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National Academy of Engineering

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FRONTIERS OF ENGINEERING

Reports on Leading-Edge Engineering from the 2014 Symposium

NATIONAL ACADEMY OF ENGINEERING
OF THE NATIONAL ACADEMIES

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Preface

This volume presents papers on the topics covered at the National Academy of Engineering's 2014 US Frontiers of Engineering Symposium. Every year the symposium brings together 100 outstanding young leaders in engineering to share their cutting-edge research and innovations in selected areas. The 2014 symposium was held September 11–13 at the National Academies' Beckman Center in Irvine, California. The intent of this book is to convey the excitement of this unique meeting and to highlight innovative developments in engineering research and technical work.

GOALS OF THE FRONTIERS OF ENGINEERING PROGRAM

The practice of engineering is continually changing. Engineers must be able not only to thrive in an environment of rapid technological change and globalization but also to work on interdisciplinary teams. Today's research is being done at the intersections of engineering disciplines, and successful researchers and practitioners must be aware of developments and challenges in areas that may not be familiar to them.

At the annual 2½-day US Frontiers of Engineering Symposium, 100 of this country's best and brightest engineers—ages 30 to 45, from academia, industry, and government and a variety of engineering disciplines—learn from their peers about pioneering work in different areas of engineering. The number of participants is limited to 100 to maximize opportunities for interactions and exchanges among the attendees, who are chosen through a competitive nomination and selection process. The symposium is designed to foster contacts and learning among promising individuals who would not meet in the usual round of professional

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meetings. This networking may lead to collaborative work, facilitate the transfer of new techniques and approaches, and produce insights and applications that bolster US innovative capacity.

The four topics and the speakers for each year's meeting are selected by an organizing committee of engineers in the same 30- to 45-year-old cohort as the participants. Speakers describe the challenges they face and communicate the excitement of their work to a technically sophisticated but nonspecialist audience. They provide a brief overview of their field of inquiry; define the frontiers of that field; describe experiments, prototypes, and design studies (completed or in progress) as well as new tools and methods, limitations, and controversies; and assess the long-term significance of their work.

THE 2014 SYMPOSIUM

The topics covered at the 2014 symposium were (1) co-robotics, (2) battery materials, (3) technologies for the heart, and (4) shale gas and oil.

The first session focused on co-robotics, or the development of robots to assist and cooperate with humans in workplaces, hospitals, and homes. Such tasks range from inventory handling and household cleaning to tele-operated minimally invasive surgery, self-driving cars, and unmanned aerial vehicles. The first talk was about Google's program for self-driving cars, which have been made possible by new algorithms, increased processing power, and innovative sensors. The next presenter provided an overview of the hardware and software required to build a robot that can safely interact with humans and perform repetitive manufacturing tasks. This was followed by a talk on the next generation of minimally invasive surgical robotics that go beyond the costly, large, less dexterous systems we see today to robots that can be designed, manufactured, and controlled on the fly for a specific patient and procedure. The last talk covered biologically inspired mobile robots. These technologies use locomotion mechanisms seen in nature to create robots with higher mobility that could even go beyond what we see in nature.

Battery Anxiety was the aptly named title of the second session because it covered the compromises among safety, energy density, power density, cost, and lifetime in batteries with a focus on fundamental and applied materials research. The talks addressed such questions as whether new chemistries that go beyond lithium ion are needed to keep pace with energy demands and whether multidisciplinary engineering can address the constraints inherent in lithium ion and other promising battery chemistries. Presentations in this session covered battery life and safety research from an automotive perspective; challenges in batteries for electric vehicles; the challenges of manufacturing the wide variety of lithium ion batteries that have been made possible through design of battery cells for specific applications; and synthesis/characterization and first principles computational modeling techniques used to develop and optimize new higher energy/power density electrode materials for lithium ion and sodium ion batteries.

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The topic of the third session was leading-edge technologies for diagnosis and treatment of heart and cardiovascular system conditions. These technologies tend to mimic natural biologic conditions and behavior in a harmonious way in order to heal, assist, or replace the heart's critical components. The first presentation provided a history of heart valves from an industrial perspective—from early design and implantation in 1955 to next-generation valves, placement techniques, and development of devices that repair rather than replace native valve function. This was followed by talks on research under way on tissue-engineered valves and state-of-the-art biomaterials for treating myocardial infarctions. The session concluded with an overview of the regulatory environment and requirements to get these new technologies to patients.

The final session of the meeting focused on the logistical, chemical, and environmental issues associated with utilization of shale gas and oil resources facilitated by the development of hydraulic fracturing technologies. These technologies are the primary reason that in October 2013, for the first time in almost 20 years, the United States produced more oil domestically than it imported. The session opened with an overview of the location and nature of domestic shale gas and oil resources and described hydraulic fracturing, including its logistical and infrastructure challenges. The next presentation covered environmental challenges associated with hydraulic fracturing, specifically the microbial ecology and biogeochemical processes that impact production of oil and gas, management of wastewater, and product quality from hydraulically fractured wells. The third speaker discussed the utilization of shale gas for chemical production vs. its use as fuels and the challenges associated with methane conversion.

In addition to the plenary sessions, the attendees had many opportunities for informal interaction. On the first afternoon, they gathered in small groups for "get-acquainted" sessions during which they presented short descriptions of their work and answered questions from their colleagues. This helped them to get to know more about each other relatively early in the program. On the second afternoon attendees met in affinity groups based on engineering discipline or interest in a particular topic such as the future of engineering education, 3D printing, or energy storage.

Each year a distinguished engineer addresses the participants at dinner on the first evening of the symposium. The 2014 speaker, Dr. Arunava Majumdar, Jay Precourt Professor and senior fellow, Precourt Institute for Energy and Department of Mechanical Engineering, Stanford University, gave the first evening's dinner speech titled, "What is Impact?" He described how the traditional ways of measuring the impact of an innovation or discovery are difficult to measure. Some innovations that have a far-reaching impact, such as the Haber-Bosch process that has affected the world's ability to grow food, may not be recognized as such. He challenged the attendees to discern what our Haber Bosch–like challenge may be, for example, providing access to electricity in developing countries or scrubbing the atmosphere of CO_2 at cost and scale.

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We also thank the members of the Symposium Organizing Committee (p. iv), chaired by Dr. Kristi Anseth, for planning and organizing the event.

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Co-Robotics

Brian Gerkey
Open Source Robotics Foundation

Carmel Majidi
Carnegie Mellon University

Historically, robots have been engineered as heavy industrial machinery for repetitive tasks such as welding, painting, and machining. These industrial robots are not typically designed for human interaction and can only be operated by a trained specialist in a controlled factory environment. However, recent advancements in robotics technology have enabled safer interaction with humans and allowed robots to enter our workplaces, hospitals, and homes. This new generation of medical and service robots assist and cooperate with humans in a broad range of "co-robotics" tasks, from teleoperated minimally invasive surgery to inventory handling and household cleaning. Advancements in robot control and automation have also led to self-driving cars, unmanned aerial vehicles, and other autonomous vehicles technologies that have the potential to revolutionize transportation, space exploration, and natural disaster relief. As these nontraditional applications of robotics continue to grow, further advancements will increasingly focus on fundamental challenges that are unique to co-robotics. These include progress in not only robotics technology but also the social, behavioral, and economic aspects of human-robot interaction.

This session began with a talk by Chris Urmson, who leads Google's program for self-driving cars, which have driven more than 700,000 miles on public roads. Next, Matthew Williamson (Rethink Robotics) presented a comprehensive overview of the hardware and software required to build a robot that can safely interact with humans and be trained to perform repetitive tasks in a manufacturing environment. The third speaker, Allison Okamura (Stanford University) described

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her work on the next generation of minimally invasive surgical robotics, which can be designed, manufactured, and controlled spontaneously for a specific patient and procedure. The final presentation, by Dennis Hong (University of California, Los Angeles), was about biologically inspired mobile robots.[1]

[1] Paper not included in this volume.

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Progress in Self-Driving Vehicles

Chris Urmson
Google

Automated driving has experienced a research renaissance in the past decade as investigators have been motivated by organized competitions to increase safety and mobility. Key advances that have shaped the field during this period have been in the application of machine learning, large-scale mapping, improved LIDAR (light detection and ranging remote sensing technology) and RADAR sensing capability, and, more recently, a deeper understanding of the human factors that will influence the form in which this technology comes to market.

WHY SELF-DRIVING VEHICLES?

Traffic accidents are the leading cause of death for individuals aged 4 to 34 in the United States (Hoyert and Xu 2012). More than 30,000 people are killed each year on the road, and over 90 percent of these accidents are due to human error. Furthermore, the ability to move in, through, and around cities is decreasing as more and more drivers, preferring individual mobility, flood roadways. Yet the importance of personal mobility in the United States is such that when individuals lose the privilege of driving, and the social connections it enables, their life expectancy drops precipitously (Edwards et al. 2009). And in developing cities the rise in traffic deaths and significant pollution is further evidence of the tragedy of the commons.

Self-driving vehicles offer the promise of addressing all of these challenges: they should dramatically reduce accidents, enable people who cannot drive to get around, and, when deployed as part of an efficient shared vehicle fleet, reduce congestion.

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A DEEP HISTORY

As early as the 1939 World's Fair, General Motors showed a concept of the automated roadway of the future. In 1950 its research and development department introduced the Firebird II concept car, capable of following buried cables that emitted a radiofrequency signal. During the 1980s and '90s the introduction of the microcomputer enabled practical, online computation on a mobile platform. Ernst Dickmanns was a pioneer in this space, introducing early versions of foveated stereovision systems (Dickmanns and Wünsche 2007).

Soon machine learning began to be applied to the problem. RALPH (a rapidly adapting lateral position handler; e.g., Thorpe and Kanade 1990) was one of the earliest applications of machine learning (neural networks in this case) to automated driving. By 1997 the combination of RALPH with a nascent forward-looking RADAR system enabled vehicles to drive thousands of miles. Elements of this technology have found their way into lane keeping assist systems, forward collision mitigation braking, and adaptive cruise control systems.

DARPA'S GRAND CHALLENGES

Much of the on-road automated driving work faded after the successful 1997 National Automated Highway Systems Consortium demonstration. The technology worked reasonably well, but automated driving research funding turned toward the military while the automotive industry slowly commercialized driver assistance systems.

In 2003 the driving research community was reenergized by the announcement of the DARPA Grand Challenges (http://grandchallenge.org/). The Floyd D. Spence National Defense Authorization Act for fiscal year 2001 called for one third of all US military ground vehicles to be unmanned by 2015. In a 2002 report the National Research Council indicated that this goal would not be achievable and that the Department of Defense should pursue other strategies (NRC 2002). Thus DARPA's Grand and Urban Challenges were born.

The initial Grand Challenges were off-road races across the desert, with the notional goal of having autonomous vehicles drive from Los Angeles to Las Vegas without remote assistance. In 2004 the challengers went only 7 miles of the 150-mile course (Urmson et al. 2004). The following year, several vehicles completed the competition (Figure 1), which was won by a team from Stanford (Thrun et al. 2006).

The vehicles featured several notable technical innovations. All of the competitors were given a rough map of the route, but several of the successful teams augmented the map data with information from other publicly available sources. The notion of fusing such information with onboard sensing data was novel at the time (Urmson et al. 2006). The approach was enabled by newly available access to

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FIGURE 1 The top three finishers in the 2005 DARPA Grand Challenge: Stanley, entered by Stanford University (left), and H1ghlander (center) and Sandstorm (right), both entered by Carnegie Mellon University.

high-resolution aerial imagery, and gave the vehicles a degree of foreknowledge of the terrain that resulted in better and safer driving.

The Stanford team used machine learning techniques extensively. For example, its vehicle used machine learning to bolster its visual system using LIDAR sensors, enabling it to drive faster than was possible using LIDAR alone. The vehicle was able to detect rough terrain and slow appropriately using a learned model of "bumpiness." The team's success in the challenge helped reinforce machine learning's value in the field of autonomous driving.

THE URBAN CHALLENGE

While the Grand Challenge was indeed a grand challenge, the vehicles operated in a world devoid of other moving vehicles: when Stanley, the Stanford vehicle, passed H1ghlander, the Carnegie Mellon vehicle, to claim the victory, H1ghlander was paused and Stanley passed an inert vehicle.

The Urban Challenge was thus the next evolution of the DARPA competition, in which the vehicles now had not only to complete the challenge with moving vehicles but also to obey a subset of driving rules that human drivers take for granted (e.g., stay in the lane, follow precedence rules at intersections, avoid other vehicles). The competition, staged in 2007, required vehicles to drive 60 miles around a decommissioned Air Force base in Victorville, California. Six vehicles

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finished the competition, with teams from Carnegie Mellon, Stanford, and Virginia Tech in the top three positions (Buehler et al. 2009).

Key technical advances came in the form of high-density LIDAR and further demonstration of the value of high-density maps. Single-plane LIDAR sensors were used in the original Grand Challenge, sometimes actuated to sweep volumes but generally carefully calibrated to sweep scan lines through the environment as the vehicle moved. The Urban Challenge introduced the concept of high-density LIDARs through a sensor developed by Velodyne. The new sensor had a spinning head that swept a set of 64 LIDAR emitters through space, generating over 1 million range measurements per second with relatively high angular resolution. This style of sensor enabled a new level of precision modelling that had until then been difficult, if not impossible, to achieve in real time.

The value of digital maps came to the forefront during the Urban Challenge. Using the maps, vehicles were able to anticipate the likely trajectory of other vehicles and focus their attention in appropriate directions at intersections. They were also able to use their limited computation more efficiently.

POST-CHALLENGE PROGRESS

In the seven years since the Urban Challenge, industry has taken up the gauntlet of advancing self-driving technology. In 2009 Google started a program to develop self-driving vehicles and since then its vehicles have driven more than 700,000 miles autonomously on public roads.

The technology being developed by Google builds on many of the themes developed during the DARPA challenges. The vehicles use high-resolution maps (now being developed at city scale) to help guide the onboard system's perception and planning behaviors as well as a combination of LIDAR, camera, and RADAR sensors to provide a partially redundant and multispectral model of the environment. The onboard software system leverages hundreds of thousands of miles of driving data and machine learning techniques to predict the behavior of other road users.

In parallel with Google's efforts, the automotive industry is broadly engaged in the development of advanced driver assistance systems, with the major car companies and their suppliers developing varying degrees of automated driving. The largest difference between the approaches of the classical automotive companies and Google is the degree to which the driver is engaged. Google is developing vehicles to be fully self-driving, requiring a rider only to tell the vehicle where to go (Figure 2), whereas the automotive companies are primarily focused on delivering advanced driver assistance systems that require the driver to remain in the steering loop. The latter approach requires a smaller incremental technical step, but is challenged by problems of driver attentiveness and skill atrophy (Llaneras et al. 2013).

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FIGURE 2 Google's prototype fully self-driving vehicle.

In the coming years advanced driver assistance systems and self-driving vehicles will become commonplace, delivering on the promise of making roads safer and more convenient for all.

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Safe, Cheap, and Smart: Collaborative Robots in Manufacturing

MATTHEW WILLIAMSON
Rethink Robotics

A recent trend in manufacturing automation is the use of what have become known as "collaborative robots." These are robots that are safe to work alongside human workers, as opposed to traditional industrial robots that are generally separated from humans by safety cages. They are also typically easy to program and inexpensive. These properties contrast with those of traditional industrial robots, which are expensive, not safe, and require an expert to program them. The properties of collaborative robots enable new classes of applications that are too low value or too variable to be cost effective with traditional robots.

This paper reviews the economics of automating tasks using collaborative robots and the kinds of new tasks enabled by their use. It describes examples of collaborative robots on the market, and some of the technologies that enable them to be safe, inexpensive, and smart.

COST AND FLEXIBILITY

A common thread in all manufacturing businesses is the desire to improve the efficiency and reduce the cost of the manufacturing process in order to increase margins and thus profits. A common way to do this is via automation, which explains why in the United States manufacturing productivity has increased steadily over the past 70 years while employment in the sector remained roughly constant (Strauss 2014).

But cost is not everything, as in recent years there has been a trend toward smaller batch sizes and more customized manufacturing, driven by consumer demand. For example, automotive manufacturing is set up to achieve economies of

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scale by mass-producing a limited range of models. However, this approach makes it difficult to respond not only to the demand for customized features per vehicle but also to the need for different volumes (e.g., demand for hot-selling models as opposed to less popular versions). Manufacturing therefore has to accommodate both cost and flexibility.

There are a variety of approaches to automation with different cost/flexibility tradeoffs, and they are driven somewhat by the properties of the automation technology used. Fixed automation, which uses custom machinery for most or all of a process, tends to be expensive to design and create but very efficient once implemented. It is, however, inflexible and so requires long production runs to justify the expense. Fixed automation is common in industries with stable, long-running production of, for example, consumer packaged goods such as diapers.

Traditional robotics is more flexible than fixed automation, but still has a high cost. Cells running robots are expensive to design and set up, and require long runs to get a return on investment. The dominant market for industrial robots is the automotive sector, where a spot welding robot can be used on a variety of models, yet be tweaked or reprogrammed as necessary as vehicle body parts and shapes change.

The most common automation method uses machinery for high-value parts of the manufacturing process and human labor to complement the machinery. For example, a Computer Numerical Control (CNC) milling machine can be used to turn metal slugs into parts (a high-value operation), while being tended by human operators (who perform the loading and unloading that is of lower value). This is a very common approach because it yields cost savings and flexibility on how a line is constructed and used, but it is more expensive in terms of running costs than fixed or robotic automation.

The technology properties of collaborative robots—safe, inexpensive, and smart—are different from those of fixed or traditional robotic automation, making them more appropriate for low-value and variable processes. The real value of their properties boils down to cost and flexibility. Safety reduces cost, both directly (there is no need to buy an industrial safety system, which are by their nature highly reliable and thus expensive) and indirectly (the floor area taken by safety systems cannot be used for manufacturing). Safety also increases flexibility: the risk assessments required for each application are the same, but there is no need to spend the time and money redesigning and redeploying a safety system for each application. Having inexpensive hardware obviously reduces overall cost, and ease of training reduces application cost, ongoing maintenance, and redeployment costs.

By offering low-cost and flexible automation, collaborative robots are appropriate for use in many areas that are not currently automated (low-value, variable tasks). These include machine tending, kitting (depositing parts into a kit for an assembly operation), line loading and unloading, and packaging, many of which are largely not automated.

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EXAMPLES OF COLLABORATIVE ROBOTS

The following sections describe some of the collaborative robots currently available. For a fuller review, see citation Robotiq.

Universal Robotics

Universal Robotics (www.universal-robots.dk/) sells two collaborative robot arms, the UR5 (with a 5 kg payload) and the UR10 (10 kg payload). These are both six-degree-of-freedom arms, with about 1 m reach. Safety for these robots comes from their low payloads and speeds, and they are inexpensive (around $35,000 for the UR5). The programming interface is very simple and easy to use, allowing quick training and retraining of the robot by users without programming skills. The company also provides support for communication with machines and other pieces of industrial automation.

Rethink Robotics

The Baxter robot, a humanoid robot with two seven-degree-of-freedom arms, is a product of Rethink Robotics (http://rethinkrobotics.com). Its safety is achieved by having arms with a low payload (2 kg) and by using an actuator technology called *series elastic actuators*, which embeds springs in each joint of the arm, making the arms inherently compliant.

Series elastic actuators, invented at MIT in the 1990s (Pratt and Williamson 1995), consist of a spring in series with the output of an electric motor and gearbox. A sensor measures the twist of the spring, and a control system is used for the output torque at the joint. The spring and control loop enable good performance with inexpensive components, because the spring naturally cleans up some of the undesirable properties of inexpensive gearboxes. In addition, the torque sensing at each joint that this type of actuator affords opens up different strategies for controlling robots, using force control rather than position control.

The use of series elastic actuators allows the cost of Baxter to be low ($30,000), and the robot comes preintegrated with sensors (e.g., force sensing, cameras) that are intended to make the integration process easier. Baxter's user interface is very different from traditional robot programming: it is programmed by demonstration and consists of manipulating higher-order primitives (picks and places) as opposed to the normal programming method (based on lower-level functionality such as moves). This opens up use of the robot to nonprogrammers.

Precise Automation

Precise Automation (www.preciseautomation.com) produces the PF-400, a small SCARA robot with a small reach (0.5 m) and payload (1 kg). Safety is

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achieved by its low power and force limiting features. The robot cost is also low (not published but likely under $20,000). The robot programming environment offers a teach-by-demonstration mode for quickly training key points in the robots environment, although it is otherwise trained like an industrial robot.

CONCLUSION

Market forces and business realities continue to prompt investment in ways to reduce cost and increase flexibility in manufacturing processes. Traditional fixed and robotic automation can offer efficiencies but tends to be inflexible and require large batch sizes to obtain return on investment. There is an opportunity for automation that can be both efficient and inexpensive enough to work on lower-value operations *and* flexible enough to be repurposed for variable or small batch sizes.

Collaborative robots are one automation choice that meets these needs. New technologies and products enable the development of robots that are safe to be around humans (which in turn has cost and flexibility benefits), inexpensive (the robot hardware is inexpensive), and flexible (their user interfaces are designed to make them easy to train and repurpose). These robots are expected to complement existing automation approaches and provide more opportunities for greater productivity in the manufacturing sector.

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Personalized Medical Robots

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Many medical interventions today are qualitatively and quantitatively limited by human physical and cognitive capabilities. Robot-assisted intervention techniques can extend humans' ability to perform surgery more accurately and less invasively using novel physical designs and computer control. Hundreds of thousands of surgical procedures are now done annually using robots, typically teleoperated by human surgeons. Commercial surgical robots such as the da Vinci Surgical System (DiMaio et al. 2011) are designed as general tools that can be used for a variety of procedures and patient populations. But because of their limited dexterity, high cost, and large footprint in the operating room, there are many scenarios in which current clinical robots cannot be used to perform minimally invasive medical procedures (Herron and Marohn 2008; Taylor and Stoianovici 2003). The next generation of medical robots will be much more personalized—capable of being rapidly designed, manufactured, and controlled for a specific patient and procedure.

DESIGN OF PERSONALIZED MEDICAL ROBOTS

Each patient presents a design opportunity. A path from a feasible entry point on the surface of the body to the target, such as a cancerous tumor or kidney stone, can be planned based on patient-specific anatomy and mechanical models of tissue acquired via new elastographic imaging techniques. Based on this path, a unique robotic steerable needle or catheter design will achieve the most minimally invasive trajectory possible, thus increasing accuracy, minimizing trauma, and ideally decreasing recovery time and chance of infection. This capacity is particularly useful in addressing the needs of specialized patient groups, includ-

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ing children and people with rare diseases, who may otherwise not receive the optimal treatment.

In many procedures, the path of least resistance from a feasible entry point on the surface of the body to a target for treatment has multiple curved segments, so a snakelike device with the ability to change its shape along its length is ideal. To avoid the "curse of dimensionality" (the challenge of modeling and controlling a system with hundreds of individual degrees of freedom), a useful robot design should require only a few input degrees of freedom, yet have the ability to achieve a large variety of physical configurations. Steerable needles (Reed et al. 2011) have this property, but require relatively large reaction forces from tissue and cannot work in free space.

One of the most promising approaches is the *concentric tube robot* (also known as the *active cannula*), which consists of nested hollow, precurved, superelastic tubes. As the curved tubes are inserted and rotated with respect to each other, they interact such that their common axis conforms to some combined curvature, causing the overall shape of the robot to change. Because concentric tube robots derive bending actuation from the elastic energy stored in the backbone, they do not require reaction forces to bend and can be used in free space. The concept for the active cannula was simultaneously developed in 2006 (Sears and Dupont 2006; Webster et al. 2006), and recent work has provided a comprehensive analysis of concentric tube robot design and kinematics (Gilbert and Webster 2013; Lock and Dupont 2011; Rucker et al. 2010; Webster et al. 2008).

One example of concentric tube robot design is given in the context of accessing hard-to-reach upper-pole kidney stones in pediatric patients (Morimoto et al. 2013). Because of their smaller body surface area compared to adults, as well as the proximity of the upper kidney to the diaphragm and the pleura, traditional straight needle- and catheter-based approaches can be dangerous. To eliminate these risks, the ideal path would begin below the 12th rib, snake up through the renal pelvis, and curve toward the upper pole of the kidney. The exact dimensions for curvatures and segment lengths of the tubes can be gauged from patient-specific CT scans. Based on kinematic models (Dupont et al. 2010; Sears and Dupont 2007; Webster et al. 2008, 2009), sets of tubes can be identified that follow the desired path through patient tissue (Figure 1).

MANUFACTURING OF PERSONALIZED MEDICAL ROBOTS

A combination of modular robot architecture and novel manufacturing techniques is beginning to enable fast manufacturing and assembly of robotic manipulators that can achieve a variety of design objectives. Primarily these robots will be long, thin, flexible devices whose actuators remain outside the body and whose components that enter the body are sterile and disposable—they are small,

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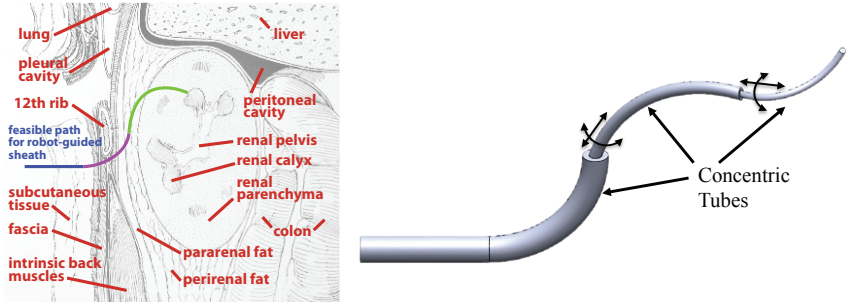

FIGURE 1 Personalized medical robot design uses knowledge of patient anatomy (left) to select the number, shape, and length of robotic elements (right) to reach a target in the safest, most minimally invasive fashion possible. Adapted from Morimoto et al. (2013).

inexpensive, and do not need to be overdesigned for repeated use. The nondisposable base of the robot can consist of modular units.

In the case of a modular concentric tube robot design, a single module includes two motors that allow a tube to be both inserted and rotated with respect to the tubes around it (Figure 2). The outermost tube to be inserted is clamped in the modular unit at the end of the base closest to the patient, while the subsequent tubes (with increasingly smaller diameters) are axially aligned in units further behind. Units can be added or removed based on the number of tubes needed for the specific procedure and patient.

The disposable components of the robot can be either specifically designed for each patient or chosen from a set that has been previously designed and optimized for a particular population of patients (e.g., children). A patient-specific design requires the manufacture of numerous disposable components. In one method for active cannula manufacturing, superelastic (e.g., Nitinol) tubes are heat treated to take on the desired shapes.

Recent work has taken advantage of advances in 3D printing to quickly and cheaply produce patient-specific devices (Figure 2). The use of 3D printing is becoming more widespread in the medical field for anatomy visualization to improve surgical planning (Dankowski et al. 2014; Schwaiger et al. 2012) and for the production of customized implants for patients with special requirements and size constraints (Abdel-Sayed and von Segesser 2011). 3D printing is also increasingly used for manufacturing medical robots, from rehabilitation devices to minimally invasive surgical robots (Roppenecker et al. 2013). The benefits of 3D printing include speed, the use of multiple materials in a single part, and the ability to embed sensors in a mechanical structure.

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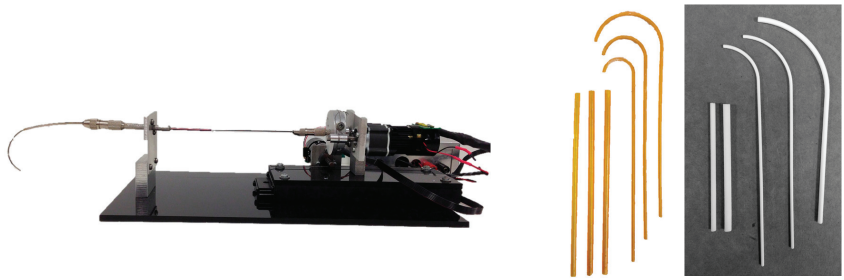

FIGURE 2 (Left) Active cannula-driving robot module. (Right) Example sets of 3D-printed tubes that can be used to construct an active cannula system.

CONTROL OF PERSONALIZED MEDICAL ROBOTS

Surgical robots that go deep into the body require a combination of low-level autonomous control and high-level human control. Human teleoperation directs the robot tip motions and treatments, while the underlying control system achieves the necessary robot configuration to minimize invasiveness. Seamless integration of preoperative plans and real-time medical imaging provide effective feedback to achieve the desired clinical outcomes. Examples of control systems that involve both low-level autonomous control and high-level human control include teleoperators that combine haptic (force feedback) guidance for steerable needles (Majewicz and Okamura 2013) and operator tip control for active cannulas (Burgner et al. 2011).

CONCLUSION

The next generation of medical robots will be personalized to enable treatment using devices optimized for a particular patient's body and malady. Advances in medical imaging, path planning, design, manufacturing, control, and human-machine interaction all contribute to this goal.

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Battery Anxiety

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Battery Anxiety

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Approximately 82 percent of energy use in the United States consumes fossil fuels such as petroleum, coal, and natural gas. In terms of sustainability, minimizing dependence on fossil fuel and reducing CO_2 emissions are compelling arguments to electrify vehicles and augment the electric grid infrastructure. As efforts to bolster electrical energy production progress, affordable, high-performance, and safe energy storage technology must also advance to enable the transition to an electrical energy economy. This session explores future energy storage needs through fundamental and applied materials research.

Batteries, fundamentally, are compromises among safety, energy density, power density, cost, and lifetime, and the materials required for batteries are actors in this compromise. In this session speakers discuss the many ways materials can be engineered to exploit or mitigate systematic coupling and the ways systems can be engineered to exploit their properties and address material limitations.

Realized in 1991, lithium ion (Li-ion) batteries were rapidly commercialized for use in microelectronics and are currently considered state-of-the-art technology for vehicle electrification. Beyond traditional battery performance metrics (e.g., the Ragone plot), widespread adoption of electric vehicles and advances in grid technology have been limited due to cost and safety constraints of current Li-ion technology. Are these constraints inherent to the technology? Can multidisciplinary engineering address these constraints not only for Li-ion but also for other promising battery chemistries? Or are new chemistries that go beyond Li-ion necessary to keep pace with future energy storage demands? These aspects are discussed in this session.

The first speaker, Alvaro Masias (Ford Motor Company), talked about battery life and safety research. The next speaker, Sarah Stewart (Robert Bosch LLC)

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linked fundamental behavior in batteries to manufacturing issues. Specifically, she shared an overview of the challenges she saw while manufacturing battery packs and spoke about how fundamental engineering research could improve the manufacturing cost and reliability of batteries. Next, Claus Daniel (Oak Ridge National Laboratory) articulated the challenges of adapting battery chemistries and large-scale manufacturing for electric vehicles and grid storage. He offered a national lab perspective on the transition between materials discovery and energy storage technology maturation. The discussion also includes technology development perspectives from the Department of Energy, automotive, and electric utility industries. The final speaker, Shirley Meng (University of California, San Diego), covered materials and battery design from the ideal or theoretical perspective, spanning a range of topics from atomic scale phenomena to nanoarchitectures, charge transport, and prototypical batteries.[1]

[1] Paper not included in this volume.

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Electrochemical Prozac: Relieving Battery Anxiety through Life and Safety Research

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Ford Motor Company

Global interest in electrified vehicles is sparked by both environmental concerns and, in practical terms, the relatively recent application of lithium ion battery technology to automotive applications. Mass adoption of automotive batteries will depend on performance improvements, so methods to optimize the prediction and design of this technology for endurance and safety are an area of active research. New analytical test tools and methods are described in this article, and their refinement and adoption will enhance the ability of lithium ion technology to supplant liquid hydrocarbon fuels in the transportation sector and thus positively contribute to the global environment.

INTRODUCTION

The governments of the United States, European Union, China, and Japan, among others, have announced increasingly strict fuel economy regulations. Thus although the fossil fuel–powered automobile has been the subject of continuous engineering improvement for over 100 years (Ford 1988), electrified automobiles are a key component of virtually all automakers' current and future product portfolios, and lithium ion batteries are enabling a new generation of electrified vehicles to be commercialized by global automakers.

In this article I explain battery performance requirements for the broad range of electrified vehicles, together with new tools to improve the identification and prediction of failure mechanisms. Safety testing and the results of recent research in this area are also presented.

By addressing the sources of uncertainty in battery failure mechanisms, whether performance (i.e., precise measurement of voltage, current, and time) or

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safety (i.e., reaction to various types of mechanical and electrical abuse) related, researchers will enable significant improvements in future generations of battery-powered vehicles.

TRANSPORTATION BATTERY NEEDS

Electrified vehicle designs can be classified by their levels of electrification. In order of increasing power and energy demands, common electrified vehicle features include stop-start (maintaining normal vehicle functions at a stop while allowing the engine to turn off), regenerative braking (converting the kinetic energy of motion into stored electrical energy using the electric machines to supplement friction braking), motor assist, and electric vehicle (EV) drive (EVs run solely on electricity). The ability of hybrid electric vehicles (HEVs), which can convert liquid fuel energy into either mechanical or electrical energy, to perform these functions allows for differentiation between stop-start, mild (<20 kW), strong (>20 kW), and plug-in electric hybrids (PHEVs), which may consume some fossil fuel.

Until recently the performance and maturity of various battery chemistries determined their EV type suitability and commercialization. Now the recent maturation of lithium ion technology is driving a migration away from nickel metal hydride batteries for most HEV and EV applications. But low-temperature, cost, and life challenges prevent lithium ion technology from supplanting lead acid chemistries in the stop-start market.

The various EV types, with their different array of electrified features, place very different power, energy, and cycle life demands on their batteries. For example, a common EV design features more than 80 kW of power and 24 kWh of energy. Cycle life is strongly affected by the extent of the battery capacity used in each cycle. Likewise, designing for high energy has a direct impact on the available power delivery as a tradeoff.

Designing a vehicle battery involves balancing competing performance figures, including energy and power. As a result, several automotive industry and government organizations—the US Advanced Battery Consortium (USABC; information at www.uscar.org), the European Council for Automotive Research & Development (EUCAR; www.eucar.be), and the New Energy and Industrial Technology Development Organization (NEDO; www.nedo.go.jp)—have created EV performance targets for energy and power, designating targets for pack-level specific energy (energy by weight) and power (power by weight).

LIFE PREDICTION

When determining the ability of a battery technology to meet future life requirements a high level of confidence is required. Consequently, qualifying a new technology for production can take several years of validation testing to meet

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the typical 10-year/150,000-mile vehicle life requirement. Testing first distinguishes between battery life decay mechanisms (use or calendar dependent) and then assesses the impacts of current levels (low, high) and temperature.

Battery Life Decay Mechanisms

Battery life decay mechanisms can be categorized as *calendar* or *use dependent*. The former are tested in high-temperature protocols that take advantage of a battery's Arrhenius kinetic mechanisms, which lend themselves well to accelerated testing. Cycle life acceleration is more problematic, as its decay mechanism is more difficult to accelerate through established techniques. High-precision battery testing has recently been proposed as a method to accelerate the understanding of cycle life–based decay mechanisms (Smith et al. 2010). To make future life predictions, it is necessary that the precision of the test data be at least as good as the decay per cycle that is being predicted. By closely measuring current, voltage, and time during a battery test, it is possible to achieve the parts per million (ppm) level of measurement precision needed to predict hundreds and thousands of cycles into the future.

Low Current

To understand the impact of imprecise battery measurements, the example of coulombic efficiency (CE) in consumer electronic cell life requirements is shown in Figure 1. Coulombic efficiency is defined as the number of electrons that leave a battery divided by the number that entered. Based on this definition, a theoretically perfect battery would have a CE value of unity or 100 percent. If a cell delivered the exact amount of coulombic efficiency (99.954 percent or a deviation of 446 ppm from ideal) required to achieve 20 percent capacity decay in 500 cycles, the curve shown on the left in Figure 1 would be achieved. Exist-

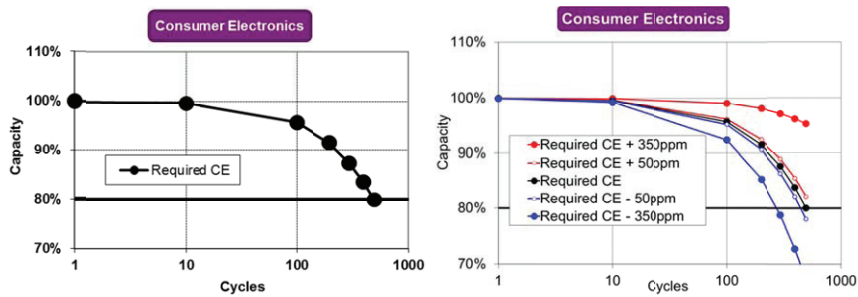

FIGURE 1 Coulombic efficiency (CE) required (L) and impact of tester imprecision (R).

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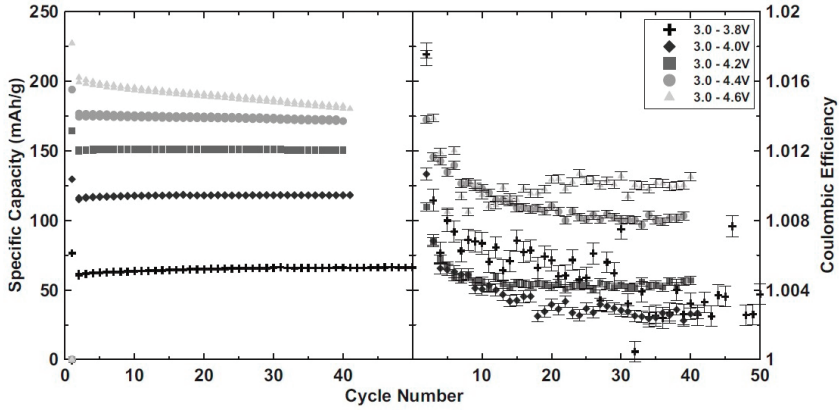

FIGURE 2 Capacity and high-precision coulombic efficiency as a function of charge voltage. Reprinted with permission from Smith et al. (2010).

ing battery testing equipment is subject to CE errors of nearly the same order of magnitude (350 ppm). To be relevant to EVs, where an order of magnitude improvement in cycles to 5,000 is desired, testers would need a corresponding error improvement to approximately 50 ppm. The righthand graph in Figure 1 shows that when the error is of about the same order of magnitude (350 ppm) as the allowable deviation (446 ppm), the predicted future capacity is uncertain. However when the tester error is reduced to 50 ppm, the predicted future capacity can be determined with more confidence.

Recognizing this opportunity for improvement, there has been growing interest in research on high-precision battery testing. Current academic systems have achieved 100 ppm error in terms of coulombic efficiency, with a goal of 10 ppm for future systems (Dahn et al. 2013; Smith et al. 2010). It should be noted that these systems are at low current rates (single-digit amps at the most). The impact of using a 100 ppm system on the imprecision of CE measurements is shown in Figure 2: the closer a battery's CE gets to unity (right side), the flatter its capacity decay cycle over time (left side).

High Current

Automotive battery testing must demonstrate the capacity to support currents of at least several hundred amps, as would be typical of vehicle conditions. The range of power and corresponding current demands varies by vehicle type. Higher currents are achieved in power characterization patterns ranging from +300 to −120 amps (A) for the various electrified vehicle types. To address the challenges associated with improving the precision of capacity predictions at

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higher current and power levels, the Department of Energy's Advanced Research Projects Agency–Energy (ARPA-E) has awarded a research contract to Ford, Arbin Instruments, and Sandia National Labs to build a commercially viable 50 ppm 200A tester.[1] Project progress is described below.

Temperature

Another significant challenge in testing at high currents is mitigation of the resulting temperature changes in the test cells and tester (e.g., shunts and amplifiers). For the test automotive cell, a thermal image can reveal temperature gradients. The order of magnitude of the gradient can vary widely depending on cell design and test pattern run, but its orientation remains the same. At the top of the cell, the connecting terminals serve as excellent thermal wicks (thanks to the highly thermally conductive metals used).

To explore the impact of high current–driven thermal gradients during high-precision testing, the Ford ARPA-E team has been developing thermal control strategies, one of which involves two thermoelectric (TE) heater/cooler assemblies surrounding a single cell. By coupling the intimate cooling capacity of the TEs with feedback (cell temperature) and feedforward (current delivery pattern and resulting cell-driven temperature change), it is possible to neutralize temperature fluctuations during the testing and study their effect (e.g., dV/dT) on precision.

SAFETY PREDICTION

Current and evolving government regulations and industry standards cover all aspects of automotive design. In the United States, these regulations take the form of the Federal Motor Vehicle Safety Standards (FMVSS), of which FMVSS 305 addresses electrified vehicles (Table 1).

As the technology and systems have evolved, FMVSS 305 has been revised numerous times since it was first issued in 2000. With the recent application of lithium ion batteries to automotive applications, the National Highway Traffic Safety Administration (NHTSA) has conducted research on the safety behavior of the technology. One of the NHTSA-sponsored research projects, conducted by Ford in collaboration with Ricardo, an international engineering and environmental consultancy, sought to develop recommendations for vehicle-level safety tests and performance metrics for NHTSA consideration. The project, completed in November 2014, included study of the behaviors of parts (e.g., cell strings, modules, and packs) to determine quantifiable vehicle-level recommended test procedures.

[1] Information about the project, for which I am principal investigator, is available at ARPA-E, "Ultra-Precise Battery Tester," http://arpa-e.energy.gov/?q=slick-sheet-project/ultra-precise-battery-tester.

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TABLE 1 US Federal Motor Vehicle Safety Standard 305 Requirements

	Section	Requirement
S5.1	Electrolyte spillage from propulsion batteries	<5L spillage total, 0 into passenger cabin 30 minutes after barrier test
S5.2	Electrical energy storage/ conversion device retention	Energy device shall remain attached to vehicle and out of passenger cabin
S5.3	Electrical safety	Maintain isolation >100 ohm/volt with monitoring or >500 ohm/ volt without monitoring

Source: DOT (2008).

The most common way to describe the response of a lithium ion battery to abuse is to use the EUCAR rating system (Table 2), which assigns a score of 0 to 7 for a range of increasingly severe battery responses. For example, a score of 5 denotes a battery that experienced a fire or flame event.

The team performed a rigorous fault tree analysis (FTA) to consider all the possible lithium ion–specific faults a vehicle could experience and produced a ranked list of priority hazards, from which the top three—crush, overcharge, and

TABLE 2 European Council for Automotive Research & Development (EUCAR) Battery Abuse Response Rating

Score	Title	Description
0	No effect	No effect. No loss of functionality.
1	Passive protection activated	Cell reversibly damaged. Repair of protection device needed. But no defect; no leakage; no venting, fire, or flame; no rupture; no explosion; no exothermic reaction or thermal runaway.
2	Defect/ damage	Cell irreversibly damaged. Repair needed. But no leakage; no venting, fire, or flame; no rupture; no explosion; no exothermic reaction or thermal runaway.
3	Leakage (Δ mass < 50%)	Weight loss <50% of electrolyte weight (electrolyte = solvent + salt). No venting, fire, or flame; no rupture; no explosion.
4	Venting (Δ mass > 50%)	Weight loss of ≥50% of electrolyte weight (electrolyte = solvent + salt). No fire or flame; no rupture; no explosion.
5	Fire or flame	No rupture; no explosion (i.e., no flying parts).
6	Rupture	No explosion, but flying parts of the active mass.
7	Explosion	Explosion (i.e., disintegration of the cell).

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short circuit—were selected for procedure development. A global survey of battery regulations and industry standards provided a baseline for the development of draft test procedures, which were then tested at three US locations. The sites evaluated string, module, and pack hardware built up with three types of lithium ion cells. The experimental testing and analysis allowed for significant test procedure refinement and confidence in battery responses.

Battery abuse tests generally fall into one of three categories: mechanical, thermal, and electrical. The following sections present the range of testing for each category and, where appropriate, the results and recommendations of Ford's research.

Mechanical Abuse

International battery safety mechanical test regulations and standards vary significantly (Table 3). The most common test combines mechanical shock and mechanical integrity testing, in which the battery is typically subjected to a mechanical crush event.

Review of the large number of existing crush-related tests led to selection of the FreedomCar procedure as a starting point (INEEL 2003). The procedure was modified to stratify the battery response by breaking up the crush motion into 20 increments of 5 percent. By crushing in many small steps over approximately one hour, it was possible to determine the impact of a fault as it progressed.

All hardware was able to be crushed to more than 13 percent displacement without a EUCAR 5 (fire or flame) response. The broad plane of the cell had the smallest ranges of response, indicative of testing consistency. Designing a parts-level crush test for the other planes of the cell is nontrivial because of the tendency of hardware to move out of the plane of crush when not constrained in a vehicle. As a result, it was concluded that crush testing should be performed only at the vehicle level and in the same manner as current FMVSS crash tests. If a battery experiences mechanical damage during these tests, the extent of battery crush can be used to assess the result.

Improvements in computing power and modeling capabilities have revolutionized automotive design and in particular crush performance development. Research in this area should seek to couple experimental results with simulations in the hopes of supplanting the need for trial and error experimentation (Sahraei et al. 2014).

Thermal Abuse

There is considerable variability in the use of thermal testing protocols (Table 4), with only two—the thermal shock and fire exposure tests—close to a consensus position among the regulatory and standards agencies.

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TABLE 3 Mechanical Safety Test Matrix

	Industry standard					Government regulation			
Test type	Freedom Car	SAE J2929	SAE J2464	ISO 12405-1	ISO 12405-3	UN 38.3	ECE R100	Q/C-T 743	KMVSS 1.48
Mechanical integrity	●	●	●		●		●	●	
Mechanical shock	●	●	●	●	●	●	●		
Penetration	●		●					●	
Immersion	●	●	●		●				●
Rollover	●		●						
Drop	●	●	●		●	●		●	●
Vibration		●		●	●	●	●	●	

Note: ECE=Economic Commission for Europe, ISO=International Organization for Standardization, KMVSS=Korea Motor Vehicle Safety Standards, Q/C-T=China Industry Standard, SAE=Society of Automotive Engineers, UN=United Nations.

TABLE 4 Thermal Safety Test Matrix

	Industry standard					Government regulation			
Test type	Freedom Car	SAE J2929	SAE J2464	ISO 12405-1	ISO 12405-3	UN 38.3	ECE R100	Q/C-T 743	KMVSS 1.48
Thermal stability	●								
Fire exposure	●	●	●		●		●		●
High-temperature storage	●							●	●
Cycle w/o thermal control	●	●	●		●		●		
Thermal shock	●	●	●	●	●	●	●		
Humidity exposure		●		●	●				
Passive propagation			●						

Note: See Table 3 for abbreviations.

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Thermal shock testing typically involves exposing a battery pack to a cycle of warm and cold temperatures and then evaluating its performance, making it more of a durability evaluation procedure than an abuse failure investigation tool.

For fire exposure investigation, an ECE regulation (R34) that calls for a fire exposure test on plastic fuel tanks in vehicles has been referenced, and the test, adapted for battery abuse testing, incorporated in a new regulation (R100) (Figure 3). It involves first directly exposing a battery to a burning pool of liquid fuel (Phase B) and then indirectly through a screen of refractory bricks (Phase C) and evaluating the hardware response (Phase D).

Electrical Abuse

The electrical subcategory of battery safety testing (Table 5) shows the greatest consistency of application: all the reviewed regulations and standards feature overcharge, short circuit, and overdischarge tests. There are minor differences in test details (e.g., in current, duration, or resistance), but the general procedures are similar.

The Ford team investigated battery responses to overcharge and found that attempts at discretizing the moment of battery response led to a start-stop approach to overcharge electrical energy delivery using twenty 5 percent state of charge intervals. No hardware had an event before it reached 134 percent overcharge. Thus, in the unlikely event that a vehicle allowed an overcharge to occur, the state of charge can be used to assess the test's outcome.

Short circuit abuse testing of batteries commonly uses shunts of specific resistances (e.g., 10mΩ), irrespective of the test hardware details. This approach ignores the Ohm's law behavior of the short circuit reaction, which dictates that the severity of the short is dependent on the relative resistance of the hardware to the shunt. By exploring a range of relative resistance values it is possible to correlate test current and shunt resistance to the likely test outcome. Review of a vehicle battery's internal resistance and limits imposed by the pack's fusing is informative of the likely abuse response.

CONCLUSION

The success of long-term vehicle electrification efforts will depend heavily on the performance of their batteries. Batteries appropriate for automotive applications have to pass extensive validation procedures to demonstrate durability, but there remain uncertainties—causes for anxiety—about battery life and safety. New testing tools are available to improve the prediction and identification of electrochemical failure mechanisms. Further research can enhance the utility and

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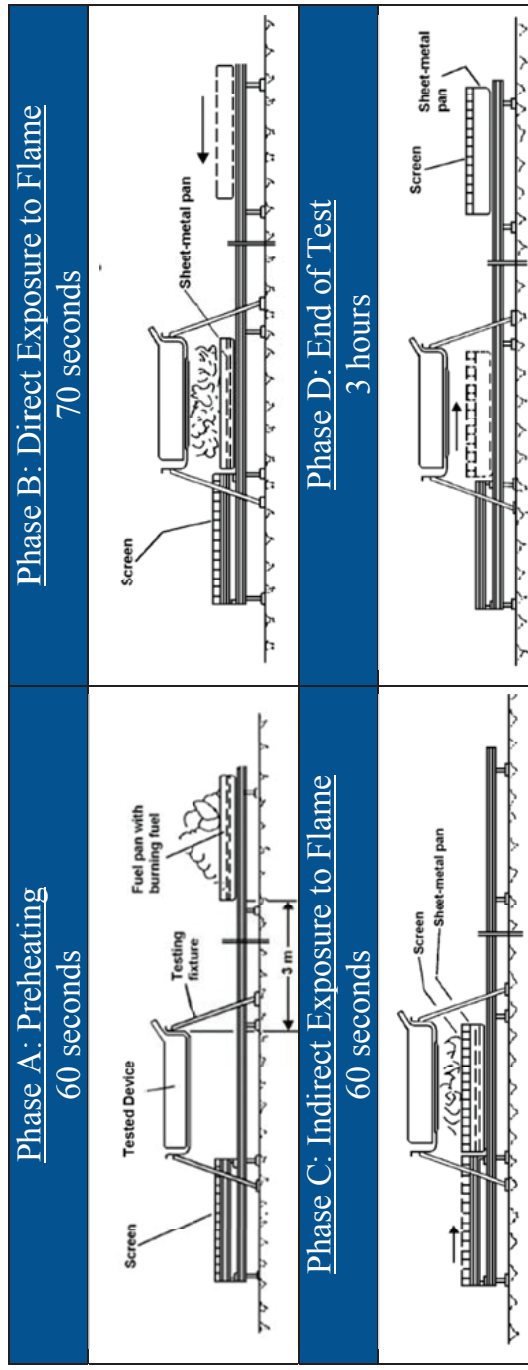

FIGURE 3 United Nations Economic Commission for Europe (UNECE) R100 Fire Exposure Test. Reprinted with permission from UNECE (2013).

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TABLE 5 Electrical Safety Test Matrix

	Industry standard					Government regulation			
Test type	Freedom Car	SAE J2929	SAE J2464	ISO 12405-1	ISO 12405-3	UN 38.3	ECE R100	Q/C-T 743	KMVSS 1.48
Overcharge	●	●	●	●	●	●	●	●	●
Short circuit	●	●	●	●	●	●	●	●	●
Over discharge	●	●	●	●	●	●	●	●	●
High voltage exposure		●							
Partial short circuit	●								
Separator shutdown			●						

Note: ECE=Economic Commission for Europe, ISO=International Organization for Standardization, KMVSS=Korea Motor Vehicle Safety Standards, Q/C-T=China Industry Standard, SAE=Society of Automotive Engineers, UN=United Nations.

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international consistency of these testing procedures to align developments and progress.

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Challenges in Batteries for Electric Vehicles

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There are many reasons why research and development in electric vehicles (EVs) is important. The world needs to reduce its production of greenhouse gases and decrease its dependence on oil (DOE 2014, Energy.gov 2014). The market for electrified vehicles is growing rapidly—Bosch predicts 12 million electrified cars by 2020 (Greimel 2013). And market research suggests that if the United States wants to compete in the future auto industry it will need to become a leader in lithium ion batteries, currently the most promising type of battery for EVs because of their high energy density (Lowe et al. 2010).

By the year 2020, 7 percent of vehicles sold worldwide may be electric (including hybrids) (Hurst and Gartner 2013). The increased use of such vehicles instead of internal combustion engines could reduce greenhouse gas emissions and dependence on oil. Recent improvements in the cost and energy density of lithium ion batteries have provided electric vehicles with a range of more than 265 miles (DOE 2014), but high initial costs limit mass market acceptance.

This paper presents current challenges and recent advances in lithium-ion batteries, and options for making electrified vehicles a more cost-effective choice.

INTRODUCTION

Electrified vehicles are battery powered either entirely (EVs) or partially (plug-in hybrid electric vehicles, PHEVs), but the batteries are expensive ($300–500/kWh). The US Department of Energy (DOE) has therefore called for a reduction in battery cost to $125/kWh by the year 2022, a target that should enable 5-year cost of ownership parity between an internal combustion vehicle and an EV (DOE 2013).

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Cost reduction can be accomplished by reducing material and manufacturing costs and/or by increasing energy density (watt hours per kilogram, Wh/kg). We estimate that lithium ion battery energy density can be doubled or tripled through the discovery of new materials and designs; for example, other chemistries, such as lithium air, may offer as much as a fivefold increase in energy density if technical challenges can be overcome.

If the battery industry can hit the DOE cost target before 2020, then a significant portion of the new vehicle market could become electric. If one assumes that most electric vehicles use 100 kWh battery packs (which should support about 400 miles of driving range—a typical distance between refueling for a vehicle powered by an internal-combustion engine), then the potential battery market is $1.4 trillion dollars.

CURRENT CHALLENGES IN EV BATTERIES

In order to achieve greater market penetration, the cost of EV batteries needs to come down. This needed cost reduction will require research and development into new materials.

Cost

Cost is the biggest challenge for EV batteries. Tesla hopes to reduce the cost of a battery pack to less than $210/kWh through economies of scale enabled by its planned "gigafactory," which is expected to double worldwide lithium ion battery production (Economist 2014).

But further cost reduction is needed to reach the DOE goal. The most promising way to achieve it is by increasing the energy content of the active materials (commonly measured in Wh/kg). The highest-energy lithium ion batteries are now about 250 Wh/kg at the cell level. We estimate that a doubling of energy density is needed to meet the DOE's cost goal.

Battery Materials: Availability and Chemistry

Significant increases in battery energy density will likely require a disruptive technology involving a lithium anode. We briefly review the materials used in lithium ion cells because these determine energy storage capacity.

Lithium is the primary component of EV batteries, and some people are concerned that there is not enough of it to supply all the batteries needed to fuel transportation. But a study from UC Berkeley into resource availability in 2011 (Wadia et al. 2011) concluded that there was sufficient lithium to replace about 10 percent of the global vehicle fleet of passenger vehicles. The paper shows that battery production is more constrained by the availability of cobalt (often used in cathode materials) than by lithium.

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In addition, researchers at the University of Michigan and Ford Motor Company looked into world lithium deposits and concluded that even with rapid adoption of electric vehicles there is enough lithium for the rest of the century (Gruber et al. 2011). They also point out that additional lithium deposits are likely to be discovered. The authors nonetheless encourage responsible use of lithium—although there is enough for the next several decades, the industry will need to conserve this resource.

A typical lithium ion battery stores energy by moving lithium ions from a mixed metal oxide positive electrode (e.g., $LiCoO_2$, $LiMnO_2$) to a negative electrode (LiC_6) during charge. When the battery is discharged, lithium ions change direction and move from the graphite to the metal oxide electrode. One can think of charging a lithium ion battery as analogous to storing potential energy as water is moved uphill: when the water is released, it produces work—as the lithium ions do when moving from anode to cathode in a battery being discharged.

To increase the specific energy of the battery (*SE*, in Wh/kg), one can increase the amount of lithium that can be stored in the electrode materials (the coulombic capacity, *C,* in Ah/kg) and/or the battery voltage (*V*), as expressed in Equations 1 and 2:

$$SE = C \cdot V \quad [1]$$

$$V_{battery} = V_{positive} - V_{negative} \quad [2]$$

Table 1 summarizes the coulombic capacities, voltages, and energy densities of some materials of interest. The table shows that replacing a conventional graphitic anode with silicon or lithium increases the anode's capacity by roughly an order of magnitude. At the practical cell level this translates into a 25–50 percent decrease in total mass when using a conventional cathode material. Using a lithium anode and replacing the cathode with high-energy nickel cobalt manganese (HE-NCM), sulfur, or air results in a theoretical specific energy and energy density that far surpass those of the currently used graphite-NCA (from 3,500 to as much as 10,493 Wh/L).

The new materials, however, come with big challenges. In the negative electrodes, silicon has a high capacity but it experiences large volume changes (~300 percent) during lithiation/delithiation, which leads to rapid capacity fade (BATT 2014). Nanostructured silicon is being explored as a way to manage the volume change, but it is a challenge to achieve high electrode mass loading and volumetric capacity when packing nanostructures in an electrode (Kim et al. 2014).

Using a lithium (Li) negative electrode results in a higher cell voltage and reduces mass significantly, enabling a higher cell-level energy density, but lithium metal has three primary challenges: low electrochemical potential, morphology changes, and dendrite formation. The low potential causes electrolyte decomposition; hence, it is difficult to find a good electrolyte to use. Morphology changes

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TABLE 1 Properties of Some Lithium Battery Electrode Materials

Electrode	Material	Theoretical coulombic capacity (Ah/kg) * Calculated based on lithiated state	Voltage (V vs. Li/Li+)	Specific energy (Wh/kg) *vs. Li/Li+	Density (kg/m^3)	Volumetric energy density (Wh/L) *vs. Li/Li+
Negative	Lithium metal (Li)	3861	0			
Negative	Silicon ($Li_{22}Si_5$)	2081	~0.3-0.4			
Negative (in use)	Graphite (LiC_6)	340	~0.1			
Positive (in use)	NCA ($LiNi_xCo_yAl_zO_2$)	~200	~3.9	780	4500	3510
Positive	HE-NCM	~250	~3.7	925	4800	4440
Positive	Sulfur (Li_2S)	1167	2.25	2625	1660	4358
Positive	Air (Li_2O)	1794	2.91	5220	2010	10493
Positive	Air (Li_2O_2)	1168	2.96	3458	2310	7989

Specific energy, density, and volumetric energy density are provided for positive electrode combinations with lithium metal. HE-NCM=high-energy nickel cobalt manganese; NCA=nickel cobalt aluminum.

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cause unstable passivation of the electrode and solvent dry-out via continuous solvent decomposition. And lithium dendrites can form and grow through the separator, posing an electrical shorting risk.

Strategies to promote stable cycling of lithium electrodes involve polymer or ceramic solid electrolytes, novel liquid electrolytes (solvents, solids, and additives), and alloying. Each has challenges (Woodford et al. 2012). The solid electrolytes have slow Li^+ transport and limited chemical and mechanical stability, and the new liquid electrolytes still have significant side reaction rates. Alloy anodes are challenged by large volume changes during cycling that disrupt the solid-electrolyte interphase (passivation layer) and lead to continued reduction of the electrolyte (Woodford et al. 2012). Some of the proposed approaches work well for low power applications (<1 mA/cm^2), but not at higher current densities.

Battery vs. Internal Combustion Efficiency

Taking into account the source of the energy used to fuel an electrified car, is a battery really more energy efficient than an internal combustion engine (ICE)? The answer depends on location. A Tesla Motors emissions calculator shows that charging an EV in California has much less carbon impact (i.e., release of carbon dioxide) than an ICE car because the state's grid generates more than one-half of its energy from natural gas (Tesla 2014). But in states where coal is used predominantly to power the grid, the carbon impact of EVs may be comparable to that of ICE vehicles. As power plants become modernized with more renewable sources of energy, EV-associated emissions will decrease further.

USE OF MODELS TO REDUCE COSTS

Big challenges must be overcome to enable battery technologies such as lithium sulfur and lithium air, but in the meantime improvements can be made in how current technologies are utilized. Physics-based models, for example, can enable more efficient battery use and reduced charge times. They are also useful to optimize the design of the cell and pack (e.g., to retain its energy storage capability while making it smaller and reducing its weight), to understand limitations and failure modes so that they can be avoided, to save money on testing, and to quickly understand the impact of new chemistries.

Battery management systems (BMS) are used to monitor and control batteries in EVs. A well-designed BMS will keep the battery in a safe operating region (e.g., ensuring that it is not overcharged, overdischarged, charged too quickly). Current BMS typically simplify the complex physics inside a battery by assuming that it is a simple RC circuit (a combination of resistors and capacitors) and using only externally available measurements (current, voltage, and temperature) for control. We have developed an approach that uses a physics-based model to predict the internal states in the battery and thus are able to extend the operational region

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(Chaturvedi et al. 2010). By increasing the envelope of battery operation, more of the battery is utilized, and it is used more efficiently. This approach is expected to significantly reduce the cost of batteries as well as typical charging times.

SUMMARY

There are some short-term hurdles to overcome (e.g., powering the grid with more renewable energy, reducing ancillary loads/parasitic current draws in electric cars), but trends indicate that developments in energy resources support the likelihood that electric vehicles will be a significant part of the world's transportation future (Oremus 2013).

Automotive batteries have a huge potential market. New chemistries are needed to achieve significant penetration in the EV market, but they are challenging and will take more years of research. In the meantime, conventional chemistries can be used more efficiently via advanced battery management software.

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Lithium Ion Batteries and Their Manufacturing Challenges

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There is no single lithium ion battery. With the variety of materials and electrochemical couples available, it is possible to design battery cells specific to their applications in terms of voltage, state of charge use, lifetime needs, and safety. Selection of specific electrochemical couples also facilitates the design of power and energy ratios and available energy.

Integration in a large format cell requires optimized roll-to-roll electrode manufacturing and use of active materials. Electrodes are coated on a metal current collector foil in a composite structure of active material, binders, and conductive additives, requiring careful control of colloidal chemistry, adhesion, and solidification. But the added inactive materials and the cell packaging reduce energy density. Moreover, degree of porosity and compaction in the electrode can affect battery performance.

In addition to these materials challenges, cost is a significant barrier to widespread adoption of this technology. Pathways are being explored to bring batteries from the commercially available 100 Wh/kg and 200 Wh/L at $500/kWh up to 250 Wh/kg and 400 Wh/L for just $125/kWh.

FUNDAMENTALS OF LITHIUM ION BATTERIES

The lithium ion battery was made possible by the discovery of lithium cobalt oxide ($LiCoO_2$), which allows the extraction of lithium ions and creation of large amounts of vacancies (without a crystal change) up to the removal of half of the existing ions. The pairing of $LiCoO_2$ with graphite allows the intercalation of lithium ions between the graphene layers that occupy the interstitial site

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between every hexagonal ring of carbon atoms (Besenhard and Schöllhorn 1976; Mizushima et al. 1980; Whittingham 1976).

The lithium ions travel during charge from the positive electrode (the cathode) through a solid or liquid electrolyte to the negative electrode (the anode) and, during discharge, in the opposite direction. At each electrode, the ion either maintains its charge and intercalates into the crystal structure occupying interstitial sites in existing crystals on the anode side or reoccupies a vacant site in the cathode that formed when the lithium ion left that crystal. While transferring the ion, the host matrix gets reduced or oxidized, which releases or captures an electron.[1]

VARIETY OF CATHODE MATERIALS

The search for new cathode materials is driven in part by important disadvantages of $LiCoO_2$. The battery has a core temperature of 40–70°C and may be susceptible to some low-temperature reactions. But at 105–135°C it is very reactive and an excellent oxygen source for a safety hazard called a **thermal runaway** reaction, in which highly exothermic reactions create temperature spikes and accelerate rapidly with the release of extra heat (Roth 2000).

Replacement materials for $LiCoO_2$ are less prone to that failure. The compounds replace parts of the cobalt with nickel and manganese to form $Li(Ni_xMn_yCo_z)O_2$ compounds (with $x + y + z = 1$), often referred to as NMC as they contain nickel, manganese, and cobalt; or they exhibit a completely new structure in the form of phosphates (e.g., $LiFePO_4$) (Daniel et al. 2014). These cathode materials all exhibit capacities in the range of 120–160 Ah/kg at 3.5–3.7 V, resulting in maximum energy density of up to 600 Wh/kg.

When packaged in real devices, however, much inactive material mass is added and the energy density tends to drop to 100 Wh/kg on the pack level. To push for higher energy density, researchers have sought higher capacity and higher voltage—and found them in lithium- and manganese-rich transition metal oxides. These compounds are essentially the same materials as NMC but an excess of lithium and higher amounts of manganese replace nickel and cobalt. The higher amounts of lithium (as much as 20 percent more) allow the compounds to have higher capacity (Thackeray et al. 2007) and a higher voltage, resulting in cathodes with up to 280 Ah/kg when charged up to 4.8 V. However, these new compounds show stability problems and tend to fade fast.

BALANCING OF MATERIALS IN CELLS

Lithium ion batteries are made of layers of porous electrodes on aluminum and copper current collector foils (Daniel 2008). The capacity of each electrode

[1] If the ion changed its state of charge, it would be called a *conversion battery* (e.g., an air battery; Daniel and Besenhard 2011).

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pair needs to be balanced to ensure battery safety and avoid risk of overcharge of the anode (which can result in lithium metal plating and short circuiting) or overdischarge of the cathode (which can result in a collapse of the crystal structure and loss of vacancies for lithium to reintercalate, dramatically reducing capacity).

Graphite has a theoretical capacity of 372 Ah/kg, double that of the available lithium in NMC cathodes. So in balanced lithium ion batteries, the cathodes typically exhibit double the thickness compared to the anode. This inherent flaw of the cell design causes problems with mass transport and kinetics, and thus prompted the search for high-capacity cathodes.

To increase cell-level energy density, inactive materials are being minimized in battery cells. For example, one way to reduce the current collector is to increase the thickness of the electrodes, but this further drives transport problems and requires a highly engineered porosity in the electrode.

COST CHALLENGES IN MANUFACTURING LITHIUM ION BATTERIES

The costs of lithium ion batteries are much higher than the automotive market will bear for full penetration of electric vehicles and a cost-neutral product compared to cars run by internal combustion engines. The US Department of Energy cost target for all electric vehicle batteries is $125/kWh of usable energy (DOE 2013). The current cost of commercial batteries is $400–500/kWh and their projected cost with current experimental materials is $325/kWh. Most of the cost reduction thus far has been achieved by energy density increases at similar cost to the older-generation products.

Further cost reduction is possible through optimization of manufacturing schemes. Lithium ion batteries are manufactured in sets of electrodes and then assembled in cells. Active material is mixed with polymer binders, conductive additives, and solvents to form a slurry that is then coated on a current collector foil and dried to remove the solvent and create a porous electrode coating. The solvent of choice, N-methylpyrrolidone (NMP), is considered an indirect material (it is needed for production but not contained in the final device), but it is expensive, exhibits flammable vapors, and is highly toxic.

The flammable vapors of NMP require all processing equipment during the production of electrodes to be explosion proof, meaning all spark-producing electrical components need to be shielded from the vapors and spaces need to be highly ventilated to keep vapor concentrations low. These measures increase the capital cost of such equipment considerably.

In addition, the electrode manufacturing plant is required to recapture the solvent from its exhaust stream, distill it, and recycle it. This is again an additional cost.

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Cost Reduction by Water-based Processing

The replacement of NMP by water is a tremendous opportunity to reduce cost in the production of lithium ion batteries. The cost of water is negligible compared to that of NMP; water is not flammable and does not produce flammable vapors; and water is environmentally benign. However, water is a polar solvent and its behavior is completely different from that of the nonpolar NMP. Furthermore, active materials tend to agglomerate and metal current collector surfaces are hydrophobic, making the coating process more difficult.

Knowledge of surface charges on particles (by measuring zeta potential) enables the design of surface polarity in the presence of water by introducing small amounts of surfactants. In the case of cathode intercalation compounds, polyethylene imide has been successfully used to introduce a surface charge large enough to repel particles so that they do not form unacceptable agglomerates (Li et al. 2013).

Understanding the surface energy of metals and the surface tension of the slurry as well as their interaction allows for optimization of the pair. Atmospheric plasma treatment of the metal surface through exposure to a corona plasma removes organic compounds on the surface and enables a slight etching and oxidation, which dramatically reduces the surface energy to values below the surface tension of the slurry. This allows perfect wetting of the surface by the slurry and creates a coating with optimized adhesion (Li et al. 2012). The result is a 75 percent operational and materials cost reduction in the electrode manufacturing and a potential cost reduction of up to 20 percent at the battery pack level for automotive applications (Wood et al. 2014). This does not include the lower equipment cost: expenses associated with the plasma processing equipment are much lower than those for the solvent recovery system and the explosion-proof requirement.

Future Opportunities for Cost Reduction

Further cost reductions will be achieved through greater knowledge of transport mechanisms and electrode architecture implications for electrochemical performance. Current research is largely focused on modeling and simulation to understand molecular mechanisms and improve the design of electrodes, electrode stacks, and battery cells. Thicker electrodes and a tremendous reduction in inactive materials will improve energy density at lower cost, reduce direct costs, and possibly enable much shorter and less energy intensive battery formation cycling.

CONCLUSION

Lithium ion batteries have tremendous potential for enabling partial to full electrification of the automotive fleet, diversifying energy sources for transportation, and supporting large-scale energy storage for a higher penetration of inter-

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mittent renewable energy supply. However, cost continues to be an issue and will need to be addressed by the development of a robust supply chain, standards in manufacturing, high manufacturing throughput, and streamlined low-cost processing methods. In addition to reducing costs, research can enhance knowledge of molecular processes and transport issues in order to optimize the design and use of available energy in batteries and increase their life time.

As shown in this paper, an increase in energy content and capacity in active electrode materials and a reduction of indirect materials in production are two ways to impact cost.

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TECHNOLOGIES FOR THE HEART

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Technologies for the Heart

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The heart is one of the most fundamental and critical organs of the human body. From athletic endeavors to artistic pursuits to intellectual discussions, the heart plays a vital role.

But an increasing number of ailments affect the heart and its ability to perform primary functions. Fortunately, scientific and medical knowledge of the heart and cardiovascular system are also growing rapidly. It is here, at the crossroads of medical knowledge and patient disease, that engineers must find new ways of transforming current medical understanding into solutions that can help to ensure the quality of human life.

Not so long ago the technologies available to "fix" heart ailments focused on a brute force approach. Large rigid external vascular assist devices were used to "aid" heart function. However, now there are many examples of miniature devices that provide a range of therapeutic options for the patient's exact heart condition. As these technologies evolve, the trend is for solutions that mimic the natural biologic conditions, constructs, and behavior as closely as possible and work together with the body rather than dominate it. As such, engineered solutions to heal, repair, assist, and/or replace the heart or its critical components in a harmonious way represent the frontiers of technologies for the heart.

This session began with a description of the basic functions of the heart to give the audience an appreciation of the complexity of the cardiovascular system, and how crucial normal heart function is to the system's stability. From there the speakers provided examples of engineered solutions to different heart problems. Specifically, a chronological overview of heart valves from their beginnings to the current best-in-class technology was provided by Erin Spinner (Edwards Lifesciences). Following on from this industrial forefront, cutting-edge research

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under way on tissue engineered valves was presented by David Merryman (Vanderbilt University). Jason Burdick (University of Pennsylvania) discussed the state-of-the-art in biomaterials for treating heart tissue that has been affected by myocardial infarction. Finally, Sonna Patel-Raman (formally FDA and now Halloran Consulting Group) concluded the session with an overview of the regulatory environment and what is required to get the newest technologies to the patients who need them. This last topic is covered in a paper in this volume by Tina Morrison (FDA).

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The History of Heart Valves: An Industry Perspective

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Edwards Lifesciences

The average heart beats 2.5 billion times in a human lifetime, during which its four valves must maintain unidirectional blood flow to maximize the heart's efficiency and provide oxygenated blood to the entire body. Although heart valves were documented by Leonardo da Vinci in some of his early sketches over 500 years ago, they have been available for implantation only since the 1950s.

Valvular disease—usually associated with advanced age, but also caused by congenital defects—can interrupt, slow, or prevent the efficient function of the valves, which lose functionality if they cannot maintain a proper seal or open completely. When any one of the valves is not working properly it may affect a person's ability to exercise or perform daily tasks and thus lead to a dramatic decrease in quality of life and even death. For these reasons, decades have been spent developing and perfecting devices to repair and replace the body's valves when they no longer function properly.

Innovation and development of replacement heart valves have largely focused on the aortic valve, which directs oxygenated blood from the left ventricle to the rest of the body. The structure of the aortic and (similar) pulmonary valves is simpler than that of the other valves—they have greater symmetry and lack the subvalvular components characteristic of the mitral and tricuspid valves—making them an attractive target for early research. The aortic and pulmonary valves consist of three leaflets of similar size and shape that are attached to the tubular vessel; in contrast, the mitral and tricuspid valves have leaflets that vary in number and size. For the mitral and tricuspid valves, these leaflets attach both directly to the wall of the ventricle at the annulus and indirectly through numerous chords (Figure 1).

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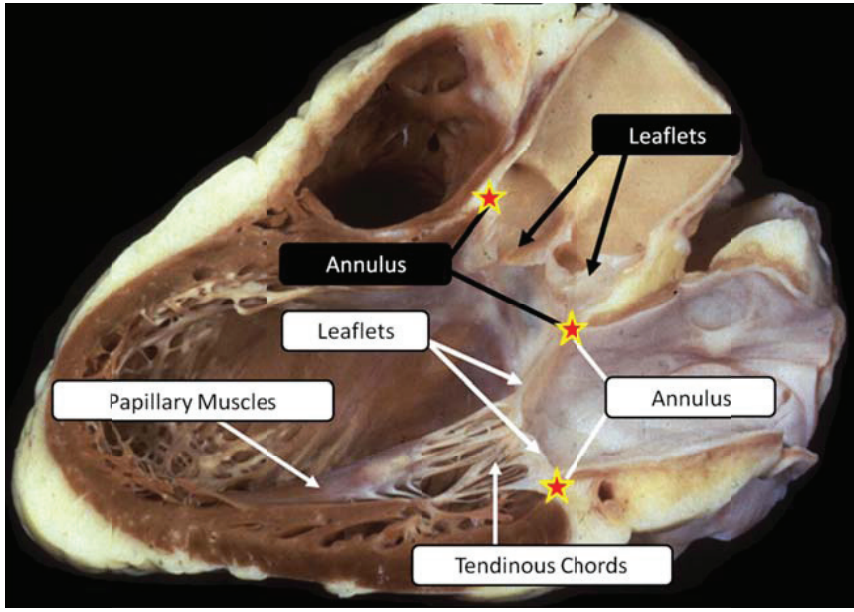

FIGURE 1 Anatomical comparison of the complexity of the aortic valve (black labels) and mitral valve (white labels). Note the subvalvular structure, including numerous chords and papillary muscles, in the mitral valve. Modified from Anderson and Kanani (2007).

Whereas past efforts focused on the aortic valve, current technologies are being developed to create devices for the more complex valves of the heart.

PAST TECHNOLOGIES

Valve replacement devices can be classified into two categories: whole valves and prosthetic valves. Whole valves consist of allografts and xenografts; prosthetic valves are composed of pericardial (tissue) and mechanical valves. The valve designs vary in numerous aspects and have evolved over time, but the goal has remained the same: an easily implantable and durable solution that increases blood flow while decreasing the risk of associated complications such as thrombosis. Each type of valve has advantages and disadvantages, which are taken into consideration when deciding which device is appropriate for an individual patient.

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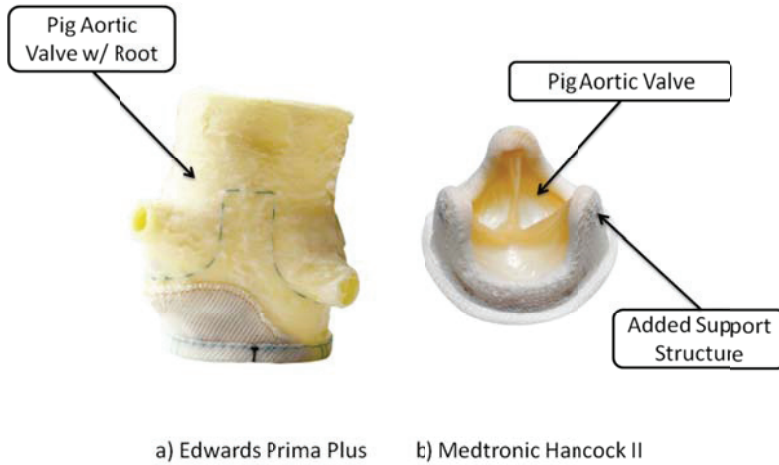

FIGURE 2 Examples of (a) stentless xenograft that uses the native support structure of the aorta and (b) supported xenograft with native aortic valve removed and added stent and sewing ring structure.

Whole Valves

Allografts are valves transplanted from another human, and xenografts are from another species. Cow and pig valves are usually selected for transplant as they best mimic the size and structure of human valves.

Attempts have been made to transplant mitral valves (Gulbins et al. 2000, 2002; Kumar et al. 2000), but the most successful and frequently used valves are pulmonary and aortic valves, which are often used interchangeably due to their similar geometry. Developments in transplanted valves have focused on improving structural support, which is necessary when the valve is removed from its native surroundings (Figure 2).

Vast strides have been made in tissue cryopreservation, which maintains high cell viability when thawed (O'Brien et al. 1987). But the appeal of allograft and xenograft valves suffers from their limited availability of size ranges and technically challenging procedure, in the case of stentless designs, which require the physician to remove the entire valve along with a portion of the aortic root to attach the replacement valve.

Prosthetic Valves

Transplanted whole valves remain a viable option, but prosthetic valves, including both mechanical and pericardial tissue valves, hold the largest share of

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the market. Of valves implanted in the United States today, most (approximately 60,000) are made of pericardial tissue; in contrast, only 10,000 mechanical valves were implanted in 2013 (Millennium Research Group 2013), although design improvements are minimizing or often eliminating the disadvantages of mechanical valves (e.g., thrombogenicity requiring anticoagulation therapy).

Both pericardial and mechanical valves consist of a sewing ring (for securing them in place), a support structure, and leaflets. Mechanical valves are similar in structure to tissue valves, but differ in the leaflet design (Figure 3). Mechanical valves have seen the greatest variety in designs, optimized through geometry, hinge mechanisms, and materials.

These designs include ball and cage, floating/tilting disc, and bileaflet (Figure 3a); the latter is the leading design in today's industry. These valves do not need to be replaced—indeed, they typically outlive the patient—but they require the constant use of anticoagulants, which is not appealing to most people and not an option for some. In contrast, tissue valves lack the longevity of mechanical valves but do not require anticoagulation, making them a preferred choice.

In contrast to mechanical valves, pericardial tissue, the sac that lines the heart, is highly durable and therefore used to construct the leaflets of a tissue prosthetic valve. The leaflets are then sewn to the stent support structure attached to the sewing ring. The attachment of the tissue to the structure is crucial to ensure durability and requires each valve to be hand assembled and sewn. The sewing ring may consist of a silicone band and cloth that support tissue ingrowth to the surrounding anatomy to provide future fixation support.

Although the overall design of the tissue valve has remained relatively unchanged throughout the years and mimics the design of the native aortic and pulmonary valves, the fixation process for the leaflets has been optimized. Vari-

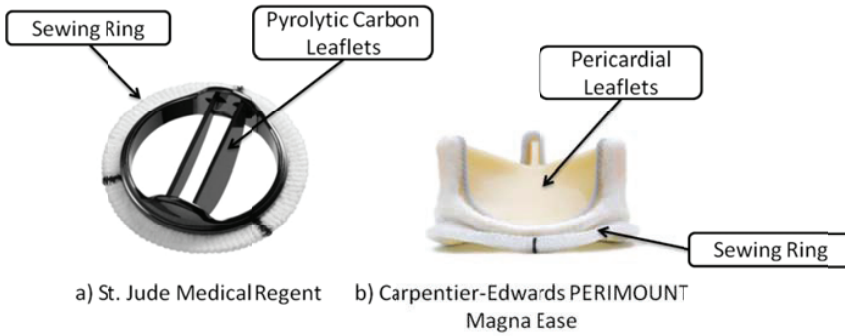

FIGURE 3 Examples of (a) bileaflet mechanical and (b) tissue prosthetic valves. Both valves shown can be used as replacements for all valves.

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ous solutions are used to crosslink the collagen fibers and ensure durable leaflet structure. The method by which tissue is fixed and preserved is a proprietary process guarded by each company.

As with any design, tissue valves also have limitations, of which the most significant is durability. Typical tissue valves currently on the market can last up to 20 years before the leaflets lose functionality and experience structural deterioration, usually due to calcification (Schoen and Hobson 1985; Schoen and Levy 2005).

CURRENT TECHNOLOGIES

Over the past 10 years, noninvasive implantation of heart valves has revolutionized the field. Implants traditionally required the chest to be splayed open to allow access to the heart, but recent advances make it possible to access the valve through the femoral vein via an incision as small as an inch. This noninvasive approach, called *transcatheter valve replacement*, is suitable for patients who are not candidates for open-heart surgery and offers a faster recovery.

The first transcatheter delivery of a valve was attempted in the 1960s, but it has only recently become accepted as a viable procedure, aided by advances in stent design and noninvasive imaging techniques. The development of transcatheter heart valves showcases the power of a multidisciplinary approach: it merges technologies from numerous devices (e.g., coronary stents and balloon angioplasty) and disciplines (e.g., interventional cardiology and cardiac surgery) to create a paradigm-shifting advance.

There are many advantages to a transcatheter approach, but added complexity arises because the valve must work with the patient's diseased anatomy. In the past the diseased valve was typically removed; now, the designs and their ability to succeed rely heavily on the patient's anatomy. For example, a transcatheter aortic valve is secured in place by applying an outward force on the calcium deposits on the native leaflets.

An additional obstacle that transcatheter technologies have had to overcome is the loss of direct visualization afforded by open-heart surgery. This is especially important when deciding where to place the valve to ensure that it is secured while avoiding the coronary ostia, which is crucial to supplying blood to the heart (Figure 4). Advances in noninvasive imaging allow for real-time imaging using multiple modalities, such as echocardiography to visualize the native anatomy and fluoroscopy to visualize the device.

FUTURE TECHNOLOGIES

The valve replacement industry is beginning to focus on the other valves in the heart and developing devices that will work in concert with the native anatomy to repair instead of replace native valve function. The number of repair procedures is on the rise as compared to replacement procedures, which have remained steady

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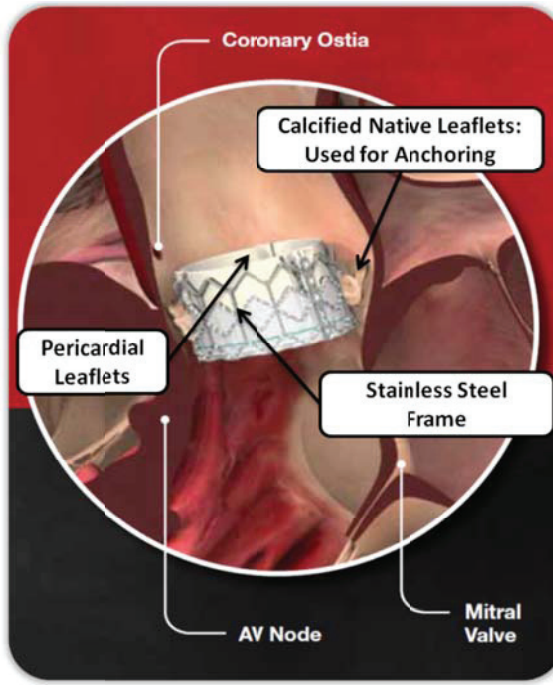

FIGURE 4 Transcatheter heart valve using the surrounding calcium in the native aortic valve to anchor. AV=atrioventricular. Source: Edwards Lifesciences.

from year to year. Recent trends favor repairing the native valve as opposed to replacing it, with approximately 32,000 mitral repairs as compared to 21,000 replacement procedures conducted in the United States in 2013 (Millennium Research Group 2013).

The introduction of transcatheter heart valves has brought new excitement to this area. Placed inside a defective tissue valve, transcatheter valves provide a way around the challenge of tissue valve durability: a tissue valve may be implanted in a younger patient with the idea that an additional valve can be placed if needed at a later date.

Valve manufacturers are expanding the number of diseases they can treat through transcatheter technologies; for example, companies are working to treat mitral valve regurgitation, a much larger market compared to aortic valve pathology. But, as mentioned, there are many hurdles in the transfer of technology and techniques to the mitral valve because it is more complex and patients tend to be in worse overall health with multiple comorbidities. That said, technology has

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advanced such that it is possible to attack more subtle pathologies and not only a valve that is completely failing.

Mitral valve repair technologies today aim at correcting a specific pathology and do so by targeting any aspect of the valve, from replacing the chords, which attach the leaflets to the ventricle, to reducing the size of the annulus and bringing the leaflets closer together to allow for sealing. In attempts to replace the valve, designs require an anchoring location as they cannot be sewn in like a traditional surgical replacement. Engineers therefore retain the native leaflets or annulus when possible as an anchor site for the replacement part.

Because of the direct interaction with and reliance on the functionality of the native valve, engineers must expand their horizons and become experts in tissue mechanics as well. The frontier of heart valve engineering is less about engineering and more about applying engineering principles in a way that requires understanding of anatomy and physiology. Collaborations of engineers working side by side with clinicians, biomedical engineers, and biologists produce the best heart valve designs.

The future of heart valves is also reliant on new engineering materials. In addition to progress in the application of synthetic materials, especially with the mechanical valve, new biological and polymeric materials are being developed. With the advent of transcatheter valves, the limits of current materials are being challenged. Tissue, polymeric, and even cloth designs are being pushed beyond what was previously thought possible in the effort to increase strength and durability and reduce the device profile. The latter requires thinner leaflets, which in turn require ingenuity to develop a strong but thin material.

New tissue treatment processes are also being developed and tested. A recent advance allows valves to be shipped dry, no longer requiring the leaflets to be stored in solution. This development allows transcatheter valves to be shipped on the delivery catheter and eliminates the need for an engineer to be present at the procedure.

These examples are a testament to the benefits of new technologies: they both enable and force development beyond what was previously thought possible.

DESIGNING FOR THE FUTURE

Next generation heart valves have brought excitement to the field, but it is also important to understand how we as engineers go from a concept to a life-saving device. We must first survey the patient population and identify a need, then develop a concept to address that need. Bench studies and animal studies are used in conjunction to test the functionality and durability of a design. Then the materials are tested in animal models to ensure that no adverse effects arise as a result of interactions with the body.

Complementing innovations in materials and design, new imaging protocols are being developed to ensure that a device is delivered to the correct location.

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Using a combination of imaging techniques (e.g., echocardiography, angiography, MRI, and CT), the implantation team can visualize both the device and the anatomy without opening the chest. These techniques are also used to determine the success of the procedure both at the time of implantation and in follow-up examinations to ensure the device's continued functionality.

When heart valves were first implanted, regulatory requirements to review the process for implantation were minimal or nonexistent. Now extensive testing is required to ensure short- and long-term success prior to implantation. The test data are submitted to a regulatory body and reviewed before implantation can be cleared. Pending full approval for general use, a first-in-human study may be conducted in compassionate cases, for patients who have no other options; these trials are usually limited to about 10 patients. If they show success a much larger clinical study is initiated, which can include hundreds of patients. From there the data are submitted to the regulatory body to get approval to commercialize the device and make it accessible to the approved patient population, ensuring that the patient's safety is the priority. When the device is made available for the masses it fulfills its original goal of saving lives.

As with many engineering creations, the design process is never complete. Once the device is implanted in humans, improvements are constantly made based on evidence from the patients. Research and development efforts seek to recreate and simulate the human environment on the bench and in animals, but there are always lessons to be learned and from there improvements.

Additionally, as new technologies and innovations are introduced to the marketplace, even in different industries, these are applied to existing devices for optimization as necessary. A great example of this is the development of new biomaterials for orthopaedic and other cardiovascular applications, in which findings and testing history can be leveraged for the valve area.

CONCLUSIONS

Now is an exciting time for heart valve development as companies are pushing the limits, expanding into new areas, and helping more patients than ever before. Advances continue to move heart valve development forward. As designs are optimized engineers are turning their attention to other disease states with next generation designs and approaches. With increased confidence in current device durability for both mechanical and tissue valves, the focus is changing from surgical to transcatheter implants and from replacement to repair devices implanted with transcatheter methods.

Each advance requires greater understanding of the disease state of the valve. The greatest successes will involve technologies and techniques that work in concert with the human body.

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Engineering Heart Valve Treatment Strategies for Tomorrow

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Heart valve disease is the third leading cause of cardiovascular mortality and morbidity in the United States and, with current aging trends, will increase in prevalence. The historical approach to valve disease treatment is open-chest, surgical replacement. While this tried-and-true approach is very good at treating a large portion of the population, it is not ideal for very young or very old patients. Researchers are exploring a variety of alternatives: tissue engineering, percutaneous methods, and pharmacological intervention.

HEART VALVES: PURE MECHANICS

Heart valves are in many ways like the simple check valves in a household plumbing system or automobile engine; they are controlled by inertial fluid forces and ensure that flow is unidirectional. Unlike toilets or cars, however, the heart is never idle—it never stops pumping blood—meaning the valves must work to near perfection for about 3.5 million cycles per year, or approximately 3 billion cycles over a 75-year lifetime. In the past decade, it has become apparent that heart valve disease is not simply a wearing out of the valve but is more accurately an active biological process that may be understood and treated in various ways.

Heart valve biomechanics has been an active research field for more than 50 years (Sacks et al. 2009). More recently, heart valve mechanobiology has become a field of great interest (Merryman 2010). The distinction between biomechanics and mechanobiology is subtle, but essentially biomechanics is the application of the principles of mechanics to study living organisms and their components, while mechanobiology is the application or analysis of the role of mechanical forces

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in eliciting a molecular response, leading to a quantifiable change in form and/or function.

In this article I first explain the two types of heart valve disease (congenital and degenerative) and then review various types of nonsurgical treatments. Each has been the subject of significant research to enhance understanding and application in the past couple of decades, but despite promising indications, challenges remain.

CONGENITAL AND DEGENERATIVE HEART VALVE DISEASE

There are two forms of heart valve disease: congenital and degenerative. Congenital valve disease is a malformation that occurs in utero and may be detected days after birth or not until decades later when the patient becomes symptomatic. Degenerative valve disease is a collective term describing age-related valve disease and occurs later in life, typically beginning around 65 years of age and increasing in prevalence with each passing year. For these two patient populations, different engineering strategies are needed.

Those with congenital valve disease usually need intervention during infancy or adolescence. The ideal solution would be a living tissue–engineered heart valve that could be grown in a laboratory, implanted surgically, and would then grow with the patient. Currently, infants receive size-matched biosprosthetic valves (porcine valves or bovine pericardium) that are chemically fixed and thus not alive. This approach is very limited because as the patient grows (quite rapidly), the implanted valve does not grow and reoperation is necessary. Some patients need up to four open-chest procedures to get to adulthood, and the mortality rate for the fourth procedure is about 50 percent.

Degenerative valve disease has been treated with improved effectiveness over the past 50 years with either bioprosthetic or mechanical valves through open-chest procedures. Although this is an effective solution for many cases of valve disease, it is not a desirable option because the morbidity associated with an open-chest procedure is significant—it is estimated that it takes up to a full year for a patient to return to previous levels of activity. As such, there have been concerted efforts to develop nonsurgical approaches for adult patients.

TISSUE ENGINEERING

Realization of a tissue-engineered heart valve that could grow with pediatric patients and would prevent the need for reoperations has been pursued for 20 years (Breuer et al. 1996; Shinoka et al. 1995). In 2000, pulmonary valves were grown in the laboratory (by combining autologous cells and a nonwoven felt scaffold) and implanted in large animals (sheep), which survived for 20 weeks. When evaluated after autopsy, the implanted valve looked very similar to the sheep's native valve (Hoerstrup et al. 2000). It was expected that this was the breakthrough needed to

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translate engineered valves to the clinic, but that has not been the case, and no other studies have been able to replicate the success reported in this seminal study.

There has also been extensive research on novel hydrogels that are much better at controlling the behavior of the valve cells (Kloxin et al. 2009; Sewell-Loftin et al. 2014; Wang et al. 2012) and on off-the-shelf scaffolds that are easy to use/mold and that closely match some of the mechanical properties of native heart valves (Engelmayr et al. 2005, 2006). Although the scaffolding component of engineered heart valve research has made progress, the cellular component to be added to the scaffold has not advanced. The primary reason for this is that it is quite unclear what cell type should be used to populate a tissue-engineered heart valve. The two cell types that make up the heart valves are unique and unlike their similar neighbors that make up blood vessels. The valve interstitial cells that are inside the tissue are essentially fibroblasts, but at the same time they are unlike most fibroblasts and are very specialized (Rabkin-Aikawa et al. 2004; Roy et al. 2000). The valve endothelial cells that cover the valve tissue are quite distinct from vascular endothelial cells (Butcher et al. 2004, 2006; Simmons et al. 2005). In other words, vascular cells from peripheral blood vessels are not sufficiently similar to serve as an appropriate cell source for a tissue-engineered heart valve, and although the field started off fast with early success, it remains a long way from clinical implementation.

PERCUTANEOUS STRATEGIES

As an alternative to an invasive, open-chest procedure, there has been considerable work to develop shorter-term solutions for adult patients, namely transcatheter aortic valve replacement. This strategy was initially created for patients that were deemed nonoperable candidates for open-chest surgery, but the early success has been encouraging and the procedure will likely expand to patients otherwise approved for open-chest surgery.

The mitral valve, unlike the aortic valve, is susceptible to a unique pathology called mitral valve prolapse in which the leaflets lose their ability to close properly and billow back into the atrium, causing regurgitant blood flow. Mitral valve prolapse is often treated with a percutaneous strategy called the Alfieri technique or "edge-to-edge" repair (George et al. 2011), but many more treatment approaches are being developed. Among these are the use of radiofrequency energy to shrink the leaflets and implantation of a "purse string" mechanism around the valve to reduce orifice area (Boronyak and Merryman 2012; Tommaso et al. 2014).

PHARMACOLOGICAL INTERVENTION

Historically, aortic valve disease, particularly calcification, was thought of as an idiopathic phenomenon likely associated with atherosclerosis. But it is now

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believed that calcific aortic valve disease is an active mechanobiological disease process and can therefore be targeted with drugs.

The contractile machinery of the valve interstitial cells that leads to calcification is of particular interest (Hutcheson et al. 2013; Walker et al. 2004; Yip et al. 2009). There are multiple potential targets that may slow or reverse the progression of aortic valve disease (Hutcheson et al. 2014), including the serotonergic pathway that was involved in some drugs that *caused* heart valve disease in the late 1990s and mid-2000s (Hutcheson et al. 2011).

CONCLUSION

Heart valve disease will continue to be a significant cause of mortality and morbidity in the coming decades; however, new treatment strategies are currently in development that should reduce the number of open-chest procedures. For pediatric patients, a tissue engineered heart valve that can grow with the child remains the ultimate goal, but this will likely not be realized in the near future unless a significant discovery occurs. For adult patients, there are many percutaneous and pharmacological treatment strategies that are in active development and will likely become available to patients within the next decade.

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Biomaterials for Treating Myocardial Infarctions

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Biomaterials are gaining attention in the development of biomedical therapies for treating patients after a myocardial infarction (i.e., heart attack). These materials may serve as mechanical restraints, vehicles for the delivery of therapeutics, or 3-dimensional scaffolds for tissue regeneration. This article focuses on one particular class of materials: injectable hydrogels, natural or synthetic water-swollen polymer networks that are a promising therapy to attenuate ventricular remodeling after myocardial infarction. They act both as acellular bulking agents to mechanically stabilize the myocardium and as delivery vehicles for cells and/or therapeutic molecules. Various materials, cells, and therapeutic molecules have demonstrated positive outcomes in the repair of cardiac tissue after infarction and provide insight for future material development and optimization. Further development of injectable hydrogels for cardiac repair will have considerable clinical impact by improving therapies to prevent progression to heart failure.

OVERVIEW OF HEART DISEASE

Heart failure affects almost 23 million individuals worldwide (Bui et al. 2011), and nearly 70 percent of these cases are due to coronary artery disease, which causes myocardial infarction (MI) (Go et al. 2014). MI occurs after coronary artery occlusion, resulting in depletion of nutrients and oxygen to the cardiac tissue and subsequent cell death (Cleutjens and Creemers 2002). The death of cells (i.e., cardiomyocytes) leads to the recruitment of inflammatory cells to remove the necrotic debris and the activation of bioactive molecules such as matrix metalloproteinases, which in turn cause degradation of the extracellular matrix (ECM) in cardiac tissue, weakening the myocardial wall and making it susceptible to global

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geometric changes, including thinning and dilation (Buckberg 2005; Dobaczewski et al. 2010; Holmes et al. 2005; Nahrendorf 2011; Spinale 2007). Infarct expansion occurs after the initial problems and is a progressive pathologic process that causes abnormal stress distributions in the borderzone regions surrounding the infarct. The process, additional cell death, and increases in borderzone stress are termed *left ventricular (LV) remodeling* and can lead to altered contractile properties and heart failure (Epstein et al. 2002; Jackson et al. 2003; Pilla et al. 2005).

TREATMENT STRATEGIES

Building on understanding of the biological and mechanical processes after MI, many strategies now utilize biomaterials for patient treatment. Several focus on treatment after significant tissue remodeling; for example, with tissue engineering, replacement cardiac tissue is developed in the laboratory and then implanted to replace damaged tissue. Another promising approach involves treating the tissue during the acute phase to try to attenuate the remodeling response before significant damage.

One option is to limit the initial infarct expansion, which has been identified as associated with the LV remodeling that leads to heart failure. Previous strategies to limit infarct expansion involved surgical reconstruction of the dilated LV and physical restraint of the ventricle or infarct region using polymeric meshed materials to prevent dilation (Batista et al. 1997; Klodell et al. 2008; Starling et al. 2007), but these approaches are highly invasive and require open-chest surgery.

Injectable biomaterials are being developed as a minimally invasive alternative to decrease damage to surrounding tissues. Among numerous potentially injectable biomaterials (e.g., microparticles), injectable hydrogels are particularly promising; they are water-swollen networks of polymer chains that have a high degree of tunability and can be formed through numerous crosslinking mechanisms (Ruel-Gariepy and Leroux 2004). They have been shown to mechanically stabilize the myocardial wall and modulate LV remodeling either alone or through the delivery of therapies such as cells and growth factors (Figure 1) (Nelson et al. 2011; Tous et al. 2011).

Acellular Approaches

Many investigators believe that post-MI regional mechanical changes and stresses in the myocardium should be addressed when designing biomaterial-based approaches for cardiac repair (Gupta et al. 1994; Holmes et al. 2005; Nelson et al. 2011). As described by the Law of Laplace (Equation 1), stress (T) is directly proportional to pressure (P) and the radius of curvature (R) and inversely proportional to the myocardial thickness (h). Therefore, the increase in R and decrease in h that occur after MI leads to an increase in T.

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$$T = \frac{P * R}{h} \quad (1)$$

Injectable biomaterials can limit infarct expansion by bulking the damaged myocardial wall through mechanical stabilization (Tous et al. 2011). Infarcts naturally stiffen over time as wound healing progresses and collagen is deposited; modifying the tissue properties of the infarct region before the body compensates for the remodeling process can limit infarct expansion and post-MI remodeling (Tous et al. 2011). Injectable hydrogels act as bulking agents by increasing the myocardial wall thickness (h) to decrease LV dilation (as measured by R) and in turn decrease wall stress (T). Theoretical finite element models have confirmed this mechanism of treatment by demonstrating that hydrogels decrease both LV dilation and myofiber stresses (Wall et al. 2006).

Injectable hydrogels can be grouped into either natural or synthetic materials. Natural materials offer advantages such as inherent biological properties, including receptor-binding ligands and susceptibility to proteolytic degradation

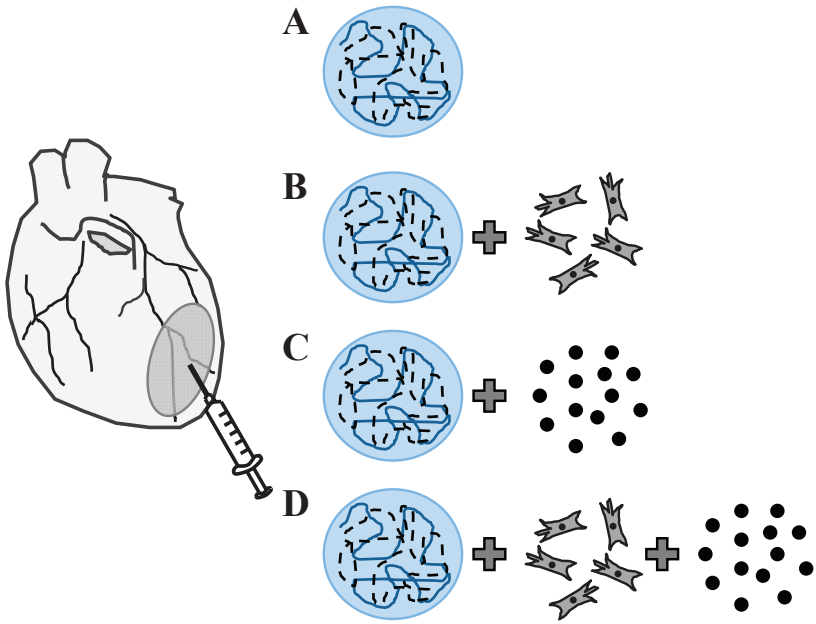

FIGURE 1 Injectable hydrogel approaches for the treatment of MI. Hydrogels (shown in the center column) can be used as (A) acellular bulking agents or a vehicle for (B) delivery of cells, (C) therapeutic molecules, or (D) a combination of cells and molecules.

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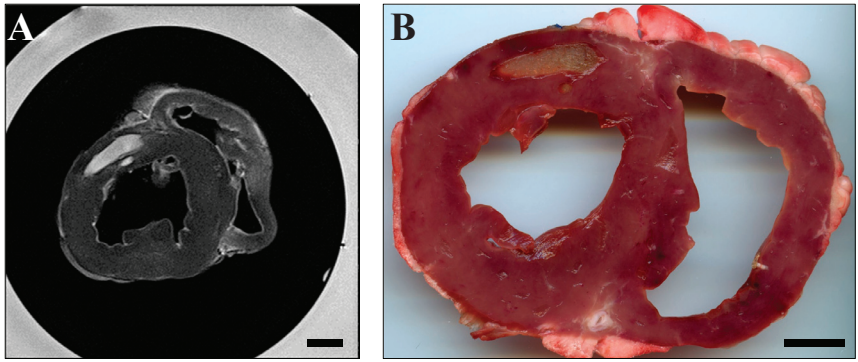

FIGURE 2 Acellular hydrogels as bulking agents for myocardial infarction repair. Injectable hyaluronic acid hydrogel distribution in cardiac tissue explant as shown by (A) magnetic resonance imaging and (B) ex vivo sectioning. Scale bar = 1 cm.

(Karam et al. 2012; Lutolf and Hubbell 2005). For cardiac applications where the goal is to replace or repair the damaged ECM, natural biomaterials more closely mimic features of the native ECM and can also be therapeutic in their degradation products through the recruitment of cells (Sui et al. 2011). Commonly used natural injectable materials for cardiac repair are fibrin, alginate, collagen, Matrigel, chitosan, hyaluronic acid, keratin, and decellularized matrices (Tous et al. 2011). But natural materials have limited tunability in properties.

Synthetic materials have defined material properties such as molecular weight, gelation, hydrophilic/hydrophobic properties, degradation, and mechanics, without batch-to-batch variations (Lutolf and Hubbell 2005). They can also be modified with cell binding sites or adhesive ligands to encourage cell interaction (Davis et al. 2005). Various synthetic materials have been explored for cardiac repair therapy, including poly(N-isopropylacrylamide) (PNIPAm)- and poly(ethylene glycol) (PEG)-based hydrogels (Tous et al. 2011). An example of an injected hydrogel based on hyaluronic acid is shown in Figure 2.

Cellular Approaches

Myocardial infarction results in the loss of over 1 billion cardiomyocytes in the infarct region, and cell delivery is one strategy used for tissue repair (Beltrami et al. 1994). A variety of cell types have been delivered—fetal or neonatal cardiomyocytes, embryonic stem cells (ESCs), skeletal myoblasts, bone marrow–derived stem cells (BSCs), adipose-derived stem cells, and cardiac stem cells (Menasche 2005; Segers and Lee 2008). Each has advantages and disadvantages for use in therapies. For example, ESCs offer the advantage of differentiating into both

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cardiomyocyte and vascular lineages, but their efficacy is limited because of their immunogenicity, risk of tumor development, and ethical concerns (Zimmermann 2011). BSCs are an autologous option that can be readily isolated and delivered to cardiac tissue, but their fate is not clear (Le Blanc and Pittenger 2005).

Although both animal models (Segers and Lee 2008) and clinical studies (Menasche 2005) have demonstrated some enhancement in cardiac function with cell delivery, these improvements are often insufficient and transient, which is believed to result from unsatisfactory cell retention, survival, and engraftment (D'Alessandro and Michler 2010). For example, less than 10 percent of BSCs delivered have been detected two hours after injection (Hofmann et al. 2005; Hou et al. 2005), and of those that stay at the injury site approximately 90 percent die within the first week because of physical stress, ischemia (due to microvasculature obstruction), inflammation, and release of cytokines and reactive oxygen species (Robey et al. 2008).

Injectable hydrogels have been explored to enhance cell retention and engraftment for cardiac repair by improving cell attachment, migration, and survival upon delivery (Huang et al. 2005). They permit both high encapsulation efficiency (cells are entrapped during gelation) and precise control over the biophysical and biochemical microenvironment surrounding cells after delivery (Bian et al. 2009).

As with acellular hydrogels, both synthetic and natural polymers have been investigated. Natural materials, such as fibrin, alginate, collagen, and Matrigel, are a popular choice for cell delivery because their inherent biological activity initiates cell-biomaterial interactions (Tous et al. 2011). Synthetic hydrogels can also be used to deliver cells for cardiac repair. With their tunability, synthetic materials can be modified to control both adhesion for cell retention and degradation for desired timing of cell release into the tissue environment. As with the acellular hydrogels, the primary synthetic materials used for cell delivery are PNIPAm and PEG (Tous et al. 2011).

INJECTABLE HYDROGELS FOR MOLECULE DELIVERY

In addition to the approaches described above to alter local mechanical stabilization and serve as a cell delivery vehicle, injectable hydrogels can deliver therapeutic molecules to address post-MI LV remodeling.

Tissue repair is a complex process controlled in part by numerous molecules, such as growth factors and cytokines, and the delivery of such molecules can modulate post-MI endogenous biological responses (Segers and Lee 2010). Delivery of therapeutic molecules alone, by either direct myocardial injection or systemic intravenous circulation, has helped restore cardiac function in some animal models, but the short half-life of the molecules and off-target complications limit clinical application (Urbanek et al. 2005).

Because of these limitations, injectable hydrogels have been used as delivery vehicles to localize molecules and tailor release kinetics through changes in

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polymer-molecule interactions, polymer hydrophobicity, and hydrogel degradation (Chen and Mooney 2003; Kretlow et al. 2007). Hydrogels can both sustain local molecule release and prolong molecule bioactivity (Langer and Folkman 1976). For cardiac applications, injectable hydrogels are useful to deliver anti-apoptotic molecules (which limit cell death after injury), angiogenic factors to promote vessel formation, or chemoattractants to recruit cells for repair and attenuation of post-MI remodeling (Tous et al. 2011).

LOOKING FORWARD

As discussed here, a range of injectable hydrogels, cell types, and molecules have been delivered with the intent of attenuating LV remodeling after myocardial infarction. Although many hydrogels have shown positive outcomes in animal models, only one (alginate) has progressed to clinical trials.[1] Research is needed to elucidate the effects of hydrogel properties, mode of delivery (e.g., direction injection vs. catheter delivery), and timing of delivery (e.g., acute vs. chronic MI) on LV remodeling. Future studies should further investigate the mechanisms by which hydrogels act on the heart, including both biological and mechanical effects, and focus on clinically relevant parameters to optimize repair outcomes.

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Regulatory Perspectives on Technologies for the Heart

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With advances in materials science, manufacturers are able to develop medical devices[1] from stronger, superelastic materials and tissue (patient-specific or otherwise), opening the door for less invasive surgical therapies and personalized medicine. Moreover, access to computers with substantial processing power enables manufacturers to use computational tools paired with patient-specific diagnostic images to simulate treatment options, almost in real time. In addition, with the increasing cost of health care alongside the aging baby boomer population, there is a need to improve quality of life, decrease the number of doctor visits and length of hospital stays, and provide more efficient treatment options that reduce costs for people living with heart disease, as highlighted in Box 1.

The objectives of this paper are to highlight the regulatory process for medical devices from an engineering perspective, to discuss how manufacturers of medical devices can leverage different tools and techniques to get their devices to the

Note: The symposium presentation on regulatory perspectives was given by Sonna Patel-Raman of Halloran Consulting Group, Inc.

[1] The FDA (www.fda.gov/aboutfda/transparency/basics/ucm211822.htm) defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

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BOX 1
America's Heart Disease Burden

- About 600,000 people die of heart disease in the United States every year—that's 1 in every 4 deaths (Murphy et al. 2013).
- Heart disease is the leading cause of death for both men and women. More than half of the deaths due to heart disease in 2009 were in men (Murphy et al. 2013).
- Coronary heart disease is the most common type of heart disease, killing nearly 380,000 people annually (Murphy et al. 2013).
- Every year about 720,000 Americans have a heart attack; of these, 205,000 have already had a heart attack (Go et al. 2014).
- Coronary heart disease alone costs the United States $108.9 billion each year (Heidenreich et al. 2011) in healthcare services, medications, and lost productivity.

market, and how regulators might evaluate innovative medical technologies for the heart.

BACKGROUND

The US Food and Drug Administration's Center for Devices and Radiological Health (CDRH) is responsible for regulating medical devices that are manufactured, repackaged, relabeled, and/or imported to be sold in the United States. Its mission "is to protect and promote the public health. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S."[2] The center's purview includes regulation of *technologies for the heart,* cardiovascular devices that treat a range of diseases that affect the heart.

Most implantable devices to treat heart disease are classified as the highest risk, Class III, because they are life sustaining and/or life supporting. Class III implantable devices include pacemakers, defibrillators, heart valves, coronary stents, ventricular assist devices, and artificial hearts. Manufacturers that wish to market Class III devices in the United States need to demonstrate that there is a reasonable assurance of both safety (i.e., the probable benefits to health outweigh

[2] Information about the Center for Devices and Radiological Health is available at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/ucm300639.htm.

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TABLE 1 Comparison of Models Used to Assess High-Risk Medical Devices

	Cost	Time	Ability to vary parameters	Evaluation involving harm	Simplifying assumptions	Relevance to clinical use	Evaluating disease state	Experimental control	Ability to interpret data and predict clinical use
Animal	moderate	moderate	limited	restricted	moderate	species variability	difficult	relatively high	limited
Bench	low	short	limited	yes	many and always	limited	simplified states	high	limited
Computer	relatively low	short to moderate	high	yes*	many and always	variable	yes*	high	yes*
Human	very high	long	not easy	no, unethical	minmal	direct	yes	low	not easy

* There is a recognized potential. Computational modeling in medical devices, as compared to other industries, is nascent and is the one model with the most potential for refinement and improvement because other models are fairly mature.

any probable risks) and effectiveness (i.e., the device will provide clinically significant results).

Comprehensive evaluation of a premarket submission for a therapeutic, high-risk medical device is typically supported by a combination of valid scientific evidence from four types of models: animal, bench, computational, and human. These models can be leveraged at different stages of a medical device's life cycle to demonstrate attributes of performance. Because each model has different strengths and limitations for predicting real-world clinical outcomes, the data portfolio for different devices and use conditions will vary. Some advantages of each model are shown in Table 1.

REGULATORY EVALUATION

Selecting the Appropriate Model for Evaluation

A firm that decides to manufacture a medical device should consider the regulatory pathway that will allow the device to be marketed in the United States. For many implantable devices to treat heart disease, a premarket approval (PMA) application is the appropriate pathway; PMA is "the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices."[3]

[3] Information about the PMA is available at www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm.

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BOX 2
Questions from a Failure Modes and Effects Analysis

- What is the device intended for?
- What could go wrong?
- Why would the failure happen?
- What would be the consequences of failure?
- What is the likelihood of occurrence?
- What is the likelihood of detection?
- What is the severity of the failure mode?

Source: ISO (2007).

The firm must also develop a plan to gather the necessary valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness. The basis of this plan will depend on the indications for use—the disease to be treated, the affected patient population, the location of the implanted device, the expected duration and in vivo conditions of the implant, and the surgical procedure. With this information, the firm can use tools such as the Device Evaluation Strategy (FDA 2013, section 6.3) and Failure Modes and Effects Analysis (FMEA) for Medical Devices (ISO 2007) to address fundamental questions about device failure and potential consequences (see Box 2).

Depending on the function of the device, the firm identifies an attribute, the potential failure mode of that attribute, potential device and clinical effects, the design characteristic intended to mitigate the risk of the failure mode, and the model (animal, bench, computational, or human) that will be used to demonstrate that the function of the device will be attained and/or that the failure mode will not likely occur.

In vivo animal studies provide anatomic and clinical pathologic information of the local and systemic responses to device use. Larger animal models, such as pigs and sheep, are typically used for cardiovascular applications because the size and response of their anatomy more closely match those of human anatomy. Bench and computational models can act as surrogates for the in vivo environment and are useful because they can challenge an isolated feature of the device (e.g., implant integrity after deployment, long-term durability). Clinical trials are used for a variety of purposes, but for Class III devices they are mainly to demonstrate safety and effectiveness in the clinical setting and evaluate the device in the in vivo human environment.[4]

[4] For other applications of clinical evaluations see FDA (2013).

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Unique Material Considerations

When a firm uses traditional materials (e.g., stainless steel, polyurethane), whose behavior is well understood, the regulatory expectations tend to be straightforward. Additional engineering and regulatory questions may arise when complex materials are introduced and their behaviors are not well established. For example, there has been a shift from bare metal stents to drug-eluting and, more recently, absorbable stents.

Questions about drug-eluting stents have focused on understanding the elution and absorption rates of the drug, in addition to the mechanical performance of the stent. With absorbable devices, a major concern is the rate of degradation: absorbable devices are not intended to be permanent implants like metallic stents, but they do need to maintain a certain amount of structural integrity. Computational methods can be used for stress analysis, but they require more complex constitutive models. Other challenges arise for drug-eluting and absorbable products when the manufacturing process changes, because this can affect the elution and absorption rates for the drug or the degradation time frame for the absorbable material, which could result in additional testing. Identification of byproducts and their biological effects is another common consideration, and can involve complex in vivo (animal model) evaluations.

For medical devices that are tissue-engineered or regenerative medicine products, the regulatory framework is a bit different. Reviewers have to consider "purity, potency, and identity" for biologically derived products,[5] and this requirement can pose limitations to traditional testing. For example, the long-term durability of permanent metallic implants (e.g., stents and heart valve frames) can be evaluated using accelerated durability bench testing and computational modeling, and the resulting data complement the outcomes from the clinical study regarding mechanical performance. This is not the case for tissue- and cell-based materials because the bench model does not allow for the cell and tissue adaptation process that occurs in vivo (e.g., cell infiltration and extracellular matrix deposition) and that may enable the product to repair itself in a normal timed setting in vivo. Therefore, manufacturers of biologic products must rely on extensive in vivo animal testing for performance evaluation.

Changes to Surgical Approaches

Another aspect of device design that can affect regulatory questions is a change in surgical technique or approach. For example, a recently introduced percutaneous (transcatheter) approach for implanting heart valves for high-risk patients engendered new questions about deliverability, deployment accuracy,

[5] Information about this requirement is available at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133072.htm.

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migration, integrity, and durability. The latter two are especially important with the new approach and are specifically assessed through a process called *preconditioning*: The heart valve is loaded onto a delivery system and guided through the arterial system, a process that subjects it to stresses and strains that do not occur in the traditional open surgical approach, in which the heart valve is directly implanted in the annulus. Preconditioning can greatly affect the integrity and durability of the implant and determine whether it is suitable for clinical use.

Unlike surgical bioprosthetic heart valves, transcatheter heart valves vary greatly in design, so the effects of preconditioning can be different for each design. Moreover, unlike surgically implanted mechanical heart valves, transcatheter valves do not usually remain circular upon implantation because the diseased leaflets and the calcium nodules are not removed, so the frame experiences noncircular deformations in vivo. The computational model is the only tool that can be used to determine changes in the stress (or strain) state of a device under different preconditioning states or implantation configurations. It can also predict the effects of preconditioning and implantation on fatigue performance (Duraiswamy et al. 2013). These predictions are then confirmed through accelerated durability testing.

Summary

Firms must provide valid scientific evidence from animal, bench, computational, and human models to support their marketing applications, and the amount of data collected from each model depends on the disease to be treated, the affected patient population, the location of the implanted device, the expected duration of the implant, and the surgical procedure. The data portfolio may change even more as companies expand their use of high-performance scientific computing to reduce time and cost in their efforts to bring safe and effective devices to patients in the United States.

TREATMENT PLANNING IN THE 21ST CENTURY

The practice of medicine is being shaped by powerful imaging capabilities, high-performance computation, wireless transmission of data, and massive storage of information. Physicians are now able to continuously monitor a patient's health from a distance and determine whether a coronary lesion is relevant and treatment necessary, whether a patient is at risk of losing heart rhythm, and whether a patient will benefit from cardiac pacing (Miller 2014). In the near future, they will be able to select the optimal heart valve size and placement and to assess treatment options within a matter of hours (Simulia Community News 2014).

Several companies make such options available in the United States. Graphium Health uses cloud computing and mobile technology to help physicians, administrators, and patients make better pre- and postsurgery decisions

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about care. HeartFlow uses patient-specific anatomy and physiological conditions to computationally estimate the amount of coronary burden due to a stenosis, alleviating in moderate cases the need for catheterization, an invasive procedure that is currently the standard of care.

Thanks to these and other tremendous advances, doctors have access to more data, information, and knowledge, and the potential to offer more clinical benefit to their patients. However, regulators are challenged with trying to determine which advances in computing and software are medical devices and, for those that are, what data are needed to support their entrance to the market in the United States (FDA, FCC, and HIT 2014).

From an engineering perspective, scientific computing is mature enough to simulate multiple design parameters and use conditions, and to visualize complex processes to revolutionize the way medical devices are investigated, treatments planned, and patient data utilized. With access to "digital patients," device designers can download anatomic and physiologic computer models of patients with a given disease.[6] They can then take their new device concepts and "deploy" them in the digital patients to simulate device performance, leading to more effective bench testing, in vivo animal studies, and (actual) clinical trials. The simulations enable detection of "soft failures," failures that occur virtually before the devices are implanted in patients.

Finally, from a clinical perspective, physicians will soon be able to use simulation to predict the safety and effectiveness of a given medical product for an individual patient, thereby truly realizing personalized medicine. However, the regulatory burden for medical devices that have the potential to predict patient-specific outcomes remains to be determined.

CONCLUSIONS

New materials and surgical approaches are generating more treatment options for patients with heart disease. Moreover, there is a huge opportunity for imaging and high-performance computing to improve net health outcomes in the United States through treatment planning and better patient understanding of options. FDA's engagement with industry and academia early on in the development of innovative products can help accelerate the field. The agency can provide the structure to help guide firms to determine appropriate models and data portfolio needs for evaluating their products. Early engagement also enables FDA to share its regulatory experience and to raise important questions that will protect patients and promote the overall health of the US population.

[6] Two such resources are available from the Virtual Physiological Human (www.vph-institute.org) and the Foundation for Research on Information Technologies in Society (IT'IS) (www.itis.ethz.ch/services/anatomical-models).

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Shale Gas and Oil

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Shale Gas and Oil

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Oil and natural gas liquids have been the feedstock for the bulk of global transportation fuel and chemical production for many decades. Natural gas, more specifically methane, is used as a feedstock on a limited scale for chemical production, and is used on a large scale for electricity generation. For many years, the United States has imported from abroad a significant portion of the oil used to power the domestic economy, and the need for these critical hydrocarbon resources has profoundly impacted our foreign policy. However, in October of 2013, for the first time in nearly two decades, the United States has produced more oil domestically than it imported from abroad. What has led to this fundamental shift in where our hydrocarbon resources are produced?

The boom in domestic production of gas and oil from shale resources has been facilitated by the development and implementation of hydraulic fracturing, or "fracking" technologies. These technologies have facilitated significant new capital investment in the United States, providing the impetus for significant domestic job creation. But with these new technologies come concerns associated with continued reliance on hydrocarbon resources for energy production and the associated carbon dioxide emissions that accompany their use. In parallel, there are concerns about water contamination associated with hydraulic fracturing technologies as well.

The light gases such as methane, ethane, and propane that are produced by hydraulic fracturing can be directly used as fuels, but their valorization as chemicals requires conversion and upgrading. Ethane and propane are readily converted in conventional technologies to make higher value products, but methane, the most abundant of the light gases, continues to challenge technoeconomic barriers for upgrading. To this end, the development of technologies that facilitate the

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conversion of these light gases into chemicals is a key research challenge facing broader utilization of these gaseous resources. This utilization can occur domestically, creating new domestic manufacturing jobs, or the resources can be exported as liquefied natural gas (LNG), positively affecting the US balance of trade. This session will provide an overview of these interconnected logistical, chemical, and environmental issues associated with utilization of the new shale gas/oil resource, identifying research problems at the forefront of this field.

The first speaker, Stephen Ingram (Halliburton), provided an overview of the location and nature of domestic shale gas and oil resources and introduced hydraulic fracturing technology, including logistical and infrastructure challenges associated with its use. The second speaker, Kelvin Gregory (Carnegie Mellon University), addressed the environmental challenges that are associated with utilization of shale gas and oil, including increased carbon dioxide production and the significant water resource challenges associated with hydraulic fracturing. Eric Stangland (Dow Chemical Company) concluded the session by discussing the utilization of shale gas for chemical production, elaborating research challenges associated with methane conversion.

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Shale Natural Resources

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The development of shale natural resources has built on engineering, chemical, and technological innovations applied with entrepreneurial spirit. Its continuing success will depend on attention to geology/geography, technology, infrastructure, and political/social elements. In this paper I discuss the circumstances and technologies associated with these four aspects.

BACKGROUND

Shale is classically defined as a fine-grained (i.e., low-permeability and low-porosity) clastic sedimentary rock composed of mud that is a mix of flakes of clay minerals and tiny fragments (silt-sized particles) of other minerals, especially quartz and calcite. These qualities can lead to uneconomic flow rates under natural conditions, hence the justification for the use of hydraulic fracturing. Most industry professionals identify permeability as the key formational attribute that distinguishes an *unconventional* formation from a *conventional* one. Some classify as "unconventional" any formation that requires hydraulic fracturing to establish economic production rates. Sondergeld and colleagues (2010) provide an excellent overview.

The technologies necessary to develop shale opportunities encompass many science and engineering domains, which are broadly described here along with other requirements and opportunities. Infrastructure requirements can be simple or complicated, and a review of the full-cycle infrastructure is necessary to identify possible barriers to economic development, in terms of both servicing the construction of the wellbore and producing the hydrocarbon.

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Shale natural resources are globally distributed, with pockets of successful activity, opportunity, and exploration in various locations. North American development is currently the most active, but development is being pursued today for opportunities existing in Saudi Arabia, Argentina, Australia, China, and Russia. Other locations, such as South Africa and Central France, with potential resources for development face barriers to economic production, so it seems likely that North America will continue to sustain the highest level of development in the near and medium term.

GEOLOGY/GEOGRAPHY

The single most important factor for developing a shale asset is the existence of subsurface conditions that promote the creation of hydrocarbons in a rock structure that is conducive to positive economic flow rates. A number of reservoir attributes are crucial to reducing the uncertainty of economic productive capacity. First is the geological structure, meaning the conditions for a large formation system of substantial hydrocarbon reserves, normally with high organic content. Over a geological period of time (pressure and temperature), surface matter is buried and begins the process of diagenesis, which converts organic matter to hydrocarbons of differing carbon chain lengths in the subsurface, subject to migration or transportation under the correct circumstances. Differing carbon chain lengths determine whether the well is gas, condensate, or oil, each of which is traded on the open market and will deliver different financial returns to the well owner.

A leading indicator of quality shale reservoirs, measured early in the exploration phase, is total organic content, typically measured as the percentage of kerogen, which is a mixture of organic chemical compounds. Kerogen has a number of properties (e.g., variable density, porosity) and can therefore be misleading for development purposes. Rickman and colleagues (2008) describe the standard industry approach for using and interpreting subsurface data for the application of hydraulic fracturing of shale reservoirs.

Other geological properties, such as permeability and porosity, are also important to the economic development of a reservoir. These include geomechanical properties, such as Young's modulus and Poisson's ratio; geochemical properties, such as clay, quartz, or carbonate content; and reservoir properties, such as temperature and pressure. There are hundreds of other important subsurface properties and considerations, and petrophysical, geological, and geophysical careers are built around their study to determine how they impact the production of reservoirs.

The combined reservoir properties are important to geoscientists and engineers for three reasons:

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- To estimate oil and gas reserve quantities
- To determine engineering needs and approaches (for drilling and completion)
- To anticipate surface impacts of development

TECHNOLOGY

The technologies necessary to develop unconventional natural resources span many domains. Technologies that enable surface seismic monitoring, downhole micro seismic monitoring, fiber optic sensing, rock and fluid sampling, and sensor physics are used to better define the shale gas reservoir. Added to these are data integration, visualization, and Big Data management.

Drilling involves top-drive flexible drilling rigs, automated pressure-while-drilling control systems, downhole rotary steerable systems, drill bit design advances, fluid chemistry, telemetry systems (mud pulse technology for data delivery), and mud motor systems. With these technologies a greater number of horizontal wellbores can be drilled faster, safer, and longer, (e.g., 6,000 feet of horizontal wellbore or longer in many cases).

Completion technologies used in unconventional development include hydraulic fracturing, fluid chemistry (specifically, viscosity generation, friction reduction, clay control, complex nanofluids ["surfactant family"], and bacteria control), surface equipment design, fueling advances, and flow-through porous media design. Technological advances in seismic interpretation and associated data integration are useful to both drilling and completion operations.

As the unconventional industry has matured, the technology focus and use has also evolved. In the 1970s, '80s, and '90s the use of hydraulic fracturing in low-permeability, low-porosity tight reservoirs was commonplace in vertical wells across the United States and abroad. After more research on fracturing applications in horizontal wellbore configurations, horizontal drilling techniques were adopted in the 2000s. The economic growth observed to date is due to a combination of vertical and horizontal technologies.

King (2010) presents a 30-year survey of seismic attributes with hydraulic fractures in horizontal wells, typically in combination with downhole microseismic data acquisition. Since 2010 the industry has evaluated and interpreted seismic datasets and made advances in data acquisition and interpretation to help reduce the risk of underperforming assets and the uncertainty of field development.

Now, three-dimensional full-azimuth wide-azimuth seismic data are the norm for new data acquisitions in the US market, and the re-processing of old datasets is being completed across most of the country. Abroad, data acquisition systems are less available and cost more to use, so the expected return on investment for such an endeavor is less favorable. Seismic technology enables the use of reservoir attributes, such as fluid type, geomechanics, and even permeability and porosity

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estimations, as well as other nascent properties, such as anisotropy (or the heterogeneous nature of rock systems). In addition to the normal use of seismic data for structure analysis, it is used for fault and subsurface barrier identification and for estimations of oil and gas in place.

INFRASTRUCTURE

Many infrastructure components are necessary for the development of an oil and/or gas project. Major infrastructure involves pipelines, facility separation, gas handling, liquid handling, surface roads, rail lines, storage, water availability, housing, living condition support, water, proppant, maintenance, and personnel.

The development of early unconventional reservoirs was in part a function of existing established infrastructure. The clearest example is the Barnett shale in North Texas, where in the early 2000s an existing highway, county road, and rail line infrastructure in proximity to the Dallas/Fort Worth metroplex, together with legacy oil and gas handling capacity, among other assets, created a low-cost working environment for entrepreneurial oil and gas companies to pioneer shale development.

After this early economic success, there was interest in expanding US shale development, but progress was limited by the slow ramp-up of the Bakken shale in North Dakota and the constrained growth of the Marcellus and Utica shales in West Virginia, Pennsylvania, and Ohio. Examples of the constraints included but were not limited to existing highways and road systems, permitting restrictions of pipelines, lack of local competent and trained human resources, limited rail infrastructure, and sufficient industrial scale water distribution infrastructure.

In the United States, it is typically within the capabilities of the economy, state and federal government, and industries to overcome infrastructure challenges and thus facilitate economic development. This is less true in other locations, such as China, Russia, Australia, Argentina, India, or Europe, where the necessary infrastructure may not exist, thus placing all or part of the burden of development on the oil and gas industry and increasing the associated costs and barriers to economic viability.

POLITICAL/SOCIAL

The fourth contributing component to the development of unconventional resources is political and social capability, including a market clearinghouse that permits profits to be obtained by all parties involved—land owners, mineral rights owners, service companies, oil and gas operators, and government entities. In this regard, there is considerable variability across both international and domestic geographies.

The United States has a significant enabling social driver to shale development: mineral rights ownership across private lands. As such, mineral rights

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owners (who may or may not be the land owners) have the right to monetize their mineral interests for economic benefit. In most of the world, this federally protected right is not available, and the mineral interest owner is a government entity. Private citizens of those nations thus have more limited access to the wealth creation of mineral rights ownership.

CONCLUSION

The sustainable success of unconventional resource development is a function of geology/geography, technology, infrastructure, and political/social elements. Each of these is integral, and without all four components, sustainable development can be constrained or even made impossible.

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Microbial Ecology of Hydraulic Fracturing

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Advances in drilling and stimulation technologies have greatly improved the economics of oil and gas production from deep, tight, hydrocarbon-rich shale formations. But the unconventional drilling required for this production is associated with challenges in the management of both the wastewater that is coproduced at the surface and the microbial communities in this water.

The focus of this article is on the microbial ecology and biogeochemical processes that impact the production of oil and gas, management of wastewater (both flowback and produced water), and product quality from hydraulically fractured wells. Hydraulic fracturing is discussed from the perspective of water management, including the volume and makeup of fracturing fluids that give rise to produced water microbiology. Recent studies of the chemistry and microbiology of produced water from the Marcellus and Barnett shale regions are discussed. Microbial ecology present at wellheads is described as well as that of stratified impoundments for produced water. The concluding section considers the implications of microbial control for unconventional production and identifies research needed to address them.

HYDRAULIC FRACTURING OVERVIEW

Horizontal drilling, a technology that has been broadly applied since the 1980s, allows access to a far greater portion of a formation than vertical wells by following the horizontal contour of the formation for thousands of meters. In this manner, horizontal wells also greatly reduce surface impacts by minimizing the number of wells required to develop a particular area. Hydraulic fracturing (often called *fracking*) is used in conjunction with horizontal wells to increase the

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permeability of a formation and extend the radius of influence of the wellbore for an overall increase in the productive area of the reservoir.

Hydraulic fracturing entails the pumping of fluid into the wellbore at a rate that exceeds the capacity of the formation to accept without fracturing. A number of fracturing fluids exist, the most common of which is a mix of water (as a solvent for chemical modifiers), sand (for proppant), and chemicals. This fluid is pumped into the wellbore at pressures of 500–900 atm, depending on the needs of the target formation. The proppant flows into preexisting and newly initiated fractures and holds them open after pumping has stopped and pressure decreases. In the Marcellus shale region, hydraulic fracturing may require 6–15 million liters of water, depending on the depth to the target formation and length of the horizontal leg of the well (Gregory et al. 2011).

FLOWBACK AND PRODUCED WATER

Generation of Fluid

After the pumping for hydraulic fracturing but before the production of hydrocarbons, the pressure in the well is allowed to dissipate; fluid returns to the surface through the wellhead and is collected and stored. This initial fluid, which is produced to the surface for about 14 days before product recovery, is called *flowback*. Thereafter, water produced to the surface (along with hydrocarbon products) over the lifetime of the well is called *produced water*. The difference between flowback and produced water is largely operational; the rate at which flowback returns to the surface is greater and the strength lower than that of produced water.

In terms of content, both flowback and produced water are a mixture of hydraulic fracturing fluid and water present in the formation. The quantity and quality of flowback vary among unconventional oil and gas plays and according to the hydraulic fracturing procedure used. In the Marcellus shale, for example, flowback returns 9–53 percent (average 10 percent) of the injected volume (Vidic et al. 2013). In terms of the quality of the fluid, the concentration of total dissolved solids (TDS, including salts and metals) in the water that returns to the surface varies over time; the earliest flowback (e.g., the first 2 days) resembles the hydraulic fracturing fluid itself and has the lowest concentration of TDS, while the later flowback (e.g., after day 10) and the produced water have much higher TDS, more like the chemistry of the formation water.

Generally speaking, the composition of produced water from a formation is similarly variable (Barbot et al. 2013). The study by Barbot and colleagues reveals that the TDS in produced water from the Marcellus varied from ~1 to 345 g/L, with an average of 106 g/L. The authors also found that the TDS in the produced water was predominantly from the ions (Cl^-, Na^+, and Ca^{2+}) and further characterized by high concentrations of magnesium, barium, and strontium. Organic compounds in produced water include those introduced with the fracturing fluid

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as well as polycyclic aromatic hydrocarbons (PAHs), heterocyclic compounds, alkyl phenols, aromatic amines, alkyl aromatics (alkyl benzenes, alkyl biphenyls), long-chain fatty acids, and aliphatic hydrocarbons (Orem et al. 2014), all of which may be used as carbon sources and electron donors for bacterial growth.

Disposition of Fluid

Most produced water in the United States is disposed through deep-well injection (Clark and Veil 2009). However, because there are few deep-well injection options in Pennsylvania, reuse of flowback as the makeup water for subsequent hydraulic fracturing has become the preferred management option in the Marcellus region. This reuse also reduces both the need for freshwater withdrawals and the costs incurred for transportation and treatment or disposal. Produced water brines are used for subsequent hydraulic fracturing, diluted with a freshwater source, and treated to remove solids and divalent cations before reuse. Although the reuse of flowback (and produced) water for hydraulic fracturing is a novel technology and management solution for oil and gas wastewater brines, a recent analysis of data from the Pennsylvania Department of Environmental Protection revealed a ~90 percent reuse rate of oil and gas brines from the Marcellus (Maloney and Yoxtheimer 2012).

Flowback is typically impounded at the surface before disposal, treatment, or reuse. While treatment or disposal may take place immediately, reuse for subsequent fracturing requires storage of a variable volume of wastewater (from 10,000 to 60,000 m^3, depending on the intended use and the number of wells served) for variable periods of time (weeks or months); for this it is either transported by truck or pumped to centralized impoundments that serve multiple wells or multiple pads with multiple wells.

In storage, microbes in the flowback and produced fluids evolve and give rise to water management challenges such as malodorous compounds, biofouling of the formation and production equipment and infrastructure, biocorrosion, and alteration of the solubility of metals including radionuclides. Issues associated with the proliferation of bacteria during oil and gas production are ubiquitous, manifest themselves throughout the production infrastructure, and are costly to manage (Ollivier and Magot 2005).

MICROBIAL COMMUNITIES IN PRODUCED FLUIDS

Microbial processes that impact oil production from conventionally developed reservoirs are well documented (Van Hamme et al. 2003). In these reservoirs, the stimulation of bacteria may result in reservoir fouling, biocorrosion, and product souring (sulfidization), or, conversely, provide benefit by enhancing product recovery and the removal of soured product and paraffins. The microbial ecology of these processes in conventional reservoirs is well understood, but there are

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few studies of the detrimental or beneficial impacts of bacteria or the microbial ecology of unconventional oil and gas development, despite similar concerns and knowledge that the microbiology is costly to control.

From Aerobic to Anaerobic Bacteria

A recent study of wellhead samples of Marcellus flowback and produced water reveals that the microbial community changes over time together with the geochemistry (Murali Mohan et al. 2013b). On day 1 of the flowback the community closely resembles that of the fracturing fluid and the source water (Figure 1). The microbes are most similar to species associated with nonhalophilic, aerobic, and phototrophic metabolisms, all of which would be expected in water from a freshwater surface source. However, later in the flowback period, the TDS increase as do the number of bacterial species that are most closely related to halophilic, thermophilic anaerobes. The rise in the abundance of halophilic anaerobes occurs at the expense of the nonhalophilic aerobes and phototrophs and at the expense of microbial diversity (Murali Mohan et al. 2013b).

Figure 1 shows a gradual decrease in *Rhodobacterales* (freshwater phototrophs) and increase in *Halanaerobiales* (anaerobic halophiles) during hydraulic fracturing of a well in the Marcellus shale. The emergence of the halophiles was concomitant with the emergence of anaerobic geochemistry (e.g., Fe^{2+} and HS^{-}) in the water and led to the loss of virtually all species present in the initial flowback except the *Halanaerobiales*, which eventually represented more than 99 percent of the community (Cluff et al. 2014). Bacteria identified in a sample of produced water were closely associated anaerobic, fermentative, and sulfur-reducing bacteria in the *Halanaerobiales*. A study of flowback from the Barnett shale revealed a community that was similarly changing with time, adapting to anoxic and saline conditions (Struchtemeyer and Elshahed 2011).

Possible Sources of Bacteria

It is important to note that next generation sequencing revealed that the anaerobic and halophilic species present in great abundance in the produced water were also present in very low abundance in hydraulic fracturing fluid. This suggests that the organisms in the produced water may originate at the surface and be introduced by hydraulic fracturing rather than native to the connate water in the deep subsurface reservoir. But there is a chicken and egg problem: trucks and equipment used for handling the water likely were exposed to brines from hydraulic fracturing, so the source of the organisms could be any equipment used for hauling the water. It is therefore difficult to pinpoint the source of the organisms in flowback and produced water.

Although bacteria are well known to inhabit deep subsurface environments (Fredrickson and Balkwill 2006), their presence in connate brine from the

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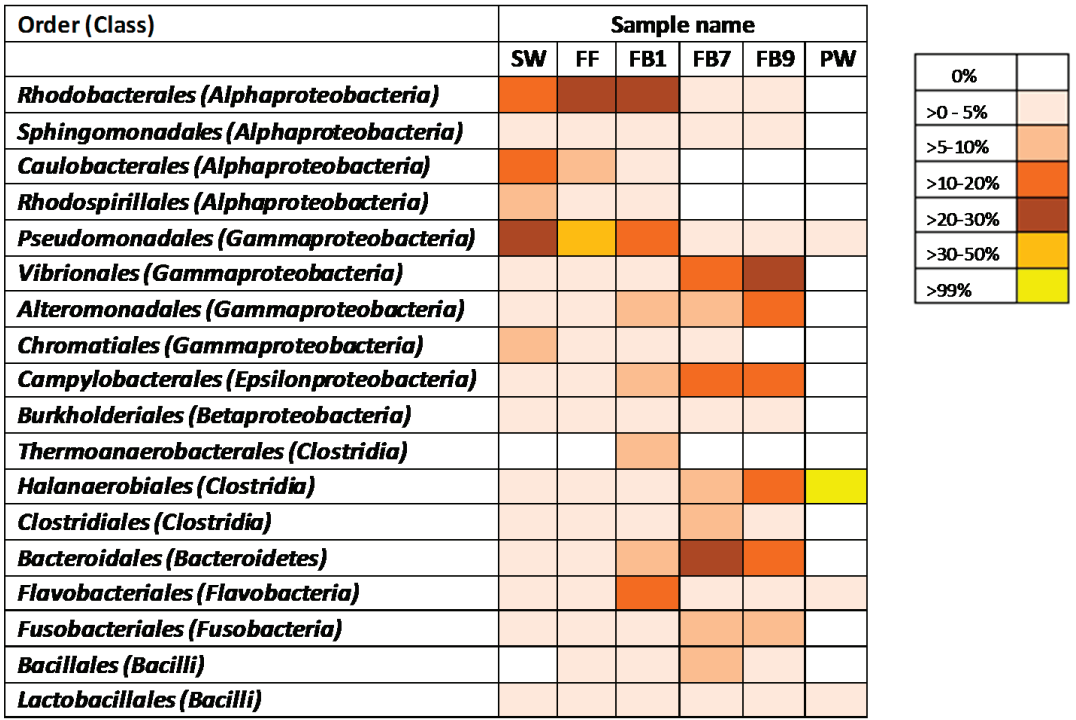

FIGURE 1 Heat map revealing the relative abundance of bacterial taxa in water samples associated with hydraulic fracturing of the Marcellus Shale as revealed by 454 pyrosequencing. FF=fracturing fluid; FB1, 7, 9=flowbackon days 1, 7, 9; PW=produced water on day 187; SW=source water.

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Marcellus and Barnett formations has not been documented. Obtaining representative samples that are assured to be free of bacterial contamination from drilling or sampling is difficult and costly as the source formations are in extremely low permeability rock. Any bacteria that were present when the formation sealed were at temperatures and pressures sufficient to produce natural gas from biosolids—more than 120°C for millions of years. With those temperatures, durations, and limited permeability for nutrient delivery, the rapidly evolving robust microbial communities in wellhead samples are not likely. However, shallow and lower-temperature hydrocarbon-rich formations and those that contain natural fractures (which may serve as pathways for the exchange of fluids, as in the Antrim basin in Michigan) are more likely to have a native community (Martini et al. 1998).

Regardless of the source of organisms at the wellhead, they come in contact with equipment for handling and transporting fluids and eventually are in an impoundment where new geochemistry, impacted by management strategy and the surface environment, drives further changes in these adaptive bacterial communities.

MICROBIAL COMMUNITIES IN IMPOUNDMENTS

Impoundments for storage of flowback and produced water have robust and dynamic microbial communities that correspond to the geochemistry of the impoundment water. Impoundments receive water and bacteria from a variety of sources, including wells, source water, drilling fluids (Struchtemeyer et al. 2011), equipment, and the environment (e.g., rain, dust, animals, runoff). Which species are capable of surviving depends on their ability to adapt to brine concentrations above 100 g/L and to the spatially and temporally dynamic geochemistry that results from environmental processes and human intervention during impoundment management.

The only study of the microbiology in flowback water impoundments finds that such microbial communities stratify with the impoundment chemistry and are impacted by management strategy (Murali Mohan et al. 2013a). The onset of anaerobic conditions in an impoundment may be detected by malodorous compounds from bacterial activity associated with volatile fermentation products and sulfide gas; this aesthetic issue is commonly controlled by the addition of biocides or aeration of the impoundment.

Samples collected at depths ranging from the surface to the bottom of aerated and unaerated impoundments revealed that the geochemistry and microbiology in the aerated impoundment were homogeneous throughout (Figure 2). Moreover, findings show that the microbial community at all depths contained species that were most similar to known aerobes and phototrophs. This follows from the expected vertical mixing of the community between the bottom and surface depths from vigorous aeration. In contrast, the untreated impoundment was geochemically and microbially stratified: bacteria that were most similar to aerobes and

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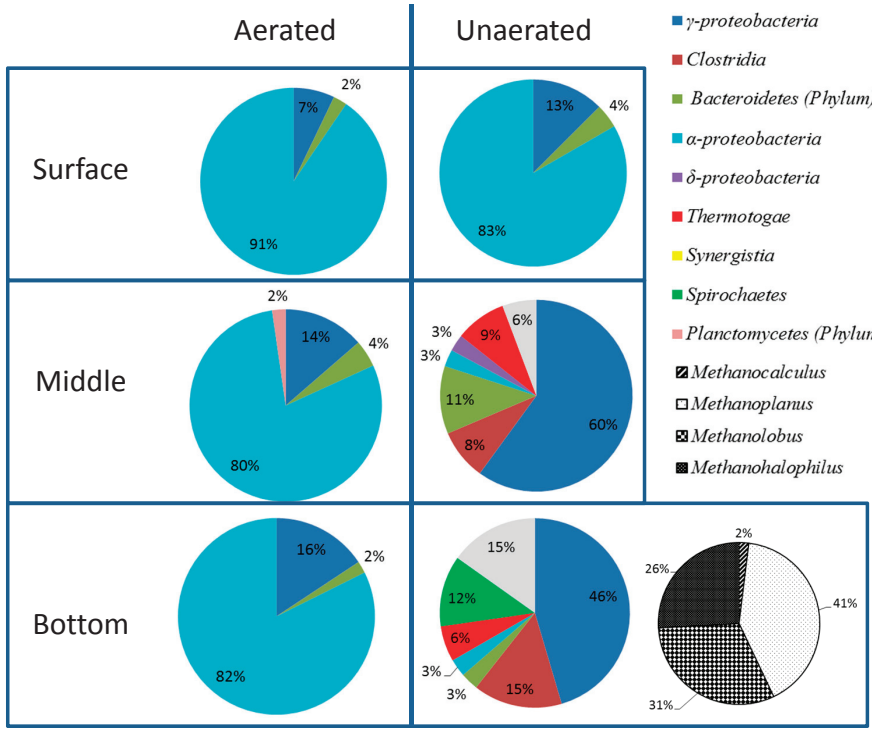

FIGURE 2 Relative abundance of bacterial taxa in flowback water impoundments at various depths. Data generated by clone libraries and subsequent sequencing of 16s rRNA genes recovered from samples. Sequences with similarity to Archaea were recovered only from the bottom of the unaerated impoundment and are shown in black and white. Data adapted from Murali Mohan et al. (2013a).

phototrophs were confined to the surface layer and anaerobes (such as sulfidogenic and methanogenic bacteria) were confined to the anoxic middle and bottom layers. In all samples, regardless of treatment or depth, the species present were most similar to taxa that are known halophiles, showing that the brine conditions of the water are an overarching driver of the ecology.

The study does not reveal the activity of the organisms, but it does suggest that the bacteria in impoundments adapt to the conditions imposed, despite the addition of biocides to the initial fracturing water (Murali Mohan et al. 2013a), as reported from studies of flowback from the Barnett shale as well (Struchtemeyer and Elshahed 2011).

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IMPLICATIONS FOR UNCONVENTIONAL OIL AND GAS PRODUCTION

Research into the microbiology of unconventional oil and gas development is a nascent focus area for engineers and scientists. There are some similarities with conventional petroleum microbiology, but many research questions remain about water management associated with unconventional development. Their answers will affect the practice as well as the economic and environmental sustainability of hydraulic fracturing for oil and gas production.

Most importantly, studies to date indicate that the microbial communities present in wellheads and impoundments appear to be dynamic in time and space, indicating that biocides may not be working or used as intended. Moreover, microbial diversity drops sharply during flowback as it becomes enriched with survivor species. The implication is that recycling of flowback and produced water for subsequent hydraulic fracturing may introduce to new wells deleterious bacteria that are adapted to the harsh environment of the well (and biocides). These bacteria grow quickly, advance the onset of sulfide production, and are more resistant to treatment options.

Studies have also shown the presence and abundance of species that are similar to *Halanaerobium congolense*, a sulfidogen. Sulfide production in wells is associated with human and environmental health risks, corrosion, and costly degradation of product quality. This organism has been identified in produced waters from conventional development, but is of significance here because it cannot reduce sulfate and instead uses thiosulfate and sulfur as electron acceptors for sulfide production. Because standardized tests for assessing sulfidogenic potential in produced water rely on the numbers of sulfate-reducing bacteria, they will yield false negative reports for sulfide production potential, a risk for the industry. New tests that enable assessment of sulfide production from sulfur-reducing bacteria are needed for unconventional wells.

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The Shale Gas Revolution: A Methane-to-Organic Chemicals Renaissance?

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The increasing availability of domestic shale oil and gas has resulted in a return to profitability for the US chemical industry, spurring 148 projects and $100 billion dollars in new capital investment over the next 10 years (ACC 2014).

A significant feature of major US shale gas plays (e.g., Bakken and Eagle Ford) is that they have large relative quantities of condensate or wet natural gas that contain ethane and propane fractions from which ethylene and propylene, the primary olefin feedstocks of the modern organic chemical industry, are derived. Ethylene, increasingly derived in the United States from the steam cracking of ethane (SCE), is the dominant organic chemical in the world, with a world production capacity of 123,000 kilotonnes per year (kta). The United States produces 24,000 kta of ethylene with a 10,000 kta increase in capacity expected over the next 10 years—a nearly 50 percent increase (Devanney 2011).

The US-produced ethane increase since 2007 has lowered the relative price such that ethane is now trading at fuel (methane) value (Figure 1). The net effect is an increase in relative profits for chemical producers after conversion of ethane to ethylene and then to polymers and derivatives. Moreover, the relative pricing of US ethane to global naphtha, which trades at the price of oil, is driving both the US competitive advantage for chemical production investment and the continuing US trend toward cracking a lighter feedstock to produce US ethylene supply. Additional US investment is garnered from announced capital and processes to directly address the decreasing amounts of heavier industry feedstocks such as propylene and C_4 that result from decreased naphtha cracking. The continued viability of these US chemical industry trends is based on the future pricing of ethane relative to other potential fungible feedstocks (such as naphtha) and is a complex function of production and global import/export dynamics.

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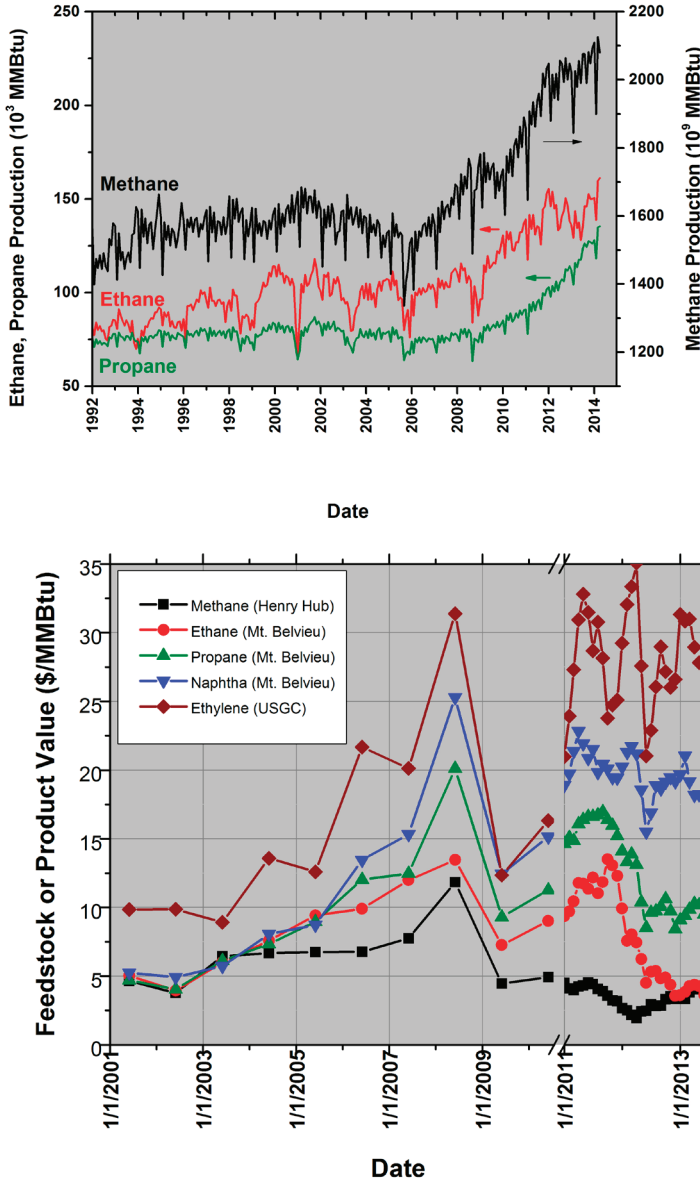

FIGURE 1 (a) Production levels of dry methane to ethane and propane from US gas wells. (b) Value of various potential fuels relative to ethylene on the US Gulf Coast (USGC). Data before the plot break (symbol and line) are plotted as the June average value for that year, whereas data after the plot break are plotted weekly. Data sources: EIA 2014a-d, ICIS Pricing Report 2014a,b.

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The chemical industry upgrades potential fuels such as ethane to ethylene and derivatives. Although wet shale sources rich in ethane are providing this US boom, Figure 1a also shows that the greatest source of natural gas is dry gas, or methane. Most methane is used as a fuel for heating value or for electricity generation (Figure 2, inset). The chemical industry derives some chemical value from methane, in the form of both ammonia and methanol, but mostly it uses methane as a fuel.

Methane has long held unrealized feedstock potential for organic chemical producers because it has typically traded below the cost of many potential feedstocks. The increasing availability of domestic methane will inevitably again raise questions about the viability of producing higher-value ethylene and propylene derivatives from this abundant natural gas resource. But the direct use of methane as a feedstock for derivatives remains an economically tantalizing and elusive challenge. To date, and not for lack of effort, no process that directly uses methane to produce olefins operates economically in the United States. After decades of research, a burning question remains for the chemical industry: Is methane a fuel or feedstock?

ETHYLENE PRODUCTION

The desired use of methane as an organic chemical feedstock unfortunately converges with certain technological and economic realities in how the world produces ethylene. The incumbent technology for ethylene production is the hydrocarbon steam cracker. In the United States this is increasingly becoming the ethane steam cracker, a mature and successful technology that fundamentally consists of two parts: a reaction plant and a separation plant (Cesar 2003; Sundaram et al. 2000; van Goethem 2006; Zimmermann and Walzl 2000).

The reaction plant is a natural gas (methane)–fired furnace in which steam and ethane react inside high-alloy metal tubes at residence times of less than 1 second to produce a mixture of unreacted ethane, ethylene, propane, propylene, hydrogen, methane, and a small amount of heavier hydrocarbons. This cracked gas mixture is water-quenched and treated to remove impurities such as CO_2 and H_2S as well as alkynes (e.g., acetylene), which are hydrogenated before downstream separations. The separation plant uses high-pressure steam generated during energy cross exchange from the cracker furnace effluent to drive compression turbines, liquefying the cracking products for separation by a series of cryogenic distillations of component pairs (olefin-paraffin) that have very similar relative volatilities.

The steam cracker is thus akin to a small power generation plant where fuel (methane) is used to generate electricity (ethylene). This technology is practiced at tremendous scales in a single plant, with single train capacities approaching 1,500 kta of ethylene, or around 175,000 kilograms of olefins processed every hour. The size of these complexes is growing as ethylene producers seek to capitalize on SCE production scaling laws that are less than unity, extracting maximum profitability for capital invested.

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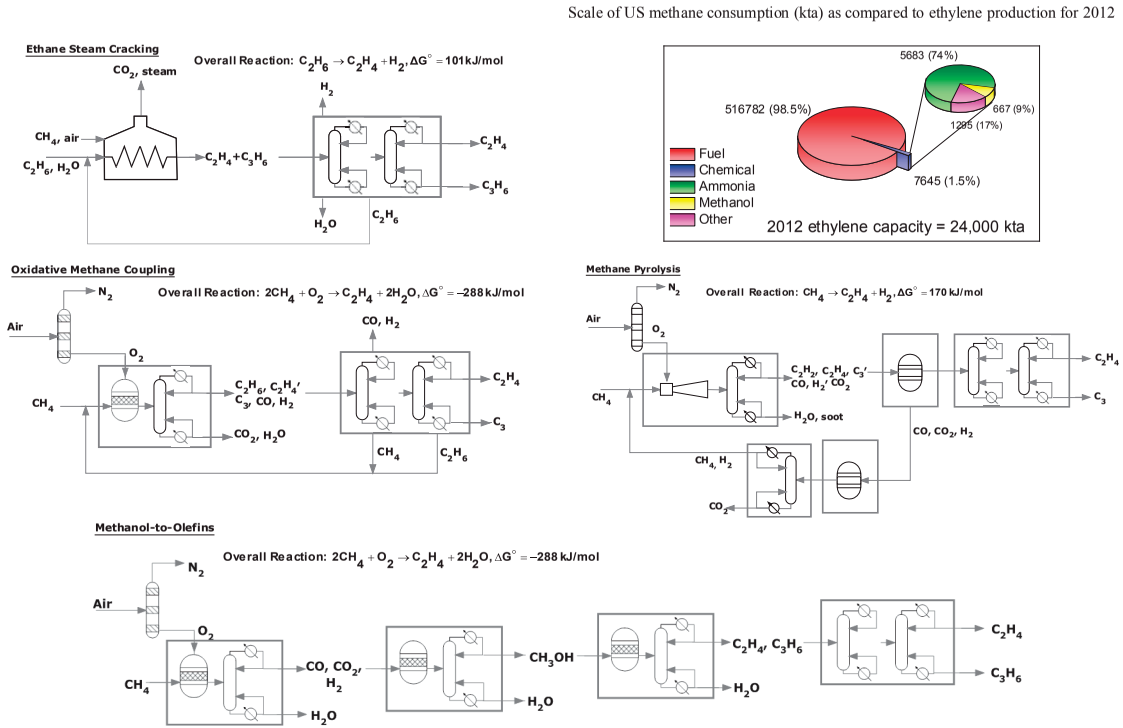

FIGURE 2 Simplified flow sheets showing an ethane steam cracker and some known processes that could produce ethylene from methane resources. Inset pie charts give additional information on the size of methane-to-chemical streams as compared to the fuels market. Labeled major reactor and separation process sections, when considering capital expenditure, are grouped into boxes, without implied meaning as to the actual complexity or real number of units in each section. Source inset data: Devanney 2013.

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The use of methane as a feedstock for ethylene, or the displacement of any part of conventional technology, will require market risk that will be justifiable only if the capital and variable cost intensity of any conceived methane process is significantly lower than conventional technology. If there is no feedstock variable cost advantage, as is now the case with methane and ethane trading at parity, then any US-built methane-to-ethylene process, with or without required oxidants, will likely require a huge capital reduction relative to the SCE process for legitimate attention (Lange 2005).

METHANE-TO-ETHYLENE

The chemical industry makes a significant amount of non-polymeric chemicals from methane, including refinery hydrogen, ammonia, methanol, and liquids (fuels) via Fischer-Tropsch synthesis. These chemicals share a common derivation from synthesis gas (CO, H_2) that is readily made from the partial oxidation of methane. Methane-to-ethylene routes have been envisioned and investigated at varied scale, but they have been historically disadvantaged by fixed capital and/or variable costs in geographies with direct access to sufficient ethane.

The utilization of a methane derivative, methanol, to produce olefins via the methanol-to-olefins (MTO) process is taking root in ethane-poor China, where regionally advantaged cheap and abundant coal resources outweigh the increased process complexity of MTO relative to SCE. MTO also has an advantage in potential methane-to-ethylene processes because its methanol feedstock is a world-fungible commodity that can be decoupled from olefin synthesis, reducing risk to producers interested only in olefins and derivatives. The technology, in effect, cheats the direct methane-to-ethylene challenge by first forming in succession the metastable products synthesis gas and methanol. The need for increased capital for MTO relative to SCE is one penalty for the cheating.

In contrast to MTO, direct methane conversion technologies, such as oxidative coupling of methane (OCM) or methane pyrolysis (MP), suffer from product selectivity losses as the conversion increases. Process flow sheets for these processes are shown in Figure 2. In OCM, the product ethane has C-H bonds more reactive to oxygen than those of methane, decreasing useful selectivity as conversion is increased to economic levels. The resulting CO_2 must be rejected as lost carbon. In MP, the high temperatures necessary to overcome the free-energy hurdle in reaction are favorable for carbon-carbon bond scission, resulting in the formation of soot instead of the desired acetylene, ethylene, and H_2. Selectivity loss can be partially overcome with unique burner design, using substoichiometric amounts of oxygen to provide enthalpy while preserving more carbon product, but significant CO_2 rejection is unavoidable. Despite these challenges, both OCM and MP are possible at large scale.

With generic polyethylene trading at an equivalent of $42/MMBtu (ICIS Pricing Report 2014c)—more than 8 times the value of methane—why is SCE still

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the preferred method for the manufacture of ethylene in most geographies? The most important answer to this question is evident from Figure 3 when considering relative capital intensity (shown in the size of the circles). Even after considering that methane is required to fuel the furnaces responsible for the endothermic ethane-to-ethylene chemistry, the steam cracker and its separation train have been remarkably energy integrated over the technology lifetime, resulting in an ethane use efficiency of greater than 85 percent and a total carbon efficiency (methane + ethane) from the plant of nearly 60 percent. Favorable SCE capacity-scaling laws per unit product give the SCE complex a total fixed capital and variable cost advantages relative to MTO, OCM, and MP in world geographies with access to cheap methane and ethane. Processes with higher capital costs for equivalently sized methane-to-ethylene plants cannot economically compete at the current valuation of ethylene derivatives in the marketplace.

Notwithstanding the success of SCE, Figure 3 also suggests that the most significant potential liability of SCE in a carbon-tax world is its overall thermodynamic efficiency of less than 20 percent—significantly less than the 50–60 percent efficiency at which combined-cycle power plants can generate electricity from natural gas. The equivalent retail value of electricity ($29/MMBtu) (EIA 2014b) relative to generic polyethylene ($42/MMBtu) shows the value society places on ethylene derivatives. Chemical producers are willing, and able, to trade lower energy efficiency, and higher greenhouse gas emissions (primarily CO_2), to deliver this product to market.

For chemical industry engineers, efforts to increase the sustainability of chemicals and chemical processes are at the forefront of many modern challenges. In the chemical industry one could define sustainability as the selection of chemical feedstocks to ensure that derived chemical processes are the most efficient from both 1st and 2nd thermodynamic law perspectives as well as from other socioeconomic factors such as the ultimate cost of those products (Banholzer and Jones 2013; IEA 2013). For most historic and US Gulf Coast chemical production, what SCE lacks in energy efficiency is compensated for by the lower risk of return on borrowed capital for plant construction and depreciation.

Figure 3, however, does provide an answer to the question: Is methane fuel or feedstock? There is obvious value in methane as a sustainable feedstock, not just a fuel. Both MTO and OCM have the potential to be more thermodynamically and carbon efficient than SCE, whereas envisioned methane pyrolysis processes fall short. The overall reactions for SCE and MP are strongly endothermic, and methane must be burned to provide energy for these plants, whereas the overall exothermic reactions for MTO, and particularly OCM, take advantage of the naturally higher energy density of methane itself to drive the relevant reactions in one vessel, albeit with the help of an oxidant. At the current valuation of ethylene relative to methane fuel, the choice of oxidants appears limited to oxygen (Lange 2005).

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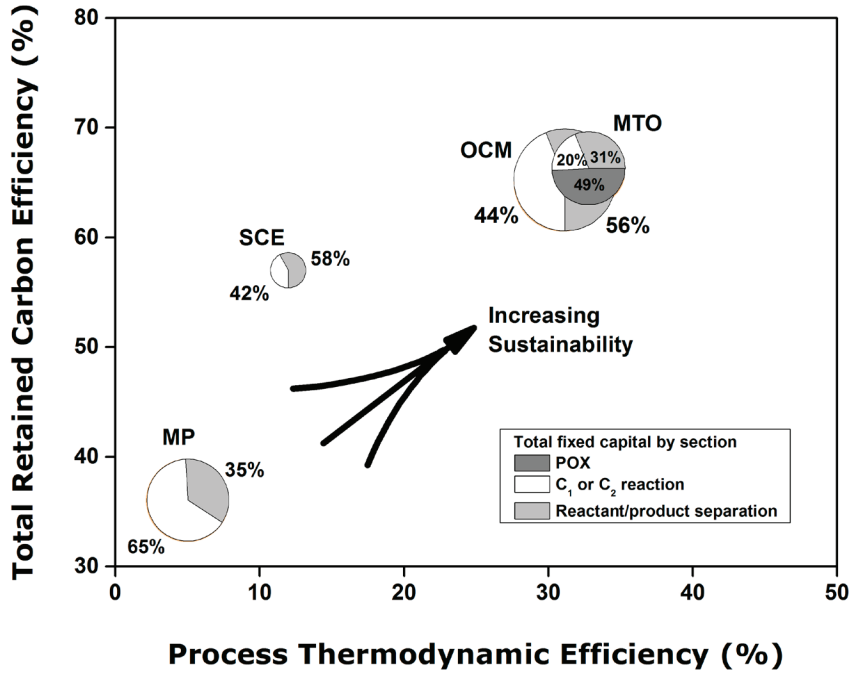

FIGURE 3 Comparison of methane-to-ethylene processes relative to ethane steam cracking (SCE) in terms of total carbon efficiency (including methane fuel usage) and 2nd law thermodynamic process efficiency. Process thermodynamic efficiency was calculated by using the ratio of the estimated process Gibbs free energy change relative to the change for primary methane reaction and separation of pure reactants and products at 298 K. The size of each pie is proportional to the total fixed capital for each process. The pie is divided by the percentage of fixed capital in the partial oxidation (POX), C_1 or C_2 reaction, and separation sections. Economics and thermodynamics have been derived from the relevant SRI or Nexant process economic reports, scaled to 1,000 kta (kilotonnes per year) olefin capacity. For the methanol-to-olefins (MTO) case, the scaling basis was 66–33% ethylene and propylene mix at 1,000 kta and for oxidative coupling of methane (OCM) it was 86–14% ethylene and propylene mix at 1,000 kta. In all processes, steam was rejected at 413 K for thermodynamic analysis. MP=methane pyrolysis; SCE=steam cracking of ethane. Data sources: Cesar (2003); IHS (1994); Nexant (2009); Wan (2007).

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ENGINEERING CHALLENGES FOR SUSTAINABLE METHANE-TO-ETHYLENE

What challenges, if solved, would allow for increased monetization of US natural methane resources to higher derivatives? First, overall methane-to-ethylene capital must be reduced. The reasons for the higher cost are evident in the tradeoffs for each chemistry: the multiple world-scale unit complexity of MTO, the low per-pass methane conversion with large CO_2-scrubbing units of OCM, and the multiple reactor capital units in MP of pyrolysis, acetylene hydrogenation, and CO_x hydrogenation needed to boost carbon selectivity. However, all of these processes share a common thread with SCE. The capital distributions shown in Figure 3 suggest that nearly 50 percent of the total fixed capital resources are tied to the separation and purification of ethylene, not the reaction step. While reaction section capital improvements in the form of catalysts or novel reactor design may reduce reaction capital, one cannot significantly reduce overall methane-to-ethylene capital without holistically addressing both the reaction and separation section.

The primary method of ethylene purification in all cases is cryogenic distillation. The low relative volatility difference between olefin and paraffin, and inherent low boiling point of C_1 and C_2 hydrocarbons, make compression and distillation a significant cost contributor to any methane-ethane conversion process that does not have 100 percent olefin selectivity. The ability of distillation to scale relatively economically, despite its high energy requirement for separation, makes it the industry separation method of choice (Neelis et al. 2008).

Replacement of distillation by lower capital and energy use options is the second challenge. The incumbency of distillation for ethylene production demonstrates the technical and economic deficiencies of potentially less energy-intensive technologies employing mass-separating agents or membranes to perform the needed separations at scale. Figure 4 makes clear that heat transfer loss and separations require the majority of energy for these processes. It is also well known that capital intensity scales with increasing needs of heat transfer duties (Lange 2001). In addition, Figure 4 shows that, on a relative basis, the operators and innovators of SCE processes have made energy integration a priority, and the energy use of SCE is low relative to alternatives despite the fact that 80 percent of the heat generated in the SCE process must be used for heat transfer and separation even after discounting for reaction enthalpy. This SCE efficiency complicates the replacement challenge.

CONCLUSION

Significant reinvestment in the US chemical industry has resulted from the influx of shale gas ethane into the marketplace. Industry is currently employing mature steam cracking technology to increase production of polyethylene to

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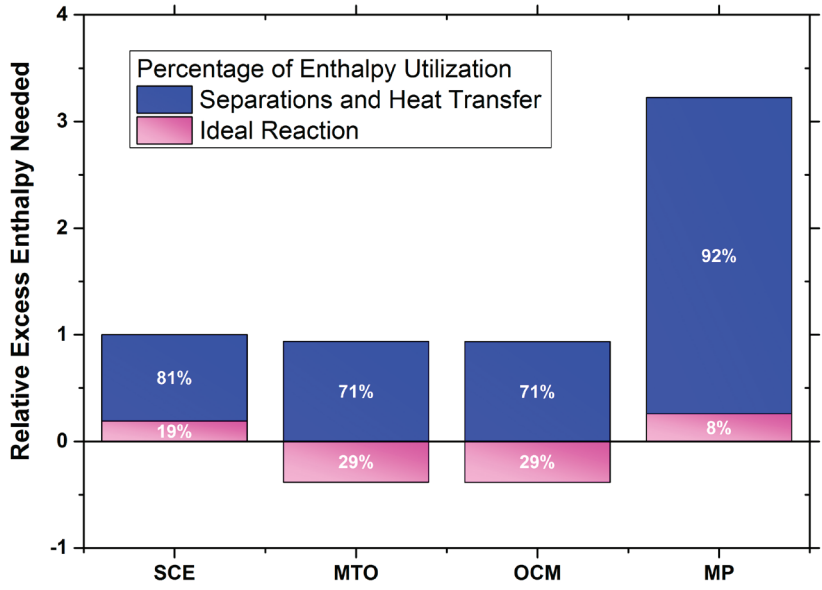

FIGURE 4 Relative energy use for the separations and reaction sections of methane-to-ethylene processes as compared to steam cracking of ethane (SCE), which is set at a value of 1 for this plot. Typical SCE energy use for this analysis was 14,440 Btu/lb ethylene. A positive excess enthalpy value represents specific heat needed in addition to any that can be recovered from any primary exothermic chemistry (a negative relative value) in the cases of oxidative coupling of methane (OCM) and methanol-to-olefins (MTO). MP=methane pyrolysis. Data sources: Cesar (2003); HIS (1994); Nexant (2009); Wan (2007).

monetize these resources. The unavoidable larger fraction of concomitant methane that accompanies shale gas liquids once again raises old questions regarding the economic viability of methane-to-ethylene transformation processes relative to methane's use solely as a fuel. Despite potential thermodynamic advantages for use of methane as a polyolefin source, all known methane-to-ethylene processes suffer from significantly higher capital intensities relative to incumbent steam cracking technology, discouraging domestic adoption. Solutions to the elusive challenge of a methane-to-ethylene process will require innovations from practitioners in multiple disciplines: chemists and chemical engineers for design of new catalysts and integrated chemical processes, materials engineers for development of new separation materials, computer and information engineers for new ways to control complex chemical processes, and executive entrepreneurs who are willing to be the first to take on the risk.

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APPENDIXES

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and regenerative medicine applications. Projects include materials for in vitro differentiation of stem cells to injectable biomaterials for tissue repair. Her lab has a strong translational focus with the main goal of developing novel minimally invasive therapies for cardiovascular disease.

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Brian Gerkey is the chief executive officer of Open Source Robotics Foundation. He builds open source software tools and libraries that enable robotics research, education, and application development. To enhance and support this software, he establishes and fosters open source developer and user communities.

Kelvin Gregory is an associate professor of civil and environmental engineering at Carnegie Mellon University. His research interests include microbiology and biotechnology, benthic and microbial fuel-cells for remote and decentralized power generation, environmental biogeochemistry, electrode-based remediation of contaminated subsurfaces, bacteriology and microbial ecology of engineered systems, and sustainable and appropriate technology in developing communities.

Dennis Hong is a professor of mechanical and aerospace engineering at the University of California, Los Angeles where his research is in robot locomotion and manipulation, autonomous vehicles, and humanoid robots.

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Christopher Jones is the associate vice president for research and New-Vision Professor in the School of Chemical and Biomolecular Engineering at Georgia Institute of Technology where his research is in the broad areas of materials design and synthesis, catalysis, and adsorption. Specific emphases are placed on design and understanding of molecular catalysts and catalytic materials for energy applications, fine chemical and pharmaceutical applications, and on adsorbents for CO_2 capture.

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Carmel Majidi is an assistant professor of mechanical engineering at Carnegie Mellon University. His interests are in multifunctional materials, soft-matter electronics, and soft machines for assistive wearable technologies and biologically inspired robotics.

Arunava Majumdar is the Jay Precourt Professor and Senior Fellow, Precourt Institute for Energy, at Stanford University. His research includes the science and engineering of nanoscale materials and devices as well as large engineered systems. He is an elected member of the National Academy of Engineering.

Alvaro Masias is a research engineer in energy storage research and strategy at the Ford Motor Company. His primary research is in batteries for transportation, focusing on safety, testing, and materials.

Shirley Meng is an associate professor of nanoengineering at the University of California, San Diego. Her work focuses on the field of energy storage and conversion materials: nano-structured electrodes for advanced rechargeable batteries, dye-sensitized solar cells and thermoelectric conversion; charge ordering, structure stability, processing structure-property performance relations in functional ceramics; and combining first principles computation with high-skill experiments for rational materials design and optimization for energy applications.

W. David Merryman is an assistant professor of biomedical engineering at Vanderbilt University. His research is focused on cardiovascular mechanobiology with emphasis on cellular response and functional changes to altered mechanical stimuli and various biochemical agents. Areas of expertise include cellular and soft tissue biomechanics, in-vitro bioreactor environments for tissue engineering, and mechanistic studies of cytokine activity and mechanical stimuli. The primary goals of his lab are to elucidate the mechanisms leading to multiple cardiovascular diseases and develop nonsurgical strategies to prevent and treat them, with particular focus on heart valves.

Tina Morrison is a regulatory advisor on computational modeling in the Office of Device Evaluation at the Food and Drug Administration. Her work advances regulatory science through modeling and simulation because she believes the future of medical device design and evaluation, and thus patient care, lies with computation and enhanced visualization.

Allison Okamura is an associate professor of mechanical engineering at Stanford University. The objective of her research is to develop the principles and tools needed to realize advanced robotic and human-machine systems capable of haptic (touch) interaction. Her interests include teleoperation, virtual environments and

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simulators, medical robotics, neuromechanics and rehabilitation, prosthetics, and engineering education.

Sonna Patel-Raman is a senior consultant at Halloran Consulting Group, Inc. Her focus is on US and global clinical and regulatory strategies for the life sciences industry. Her expertise is in cardiovascular clinical trial design, pre-clinical bench testing, human factors, informed consent and patient rights, and risk analysis/failure modes and effects analysis. She also has experience with a variety of medical devices and drugs used in the respiratory and gastrointestinal system, plastic and reconstruction surgery, and orthopedic surgery.

Ashley Peterson is a principal research and development engineer in the Aortic and Peripheral Vascular Group at Medtronic. His focus is on combining computational and experimental methods in fluid and structural mechanics. He has overall technical responsibility for computational fluid dynamics and structural finite element simulations and hemodynamic testing of stent grafts. Previous research concentrated on the creation of high efficiency energy generation devices and multi-physics turbomachinery design.

Jeff Sakamoto is an associate professor of mechanical engineering at the University of Michigan where he studies solution-based synthesis of porous materials. The ability to order interconnected porosity at multiple length scales provides a modular experimental platform enabling investigations into the interplay between micro-meso-macro pore morphology and mass/charge transport for energy storage and biomedicine.

Erin Spinner is a biomedical research engineer in the Advanced Technologies Department of Edwards Lifesciences. Her focus is on translational research and heart valve device development from design ideas to first-in-man trials. She believes better understanding of the native anatomy and physiology is critical to applying engineering principles to innovative device development. This is aided through non-invasive imaging techniques and in vitro testing.

Eric Stangland is a principal research scientist at The Dow Chemical Company within the Core R&D division. His research interests include heterogeneous catalyst material and process development, porous material characterization, and rate- and equilibrium-based adsorbent material design.

Daniel Steingart is an assistant professor of mechanical and aerospace engineering at Princeton University. His interests are in the formation, degradation, and maintenance of cyclical and long-term structures created through electrochemical processes. These include products created through primary metal production facilities, electrochemical energy storage devices, and corrosion/passivation products.

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Sarah Stewart is a senior research engineer for the Research and Technology Center at Robert Bosch LLC where her work is in developing next-generation batteries for use in vehicle applications. Currently, she is developing physics-based models to predict the behavior of batteries. These models can be used as tools to design batteries for optimal performance, as well as to control the use of the batteries in order to minimize degradation and performance limitations.

Chris Urmson leads the Self-Driving Car Project at Google. He leads a team focused on addressing the technical, regulatory, and social challenges necessary to field a commercially viable self-driving vehicle.

Matthew Williamson is the director of technology at Rethink Robotics. He leads a group developing technologies for a low-cost collaborative robot used in manufacturing.

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Program

NATIONAL ACADEMY OF ENGINEERING

2014 US Frontiers of Engineering Symposium
September 11–13, 2014

Chair: Kristi Anseth, University of Colorado, Boulder

CO-ROBOTICS

Organizers: Brian Gerkey, Open Source Robotics Foundation, and Carmel Majidi, Carnegie Mellon University

Progress in Self-Driving Vehicles
Chris Urmson, Google

Safe, Cheap, and Smart: Collaborative Robots in Manufacturing
Matthew Williamson, Rethink Robotics

Personalized Medical Robots
Allison Okamura, Stanford University

Biologically Inspired Mobile Robots
Dennis Hong, University of California, Los Angeles

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BATTERY ANXIETY

Organizers: Jeff Sakamoto, University of Michigan, and
Daniel Steingart, Princeton University

Electrochemical Prozac:
Relieving Battery Anxiety through Life and Safety Research
Alvaro Masias, Ford Motor Company

Challenges in Batteries for Electric Vehicles
Sarah Stewart, Robert Bosch LLC

Lithium Ion Batteries and Their Manufacturing Challenges
Claus Daniel, Oak Ridge National Laboratory

Materials Design and Diagnosis for Rechargeable Battery Energy Storage
Shirley Meng, University of California, San Diego

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TECHNOLOGIES FOR THE HEART

Organizers: Karen Christman, University of California, San Diego, and
Ashley Peterson, Medtronic

The History of Heart Valves: An Industry Perspective
Erin Spinner, Edwards Lifesciences

Engineering Heart Valve Treatment Strategies for Tomorrow
W. David Merryman, Vanderbilt University

Biomaterials for Treating Myocardial Infarctions
Jason Burdick, University of Pennsylvania

Regulatory Perspectives on Technologies for the Heart
Sonna Patel-Raman, Halloran Consulting Group, Inc.

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SHALE GAS AND OIL

Organizers: Billy Bardin, The Dow Chemical Company, and Christopher Jones, Georgia Institute of Technology

Shale Natural Resources
Stephen Ingram, Halliburton

Microbial Ecology of Hydraulic Fracturing: Implications for Sustainable Resource Development
Kelvin Gregory, Carnegie Mellon University

The Shale Gas Revolution: A Methane-to-Organic Chemicals Renaissance?
Eric Stangland, The Dow Chemical Company

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DINNER SPEECH

What Is Impact?
Arunava Majumdar, Stanford University

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