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FUNDAMENTALS

Understanding the building blocks of life

Note from the Editorial Board

Dear Reader,

The *Dartmouth Undergraduate Journal of Science* was founded in 1998 with the mission of uniting the scientific community at Dartmouth and providing an interdisciplinary forum for undergraduates to enrich their scientific knowledge. Today, the *DUJS* is an award-winning publication produced by undergraduates who are committed to enhancing the goals of science, technology, engineering, and mathematics – or STEM – at Dartmouth and beyond.

This year, the *DUJS* reaffirmed our mission by hosting the College's first *STEM @ Dartmouth* Panel & Activities Fair, publishing an undergraduate-focused *STEM Guide*, and sponsoring the third annual *International Science Essay Competition (ISEC)* with Dartmouth College's Office of Undergraduate Admissions.

STEM @ Dartmouth is an initiative aimed at increasing scientific awareness and fostering peer mentoring at Dartmouth. At the Panel & Activities Fair hosted by the *DUJS* on October 28th, 2014 in Collis Common Ground, five senior-year panelists discussed their diverse classroom, extracurricular, and career experiences. Following the panel, thirteen prominent STEM-related organizations on campus participated in an Activities Fair that provided students the opportunity to learn about academic and service groups operating outside the classroom.

To promote the student-driven component of the event, the *DUJS* published the first version of the *STEM Guide*, a centralized resource of information about coursework, clubs, and careers in the sciences at Dartmouth. Today, the *Guide* can be found online at dujs.dartmouth.edu/stem-guide, and we are excited to report that a second version is currently in progress.

This issue of the *DUJS* published in Winter 2015 is entitled *Fundamentals*, highlighting a focus on the foundational building blocks of knowledge that underlie the study of science. In addition to the exceptional work by our staff writers, the issue features two original research submissions from students at Dartmouth College and two essays by the first and second place winners of the *2014 International Science Essay Competition (ISEC)*, who were selected from over 260 entries representing 21 countries around the globe.

I am proud to be part of the ongoing *DUJS* community, which includes the writers, editors, staff members, and faculty advisors who are involved in various parts of the publication process. As the *Dartmouth Undergraduate Journal of Science* embraces a new Editorial Board for 2015-2016, we look forward to a bright future as we celebrate one of the most influential years in our seventeen-year history.

Thank you for reading the *DUJS*, and we hope you enjoy the issue.

Sincerely,

Scott W. Gladstone
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The Dartmouth Undergraduate Journal of Science *aims to increase scientific awareness within the Dartmouth community by providing an interdisciplinary forum for sharing undergraduate research and enriching scientific knowledge.*

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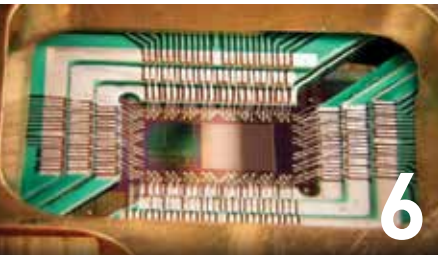

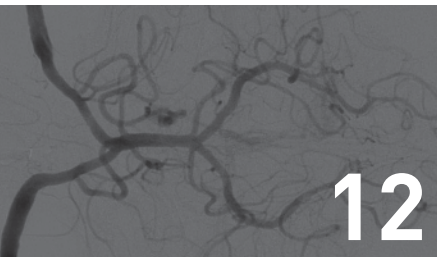

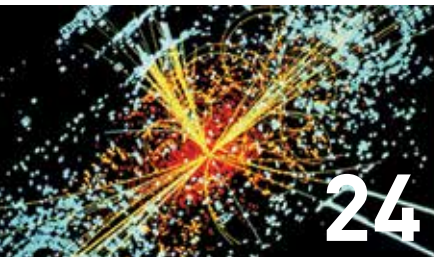

2014 ISEC WINNERS

ORIGINAL RESEARCH SUBMISSIONS

Free Samples as a Pharmaceutical Marketing Tool

Navigating America's Health Care System under the Influence

Image courtesy of Chaos. Available at http://commons.wikimedia.org/wiki/File:VariousPills.jpg

BY JONATHAN BUSAM

Introduction

When describing the American health care system, common phrases include "ethically compromised," "mind-boggling," "rising costs," and "quality problems" (1,2). A myriad of factors contribute to these descriptions, including free samples and other small gifts provided by pharmaceutical companies (1-4). Many physicians do not believe these free items can influence their behavior, yet data suggests that gifts, regardless of size, subconsciously affect the recipient's actions to favor the gift-giver (5-9). Current health policy aims to enable doctors to practice evidence-based medicine by reducing the confounding psychological effects of gifts (10). Such policy targets pharmaceutical marketing techniques involving, but not limited to, branded trinkets, "free meals," and product samples that do more to engender familiarity with the drug than to show its objective efficacy (5,10-12). To date, government-led transparency initiatives aimed at improving patient care have produced ambiguous results with respect to the improvement of delivered value (13-16).

The Evolution of Pharmaceutical Marketing

Since the beginning of the twentieth century, pharmaceutical marketing campaigns with ever-increasing budgets have shifted their target audience from pharmacists to physicians and patients (17). J.A. Greene, an associate professor of medicine and the history of medicine at Johns Hopkins University, chronicles this journey in his 2007 article, "Pharmaceutical marketing research and the prescribing physician" (17). He notes that drug companies initially focused their marketing efforts on persuading pharmacists to stock particular medications in local and regional pharmacies. During the 1940s, the surge of supply and demand for new, brand name, prescription-only pharmaceutical drugs increased the importance of prescriptions. As doctors became gatekeepers between the pharmaceutical industry and patient consumers, the pharmaceutical industry recognized that targeting physicians would yield the greatest benefits in terms of increased sales at the lowest cost (24). The industry did not stop there; it increased its profits further by targeting highly influential physician leaders as opposed to all physicians and consumers directly through advertisements. These advertisements only use data to describe drug efficacy 13 percent of the time, which may not constitute patient-centered, evidence-based medicine (2,3).

Gifts and their Influence on Behavior

Many doctors believe that gifts fail to influence their behavior and that a lack of resistance to these sorts of pharmaceutical marketing strategies would constitute a breech of their commitment to act ethically in prescribing the drug most likely to benefit the patient (5-6). Nonetheless, several studies show that marketing efforts have a demonstrable effect on physician behavior (5). One study revealed that doctors who participated in "free" pharmaceutical-sponsored educational trips more than doubled

Figure 1: Since the 1940s, prescription pharmaceutical drugs have been on the rise. Pharmaceutical industries recognized that targeting doctors yielded the most benefits, though at a potential cost to patient care.

their prescriptions of the corresponding brand name drug within the following year and a half. Although doctors claimed that the trip did not influence their behaviors, their change in prescription patterns significantly deviated from national standards of care (5). Other studies suggest that much smaller gifts, such as soft drinks and stationary, have a role in subconsciously modifying prescription preference in favor of the gift-giver, even at the expense of the patient (6,7). Through the giving of gifts, the pharmaceutical industry is able to influence the prescribing habits of physicians despite their conscious efforts to remain objective.

The industry has used the social psychology and anthropology principal of "reciprocity" to strongly influence physician and patient behavior. Through this lens, gift giving is not "voluntary, spontaneous, or disinterested" (18). Instead, pens, pads, and mugs serve to constantly keep brand names in the minds of physicians. These gifts not only made brand names ubiquitous, but also triggered reciprocity norms, leading doctors to aid the gift-giver by writing prescriptions for their drugs (20). Gift giving practices began to be more strictly monitored in 2008, when the Pharmaceutical Research and Manufacturers of America (PhRMA) modified its "Code on Interactions with Healthcare Professionals" (12,19). However, free samples, which are still permitted under the new code, have been shown to have similar effects on patients, leading to an increase in demand for particular products and brands regardless of the proven efficacy of the drug (5,6). Most often, patients do not inquire about drugs which they have not been exposed to and free samples often serve as the first step in developing patient familiarity with a product.

The Sunshine Act

Transactions between doctors and pharmaceutical companies over **$10** must be made public

Failure to submit info can result in fines up to **$10,000**

Knowingly failing to submit info can result in fines up to **$1,000,000**

The Government Response

The sense of obligation the gift receiver feels toward the giver has the potential to compromise the ideals of evidence-based medicine (23). Strong suggests that health policy should work to restore the possibility of objectivity in prescribing practices by eliminating all gifts from the scope of medical practice (23). Growing conflict-of-interest concerns led to recent policy measures to increase transparency in pharmaceutical payments to physicians with the aim of increasing the quality of patient care (10). Studies revealed that physician relationships with marketers representing pharmaceutical companies led to increased prescriptions of drugs produced by those companies, which contributed to worse patient outcomes in some cases (21). These studies spurred legislators to create the Physician Payment Sunshine Act (22).

The Sunshine Act mandates the public disclosure of transactions between physicians and pharmaceutical devices exceeding $10 in value (11). While the Sunshine Act increases transparency, it fails to stop the flow of all gifts from pharmaceutical companies to physicians. Instead, the act makes some gifts transparent in the hope that patients will make "better informed decisions […] and deter inappropriate financial relationships which can sometimes lead to increased health care costs" (25). Transparency has the potential to address the conflict of interest issue, but the effect of the Sunshine Act has been minimal since the available data are incomplete, ambiguous, and susceptible to misinterpretation in some cases (13,15). If patients cannot easily locate or understand the information made available by the act, they will not be able to realize and respond to physician biases in prescription writing, or to make fully informed decisions (15). A complex website that is difficult to navigate and comprehend limits the ability of the Sunshine Act to allow for objectivity in prescribing (11).

Furthermore, the Sunshine Act does not mandate monitoring or reporting of the distribution of product samples, which has a variety of implications for patients (26). Pharmaceutical companies are increasingly using samples for marketing purposes (5). Without the need for public disclosure, it is likely that this trend will continue. Product samples provide information on how different demographics respond to a particular drug and help uninsured patients (5). Many patients enjoy receiving free samples simply because they are free. In the long run, however, these samples have a price. Some of the samples that are most widely available are particularly expensive, or are novel enough that it is difficult to get an accurate sense for the most common potential side effects (5). Once a patient uses these samples, he or she will likely ask for and receive a prescription from his or her physician that may not necessarily provide the best benefit in terms of health outcome per dollar spent (3).

Conclusion

In recent years, the pharmaceutical industry has pioneered drug and technology options that have substantially improved the quality of life for millions of patients. This productivity and innovation would not have been possible without the free market. If industry is to continue this productivity, there must still be a profit incentive to conduct expensive research. However, this same incentive leads pharmaceutical companies to heavily market drugs they have already developed (1).

With increased innovation in the pharmaceutical industry and perpetual proliferation of drug-related information and marketing, consumers need to boost their savviness when it comes to understanding the

risks and benefits of novel treatment options. Unfortunately, there is a growing amount of literature to review, and obtaining the truth has become increasingly difficult (2). Instead of examining this mass of data, consumers often turn to press releases and pharmaceutical advertisements, the latter of which provide little sound information.

Many drug development gains are made at the margin, and pharmaceutical companies can use statistics to make such gains seem extraordinary in their press releases. For example, in 2008 AstraZeneca trumpeted that Crestor reduced the risk of adverse cardiovascular events by 56 percent (2). As Hadler notes, however, "I'd have to treat about 200 well people with Crestor for a year to spare one of these cardiovascular events… about 400 well people for a year to spare one heart attack and about 600 to spare one stroke. I am unwilling even to suggest a life-saving benefit" (2). The seemingly marvelous 56 percent reduction statistic arises from comparing the 0.77 rate of an adverse event for patients on Crestor and the 1.36 rate of an adverse event for patients not on the drug -- a less grand comparison in absolute value (2). The irreproducibility of the results favoring Crestor coupled with AstraZeneca's use of statistics should cause patients to approach their understanding of drug benefits with healthy skepticism and seek out additional information beyond pharmaceutical companies (2).

Knowing the true benefits of drugs and understanding susceptibility to marketing techniques used by pharmaceutical companies should make consumers think twice before requesting the newest treatments. Hopefully, instead of seeing an advertisement for drug X, picking up a few free samples of drug X at the physician's office, and ultimately asking for a prescription for drug X, consumers will begin to engage in a more open dialogue around which prescription drug might be best suited for their particular condition. This dialogue may enable patients to make more scientifically informed decisions and improve the value of health care in America. Both physicians and patients, armed with better information, can work to improve prescribing habits. D

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"Knowing the true benefits of drugs and understanding susceptibility to marketing techniques used by pharmaceutical companies should make consumers think twice before requesting the newest treatments."

How Quantum Computing Could Change the World

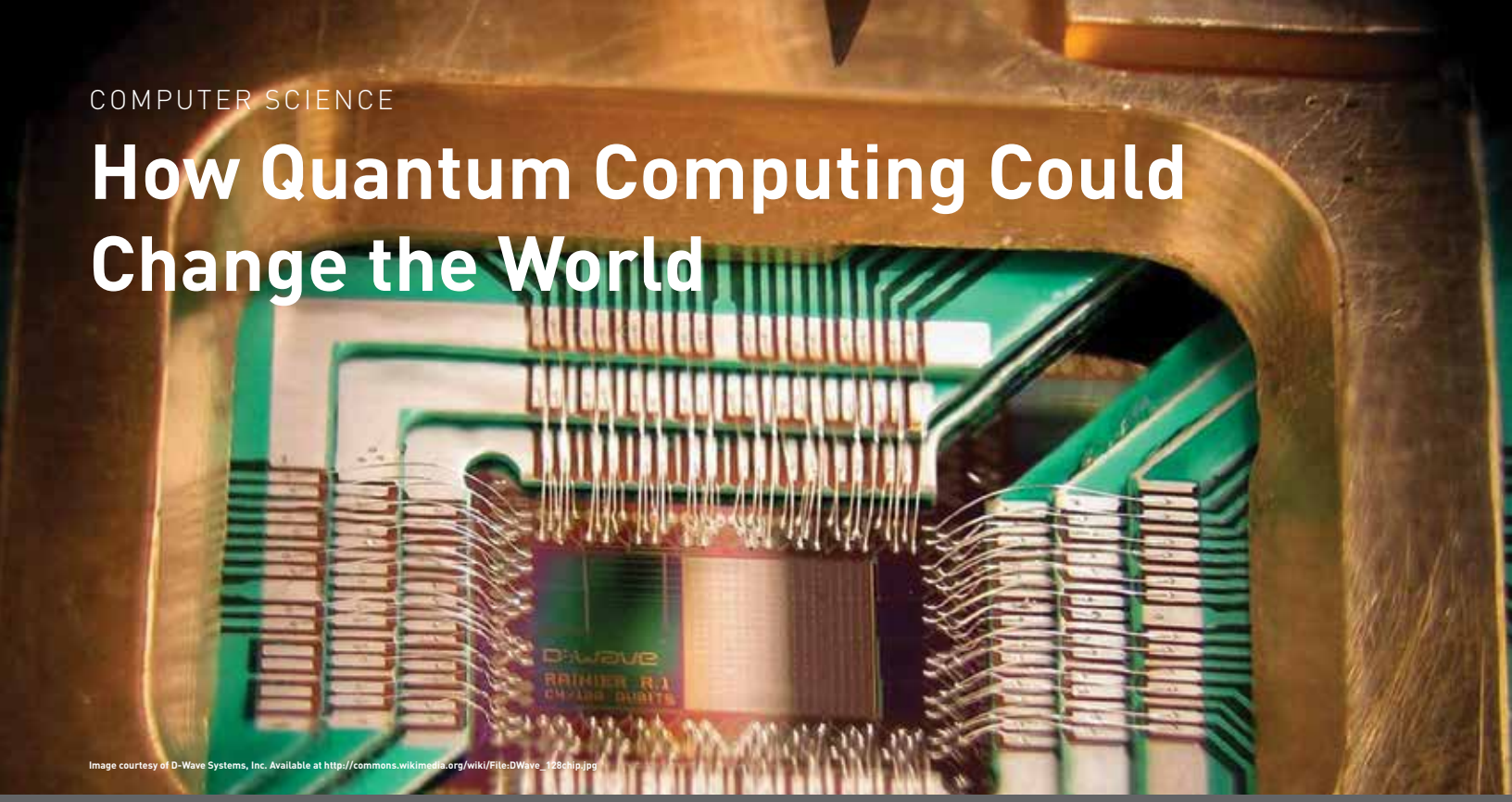

Image courtesy of D-Wave Systems, Inc. Available at http://commons.wikimedia.org/wiki/File:DWave_128chip.jpg

BY MERRITT LOSERT

Figure 1: The processor inside D-Wave's quantum computer.

In 1965, Gordon Moore, then working with Fairchild Semiconductor, noted that computer manufacturers were doubling the density of components on integrated circuits at regular time intervals. Advancements in chip manufacturing allowed companies to produce finer and finer features with fewer imperfections. In 1975, Moore revisited this prediction, claiming that component densities would double roughly every two years. While seemingly innocuous, this observation, dubbed Moore's Law, has been quite prophetic. For the remainder of the twentieth century and into the twenty-first, Moore's Law has accurately predicted the growth of microchip computing power (1).

Moore's Law might not hold indefinitely, however. In 2014, Intel released its next-generation Broadwell chip, with a 14 nanometer die construction, meaning that each layer of semiconductor with a circuit is 14 nanometers thick (2). While these tiny die allow manufacturers to pack many transistors onto a single chip, former Intel architect Robert Colwell still predicts the death of Moore's Law, perhaps as early as 2020 (2). He explains that it might be possible to scale chips down to a size of 5 nanometers, but that anything smaller will become prohibitive expensive (2).

Other technologies exist that might preserve Moore's Law and continue to increase computer performance at an exponential rate. Materials other than silicon show promise, as does the use of graphene nanoribbons in integrated circuits (2). The power of semiconductor processors will certainly continue to improve performance, but perhaps at a slower rate.

However, there exists another idea in computing that could turn Moore's Law on its head, namely, quantum computing. At its core, a quantum computer uses the laws of quantum mechanics to do computations (3). In theory, a quantum computer could greatly outperform any classical computer (4).

Understanding Quantum Mechanics

To understand what makes quantum computers unimaginably fast in theory, one must first understand a few features of quantum mechanics, the branch of physics that describes matter on an atomic scale. As it turns out, matter behaves very strangely when observed at the atomic level. The distinction between waves and particles becomes unclear: small particles like electrons, atoms, and even molecules exhibit wave-like properties (5).

Looking at the famous double slit experiment provides some insight into the strange nature of quantum mechanics. When coherent light is shined through two closely spaced slits in an opaque material, the light produces an interference pattern behind the slits (6). Since light is a wave, this interference pattern is expected. Surprisingly, these results have been replicated for beams of particles

of matter, like electrons, suggesting that they have wavelike properties as well (6).

Even when only one photon or electron passes through the slits at a time, the same interference pattern persists. However, if a detector is used to measure which slit an electron or photon passes through, the detector will only register the particle in one slit, and the interference pattern disappears (6). Until it is measured, each particle can be said to pass through both slits at once. When observed, the motion of the particle is disturbed, such that it is only able to pass through one slit and the wavelike properties of the particle are eliminated (6). In other words, the system decoheres and the superposition disappears. The very act of measurement, then, can be seen to influence a quantum system.

This experiment highlights an important idea in quantum mechanics: superposition. Quantum mechanical superposition is the idea that a particle exists in all possible states at the same time, until its state is measured. In the double slit experiment, each photon or electron passes through both slits at the same time. If the experiment is designed to detect which slit a particle passes through, though, the superposition is lost and the particle is observed to pass through only one slit (7).

While the double split experiment demonstrates this core idea in quantum mechanics, it fails to demonstrate the property of entanglement, which stands as one of the least intuitive features of quantum mechanics. If two particles are entangled, then measurements of the states of those particles will yield correlated results. For example, two entangled photons might always be observed to have opposite polarizations. When measured individually, the polarization of each photon is completely random. However, when both photons are measured together, they always give opposite results. This suggests that photons are somehow able to communicate instantaneously across space (8).

Using Quantum Mechanics to Compute

The fundamental unit of every computer is a bit, short for binary digit. In a classical computer, a bit can have a value of zero or one. Operations performed on these bits drive the function of the computer. Bits are physically represented by positive or negative charge in chips, or by the direction of a magnetic field in hard drives (9).

A bit in a quantum computer, dubbed a qubit, is represented by something much smaller, such as the spin of an electron or the orientation of an ion (4). Due to their small size, these objects are fundamentally quantum in nature. As observed in the double slit experiment, quantum objects behave very strangely.

Here, the idea of superposition becomes incredibly important in quantum computing: the objects that make up qubits do not have to have definite states. An electron, for example, can have an up spin, a down spin, or any combination of the two. Thus, while a classical bit is either zero or one, a quantum bit could be zero *and* one at the same time (10).

As seen in the double slit experiment, however, superposition disappears once the state of a quantum object is measured. A qubit can only exist as a combination of zero and one until its value is measured—at that point, the qubit is forced to "decide" which value to take. For this reason, the superposition of states in a qubit is best regarded in terms of probability. If a qubit is 70 percent zero and 30 percent one, then 70 percent of the time an identical qubit is measured, it will be zero; 30 percent of the time, it will be one. Qubits can have any possible superposition of zero and one, as long as the probabilities of getting one or the other add up to 100 percent.

Moreover, qubits can be entangled to varying degrees. Two qubits might have any degree of correlation between no correlation and complete correlation in measurements of their states (8).

The potential of quantum computation stems directly from the superposition and entanglement of the states of qubits. A collection of 10 classical bits can only represent one 10-digit number at a time. In contrast, a collection of 10 qubits could represent *all* 10 digit numbers at once through superposition. Mathematically, a collection of n qubits has a state space of 2^n dimensions, meaning it contains exponentially more information than the same number of classical bits (10). Since these qubits contain so much information, they could theoretically perform massive parallel computations exponentially faster than a classical computer (4).

Problems with Quantum Computation

Measuring a quantum system causes the system to decohere, and any superposition in the system is lost. Thus, only when a computation is finished can the system be measured. Otherwise, the system would decohere, losing the precious information stored in the superposition of the system. Unfortunately, this poses a huge problem for quantum computation. The smallest disturbance could decohere a complicated

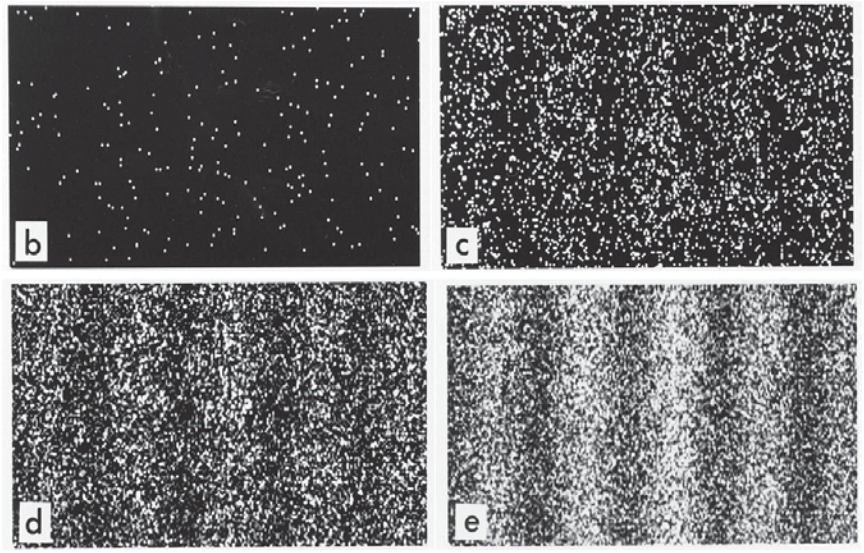

Image courtesy of Dr. Tonomura and Belsazar. Available at http://commons.wikimedia.org/wiki/File:Double-slit_experiment_results_Tanamura_four.jpg

Figure 2: In the double slit experiment, an interference pattern develops even when one photon passes through the slits at a time.

quantum system (11). Building a functional quantum computer is therefore very difficult.

Creating quantum algorithms poses an equally challenging problem. Scientists know of only a few algorithms that work on quantum computers (4). One such algorithm computes the prime factors of numbers. While this algorithm could theoretically factorize very large numbers far faster than any quantum computer, it has proven difficult to implement experimentally. So far, the largest number a quantum computer has successfully factorized is 143 (12).

Is There Hope for Quantum Computers?

While the development of quantum computers has been remarkably slow thus far, some recent developments point to a promising future in the technology. In 2012, D-Wave Systems, a company that builds quantum processors, claimed that its quantum processor could solve a difficult mathematical problem very quickly using 84 qubits (13). The company has even marketed and sold its quantum computers to companies like Google and Lockheed Martin (14).

D-Wave's computer is not yet bringing about a revolution in quantum computing, however. It uses a process called quantum annealing, which works well in solving optimization problems, but is otherwise not very useful. Many scientists question whether D-Wave's machine is a quantum computer at all, citing the fact that D-Wave's results could easily have come from a classical computer (15). In truth, nobody can tell for sure.

At best, D-Wave's computer is an expensive but weak quantum computer that can solve only certain types of problems. However, if D-Wave's claims are true and the machine really does work on a quantum level, it may serve as an important step toward realizing the potential of such machines. At last, these computers might become more than a scientific daydream. D

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The Untapped Power of Viral Gene Therapy

Image courtesy of Dr. Graham Beards. Available at http://commons.wikimedia.org/wiki/File:Adeno-associated_viruses.jpg

BY WILLIAM TACKETT

Introduction

Given how minuscule viruses are, their capacity for destruction is staggering. Though they range in size from 20-400 nanometers, they are responsible for a wide array of diseases and have caused millions of deaths throughout history. Smallpox, for example, killed 300 million people in the 20th century alone, while influenza kills 250,000 to 500,000 yearly (1,2). However, researchers in gene therapeutics are working on harnessing the capabilities of viruses for something more beneficial: treating and curing genetic diseases.

Gene therapy is a relatively new field in biomedical research. The first FDA-approved gene therapy experiment was carried out in 1990 on a child with adenosine deaminase deficiency, a genetic disease that compromises the immune system (3). Gene therapy's progress plateaued in 1999 after a University of Pennsylvania gene therapy trial ended in the death of one subject. However, successful gene therapy experiments since 2006 have renewed optimism within the scientific community around gene therapy as a potential treatment (3). While gene therapy is still very much an experimental treatment, it has had success in trials for a range of genetic diseases, including Leber's Congenital Amaurosis (a form of blindness), hemophilia, X-linked Severe Combined Immune Disorder, Parkinson's and even some forms of leukemia (3,4).

Gene therapy treats diseases by replacing dysfunctional genes with properly functioning DNA. Scientists deliver the correctional gene to subjects using a vector; there are two categories of vectors: viral and non-viral. Each method has its trade-offs. For instance, viral gene therapy has had higher levels of transduction in cells (which means it infects the highest number of cells), while non-viral gene therapy elicits a weaker immune response (which can help to avoid danger to the patient and detriment to the success of the treatment that can result from strong immune response). This article will focus on viral gene therapy.

How It Works

Viruses generally have two parts: a protein capsid and an RNA or DNA genome which the capsid encloses. Sometimes a membrane also surrounds the virus. Viruses cannot reproduce their genome on their own, so they have to infect a host. The specifics of how they infect host cells depends on the type of virus, but there is a general pattern. A virus particle, or virion, begins by attaching to a specific receptor protein on a host cell in a process called receptor-mediated endocytosis. During this process, a piece of membrane surrounds the virion and pinches off. As the vesicle becomes more and more acidic, the virion must escape. Most viruses do this with a fusion protein that activates in response to the change in pH. Direct membrane fusion is also possible if the virus has a fusion protein that activates as a direct response to binding to the receptor (5).

The steps of replication depend on the type of viral genome. Viruses with a double-stranded DNA (ds-DNA) genome usually enter the cell nucleus. Because of this, they are dependent on the cell cycle to replicate. Some ds-DNA viruses use the cell's polymerases to replicate, while others make their own. Adenovirus is one example of a ds-DNA virus used in gene therapy. Single-stranded DNA (ss-DNA) viruses, though less common, replicate in a similar manner to ds-DNA viruses. However, they must first form a double-stranded DNA molecule by synthesizing a complementary DNA strand. One ssDNA virus commonly used in gene therapy is the adeno-associated virus (AAV), aptly named because it relies on the presence of adenovirus in order to infect a host. Another type of virus—retroviruses—use an enzyme called reverse transcriptase to convert their single-stranded RNA genomes into ds-DNA. They integrate this DNA into the host genome using an enzyme called integrase. The host cell's polymerases then proceed to replicate the viral genome. The retrovirus most commonly

Figure 1: A cluster of adeno-associated viruses (AAV), whose vectors are commonly used in gene therapy.

used in gene therapy is the lentivirus. There are also double-stranded RNA viruses and other types of single-stranded RNA viruses, but these are not commonly used in gene therapy (5).

How does gene therapy take advantage of viral behavior to treat diseases? First, scientists modify the virus, removing its genome and replacing it with new genome, which contains the functioning version of the gene that is damaged or missing in the patient, as well as genes that aid in the replication of the replacement gene. Next, researchers deliver a dosage of this viral vector to the cells that need the new gene. There are two methods of accomplishing this: in vivo and in vitro. The in vivo method involves an injection of the vector or an IV directly into the tissue. The in vitro method requires that some of the patient's cells be removed. Scientists then add the vector to the cells in the laboratory and reintroduce them to the patient (6).

Once the vector is in the patient it will behave like a normal virus, attaching to cell receptors and crossing the cell membrane through one method or another. Once in the cell, it travels to the nucleus. Depending on the virus, it will either integrate into the host genome or simply sit in the nucleus. In either case, the polymerases of the host cell will replicate the genome and synthesize the appropriate mRNA molecules and its ribosomes will manufacture the therapeutic proteins out of this mRNA.

HOW GENE THERAPY WORKS

Replace viral genome with genes of interest

↓

Deliver viral vector

↙ ↘

In vivo In vitro

Notable Gene Therapy Experiments

One of the most promising of the latest gene therapy experiments has been a 2008 trial involving Leber's congenital amaurosis (LCA). LCA is a set of hereditary diseases that cause blindness from childhood. One form of the disease, LCA2, is caused by mutations in the retinal pigment epithelium–specific 65-kDa protein gene (RPE65). RPE65 is a part of visual phototransduction, the process by which light is converted into electrical signals in the retina. It is responsible for isomerizing all-trans retinyl ester into 11-cis retinal. Without 11-cis retinal, opsins, a kind protein in photoreceptor cells, cannot perform their main function: capturing and converting light into electrical responses. This biochemical defect results in severe visual impairment, with vision deteriorating into full blindness over time (7).

The trial used RPE65 complementary DNA (cDNA) packaged in a recombinant adeno-associated virus (AAV) vector. 1.5×10^{10} copies of the vector were injected subretinally in three patients. All three patients showed improved pupillary light reflexes (effects of light on pupil size) and a decrease in nystagmus (involuntary eye movement). The patients also showed improvements in visual acuity. However, in the test of ability to navigate an obstacle course, two of three patients showed less promising results, bumping into obstacles and straying off course, while the third was challenged only by objects in her peripheral vision. One patient developed an asymptomatic macular hole (a small break in retinal tissue), but this adverse event was not linked to the AAV vector. Overall, the results of the study were very promising; efficacy of the treatment could be improved if administered before retinal degeneration occurs (i.e. in children) (7).

Hemophilia B is another disease that has been a major target for gene therapy. Hemophilia B is an X-linked bleeding disorder caused by mutation in clotting factor IX (FIX). FIX is a vital part of the coagulation cascade which closes up blood vessels when they are cut; without it, the body is incapable of stopping bleeding. Hemophilia B can be treated with injections of the protein itself into the blood of patients two to three times a week, but this treatment is expensive and inconvenient. It is, however, a viable candidate for gene therapy because it is caused by a defect in a single gene and because patients only require one percent of normal levels of FIX for an improvement in quality of life (8,9).

In a 2011 clinical trial, researchers took steps to make the therapy more effective. The first was to use an AAV vector that they modified to be double-stranded. Usually single-stranded DNA viruses like AAV must create a complementary DNA strand before they can replicate, which slows them down. By making the genome double-stranded beforehand, the researchers ensured that the vector would be more effective. The second way they improved efficacy was by using the capsid of a type of AAV known as AAV8. AAV8 is much less common in humans, which reduces the risk of neutralizing antibodies impeding expression. The third step was to limit the invasiveness of the injection itself by injecting into the peripheral veins, which are in the hands, arms, legs, or feet. Injecting in this manner is possible due to AAV8's strong liver tropism, meaning it has a high tendency to go to and transduce liver cells. This is advantageous because FIX is produced in the liver, so the vector progresses naturally to the site of production (9).

Results of the study have been very promising. All six patients saw expression of FIX at two to 11 percent of normal levels. One patient of the high-dose group saw high levels of serum aminotransferase levels in the peripheral blood, a phenomenon associated with T-cells specific to AAV8 capsid. Another had a slight increase in liver enzyme amounts. These effects were successfully treated without loss of gene expression. Despite these minor roadbumps, the trial can be called a success due to the stable and therapeutic levels of FIX gene expression (9).

Challenges to Progress in Gene Therapy

Despite its recent success, a number of fundamental barriers limit the effectiveness of gene therapy. The first concern is its longevity. Gene therapy is currently most effective in cells that do not divide often. Unless the viral vector integrates the gene into the host genome, the effectiveness of the therapy will not last long. In dividing cells, the therapeutic gene will not be passed to any of the daughter cells of the initially transfected cell without integration. Under these circumstances, patients would have to receive multiple rounds of gene therapy throughout their life. With viral vectors that do integrate their genome, other issues arise. Integration into the wrong location in the host genome could result in detrimental mutations or even cancer (10). In one gene therapy trial that lasted from 1999 to 2006, the therapy restored a critical gene in immune cells. Later, however, five of the patients developed leukemia because the therapeutic gene integrated into a gene that helps to regulate cell division (10).

Another roadblock for viral gene therapy is the immune system. The immune system attacks any foreign entities entering the body, including viral vectors. The immune system will attack vectors and prevent them from infecting cells and replicating. When this happens, the treatment is much less effective. More important than effectiveness, however, is when an immune response is particularly intense and becomes dangerous for the patient. The most famous example of this phenomenon is Jesse Gelsinger. Gelsinger was the patient in the aforementioned University of Pennsylvania gene therapy trial who died. His death was caused by an inflammatory immune response to a dose of adenovirus vector (11).

Yet another major hindrance to progress in gene therapy research is its cost, as gene therapy focuses on rare single gene disorders. Drug companies considering funding gene therapy research recognize that the market is small in terms of the number of patients who might benefit. It would be difficult to recoup the costs of very expensive research. While gene therapy is also being developed for more common diseases, like some cancers, these treatments would have to be individualized and therefore expensive.

AAV and the Future of Viral Gene Therapy

Gene therapy scientists are working on addressing these issues by introducing a new type of virus called AAV as a vector. Both of the clinical trials discussed in this article used a type of AAV as the viral vector. AAV offers some advantages over other types of viruses. For one, its immunogenicity, or tendency to elicit an immune response, is low, a trait especially valuable in the post-Gelsinger era. AAVs are harmless, even in a non-modified state. They are non-pathogenic, so they are not associated with any kind of disease and do not elicit a dangerous immune response (11). In some respects, they are also more effective at delivering a therapeutic gene than other viruses. As researchers have studied these viruses more, they have discovered that different types have "specialties." For example, AAV8 is extremely effective at transducing liver cells. Another type, AAV9 actually crossed the blood-brain barrier, an unprecedented achievement for a gene therapy vector (11). With this new virus paving the way, gene therapy has reached new heights after almost completely failing in the early 2000s. Much has yet to be overcome, but the field has regained some of the promise that scientists thought it had when it was first conceived. With more clinical trials being conducted than ever before, gene therapy is now back on its way to becoming a reality in medicine. D

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"AAV9 actually crossed the blood-brain barrier, an unprecedented achievement for a gene therapy vector. With this new virus paving the way, gene therapy has reached new heights after almost completely failing in the early 2000s."

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Nanoparticles for CNS Drug Delivery: Crossing the Blood-Brain Barrier

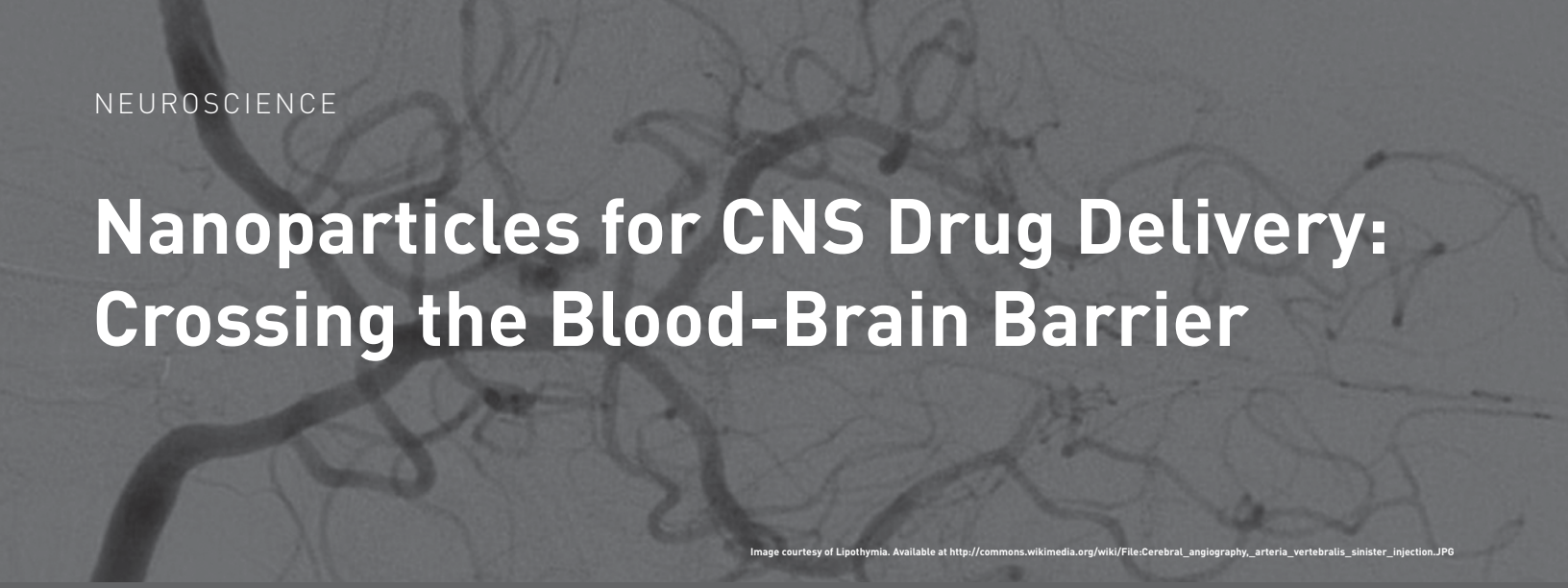


Image courtesy of Lipothymia. Available at http://commons.wikimedia.org/wiki/File:Cerebral_angiography,_arteria_vertebralis_sinister_injection.JPG

BY STEPHEN OFORI

Figure 1: Depiction of cerebral circulation. The blood-brain barrier allows essential nutrients to pass but keeps foreign materials out of the brain. This has been a problem for drugs that need to reach the central nervous system.

Introduction

The brain is a highly sophisticated and sensitive organ that is responsible for both conscious experience and involuntary metabolic actions. Everything that humans taste, feel, smell, think, and see is the result of complex neuronal activity. With such a profound responsibility, the brain must operate in a biochemical environment that ensures its optimal performance. A specialized system called the blood-brain barrier maintains the homeostasis of this specific biochemical environment by allowing access to essential nutrients and denying other objects. However, this same barrier that protects the brain from foreign objects also deters therapeutic drugs from reaching the central nervous system. Thus, there is an urgent need for the modification of pre-existing drug delivery methods that treat neurological disorders and diseases. Progress in the field of nanotechnology has provided numerous nano-sized vehicles for improved CNS drug delivery. Nanoparticle drug delivery proves to be one of the most promising approaches for crossing the blood-brain barrier.

A Remarkable Discovery

The discovery of the blood-brain barrier began about 100 years ago with the experiments of a bacteriologist named Paul Ehrlich (1). Ehrlich was searching for different dyes to stain and kill the deadly parasite, *African trypanosomiasis*. After testing several different dyes, he settled on one because of its low toxicity. In hopes that it would kill *trypanosomiasis*, the dye was nicknamed trypan blue. Initial effects of trypan blue were promising; however, patients began relapsing several months after treatment. Ehrlich's study ended in 1905 with no success. In 1913, Edwin E. Goldmann used trypan blue dye in his tumor research again for its low toxicity and ability to spread quickly throughout the body. Upon injections of trypan blue into several animal species, Goldmann observed how the dye stained the entire body while leaving the brain and spinal cord "as white as snow" (1). Following injection of trypan blue into the subarachnoid space at lumbar level, dye flowed rapidly throughout the central nervous system (CNS), staining it blue. From this, Goldmann concluded that there must be a lack of dye penetration from the blood into the CNS and a compartmentalization between the CNS and its vasculature (1). The blood-brain barrier was, for the first time, demonstrated and visualized. (1)

There are approximately 100 billion capillaries in the human brain, the net surface area of which cover approximately 20 square meters (2). Due to this extremely large surface area, one would expect the penetration of substances from the blood into the brain to be very high. However, the interactions between the brain and its vasculature remain minimal, only allowing certain substances into the CNS. To understand the selective permeability of the blood-brain barrier (BBB), it is crucial to understand its structural components as well as the factors that regulate penetration of the substances (2).

A Close Look

Neuroscience research has proved that the brain's capillary system is organized into neurovascular units, which are involved in the regulation of cerebral blood flow. If one were to examine a cross section of one neurovascular unit, one would see endothelial cells, the basal lamina, a pericyte, and astrocytes (3). The endothelium lines the cerebral capillaries, and the interactions between endothelial cells perform the main function of the BBB. Adjacent endothelial cells form tight junctions, which are belt-like adhesive regions (3). They contribute to selective permeability by forcing substances

to travel across the endothelial cell (trans-cellular transport) rather than in between the cells (para-cellular transport). Surrounding the endothelial cells is the basal lamina, which serves as an anchor for other components of the BBB, acts a signaling site for cell-to-cell interactions, and provides structural support for cerebral capillaries (3). Inside the basal lamina is a cell called the pericyte. Pericytic cells are similar to the nearby endothelial cells in terms of their physical characteristics, and the two cell types signal to one another to regulate BBB permeability. As contractile cells, pericytes also induce BBB "tightness" for reduced permeability.

Astrocytes are a type of glial cell in the CNS, and they have terminal ends on neurovascular units (3). Through these terminal ends, astrocytes aid nutrient uptake of substances from the blood that are allowed to cross the BBB and transport nutrients to nervous tissue. Research suggests that astrocytes may also contribute to BBB tightness, like pericyte cells. Astrocytic cells also secrete various hormones and neurotransmitters in addition to aiding nutritional uptake and transport. Thus, they are crucial for the homeostasis of the biochemical environment in the brain and other metabolic processes (3).

A Closer Look

Examining the structural components of the BBB gives useful information about how it maintains the microenvironment of the brain. However, the efficiency of this system is most apparent at the molecular level. The tight junctions of endothelial cells are composed of many proteins, the two most important being occludin and claudin (3). In between each endothelial cell, these proteins are anchored to each other and to actin filaments on each endothelial cell, forming a physical barrier. Only water and small hydrophilic molecules may pass through the tight junctions. Other substances are either denied passage into the CNS or must enter through a transmembrane pathway. There exist several mechanisms of active transport across the BBB, and different substances often use different mechanisms of transport (3).

For example, small hydrophobic molecules, such as oxygen gas and carbon dioxide, may diffuse freely through the BBB. Additionally, the lipid membrane on endothelial cells means that lipid-soluble molecules may also enter the CNS (3). This is a passive type of transport caused by a concentration gradient. Due to the large surface area of the lipid membrane, simple diffusion is the primary method by which therapeutic agents reach the CNS. Endothelial cells also contain transport proteins for carrying nutrients across the BBB (3). Some are bidirectional, capable of carrying substances to the CNS and away from the CNS into the bloodstream, and some are energy dependent. These transport proteins include the carrier for glucose (GLUT1), the carrier for amino acids (LAT1), and carriers for many other substances including purine bases, nucleosides, and choline (3).

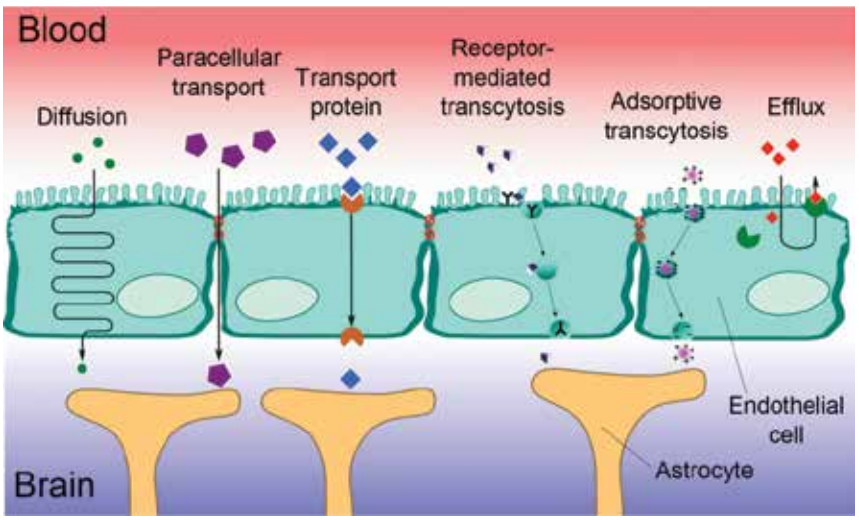
Another mechanism of transport is receptor-mediated transcytosis. This mechanism involves receptors on the endothelial surface that are sensitive to specific molecules. Once a molecule has joined with its corresponding receptor, the first step of the mechanism has initiated; the molecule is absorbed into the cell by endocytosis (3). The molecule is then transported across the endothelial cell, past the BBB and into the CNS. Substances that are subjected to this type of uptake include insulin, leptin, and iron. The final known mechanism of transport across the BBB is called adsorptive-mediated transcytosis, which utilizes positively charged cargo in a non-specific manner. Serum proteins use this transportation method.

The Problem

The intricacy of the transport mechanisms across the BBB reflects its proficiency in maintaining the biochemical environment of the brain. Protecting the CNS from various blood-derived compounds ensures that external forces do not affect neurological processes. However, individuals with neurological disorders such as schizophrenia need certain drugs delivered to the CNS for treatment. It is difficult for these drugs to diffuse through the blood into the CNS because the BBB restricts the passage of most drugs by diffusion or active transport (4). The BBB identifies most drug therapies as foreign objects and prevents 98 percent of drugs from reaching their CNS targets (6). In fact, a recent study of the comprehensive medical chemistry database showed that only five percent of 7000 drugs

Figure 2: Substances may enter the CNS via these mechanisms of transport across the BBB.

Image courtesy of Armin Kübelbeck. Available at http://commons.wikimedia.org/wiki/File:Blood-brain_barrier_transport_en.png



analyzed affected the CNS, treating disorders such as depression, schizophrenia, and insomnia (5). It is in this way that the same system that protects the CNS could also contribute to its disturbance by depriving it of helpful drug therapies.

Thus, there is an urgent need to overcome the BBB to allow for successful drug delivery. One method of achieving this is to use ultrasound to loosen the tight junctions between endothelial cells. However, forcibly opening the BBB in this fashion may cause structural damage, creating further issues for the patients. Many psychoactive drugs also disrupt BBB function by loosening endothelial tight junctions, allowing large amounts of the drug to enter the CNS. However, this method is also associated with a variety of risks. Flooding the brain with therapeutics causes osmotic imbalances that largely affect BBB permeability and restrict normal supply of nutrients. Additionally, loosened tight junctions throw off the homeostasis of the brain, resulting in compromised brain function. Safe, noninvasive drug delivery to the CNS is a complex problem that calls for an unorthodox solution (4).

The Solution

Nanotechnology is the result of the manipulation of matter on the atomic and molecular scale of observation. It has received a great deal of attention over the past three decades, and its progress has given us a variety of tools in engineering and the sciences (7). Biomedicine in particular has seen significant progress due to the advent of the nanoparticle. There has been extensive research on the application of nanoparticles as drug delivery systems that function to deliver drugs to specific cells at predetermined rates over a set course of time (8). Nanoparticles differ in composition with respect to their targeting sites in the body. The drug delivery system's ability to target specific sites greatly enhances therapeutic potency while sparing healthy tissue. Javad Safari and Zohre Zarnegar claim that: "Micro- and nano-scale intelligent systems can maximize the efficacy of therapeutic treatments in numerous ways because they have the ability to rapidly detect and respond to disease states directly at the site, sparing physiologically healthy cells and tissues and thereby improving a patient's quality of life" (8).

Given that the mechanisms of BBB function operate on the molecular and nano-scale level, the application of nanoparticles is the most promising approach for crossing the BBB. The ideal set of characteristics for nanoparticles is to be smaller than 100 nanometers, biodegradable and non-toxic, BBB-targeted, long-lasting, and cost effective (5). Nanoparticle composed of a liposomal shell are found to be non-toxic and biodegradable (9). BBB targeting is achieved by constructing the nanoparticle with ligands on its surface that correspond to receptors on the BBB (9). Once bound to the receptor, the nanoparticle undergoes receptor-mediated transcytosis (9). A dissociation of the receptor from the nanoparticle leads to its acidification and the release of the drug into the brain (5). The particles may also be constructed with cationized ligands so that it may pass through the BBB by adsorptive-mediated transcytosis. The efficiency of nanoparticles lies in their ability to operate under the same transport mechanisms as endogenous CNS particles.

Conclusion

The BBB allows the CNS to operate in a distinct biochemical environment from the rest of the human body. However, this same protective barrier also hinders conventional drug delivery to the CNS. One must study the BBB deeply to confront this problem, going deeper than its superficial structural components and observing its molecular anatomy. Given the delicate balance of small particles involved in maintaining normal brain function, innovative strategies are necessary to allow for the entry to CNS drugs without compromising the stability and defense conferred by the BBB. D

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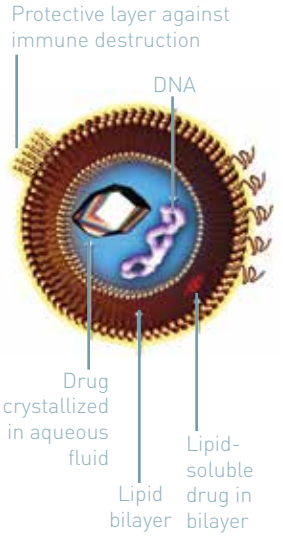
Liposome for Drug Delivery:
An Example of Nanotechnology in Medicine



Original image courtesy of Kosi Gramatikoff. Available at http://en.wikipedia.org/wiki/File:Liposome.jpg

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Nanoscale Technology: The Key to Accessing the Previously Inaccessible

Image courtesy of National Oceanic and Atmospheric Administration: Office of Response and Restoration

BY HAE-LIN CHO

Introduction

Despite enormous progress in science and engineering, there are locations far out of the reach of human exploration. Exploring places such as outer space and the inner human body has proven extraordinarily difficult.

Scientists now believe that the key to accessing these regions lies not simply in better tools, but in smaller ones - specifically, those whose sizes are on the nanoscale—on the order of 10^{-7} to 10^{-9} meters (1). Reflecting the current trend of shrinking technology, nanotechnology has recently gained traction in experiments despite a variety of size-related technical and practical challenges behind its realization. Its unique properties stem from the characteristics of particular materials at the nanoscale level, and give it potential in a wide variety of fields (2).

Exploring Outer Space

Although common sense seems to dictate that larger, heavily enforced structures would better survive the harsh conditions of outer space, current data suggests that miniscule nanorobots may have the most success exploring the cosmos.

In 2005, scientists at the National Aeronautics and Space Administration (NASA) introduced the idea of "autonomous nanotechnology swarms," otherwise known as ANTS, which gave birth to multiple related projects (3). Rather than using singular and static structures, engineers at NASA hope to use nanotechnology to send up small parts of robots or multiple interacting robots that could dynamically adapt to their environment for better space exploration (3). Nanorobots forming a swarm could be sent in a capsule to distant planets, released, and programmed to explore. They could also combine to form structures, like antennas, to help travel and communicate (3). By sharing information and adapting different structures, nanorobots could better navigate their environment.

One of the main ANTS projects is the Tetrahedral Walker Project. The "TETWalker" robot prototype is designed as a triangular pyramid with electrical motor nodes at corners with struts connecting each of the nodes (3,4). Swarms of miniaturized TETWalkers could potentially be sent to the moon, Mars, asteroids, or other planets. They could also potentially survive longer and transmit more information than conventional craft; TETWalker's most recent design managed to travel 10 km in a day. However, further research and developments seem to have ceased according to the NASA ANTS research website (4).

Other possibilities of nanotechnology in space exploration have since emerged, including that of carbon nanotubes. Stronger than steel and $1/100{,}000^{th}$ the diameter of a strand of human hair, carbon nanotubes offer a great deal of structural potential (2). In addition, carbon tubes conduct heat and electricity very well in comparison to other common materials, making them excellent thermoregulators for space-traveling vehicles to help protect against lightning strikes or other temperature-related emergencies (2). By maximizing strength and minimizing weight better than the currently used materials, carbon nanotubes are ideal building blocks for future space technology (2).

ANTS, carbon nanotubes, and other related nanomaterials could enhance space exploration by downsizing vehicles, decreasing the energy requirements due to weight, and even generating their own thermoelectric energy (5). These materials could also be used to build the sensors on spacecraft and rovers, which would allow engineers to equip smaller instruments with multiple capacities like mapping and monitoring (5).

Figure 1: Oil from future spills resembling the Gulf of Mexico spillage in 2010 may be recovered using nanotechnology developed by researchers at the Massachusetts Institute of Technology. By using ferrous nanoparticles and powerful magnets, the researchers believe that oil and water can be effectively separated.

Figure 2: Although the TETwalker remains a prototype, yet to achieve nanoscale, it represents the potential of nanotechnology in interstellar exploration using "swarm" technology. This and other uses of nanotechnology, like carbon nanotubes, are being explored by organizations such as NASA.

In the Human Body

Experimenting on and repairing the human body requires a large degree of delicacy and precision. Even before nanotechnology, surgeons and medical practitioners have been refining their practice via minimalization (6). For example, the transition from crude saws to scalpels allowed surgeons to perform a variety of procedures in a much safer fashion. Surgery, initially limited to external and rather violent procedures that required large, dangerous incisions into the human body, expanded as the tools that performed it shrunk (6).

This emphasis on finding minimally invasive techniques evolved into the current-day focus on nanorobotics. The small size of nanorobots could not only allow better access to certain parts of the human body, but also decrease the potential and extent of damage. After all, nanotechnology is built on the same size scale as viral particles and proteins, both of which have relatively easy access to human body systems (1).

Since only materials smaller than 400 to 600 Daltons can pass through the blood-brain barrier (BBB) that protects the brain, neurological conditions like Alzheimer's Disease, which require early detection and delivery of potent drugs across the BBB, can prove difficult to diagnose or treat (1). However, nanotechnology may provide better detection of Alzheimer's by using more sensitive microscopy and assays. These techniques measure the level of protein build-up in the brain, which is correlated with the potential for disease (1,7). In addition, since nanobots can be made small enough to pass the BBB, they can provide much more effective delivery of drugs to the affected brain tissue. In fact, some scientists believe that nanotechnology combined with stem cell therapy may one day be able to cure Alzheimer's Disease outright (7).

Delicate surgical procedures like eye or fetal surgery may also benefit from nanotechnology, which would significantly decrease the potential for internal trauma of the patient (8). In the case of retinal surgery, surgeons may be able to bypass the risk of damaging the eye entirely by injecting the nanobots into the blood vessels of a safer area and then directing the robots to the eye via remote control (8). Such a degree of control would allow for safer and less invasive surgical operations in the brain and may even allow for nerve repair. This strategy could also allow faster recovery times for the patient (8).

Not content to simply deliver drugs, scientists believe that nanotechnology can provide valuable information about a patient via surveillance and imaging (1,8). For example, nanobots may be able to measure vital signs like heart rate or blood pressure from inside a patient's body. Some researchers hope that using the same "swarm" technology that NASA hopes to achieve with ANTS will not only be able to detect critical changes in vital signs, but also fix the underlying cause by joining with other nanobots, sharing information, and responding appropriately (8). These situations could involve breaking down clots or surrounding and destroying pathogens.

Nanoparticles have also shown potential in fighting various diseases. Scientists at Washington University in St. Louis, for example, designed nanoparticles that contain bee venom. These particles can kill the human immunodeficiency virus (HIV) without harming the surrounding host cells. Realizing that HIV is smaller than the nanoparticle while human cells are larger, the scientists designed the nanoparticle with bumpers that prevent host cells from making contact with melittin, the toxin in bee venom. HIV, however, slips through the barrier and is eradicated (9). Researchers hope to develop this technology into a vaginal gel to prevent HIV transmission, but their results suggest even more potential uses. In addition to killing HIV, nanoparticles containing melittin also attacked and killed tumor cells (9).

Acting in an opposite manner to nanoparticles, "nanosponges" absorb rather than distribute materials, but appear similarly promising. Nanoengineers at the University of San Diego believe that non-specific nanosponges can remove toxins released by infectious bacteria, particles, and even the venom of snakes and bees (10). In fact, these nanosponges improved survival rates in mice injected with the MRSA toxin both when the sponges were injected before the toxin and when they were injected after, highlighting their versatility (10).

Cancer research is another potential field for nanotechnology. Much like melittin-carrying nanoparticles, other nanobots may be able to attack cancerous cells from within the body. They could also help deliver necessary drugs to remote locations within the human body, like the inside of the blood brain barrier. In the future, scientists hope that nanotechnology as a cancer therapy will be made even more effective by using multiple waves of nanobots to better target cancerous tissue and avoid harming healthy cells (8).

Whether as surgical tools, information gatherers, or delivery vehicles, nanotechnology signals exciting possible developments in the field of medicine. Although the current designs and mechanisms of nanotechnology remain primarily theoretical, its actualization could revolutionize treatment and improve the standard of care for patients all over the world.

Environmental Toxins

In addition to aiding medical and astronomy research, scientists believe that nanotechnology could also help clean environments made inaccessible by pollution, radiation, and

other toxic materials. Nanoscale dry powders varying from silver to nickel are already being manufactured and used as neutralizers for chemicals and other toxins (2).

One example of such an application involves groundwater purification to prevent arsenic poisoning, which remains a global problem that affects millions of people. Arsenic poisoning is not only capable of causing acute illness, but is also carcinogenic (11). In 2006, when large-scale technology proved ineffective in removing arsenic and providing safe drinking water, scientists at Rice University decided to go to the nanoscale level. A group of researchers at Rice's Center for Biological and Environmental Nanotechnology (CBEN) developed a design coined "nanorust." Nanorust consists of miniscule iron oxide particles that bind with arsenic and can produce sand-like filters to purify groundwater (11). The first tests began in 2009 in Guanajuato, Mexico (11). Similarly, nanoscale titanium dioxide, a component of some sunscreens, has been shown to neutralize harmful bacteria like *E. coli* in water (2).

On a related front, a team of researchers at the Massachusetts Institute of Technology (MIT) led by Shahriar Khushrushahi published a paper that describes how water-repellent iron nanoparticles can be used to separate oil from water in the event of an oil spill (12). By mixing the nanoparticles into the oil, it can be safely and effectively separated from water using a perpendicular, cylindrical design of magnets called the Halbach array (12). The separated oil can then be recycled and reused. Although this design requires water to be run through multiple times to remove all the oil, its simplicity allows it to be used with minimal energy consumption and maintenance (12). However, in order to keep nanoparticles themselves from polluting the environment, the current design calls for the oil-water suspension to be held in separate vessels (12).

Just as nanosponges are used to absorb toxins in the human body, nanoparticles can help reduce the damages incurred on the environment. With relatively recent incidents such as the Fukushima nuclear meltdown in 2011 and the ongoing issue arsenic poisoning, environmental damage control represents another major area of potential for nanotechnology.

Conclusion

Although nanotechnology in the aforementioned applications remains largely experimental and prototypical, its already enormous potential continues to grow with the imagination and innovation of experimenters and researchers. It may take years to achieve a practical control of nanotechnology. The self-assembly necessary to create nanobot swarms and the motion dynamics of bots within the environment are especially difficult problems. However, further research may lay the foundation for important advances in the future - advances that could unlock places that have remained previously unexplored. D

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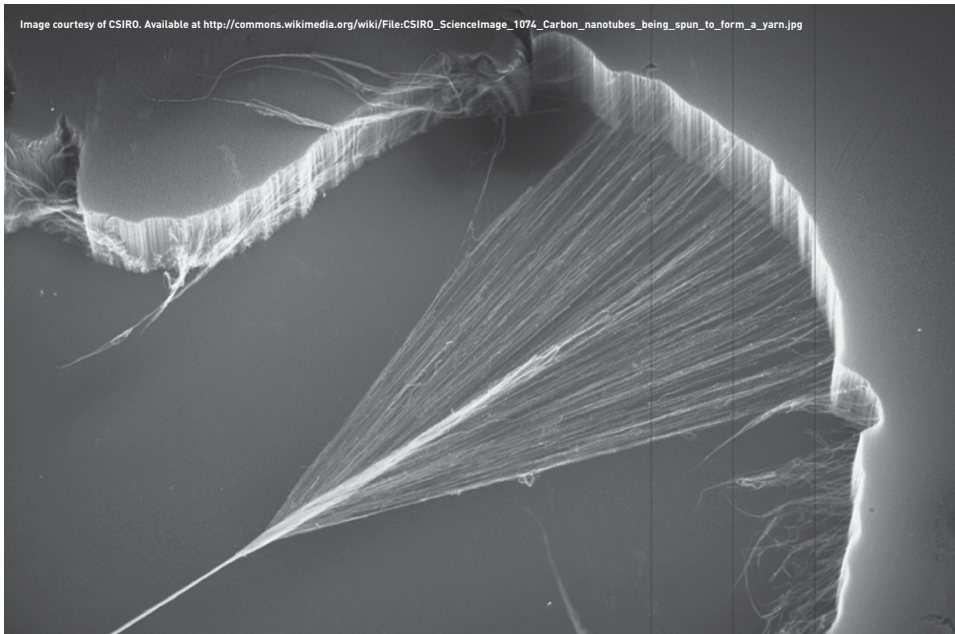

Figure 3: Individual fibers of carbon nanotube are being spun into yarn. Carbon nanotubes have huge potential in the world of nanotechnology.

Optimizing Distributed Computing With Communication Complexity

Image courtesy of Cncplayer. Available at http://commons.wikimedia.org/wiki/File:Binary_Code.jpg

BY MATTHEW JIN

Figure 1: Bit strings are composed of 0's and 1's, as is everything in binary code.

Overview

Suppose that Alice has a bit string (a string of 0's and 1's) x of length n and Bob has a bit string y of the same length. Additionally, suppose that Alice and Bob wish to compute a boolean function $f(x, y)$. Alice is the only one who knows x and Bob is the only one who knows y, therefore Alice and Bob will have to communicate in order to compute $f(x, y)$. The goal of communication complexity is to compute $f(x, y)$ with high accuracy while exchanging a minimal number of bits.

Recall that big-O notation describes how fast a function grows or declines with respect to a variable. In our particular case, a communication cost of $O(n)$ implies that communication grows linearly with the size of the bit string n. Similarly, a communication cost of $O(1)$ implies that a constant amount of communication is required regardless of n. Trivially, in order to compute $f(x, y)$, Alice could send her entire string x to Bob, which requires n bits of communication and results in a $O(n)$ communication cost. However, this is expensive if n is extremely large.

Communication complexity is thus concerned with finding methods to compute functions with less than $O(n)$ communication. These methods are more formally called protocols. They are the rules of communication that dictate who sends the next bit as well as the value of this bit. The value of the bit depends on the sender's input as well as the communication so far.

Deterministic and Randomized Communication Complexity

The difference between a deterministic and a randomized protocol is that a randomized protocol involves randomness when computing f, whereas a deterministic one does not. The cost of a deterministic protocol is the worst case number of bits that need to be exchanged in order to compute $f(x, y)$. The deterministic communication complexity of a function f, denoted $D(f)$, is the lowest cost among all protocols that compute f.

An important early problem in this field was determining the communication complexity of equality. In other words, Alice and Bob might wish to determine whether they had the same files or databases. As proven by A.C. Yao in 1979, it is in fact impossible to improve over $O(n)$ deterministic communication complexity for computing

equality (1). However, as we will see later, we can achieve $O(\log(n))$ or even $O(1)$ communication cost in accurately computing equality using randomized protocols.

In the randomized model, Alice and Bob tolerate a small chance of computing $f(x, y)$ incorrectly. They also each have a fair coin that they can use to randomly determine what messages they wish to send. Each message sent is a function of an input from the sender as well as all of the messages that have been sent so far. Furthermore, in order for a protocol to compute a function, it must succeed on all possible (x, y) with high probability, and not merely on most (x, y) with high probability; the accuracy of the protocol must depend on the random choices that Alice and Bob make at each step, as opposed to their particular (x, y). The randomized communication complexity of a protocol P, $R(P)$, is the worst case number of bits exchanged among all different inputs (x, y) and random choices. The randomized communication complexity of a function f, $R(f)$, is the lowest cost among all the randomized protocols that compute f.

The accuracy of the protocol does not need to be extremely high in order for one to say that the protocol computes the function. For example, if Alice and Bob have a protocol that is correct 3/4 of the time, then it can be repeated k times, reducing the error probability to a potentially very small $(1/4)^k$, while only increasing the overall communication cost by a constant factor. This technique is called amplification.

Equality: An Example

Equality can in particular be computed with significantly reduced communication cost using randomized protocols. We discuss two different such protocols: a public coin protocol, in which Alice and Bob both have access to the same random number generator, and a private coin protocol, in which they don't. We will analyze them for accuracy and the amount of communication that they require.

Public Coin Protocol

Suppose a random bit string r is generated by flipping a coin n times, recording either a 0 or a 1 each time depending on whether a heads or a tails is flipped. Because the coin is public, r is known to both Alice and Bob. Using this protocol, Alice computes

$$a = \sum_{i=1}^{n} x_i r_i \pmod 2$$

Alice then sends a to Bob. Then, Bob computes

$$b = \sum_{i=1}^{n} y_i r_i \pmod 2$$

He then compares a to b, and outputs 1 if $a = b$ and 0 otherwise. If $x = y$, then certainly $a = b$ regardless of r, thus the output would always be correct in this case. On the other hand, if $x \neq y$, half of all possible r can result in a false conclusion of $a = b$, implying an error rate of 1/2.

However, if this process is repeated m times, then the probability of the protocol incorrectly predicting equality all m times is $(1/2)^m$. Alice and Bob can thus achieve a small constant ε error rate with constant bits communicated. This protocol therefore computes equality with randomized communication complexity $O(1)$, which is a tremendous improvement over the deterministic communication complexity $O(n)$.

Private Coin Protocol

Unlike the public coin protocol, Alice and Bob do not have access to the same random bit string in the private coin protocol. In this protocol, Alice essentially randomly picks a random number w and computes her polynomial function $A(w)$ of it. She sends both numbers to Bob, who computes his own polynomial function value $B(w)$ and predicts equality if $A(w) = B(w)$. The high accuracy of this prediction comes from polynomials having relatively few roots, which are the error cases.

More rigorously: let Alice's bit string be represented as $x = x_0x_1...x_{n-1}$ and Bob's bit string be represented as $y = y_0y_1...y_{n-1}$. Additionally, suppose Alice has a polynomial function

$$A(t) = x_0 + x_1t + x_2t^2 + ... + x_{n-1}t^{n-1} \pmod p$$

Bob has a polynomial function

$$B(t) = y_0 + y_1t + y_2t^2 + ... + y_{n-1}t^{n-1} \pmod p$$

Alice and Bob agree beforehand on a fixed prime number p such that $4n^3 < p < 8n^3$. Such a prime is guaranteed to exist by Chebyshev's theorem on the distribution of prime numbers (Kushilevitz). Then, Alice picks with uniform probability a number w from the set 0, 1, 2, ..., $p - 1$ and computes $A(w)$. She then converts the values w and $A(w)$ into binary strings, which will be of worst-case length $\log_2(p)$, and sends them to Bob. The total amount of communication is $2*\log_2(p)=O(\log n)$.

Bob then computes $B(w)$, returning a 1 if $A(w) = B(w)$ and 0 otherwise. In order to find the probability of error, we must determine

how many of the possible values of w can result in a false conclusion. We consider the two cases $x = y$ and $x \neq y$.

If $x = y$, then certainly the polynomial $A(t)$ will be equivalent to $B(t)$. No matter what w is, the protocol will correctly predict that $x = y$. However, if $x \neq y$, then $A(t) - B(t)$ is a polynomial of degree at most $n - 1$, which can have at most $n - 1$ roots. This implies that there are at most $n - 1$ values for which $A(t) - B(t) = 0 \Rightarrow A(t) = B(t)$. Thus there are at most $n - 1$ values out of p possible values that w can take on that would lead to an incorrect conclusion of equality. Therefore, the probability of error is at most

$$\frac{n-1}{p} < \frac{n}{p} < \frac{n}{4n^3} = \frac{1}{4n^2} \leq \frac{1}{4}$$

The resulting probability of successfully computing equality with this protocol is at least 3/4, and its cost is $O(\log n)$. The two protocols demonstrate that as long as we permit error, we can significantly decrease the amount of communication needed to compute equality between two bit strings.

The primary difference between the two is that the public coin protocol is able to compute equality with a constant amount of communication regardless of the length of x and y, whereas a private coin protocol requires an amount of communication that grows logarithmically as the length of x and y. However, the private coin protocol is more general, because unlike the public coin protocol, it does not require that both Alice and Bob have the same random number generator.

More Applications of Communication Complexity

One important application of communication complexity is in understanding area-time tradeoffs in very-large-scale integration (VLSI) chips, which are chips consisting of hundreds of thousands of transistors. The two most important measures of complexity in such chips are its area A and the time T for the chip to compute a function f. A designer of VLSI chips wishes to minimize both A and T.

The communication complexity of a function f that the VLSI chip computes is a lower bound on the quantity AT^2. An understanding of the area-time tradeoff allows VLSI circuit designers to minimize energy consumed by making communication between the parts more efficient during a distributed computation.

Communication complexity is also intimately tied to data structures, because communication complexity bounds provide information on the space-time tradeoffs in data structures. For instance, consider this common static data structure problem: given a set $B \subseteq 1, \ldots, n$, we wish to be able to answer queries as to whether $i \in B$ while minimizing the amount of space the data structure takes up, as well as the amount of time it takes to answer the query. In the communication complexity formulation of the problem, one party has B and the other has i, and the goal is to determine whether $i \in B$. It can be shown that for any implementation for the data structure problem there is a protocol for the communication complexity problem whose complexity depends on the time and space complexities in the data structures problem. In other words, communication complexity bounds yield time-space tradeoffs in the data structure problem.

Other applications of communication complexity include proving lower bounds for space-time tradeoffs in Turing machines and decision-tree depth. Another important application is proving lower bounds on communication time in computer networks, which in turn can be useful for network optimization. Communication complexity also has applications in boolean circuit complexity, streaming algorithms, game theory, and differential privacy. D

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How Far Down The Rabbit Hole Can We Go?

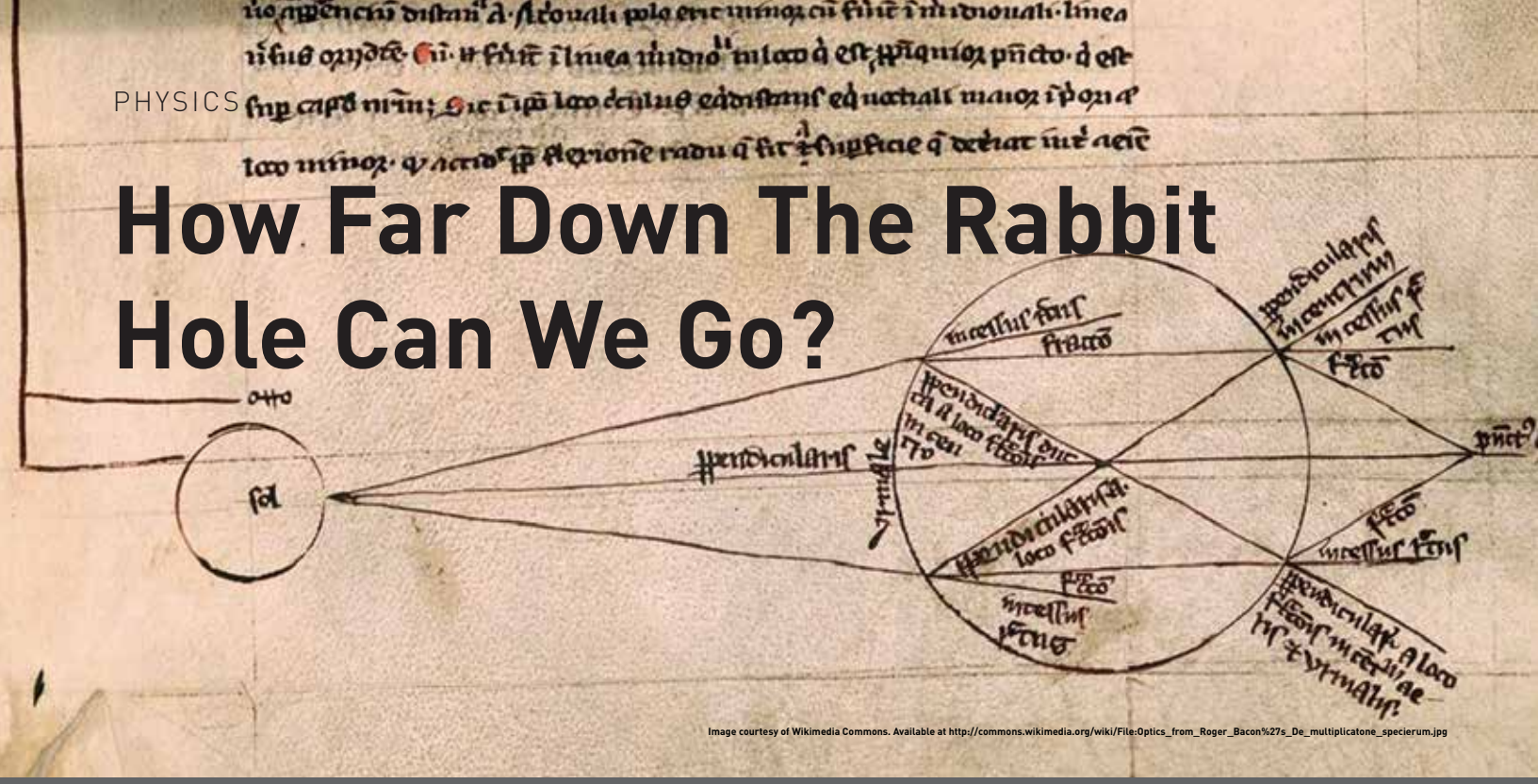

Image courtesy of Wikimedia Commons. Available at http://commons.wikimedia.org/wiki/File:Optics_from_Roger_Bacon%27s_De_multiplicatone_specierum.jpg

BY JAMES HOWE

Introduction

In 1665, Robert Hooke published *Micrographia*, one of the most important biological texts in history. In it, he made a description that provided the foundation for microbiology: "I could exceedingly plainly perceive it to be all perforated and porous, much like a Honey-comb, but that the pores of it were not regular…these pores, or cells… were indeed the first microscopical pores I ever saw, and perhaps, that were ever seen, for I had not met with any Writer or Person, that had made any mention of them before this" (1).

These were the first cells ever seen, only visible due to Hooke's invention of the compound microscope, which allowed him to the push the boundaries of the size of structures that could be visualized. Visual advances like this are necessary for the observation of many new phenomena. However, each medium is inherently limited by simple physics, and eventually new methods must be developed once current boundaries have been reached.

The Human Eye

The very first visual tools available to humans were the human eyes. Vision tends to be the primary sense humans use to interact with the world, and for good reason. Primate eyes have a relatively high density of cones, or cells in the retina that allow us to see fine details in color (2). Humans are also one of only a few trichromat primate species, possessing three different types of cones. This allows them to see a larger portion of the color spectrum than most other animals, who tend to be dichromats (3). The combination of high cone density and trichromacy allows humans to have one of the best senses of sight among all of M*ammalia*, with comparatively high fine detail (human eyes are able to discern details as small as 0.09 mm from a foot away) and color perception (3). However, as good as human vision is naturally, it still has lower boundaries above the level needed to resolve nature at the microscopic level.

To fully understand how optics work, it is necessary understand how magnification works in the human eye. The mammalian eye has a lens that focuses incoming light onto the back of the retina. The light is pinpointed onto a retinal surface with a very high density of cones, the fovea centralis, which is roughly 20 mm away from the lens (4). The focus is sharpest when the object being viewed is around 25 cm away, a position known as the nearpoint (4). Both of these distances become important in the magnification equation, where the magnification of an object is equal to the distance from the lens to the image divided by the lens to the object, or d_i/d_o (4). Using this equation, where d_i is 20 mm and d_o is 25 cm, the maximum proportion of the size of the image on the retina to the size of the object, or the magnification (m) is .08.

Figure 1: Roger Bacon's original notes on the magnifying glass. The small circle to the left is the object of interest, and the larger circle is the lens, with the rays of light between the two objects being bent by the lens.

Simple Magnification

The first device to increase visual acuity, the magnifying glass, was described by the philosopher Roger Bacon in 1268 (5). While the magnifying glass itself consists of one lens, it actually uses two: the glass itself and the lens in the viewer's eye. Magnifying glasses are fixed lenses, with only one possible level of magnification by the lens itself. The magnification is dependent on its index of refraction of the constituent material (how much it slows the light) and the curvature of the lens, with more convex lenses bending the light to a greater degree and focusing the rays closer to the lens (6).

The external lens magnifies images by focusing all of the light onto the lens of the eye, which is then projected onto the retina. When viewing images, the brain traces the path of the light rays back to their supposed origin (7). The bending of these rays causes the brain to perceive the source of these rays at the nearpoint to be larger than it actually is. The maximum magnification possible with the lens is limited mainly by its diameter, where the power of the lens (maximum ratio of the magnified image to the normal image, 4x is equal to 4 power) is limited to double the diameter of the lens in mm (8).

Compound Microscopy

Because magnification is directly dependent on the size of the lens, there is a practical limit to the magnification possible with only one lens. This led to the invention of the compound microscope in 1597 by Zacharias Janssen (9). In order to further magnify very small objects, he added another small lens, the objective lens, very close to the object. The objective lens is convex, and scatters the light coming from the object of interest. This creates a larger image on the surface just past the objective lens, called the intermediate image plane (7). The image is then magnified by another larger lens near the viewer, called the eyepiece. This lens acts like a magnifying glass on an already-enlarged image. The result is an even larger image at the nearpoint (7).

The compound microscope allows a very high level of magnification, as the maximum resolution is limited by neither the size of any of the lenses nor the angle the lens focuses light at, but by the light itself. At such high levels of magnification, the main limiting factor is the index of refraction of the medium, or the material used to view the specimen (7). As the index of refraction increases, so does the deviation of rays of light from the original path, allowing for less loss of light (10). Air, with its relatively low index of refraction, can be replaced by oil, which has a higher index, increasing the fidelity of the image being projected (10). With oil as the medium, very powerful compound microscopes can resolve structures down to 150 nm away from each other, a limit imposed by the wavelength of light itself (11).

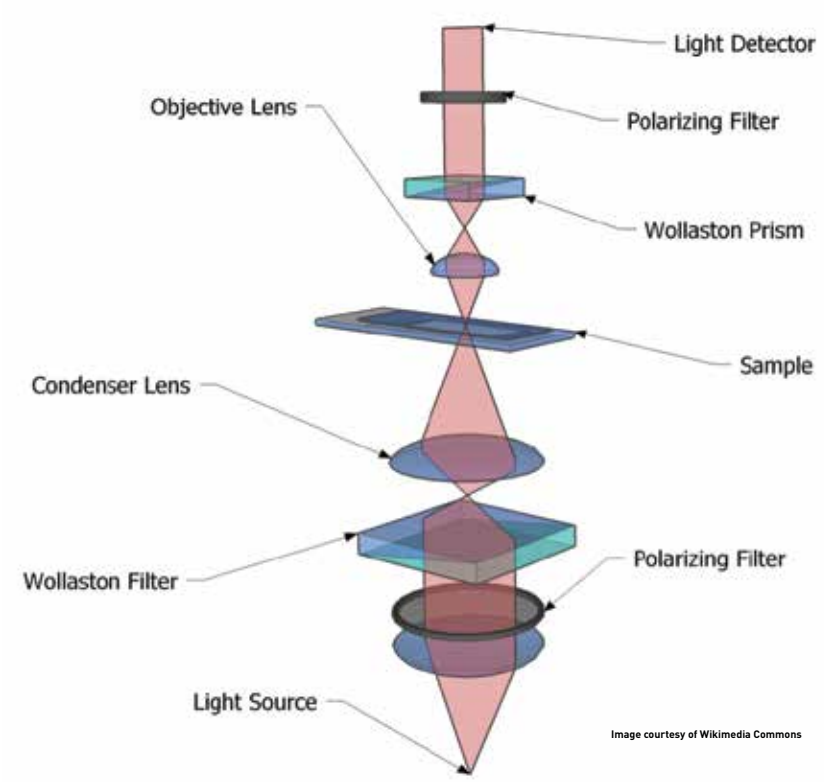

Figure 2: Diagram showing how a compound microscope functions. A number of filters can be used to increase the clarity and/or contrast of the image.

Electron Microscopy

In order to bypass this physical limit, two German engineers invented the electron microscope in 1931 (12). Instead of using glass to bend light, its lenses use magnets to focus electrons. These electrons are emitted by a heated filament, and their trajectories are bent by the magnets towards the specimen (12). When the electrons bounce off of the specimen at different angles, they come into contact with a sensor that measures the angles to visualize the image (12).

Using electrons to visualize the image allows the detrimental effect of high wavelengths, the ultimate limit of resolution in light microscopes, to be minimized. Unlike light, an electron has mass. Mass and wavelength are inversely proportional, so any particle with mass has a much lower wavelength than massless light waves, and thus much higher maximum resolution (13). Electron microscopes can magnify objects up to two million times larger, allowing them to resolve distances of up to .05 nm (50 pm), which is small enough to distinguish

individual atoms (14). Increasingly for many fields, the limiting factor for resolution is not based on the microscope, but rather on small imperfections in the specimen being imaged, causing slight distortions in the image (15).

The electron microscope has such high resolution that more recent microscopy techniques, such as atomic force microscopy and scanning tunneling microscopy (both of which use probes to detect the forces of individual atoms) are unable to significantly improve on the images produced (16). As of now, electron microscopy remains one of the highest-resolution tools known. Additionally, given the degree of conceptual resolution already available, such as the visualization of individual atoms and covalent bonds, it is becoming increasingly unclear whether further developments in microscopy techniques will be able to resolve higher magnifications.

The Smallest Measurement Ever Made

Early in 2014, a group of researchers at UC Berkeley managed to record a force of 1 x 10^{-24} newtons by adding very small amounts of force to a cloud of ultracold (just above absolute zero) atoms (17). This amount of force is not only incredibly small, but also very close to the theoretical limit of any measurement, known as the quantum limit. At such low levels of force, feedback is limited by quantum effects, specifically the Heisenberg uncertainty principle. The uncertainty principle describes the inherent imprecision in all measurements, which is caused by randomness found in all matter at infinitesimally small scales (17). At the quantum limit, a measurement becomes so small that it cannot be distinguished from the noise produced by the sensor simply existing (17).

If scientists can make measurements of force that approach limits set by the universe itself, then it should be possible to take an even closer look at matter. When resolving images at the atomic scale, we are not yet limited by quantum physics, but by the current scale of engineering. The current level of scientific growth, coupled with the efforts of engineering, suggests that we could soon be taking ever closer views of nature. D

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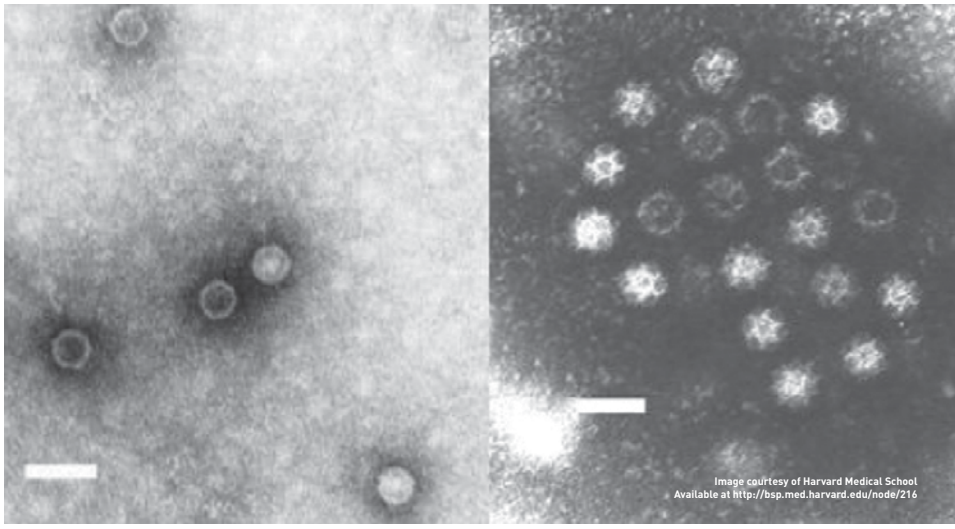

Figure 3: Electron microscopy images of Poliovirus (left) and Calicivirus (right). Many important biological phenomena, like viruses and proteins, are only able to be visualized at a scale requiring an electron microscope. The white bar for scale is 50 nm.

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The Higgs Boson and Its Implications

BY KEVIN KANG

Figure 1: Image of the tunnel of the Large Hadron Collider, the world's largest and most powerful particle collider, which was used to confirm the existence of the Higgs boson.

The Theory Behind the Particle

An object's mass is often thought of as the amount of material the object contains. The mass of a macroscopic object comes from its constituent atoms and molecules. These atoms and molecules are in turn composed of fundamental particles: electrons and quarks. In the late twentieth and early twenty-first century, particle physicists formulated equations that modeled the behavior of these fundamental particles using experimental data. However, these equations only matched the data when the particles were considered massless. Thus, the physicists encountered a dilemma: they knew that fundamental particles had mass, but giving these particles their masses yielded inconsistencies.

In 1964 physicist Peter Higgs postulated the existence of a theoretical, omnipresent field responsible for the masses of all fundamental particles in the universe: the Higgs field. According to Higgs' theory, the Higgs field is present even within a vacuum, permeating all matter and uniformly occupying space (the Higgs field must be considered uniform because if it were not uniform, then particles' masses would vary depending on their directions of travel). When a particle accelerates, the Higgs field exerts a "drag force" on this particle: this resistant drag force can be interpreted as the particle's mass. Particles that interact more with the Higgs field will experience a larger "drag force" and thus will have greater mass. A common analogy used to explain the Higgs field is that of a ping-pong ball submerged in water. Since it is more difficult to move the ball while it is submerged, the ball's interactions with its aquatic environment have the effect of endowing the ball with more mass. Likewise, the Higgs field endows subatomic particles with mass while these particles interact with the field.

When it was first submitted in 1964, Higgs' proposal was rejected because the premise of an invisible field permeating all of space was too outlandish for physicists at the time. However, particle physicists soon began to appreciate the genius of Higgs' proposal: it allowed their mathematical expressions to retain their validity and elegance, while providing an explanation for why some fundamental particles are massless (like photons) and other particles have varying amounts of mass (like quarks). Photons and other massless particles do not interact much with the Higgs field, while quarks and more massive particles do. By the mid-1980s, the physics community had essentially accepted the notion of the Higgs field, and physicists were beginning to devise experiments that could finally confirm its existence.

Discovery of the Higgs Boson

According to the principles of quantum mechanics, energy fields are made up of discrete particles. Therefore, in order to confirm the existence of the Higgs field, scientists sought to find its smallest possible constituent, the Higgs

boson. However, in order to "disturb" the Higgs field and displace a Higgs boson, a massive amount of energy must be generated within the field. Scientists have developed the Large Hadron Collider in Geneva, Switzerland for this very purpose.

The Large Hadron Collider (LHC), which became operational in 2008, is the world's largest particle accelerator. The LHC is about 17 miles in circumference and lies 175 meters underground, beneath the Franco-Swiss border. It was built through the collaboration of over 10,000 scientists from over 100 different nations. The LHC contains about 9000 superconducting magnets, which accelerate protons to speeds greater than 99 percent of the speed of light. Each second, these protons traverse the LHC about 11,000 times, engaging in millions of collisions and generating massive amounts of energy. Large detectors carefully study the debris resulting from these collisions, hoping to find traces of the Higgs boson and other unidentified particles. Mathematical calculations suggest that if the Higgs field does exist, then the powerful proton collisions should occasionally be able to displace a Higgs boson. Furthermore, these calculations predict that the Higgs boson would decay in a fraction of a second. As a result, sophisticated computers have to carefully study the pattern of decay products for evidence of the Higgs boson.

On July 4, 2012, scientists at the LHC announced that they had found strong evidence of a particle that resembles the Higgs boson. Since that announcement, these scientists have continued to study the particle, trying to determine whether this particle has the same properties as the Higgs boson predicted by the Standard Model, the dominant framework of particle physics. The Standard Model is a theory encompassing all of the particles and forces in the universe and attempts to explain the connections among them, and its underlying logic is rooted in mathematics. The Standard Model holds that there are 17 fundamental particles, or particles that cannot be divided into smaller units. These particles are divided into two groups: the fermions and bosons. The fermions are the fundamental building blocks of matter, and there are twelve of them: the six (up, down, top, bottom, charm, and strange) quarks, the electron, the muon, the tau, and the three (electron, muon, and tau) neutrinos. The bosons, by comparison, are the five force-carrying particles: the gluon, the photon, and the three (W, Z, and Higgs) bosons. According to the Standard Model, the Higgs field, composed of Higgs bosons, endows all fundamental particles in the universe with mass. The Higgs boson has a certain mass, no spin, and decays into fermions.

Since the discovery of the Higgs boson candidate in 2012, scientists at the Large Hadron Collider have spent two years conducting additional experiments to determine if the discovered particle is in fact the Higgs boson predicted by the Standard Model. Their results demonstrate that the discovered particle has a mass very similar to the mass predicted by the Standard Model, has no spin, and does indeed decay into fermions. Thus, it is highly likely that the particle found at the LHC is in fact the famous Higgs boson.

Figure 2: An aerial view of CERN over Geneva, with the LHC marked in yellow.

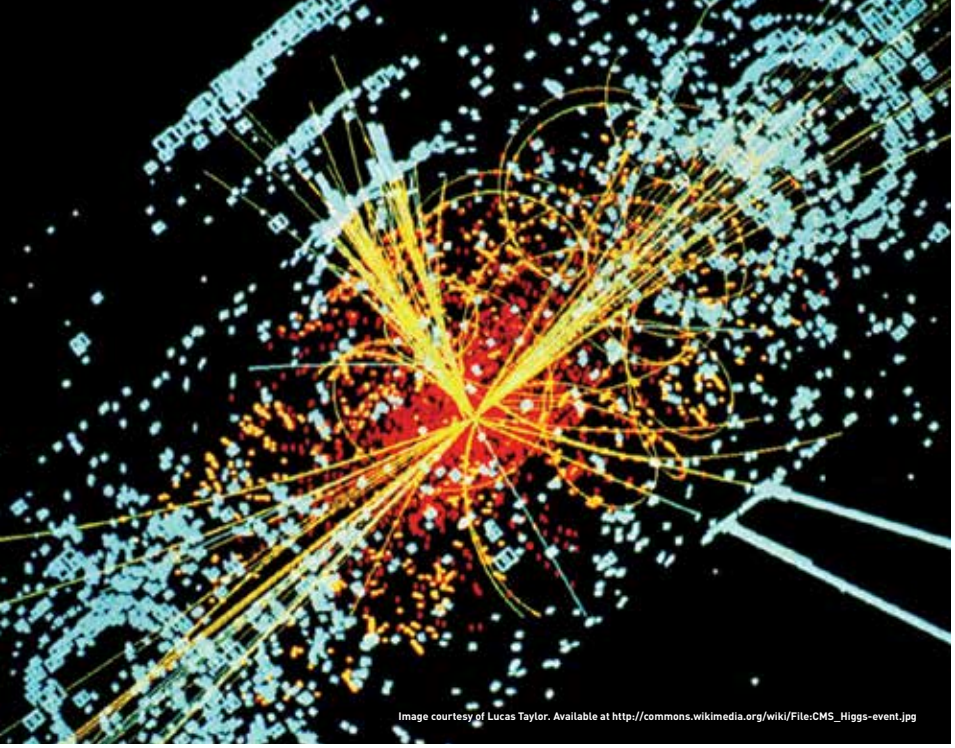

Figure 3: A close view of a typical candidate event in which protons vigorously collide and decay into smaller particles. Physicists at CERN studied the debris of images like this one in order to find evidence of the Higgs boson.

Implications of the Higgs Boson

The Higgs boson has numerous implications for the human understanding of the universe. First of all, the Higgs field is the only known energy field that apparently uniformly fills all of space. Hence, the Higgs field is fundamentally different from any other physical field ever encountered; gravitational fields, electric fields, and magnetic fields all originate from some source and can be "turned off" by eliminating that source. However, The Higgs field has no discernable "source"; it uniformly and permanently fills the entire universe. The discovery of an invisible, uniform field suggests that other unknown uniform fields could exist.

Secondly, the Higgs boson has no spin. In the early twentieth century, physicists realized that fundamental particles have three defining features: mass, charge, and spin. However, unlike the spin of a top or wheel, a particle's spin is an intrinsic feature that does not speed up or slow down over time. Electrons, quarks, and photons all have characteristic spins. Physicists have long predicted that the Higgs boson, unlike any other particle, would have no spin. Experiments at the LHC have confirmed that the Higgs boson indeed has no spin and thus represents an unprecedented type of particle.

Thirdly, the discovery of the Higgs boson has led some prominent physicists, such as Stephen Hawking, to predict a catastrophe that will end the universe. Clara Moskowitz states that: "The mass of the new particle is about 126 billion electron volts…its mass turns out to be just about what's needed to make the universe fundamentally unstable, in a way that would cause it to end catastrophically in the far future." Because the Higgs boson occupies the vacuum, the stability of the boson directly impacts the stability of the spatial fabric. Thus, an instability of the Higgs field may someday create an unstoppable vacuum bubble, spelling doom for the universe. Stephen Hawking elaborates: "The Higgs potential has the worrisome feature that it might become metastable at energies above 100 billion gigaelectronvolts. This could mean that the universe could undergo catastrophic vacuum decay, with a bubble of the true vacuum expanding at the speed of light." Such a vacuum bubble would approach us at the speed of light, so we would not see the catastrophe coming. Nevertheless, physicists have predicted that this catastrophe most likely will not occur for 10^{100} years. Joseph Lykken, a theoretical physicist at the Fermi National Accelerator Laboratory in Batavia, Illinois, advises: "[You] probably shouldn't sell your house and you should continue to pay your taxes."

Conclusion

The discovery of the Higgs boson is one of the most influential discoveries of the twenty-first century thus far. It represents a new type of particle, substantiates many of our predictions based on the Standard Model, and suggests that the theoretical field of particle physics has been moving in the right direction for the past forty years. The discovery is also triumph for the ability of mathematics to predict natural phenomenon, as mathematical calculations have implied the boson's existence for decades. Of particular importance is the construction of the Large Hadron Collider, where scientists will continue to gain further insight into the properties of this unique particle and attempt to learn more about the universe in which we live. D

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Nanotechnology and the Petroleum Industry

Image courtesy of Jstuby. Available at http://commons.wikimedia.org/wiki/File:Porosity_thin_section_GP.jpg

BY ANNIE (YI) SUN

Introduction

For the past few decades, nanotechnology has been a buzzword reaching almost every industry, bringing with it the promise of revolutionizing existing technologies. Defined as the study of manipulating technology at the nanoscale (<1 to 1000 nm), nanotechnology has existed for hundreds of years. Unaware of the nanoscale processes underlying their art, constructors of stained-glass windows in medieval churches used alternate-sized silver and gold nanoparticles to create vivid colors (1).

In 1959, Nobel Prize-winning physicist Richard Feynman, recognized as the father of nanotechnology, gave the famous lecture "There's Plenty of Room at the Bottom," describing the possibilities of controlling individual molecules and atoms (1). The nanotechnology of the present has progressed greatly towards enabling this sort of fine-tuned control on the molecular level. For example, post-doctoral researcher Wim Noordiun created self-assembling flowers by carefully controlling pH and temperature (Image 2).

Although Feynman laid out ideological beginnings, the term "nanotechnology" was not coined until a decade later when Professor Norio Taniguchi explored ultra-precision machining (1). The modern era of nanotechnology did not properly begin until the inventions of the scanning tunneling microscope and the atomic force microscope made imaging on the nanoscale possible in the 1980s (1).

Since the 1980s, the United States has created and poured more than $3.7 billion into the National Nanotechnology Initiative for developing nanoscale technologies (1). The electronics, optics, aeronautics, medical, automobiles, and even sports industries have benefited from nano-inspired products. Cars manufactured with nanomaterials are lighter, more fuel-efficient, and stronger. New coatings containing nanoparticles allow for golf balls to fly more accurately (1,2).

At the nano level, classical physics no longer applies. Thus, nanomaterials take on a novel set of chemical and physical properties that have the potential to greatly improve existing materials. They may be stronger, lighter, better catalysts, or otherwise push long-accepted limits in the field of materials science (2).

Why is Nanotechnology Important to the Oil and Gas Industry?

Oil is found in geological traps of porous sedimentary rock such as limestone or sandstone. Oil is typically collected by flooding water down a well to create pressure underground, forcing the oil upwards through the pores and channels of the geological formation. However, this technique leaves as much as 70% of the oil present in the well unattainable. Billions of barrels of oil are left underground in wells after the drilling treatment is completed (3).

Besides economic and industrial incentives for the oil and gas industry, the improved recovery of fossil fuel resources is of interest to the entire world. In their 2006 report, the International Energy Agency (IEA) forecasted that remaining fossil fuel resources will last at least until 2030, though it also noted that the global supply of oil will remain tight in the medium and long term (4).

Oil collection may be further enhanced by recovery techniques such as the injection of gases (i.e. CO_2) to keep underground pressure high, or the use of gels and surfactants to

Figure 1: Purple regions represent porosity (and oil) between carbonate grains. In an oil reservoir, the most oil would be produced out of the well if the hydrophobic oil molecules associate little with the pore surfaces.

prevent the oil from adhering to the rock pores (3). However, due to the uniqueness of each reservoir in terms of oil viscosity, pore size, temperature, and geology, the use of any particular treatment does not always guarantee enough oil recovery to justify the cost of the treatment.

The focus of the oil and gas industry on nanomaterials has been fairly limited until recently (5). Nanoparticles have been successfully used in drilling for the past fifty years. Increasingly, however, challenges in conventional wells—as well as challenges created by harsh conditions (high-temperature and high-pressure geological formations), deep-water or arctic locations, and nonconventional reserves—have instigated a closer look into the potential of nanotechnologies (5).

Nanotechnology presents a number of new solutions to old problems found in the oil and gas industry—in particular, this article will highlight applications of carbon nanotubes and nanoparticles. Nanomaterials show a variety of promising properties such as enhanced lightness, mechanical strength, and corrosion resistance (5).

Carbon Nanotubes

These allotropes of carbon can be thought of as cylindrical, continuous "buckyballs" with a hollow center. They is held together by sp^2 bonds, like the 2010 Nobel Prize-winning graphene (a single sheet of honeycomb-like carbon bonds) (6). Importantly, these sp^2 bonds that hold together carbon nanotubes (CNTs) are stronger than the sp^3 bonds of diamond (6).

The oil and gas industry has found applications for carbon nanotubes as filters. In 2004, Srivastava reports the creation of cylindrical membranes using CNT walls. These high surface-area membranes may be used as filter materials such as heavy hydrocarbons or bacterial contaminants from water or petroleum (6).

The CNT membranes are thermally and mechanically stable due to their strong carbon bonds; consequently, they are also reusable (6). Ultrasonication and autoclaving enables the membranes to be used again for further filtration. In addition, the membranes are easily and inexpensively made when compared to polymer- or ceramic-based filters currently on the market (6).

These carbon nanotubes filters, when combined with boron, are particularly useful in environmental remediation. Doping, the process by which boron is deposited via chemical vapor between CNT carbon atoms, creates a material with highly desirable chemical properties. When wedged between the individual CNTs, boron is able to interact with the electron structures of the carbon atoms in order to bend the linear nanotube structure (7).

The resulting material is lightweight, extremely hydrophobic, and highly porous, in addition to possessing mechanical and thermal stability (8). The boron-doped CNT is useful as a novel absorbent framework that may leech oil out of contaminated seawater; because of the CNT's reusability, the material is a viable and potentially groundbreaking tool for cleaning oil spills (8).

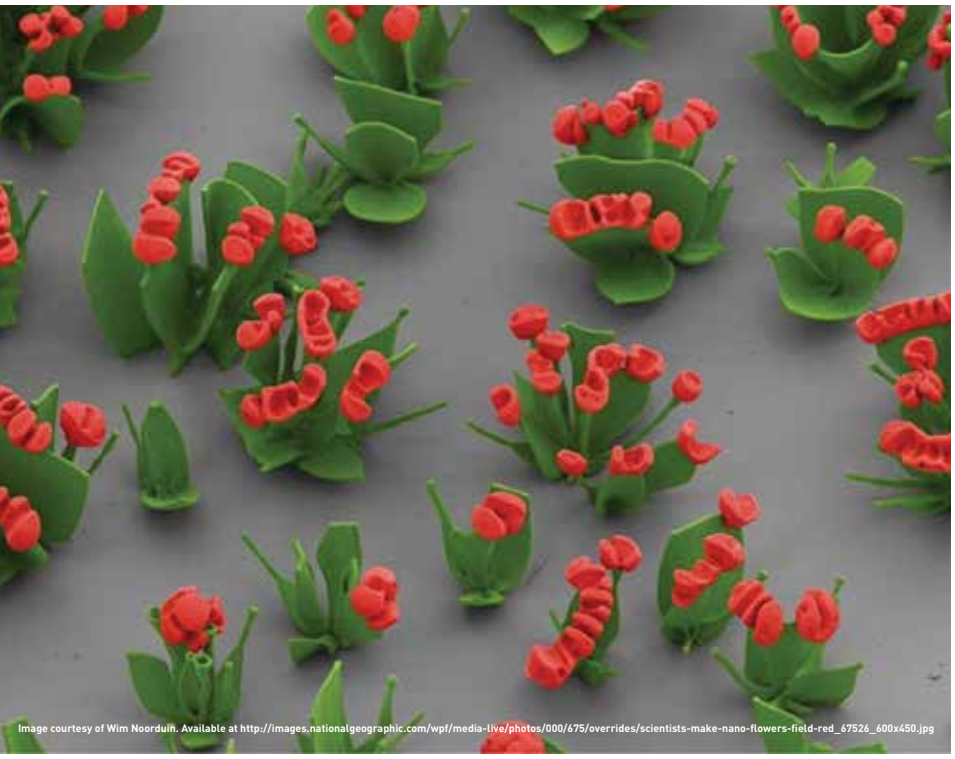

Image courtesy of Wim Noorduin. Available at http://images.nationalgeographic.com/wpf/media-live/photos/000/675/overrides/scientists-make-nano-flowers-field-red_67526_600x450.jpg

Figure 2: These microscopic flowers were grown in a laboratory at Harvard University using a solution of barium chloride and sodium silicate in water under very carefully controlled pH and temperature.

Nanoparticles

A key factor for enhanced oil recovery (EOR) with the use of nanoparticles is changing the "wettability" of a formation (9). Oil, primarily composed of hydrocarbons, is hydrophobic; if the formation pore surfaces are also hydrophobic, or "oil-wet", then the oil will be inclined to interact with the surfaces rather than escaping to the surface. If the pore surfaces can be made to be more hydrophilic, or "water-wet", more oil will be produced (3).

To improve the "wettability" of the formation, the nanoparticles used are oftentimes nanoscale inorganic crystals selected for their reactivity. In the study conducted by Ogolo *et al.,* nanoparticles used included magnesium oxide, aluminum oxide, zirconium oxide, as well as silicon oxide treated to be hydrophobic (9). Because of the extremely small size of nanoparticles, they have an enormous surface area to volume ratio and react quickly.

Ogolo's team found that some nanoparticles such as silicon oxide and magnesium oxide were effective at improving the wettability

of the formation—this opens up the potential for enhancing hydrocarbon production (9). In addition, they reported that the use of ethanol (a polar solvent) further improved the performance of some nanoparticles (9).

In addition to working well on their own, nanoparticles may be applied to aid viscoelastic surfactant (VES) fluids. VES fluids naturally arrange into structures called micelles—when in water, they arrange themselves such that the nonpolar tails cluster into the center, while the polar heads remain in contact with the polar water molecules.

These structures can help to increase the viscosity of fluids pumped underground; they need to remain viscous to continue carrying proppant (sand and other small particles that help to prop open underground cracks). Early deposition of the proppant from the fluid matrix clogs the rock pores prematurely and chokes off oil production. VES fluids, however, cannot be used at high temperatures since they tend to decrease in viscosity and leak off into surrounding rock when heated past a certain point (10).

In the past, this has limited the use of VES fluids to primarily lower-temperature applications. The research from Kaputa *et al.* discusses the use of nanoparticles, which would associate with the VES micelles via surface-charge attraction to help maintain viscosity at high temperatures (10).

After the treatment has been completed, a "breaker" fluid can be flushed underground to shatter the VES micelles. The thick, built-up fluid would become much less viscous, and consequently become available to flow back to the wellbore. The nanoparticles, being very small, would flow right back up within the formation fluid without becoming trapped within the pore spaces (10). With the help of nanoparticles, the benefits of VES fluids may be extended to high-temperatures as well, with the result of enhanced oil recovery.

Conclusions

Nanotechnology remains an extremely promising field due to its versatility and interdisciplinary nature. Certain nanomaterials with exceptional properties may be applied to not only the oil and gas industry, but to many other industries to improve quality of life and deliver continually improving products.

Plainly, nanotechnology is a very broad science—the advancements in even a single industry cannot be contained in a single article. However, the incremental benefits of each improvement in oilfield technology are vital to the continued production of oil and gas in the future years, as hydrocarbons remain a bridge fuel to more renewable sources. With up to 70 percent of discovered oil left underground after production, even small improvements to technology are significant to maximizing limited hydrocarbon resources. D

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Figure 3: The 2mm diameter sphere shown in this photograph is two million times larger than a nanometer—the scale at which nanotechnology is conceived and implemented.

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Weighing in on Testosterone Treatments: Risks and Benefits

Image courtesy of the Drug Enforcement Administration

BY ANIRUDH UDUTHA

Figure 1: Vials of various injectable anabolic steroids, which are used for their medical and ergogenic properties.

Introduction

In December 2014, two major studies shocked researchers hopeful for a viable treatment for Traumatic Brain Injury (TBI). Dozens of previous animal experiments and two preliminary clinical studies suggested progesterone, a female sex hormone, could help reduce inflammation, cell death, and behavioral effects in TBI. However, two large multicenter, placebo-controlled studies, showed no significant difference between patients who had received progesterone versus those who received a placebo injection. The authors of these studies pointed to the heterogeneity of TBI and the complex injury pathways in TBI that can damage the brain (1,2).

Despite the failure of progesterone to treat TBI, the use of testosterone, a similar molecule, continues to be actively studied as a treatment for a variety of diseases. Although testosterone is well known as a male sex hormone, or androgen, the steroid hormone is involved in a variety of biochemical pathways throughout the body. Many clinical studies link testosterone to metabolic syndrome, type 2 diabetes, and cardiovascular disease, and testosterone replacement therapy (TRT) may help some men manage or prevent these conditions (3,4).

Background of Testosterone Research

Testosterone administration has been known to improve angina pectoris, chest pain usually due to obstruction of the coronary arteries, since the 1940s (5). However, the therapeutic use of testosterone has been overlooked for decades, likely due to reports of cardiovascular damage in athletes who abused anabolic steroids as well as the observed benefit of reducing testosterone function through androgen deprivation therapy (ADT) in prostate cancer patients. Studies have produced no signs that testosterone replacement to the physiologically healthy range leads to cardiovascular disease or prostate cancer. As testosterone levels naturally decline with age and inflammation of blood vessels naturally increases with age, scientists hypothesized that testosterone was critical for healthy maintenance of cardiovascular function (3). More recent studies show that low testosterone levels in men of all ages often predispose patients to cardiovascular disease as well as reduction of muscle mass and increases in body fat (4).

Cardiovascular Nature of Testosterone

Some scientists have proposed that low testosterone is simply a marker of a general decline in health, which they suggest is the true cause of the cardiovascular disease and resulting mortality. However, studies of elderly men with naturally high testosterone levels who had fewer cardiovascular events and the increased risk of coronary heart disease, diabetes, and cardiovascular death in patients receiving ADT for prostate cancer suggests that testosterone does play an active role in cardiovascular health. Furthermore, sex hormone receptors and enzymes that act on testosterone are present in the lining of arteries. Although scientists still urge for a placebo-controlled, long-term clinical trial of testosterone to definitively determine a causal relationship between testosterone

and cardiovascular health, much research still supports the relationship between testosterone and cardiovascular disorders (3).

Studies have also shown that testosterone can decrease exercise-induced cardiac ischemia, or restriction of blood supply, as well as increase exercise time in men with reduced natural levels of testosterone and chronic angina. Importantly, these improvements remained without decreasing in strength over a 12 month period of testosterone treatment. Many other studies also suggest testosterone can dilate arteries, although there is some evidence of specific instances where testosterone administration constricts arteries. Research suggests this vasodilatory function of testosterone is due to voltage-gated and Ca^{2+}-gated K^{+} channel modulation in the smooth muscle cells of arteries as well as stimulation of nitric oxide (NO) release, which has strong vasodilatory properties (3).

Testosterone has also been known to have anti-inflammatory properties on the vasculature. Furthermore, testosterone replacement therapy (TRT) in men with low levels of testosterone can reduce atherosclerosis and even potentially help patients with cardiovascular disease. This modulation of unhealthy vascular tissue is thought to be caused by gene transcription regulation, rapid intracellular signaling pathways, ion channel modulation, or another cell membrane receptor (3).

Metabolic Nature of Testosterone

Initial studies that suggested a bidirectional relationship between obesity and low testosterone lead to the creation of the hypogonadal (low testosterone) – obesity cycle hypothesis. Adipocytes, or fat cells, contain the enzyme aromatase, which converts testosterone into estradiol in a process called aromatization, decreasing total testosterone levels as fat tissue accumulates. Low testosterone levels then further promote fat deposition. In addition, the usual negative feedback cycle that would make up for dropping testosterone levels is dependent on aromatization; thus, excess aromatization by adipocytes would disrupt this feedback, worsening the hypogonadism. More current research promotes the hypogonadal–obesity–adipocytokine hypothesis. In this model, estradiol and adipocytokines, which are fat cell signaling molecules, inhibit production of GnRH, a hormone which leads to testosterone secretion. In addition, excess leptin, another hormone released by adipocytes, which would normally promote GnRH secretion, overwhelms GnRH-releasing neurons in the brain, inhibiting GnRH release (4).

In recent years, there has been a significant rise in type 2 diabetes as well as metabolic syndrome (MetS). MetS occurs when a patient has three of the following: obesity, high blood sugar, high blood pressure, high triglycerides, and low HDL cholesterol, a type of 'good' cholesterol that reduces excess cholesterol in the blood. Low testosterone has been negatively correlated with high LDL and triglycerides and positively correlated with HDL. Importantly, TRT reduced cholesterol in older men who were already taking statins; furthermore, TRT reduced triglycerides in another study of men who had type 2 diabetes and low testosterone. In addition, numerous studies of prostate cancer patients receiving ADT have suggested that ADT predisposes patients to type 2 diabetes and MetS, both of which are risk factors for cardiovascular disease (4).

In the liver, testosterone has been shown to increase expression of the insulin receptor, thereby increasing insulin binding. The promoter region for the insulin receptor gene has also been found to have estrogen binding elements; as testosterone can be converted into estrogen, some scientists believe testosterone uses these estrogen binding elements to affect insulin receptor levels (4).

Testosterone injection has also been linked to significant reduction in abdominal fat. In addition, research suggests that it may reduce fat deposition and triglyceride uptake as well as increase fat metabolism and muscle mass and thereby counteract the progression of obesity (4).

Future Implications

Although many studies have established associations between low testosterone and diseases such as type 2 diabetes and MetS,

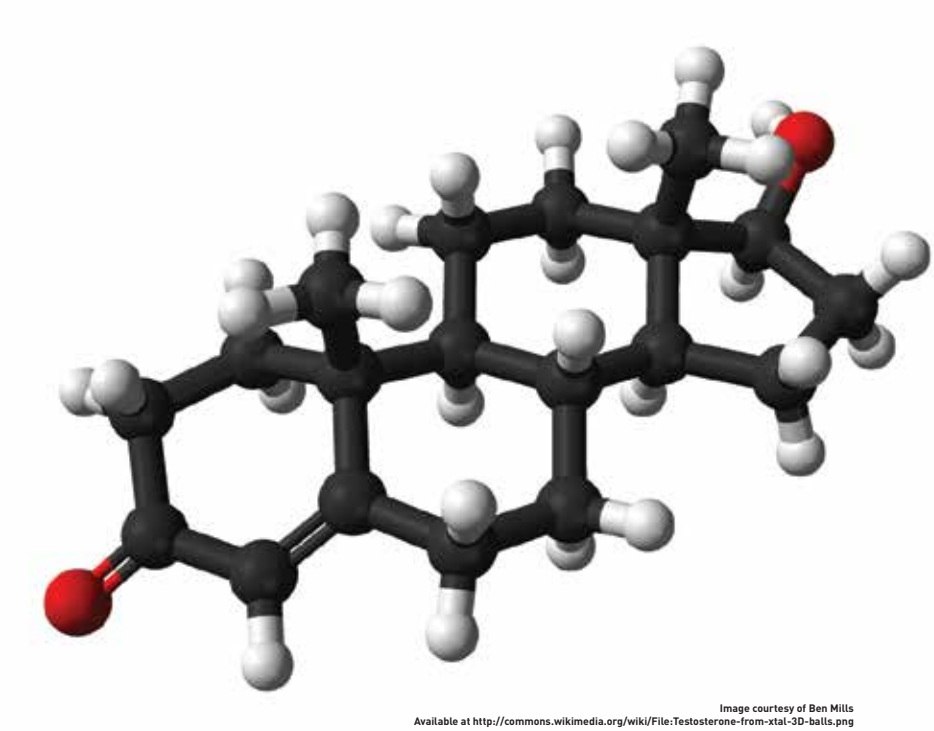

Figure 2: Molecular structure of testosterone, $C_{19}H_{28}O_2$.

Image courtesy of Ben Mills
Available at http://commons.wikimedia.org/wiki/File:Testosterone-from-xtal-3D-balls.png

"In addition to numerous studies contradicting each other about TRT's effectiveness, no researchers have conducted a long-term, placebo-controlled study of TRT and its effects, prolonging the back-and-forth nature of this debate."

scientists also agree on the necessity of large-scale, randomized, placebo-controlled clinical trials to definitively determine the utility and safety of testosterone replacement. Years ago, female hormone replacement therapy (HRT) was widely popular and was prescribed for postmenopausal women to reduce risk of coronary heart disease after observational data suggested such an effect for HRT. However, large, randomized, placebo-controlled studies of HRT demonstrated health risks that outweighed potential benefits, leading to a significant decline in usage of HRT (6). Nevertheless, current knowledge of how testosterone functions does offer clues for potential treatments for diseases associated with low testosterone. For example, a one week treatment of aromatase inhibitor for healthy men increased insulin sensitivity and decreased triglyceride levels. Another study of a year-long aromatase inhibitor treatment in elderly men with low testosterone resulted in decreased bone mineral density; however, the estradiol levels of these men were lower than what would be expected from hypogonadism in obese men. Similar aromatase inhibitors may be able to treat obesity-related hypogonadism, but further research is necessary. Furthermore, some research suggests long-term treatment with kisspeptin, a critical regulator in testosterone secretion, for hypogonadal men with type 2 diabetes can improve testosterone levels (7).

As historical research suggests testosterone stimulates growth of prostate cancer once the tumor appears, prostate cancer is often treated with androgen deprivation therapy (ADT) where the patient is given drugs that chemically disrupt androgen function. However, prostate tumors often develop resistance to ADT over time through overexpression of androgen receptors. A recently study published in *Science* suggests that testosterone injections coupled with continued ADT can exploit this overexpression and reduce tumor size as well as increase receptiveness to ADT (8).

In addition, a recent literature review supports the monitored and cautious use of TRT for hypogonadal men as well as the beneficial effects of TRT on MetS in these men. This review also questions the reliability of previous research regarding claims that TRT increased CVD or prostate cancer risk, although these authors also acknowledge the need for larger, placebo-controlled studies of TRT (9). Nevertheless, another recent publication questions whether the current model for how androgens affect prostate cancers fully accounts for the diversity observed in prostate cancers and again emphasizes the lack of definitive studies regarding the effects of TRT on prostate cancer risk (10).

Conclusions

Despite decades of research into the relationship between the primary male sex hormone and diseases such as type 2 diabetes and cardiovascular disease, these studies are still not conclusive on the benefits and safety of TRT for hypogonadal men. In addition to numerous studies contradicting each other about TRT's effectiveness, no researchers have conducted a long-term, placebo-controlled study of TRT and its effects, prolonging the back-and-forth nature of this debate. Some scholars attribute this to the high cost of recruiting a diverse sample of men to be treated over a long period of time with expensive follow-ups (9). In the meantime, current scientific knowledge of testosterone's importance as a critical vascular and metabolic hormone sustains the possibility of its future use in helping treat a variety of cardiovascular, metabolic, and other diseases. D

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Nanotechnology: The Nanofiber

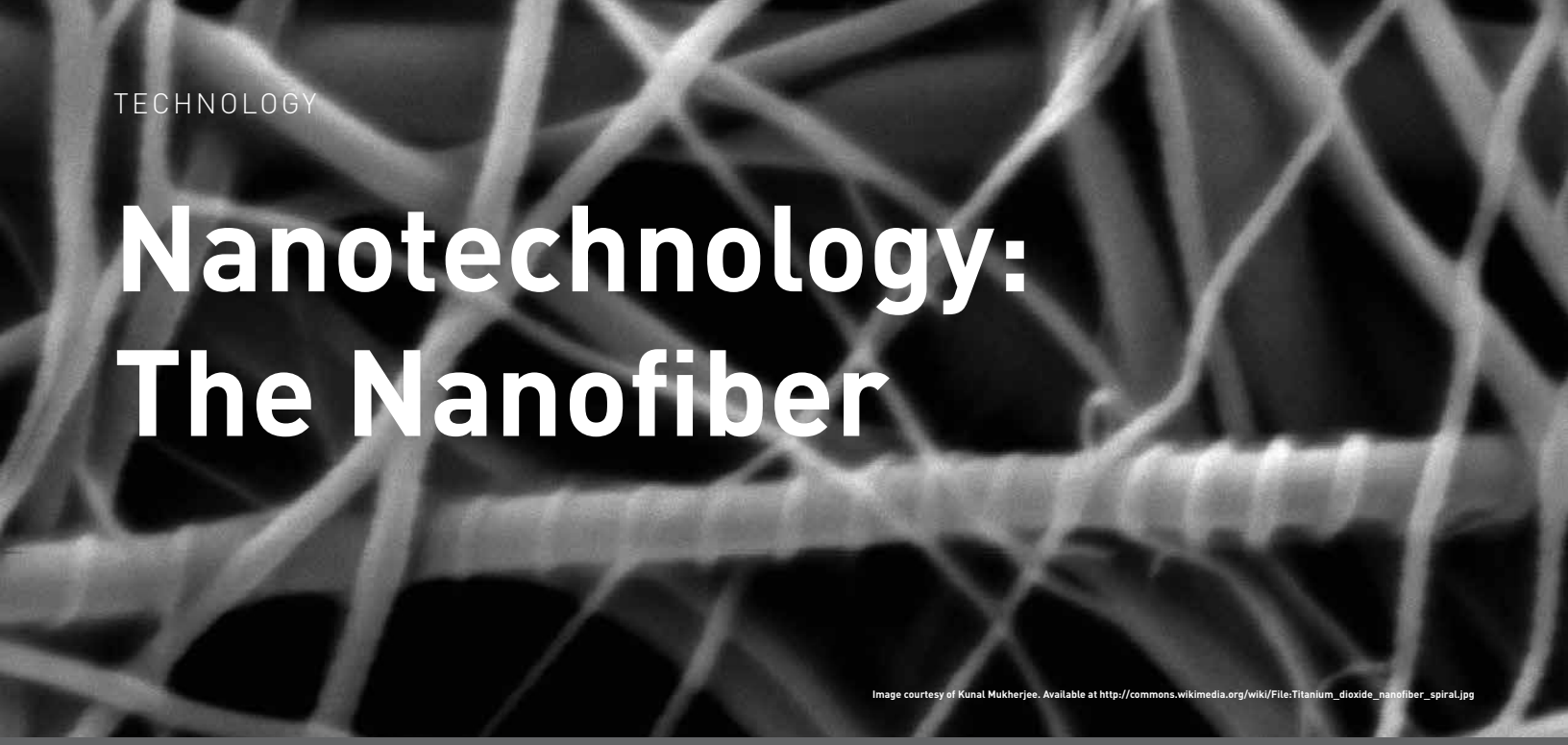

Image courtesy of Kunal Mukherjee. Available at http://commons.wikimedia.org/wiki/File:Titanium_dioxide_nanofiber_spiral.jpg

BY SUMITA STRANDER

Introduction

Nanotechnology operates science on the nanoscale. Its unit of measurement is the nanometer, which is one-billionth of a meter. Nanoparticles, then, are usually thought to be particles with a dimension that is between one and one hundred nanometers in length (1).

The nanofiber, a nanoparticle with a thread-like structure, has a diameter within this range. The fact that a single human hair has a diameter of roughly 80,000-100,000 nanometers demonstrates the incredibly small size of these particles (1). Several titanium dioxide nanofibers are shown in Figure 1.

History

Nanotechnology is often deemed one of science's fastest growing areas. This is not surprising, considering the fact that it only formally emerged as a discipline in the mid-twentieth century.

Many point to December 29, 1959, as the launch date of the field. On this day, at the California Institute of Technology, physicist Richard Feynman gave a talk called: "There's Plenty of Room at the Bottom" (1). This talk discussed the potential associated with studying single atoms and molecules. Although Feynman did not specifically use the term "nanotechnology" in his presentation the idea of studying science on such a small scale turned into what is known to be nanotechnology today.

The ability to recognize the single atoms and molecules Feynman mentioned did not become feasible until 1981 with the scanning tunneling microscope (1). Interestingly, artists inadvertently employed nanotechnology in the Middle Ages when they created stained glass windows (Figure 2). The artists were not aware that gold and silver nanoparticles were required to produce the striking effect seen in these windows (1).

Nanofiber technology has become prominent more recently. BBC researchers have followed the presence of nanofibers for only about a decade, which indicates the field's novelty. In fact, they have suggested that, based on a compounded annual growth rate of around 20 percent, the nanofiber market is expanding faster than many others within the realm of nanotechnology (2).

Unique Properties

This exponential growth of the nanotechnology industry is due to the appeal of several properties that nanoparticles, including nanofibers, possess. Quantum effects dictate that properties such as conductivity, melting point, and fluorescence depend directly on the size of the particle (1).

For example, the stained glass windows previously mentioned were made possible by the ability of gold nanoparticles to appear a red or purple color (1). This, in turn, was due to the fact that movement of these particles' electrons is different than that of "normal" gold particles' electrons. Furthermore, when examining particles at the nanoscale, small changes in size result in discernable changes in these properties.

This relationship between size and properties expressed does not hold true on larger

Figure 1: Titanium dioxide nanofibers shown above. Properties associated with these extremely small particles allow them to have novel applications in various fields.

scales. It is helpful to think of the relationship like a mathematical function, where size is the independent variable and property variation the dependent variable. Thus, an important implication of quantum effects is the ability to "design" favorable properties by adjusting the particle's size. This design process is often referred to as "tunability" (1).

Nanoparticles are not only appealing because their properties can be altered, but also due to their potential in understanding and affecting biological processes. This is because many of biology's building blocks and most important elements have dimensions in the nanoscale. For example, a single strand of DNA has a diameter of roughly two nanometers, while the protein hemoglobin has one of around 5.5 nanometers. Since scientists now have access to materials with similar dimensions, they can customize them so that they can directly interact with these small biological components.

For example, researchers at Northwestern University developed a method to find certain biomarkers for prostate cancer in human blood. They did this by forming the first bio-barcode assay, using gold nanoparticles (1). Although this assay was used specifically for the prostate cancer biomarker, the technology can be applied to create assays for other types as well.

There is one other major benefit of nanotechnology: a much higher surface area-to-volume ratio than larger particles. That is, for the same volume (or mass) of substance, nanoparticles offer a much higher surface area value than do their bulk counterparts. Imagine a set weight of a hypothetical substance. On the "normal" scale of science, this weight would be composed of so many fewer particles than it would be on the nanoscale, since each nanoparticle is so much smaller and thus weighs so much less.

This increased surface area is important because it allows for more efficient catalysts. Catalysts are substances added to reactions to increase the rate at which they take place. They do this by lowering the activation energy – the energy required for the reaction to occur – by providing the reaction with an easier path to take (3). Furthermore, catalysts are not consumed in reactions and often may be reused. Catalysis has many useful applications, particularly related to processes using chemicals and oils. For example, catalysts are used in a class of chemical reactions called hydrogenation to convert crude oil into the gasoline that operates vehicles. It has been estimated that over 99 percent of the gasoline that is developed depends on the use of catalysts (4).

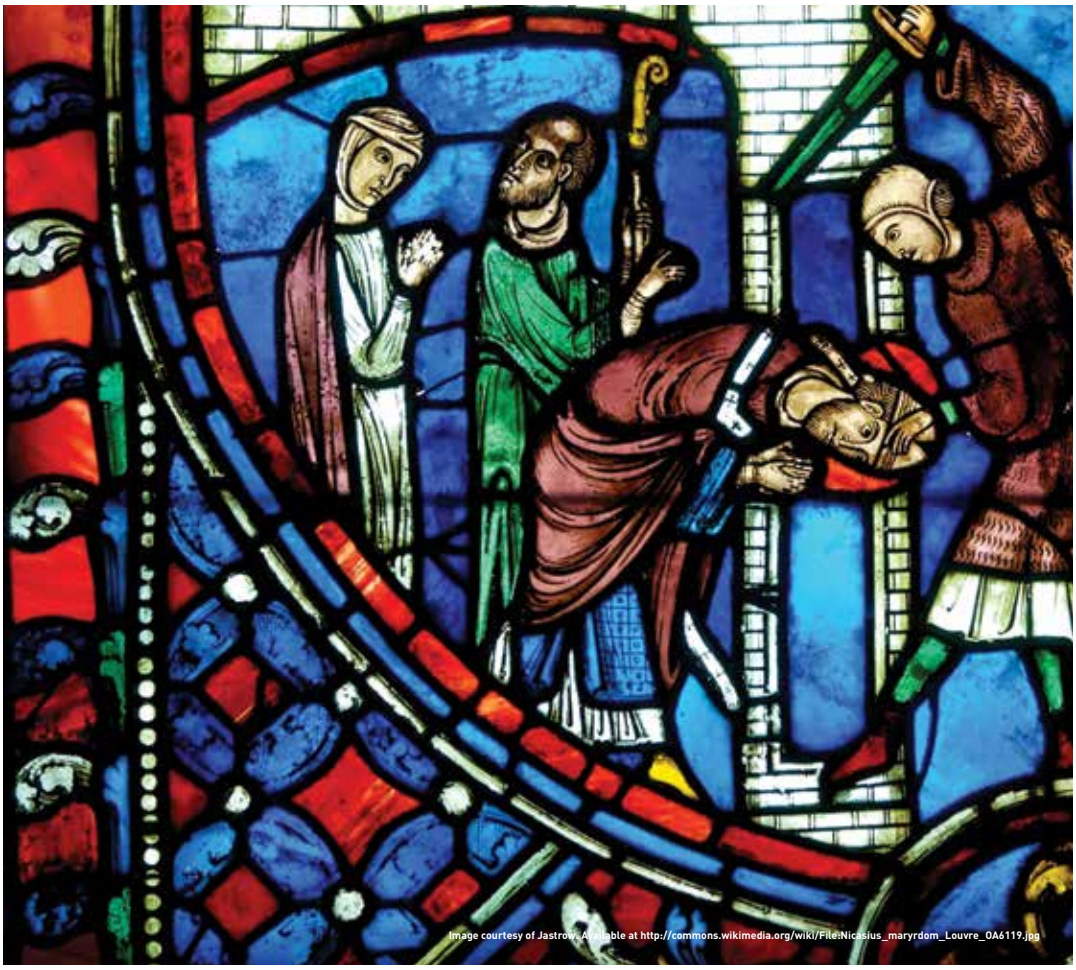

Figure 2: A medieval stained glass window. Artists of stained glass windows often inadvertently used nanotechnology to create this effect.

The question that remains is how nanotechnology affects the quality of a catalyst. The answer lies in the concept that catalysts work through contact with the reactants. That is, the more contact that exists, the more reactant that can be converted into product in an allotted measure of time (5).

Since reactions are measured by the conversion of reactants to products, converting more reactants by using the same mass of catalyst would entail higher reaction efficiency. Higher contact can be established by increasing the surface area of the catalyst without increasing the mass. The way to do this is by utilizing catalysts that are comprised of nanoparticles.

A Closer Look at Nanofibers

As previously mentioned, nanofibers are a specific class of nanoparticles that are long and tubular. Nanofibers can be constructed from both natural and synthetic materials. Some popular natural materials include collagen, chitosan, and hyaluronic acid (7). The most common method of forming nanofibers from these materials is the process of electrospinning, which relies on the application of high voltage to create an electrified jet, which is then stretched to become a long, tubular fiber (8).

Although they form a particularly new variation of nanoparticles, they are undoubtedly in high demand. This is largely because they too experience the unique and beneficial properties general nanoparticles possess. Additionally, they have some remarkable and specific characteristics that differentiate them from other types of nanoparticles.

One of these characteristics is tensile strength, which is important for a material to be successful as a fabric. Specifically, the tensile strength of nanofibers is thought to be as much as 40 percent greater than that of their larger equivalents (6). Therefore, just as in the case of catalysis, the fabric would be just as strong with a smaller number of fibers, creating a niche for nanoparticles in the textile industry. It has been suggested that nanofibers also possess unique capabilities to insulate material and store energy, creating applications in products like batteries (6). One of the reasons nanoparticles are so important is because they are on the same scale as many of the biological structures currently being studied. Because of this property, they have promising applications in the healthcare industry in areas such as wound healing, tissue engineering, and antibiotic delivery. In all three cases, the high surface area that nanofibers boast is essential. In antibiotic delivery, this allows the drug in question to be transferred at a faster rate. In wound healing, higher surface area increases the exposure of the wound to the medicated dressing composed of these nanofibers (6). Finally, in tissue engineering, the nanofibers are used to imitate the extracellular matrix of the cell, which surrounds and supports the cell. Here, high surface area (along with porosity) aids processes like cell adhesion, proliferation, and differentiation that are important for tissue success (7).

Conclusion

Nanotechnology is undoubtedly a rapidly expanding field. Although it only rose to prominence in the mid-twentieth century, its effects have been witnessed for centuries. With the advent of novel instrumentation, the study of what were initially unperceivably small particles became not only routine but also extremely valuable. It was quickly realized that particles this small do not abide by the same rules as particles of a more convention size. This difference could be employed to tweak the nanoparticle properties.

Furthermore, nanoparticles possess many exciting applications to biology and catalysis and remain a popular topic of research in these fields. Under the umbrella of nanoparticles, nanofibers have even more specific and equally attractive aspects as those of other nanoparticles. These properties have given rise to extremely diverse applications of nanofibers, in areas from clothing to electrodes to synthesized human tissue. Even though it may be unclear as to where and when the next nano-breakthrough will emerge, it remains certain that there is still "plenty of room." D

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Dye Sensitized Solar Cells

BY YIXUAN HE

Figure 1: Dye sensitized solar cells may replace traditional rooftop solar cells due to its cheap production, easy assembly, and high efficiency.

In the past few years, natural resource exploitation has increased dramatically. Humans use around 50 percent more natural resources than compared to 30 years ago (1). At the current rate, earth's oil and natural gas reserves will run out in this century (2). A major energy crisis will undoubtedly occur unless renewable resources can replace fossil fuels. The need for a new and cleaner source of energy is also heightened by the major environmental pollutions that occurred recently as a direct result of fuel extraction. The 2010 *Deepwater Horizon* oil spill in the Gulf of Mexico marked the worst spill in the United States history, killing 11 people, causing severe recreation revenue loss, and destroying the habitats of thousands of birds, sea turtles, and other marine mammals (3).

Fortunately, the sun is capable of supplying over 3 x 10^{24} Joules of energy per year, which more than 10,000 times the amount of energy consumed currently by the entire human race (2). By covering only 0.1 percent of the earth's surface with solar cells with an efficiency of 10 percent, the energy demand would be met (2). The challenge is to design and implement efficient, yet inexpensive solar cells.

A traditional silicon solar cell, or photovoltaic cell, is made from two types of semiconducting silicon plates, negative (n) and positive (p) types. Electrons from the n-type silicon flow into the p – type to equalize the charges. The flow of electrons creates a current, and the electric field of the cell creates a voltage. When an external power (such as a light bulb) is attached, electricity flows through the cell (4).

The amount of energy generated from electron transfer is about 0.6 to 0.7 volts per cell in traditional silicon solar cells (4). The major drawback, however, of silicon solar cells is the cost. Silicon processing is expensive, leading to high production costs for silicon solar cells.

Dye-sensitized solar cell (DSSC) provides an efficient yet cheap alternative. In 1991, Brian O'Regan and Michael Grätzel reported the modern dye-sensitized solar cells, which are semi-transparent and simple to assemble (5). The mechanism of DSSC is similar to that of light harvesting chlorophyll in plants. Conductive plates are lined with nanoparticles of titanium oxide coated with a monolayer of organic dye. The dye contains photosensitizers that become excited when struck by light. At the excited state, an electron is "injected" into a conduction band, which then travels to the anode to produce electricity. Thylakoid vesicles in the green pigment of plants behave similarly in sunlight to generate energy.

The titanium dioxide particles are each roughly 20 nanometers in radius. They act as conductors for the cell. Electrons move from one titanium dioxide particle to another to bring the electrons to the bottom of the cell.

Though the monolayer of dye is less than 1 nanometer thick, it plays a large role in determining the absorption rate and efficiency of DSSC. Most of the commonly used dyes have poor absorption in the red part of the spectrum, thus limiting the efficiency of the cell. Scientists

are now working to improve the absorption efficiency of the dyes throughout the entire spectrum. Recently, there have been DSSC prototypes developed with efficiencies as high as 15 percent (6).

DSSCs are the most efficient third-generation solar cells available (7). This new generation of solar cells includes cells made from materials other than silicon that focuses on lowering the cost of already commercially available solar cells. In many cases, however, efficiencies are compromised in traditional solar cells to try to lower the cost. Current commercial rooftop solar collectors have efficiencies of between 5 percent and 13 percent. DSSC is an attractive replacement due to not only their low cost, but also their lightness and robust construction.

There are several other advantages of DSSC. While traditional solar cells need direct sunlight to work efficiently, DSSC operate even in low light conditions, such as under cloudy skies and in settings with indirect sunlight like when indoors. The mechanism of solar cells is also indirectly proportional to the temperature. The DSSC's thin conductive plastic structure radiates heat faster and thus has higher efficiency (8).

Interview with Hongshan He, Eastern Illinois University

Dye sensitized solar cells are becoming increasing popular in the research community as more and more scientists work to improve DSSCs. Below is an interview with Professor Hongshan He of Eastern Illinois University (EIU) who has done extensive research in the field of DSSCs. Dr. He is an experienced materials chemist. His research has been supported by the National Science Foundation, the American Chemical Society Petroleum Research Fund, as well as EIU President's Funds for Research and Creativity Activity. Dr. He was also a lead organizer of two symposia for the Materials Research Society (MRS) and is an author of more than 70 peer-reviewed publications. His current research group includes two graduate students, two undergraduates and one visiting professor. Dr. He can be reached by the email: *hhe@eiu.edu.*

What does your research focus on?

My research focuses on photoactive materials with broad applications in renewable energy, medical diagnosis, and chemical synthesis. The research is interdisciplinary— spanning from inorganic/organic synthesis, nanofabrication, theoretical modeling, and crystallography to catalysis. However, the photoactive nature of studied materials is the core of my research. For example, the dye molecules in dye-sensitized solar cells, which play a critical role in harvesting sunlight efficiently, are photoactive materials.

> "It is estimated that in one hour more sunlight falls on the earth than what is used by the entire population in one year. If a small fraction of this solar energy is converted into electricity at a reasonable cost, then a continuous and reliable energy supply should be achievable, as well as a concomitant reduction in carbon dioxide emission to help abate global warming."

Can you describe your past and present research projects?

I have been working on several projects. The first one is focused on light-harvesting materials for dye-sensitized solar cells. One primary focus is to develop highly functionalized porphyrin dyes with broader light absorption to increase energy conversion efficiency. A DSSC functions much better when dye molecules absorb broadly in the solar spectrum and are anchored strongly on the TiO_2 surface. Current state-of-the-art dyes suffer from their narrow absorption of sunlight and weak binding capacity to the semiconductor. I am working along with my students to address these limitations by first, making the fabrication of a DSSC much easier, more controllable, and more reproducible; second, enhancing the binding strength of dye molecules on the titanium dioxide nanoparticles, and therefore, cell's long-term stability; and third, using an Förster resonance energy transfer process to realize complimentary light absorption. We have made significant progress in this area and some results have been published in peer-reviewed journals. Currently, this work is supported by Eastern Illinois University President Research and Creativity Fund.

The second project is on near-infrared materials for biomedical diagnosis. The goal is to develop photoactive materials that can emit in the near-infrared region under illumination of red lights. Those materials can be used as optical probes for sensitive detection of tumor markers for early prevention. Such probes can overcome several disadvantages of the state-of-the-art probes on the market. A recent review article in the *Coordination Chemistry Reviews* (2014, 273-274, 87-99) summarizes my work in this field.

The third project is also related the development of photoactive materials. In this

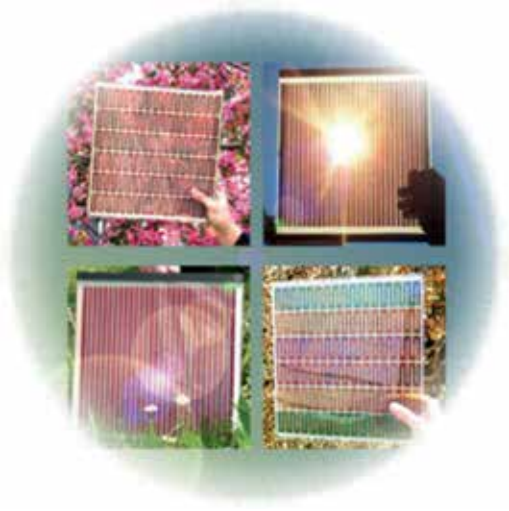

Figure 2: Dye sensitized solar cells are becoming more popular as the demand for renewable energy increases. The transparency of DSSC makes it attractive for commercial use as well.

Image courtesy of Ronald Vera Saavedra.
Available at http://commons.wikimedia.org/wiki/File:Dye.sensitized.solar.cells.jpg

direction, we are trying to use photoactive materials to catalyze chemical reactions to make the reaction efficient. One typical example is the Sonogashira coupling reaction of aryl bromides with terminal alkynes at elevated temperature. The idea is to develop a photocatalyst that will speed up the Sonogashira reaction under visible light illumination. This work is currently supported by the American Chemical Society Petroleum Research Fund.

How did you become interested in DSSC's?

When I was a child, I was very fascinated by how the small blue window panel on the top of the calculator could provide enough electricity for the device to work. That fascination inspired me to pursue an education and career in photoactive materials. Solar energy is an environmentally friendly alternative energy source that can make a significant contribution to solving worldwide energy problems. It is estimated that in one hour more sunlight falls on the earth than what is used by the entire population in one year. If a small fraction of this solar energy is converted into electricity at a reasonable cost, then a continuous and reliable energy supply should be achievable, as well as a concomitant reduction in carbon dioxide emission to help abate global warming. However, the current dominant technology for converting solar energy to electricity is based on silicon solar cells, which are quite expensive due to the high cost of manufacturing.

Thus I began to work with an alternative technology, dye-sensitized solar cell (DSSC), which has been recognized as a cost-effective device. They are lightweight, made from inexpensive materials, and can be adapted for a variety of indoor and outdoor applications with significantly reduced environmental impact.

How do you see the future of DSSC's?

Since its discovery by Grätzel and Oregan in 1991, DSSCs have been extensively investigated; however, only recently have large breakthroughs been reported. Scientists around the world are now trying to address aforementioned challenges in order to improve its efficiency and lower its costs. They are strong candidates for indoor and outdoor applications. For an example, it is possible to make flexible DSSCs, which can be used to charge small portable electronic devices. In addition, due to the their transparency, DSSCs can also be effectively incorporated into windows to produce electricity. A bright future lies ahead for DSSCs.

Dye sensitized solar cells are becoming increasingly as commercial solar cells. There is a high demand for efficient renewable resources to replace the depleting natural resources.

Despite the simple structure of DSSCs, the nanoparticles that make up the cells play large roles in determining the efficiency and cost of this new category of solar cells. Dr. He, along with researchers from across the world, is working together to make DSSC an even better source of alternative energy. **D**

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Bona Fide Beauty Led Off by Bona Fide Change

KEVIN JONG-HYEON SHIN (SEOUL INTERNATIONAL SCHOOL, SEOUL, SOUTH KOREA)

Since the First World War, humans have sought ways to correct deformities and facial damage inflicted during the horrors of combat. Additionally, many more individuals seek ways to correct hair lips, cleft palates, and other facial problems (1). Modern medicine and surgery have pursued many ways to help those afflicted by flaws and imperfections; and now we may have an answer.

Perhaps the most pervasive inducer of stress in the modern world is related to our aesthetic beauty. As elementary as this conflict may sound, it is simple for some to assert that cosmetic surgeries will resolve such conflict at all costs. Nonetheless, there are potential consequences for any action one takes, and this is no exception in the world of plastic surgery. Though the probability of post-surgery side effects is noted to be so minuscule that it can be neglected due to the unparalleled technological developments in these operations, even such trifling possibility triggers anxiety within patients and practitioners. Yet, what if we found a possible panacea for the backlashes of surgery complications? In other words, what if someone avowed that, in the world of plastic surgeries, it is possible to correct aesthetic imperfections without any potential consequence?

Of course, it is farfetched to argue that there is a zero-percent risk during or following any operation, as nothing is guaranteed in this world. Yet, humans always strive to improve themselves, and this is the same in the domain of beauty. Nitrogen plasma surgery, a surgical operation set forth by Portrait, opens a new gateway for the medical field to explore operative care while minimizing unwanted and hazardous repercussions. By using plasma to produce a thermal profile at and beneath the skin's surface, this procedure replaces old collagens with new collagens while leaving the outer epidermis intact (2,3). As implausible as this claim sounds, the merits brought forth by this technological development potentially represent a scientific advancement in the field of cosmetic surgery, placating the fears faced by thousands of potential patients. From a cosmetic perspective, this offers a revolutionary change, which demands further scrutiny.

It is necessary to delve into the history of cosmetics to understand the logistics of nitrogen plasma surgery. Plastic surgery dates back to the Old Kingdom of Egypt, which existed from 3000 to 25000 BCE. At this point, plastic surgery consisted of no more than inchoate procedures with the aid of rudimentary utilities. No practical developments were made during the period between the ancient world and the twentieth century until Sir Harold Gillies, known as the father of modern plastic surgery, pioneered modern facial reconstructive surgery in order to help soldiers who suffered grievous injuries during World War I (1). Yet with the finite amount of technology and knowledge available at that time in history, plastic surgery was used to simply lessen the severity of one's facial deformities (4).

Nevertheless, in a matter of few decades, plastic surgery had advanced sufficiently to serve a purpose of reconstructing and beautifying one's appearance. No matter what type of cosmetic surgery one decides to pursue, the basic procedure involves removing the outer epidermis, manipulating the tissue beneath, and then closing the epidermis after alterations are complete (4). Hence, it is inevitable for physical scars to form following the process of these surgeries. As a result, afflictions and infections are inadvertently sustained, creating grief, discomfort, and despair among patients, many of whom become afraid to expose their modifications (5). Though developments are being made to reduce the possibility of these unintended misfortunes, it is impractical to wish for a risk-free operation in perfecting one's appearance. This underlying danger forced plastic surgeons to concede the inherent risk assumed by patients in order to protect themselves against malpractice lawsuits (6). Yet, with the dawn of nitrogen plasma surgery, these threats are beginning to recede.

The Portrait Plasma Skin Regeneration is a leap forward in terms of maximizing the surgeries' efficiencies, while reinforcing a path for ongoing development in the world of aesthetics. This new technology employs the fourth state of matter, known as plasma, to produce a thermal profile at and below the skin's surface (7). The hand piece delivers micro-pulses of plasma directly into the epidermis while keeping the outer skin layer intact (4,8). The gravity of this new technology lies in the notion that the outer layer of skin is undisturbed and unmarked by the surgical process. In other words, neither patients nor other individuals will be able to perceive that the surgery ever took place.

To serve the uttermost needs of the patients, nitrogen plasma surgery utilizes its effectiveness in multiple dimensions. There are three different regimen types of nitrogen plasma surgery, which are named PRS1, PRS2, and PRS3 (7,9,10). Each of these regimens is a form of nitrogen plasma surgery with a specific role to fulfill. PRS1 divides the treatment into three to four low energy sessions and is primarily used to treat mild sunburns and wrinkles. PRS2 is employed when the patient has severe wrinkles or major skin damage. The skin will gradually darken into a brown tone, showing signs that the skin beneath is remodeling and reshaping itself. PRS3 is an extension of the aforementioned operations with more extensive resurfacing of the skin (9,10). Each distinguished treatment is based on the individual patients' needs, allowing patients to choose the therapy that suits best for them. Such diverse treatment is not easily found in orthodox facial operations prevalent in nations such as the United States and South Korea.

Up until today, there has been overwhelming evidence of convenience and satisfaction for users of nitrogen plasma surgery. Out of 272 investigated procedures using nitrogen plasma surgery, there were only a total of five complications, meaning the percentage of dissatisfaction or unwanted disfigurement out of the procedures taken was a mere 1.8 percent (11). The surgery's ability to predict the approximate depth of the tissue injury and the post-treatment healing process that allows Portrait to maximize the convalescent's needs enables the procedure to achieve an unprecedented success rate. Furthermore, the percentage of tissue undermining is 0.2 percent, meaning only one out of 475 treated areas with plasma surgery suffered difficulties related to the inner tissue (12). The statistics not only demonstrate the safety of these surgical procedures, but also indicate a heightened level of patient fulfillment. It is important to note that the priority in the medical world is not only to pronounce premier outcomes to the public, but also to provide verification with actual results. Nitrogen plasma

surgery achieves this goal with its innovative development in the field of aesthetic surgery.

Another impressive factor regarding nitrogen plasma surgery is the flexibility with which this procedure can handle different situations. Regeneration using nitrogen plasma can occur after traditional procedures, including operations to the forehead and mid-face regions. This procedure yields the double benefit of the traditional treatment the patient may need and the plasma procedure which amplifies the textural structure and appearance of the skin. Such procedures minimize thermal injury and laser tissue interaction, while producing a natural skin tone (9). Though this technology is still maturing, the safety and flexibility achievements of nitrogen plasma surgery deserve special recognition. Undoubtedly, the world of aesthetics has never seen an operation that can offer such high success rates in safety and accuracy as nitrogen plasma surgery.

To neglect the sophisticated advantages of nitrogen plasma surgery is to forgo a revolutionary progress in the field of aesthetic surgeries. There is no doubt that plasma surgery requires further development before reaching its finest potential. Nonetheless, the scientific advantages and implications it elicits are aspects to keenly observe. The handpiece allows computer-controlled diffusion of plasma into the intended skin layer, prohibiting hindrance of the nervous system and minimizing the possibility of human error (8). This development avoids additional anesthesia meaning the possible repercussions regarding stimulation of the nervous system are mitigated. Such enhancement is not only significant in the field of cosmetics, but also in the world of other scientific endeavors that require the usage of anesthesia. Hence, nitrogen plasma surgery has prompted in reducing the need for anesthetics, marking a breakthrough in the field of surgeries.

All forms of cosmetic surgery deals with the epidermis, the largest organ of the human body. No matter what type of aesthetic surgery one decides to take, the patient is attempting to alter an organ made up of complicated tissues composed of millions of cells. The primary difference between nitrogen plasma surgery and more established or contemporary alternative surgeries is that nitrogen plastic surgery does not require incisions or other compromising procedures. Rather, nitrogen plasma surgery keeps the epidermis intact, while alternative methods require risky and invasive measures which compromise the very same organ said procedures seek to heal or improve (8,13). Doctors' awareness of cosmetic surgery's inherently counterproductive mandate – healing or improving only after a patient is willing to risk scarring and infection – is what prompted the creation of national plasma surgery. Previous surgeries which sought to "unzip" the largest organ in the human body and make alterations beneath the skin did not adequately address safety and dependability issues during or after surgical procedures (6). Nitrogen plasma surgery, on the other hand, does not involve any sort of physical opening of the skin, precluding many forms of infection which were present in traditional procedures. Though it may sound farfetched, nitrogen plasma surgery may very well precipitate the dawn of closed-skin organ surgery such as a closed-skin heart surgery. This hope, while ambitious, is based upon science's marked ability to build upon the foundations of preceding experiments.

All in all, patients are the number one priority in any surgical procedures, and this goes the same for the realm in cosmetic surgery. Every year 14.6 million patients worldwide are taking the risk of potential backlashes during or after cosmetic surgeries (12). This potential backlash demonstrates how urgent it is to not only reduce the potential harms after these aesthetic surgeries, but also to alleviate the psychological damages patients may go through after their procedures. To mitigate the mental breakdown patients go through due to the lack of success in the operations they eagerly awaited for, the priority is to produce optimum results in the surgical procedures (14). It is that simple. A change in the system itself not only assembles better results, but also elevated satisfaction within patients.

The world of surgeries is a continuous process. What this means is that a success in the procedure will lead to a contented patient; on the other hand, a failure in the procedure will lead to a malcontented patient. Favorable results recondition both the patient's inner and outer beauty and nitrogen plasma surgery can serve as the finest assurance (5,15). If one is not able to embrace a mere 0.2% of potential harm, no operation in this world will possibly satisfy oneself (11).

The world of science is too convoluted for a single breakthrough to change the entire field. Nonetheless, history has shown that a single discovery can branch off to multiple innovations. Though we hear time to time to never judge a book by its cover, it is the innate behavior of all humans to make first impressions out of anyone or anything they perceive. This implants the thought within us that more beauty will lead to more success. A dawn in cosmetic surgeries originated from this simple belief, and it is too late now to try to alter this perception. For science to develop and for the world to enhance, it is the job of those capable to make a potential into a reality. And in this consumer world, there seems to be nothing more important than beautifying the faces of millions of people. As idealistic as this claim sounds, plasma nitrogen surgery may be the breakthrough we have been anticipating.

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Graphene: The Hope For Renewable Energy

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A new scientific discovery can often generate a chain reaction where additional breakthroughs take place, expanding on existing technology and generating new findings. For example, after single-layer graphene was experimentally isolated in 2004, the two-dimensional material rose to prominence in the scientific community and later earned Andre Geim and Konstantin Novoselov the Nobel Prize in Physics in 2010 (1-3). Graphene has inspired developments in a variety of areas, including in electronics, field emission, gas sensing, energy storage, and energy conversion (3).

Because of the rapid depletion of fossil fuels, a major challenge facing the twenty-first century scientific community is trying to find a clean, efficient, and renewable energy source (1). In addition to acting as a replacement for presently diminishing sources of energy, renewable energy can be a much more effective and environmentally friendly alternative to nonrenewable sources of energy (4). One of the most promising existing energy sources is the fuel cell, an electrochemical device which derives power from converting chemical power into electrical energy through chemical reactions on the surface of an electrode and an electrolyte (1). Fuel cells have many additional benefits over presently used energy sources, such as the fact that they produce no harmful emissions, thus reducing the output of greenhouse gases and air pollutants in the Earth's atmosphere. As fuel cells gain more popularity, scientists are always looking for new ways to improve their efficacy by utilizing new technology. Methods they are using range from reducing system size to decreasing cost and increasing durability (4).

Fuel cells use electrocatalysts in order to accelerate oxygen reduction reactions (ORR) within the cell (1,4). Currently, the catalyst of choice is platinum because it exhibits the highest electrocatalytic activity of available materials (1). However, a major obstacle which prohibits the mass production of fuel cells is their use of platinum catalysts. These catalysts are not ideal due to their high cost, low reliability, and inefficiency (6-8). If platinum catalysts were replaced with a more efficient material, fuel cells could possibly replace current nonrenewable energy sources.

Graphene is one of the materials proposed to replace platinum. It is extremely versatile, having the ability to be shaped into 0D fullerenes, rolled into 1D nanotubes, or stacked into 3D graphite (3). Its versatility and other unique properties such as high charge carrier mobility allow it to be applied in a variety of fields, from biosensing to electronics (2,9). In addition, it possesses high thermal and electrical conductivity and flexibility (9). It is also much stronger than platinum; in fact, researchers at Columbia University once lauded it as the 'strongest material in the world' (10). Being a 2D material, it has a large surface area, which makes it optimal for use not only in electronics, but also as a catalyst support in fuel cells (1,9).

Although graphene has a multitude of properties which enable its potential usage in many different fields, it still contains innate flaws which need to be improved before it can be used in real world applications. For example, pristine graphene has predetermined energy levels which restrict its ability to be used in many existing electronic devices (9). The most effective method of mitigating graphene's defects seems to be doping the graphene sheet. Doping is when carbon atoms within the graphene sheet are substitutionally replaced with other elements (9). Doping can alter the electronic properties and change the local chemistry of graphene, which allows aspects of the graphene sheet to be adjusted to suit different purposes (11). The modification of these properties can also be beneficial in fuel cells because it can increase electrochemical activity.

Carbon-based nanomaterials show high electrocatalytic activity during ORR and are relatively inexpensive and environmentally friendly. Therefore, they provide a welcome alternative to platinum catalysts. Graphene sheets doped with elements such as nitrogen or phosphorus have been displayed even higher electrocatalytic activity than do pure graphene and other carbon-based nanomaterials (7). Originally it was hypothesized that the increased activity of the nitrogen-doped graphene sheet was due to the fact that nitrogen atoms (electronegativity (EN): 3.04) are much more electronegative than the carbon atoms (EN: 2.55) that comprise the graphene sheet. This disparity in charge then created positive charge density in the carbon atoms adjacent to the doped nitrogen atoms, causing increased electrocatalytic activity. However, when atoms such as phosphorus (EN: 2.19) and boron (EN: 2.05) were used as dopants, these doped graphene sheets *also* exhibited increased activity even though boron and phosphorus atoms possess electronegativities lower than that of carbon. This led to the rationale that positive and negative sites led to increased O_2 adsorption in ORR (5). In addition to introducing asymmetrical charge distribution, dopants within the graphene sheet also have the added benefit of providing anchoring points for the adsorption of isolated atoms such as O_2 in ORR, further increasing electrocatalytic activity (6).

Another notable advantage of doped graphene is that, depending on the dopant atoms, doped graphene can be a metal-free catalyst. An advantage of metal-free catalysts is that they are not susceptible to gas poisoning and also show tolerance to methanol crossover effect, which can be beneficial in methanol fuel cells (12,13). However, there are still problems with using doped graphene as catalysts. Methods of producing doped graphene often yield low concentrations of the dopant element within the graphene sheet. For example, when researchers used a thermolysis method to synthesize phosphorus-doped graphene, the graphene sheet had a phosphorus concentration of less than 0.3% (13). Since the concentration of dopant atoms in the graphene sheet correlates with the amount of charge introduced into the sheet and the number of anchoring points for oxygen atoms, the creation of a graphene sheet with a low dopant concentration is not ideal (4). However, synthesizing phosphorus-doped graphene sheets is much more difficult than with other dopant atoms because phosphorus atoms are much larger than the carbon atoms. Recent methods such as

using graphite oxide and triphenylphosphine to synthesize phosphorus-doped graphene have proven successful. The resulting phosphorus-doped graphene sheet acted as an efficient catalyst in ORR (13).

Since single-atom doped graphene has shown higher electrocatalytic activity than pure graphene, some researchers have experimented with graphene doped with two or more elements. Graphene doped with more elements is harder to synthesize, but has been shown to have significantly higher electrochemical activity than single-atom doped graphene.

Researchers at the Korea Advanced Institute of Science and Technology attempted to dope graphene with a combination of boron, nitrogen, and phosphorus elements. They obtained results which state that boron nitrogen-codoped graphene showed 1.2 times higher ORR activity than nitrogen-doped graphene. Phosphorus nitrogen-codoped graphene exhibited even higher ORR activity, having results which were 2.1 times higher than that of nitrogen-doped graphene. However, in conjunction with the previous theory that higher electrocatalytic activity was due to the asymmetric charge density and the anchoring points introduced by dopants, the ternary-codoped graphene sheet had the highest activity, 2.3 times higher than that of nitrogen-doped graphene (14).

These researchers also provided additional reasons to explain why doped graphene yielded higher electrochemical activity than pure graphene. They asserted that phosphorus doping increased the difference in charge between the carbon atoms and the number of edge sites within the graphene sheet. Therefore, since introducing phosphorus into the graphene sheet provided the largest difference in electrochemical activity, they concluded that the number of edge sites and charge delocalization in the graphene sheet was the major factor in determining ORR activity (14).

The feasibility of graphene replacing platinum catalysts in fuel cells is high, as in October 2014 researchers at Rice University developed boron and nitrogen-doped graphene quantum dots which outperformed commercial platinum catalysts in fuel cells by about 15 millivolts in the ORR. These quantum dots also showed about 70% higher charge density than the platinum catalysts. These dots were synthesized from graphene quantum dots (GQD) and graphene oxide, which makes them much more inexpensive than commercial platinum catalysts. Using the GQD-graphene oxide hybrid, these quantum dots combine the overall advantages of graphene (15). The GQD dots add to the number of edges sites, which Choi *et al.* found was beneficial in increasing electrochemical activity, while the final hybrid quantum dots retain the large surface area and high electrical conductivity of graphene (14, 15).

Replacing the platinum catalysts in fuel cells with graphene catalysts is the best option for an alternative to non-renewable energy. Graphene solves the two major problems platinum incurs—its high cost and inefficiency. Carbon-based nanomaterials are much more inexpensive than metal catalysts such as platinum, and both theoretical and experimental studies have proven that pure graphene exhibits higher electrocatalytic activity than their platinum counterparts. Doped graphene, both single-doped and codoped, exhibits even higher electrocatalytic activity than pristine graphene. The possibility of graphene catalysts is no stretch of the imagination. Researchers such as those at Rice University are already developing graphene catalysts which can be commercially sold. The substitution of platinum with graphene may finally make fuel cells widely accessible, providing an environmentally friendly energy source and eliminating the need for fossil fuels.

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Energy allocation in morphological features varies throughout life span and between sexes of *Pterois volitans*

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Abstract

The invasion of lionfish, Pterois volitans*, poses one of the most significant threats to native reef fish communities in the Caribbean to date. Understanding how lionfish are able to maintain life history strategies of rapid growth rate and high fecundity through allocation of resources may help to explain the mechanisms underlying their competitive advantage. We tested how relative size of morphological traits key to survival changed with body weight and how investments in relative fat and gonad mass differed between mature males and females. As lionfish weight increased, their relative total body length and morphological features relating to defense and apparent size decreased. Both female and male lionfish invested more in relative gonad weight as their body weight increased, but only males had a higher relative fat mass as their body size increased. These findings suggest that as lionfish grow, their reproductive capability and ability to withstand environmental stressors continue to increase.*
keywords: lionfish, invasive, Pterois volitans, *resource allocation*

Introduction

Lionfish, *Pterois volitans*, were introduced to southern Florida in the early 1990s and have spread prolifically throughout the Caribbean (Albin & Hixon 2008). As top predators, lionfish can adversely affect reef ecosystems through competition with native piscivores and consumption of a variety of native reef fishes, crabs and shrimps (Hare & Whitfield 2003). In addition to advantages incurred from living outside of its native range, the competitive advantage of this species stems from life history strategies including rapid growth rate, high fecundity, and venomous spines (Morris et al. 2011). Examining how lionfish allocate resources throughout their life span and between sexes may help to explain the success of many of these strategies.

All organisms are constrained by the limited resources and the trade-offs of resource allocation. The principle of allocation (Cody 1966) suggests that evolution selects for organisms that allocate resources in ways that maximize fitness. Resource allocation often varies across life stages to optimize fitness. In juvenile fish growth and survival are prioritized, as rapid growth and investment in particular shapes may enable fish to reach a size refuge from predators (Brönmark & Miner 1992). Resources are also invested differently by sex to balance reproduction, maintenance, growth and defense. We studied how energy allocation varies through life history and between female and male *Pterois volitans* by measuring morphological characteristics relative to body weight.

Since lionfish exhibit indeterminate growth (Heino & Kaitala 2001), allocation to morphological features may vary with size, particularly before and after sexual maturity (Taylor & Gabriel 1992). We tested the hypothesis that larger lionfish invest less in survival relative to smaller juveniles. We predicted that as lionfish grow, they invest less in morphological features that deter predators and make them appear larger. These features include long venomous spines and protruding fan-like pectoral fins. Alternatively, larger lionfish may not be investing relatively less in survival and instead the length of these morphological traits may be a function of body size.

Lionfish reach sexual maturity at approximately 100 mm for males and 180 mm for females (Morris & Whitfield 2009). Sexually mature males and females likely allocate energy resources differently as mature females have a lower body fat mass, in relation to body length, than males (Costello et al. 2012). We predict that females are allocating more resources to reproduction than males as they grow and will thus have a lower relative body fat mass and a higher relative gonad size to males. In many indeterminate species, reproduction is seasonal and females often invest energy resources into growth during the non-reproductive season (Heino & Kaitala 2001). Female lionfish in the Caribbean can reproduce as frequently as every four days and this pattern of shifting resources may appear during the reproductive cycle. In this case, we would expect to see higher percent body fat in females with eggs than females without eggs. Alternatively, if female lionfish are continuously allocating resources towards reproduction, not towards fat storage or growth, percent body fat then there would be no difference in relative fat mass between females with and without fully developed eggs.

Methods

Twenty-seven juvenile lionfish were collected and frozen in the months of February and March from various

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locations on Little Cayman Island, including Mary's Bay, Pirate's Point Dock, and South Hole Sound. Ten lionfish were culled at Joy's Bay on the evening of March 5, 2014 and after being kept on ice overnight, were dissected. We weighed all lionfish and measured total body length, pectoral fin length, and both dorsal and pectoral spine length. Total length was measured as the distance from the mouth to the tip of the caudal fin. Pectoral fin length was measured from the base of the fin to its longest point. The longest dorsal spine and the first pectoral fin were measured using SPI 2000 calipers.

In mature fish, we determined sex and then removed and weighed gonads. We noted stage of eggs in ovaries as developing or fully developed. We also determined body fat mass by removing and weighting all fat in the body cavity. All weights were made using an Adventurer™ OHAUS. We also used data collected in Little Cayman in March, 2012 by Costello et al. (2012) in our analysis

Statistical analysis

All morphological measurements and total body weight of lionfish were log transformed to linearize their relationships. This enabled us to determine the differential growth ratio between a morphological trait and weight using the slope of the linear equation between log-transformed variables. In doing so, we were able to determine how lionfish invest their energy. If a morphological feature had a higher growth rate than body weight, the slope of the log-transformed relationship was greater than one (positive allometric relationship). If a morphological trait had a lower growth rate than the body weight as a whole, slope was less than one (negative allometric relationship). If the growth rate of a feature was equal to that of the body weight, the slope was equal to one (isometric relationship).

To test investment in survival throughout life-stages, we performed a regression analysis of lionfish body length, pectoral fin length, pectoral spine length, and dorsal spine length, with respect to weight. To test investment in energy reserves and reproduction in sexually mature lionfish, we regressed fat mass and gonad mass with weight in males and females. We performed an analysis of covariance (ANCOVA) of gonad mass and fat mass in males and females. To test the difference between fat mass in females at various stages of their reproductive cycle, we performed an ANCOVA of fat mass in females with developed eggs and those without. All analyses were performed using JMP® 10 statistical software (SAS Institute, Cary, NC).

Results

Lionfish total weight ranged from 0.6 g to 720.1 g and body length ranged from 57 mm to 381 mm. There was no difference in the upper size range of lionfish caught in 2014 and those caught in 2012. As lionfish weighed more, their relative total body length decreased (slope = 0.28 ± 0.02, $P < 0.0001$, $r^2 = 0.99$: Fig. 1). Likewise, as lionfish weight increased, the relative size of their pectoral fin, dorsal spine and pectoral spine lengths all decreased (slope = 0.20 ± 0.10, $P < 0.0001$, $r^2 = 0.54$; slope = 0.031 ± 0.07, $P < 0.0001$, $r^2 = 0.94$; slope = 0.24 ± 0.06, $P < 0.0001$, $r^2 = 0.94$ respectively: Fig 2).

In sexually mature adult lionfish, the trends in relative fat mass differed between females and males ($F_{1,53} = 3.87$, $P = 0.05$). Heavier females tended to have lower relative fat mass, although this relationship was not significant, while heavier males had higher relative fat masses (females: slope = 0.77 ± 0.44, $P = 0.07$, $r^2 = 0.16$; males: slope = 1.45 ± 0.26, $P < 0.0001$, $r^2 = 0.79$: Fig. 3). There was no difference in the relative fat mass in females with and without developed eggs ($F_{1,15} = 2.04$, $P = 0.17$) Relative gonad mass was higher as weight increased in both female and male lionfish (female: slope = 2.58 ± 0.32, $P < 0.0001$, $r^2 = 0.82$; male: slope = 1.77 ± 0.17, $P < 0.0001$, $r^2 = 0.89$: Fig. 4). However female's relative gonad mass increased at a greater rate than male's ($F_{1,53} = 9.85$, $P = 0.003$).

Discussion

Resource allocation to growth and survival vary with lionfish size and corresponding life stages. Larger fish are not investing as much in growth (Fig 1) and invest relatively less in morphological traits aiding in survival (Fig. 2). Juvenile lionfish likely grow rapidly lengthwise and invest in morphological traits that increase apparent size in order

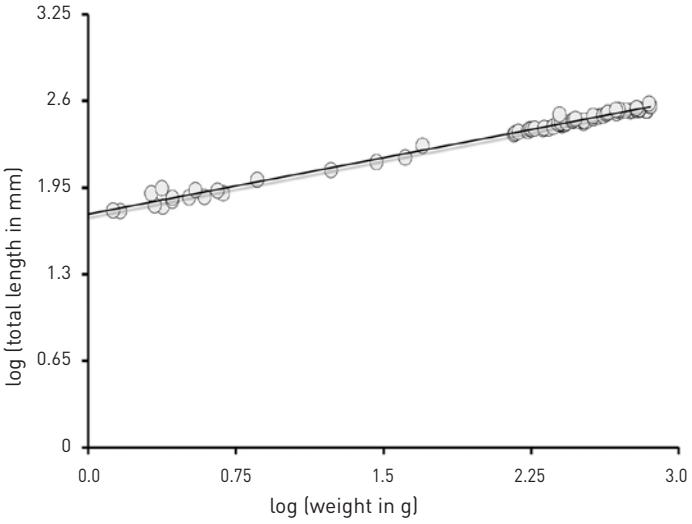

Figure 1: Lionfish length had a negative allometric relationship with weight.

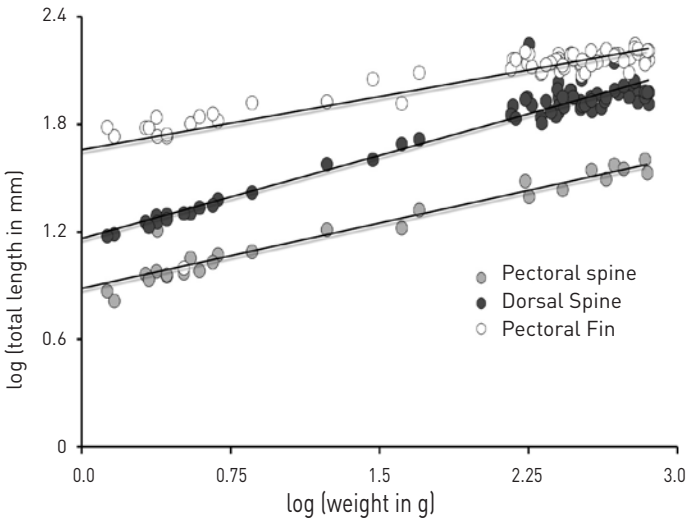

Figure 2: Pectoral fin, dorsal spine, and pectoral spine lengths all had negative allometric relationships with lionfish weight.

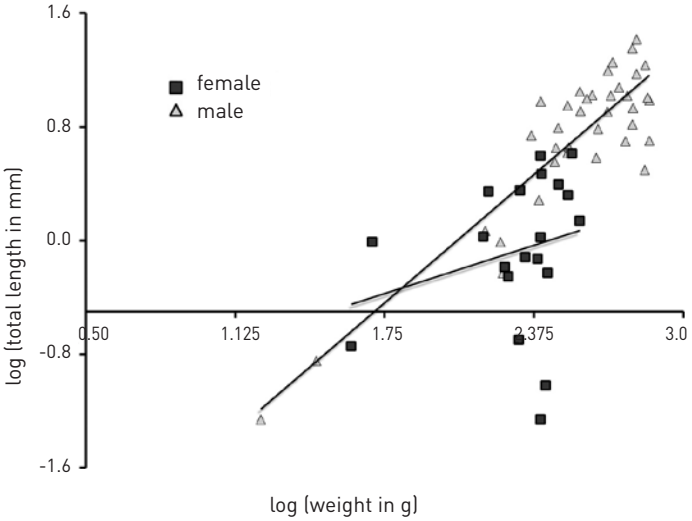

Figure 3: Fat mass had a negative allometric (slope = 0.77 ± 0.44) relationship with weight in females and a positive allometric (slope = 1.45 ± 0.26) relationship in males.

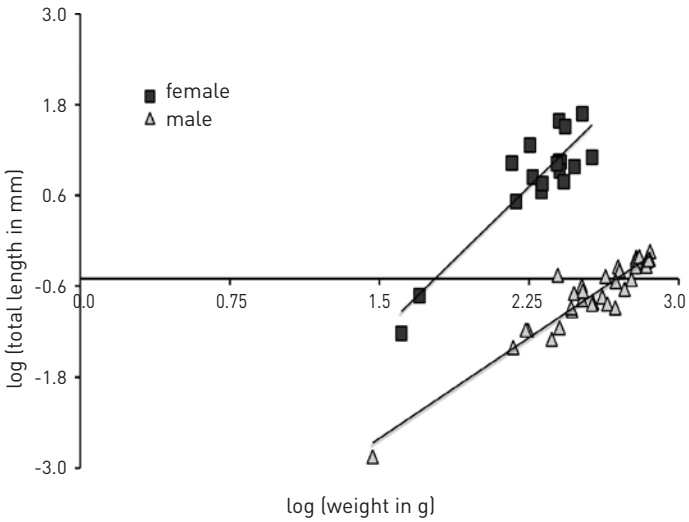

Figure 4: Gonad mass in both females and males had a positive allometric relationship with weight.

to reach a size refuge from predators.

As lionfish grow and reach a size threshold, they invest relatively more in gonad weight and fat storage (Figs. 3 & 4). However males and females are allocating resources slightly differently. Unlike males, as females increase in weight, they do not invest more energy towards accumulating fat stores (Fig. 3), probably due to increased investment in reproduction. Both female and male lionfish increased relative gonad mass at a greater rate as body weight increased (Fig. 4), however females did this to an even greater extent. This indicates that as females grow, more resources are allocated towards reproduction than fat storage as compared to males. Relative body fat did not change when females carried eggs, suggesting that energy allocated toward reproduction in place of fat storage remains consistent throughout the reproductive cycle.

The high level of investment in reproduction in female lionfish has major implications for the reproductive success of this invasive species in the Caribbean and central Atlantic. Female lionfish evidently have high fecundity, and also produce more eggs as they become larger (Heino & Kaitala 2001). Likewise, as relative body fat increases in males, their ability to withstand prolonged starvation and other environmental stressors also increases. If lionfish truly are growing to sizes beyond those found in their native range (Darling et al. 2011), this could greatly increase their reproductive success and proliferation.

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Laparoscopic versus Open Colorectal Surgery: Through the Lens of the Enhanced Recovery Program

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Abstract

Background: *The Enhanced recovery program (ERP) is a multimodal intervention with the main goals of minimizing pain and reducing postoperative length of stay (LOS). The program focuses on enhancing patient engagement across the care continuum. Patients who enter the ERP experience less pain, reduced morbidity and faster return of normal bowel function. RCT's regarding ERP demonstrate improved outcomes for laparoscopic over open colorectal surgery.*

Method: *A meta-analysis of RCTs and review articles comparing outcomes following ERP protocols to standard care and comparing laparoscopic to open colorectal surgery. Researchers published these studies in North America and Europe.*

Results and Conclusion: *Available data demonstrates that patients following ERP protocols have a faster physiological recovery. Patients receiving laparoscopic surgery in conjunction with ERP care have lower rates of complications and morbidity, along with faster return to normal gut function.*

The multimodal approach: *ERP combines several interventions in the perioperative setting to ensure physiological wellbeing of the patient. The ERP protocols are described in the table on the following page.*

Discussion of Protocols

Preoperative fasting

The long held practice of "nil by mouth," meaning no eating and drinking from midnight before surgery, could cause unnecessary physiological harm and deter patient recovery. Patients should be well hydrated up to 2hrs before surgery. Hydration and carbohydrate loading minimizes insulin resistance post surgery (3).

Mechanical Bowel Preparation

MBP before colorectal surgery was commonly used to prevent leakage of stool into the peritoneum, which is the membrane lining the abdomen. However, the intestinal liquid residue remaining after MBP may result in a higher risk for postoperative complications including wound infections (4).

Anesthetic Protocol

During mobilization after surgery, patients who receive EA (epidural analgesia) rather than LA (local anesthesia) give lower pain scores. For the EA group, patients returned to normal gut function sooner and had a shorter LOS (5). In addition to epidural anesthesia, another postoperative pain management protocol may consist of intrathecal morphine (ITM) along with local anesthesia (LA). Patients who receive ITM +LA consume significantly less morphine for pain control (6).

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Preventing intraoperative hypothermia

Maintaining body temperature as close to normal prevents postoperative complication including surgical site infection (SSI), blood loss/need for transfusions, and adverse myocardial events (7).

Preventing postoperative nausea and vomiting (PONV)

PONV is a frequent occurrence following surgery, which could be reduced in patients following ERP protocols. Adhering to a multimodal analgesia protocol while eliminating opioids may help eliminate PONV. In addition, antiemetic medications may include ondansetron, dexamethasone, and droperidol (8).

Comparing Laparoscopic and Open Surgery

Short Term Outcomes

Minimally invasive surgery shows benefits over open colorectal surgery across colorectal cases from colorectal cancer to diverticulitis. Compared to open operation, minimally invasive surgery (MIS) shows lower rates of wound infection, less need for blood transfusions, and faster recovery (9).

Patients who received either laparoscopic or open colorectal resection were assessed for rates of morbidity and surgical site infections, length of stay, lymphocyte proliferation and gut oxygen tension. For the laparoscopic group the morbidity rate was 20.6 percent compared to 38.3 percent in the open group. Surgical site infections occurred in approximately half the number of MIS patients compared to the open group and their mean length of stay was two days shorter. 15 days after operation the lymphocyte proliferation returned to baseline values only in the laparoscopic group meaning that they had a weakened immune response post surgery causing less physical stress. Gut

Table 1: Protocols for ERP (2)

Item	*Protocol*
Preoperative	
Pre-admission information and rehabilitation	Provide guidelines on how patients can their enhance recovery by following pre/post surgical protocols.
Prehabilitation	Adherence to an exercise regime prior to surgery to improve patients' postoperative physical function and reduce complications. Patients should abstain from smoking and limit alcohol intake for a month prior to surgery.
Preoperative fasting and carbohydrate loading	Patients should not consume solid foods for 6 hrs before surgery and clear liquids up until to 2 hours before surgery.
Bowel preparation	Discourage preoperative mechanical bowel preparation.
Preanesthetic medication	Minimize sedating medications within the 12 hours before surgery.
Intravenous Antimicrobial prophylaxis	Patients should receive a single dose of antibiotic prophylaxis against anaerobes and aerobes 1hr before surgery.
Intraoperative	
Anesthetic protocol	Patients should receive mid thoracic epidural analgesia (EA) or a Transversus abdominis plane (TAP) for pain control.
Drainage of peritoneal cavity	Do not drain peritoneum. Draining does not prevent wound infection and it may decrease postoperative mobilization.
Surgical incision	Use a midline or transverse laparotomy incision. Smaller incisions reduce surgical site infections.
Preventing intraoperative hypothermia	Maintain normothermia during surgery through upper-body forced area heating. Use heating blankets, warming mattress, warm clothing and warmed intravenous fluid.
Nasogastric intubation	Avoid use of nasogastric tube and only use when a postoperative ileus develops.
Perioperative fluid management	Intraoperative and postoperative fluid restriction in major colonic surgery reduces morbidity.
Urinary drainage	Urinary drainage is recommended. Manage postoperative urinary retention to prevent UTI, catheter-related complications or bladder over-distension.
Postoperative	
Preventing postoperative nausea and vomiting (PONV)	Patients at risk of developing PONV should receive medication to prevent or reduce these symptoms.
Prevent postoperative ileus	Reduce postoperative ileus by using mid thoracic epidural analgesia, opioid antagonists, local anesthetics and avoidance of fluid overload. Resume normal diet as soon as tolerated.
Postoperative analgesia	Provide continual epidural mid thoracic low-dose local anesthetic and opioid analgesia for 48 hours post surgery. Epidural boluses are for breakthrough pain. Give NSAIDS after epidural is removed for pain management.
Postoperative nutritional care	Patients resume oral intake upon return of bowel function. Prescribe oral nutrition supplements until commencement of a sufficient solid caloric intake.
Early mobilization	Mobilization for 2 hours the days of surgery and 6 hours the days following.

oxygen tension in this group was higher meaning the value was closer to normal (10).

The MIS technique can be used for extensive colorectal surgery including total mesorectal excision (LTME). Compared to patients who received open total mesorectal excision, LTME patients had decreased blood loss, a sooner return to normal diet, less pain, less consumption of narcotics and less immune response (11). Minimally invasive surgery is safe and effective for total abdominal colectomy (TAC) and protocolectomy (TPC), The rate of complications and mortality may be even lower compared with the open technique (12).

Laparoscopy for colectomy also accelerates restoration of bowel function. When patients in the laparoscopic and open groups both received traditional preoperative care, the laparoscopic group had earlier bowel movements, lower pain scores, and shorter length of hospital stay.

Overall in several studies using varying forms of perioperative care from standard care to ERP, laparoscopic surgery leads to faster patient recovery compared to open surgery. Therefore, laparoscopy combined with ERP should be the recommended technique for colorectal surgery.

Long Term Outcomes

The UK Medical Research Council assessed patients five years after they received either laparoscopic or open colorectal surgery. There was no difference between the patient groups regarding overall survival, and cancer recurrence rates. The 5-year follow up shows that laparoscopic surgery is as effective as open surgery (14).

Cost Analysis

Laparoscopic surgery has a higher monetary price due to surgical instruments used and longer operative time. However, after open surgery patients are more likely to have complications that may double patient care costs. The difference in cost between the two techniques is narrowing as the equipment for laparoscopic surgery becomes more common (15).

Conclusion

Combining LPS and ERP leads to a better allocation of hospital resources and enhances patient care. The enhanced recovery program combines both clinical and nonclinical approaches to improve patient outcomes. Hospital staff should implement these evidence-based guidelines. At certain institutions, these protocols may contrast with traditional perioperative management. Therefore, several measures have to be taken in order to introduce and implement these protocols. ERP supports the laparoscopic technique since it leads to both short and long-term benefits. ERP and the laparoscopic technique have independently been shown to improve patient outcomes. When combined, patient recovery is further enhanced.

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