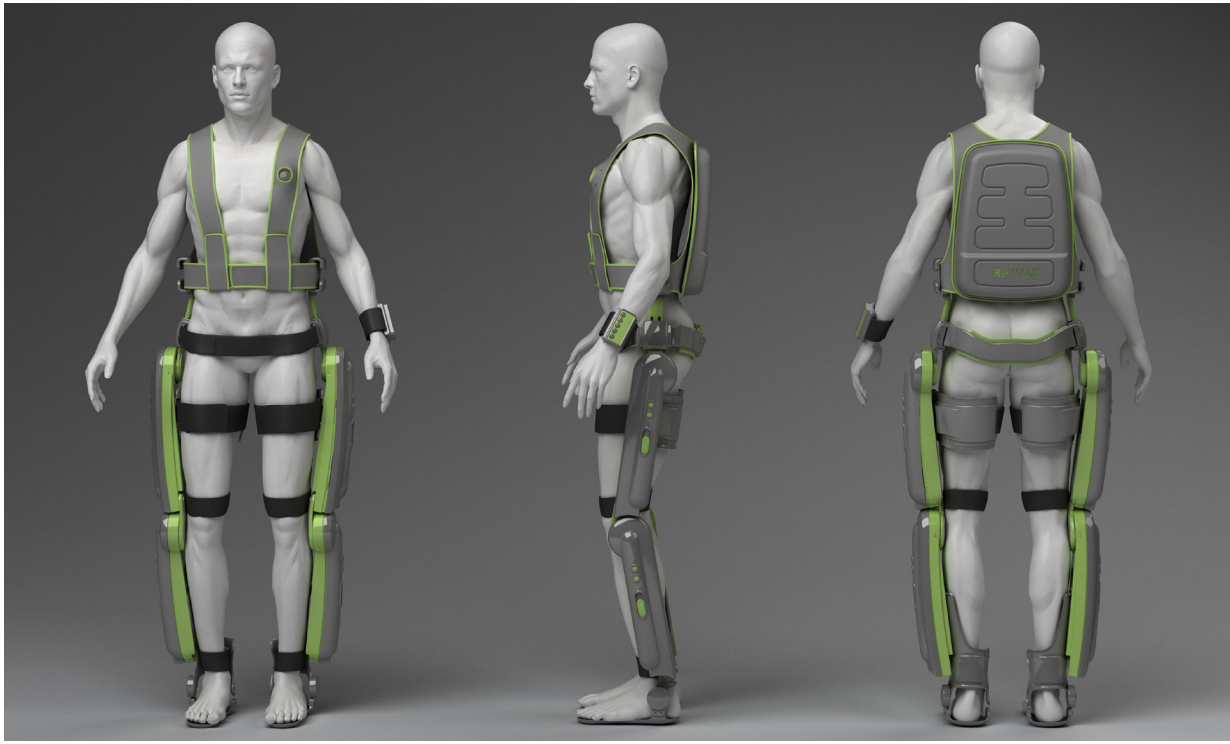
A CLOSER LOOK AT PERSONALIZED HEALTH

IMPROVE HEALTHCARE AND THE PATIENT EXPERIENCE WITH UNIFIED 3D DESIGN, SIMULATION AND ADDITIVE MANUFACTURING TECHNOLOGIES

Healthcare is changing. That's never a surprise. The need to improve treatments, save lives, and blunt the impact of disease drives a tremendous commitment of intellectual and material capital to advance medical knowledge and capabilities. At the same time, the emergence and maturation of new technologies empowers researchers, practitioners, medical device developers, and others to explore and pursue an expanding range of possibilities, and to drive innovations that would have seemed impossible only a few short years ago.

Perhaps the most significant change has been surrounding medical care—particularly, challenging the idea that treatments must necessarily be generalized to serve broad numbers of patients. While historically, medical research has necessarily been focused primarily upon "macro" solutions to large-scale problems—such as the development of antibiotics to combat communicable disease—there is a growing understanding that highly specialized "micro" solutions are possible, practical, and desirable. Researchers and practitioners are increasingly working to develop treatments and solutions keyed to the needs of certain types of populations and, in some cases, individual patients, with the goals of optimizing treatment efficiency and improving treatment outcomes while containing costs.

Researchers are now developing treatments keyed to the needs of individual patients, showing that highly specialized healthcare solutions are now possible, practical, and desirable.



A convergence of diverse circumstances is driving these changes—and making them possible. Throughout the developed world, there is an increasing emphasis on proactive, patient-centered therapy, with the quality of the patient experience and improved treatment outcomes deemed to be of greatest importance. At the same time, the business climate has enabled a new generation of agile, venture-funded startup firms to pursue development of innovative and highly specialized medical treatments, devices, and products. Perhaps most significantly, new technology—often drawn from realms outside of traditional medical practice—is making pursuit of these innovations possible, practical, and affordable.

3D design, simulation, and additive manufacturing technologies are central to these developments. Traditionally employed in sectors such as aerospace, defense, and consumer products, these technologies are now being employed directly and indirectly to repair and restore the most complex machine of all: the human body. In so doing, they are unlocking new possibilities within life sciences, and creating the potential for a new era of patient-centric medical practice and treatments. Innovations made possible through 3D technologies are already generating powerful results across a wide spectrum of medical specialties, resulting in improved health and quality of life.

THE ERA OF MULTI-DIMENSIONAL THERAPY

In the quest to cure or compensate for the effects of injury, aging and disease, doctors and scientists continually struggle to push past the limitations of knowledge and tools available to them. The emergence of 3D design and simulation technologies as a viable tool for researchers and clinicians empowers these professionals to adopt a new approach to their work. As a consequence, this generates a new, multi-dimensional approach to treatment. The expanded range of design, testing, simulation, and additive manufacturing capabilities these technologies make possible, along with the gains in speed and efficiency in executing them, helps to bring a tantalizing new possibility within reach: the prospect of truly personalized care, devices, and treatments.

THE PROJECTED ANNUAL COST OF CANCER CARE IS ESTIMATED TO RISE TO

$157

BILLION IN 2020

STAT SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE/NATIONAL INSTITUTES OF HEALTH

HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC3107566/

There is more acceptance than ever before that personalized care is desirable and necessary – and an expanding recognition that technology is making it possible. There is a growing body of evidence emerging from across a spectrum of life sciences and health care specialties that 3D design, simulation, and additive manufacturing technologies are having a transformative effect upon patient care and treatment outcomes. Cardiology, oncology, orthopedics, audiology, prosthetics, dentistry – all are undergoing rapid transformation as a result of these technologies' influence.

The following sections will explore an array of new personalized therapies, devices, and treatments with the power to transform the quality of care and improve the patient experience. These include:

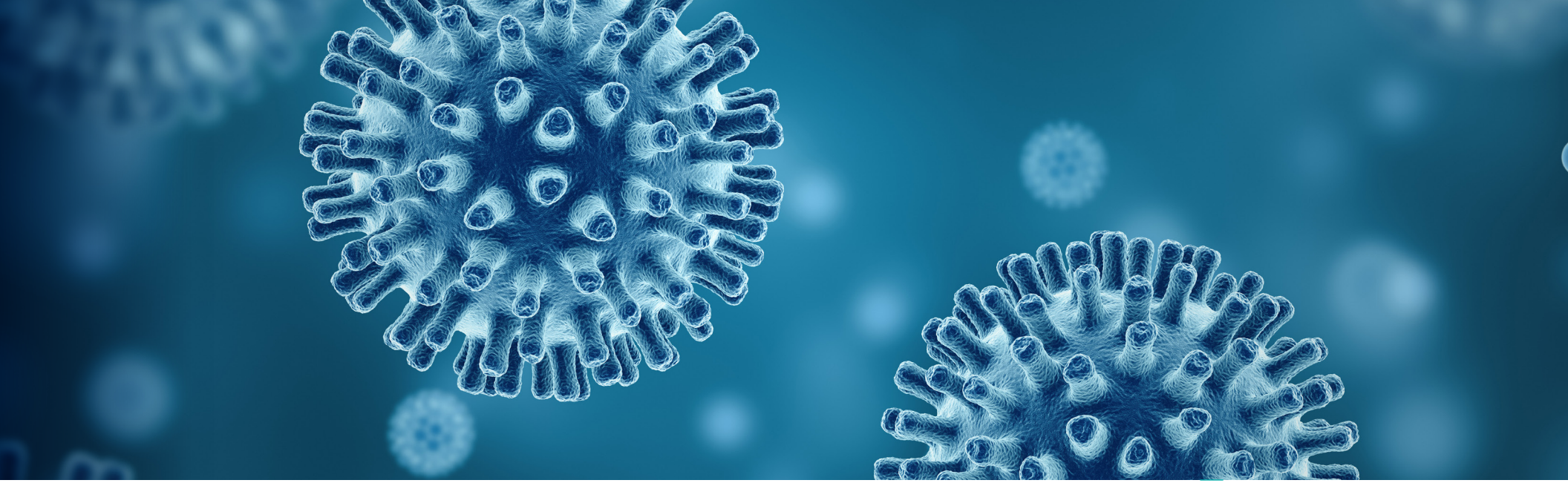
- **Individualized Cancer Care** – 3D design, simulation, and additive manufacturing technologies are changing the face of cancer care by optimizing both internal and external radiotherapy treatment regiments for individual patients
- **Accelerated Innovation** – New 3D technologies facilitate efficient and effective collaboration, enabling the rapid development of new devices and treatments
- **Sharing Learning and Knowledge** – Unified design, simulation, and analysis platforms foster closer working relationships between researchers, medical practitioners, device manufacturers, enabling development of a new generation of diagnostic and learning tools
- **Engineering the Invisible** – Advanced simulation technologies enable users to model chemical behaviors and outcomes at the atomistic level to develop new pharmaceutical therapies

Companies are utilizing 3D design, simulation, and additive manufacturing technologies to individualize personal healthcare. Explore the ways throughout the ***Designing Personalized Healthcare ebook.***

DESIGNING FOR ONE

HOW 3D DESIGN, SIMULATION, AND ADDITIVE MANUFACTURING TECHNOLOGIES MAKE INDIVIDUALIZED CANCER CARE A REALITY

CHAPTER 1



A charged particle is a powerful thing. These infinitesimal objects, properly directed, have the ability to hold some of humanity's most feared diseases in check, or eradicate them altogether from the body. Applied indiscriminately, they can destroy healthy tissue, cause countless side effects, and have the potential to permanently compromise the health of the patient. The success or failure of radiation therapy in treating cancer depends upon the physician's ability to strike a careful balance: Just enough radiation, in just the right place, at just the right time to optimize effectiveness without compromising the health of adjacent areas of the patient's body.

No two human beings are the same. Neither are any two cases of cancer. Historically, however, it hasn't been possible to apply a radiation treatment regimen matched perfectly to an individual patient. For optimal results, treatment would need to not only be perfectly matched to each patient's external physical body, but to each patient's tumor—typically within the body, and invisible to the eye. X-rays, CT scans and MRI scans can provide doctors with general guidance as to where to direct beams and where to apply shields to protect healthy tissue, but absolute precision seemed impossible.

Enter a company called .decimal. .decimal's management, scientists and engineers felt that there had to be a better way to direct, control, and contain the power of protons, photons, and electrons—and that by leveraging integrated 3D design and CAM technology, they could provide it.

THE NUMBER OF CANCER SURVIVORS WILL RISE TO

18.1

MILLION IN 2020, UP BY

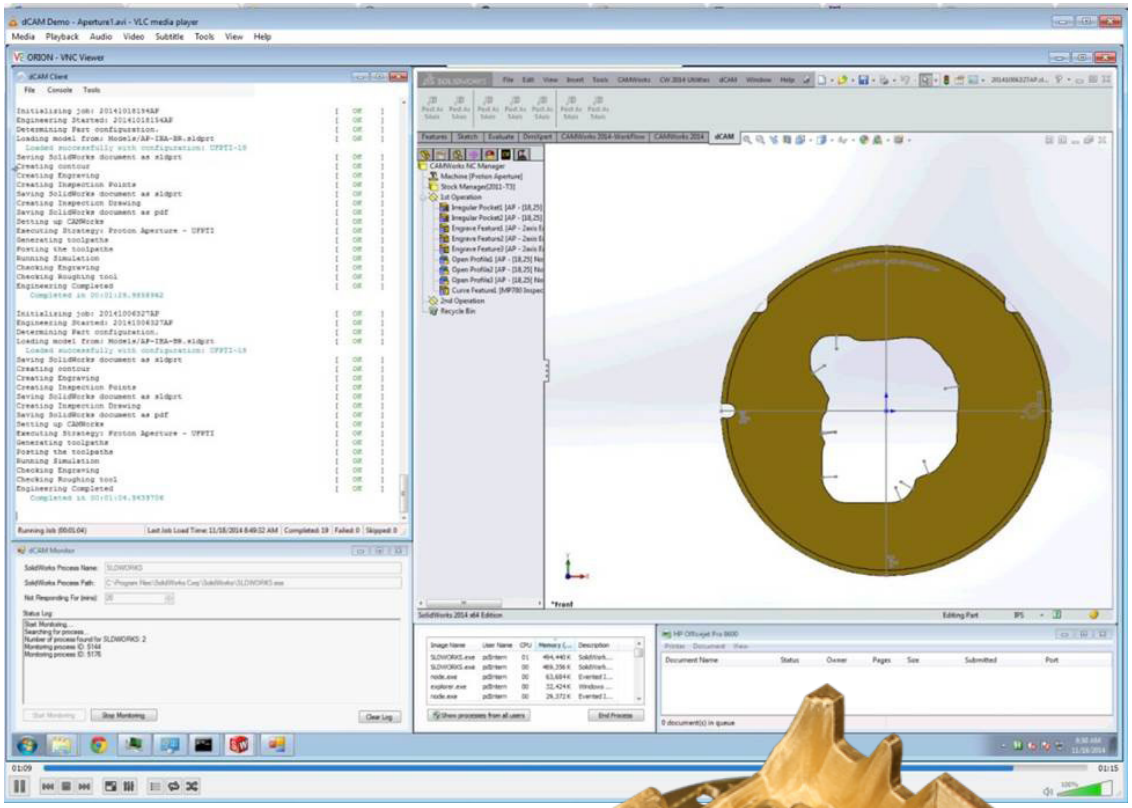
30%

OVER 2010

STAT SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE/NIH

HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC3107566/

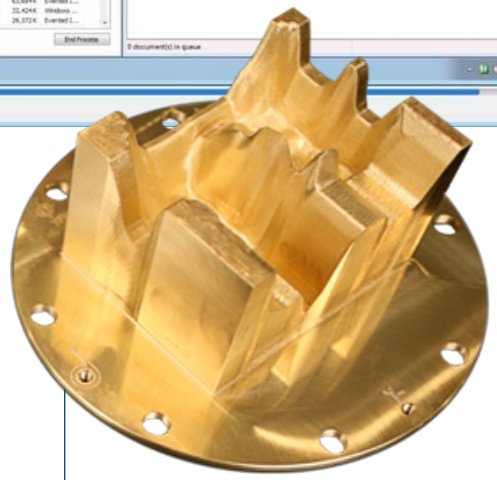
.decimal dedicated itself to designing, manufacturing, and delivering one-of-a-kind, patient-specific devices for cancer treatment. .decimal defined a process in which CT scan data provided by the hospital could be imported into 3D design software in order to develop fully customized devices precisely tailored to the individual patient, the specific area of the body to be treated, and specific radiation type to be used. The device types vary depending on the treatment described—a form-fitting bolus, applied directly to the patient, serves to direct rays to the treatment area while shielding healthy tissue; a custom-cut brass aperture, used on the radiation device, guides rays to match the specific shape of a patient's tumor; an acrylic range compensator controls the depth that treatment rays penetrate into the body.



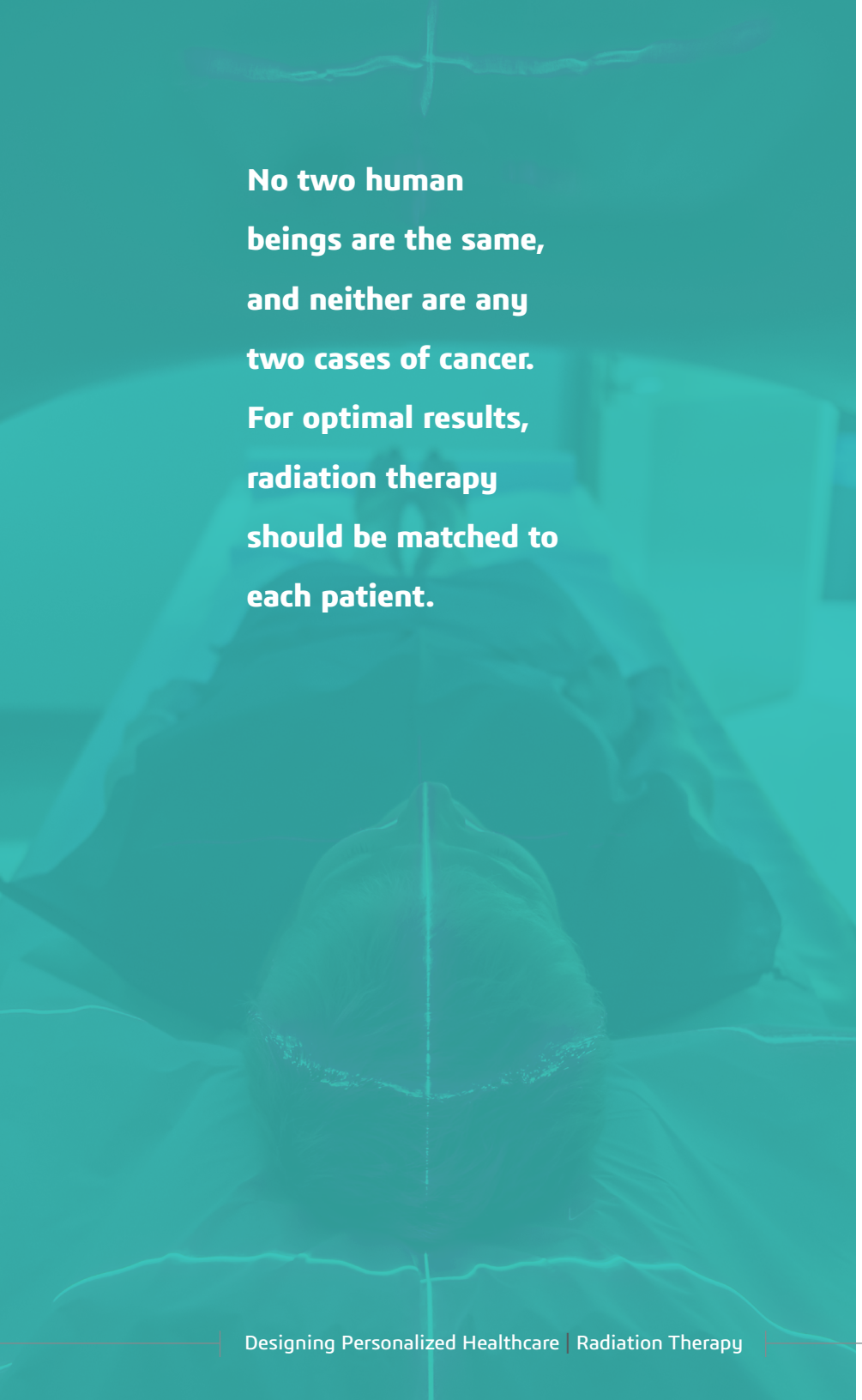
Once the design phase is complete, data is seamlessly ported into the application's integrated CAM functionality, generating tool paths for use in an almost fully-automated manufacturing process: Computer-controlled laser cutters, milling machines, molding machines, and 3D printers go to work to fabricate these precision components to exacting specifications, whereupon they are shipped to the hospital and the treatment is applied.

From the time an order is placed and CT scan data is supplied, the entire process to design, fabricate, and ship the completed devices consumes not days or weeks, but hours. According to the company, orders placed by noon typically ship the same day. It's a far cry from the labor-intensive, time-consuming standard process—manually measuring, making molds, and fabricating devices by hand. For physicians, patients, and hospitals alike, it makes a big difference: Treatments are provided sooner, and more precisely; damage to healthy tissue is minimized.

The efficient, highly automated device fabrication process provides care facilities with an additional important benefit: greatly heightened efficiency. By dispensing with the need to hand-fabricate treatment devices on site—and with the associated expenditure of time and resources—hospitals are able to provide treatment to more patients. One facility using .decimal's services schedules 114 patients for therapy on a daily basis, and it states that it would be impossible to do so using a different process.



Custom 3D-printed shields matched precisely to each patient's body focus radiation therapy where it's needed—sparing areas where it isn't.



No two human beings are the same, and neither are any two cases of cancer. For optimal results, radiation therapy should be matched to each patient.

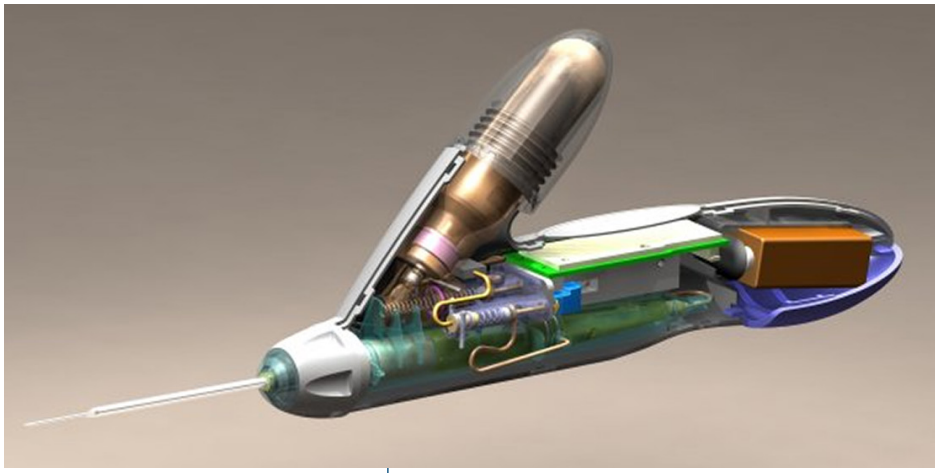
Integrated 3D design, CAM, and simulation technologies are also having a similarly transformative effect in areas of oncology beyond externally applied radiation therapy. Brachytherapy is a form of radiation therapy administered using tiny implantable radioactive "seeds," which destroy cancer tissue when applied directly in proximity to a tumor.

Like external radiotherapy using targeted beams, brachytherapy's goal is to maximize the exposure of diseased tissue to radiation treatment while sparing healthy tissue. This is accomplished by using a hollow needle to insert radioactive "seeds" made from palladium 103 to areas within or close to diseased tissue. Accurate seed placement is vitally important, both from the standpoint of maximizing the treatment's effectiveness and sparing damage to healthy areas. To provide effective treatment, each seed must be placed within a scant few millimeters of the area it is intended to treat—and in the case of larger tumors, possibly dozens or hundreds of seeds must be placed within these tolerances.

3D Design & CAM are Transforming Brachytherapy. To achieve this level of precision, Okolohealth uses integrated 3D design, simulation, and CAM software along with additive manufacturing, or 3D printing, to generate physical facsimiles of the specific treatment area of an individual patient's body with a dimensionally near-perfect replica of the specific tumor placed precisely within it. In the case of breast cancer, CT scan data is used to generate an accurate digital model of the treatment area and tumor; this in turn is utilized within CAM software to create mirror-image molds used to form a gelatinous replica of the body.

The 3D and CAM software is used again to fabricate a tumor model, made from a material of slightly varying density, which is then placed within the replicated body. The completed model is then used by the physician to "practice" the precise placement of the individual seeds. When the practice is completed, the model can be scanned to assess the accuracy of placement, allowing for corrections to the placement process, ***before*** any actual surgery takes place. This minimizes risks to the patient and improves prospects for the treatment's success.

Okolohealth is working on additional ways to leverage the integrated 3D technologies to optimize treatment effectiveness. The company is developing 3D-printed devices, tailored to match each individual patient, to guide the placement of needles and seeds. Created in collaboration with physicians and using the same CT scan data, 3D guide devices with pre-drilled holes will direct the placement needles into exactly the proper point on the body, helping to further minimize any placement variance. The company has already produced a customized needle placement device, currently in use, to replace an awkward and less-precise articulated arm device.



This medical injector can be used during brachytherapy to insert pellets used during radiation treatment.

Since the company works with physicians and facilities that may be hundreds of miles away, the integrated 3D system's simulation and visualization capabilities play a vital role in the treatment process. Okolohealth is capable of providing a three-dimensional eDrawing to the on-site treatment team, illustrating the specifics of device usage and the optimal treatment process. The on-site users can work with this visual model, collaborating remotely with the Okolohealth team to make revisions or modifications and to plan their approach to the procedure.

Okolohealth's Medical Physicist Michael Roumeilotis stresses the importance of these integrated visualization and collaborative capabilities in developing effective physician- and patient-specific devices and models. "Being able to send such a model is paramount to the success of this project, because it's very difficult to describe how something like this is going to work," he explains. "The cycle for how quickly we're able to alter the design based on feedback from these people is important. It's not a case of sending them a part and them finding that 'oh, it will interfere with this other person.' I've got all that data, a virtual operating room, on the screen. It makes a very complex program function easy for people who otherwise would not be able to use it."

As a result of the integrated 3D system's varied capabilities, Okolohealth and .decimal are discovering new ways to approach cancer treatment—and developing new devices and methods to optimize chances for success. Though their businesses consist of making physical devices, they see their missions as something more meaningful. "Each of our devices is unique, and is used to treat a grandmother, grandfather, son, daughter, or mother," says .decimal's Daniel Patenaude. "The work we do here is important, and we're treating cancer with everything we ship out the door. It means a lot when you see a product you work on make peoples' lives longer and better, and treat cancer more efficiently."

By using 3D design, simulation, and additive manufacturing solutions in developing their products and processes, companies like .decimal and Okolohealth are expanding the range of possibilities available to physicians—and expanding the scope of oncology to include a new dimension: The individual, human one.

ACCELERATING EXCELLENCE

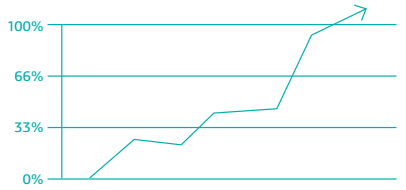
HOW 3D DESIGN, SIMULATION, AND ADDITIVE MANUFACTURING TECHNOLOGIES ACCELERATE COLLABORATIVE INNOVATION, TIME TO TREATMENT AND TIME TO MARKET

CHAPTER 2

A person confronting a major medical challenge typically faces one major enemy apart from their specific medical condition: Time. Recovery typically requires the intervention of skilled physicians, the application of effective treatments, and the use of suitable medical devices. Any delay in getting them results in continued suffering, or possible progression of disease. On a societal scale, prolonged delays in delivering treatment are enormously costly; on an individual level, they are often tragic.

It is almost always a practitioner's goal to deliver effective treatment as quickly as possible, but that is often easier said than done. A number of factors can affect the availability of care and the speed with which it is provided, including the availability of proven, approved, effective treatments; the patient's proximity to care providers; and access to necessary technology, resources, and materials.

The emergence of integrated 3D design, simulation, and additive manufacturing solutions is helping to bridge some of these gaps, dramatically increasing the speed with which patients are able to access needed devices and treatments. The effectiveness and quality of treatments can also be dramatically



DEMAND FOR PROSTHETIC LIMBS IS EXPECTED TO INCREASE BY

100% BY 2050

STAT SOURCE:ZIEGLER-GRAHAM K, MACKENZIE EJ, EPHRAIM PL, ET AL. 2008. "ESTIMATING THE PREVALENCE OF LIMB LOSS IN THE UNITED STATES: 2005 TO 2050." ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, 89(3).

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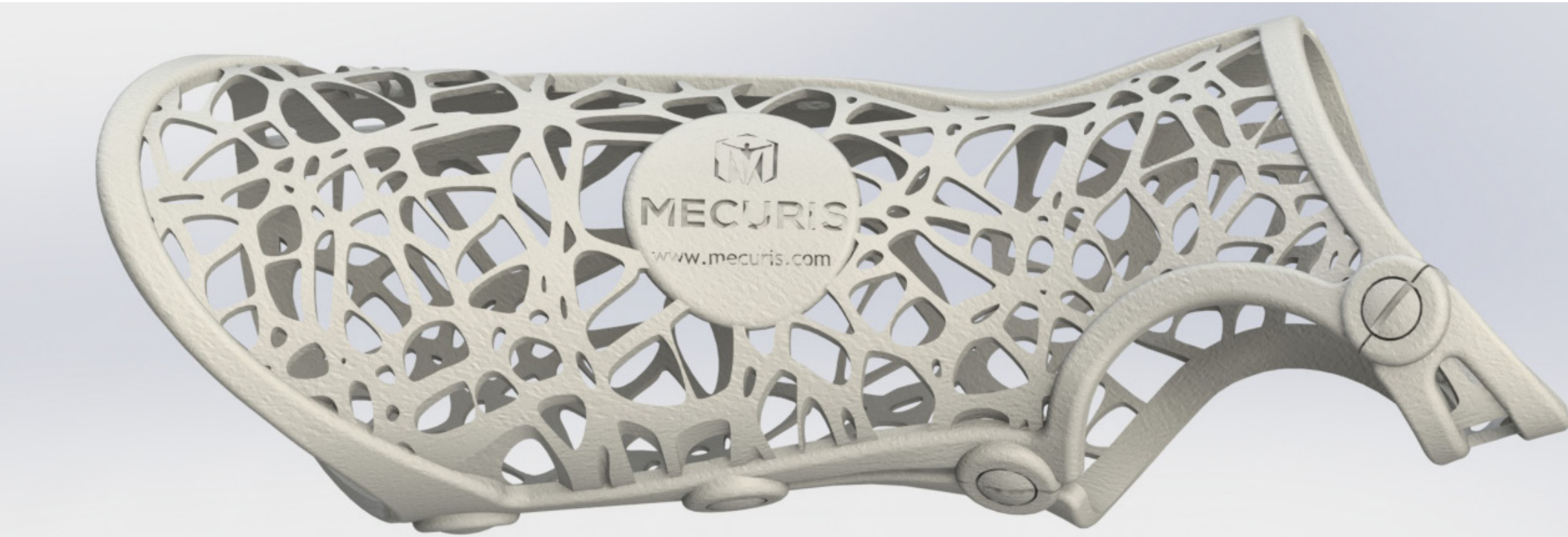
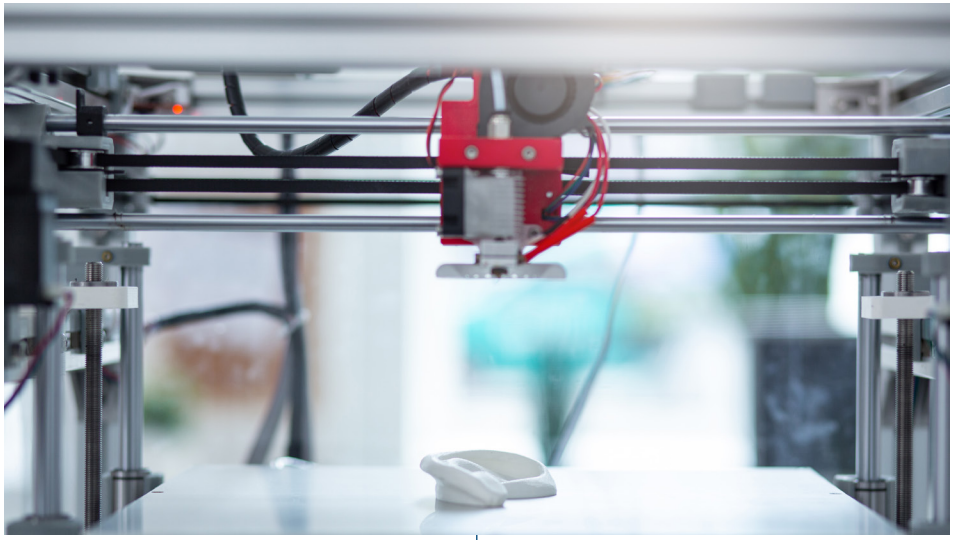


improved through increased personalization, with additive manufacturing (3D printing) making custom devices and materials rapidly available when and where they are needed.



The French-American startup Biomodex specializes in creating lifelike, functional 3D replicas of specific patient organs and parts of the anatomy for use by physicians in practicing complex operations. Using CT scan data, Biomodex replicates complex systems, such as the area of a patient's brain surrounding an aneurysm, isolating the network of veins requiring treatment. These are 3D printed using materials of varying density so as to replicate the relative flexibility and firmness of specific areas. The model is then mounted on a functioning base that pumps heated fluid through the network. The surgical team can then leverage this model to rehearse and pre-plan all aspects of the procedure, including the imaging setup, avenues of access, and the size of medical devices to be used.

According to Biomodex CEO and Chairman Thomas Marchand, "the goal is to drive decision-making prior to the surgery in a safe, replicable environment, rather than on-the-fly during an operation." Working remotely within a secure online environment, the company is able to receive needed data from a medical team anywhere in the world, and provide the necessary digital and physical models within five to seven days. Marchand expects to reduce this time frame to a single day with the placement of a compatible 3D printer within the hospital. "This is a game changer in surgery today," Marchand said, citing the technology's ability to mitigate risk, lower the number of adverse events, and reduce patients' exposure to x-rays.

Marchand also cited the company's ability to enable successful treatment of particularly complex cases, including enabling procedures upon patients who would otherwise not be eligible for treatment. He quotes Jacques Moret, the inventor of interventional neuroradiology, who shared a specific example in a public presentation, stating "Without the Biomodex model, I wouldn't have taken the risk to operate on this patient." In this case, access to a tactile model and the ability to test surgical scenarios beforehand was critical in achieving a successful outcome.

3D technologies help to minimize risk, reduce the number of adverse events, and reduce X-ray exposure, improving patient outcomes.

Collaborative 3D design, simulation, and additive manufacturing capabilities are also having a profound effect in a more broad-ranging area of need: meeting the growing demand for prosthetic limbs. The U.S. Centers for Disease Control have estimated that over 180,000 new patients annually* need prosthetics in the U.S. alone; at the time of a study in the early 2000s, demand was expected to grow by 47 percent by the year 2020, and to more than double by 2050. Extrapolated worldwide, the total need for prostheses can be estimated in the tens of millions – a need that often goes unmet due to high cost and lack of availability.

Historically, the manufacture of prosthetic limbs has been a high-cost, time-intensive endeavor requiring a high level of specialized skill. The correct fitting of a customized prosthesis typically has required repeated rounds of measurement and adjustment, as well as manual fabrication and modification of the limb by trained specialists. A new breed of startup companies has begun to leverage 3D technology to produce high-performance, fully customized prostheses within a dramatically shorter time frame – and often at a fraction of the usual cost.

The German company Mecuris is leveraging Dassault Systemes' technology to digitize the fitting processes, automate design, and rapidly fabricate customized prostheses for patients throughout the world. Using the company's online interface, an orthopedist can submit digital scan data or measurement information that Mecuris will use to create a patient-specific device that can be readily

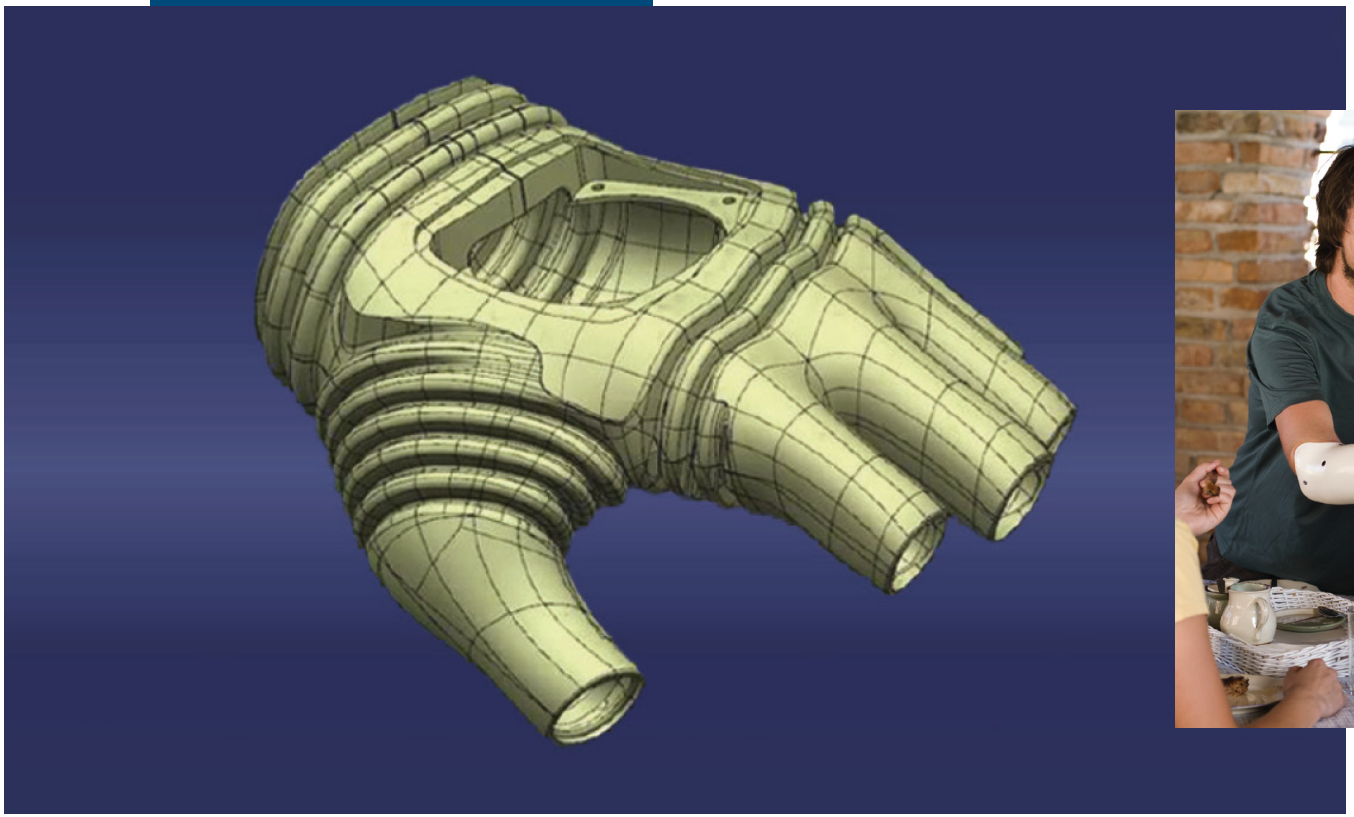
*STAT SOURCE: ZIEGLER-GRAHAM K, MACKENZIE EJ, EPHRAIM PL, ET AL. 2008. "ESTIMATING THE PREVALENCE OF LIMB LOSS IN THE UNITED STATES: 2005 TO 2050." ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, 89(3).

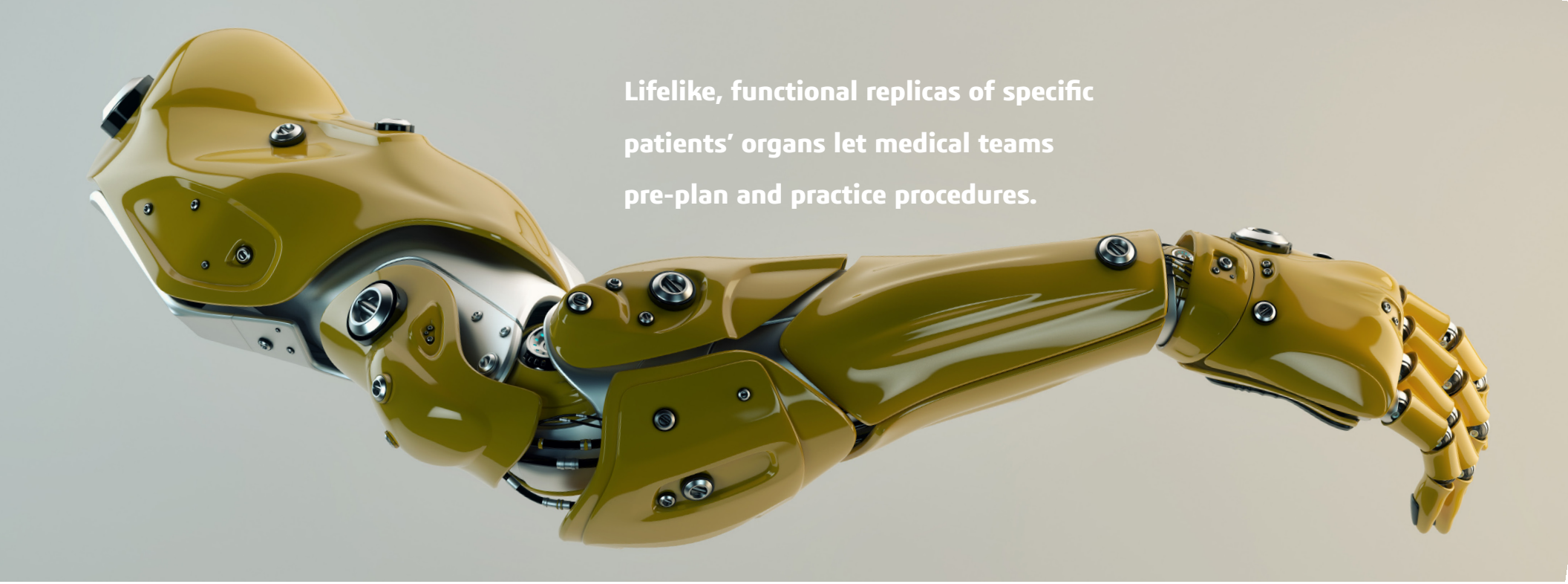
AS QUOTED AT:HTTP://KK.ORG/EXTRAPOLATIONS/PROSTHETIC-LIMBS-FORECAST-TO-2050/

Automated design and manufacturing processes result in perfectly fitted prosthetics – delivered in 24 hours.

3D printed. The Mecuris system relies upon the software's ability to maintain multiple design configurations: Patient-and situation-specific data, such as foot and limb measurements, patient weight, and usage loading conditions, drive an automated design process —consuming seconds, rather than the usual days or weeks, to output a completed design. This design can then be aesthetically customized according to the patient's preferences before being output through a 3D printer as a finished product.

Because Mecuris's designs leverage a readily available, high-strength thermoplastic, the company has the ability to output its finished devices through a 3D printing service bureau virtually anywhere in the world. This makes its prostheses available to a global population ordinarily underserved by traditional device manufacturers. Taken together, Mecuris' accessible online ordering, automated design, and output-anywhere methodology results in overall production time reduction to a mere 24 hours, rather than weeks or months – while delivering a fully individualized, perfectly fitted product.



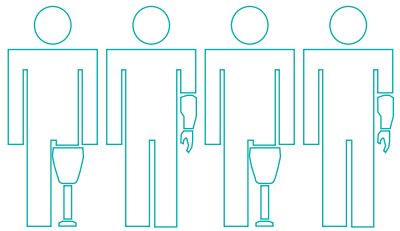


Lifelike, functional replicas of specific patients' organs let medical teams pre-plan and practice procedures.

The new U.S.-based firm Unlimited Tomorrow is taking its 3D design, simulation, and additive manufacturing-oriented approach a step even further and "empowering amputees by using an intuitive scalable model to create custom devices from start to finish." The company is working to create fully articulated, functional, bespoke artificial limbs at the lowest possible cost, making them broadly accessible, including to residents of remote, underprivileged communities.

Unlimited Tomorrow is currently focused on development of practical and functional hands and arms modeled directly from the patient. Using 3D scanning technology, the company digitally maps both the client's residual limb and, if available, the existing opposing limb. Through the design application, the opposing limb is mirror-imaged to model the appearance of the new prosthesis. Mechanical and robotic design elements are then robotically placed within the model, which is then able to be output through 3D printers anywhere in the world.

Following extensive research, Unlimited Tomorrow created an initial working prototype, fitted to a ten-year-old girl. The finished product, modeled directly from the girl's existing arm, is a muscle-controlled, one-pound



185,000

AMERICANS LOSE A LIMB EACH YEAR

SOURCE: AMPUTEE COALITION OF AMERICA, QUOTED AT HTTPS://WWW.CNBC.COM/2013/11/28/THE-BUSINESS-OF-BIONICS-IMPROVING-THE-LIVES-OF-AMPUTEES.HTML

device with individual finger movement. Internal robotics are controlled by electronic sensors attached to the girl's residual limb.

The company has demonstrated its commitment to maximum accessibility and affordability for patients by making much of its technology available on an open-source basis, enabling others to modify and build upon its achievements. The firm also believes that ultimately it will be able to produce its prostheses, even with the high degree of customization and technological sophistication, for a fraction of the price of traditional customized limbs.

Dassault Systèmes' Director of Additive Manufacturing & Materials, Subham Sett, sees the emergence of collaborative 3D design, simulation, and manufacturing solutions such as the company's 3DEXPERIENCE platform as instrumental in accelerating the development of such emergent technologies and shortening their time to market. These are critical considerations for new, emerging companies lacking the capital to support lengthy development processes as well as larger enterprises seeking to transform their businesses and stay ahead of the competition.

According to Sett, the cumbersome nature of typical design-to-manufacturing processes previously slowed the life sciences' adoption of additive manufacturing technology. "For an additive engineer to go from design all the way to production, a user would be touching upwards of 12 software pieces. From an efficiency perspective, it was really killing the adoption of additive, and many of the designs never made it into production because it was so time-consuming to bring it back into design after simulation—people were giving up," he said.

The emergence of collaborative systems such as the 3DEXPERIENCE platform is rapidly changing this landscape. Sett cited integrated simulation capabilities as a key to increasing efficiency and speed. "If you are doing a lot of trial and error (using 3D printing), you're using your hardware for research, not for production," he explained. "That's where simulation comes in: you can do the trials and calculate errors much faster, and save on materials and machine downtime. You move towards production much faster by being able to do it virtually. What we've done is to connect the dots from design to simulation to manufacturing through the 3DEXPERIENCE platform."

Faster research, product development, and custom manufacturing are welcome developments for innovators within the life sciences industry—and life-changing for patients, whose vital treatments can't possibly come too soon.

REFERENCES

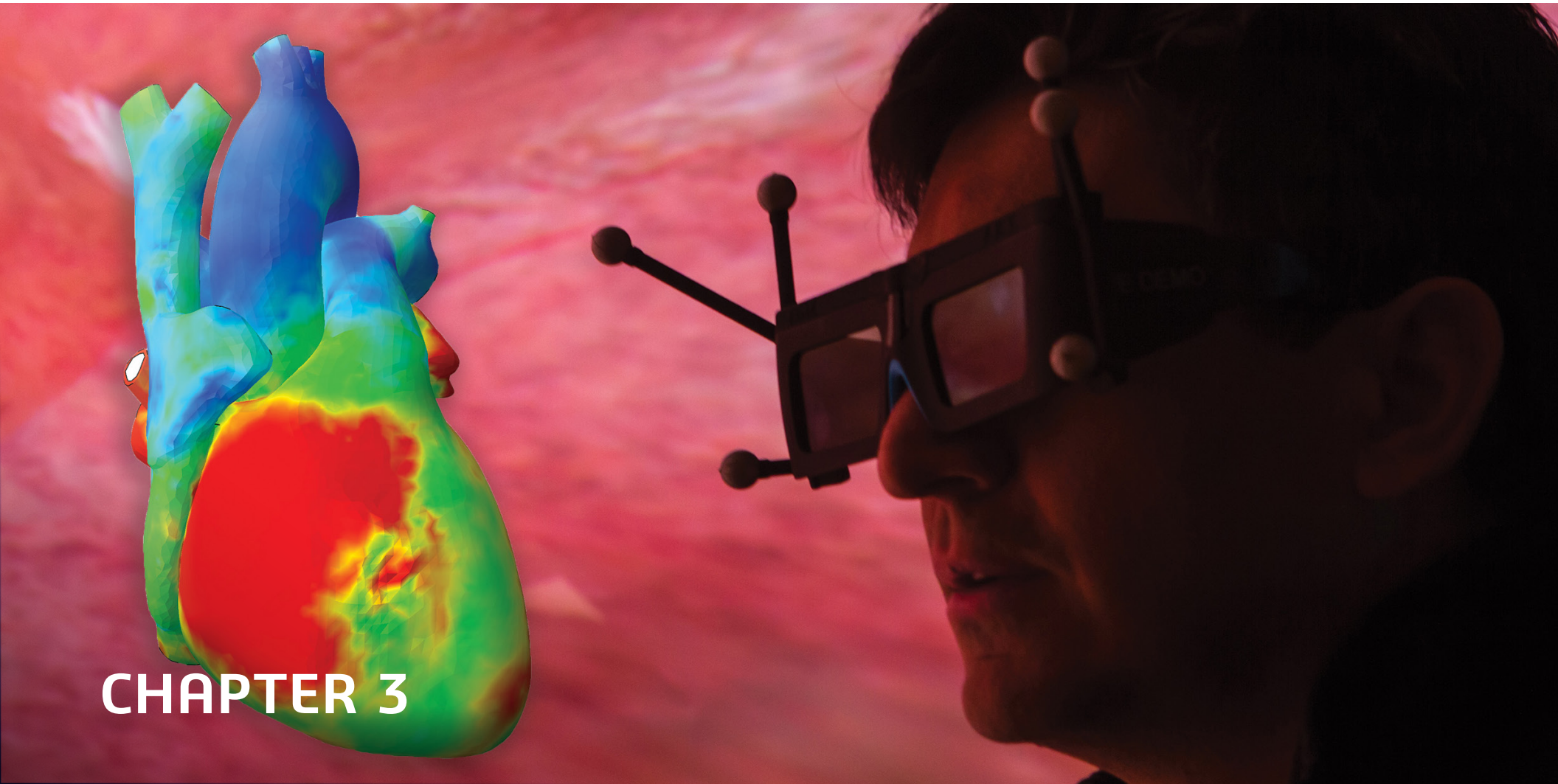
*Ziegler-Graham K, MacKenzie EJ, Ephraim PL, et al. 2008. "Estimating the prevalence of limb loss in the United States: 2005 to 2050." Archives of Physical Medicine and Rehabilitation, 89(3).

DASSAULT SYSTEMES

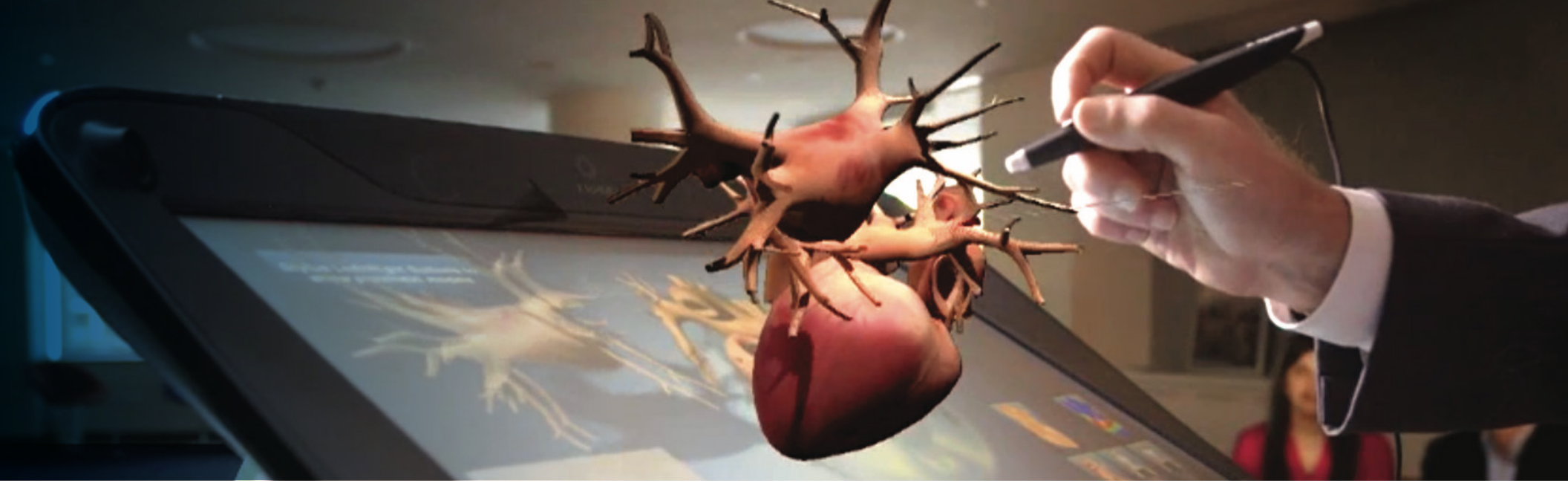
vias3D

LEADING THROUGH LEARNING

HOW CLOSER WORKING RELATIONSHIPS BETWEEN SCIENTISTS, PRACTITIONERS AND DEVELOPERS RESULT IN MORE POWERFUL APPLICATIONS AND MORE EFFECTIVE TREATMENTS



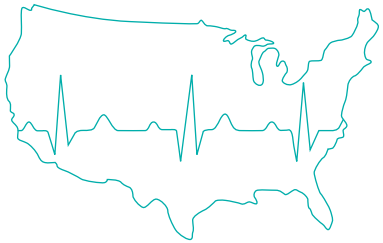
CHAPTER 3



Even for seasoned physicians and scientists, it's hard not to marvel at the human heart. This amazing, incredibly complex organ is the cornerstone of human life — a self-regulating, always-running engine supplying the body and brain with vital oxygen and nutrients through a labyrinthine vascular network. Even before the moment of birth, its layers upon layers of specialized fibrous tissue seamlessly interoperate to deliver blood to the furthest reaches of the body, adapting flow and function automatically as necessary to compensate for changing physical circumstances.

That is, until it doesn't. The effects of a compromised, malfunctioning, or injured human heart are instantly reflected in a corresponding decline in the other bodily systems it supports; when sufficiently damaged, the inevitable consequence is death.

It is a catastrophic outcome for individual patients and their families, and an incredible cost for human society. Cardiovascular disease is the world's leading cause of death, and is responsible for more than 30 percent of annual deaths*. Additionally, some 40 percent of the world's population will ultimately suffer from some form of cardiovascular disease. In the United States, recent statistics show that treating cardiovascular disease costs approximately $555 billion annually**, a figure likely to rise to $1 trillion by 2035 according to a recent study by the American Heart Association.



IN THE US, CARDIOVASCULAR DISEASE TREATMENT CURRENTLY COSTS APPROXIMATELY

$555 BILLION ANNUALLY

SOURCE: HTTPS://HEALTHMETRICS.HEART.ORG/WP-CONTENT/UPLOADS/2017/10/CARDIOVASCULAR-DISEASE-A-COSTLY-BURDEN.PDF

* SOURCE FOR PREVALENCE/DEATH STATISTICS: HTTP://WWW.WHO.INT/NEWS-ROOM/FACT-SHEETS/DETAIL/CARDIOVASCULAR-DISEASES-(CVDS)

**SOURCE: HTTPS://HEALTHMETRICS.HEART.ORG/WP-CONTENT/UPLOADS/2017/10/CARDIOVASCULAR-DISEASE-A-COSTLY-BURDEN.PDF

"We began with the drive to use digital technology to improve life as we knew it... "

– Dr. Steve Levine, head of Dassault Systèmes' (DS) Living Heart Project

It's clear that the need to develop more effective means of treating and preventing heart disease is both pressing and universal. While the medical sciences have achieved tremendous breakthroughs in knowledge and treatment, the pace of advancement has been constrained by our limited ability to look inside a functioning heart or subject it to experimentation, placing researchers and practitioners at a disadvantage.

The need to learn more about how the heart works and how its afflictions might be treated led Dassault Systèmes to launch the Living Heart initiative, an ambitious collaborative project aimed at developing a comprehensive digital functional model of the heart. Beginning in 2014, the company drew together researchers, clinicians, regulators, and industry representatives to share their information and expertise to advance this objective. Attracted by its stated mission to "advance development of safe and effective cardiovascular products and treatments by uniting engineering, scientific, and biomedical experts to deliver validated models and translate simulation technology into improved patient care," the initial twelve-member team set to work using Dassault Systèmes' 3DEXPERIENCE cloud-based shared development platform.

"We began with the drive to use digital technology to improve life as we knew it," says Dr. Steve Levine, head of Dassault Systèmes' Living Heart Project. "Could we simulate something as profound as the human heart? Could we understand the physics, the electromechanical behavior, and predict how devices would interact—to make them better, test them, and make them safer, and more reliable, before they're ever put into a human body?"

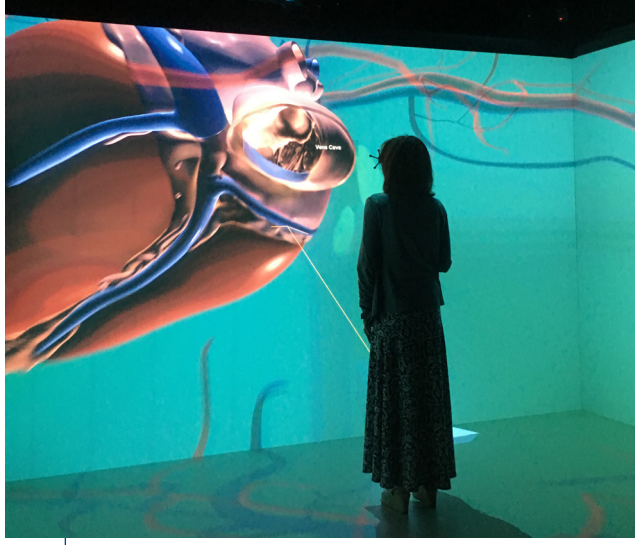
Building from an existing baseline data set, the team began to answer this question by refining the system's models for electrical conductivity, including the electrical behavior of human tissue. Team members contributed additional data drawn from their own areas of specialty, working collaboratively to ensure accuracy. The group then created the first iteration of the Living Heart—a dynamic 3D virtual model of a living human heart that could be viewed internally and externally from all angles, cross sections, and dimensions.

The project has since grown to include the contributions of 49 research partners, 35 corporate partners, and ten clinicians from around the world, and has secured the support of the Food and Drug Administration and the Medical Device Innovation Consortium. Through the contributors' combined knowledge and diligent efforts to refine the project's methodology and model, the current iteration of the Living Heart has become capable of accurately modeling virtually the full spectrum of heart functions—flows, volumes, mechanical functions, and electrical functions.

With these capabilities, researchers and device developers gain the ability to introduce models of specific devices or treatments, simulate their performance in conditions nearly identical to "real life" circumstances, and gauge their efficacy and impact with a high degree of certainty. This permits a level of experimentation and testing impossible to achieve using live animal studies, and which typically cannot be undertaken at all using human subjects. In addition, since modeling and simulation do not consume the same time, expense, or physical resources as animal or cadaver studies, tests can be quickly conducted and iteratively repeated, enabling devices and methodologies to be continually refined.

More significantly, the Living Heart has transitioned from the generic to the personal. CT, MRI, EKG, and other data from individual patients can be imported into the system, analyzed, and rendered as a functioning model of the patient's specific heart—including any abnormalities, defects, diseases, or

The Living Heart enables researchers to simulate the performance of devices and treatments nearly identical to "real life" — including testing that's impossible to conduct through animal or human studies.



dysfunctions. As a result of this development, clinicians and surgeons gain additional vital insights into a patient's specific circumstances and needs; testing and simulation can forecast outcomes of specific surgical procedures, drug treatments, or device implantations; surgeries and procedures can be practiced beforehand, optimizing their efficiency and efficacy; and, through the gaining of greater knowledge of the individual heart's specific function and physiognomy, unnecessary risks can be averted. All of this adds up to the likelihood of improved patient experiences and treatment outcomes.

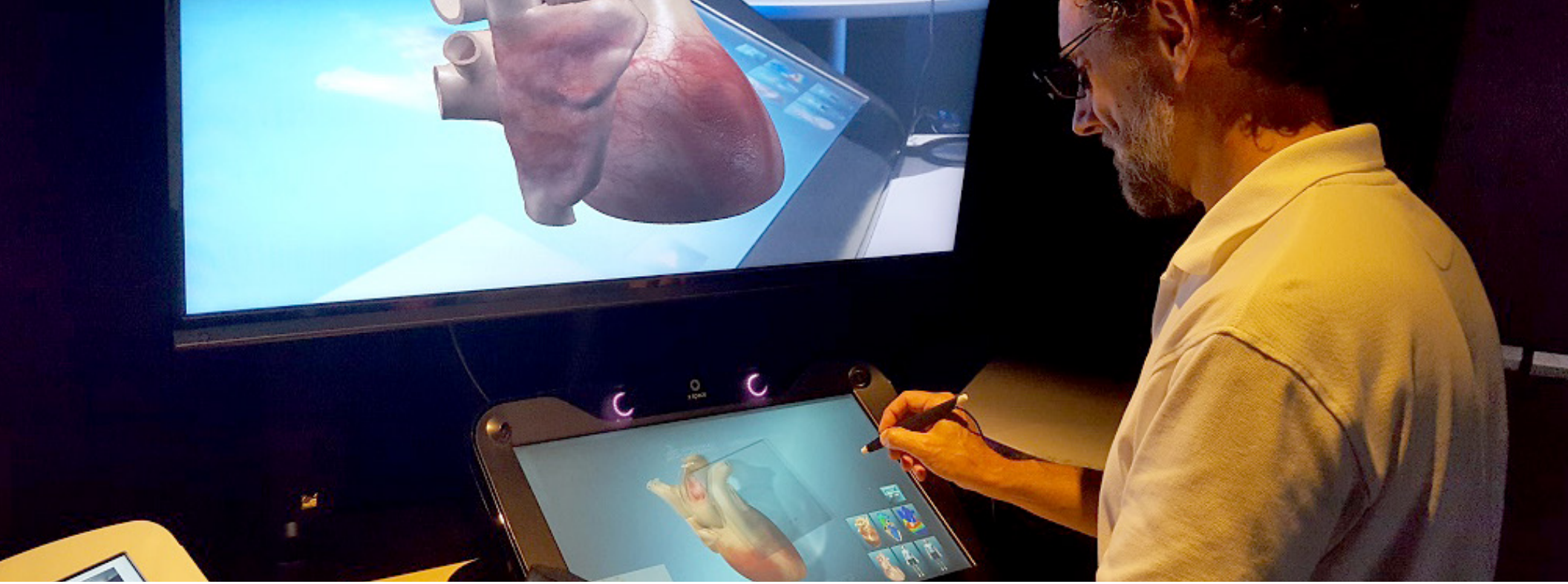
Beyond development of the world's most advanced, openly accessible human heart model, the Living Heart Project achieved another notable milestone: Developing a template and framework for 3D experience-based collaboration, knowledge sharing, and scientific advancement that could be applied to other Life Sciences specialties. The project's success in developing a viable model of one of the body's most complex, delicate organs served as validation of the technology and the methodology for developing equally powerful models for other organs and systems, as well as for testing treatments and devices related to them.

Pursuit of the Living Heart Project provided Dassault Systèmes developers with a rare opportunity to work with a global, cross-disciplinary team using their products, and to gain vital, immediate feedback. The team was able to see firsthand how a wide range of professionals from multiple disciplines used the 3DEXPERIENCE technology, and to use this knowledge as the basis for future refinements as well as possible specialized functions keyed to specific interest and practice areas.

"As society seeks personalized health care while ensuring optimum industrial security, the time has come for Life Sciences to, at last, leverage the tremendous power of the virtual world. Digital environments are pushing the boundaries of possibility to transform research, science, the pharmaceutical industry and medicine in general," says Bernard Charlès, Chief Executive Officer of Dassault Systèmes. "Innovation is about imagining worlds that don't yet exist—worlds that await us in the future. Digital is about making these new worlds possible."

The practical ramifications of the Living Heart project are only beginning to be felt as scientific papers are published, new treatments are developed, and new products are refined leveraging the technology. As they prove their worth through peer review and in practice, the Living Heart project and the collaborative methodology and simulation model supporting it stand to radically transform medical research and practice, including the process of gaining regulatory approval.

As a result of the Living Heart Project, clinicians and surgeons gain vital insights into a patient's specific circumstances and needs; testing and simulation can forecast outcomes of specific surgical procedures, drug treatments, or device implantations optimizing their efficiency and efficacy.



In response to the success of the Living Heart and other advanced simulation initiatives, regulators are growing increasingly responsive to computational modeling and simulation as a component of medical device development and testing processes. The FDA recently launched a new Medical Device Development Tools program, which includes a category for nonclinical assessment models incorporating computer modeling and simulation. "The Living Heart Project opened a Pandora's box on this whole new paradigm of modeling and simulation within medical devices and working in collaboration with the FDA," says Arieh Halpern, Life Sciences Director for Dassault Systèmes. "It's a whole new era that the FDA and the industry see as extremely valuable in being able to bring newer products to the market safer and faster."

By combining the knowledge and expertise of experts from around the world within a sophisticated collaborative environment and leveraging that knowledge to present a dynamic, accurate model of individual heart structures and functions, the Living Heart Project creates a new avenue of hope for millions of cardiac patients. Perhaps more importantly, it blazes a new trail for future innovation. The collaborative, technology-driven methodology driving the project serves as a possible model for unlocking the secrets of other organs, ailments, and treatments - with the potential to transform medicine and impact millions of lives.

DASSAULT SYSTEMES

vias 3D

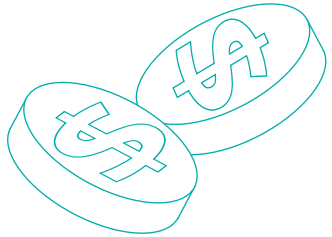
DISCOVERY ON THE INVISIBLE FRONTIER

DESIGNING BETTER CARE, BETTER CURES, AND BETTER LIVES—AT THE MOLECULAR LEVEL

CHAPTER 4

Pharmaceutical development has never been easy, fast, or inexpensive. The drug development process has historically been time, labor, and cost-intensive, requiring tremendous volumes of painstaking, detailed work performed by highly trained personnel. At the same time, the barriers to the successful introduction of a new drug are daunting: As of 2015, it was estimated that it took more than ten years to bring a new drug to market, at an average cost of more than $2.6 billion. Of those which finally reached the marketplace, only 2 in 10 generated enough revenue to cover development costs.

Even in a comparatively static environment, the process of launching a new drug would pose tremendous challenges to researchers and firms—but this is not a static environment. Technological change, rising costs, shrinking profit margins and an increasingly rigorous regulatory landscape all serve to heighten the pressure. In addition, the nature of drug development has changed: more and more companies are turning towards complex biologics—a development path that technology has only recently made possible—in an effort to develop the breakthrough treatments and personalized solutions that many of the most severe and intractable medical problems demand. For the millions of patients suffering from conditions such as heart disease, myeloma, melanoma, lymphoma, macular degeneration and countless other conditions, cutting-edge biotherapeutics offer their best and, sometimes, only hope.



AVERAGE COST TO BRING A NEW DRUG TO MARKET:

$2.6 BILLION

STAT SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE/ NATIONAL INSTITUTES OF HEALTH

HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/ PMC3107566/

Only 20% of drugs produce enough revenue to cover development costs.*

Considering the sophisticated processes, advanced knowledge, and expensive technologies needed to pursue cutting-edge biotherapeutic development, it becomes evident that upward pressure on development costs and time requirements will continue, if not accelerate. At the same time, there is little indication that there will be a corresponding rise in revenues to compensate for these expenses. It becomes increasingly important for researchers and pharmaceutical companies to maximize efficiency and contain costs throughout the entirety of the ideation-to-delivery process, even as they expand the scale and scope of the tasks they undertake.

To make this possible, researchers and companies are turning to a new generation of highly specialized, automated and integrated tools for design, simulation, testing, quality and manufacturing, as part of a common enterprise platform. This new approach will help drive corporate efficiency and deliver innovative therapies faster to the patient.

STRUCTURE-BASED DESIGN

Historically, efforts to determine the efficacy of a new pharmacological compound were a process of "trial and error:" an endless procession of manually-conducted physical experiments whose results would be duly noted in each instance—usually in disparate electronic systems requiring manual, paper-based intermediary steps—before being analyzed and contrasted. Even at its best, it is a time-consuming and error-prone process whose difficulty is compounded as the number of research participants increases.

The maturation of design and simulation technologies has provided researchers with a means of accelerating this cumbersome process. Dedicated tools now enable scientists to engineer at atomistic, molecular, and protein levels. When coupled with connected exhaustive data sets and powerful 3D modeling capabilities, these tools are allowing researchers to engineer new compounds and reliably simulate their behaviors using faster, largely automated processes.

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* STAT SOURCE: HTTPS://FDS.DUKE.EDU/DB?ATTACHMENT-25--1301-VIEW-464
HTTP://BLOGS.SCIENCEMAG.ORG/PIPELINE/ARCHIVES/2016/03/30/ONLY-TWO-OUT-OF-TEN-DRUGS-REALLY

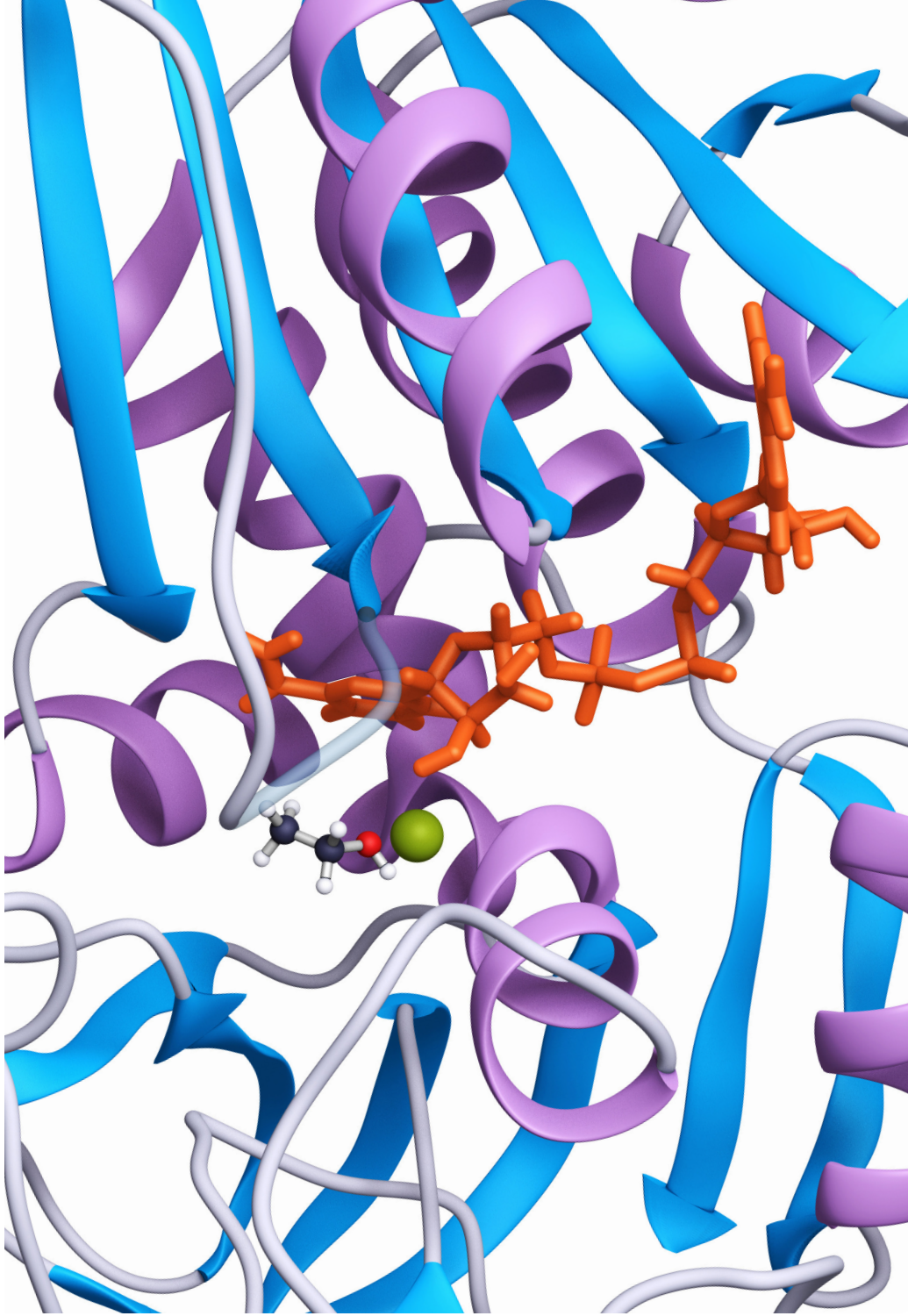
EXPERIMENT SIMULATION

Researchers face particular challenges when it comes to testing the safety, efficacy, and other properties of new products. Ethical considerations, legal constraints and the prospect of liability severely inhibit the ability to conduct in vivo testing with human subjects. Other forms of experimentation, such as in vitro, can provide unreliable results and can be costly and time-consuming. As technology permits, researchers are increasingly turning to in silico (simulated) experimentation alongside physical experimentation. This allows them to quickly identify promising avenues for development while efficiently eliminating "dead ends," and dramatically accelerate development time frames and reduce costs as a result.

Utilizing baseline shared data and data incorporated from previous related experiments, scientists can project the likely behavior of modeled small molecules or protein chains in relation to relevant metrics. These may include considerations such as efficacy, bioavailability, selectivity, propensity for autoxidation, interactivity with other compounds, and a host of other considerations. Carefully applied methods enable users to accurately predict the outcomes of physical experiments without the time, or material resources needed for physical experiments.

The ability to accurately experiment in silico using engineered digital molecular and protein formations (which are designed to accurately represent the characteristics of their "real world" counterparts) can help researchers and pharmaceutical manufacturers achieve a variety of important objectives:

- Increase innovation – the ability to conduct more experiments in less time, while consuming fewer resources, enables more experiments to be conducted, including those for comparatively risky projects



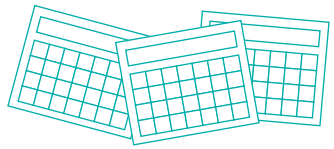
- Improve R&D Efficiency – the speed of simulation and the ability to quickly identify non-fruitful development paths enables researchers to devote resources towards high-potential development efforts
- Shorten overall time to market
- Contain development costs
- Identify new research and innovation possibilities by leveraging data in silico

Ultimately, these benefits constitute significant economic and competitive advantages—advantages whose importance increases in proportion to the complexity of the research and development work being undertaken. The rise of biologics and the emergence of individualized "precision medicine" stand to make these benefits critically important in years to come.

THE DIGITALLY-CENTERED LAB

Laboratory operations provide one of the best opportunities to actualize efficiency and cost-containment gains. Research, development and quality processes are becoming increasingly collaborative, often involving the participation of researchers and facilities around the world. While pharmaceutical firms benefit from the specialized expertise external collaborators can provide, the development process can be hamstrung by operational inefficiencies within individual labs and the lack of standardization in applications and procedures from one organization to another.

Leading Life Sciences companies are striving to implement standards-based, flexible data management platforms to drive operational efficiency throughout the product development lifecycle. By implementing such a platform, companies can enhance their collaborative capability across the broadly distributed chain of research partners—often separated by languages and continents—who are contributing to the development process.



AVERAGE TIME TO BRING A NEW DRUG TO MARKET:

12 YEARS

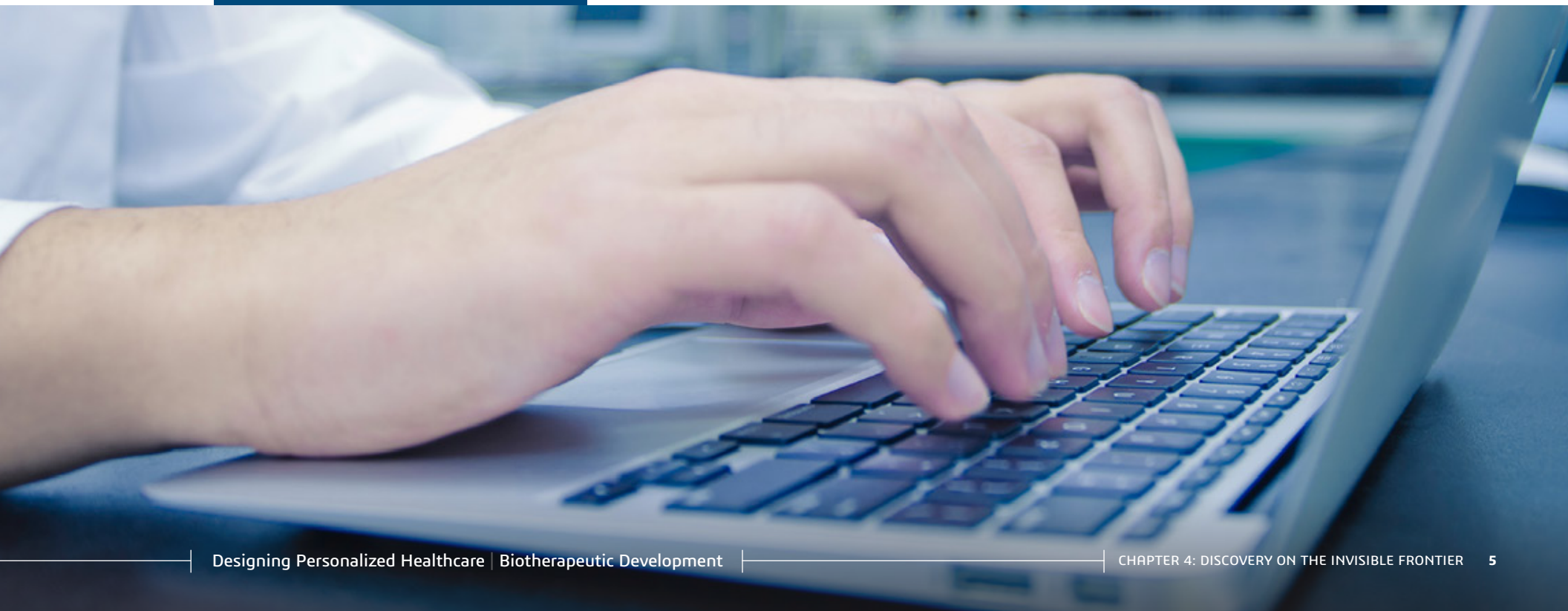
STAT SOURCE: HTTPS://WWW.MEDICINENET.COM/SCRIPT/MAIN/ART.ASP?ARTICLEKEY=9877

More and more, companies turn to complex biologics to develop breakthrough treatments—and personalized solutions.

Even today, many labs rely on cumbersome processes based on disconnected systems and manual data transfer for recording results and recordkeeping, sometimes even paper-based. This makes it much more difficult for researchers to effectively share data or to access data that they need, which leads to a number of significant negative consequences:

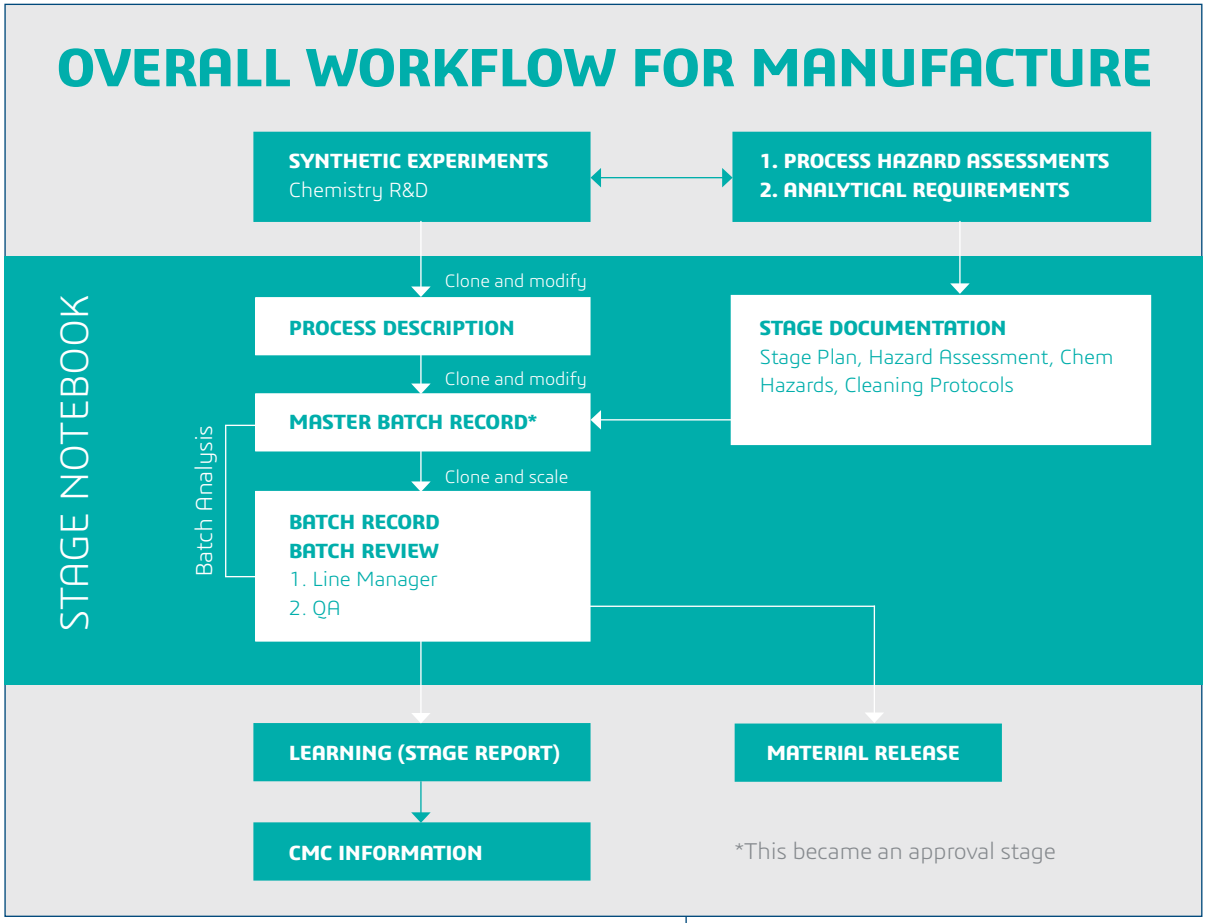
- Many experiments are needlessly duplicated, consuming time and incurring unnecessary expense
- Experiment data and results must often be manually keyed into a siloed system in order to be documented, catalogued or shared
- Complex annotation and indexing protocols must be established and adhered to in order for information to be accessed later
- Mandatory reporting to meet regulatory requirements can only be achieved through labor-intensive manual processes

In recent years, Electronic Lab Notebooks (ELNs) have become the instrument of choice for organizations seeking to streamline and standardize their data collection, inventorying, documentation and workflow management capabilities. As pharmaceutical research becomes increasingly decentralized, with any given



project potentially involving the work of multiple collaborating organizations around the globe, the need for a standards-based and shareable form of data management has increased. While siloed ELNs have existed for some time, the new paradigm focuses on a cross-functional ELN capable of addressing needs across the entire development-to-manufacturing chain—and capable of serving a geographically diffused user base, enabling information sharing through a single centralized point of truth.

Millennium, the Takada Oncology company, found that collaboration between different teams and the ability to rapidly develop new drugs were hampered by the differing information management systems used by chemists and biologists. To address this problem, the company elected to deploy a highly configurable ELN system. The company considered it especially important to develop a means of effectively searching and retrieving critical information—data that normally would be contained within paper notebooks.



The company began by deploying an ELN used by chemists, coupled with a carefully tailored workflow designed to standardize procedures for users. Prior to its rollout, chemists had experienced considerable difficulty in swiftly obtaining proprietary chemical information, owing to the paper-based systems previously in use. Following deployment, the company and its researchers soon realized some considerable benefits:

- Greatly expanded searchability and speed of access to proprietary chemistry data
- Streamlined workflow through increased re-use of existing data
- The ability to access multiple data sources through a single ELN interface, rather than through separate systems

AstraZeneca's overall manufacturing workflow requires the transfer of experimental and analytical data to process chemistry. Rather than trying to develop a single document to encompass all of this information, AstraZeneca used a single folder—the stage notebook—to keep all the relevant documents in one place.

The company subsequently elected to implement the ELN, with some customization, for biologic research. The comparative complexity of the research, coupled with the fact that the biologic ELN encompassed ten separate departments using different equipment and methodologies, posed particular complexity challenges to implementation. Nonetheless, Millennium's biologic ELN emerged successfully as an information hub, enabling researchers to quickly access critical summary data for experiments from anywhere within the organization.

Ultimately, Millennium found that by digitizing its information capture and management through the ELN, it was able to facilitate greatly improved collaboration and increased productivity on the part of both chemists and biologists. Scientists were able to save time through data re-use and improve the quality of recordkeeping, while drug candidates were able to move more swiftly into pre-clinical and clinical review.

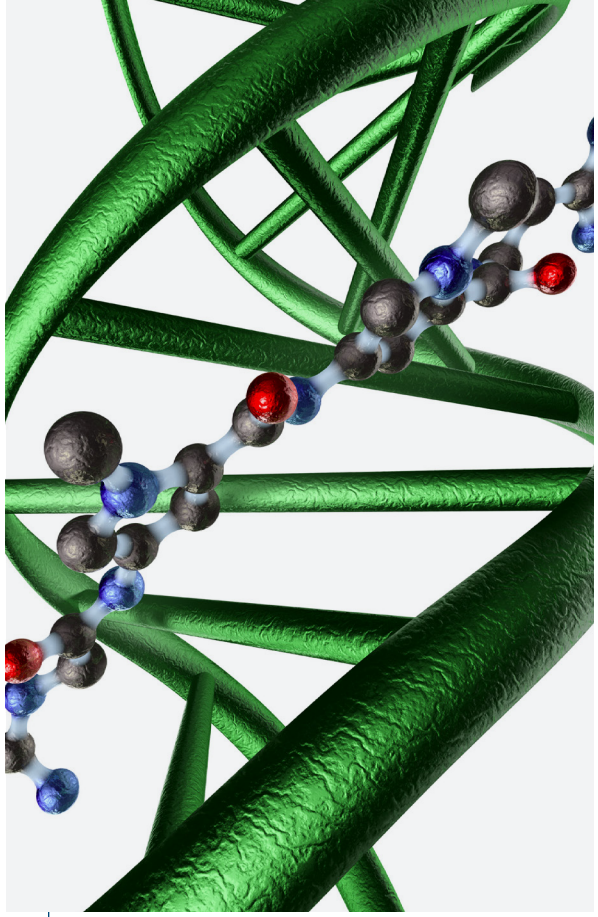
ACCELERATING COMMERCIALIZATION OPPORTUNITIES WITH DIGITAL MANUFACTURING

Pharmaceutical organizations develop and produce therapeutics to address patients' changing needs, and in the process, assume significant responsibility for providing consistent product quality and efficacy wherever they are manufactured. Ensuring that these therapies are produced 'As designed' and 'As registered' is both vitally important and a continuous challenge.

Advances in translational sciences, genomics, and biotechnology-based medicines are facilitating a global shift towards precise medicine. As the manufacture of biologic compounds differs significantly from the processes used in small molecule therapeutics, their production requires significant changes to manufacturing organizations.

Simultaneously, as biologic medicine patents start to expire, the first generation of biologics are beginning to face competition from biosimilars or bioequivalents. This shrinks the revenue margins of therapeutics with high production costs.

All of these changes are creating a paradigm shift in pharmaceutical manufacturing towards more predictive and adaptive facilities that leverage modular technology, disposable components, PAT, the Internet of Things, smart objects, remote control, and augmented reality. These new elements greatly influence the design, construction, layout, and operation of a plant—and, consequently, the timing and cost of production.



Current design and simulation technologies let scientists engineer solutions on the atomic, molecular, and protein levels.

With investments in next-generation manufacturing, pharmaceutical and bio technology companies will significantly extend their competitive advantage and move toward their objectives of globalization, market differentiation, and speed to market—all while controlling costs and continuing to focus on total quality.

To meet these objectives, executives require comprehensive visibility with real-time access to critical KPIs.

The ability to better understand and manage their processes gives them the agility to improve profitability and product quality while ensuring compliance with regulations, protecting brand reputation, and improving time to market.

Managers need to be able to track and report project status in real time, identify process issues and take immediate corrective action before problems arise. In a GMP environment, regulatory actions and quality issues that aren't managed proactively by monitoring and analyzing critical parameters can negatively impact operations.

The capability to control and manage critical process parameters can enable better understanding and management of design spaces used in the biopharmaceutical manufacture of therapeutic solutions.

A platform that provides visibility across the enterprise to identify, monitor, and operationalize critical production processes helps data-driven decision making.

Combining this process-level understanding with virtual commissioning that accelerates the calibration and validation process of manufacturing lines helps reduce costly and time-consuming activities between equipment OEMs and manufacturers, and can transform regulatory compliance from a constraint to an asset.

IMPROVING QUALITY AND REGULATORY COMPLIANCE

As part of a heavily-regulated industry, pharmaceutical researchers and firms must maintain scrupulous documentation of all processes and procedures. This documentation must also be correctly formatted and readily available upon short notice to meet the reporting and evidentiary requirements of the FDA and other bodies. By integrating design, experimentation, quality assurance and manufacturing processes within a comprehensive platform incorporating centralized information management capabilities, researchers can maintain information reliability and integrity throughout the entire development and production process. Since regulatory compliance requirements result in significant additional development expenses, efficiencies gained in terms of time, effort, and accuracy bring a significant benefit to organizations adopting these kinds of platform-based solutions.

ADVANCED INNOVATIONS DEMAND ADVANCED DESIGN SOLUTIONS

As researchers and developers move further and faster into new and uncharted therapeutic territory, the risks and opportunities both stand to rise exponentially. It is likely that more and more organizations will discover that they simply cannot rely upon fragmented processes, discrete technologies, and rigidly-siloed practice areas if they wish to make meaningful advances on therapeutics' new frontiers. The complex, mutable nature of modern pharmaceutical research demands new levels of collaboration, interoperability, process fluidity and advanced information sharing that only a sophisticated, adaptable toolset staged on a unified enterprise platform can provide. As such environments become more versatile and available, more of the incredible potential to be discovered on these frontiers will become visible—and become the treatments and technologies that transform lives.

DESIGNING A HEALTHIER FUTURE

COLLABORATIVE 3D APPLICATIONS CHART THE PATH TO FUTURE BREAKTHROUGHS—AND BETTER CARE

"With Dassault Systèmes' 3DEXPERIENCE platform we enhance business efficiency and develop higher-quality medical device products that comply with international regulations."

– Kim Tae-yong Head of the information system management team, Osstem Implant

A company creates a patient-specific surgical guide that enables doctors to pinpoint and destroy cancerous tissue from the inside.

A team develops innovative 3D-printed prosthetic limbs, tailored to individual patients, that can be delivered anywhere in the world quickly and at a fraction of their usual cost.

A consortium of scientists, regulators, and application developers collaborate to create a system that digitally replicates individual human hearts, expanding physicians' knowledge—and improving patients' outcomes.

Pharmaceutical companies are engineering better care, better cures, and better lives—at the molecular level.

Only a few years ago, each of these would have been an idealistic vision; the stuff of science fiction and utterly unattainable given the technology available at the time.

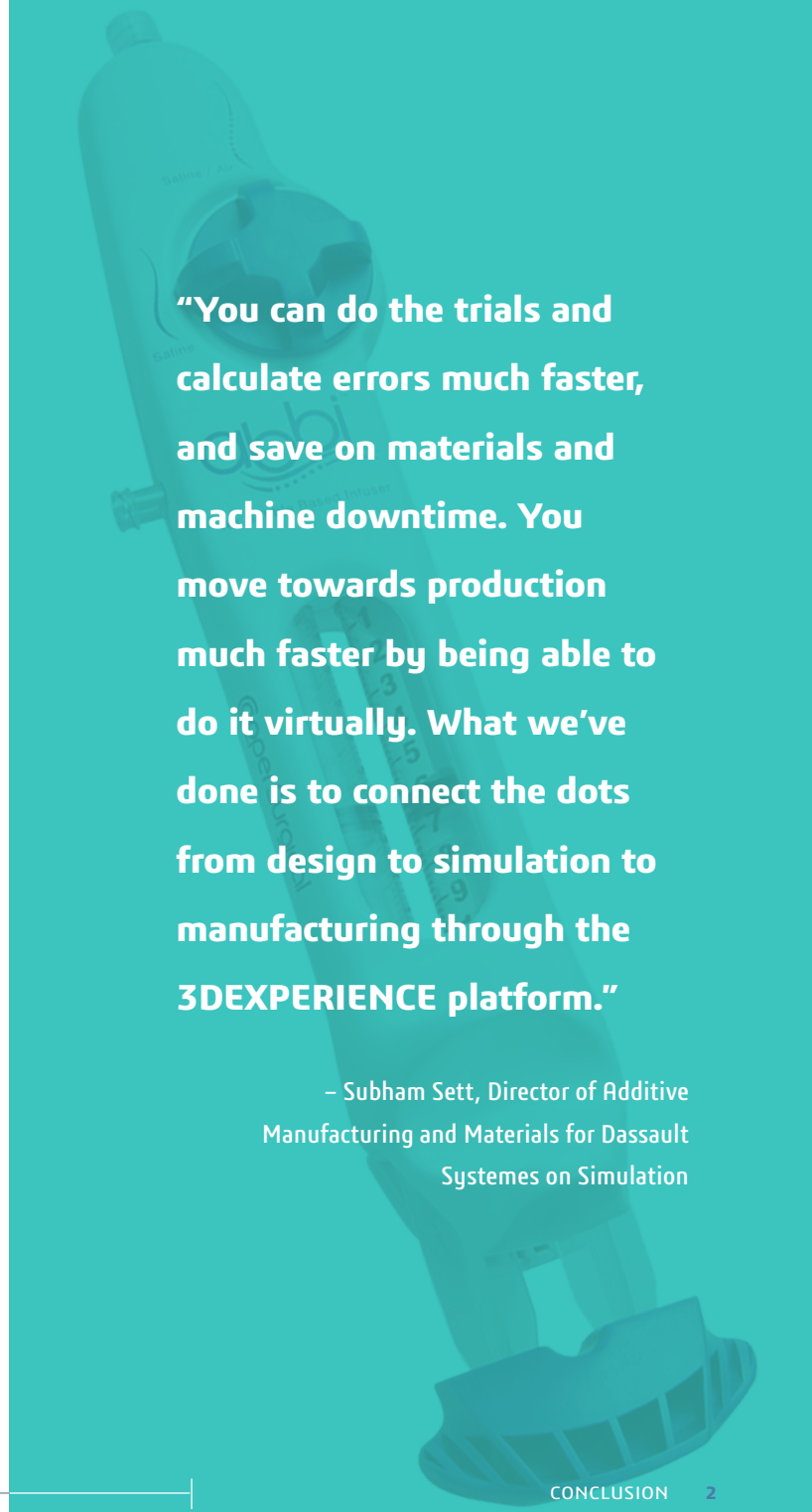
Technology, of course, has a way of advancing. And fortunately, human thinking tends to advance along with it. New capabilities generate new ideas, and empower professionals committed to turning them into realities. When needs, capabilities, and visions converge, yesterday's idealistic visions become new diagnostic tools, treatment devices, and cures, such as a bespoke surgical device, targeted biotherapeutics, an individualized prosthetic, or the Living Heart Project.

Turning visions into realities isn't an easy, straightforward process. In the life sciences field, innovation and isolation don't always work well together. Shared knowledge, committed teamwork, and a firm foundation for collaboration are cornerstones of scientific advancement, and the basis for the new tools and treatments that the world so desperately needs. Fortunately, digital technology can support all three when properly conceived, developed and applied.

The pace of discovery accelerates when researchers and practitioners have the tools to meet the right challenge, at the right time. As doctors and researchers expand their scope of inquiry to incorporate new concepts, such as the digital modeling of the human body or additive manufacturing as a means of creating needed devices and materials, the need grows for applications that are aligned with specific objectives. At the same time, they must remain flexible and extensible, facilitating participation of—and collaboration between—everyone involved in bringing a cure from idea to fruition, from the earliest conceptual stages through design, simulation, testing, validation, and final rendering or manufacture.

It's a challenge that Dassault Systèmes understands. Dassault Systèmes' applications play essential roles in an exhaustive range of industries, from consumer products to aerospace and defense—industries where accuracy, efficiency, interoperability and versatility are pivotal to project success. Through hard-won experience, Dassault Systèmes has learned that providing a tool optimized for a single discipline or vertical is almost never enough: Information and capabilities need to be broadly shared so as to harness the full team's contributions.

The 3DEXPERIENCE platform is created with the goal of providing users at every stage of the project chain a single source of truth for project data in order to enable effective collaboration. The platform connects people and data with rich 3D model-based applications, and digitizes ideas and processes to provide a continually evolving, continually updated project environment, enabling a seamless development environment. By dissolving barriers between applications, specialties and disciplines, the system strives to streamline the innovation process, facilitating contributors' ability to work effectively within their disciplines—and contribute efficiently across them.



"You can do the trials and calculate errors much faster, and save on materials and machine downtime. You move towards production much faster by being able to do it virtually. What we've done is to connect the dots from design to simulation to manufacturing through the 3DEXPERIENCE platform."

– Subham Sett, Director of Additive Manufacturing and Materials for Dassault Systemes on Simulation

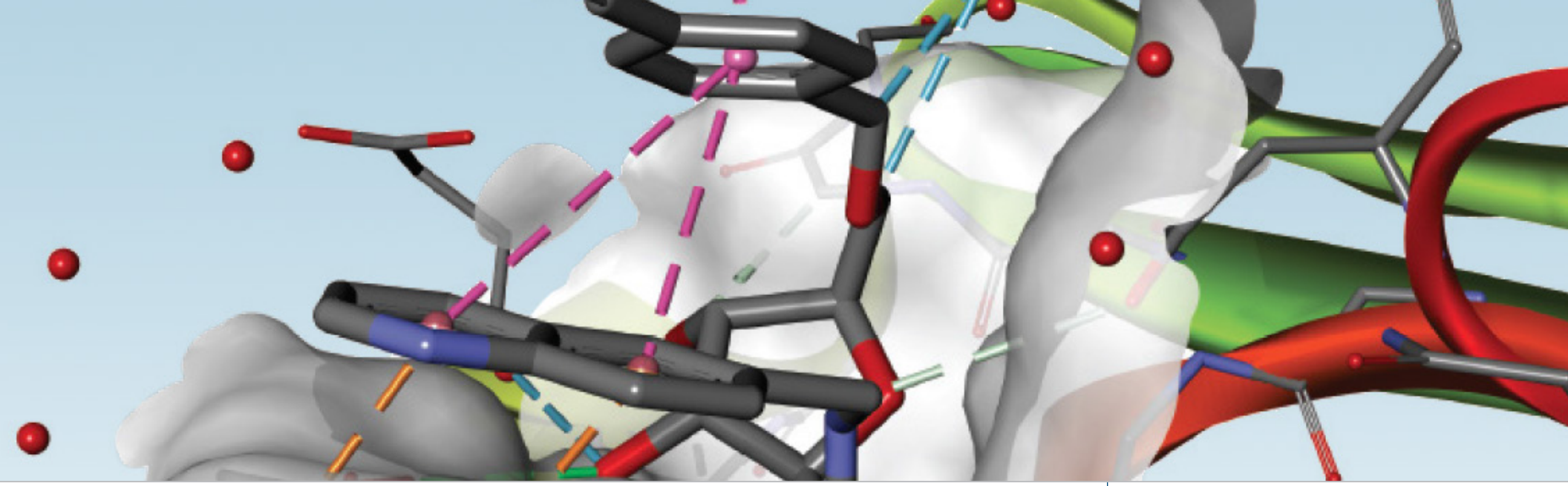
Dissolving barriers between applications, specialties, and disciplines enables contributors to work across disciplines within a seamless development environment.

A NEW STANDARD FOR EXCELLENCE: THE ADAPTIVE, COLLABORATIVE DEVELOPMENT & PRODUCTION ENVIRONMENT

More than ever, life sciences researchers require a comprehensive, yet flexible set of tools accessible on an enterprise platform that connects all the contributors in the value stream, drawing together all participants in a project to foster collaboration and speed advancement. The 3DEXPERIENCE platform is the foundation for continued development and refinement within the life sciences industry. By working closely with researchers, physicians, solutions developers, regulators and other constituencies, Dassault Systèmes gains insight into the emerging challenges that researchers face, and works collaboratively to develop the tools needed to meet them.

Today, researchers are exploring a broad range of tantalizing new possibilities, any or all of which stand to transform the face of medicine, address some of its most intractable challenges, and dramatically improve patient experiences and outcomes:

- 3D-printed "replacement" human organs, comprised from organic materials and cells culled from the patients they will treat
- Molecular-level engineering of bespoke pharmacological compounds and targeted biotherapeutics to treat patient-specific diseases



Structure-based Design in BIOVIA Discovery Studio: 3D pocket views of a novel adenosine inhibitor bound inside the active site of the 70 kDa heat shock protein [PDB: 3FZM].

- Cellular-level modeling of patient-specific organs and tissues, enabling the development of precise patient-suited treatments
- Next-generation immersive instructional tools for the training of physicians and researchers

All may sound fantastic or impossible—just like the countless breakthroughs that have preceded them. Like any number of earlier innovations, they stand to transform both medical practice and human lives.

Dassault Systèmes is dedicated to advancing the life sciences industry and to serving as the indispensable partner of leading medical technology companies, health care facilities, and educational institutions across the globe. We strive to continually expand the range and improve the quality of our solutions, delivering them through a holistic enterprise platform so as to provide the life sciences ecosystem with a powerful means of advancing innovation and improving patient care.

The future of innovation in medicine is unwritten. Through the 3DEXPERIENCE platform, Dassault Systèmes pledges its unswerving support to those who will write it.

LEARN MORE:

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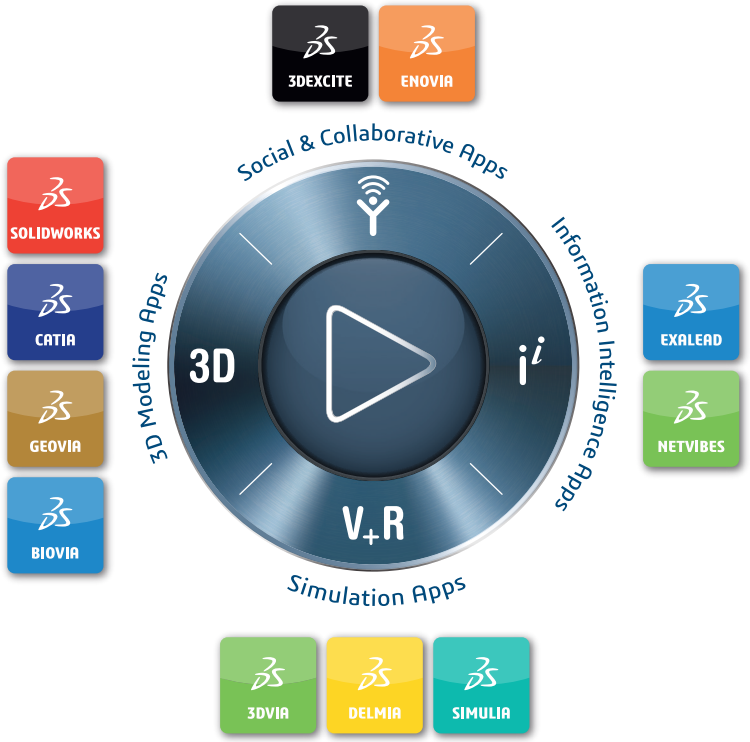
Our **3D**EXPERIENCE® platform powers our brand applications, serving 12 industries, and provides a rich portfolio of industry solution experiences.

Dassault Systèmes, the **3D**EXPERIENCE® Company, provides business and people with virtual universes to imagine sustainable innovations. Its world-leading solutions transform the way products are designed, produced, and supported. Dassault Systèmes' collaborative solutions foster social innovation, expanding possibilities for the virtual world to improve the real world. The group brings value to over 220,000 customers of all sizes in all industries in more than 140 countries. For more information, visit **www.3ds.com**.



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