modalities with characteristics in actual tissue extracted through biopsies or surgery. "Instead of just saying, 'Yes, we saw cancer,' and 'Yes, Wendy says it's cancer,' we [try] to think of things that were happening in the tissue . . . that could be measured," says Wells. That is, the characteristics that created the image.

Mammograms, she explains, look at architectural distortions and masses in breast tissue. So clinical pathologists are trained to look for their correlates—accompanying changes in the structure of cells in those tissues. But the new modalities look at totally different things. They look at oxygenation, hemoglobin concentration, elasticity, conductivity, permittivity (a measure of a tissue's ability to store electrical energy)—"all these things that, to be quite honest, I didn't have a clue as to what the underlying tissue correlates might be," admits Wells. "So we had to all sit down and figure out what the correlates were supposed to be. . . . That required me to do some really abstract lateral thinking."

Now, instead of focusing on cytology and epithelial architecture, Wells looks at blood vessels, fat content, water content, and various characteristics of the stroma (the supporting tissue) when she's working with tissue samples from the breast imaging projects. It fascinates her, she says, that in her clinical, non-research work, "I make all these diagnoses on one category of cells, and it turns out that tons of information is happening around it that I don't even register."

Finding the tissue correlates for the modalities is "a huge amount of tedious work," she admits. But "if those modalities can be validated in a way that can either prevent multiple [mammography] follow-ups or screening biopsies, that's a big deal." That's because many women would know sooner whether they have breast cancer or not and thus could avoid the stress and expense of those additional procedures.

However, all the clever engineering and innovative pathological techniques won't matter much if the modalities don't help real, live patients. And figuring out whether they are able to do that is resting on the generosity of hundreds of women who have agreed to participate in trials of the research.

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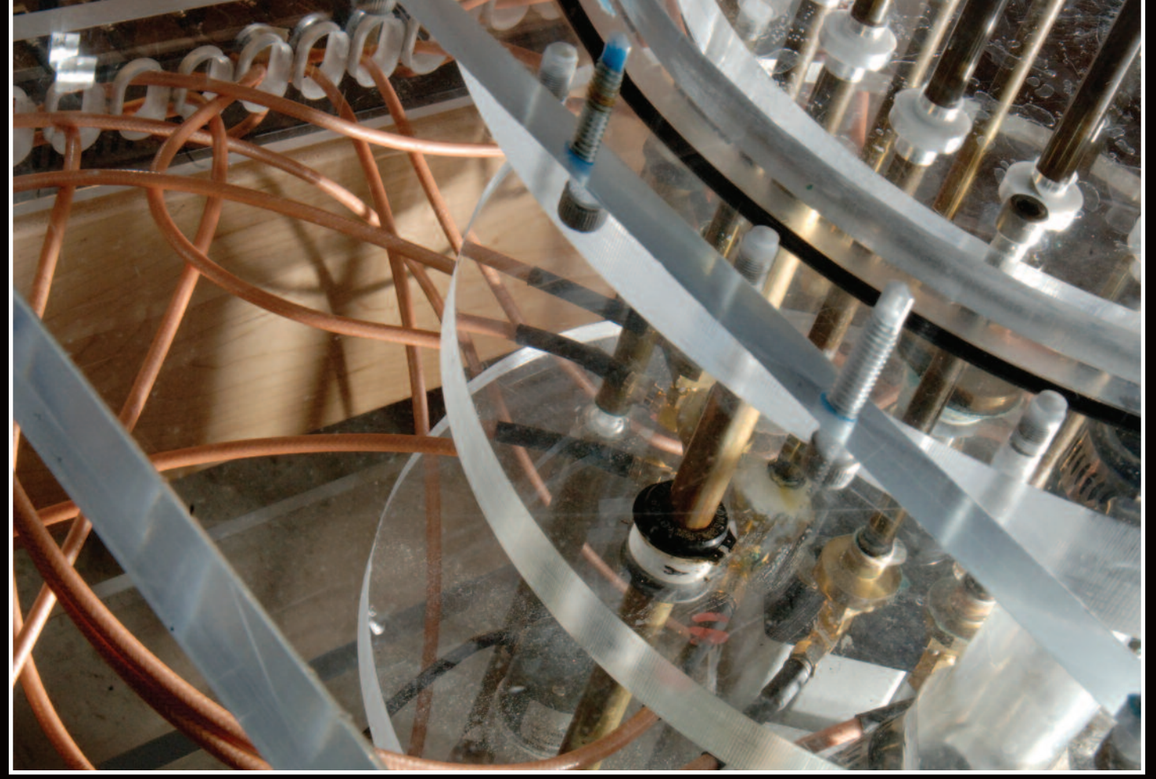


Microwave Imaging Spectroscopy (MIS)

The premise: Most people think of microwave technology as having to do with "radars, World War II submarines, or something like that," says Paul Meaney, who leads the MIS breast-imaging project. Engineers have considered biomedical applications for microwaves "for a long time," he adds, but the technology "never really caught on." That may be changing.

For 10 years now, Meaney has been developing an imaging system that uses microwaves and specialized software to measure the electromagnetic properties of breast tissue. Those measurements form the basis for high-contrast images that can be used to diagnose breast cancer and monitor tumors that are getting shrunk with chemotherapy prior to surgery.

Early on, Meaney and Keith Paulsen, who helped create the software, decided to patent the MIS system. They formed a small company, Microwave Imaging System Technologies (MIST), with the help of the Dartmouth Entrepreneurial Network. Recently, a government research institute in South Korea licensed MIST's software; the Korean group plans to build and market their own imaging system.

Meanwhile, Meaney and his team continue to improve the MIS software and hardware. A third generation of the system will come online soon in clinical research space at DHMC.

The procedure: During MIS, a woman lies face down on a table with one of her breasts submerged in a bath of water and glycerin. Most women find this modality to be the most comfortable one, says Christine Kogel, the project's clinical research coordinator. "We advertise it as a facial for their breast tissue," she quips. Sixteen antennas surround the breast but don't touch it. In fact, women don't feel anything but the liquid during the procedure.

The microwaves are transmitted from one antenna, hit the breast, are deflected in various patterns depending on the tissue's composition, then are received by the other 15 antennas. The waves' power is about 1/1,000th the strength of a cell-phone signal. Each antenna takes a turn as the transmitter until the whole array is used. The array can be raised and lowered to image different planes of the breast, but for time and data manageability, usually only about seven planes of data are collected.

A bath of glycerin and water fills the tank (shown above and on the upper left) when a woman's breast is being examined (as shown on the lower left). The mixture provides enough resistance so that if a signal bounces off the wall of the tank, it is too weak to interfere with the primary measurements.

"Recruiting these women is extremely difficult," says Kogel, because they have just been told that they may have breast cancer. Many women feel too overwhelmed to even consider participating in research that they are probably not going to benefit from themselves. Yet some women agree to participate because they have had relatives or friends who have had breast cancer. And some are just altruistic.

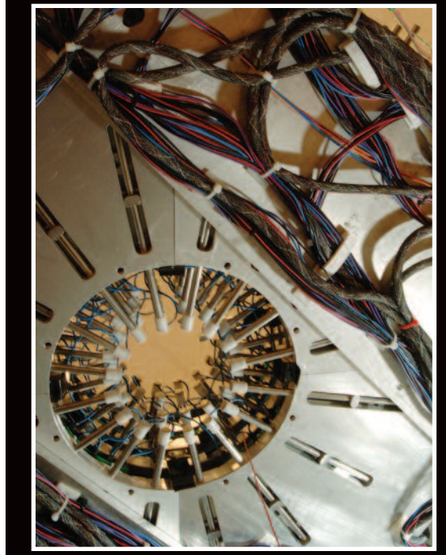
As the project's clinical research coordinator, DHMC nurse Christine Kogel recruits women to participate in the breast imaging studies. In the main branch of the study, women who have been called back for a biopsy have their breasts imaged by some or all of the new modalities. "Recruiting these women is extremely difficult," says Kogel, because they have just been told that they may have breast cancer. Many women feel too overwhelmed to even consider participating in research that they are probably not going to benefit from themselves. Yet some women agree to participate because they have had mothers, sisters, other relatives, or friends who have had breast cancer. Others are drawn to the possibility of creating any way other than mammography to detect breast cancer because of the discomfort involved in compressing breast tissue. And some are just altruistic, explains Kogel.

The other branches of the clinical studies depend on women who have already been diagnosed with breast cancer. In what the researchers call the neoadjuvant branch, women who are receiving chemotherapy to shrink their tumor before surgery agree to have their breasts imaged at set intervals: before chemotherapy, 48 hours after the first dose of chemo, one week after the first dose, every subsequent time they come in for chemo, and one last time before surgery. In this study, the researchers are interested in seeing whether the modalities can help monitor the effectiveness of chemotherapy.

In the third branch, measurements of a tumor are taken with a probe: first in the operating room, while the tumor is still in the woman's breast, and then later in the pathology lab. The hope here is to better correlate the images with the actual tissue.

Paulsen and Poplack hope that the data gleaned from the latest round of clinical trials will help determine which modalities to take to the next level—a large, national, multicenter trial. The current clinical trials will also help clarify where these modalities might fit into the clinical setting. But it will be several years before the teams reach either of those goals.

The comprehensive results from the first round of clinical trials were just published, in May 2007, in the journal *Radiology*. The results were "reasonable, probably better than I might have expected when we first started," says Paulsen, but "not eye-popping." None of the electromagnetic modalities (EIS, MIS, and NIR) were fantastic at detecting malignant breast tumors by themselves. (MRE was not included in the study because it is not as developed, and so the researchers did not have as much data.) Each electromagnetic modality showed



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Electrical Impedance Spectroscopy (EIS)

The premise: "Imagine little plastic bags full of stuff floating in interstitial fluid." That's how Alex Hartov, the project leader of the EIS research initiative, describes the cells that make up breast tissue. Interstitial fluid—the fluid between cells—conducts currents, he explains. Cell membranes, however, do not. Therefore, the kind of cells and the number of cells in a given region directly affect tissue conductivity. Different tissue types—normal, fatty, cancerous—have different electrical properties.

The EIS modality (like MIS) is designed to measure those properties throughout the breast and then use that information to create a kind of tissue map, which shows an obvious contrast between normal and cancerous tissue.

One way that Hartov's team is both validating and improving EIS is by taking readings of a tumor in the operating room, before it is removed from a woman's breast, and then taking readings again, after the surgery, when the tumor is in the pathology lab.

"If one were ambitious," says Hartov, "one could imagine that we could conceivably supplant mammography completely [with EIS], which I am sure a lot of women would really like. A more reasonable goal would be to supplement it by being a second-step exam to decide whether or not to do a biopsy. Biopsies are still a pretty big deal in terms of cost, pain, and other annoyances."

The EIS procedure, however, is inexpensive, painless, and relatively quick, he points out.

The procedure: During EIS, the woman lies face down on a table with one of her breasts positioned through an opening. A technician places from one to four rings of electrodes in contact with the breast; the number of rings used depends on the size of the breast. Each ring contains 16 electrodes, and all 16 electrodes on a ring must touch the breast. This can be tricky sometimes, since most breasts are not perfectly round.

Using one ring at a time, small currents of varying frequency are then passed through the breast; the current is sent from each electrode in sequence to the other 15 in that ring. As in MIS, the currents are of such low power that the women do not even feel them.

Skeins of wires (visible in the upper left photo) power the four rings of electrodes (above) that come into contact with the breast during an EIS exam. Built into a retrofitted breast biopsy table (shown on the lower left), the EIS system measures electrical properties of normal and abnormal breast tissue.

There's no question that the DMS-Thayer collaboration is at the forefront of alternative breast-imaging research nationwide, even worldwide. A few other research groups are working on some of the techniques. But no other initiative in the world is as comprehensive and as well developed as the Dartmouth collaboration.

strengths, however. EIS showed good sensitivity (meaning that it was good at detecting abnormalities) but relatively poor specificity (meaning that it wasn't good at distinguishing between malignant and benign abnormalities). MIS and NIR were more specific, and, when used in conjunction with mammography, they dramatically improved the probability of a correct diagnosis.

Such mixed results were not surprising. Developing and refining technologies like these is "an incremental process," says Paulsen. Even MRI, which "is viewed as the most advanced medical imaging technology . . . wasn't eye-popping in imaging the breast because [breast cancer] is complicated."

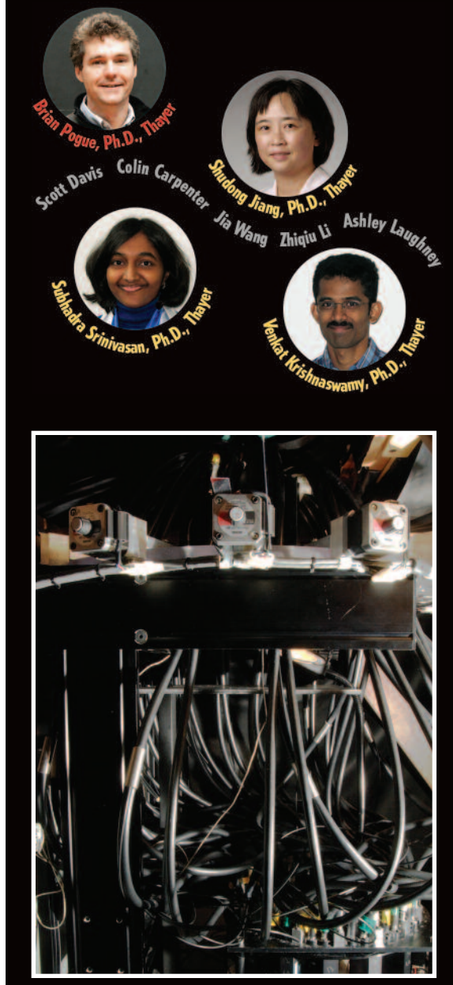
None of the project leaders foresee their modalities replacing mammography, at least not any time soon. Mammography has been improved and developed over such a long period of time that it is firmly entrenched in the medical infrastructure of the United States. So instead of trying to supplant mammography, the researchers are looking for ways to supplement mammography. One way to gain a "toehold," says Paulsen, is to look at the settings in which mammography performs poorly, such as in dense breasts.

Advances in breast imaging tend to draw a lot of attention, Paulsen continues, "but in practice, these things move relatively slowly. I don't know of anything else that's on the horizon that is going to take over, so to speak. Tomosynthesis [which uses x-rays to create a three-dimensional view of the breast] is interesting, but it's a small perturbation on an existing idea."

There's no question that the DMS-Thayer collaboration is at the forefront of alternative breast-imaging research nationwide, even worldwide. Researchers at several other institutions are working on NIR techniques (and all of them are collaborating with Dartmouth); a few teams elsewhere are in the early stages of exploring microwave-imaging technologies; a handful of centers are experimenting with MRE to image other parts of the body; and there have been at least a couple of commercial ventures using electrical impedance. But no other research initiative anywhere in the world is as comprehensive and as well developed as the Dartmouth collaboration.

"We're looking at all four [of the modalities] in a common setting," explains Paulsen, so that "we can look at them together and comparatively and synergistically."

The key to the success of the collaboration, says Paulsen, is the size of Thayer, DMS, and DHMC. "It's sort of the big company/small company para-



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Near-Infrared Spectral Tomography (NIR)

Sixteen sets of optical fibers (above) surround the breast during an NIR procedure (pictured on the lower left), which must take place in complete darkness. The cables and circuitry (upper left) that power the optical array are usually hidden from view underneath the exam table and behind a black curtain.

The premise: Location. Location. Location. It's important in real estate and in NIR, too. NIR uses an approach similar to the idea behind MIS and EIS. But because of near-infrared's location on the electromagnetic spectrum, this modality can measure hemoglobin concentration and oxygen saturation levels—key indicators of microvascularity. (Tumors are hungry little beasts that require a lot of tiny blood vessels to keep them fed.)

The NIR modality has the ability to operate in two environments—in a free-standing system that Thayer engineers built and in a smaller unit that functions inside an MRI scanner. "I have a very practical focus," says Brian Pogue, the NIR project leader. "We're not going to replace mammography or magnetic resonance." So his team is looking for ways that NIR can add useful information to mammography and magnetic resonance imaging.

In the free-standing unit, the researchers use NIR to monitor tumors that are being shrunk with chemotherapy prior to being removed surgically. In the MRI scanner, they use NIR to help diagnose abnormal tissue, with the goal of preventing unnecessary biopsies. MRI makes it possible to zoom in on the tumor, while NIR can categorize it, explains Subhadra Srinivasan, a research scientist at Thayer who works with Pogue. Her job is to figure out how to use the MRI data to produce better NIR images in a three-dimensional format. Pogue, Srinivasan, and several colleagues recently published some of their results in the journal *Optics Letters*.

Unlike the other modalities, NIR is being explored by several research teams elsewhere. But what sets the Dartmouth NIR work apart is the aspect of integrating it with MRI.

The procedure: NIR must be conducted in complete darkness. During a free-standing NIR procedure, the woman lies face down with one of her breasts positioned over an opening. A circle of optical fibers surrounds and touches the breast. Light is sent from one fiber and is then picked up by all the others. The light is emitted in sequence from all the fibers, and several different wavelengths within the near-infrared spectrum are used.

The process in an MRI is roughly the same.

The deans of both Thayer and the Medical School are keen to exploit the strengths that Paulsen describes. . . . "What distinguishes [Dartmouth] and gives us vitality . . . is our collaborative spirit," DMS's dean, Stephen Spielberg, has pointed out. And that spirit is what has made the breast imaging projects so robust.

digm," he explains. A big company "can continue to do its own thing, but to really turn it or adapt it quickly to something new just doesn't work because there's huge infrastructure and huge investment in teams. . . . We're a much more nimble, small enterprise." There are not too many places where radiologists, pathologists, and other clinicians are so accessible to medical engineers, he adds.

The deans of both Thayer and Dartmouth Medical School are keen to exploit the strengths that Paulsen describes. "What distinguishes [Dartmouth] and gives us vitality . . . is our collaborative spirit," DMS's dean, Stephen Spielberg, M.D., Ph.D., has pointed out. He and his Thayer counterpart, Joseph Helble, Ph.D., formed a committee composed of three DMS and three Thayer faculty to look at creating a new curriculum and new educational tracks, to formalize the merging of medicine and engineering that has been taking place informally for some time now.

Helble sees great promise in the openness on the part of DMS faculty to sharing their expertise and clinical space with engineering students and faculty. "As medicine becomes more and more technologically based," he says, "it's really important that the next generation of practicing physicians have a good understanding, a fundamental engineering understanding, of the capabilities and limitations of the technology they are going to be using."

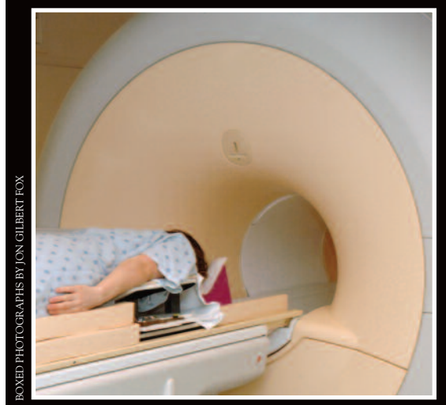
Spielberg and Helble also make a special effort to encourage the faculty at both schools to work together. When either DMS or Thayer is interviewing a candidate for a faculty position who has interests in engineering or medicine, respectively, they make sure that the candidate also meets with faculty members at the other school.

"If you're looking for a place where there are going to be three or four people just like you," Helble says he tells prospective faculty, Dartmouth "is not the right place. . . . If you believe that all the intellectual excitement is at the interface between individual problems, then this is the place."

That willingness to collaborate across disciplines and to apply various approaches to the same research problem is what has made the breast imaging projects so robust.

Although it's likely that some of the modalities will progress farther and faster than others, none of the teams seem to view each other as competitors. They share computational and clinical resources and exchange information freely. Their attitude is that a lesson learned by one of the teams is a lesson that benefits all of the teams.

And ultimately, of course, patients. ■



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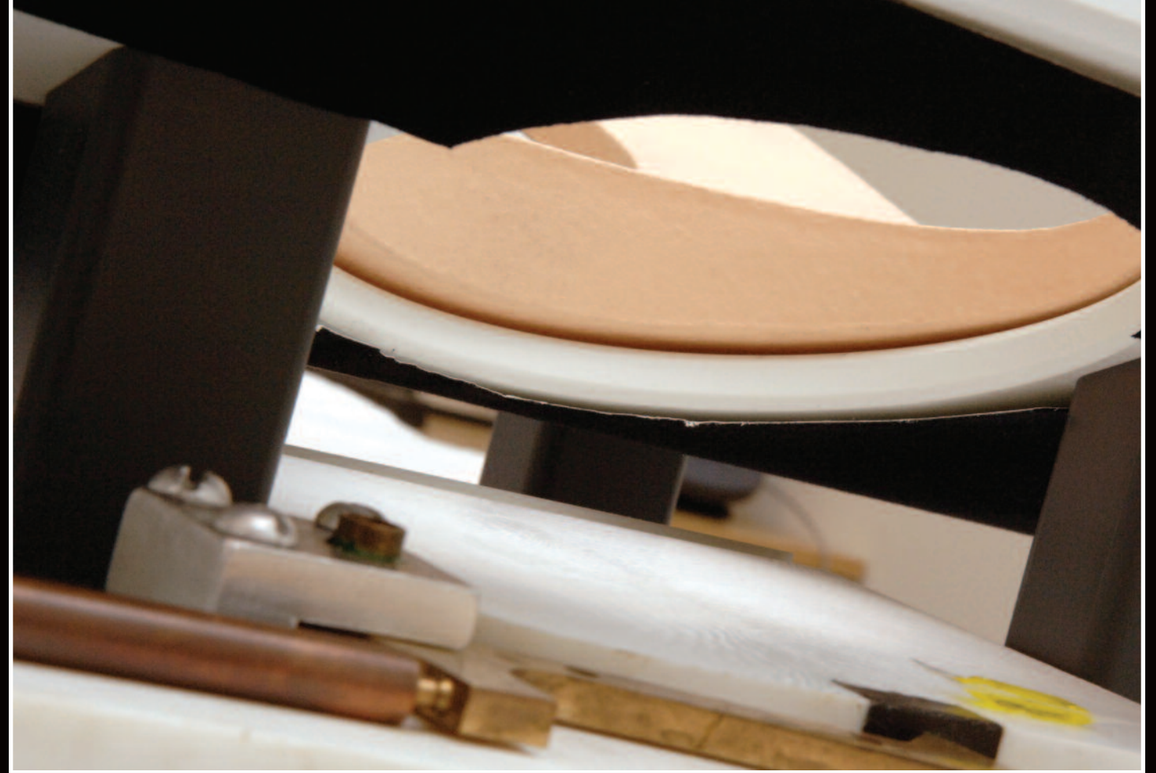

Magnetic Resonance Elastography (MRE)

The premise: "The trick here is that things that are really stiff, when you move them, they all move together," says John Weaver, the MRE project leader. A well-known property of cancerous tissue is that it is stiff—as any woman who has found a lump in her breast knows.

Imaging researchers will often invent a way to capture a picture of a certain property, explains Weaver, and then try to figure out whether it offers any useful information. With MRE, Weaver began with something known—the fact that cancer is stiff—and is working backwards to capture an image of it.

In MRE, very-low-frequency waves pass through the breast and vibrate the tissue. An MRI scanner with specialized software measures that motion and estimates what distribution of stiffness within the breast would cause those measurements. Until a couple of years ago, DHMC did not have an MRI scanner designated exclusively for research. So in order for women to participate in the MRE study, they often had to come in for the investigational exam late at night, when the clinical MRI machines were not in use. This scheduling hurdle made it difficult to develop the technology as quickly as the other modalities. Now, however, DHMC has an Advanced Imaging Center, so Weaver is making much faster progress.

The Dartmouth team is not the only group in the world looking at MRE for breast imaging, but its findings are among the most developed, according to Weaver. He anticipates MRE being used to better diagnose abnormal tissue and to avoid unnecessary biopsies, as well as to monitor the success of chemotherapy treatments.

The procedure: From the patient's perspective, an MRE exam is very similar to a standard MRI. The main difference is that the woman lies face down, with her upper torso on a sliding apparatus that looks like a rolling cart or tray. The tray has two holes for her breasts, and the breast being examined rests on a vibrating plate. The low-frequency vibrations can be felt by the patient but are not uncomfortable.

Inside the device are coils that sense the vibrations in the tissue and interact with the MRI magnet to actually create the images.

The MRE apparatus (pictured in the upper left photo) consists of coils—which surround the breasts and interact with the MRI machine (pictured on the lower left)—plus a plate (pictured in a close-up view above) that uses piezoelectric crystals to create controlled vibrations in the breast tissue.