BIOMEDICAL ENGINEERING
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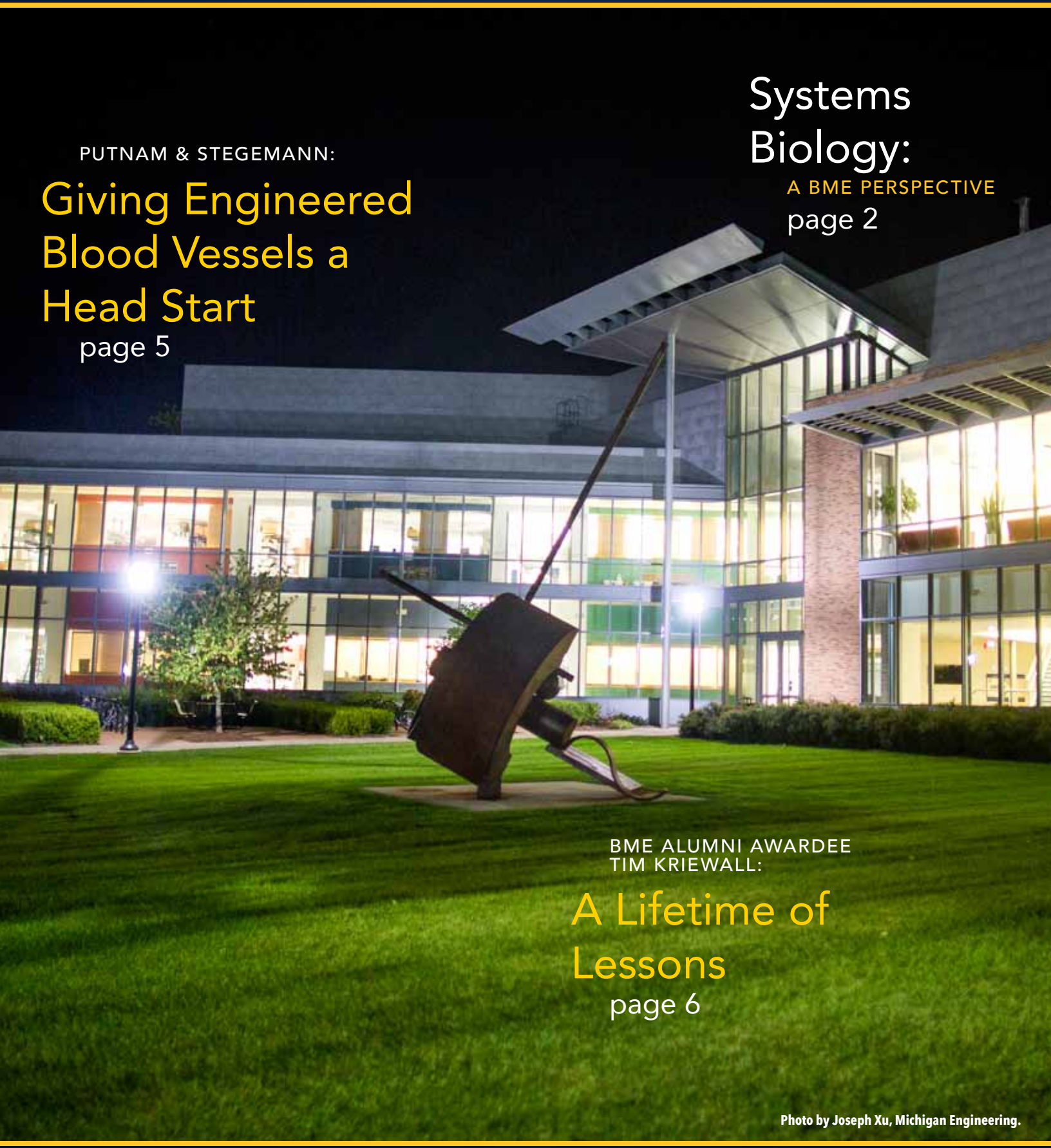

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Photo by Joseph Xu, Michigan Engineering.

Systems Biology: A BME Perspective

by Aimee Balfe

On first glance, there's not much overlap among researchers studying the cardiovascular physiology of the rat, the interactions among bacterial colonies in the human microbiome, or the mechanism by which certain drugs affect the cytoskeleton.

But look more closely, and you'll see these are all topics being addressed by BME researchers using a common approach: systems biology. And it's an approach that's poised to grow in importance within the department and across campus, given its potential to illuminate the dynamic functioning of numerous biological systems.

But what is systems biology and how are BME faculty using it to answer key scientific questions? We've invited a sampling of researchers to share their perspectives.

David Sept. Photo by Joseph Xu.

DAVID SEPT: CORE FACULTY WITH A COMPUTATIONAL MODELING FOCUS

Associate Professor **David Sept**, PhD, is perhaps the BME core faculty member most intimately associated with the systems biology approach. When asked how he defines it, he chuckles. "I taught a class on the subject," he says, "and I'd start by saying, If you ask five people what 'systems biology' means, you'll probably get six different answers."

That may be no exaggeration. There are message boards and opinion pieces teeming with disputes over where the boundaries of bioinformatics, computational biology, and systems biology begin and end – if they exist at all. But Sept provides a useful, 35,000-foot conceptualization:

"In a sense, systems biology is really the antithesis of where we've been going in biology for most of its history. We've taken a reductionist approach, studying smaller and smaller pieces down to the levels of individual proteins and molecules. That's been invaluable, but we're realizing that when we put those pieces back together, they don't behave as they did in isolation. You see things coming out of the system, whether it's a signaling network or a group of enzymes, that you didn't see when you studied the parts by themselves."

These are the so-called "emergent phenomena" that bubble up when elements of the system are reintegrated and studied cooperatively. Doing this requires methods as cooperative as the systems themselves. The process, says Sept, is an iterative one, where experimental data from the wet and/or animal lab are fed into a computational model that tries to explain them. The model in turn generates additional hypotheses to be tested experimentally.

Sept's strategy has been to carve out one element for himself – the computational modeling portion – and to collaborate with experimentally minded labs on questions of mutual interest. It's a tactic that has allowed him to address relatively disparate questions in realms both fundamental and applied.

Sept has had a longstanding interest in the cytoskeleton – specifically the actin filaments and microtubules that give cells their shape and help them divide and move. He's interested in how the cell regulates their assembly, how they interact with other cellular components, how they function in a normal cell and what goes wrong in the case of disease, and how various drugs affect them.

He's already done much to reveal the dynamics of actin assembly. He's modeled the molecule's polarity and how its ends grow at different rates. He's also clarified the role of the protein cofilin in this process. Cofilin plays an important role by severing actin filaments, generating ends that will be either rapidly reassembled for cell migration or disassembled for remodeling of the actin network. Sept's lab, together with a collaborator from Yale, developed a comprehensive model showing that the binding of one cofilin molecule alters how

subsequent molecules bind and unbind. The model revealed that the cofilin-actin filament must exist in two different states, a feature that could not be directly observed in experiments.

On the applied side, Sept is using his understanding of the cytoskeleton to study drugs that target it. His was one of the early labs to model how the chemotherapy drug Taxol stops tumor growth by hyperstabilizing microtubules and preventing cell division. "Our computer modeling gave rise to some surprising results," he says. "It turns out that most of us still have a very 1950s view of how drugs work, expecting that if a drug binds to a particular site on a protein, it will have a very local effect. But it looks like Taxol has an allosteric effect – action at a distance if you will. It actually changes the dynamics of the polymer at a region distal to where the drug binds. This is what prevents depolymerization."

He's now interested in designing drugs capable of targeting the parasitic cytoskeleton without affecting the host's. To do this, he must understand and exploit the differences between them. From giardia to malaria, parasites have cytoskeletons that can be from 15 to 50 percent divergent from humans'. Sept and colleagues from Washington University recently published an article in *Nature Communications* demonstrating that actin filaments from the parasite *Toxoplasma gondii* polymerize in a completely novel way – quite differently from the actin in animal cells.

His lab is using these insights to take lead compounds that show promise against the parasitic cytoskeleton and tweak them to be more effective and better tolerated by humans. Using that characteristic iterative process, their computer-modeled designs are synthesized, tested in a microbiology lab, and further refined based on the results.

> "I'd start by saying, If you ask five people what 'systems biology' means, you'll probably get six different answers."

But his work also has implications for diseases like Alzheimer's, cancer, and tuberculosis (TB). For example, it was his modeling, in conjunction with experimentation in the lab of BME Associate Professor **Michael Mayer**, that revealed the danger posed by medium-length aggregates of amyloid beta peptides (see **BME News Spring '12**). These peptides form the characteristic "senile plaques" in Alzheimer's patients. Again using a system-level approach, their research revealed that aggregates of 4 to 13 peptides were the toxic species, creating pores in neuronal membranes and causing cell death.

Sept is also plying his skills in the area of pharmacokinetic modeling. A recent paper on the subject challenged the view that chemotherapy is thwarted from entering tumors because of their high interstitial pressure. By modeling experimental bioluminescence data, he and his collaborators showed that as tumors grew, the growing efflux of drugs was a more significant problem than reduced influx.

He's now teaming up with researchers in South Africa to use his models to develop a more streamlined treatment for drug-resistant TB. "Our goal is to replace the current cocktail of drugs that must be taken every day for many months with, say, a weekly injection," he says. "It could make a huge impact on patient compliance and drug resistance. To do that, we're looking at nanoparticle therapeutics – designing ideal kinetic profiles so the various drugs are released from their nanoparticle carrier in just the right way to achieve just the right concentrations over time. This involves a lot of moving pieces that you can only optimize with a large-scale model."

DANIEL BEARD: AN ESTABLISHED SYSTEMS BIOLOGIST WITH FULL-SPECTRUM FACILITIES

Another approach to systems biology is embodied by one of the newest members of the BME Department, Professor **Daniel Beard**, PhD. A noted systems biologist with a primary appointment in molecular and integrative physiology, Beard heads up a National Center for Systems Biology, which has moved with him to U-M.

Daniel Beard.

While Beard's scientific questions are in some ways more tightly focused than Sept's, his lab comprises the whole systems biology enterprise – computer modeling, wet labs, and small-animal work.

Beard's general interest is in cardiovascular physiology, enriched by a focus on energy metabolism. To address these issues from a systems biology perspective, his center has launched the Virtual Physiological Rat (VPR) project, which works to integrate experimental and computer modeling efforts at nine different institutions. "The project's ultimate challenge," says Beard, "is to integrate everything we know about cardiovascular physiology into computer models that can not just simulate the cardiovascular function of the rat – but actually *predict* how genetic variation will interact with environmental variables like diet to produce various cardiovascular phenotypes. We're building models to analyze

current data and designing new experiments that will give us insight into the causes and consequences of complex diseases like hypertension and heart failure."

A challenge of this scope requires his team to integrate data from various scales – from the granular details of ion handling in cardiac mitochondria all the way up to functional interactions among the heart, autonomic nerves, blood vessels, and kidneys.

"It is a building process," he says. "We do lab experiments on enzymes from mitochondria that we purify from cardiac tissue. Based on our enzyme models, we build models of the mitochondria, then of cellular metabolism, then of heart metabolism, including extraction of oxygen and substrates from the blood. After that, we integrate these with the pumping of blood and its flow. Pretty soon we've combined enough things to produce a high-level phenotype like blood pressure."

It's a process that allows his lab to tackle a range of questions, from how heart tissue selects different energy substrates to how multiple genes combine with the environment to raise cardiovascular risk. This is only possible within a systems biology perspective.

Nina Lin. Photo by Joseph Xu.

NINA LIN: A SYSTEMS BIOLOGY APPROACH TO MICROBES

Chemical Engineering and BME Assistant Professor **Nina Lin**, PhD, applies a systems biology approach to her research on microbial processes in areas as diverse as engineered biofuels and the human microbiome. She combines computational modeling, traditional wet-lab experimentation, microfluidics and other techniques to study both the complex functioning of individual cell types and the interactions within diverse microbial populations.

In terms of the former, her lab is engineering microbes like *E. coli* to produce the biofuel isobutanol from corn stover and other cellulosic biomass. Because the chemical is actually toxic to the bacteria, her lab is using a systems biology approach to identify genes that might help *E. coli* tolerate isobutanol so it can be produced in higher concentrations. "It turns out that it's not just one gene, or even a few, but many genes involved in enabling the cell to tolerate toxic chemicals," says Lin. "Using genome evolution, we've found over 100 genetic loci that might matter. Now we're using multiplexed genome engineering to change up to 40 genes at a time to see which ones might come together to help us make a strain that is more robust and efficient."

She's also using the systems biology approach to study the human microbiome – the hundreds of species of microbes that live in and on our bodies. For instance, her lab has teamed up with faculty in dentistry and public health to investigate the complex interactions among the microbes of the mouth to determine how they either support health or cause plaque and disease.

SYSTEMS BIOLOGY AT U-M

All three researchers say that U-M is an ideal environment to employ a systems biology perspective because of the institution's depth and breadth of research and penchant for collaborative, interdisciplinary work. "Systems biology is so interdisciplinary that you can't really do it by yourself," says Lin. "You have to collaborate with people who have complementary expertise, experiences, and views."

Sept says U-M has thus far taken a fairly decentralized approach to systems biology, which he thinks reflects both the institutional culture and the "field" itself. "As systems biology developed, a lot of places quickly established departments under this name," says Sept. "We may have been wise to hold off. Systems biology isn't necessarily a 'field' so much as an interdisciplinary approach – a reflection of where the whole field of biology is going."

No matter how it's framed, systems biology is certainly fertile ground for biomedical engineers. "Engineers have always been comfortable with systems-level descriptions and the differential equations we use in modeling," says Sept. "When you add the biological savvy, they are perfectly positioned to see what needs to be included in a model and what can be ignored. This will undoubtedly be a growth area for BME, both in terms of faculty hires and where students are likely to gravitate in the future."

PUTNAM & STEGEMANN:

Giving Engineered Blood Vessels a Head Start

by Aimee Balfe

If BME Associate Professors **Andy Putnam**, PhD, and **Jan Stegemann**, PhD, have their way, patients with coronary artery disease may one day have a pasty injection of cells to thank for a new lease on life. The pair has teamed up with U-M interventional cardiologist Michael Grossman, MD, to assess a modular tissue engineering technique they've developed that aims to grow healthy new vessels to take over from narrow, plaque-filled ones. Their goal is to rapidly restore blood flow in a range of ischemic conditions, from coronary and peripheral artery disease to diabetic ulcers.

Jan Stegemann. Photo by Joseph Xu.

The project is the result of a four-year, $1.5 million NIH grant that capitalizes on each investigator's strengths. It combines expertise from the Putnam lab in the mechanism of angiogenesis, including which cell types grow the most robust vasculature; the Stegemann lab in modular tissue engineering and the delivery of cell-based therapies; and Grossman's experience treating ischemic conditions and exploring the use of growth factors to promote revascularization.

In recent years, cell-based approaches have shown significant promise in revascularizing tissue. The big question has been how best to deliver them. On one end of the spectrum is a liquid injection of cells. Though minimally invasive, this technique has generally not formed vessels quickly enough to restore blood flow to oxygen-starved tissue. On the other end is the implantation of a prevascularized tissue slab. While such tissues have been shown to connect with host vessels in as few as three days, they require an invasive surgery.

Andy Putnam. Photo by Joseph Xu.

The collaborators' approach aims to combine the benefits of both methods – injectability plus rapid vascularization. It incorporates cell types identified in Putnam's lab with Stegemann's modular delivery system. "We encapsulate cells in hydrogel microbeads," says Stegemann. "These represent the 'modules.' Each bead contains a small number of endothelial cells, which line the blood vessels and form capillaries, and mesenchymal stem cells, which provide support and produce various biochemical factors that promote vascularization."

The beads serve as tiny nurseries, where the cells can begin self-assembling into primitive capillary fragments. This is what gives Stegemann's approach a key potential advantage relative to other modular strategies: It allows the team to "jump-start" vessel formation outside the body. The idea is that by injecting a paste of these beads at the site of reduced blood flow, the preformed capillary fragments can quickly start connecting with each other and with the host's vasculature to form a healthy new vascular bed.

The team will test their method in a mouse model of hind limb ischemia to see how it compares to liquid cell injection and implantation of a preformed slab. They're interested both in how quickly the vessel fragments form within the microbeads – since this is critical to identifying the optimum time for injection – and in how quickly these methods form viable vasculature within the body.

Putnam is exploring other elements on the basic science side, such as how neighboring vascular units find and connect with one another – perhaps by sensing the tractional forces between them. However, he and Stegemann are quick to point out that their primary goal is translation. "The approach we've outlined is particularly translatable," says Putnam. "Jan's hydrogel uses all FDA-approved materials, and we could potentially get all our cells from the patients themselves. If this goes well and we demonstrate efficacy, there's no reason to think that in 8 to 10 years you couldn't do this in a patient."

As promising as their approach is, the pair is especially excited by its potential as a "platform" technique. The modules could be filled with a range of cell types and biochemicals, and used to "incubate" fragments of various tissue types. In fact, Stegemann originally developed the method for bone regeneration. Putnam heard him lecture and proposed they team up on a grant.

"This project is so exciting because it taps our complementary expertise," says Putnam, "and offers the opportunity for real translational impact."

BME ALUMNI AWARD WINNER TIM KRIEWALL:

A Lifetime of Lessons

by Aimee Balfe

2013 BME Alumni Society Merit Award winner, Timothy Kriewall, PhD, has had a rich, and oftentimes surprising, career. He's leapt from circuit-board designer at Bell Labs to OB/GYN faculty at U-M. He's spent decades in medical device development, served as the unlikely president of a liberal arts college, and led one foundation's efforts to change the way we teach engineers. And he's "retired" at least three times along the way.

As he looks back over his career – its twists and turns, the dizzying highs and the occasional, heart-wrenching low, he realizes it embodies a multitude of lessons – lessons he hopes to share with students and graduates now shaping careers of their own.

LESSON 1: DON'T PLAN; DO WHAT YOU LOVE

Kriewall began fresh from U-M's electrical engineering program with a job offer from R&D powerhouse Bell Laboratories. The offer required a master's degree, so he used Bell's backing to head to Stanford, marrying his high-school sweetheart along the way.

In California, his wife worked as a nurse in one of the country's first neonatal intensive care units. He'd have dinner with her at the hospital and look in on the premature babies on their apnea monitors. Something inside him stirred. "I loved electrical engineering," he says, "but I wanted to help people more directly than I could by making a power supply for a radio."

Kriewall returned to Bell Labs, where he was tasked with circuit design and software development. Without setting out to, he and his officemate tinkered their way into developing what Kriewall thinks was the world's first P-CAD system. When the circuit board for a high-profile power station failed, the duo used their system to design a new board in two days instead of the standard eight weeks. "It was incredible," he says. "We had an audience with the executive board at AT&T. And we couldn't have planned this; it was just two kids having fun."

While he was flourishing professionally, he and his wife were making progress of their own by starting a family. The experience only reinforced his interest in perinatology. "I was amazed at how little the doctors knew about the birth process," says Kriewall. "My wife was told she was experiencing false labor, only to have the baby later that night. We were in the early part of the space program, and I remember marveling that we knew everything about the astronauts up there – their heart rate, their physiology – yet here were these infants a few centimeters from the abdominal wall, and we knew almost nothing about them."

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About this time, he learned of a new program that would allow him to focus on questions like these. He applied for an NIH Special Fellowship in Bioengineering and used the award to return to U-M. "I liked that Michigan allowed you to create your own path to a PhD," he recalls. "You weren't preselected to work in someone's lab." While many BME students were following the NIH funding into cardiology, Kriewall took a different route. He connected with the college roommate of the couple's former obstetrician. This OB not only would deliver their second baby but would partner with Kriewall on his early BME research.

LESSON 2: LEARN LATERAL LEADERSHIP

When this mentor moved on, Kriewall connected with a perinatologist and began his dissertation on the real-time measurement of cervical dilatation. Assembling his committee helped Kriewall develop another important skill. "The program's loose structure taught me how to get people to work for you when you have no authority over them," he says. "You had to get busy faculty to share their lab, their know-how, and their time. It helped me become an effective leader on cross-functional teams later in my career."

The work was insightful, too. Kriewall developed a technique for the continuous measurement of dilatation and in the process discovered why contractions must occur at least every five minutes for labor to progress.

LESSON 3: LOOK FOR QUESTIONS

With his PhD complete, Kriewall received an invitation to the join the faculty in OB/GYN. The clinical environment offered an advantage he couldn't resist: access. "I could walk into the labor room just like a resident and talk to nurses, obstetricians, and patients," he says. "I knew these

people weren't going to walk across campus to share a problem that needed a technical solution; I had to see or hear about it for myself."

He was introduced to his first project in the most personal way imaginable – through the birth of his second child. "She was the result of a precipitous labor and emerged with an elongated, banana-shaped head," he says. This got him wondering how much a baby's head could be molded before there were negative consequences.

"Too many kids were born with cerebral palsy, and people wondered whether it was the result of a mismanaged labor," he says. "But it's hard to accuse doctors of this if they don't have the instrumentation or data to know whether pressures on the skull are too high or too long or whether there is too much skull molding. I wanted to contribute to that."

So he undertook research on fetal skull molding that is still cited today. He examined donated skulls from premature babies, measuring calcification and performing flexion testing at the Highway Safety Research Institute. He also measured newborns' heads to learn how they returned to their more natural state postpartum. In the process, he and his collaborators turned much of the accepted wisdom, so to speak, on its *head*, and taught doctors why, for example, premie's skulls were so vulnerable to pressures during delivery.

"We learned a lot," says Kriewall, "but the point is that nobody asked us to do this. We saw an issue and explored it. That's what I tell biomedical engineers all the time: Look for questions; don't wait to be asked."

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Tim Kriewall, PhD '74, received the BME Department's 2013 Alumni Society Merit Award at an awards dinner on October 4. Photo by Brandon Baier.

LESSON 4: PREPARE FOR RESISTANCE

Not only did this work yield insights, it led Kriewall to another opportunity – the chance to bring real-time ultrasound to obstetrics at U-M.

Because he'd been teaching a BME course on ultrasound and was positioned in the OB/GYN department, Kriewall was approached by a medical device company offering a free ultrasound unit to demonstrate its value in prenatal diagnosis.

"I ran to the chair," says Kriewall, "and he absolutely wasn't interested. 'I have 25 years of palpating abdomens,' he said. 'I don't need a machine to tell me a fetus is breech.' I said, 'Yeah, but it can probably tell us other things.' He said, 'I doubt it.' It wouldn't be the last time someone resisted a new technology because the old way was plenty good enough."

The chair relented, and Kriewall found a willing audience among the medical students and residents who were not yet confident in their clinical skills. They found, of course, that they could see not only if a baby was breech, but other things as well – water on the brain, a missing head, too much or not enough fluid in the uterus, placenta previa, and perhaps most excitingly at the time – the presence of twins. "It was the mid-1970s," he says, "and 50 percent of all twins went undiagnosed until birth. This is dangerous because the placenta may begin to detach after the arrival of the first baby, so the second can be oxygen-starved. But until real-time ultrasound, doctors may not have known what was coming."

The faculty soon saw its advantages, and Kriewall designed a course to teach ultrasound to the practicing OBs through Towsley Medical Center.

LESSON 5: LEARN FAILURE ANALYSIS

About this time, Kriewall was approached by a former colleague to join 3M. He

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BME News

Wayne Barlin, Coulter Foundation VP & Doug Noll, BME Professor. Photo by Brandon Baier.

COULTER CENTENNIAL

BME celebrated the 100-year anniversary of the birth of philanthropist Wallace H. Coulter with a lecture honoring his legacy on October 23 in the Michigan League. Headlining the event was J. Paul Robinson, PhD, professor of cytomics in the School of Veterinary Medicine and professor of biomedical engineering at Purdue University. His lecture was titled, "Wallace H. Coulter: The Man, Engineer, and Entrepreneur."

For more information, see:
bme.umich.edu/coulter100

The U-M Coulter Translational Partnership features a $20 million endowment that supports translational research between clinicians and biomedical engineers.

INAUGURAL HUNT LECTURE

On November 15, the department hosted the first **Alan J. Hunt** Memorial Lecture, honoring the beloved BME professor who passed away last year after a prolific, 14-year career at U-M. The featured speaker was longtime Hunt lab collaborator David Odde, PhD, a professor of biomedical engineering at the University of Minnesota. Odde spoke on microtubule dynamics at the nanoscale.

For more info and to donate, see:
bme.umich.edu/huntlecture2013

GRANT SEEKS TO STARVE TUMORS

An NIH grant renewal supported by three BME faculty aims to test the ability of their novel gas embolotherapy technique to starve tumors of their blood supply. The approach involves injecting tiny encapsulated perfluorocarbon droplets into the vascular system, then using ultrasound to turn these droplets into bubbles large enough to block the microcirculation supplying a tumor. The grant is titled, "Dynamics of Vascular Microbubbles and Microdroplets in Gas Embolotherapy." The PI is **Joseph Bull**, PhD, the Arthur F. Thurnau Professor of Biomedical Engineering. His co-investigators include: **Mohamed El-Sayed**, PhD, assistant professor of BME and macromolecular science and engineering; **Brian Fowlkes**, PhD, professor of radiology and BME, and Jonathan Rubin, MD, professor of radiology.

GRANT TESTS MRI FOR RADIATION THERAPY

Two BME professors are involved in an NIH grant designed to determine whether magnetic resonance imaging (MRI) is accurate enough to supplant computed tomography (CT) for radiation therapy applications. The grant is titled "Optimizing MRI for Radiation Therapy Treatment Planning." Its PI is **James Balter**, PhD, a professor of radiation oncology and BME. He is supported by **Douglas Noll**, PhD, the Ann and Robert H. Lurie Professor of Biomedical Engineering, and U-M collaborators in radiology and radiology oncology.

NEW TISSUE ENGINEERING GRANTS

BME Associate Professor **Jan Stegemann**, PhD, is a PI on three new NIH tissue engineering grants. The first is featured on page 5; the others include:

Quantitative Ultrasound Imaging for Noninvasive Assessment of Engineered Tissues: A collaboration with BME Professor **Cheri Deng**, PhD, which aims to use high-frequency spectral ultrasound imaging and acoustic radiation force elastography to characterize the composition, structure, and mechanical properties of bone and other mineralized engineered tissues.

Modular Assembly of Interdigitated Osteochondral Interfaces: A collaboration with BME Assistant Professor **Rhima Coleman**, PhD, that aims to improve the integration of engineered bone and cartilage using Stegemann's modular, microbead-hydrogel approach.

3D-PRINTED AIRWAY SPLINT HONORED

Scott Hollister & Glenn Green. AP Photo/University of Michigan Health System.

BME Professor **Scott Hollister**, PhD, and Otolaryngology Associate Professor Glenn Green, MD, won a Breakthrough Innovator Award from *Popular Mechanics* magazine for their custom-designed, 3D-printed, bioresorbable tracheal splint. The device saved the life of a baby suffering with severe tracheomalacia, or windpipe collapse, after the FDA granted emergency clearance to use it in February 2012. The case is believed to be the first of a 3D-printed device saving a life. Hollister and Green are one of 10 teams that received awards at a ceremony in New York City on October 22.

Their *Popular Mechanics* story is available at:
http://bit.ly/18sV4FJ

FAN LAB WINS 5 GRANTS

Sherman Fan. Photo by James Rotz.

BME Associate Professor **Xudong (Sherman) Fan** has recently won four NSF grants and a U-M Global Challenge grant. They include:

I-Corps: Development of Integrated Optofluidic Enzyme-Linked Immunosorbent Assay (ELISA): Explores how to commercialize the lab's novel integrated optofluidic ELISA technology that is substantially faster, more sensitive, and more cost-effective than current devices.

Sensitive Dual-Mode Microfluidic Optomechanical Analysis of Biomolecules: Aims to develop a microfluidic optomechanical (FOM) resonator for dual-mode optical and acoustical detection of biomolecules in liquid. A collaboration with The Technion – Israel Institute of Technology.

Plasmonically Enhanced Optical Ring Resonators (PEORR) for Label-Free Single Molecule Detection: Aims to achieve the "Holy Grail" of sensor development: label-free detection of single molecules. Combines the sensing resolution of the ring resonator, the sensitivity of plasmonic nanostructures, and the carousel effect from the ring resonator for efficient capture and transport of biomolecules. A collaboration with the Polytechnic Institute of New York University.

PFI AIR Technology Translation: Leverages two prior NSF grants and related patent applications to prototype and assess the commercialization potential of a smart, multi-dimensional micro-gas chromatography instrument with unprecedented peak capacity.

Real-Time Monitoring of Environmental Impact on Plants Through a Plant-Machine Interface Network: A U-M collaboration that aims to develop a technology capable of continuously analyzing plant-emitted volatile organic compounds to quantify the impact of stressors such as drought, disease, and environmental change for improved crop and forest management. See: **http://thirdcentury.umich.edu/plant-machine-interface/**

Fan was also recently elected as a fellow of the Optical Society of America.

LEE WINS RACKHAM CENTENNIAL FELLOWSHIP

BME PhD candidate **Paul S. Lee** won a Rackham Centennial Fellowship for his work with BME Professor **Mary-Ann Mycek**, PhD, developing a Ray-Traced Monte Carlo simulation technique to enable complete light path analysis incorporating optical probes and tissue optics. This technique can be used to design optical probes for early cancer diagnosis and the assessment of engineered tissue.

RAO WINS TERMIS AWARD

Ram Rao (BME PhD '13) received the 2013 Mary Ann Liebert, Inc., Outstanding Student Award from the Tissue Engineering and Regenerative Medicine Society (TERMIS)-Americas. Rao worked with BME Associate Professor **Jan Stegemann** on the design of a two-phase tissue for bone regeneration.

TAKAYAMA WINS MICROFLUIDICS TRAINING GRANT & AWARD

In September BME Professor **Shuichi Takayama**, PhD, took on the directorship of the Microfluidics in Biomedical Sciences Training Program, which offers a variety of microfluidics-related training opportunities to PhD students. This NIH-funded program engages 45 faculty members across campus; awards 6 fellowships; and engages students through an annual symposium, seminar series, and coursework.

Information is available at:
www.umich.edu/~ufluids/

Takayama was also awarded the 2013 Lab on a Chip/Corning, Inc. Pioneers in Miniaturization Prize for his outstanding contribution to the field of microfluidics.

COULTER PROGRAM DIRECTOR & HR SPECIALIST JOIN STAFF

Tom Marten joined BME in November as the Coulter Program Director. Marten founded Pharmacision LLC in 2007 through which he's consulted companies in the medical device, therapeutics, diagnostics, and life science arenas on commercialization and start-up efforts.

Tom Marten. Photo by Joseph Xu.

Jennifer Rieger joined BME in July to provide human resources (HR) support to the department. She's been at U-M for six years and formerly managed HR in the Chemistry Department.

Jennifer Rieger. Photo by Joseph Xu.

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was drawn to the company's focus on organic development – its support for foundational research and development from the patent on up. He soon found himself on a thrilling project, serving as technical lead for a cochlear implant. The device provided him a major claim to success – it was the first FDA-approved replacement for one of our five senses. However, it would also teach Kriewall the most painful lesson of his career.

The project began as an acquisition from another company, and Kriewall's team knew they could improve it. They replaced short-lived plastic parts with titanium-encapsulated receivers. The welding was hermetically sealed by a company contracted with NASA. They even devised a "belt and suspenders" design to ensure electrical continuity if a weld ever failed. In short, they aimed for a rock-solid device.

After years of work and FDA approval, they were ready to implant in 16 test patients. But when the time came to power them up, almost a third failed immediately. Yet the x-rays looked fine. Everyone turned to Kriewall for answers.

"It was agonizing; I spent nine sleepless months," he says. "I didn't know what to fix because we had no idea what broke. I didn't even know which questions to ask. I had spent my career focused on research; I knew nothing about failure analysis."

He recognized that, at a minimum, they had to remove and analyze all the implants. In the process, they discovered two things. First, their belt and suspenders design had backfired; the device was too inflexible for the implantation procedure. Second, the NASA supplier's "certified" hermetic seals were not living up to their claims.

With this information, Kriewall's team was able to change the design and manufacturing process – and more importantly develop the design specifications needed to test the new product to failure. "I learned this process from the scientists at the FDA," he says. "It was the most important lesson of my life, yet it's the hardest to convey to students. I tell them: When you have a design, break it! But it doesn't sink in. They're so excited about their new, low-cost prosthetic or whatever. But if your device gives an amputee hope that he can walk again and the thing fails in six months, how does that affect him psychologically? Students think failure analysis is extra work they don't have time for, but it's critical."

Kriewall led the development of the first FDA-approved cochlear implant. An early implant allowed this child to mainstream with hearing children without the need for sign language or lip reading.

LESSON 6: CONSIDER THE CULTURE

Despite all their investment, 3M considered the implant's risk-to-benefit ratio too high and sold it off. Seeing the writing on the wall, Kriewall took preretirement to ponder his next step. But Medronic had already come calling. Kriewall was intrigued by their intrepid focus on medical devices. "They routinely go where angels fear to tread," he says. "They develop products other companies won't touch and do extraordinary things with them."

Kriewall spent six years with Medtronic leading product development efforts in ear, nose, and throat instruments; blood diagnostics; and cardiovascular surgery. But he came to realize that the flip-side of 3M's "organic development" process had challenges all its own. "Compared to 3M, Medtronic was more interested in buying the field after oil was discovered," he says. "They would acquire medical device companies once they'd proven a technology's potential." His job was to integrate the culture of the new company with Medtronic's. But it was often difficult to retain key scientific and engineering experts, he says, because their passion was in the start-up; they weren't always interested in the corporate milieu. It was an up-close lesson in the value of understanding a company's culture and whether you, as an employee, can sync with it.

LESSON 7: KNOW YOUR VALUE

The time was right for a transition when Kriewall was invited to throw his hat in the ring for the presidency of Wisconsin Lutheran College, a comprehensive liberal arts school, which, incidentally, offers no engineering. Though perhaps not an obvious fit, Kriewall felt he had something important to teach the students. "I learned in my career that liberal arts graduates bring something critical to product development," he says. "Engineers are wonderful problem solvers, but it's the liberal arts graduates with their well-developed right brains who introduce things like color, descriptive text, and graphical user interfaces."

But what these students needed, he thought, was to understand their value in business. He worked during his tenure to encourage them to discover the skills they most enjoyed using, identify industries in need of those skills, and articulate their unique value proposition in each industry's language.

LESSON 8: SEE THE NEED

Kriewall "retired" again, only to find himself back at work the next day, this time for the Kern Family Foundation. His charge was "to keep the U.S. in its technical leadership position by instilling the 'entrepreneurial mindset' in engineering graduates." The foundation targeted a network of small private schools eager to teach engineering students to recognize the needs around them and find ways to deploy technology to improve people's lives throughout the world.

Kriewall giving advice to current students at the alumni tailgate. Photo by Joseph Xu.

The aim, Kriewall says, was not to create engineers who would launch businesses, but to instill a habit of watching for needs and asking good questions. "Generally, people can't tell you what they need," he says. "You have to drill down." For example, OBs didn't think they needed real-time ultrasound, but they knew they'd benefit from identifying twins in utero. Engineers can only provide a solution if first they see the need.

Kriewall retired again last year, though he still makes himself available for consulting. He says he was pleased to receive the Alumni Merit Award for the opportunity to share both his life's lessons and a long-overdue thank-you to the university and department that trained him. He urges today's students to do the same. His parting lesson? "Say thank you," he says, "before it's too late."

Students' Summer Experiences

Kaitlin Grove (master's student) worked in Regulatory Affairs for Zimmer Trauma in Warsaw, Indiana, where she helped complete international registrations for an intramedullary nail product.

Matthew Kolevar (senior) worked with the Surgical Solutions Division of Covidien in Boulder, CO, testing electrosurgical handsets on a new platform for emerging markets.

Sibu Kuruvilla (PhD student MSE) developed a curriculum and helped implement engineering and sustainable agriculture summer camps for high school students in Liberia, Africa.

Sibu (center) with Peace Corps volunteers who also taught camps through Excellence in Higher Education for Liberian Development.

Anastasia Ostrowski (sophomore) participated in a Johns Hopkins Research Experience for Undergraduates. She worked in the Computational Sensing and Medical Robotics Laboratory, developing simulations to test the feasibility of using transcranial photoacoustic imaging in endonasal surgery.

Jordan Pollack (master's/SGUS*) served as an R&D intern at Baxter Healthcare in Round Lake, IL, where he worked on a new cycler for peritoneal dialysis.

Ryan Thomas (sophomore) studied Spanish and conducted independent research in the Dominican Republic on the influence of socioeconomic status on leptospirosis awareness.

Brandan Walters (PhD student) volunteered with 10 U-M students in mobile clinics in Tanzania, Africa. The trip was organized through Medlife, a campus organization that provides health care in developing countries.

Brandan and other Medlife volunteers in Tanzania.

*Sequential Graduate/Undergraduate Study (SGUS) is a five-year program that combines undergraduate study in an engineering field with a master's degree in biomedical engineering.

COLLEGE OF ENGINEERING & MEDICAL SCHOOL
BIOMEDICAL ENGINEERING
UNIVERSITY OF MICHIGAN

Department of Biomedical Engineering
University of Michigan
2200 Bonisteel Blvd.
1107 Carl A. Gerstacker Building
Ann Arbor, MI 48109-2099

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