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EXPECTATIONS

Past, present, and future possibilities

Spotlight on Faculty

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Joseph J. BelBruno

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Note from the Editorial Board

Dear Reader,

Expectations in science are constantly evolving, with some discoveries living up to the hopes of the general public and scientific community, and others falling short. Past and present advancements in science, technology, engineering, and math have influenced aspects of society ranging from health outcomes to consumer choices to the increased role of technology in everyday life. In light of the increasing importance and role of scientific discoveries in society, we examine past and present expectations for progress across a range of scientific disciplines in this issue of the *DUJS*.

Melvin King evaluates the implications of advancements in genetics for developmental biology and understanding pregnancy. Moving from biology to technology, Nan Hu discusses previous expectations for artificial intelligence, starting with its inception at Dartmouth College. Kevin Kang takes a look at the hopes of dieters and the contrasting realities of different fad diets.

Next, Heeruk Bhatt examines the potential of age reversal in mice for aging in humans, while Ali Siddiqui discusses past disease outbreaks and predictions for potential cures and epidemics. Exploring recent expectations in medicine, Hae-Lin Cho evaluates the new prospects presented by immune-based treatments. Sam Lee provides a history of MSG usage and its association with Chinese food in the United States.

Bringing the focus somewhat closer to Dartmouth, Katie Billings reviews a new treatment for depression studied by researchers at Dartmouth-Hitchcock Medical Center. Sumita Strander emphasizes the underrepresentation of women in science, technology, engineering, and math, considering both the psychological underpinnings of and possible solutions for this phenomenon. Finally, Alexandra Dalton gives the reader a glimpse into the growing field of molecular dynamics.

Our spring issue features a faculty interview with Professor Joseph J. BelBruno, where he discusses the transformation of his research on sensors into his new company FreshAir Sensors. We also have two original research submissions in this issue. James Brofos, Rui Shu, and Matthew Jin of Dartmouth College evaluate optimization techniques for mathematical functions. An outside submission from Daniel Conti, Keiosha Hunt, Mackenzie Piper, Clarence Shields, and Heather Tarleton assesses the potential success of a new fitness program in reducing obesity in sedentary urban adolescents.

We would like to thank our writers, editors, staff members, and faculty advisors for making this issue of the *DUJS* possible. Without the support of the Dartmouth community, we would not be able to maintain our continued success as an outstanding scientific outlet.

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

Sincerely,

Stephanie Alden
Editor-in-Chief

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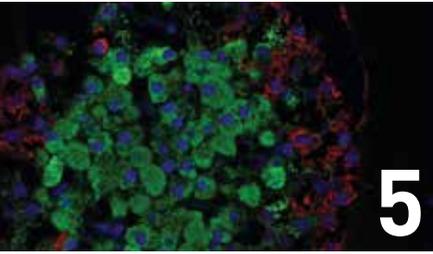
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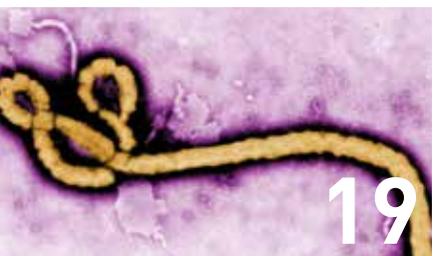
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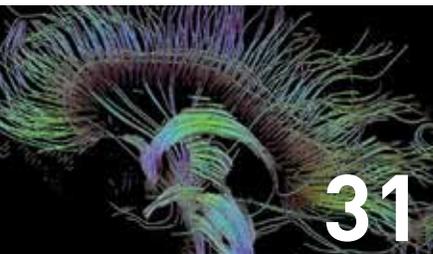


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Heather P. Tarleton*



Professor Joseph J. BelBruno earned his bachelor of science from Seton Hall University and his Ph.D. in physical chemistry from Rutgers University. He has served as a visiting professor at the Norwegian University of Science and Technology in Trondheim, Norway and as an Alexander von Humboldt Fellow at the Technical University in Munich. Professor BelBruno is the author or co-author of more than 130 publications and 9 patents. His current field of expertise is experimental and computational study of clusters, sensors, surface interactions, and nanomaterials. At Dartmouth, he currently teaches general chemistry, honors general chemistry, and physical chemistry II. In 2013, Professor BelBruno and Jack O'Toole, a graduate of the Tuck School of Business, founded the company FreshAir Sensors.

How did you come up with the idea of your company FreshAir Sensors?

My research at Dartmouth is on sensors. I have been working on sensors for ten years, 15 if you include the fundamental work that led to sensors. We have been trying to detect different types of molecules. A group of faculty at Dartmouth's Geisel School of Medicine brought nicotine to my attention. They were studying cancer, focusing on the effects of secondhand smoke on small children and people with various kinds of illnesses. That helped direct my research towards detecting nicotine in the air. Eventually, I thought it would be an interesting change to take it from the lab to a company. I soon met with Jack O'Toole from the Tuck school, and we founded the company together. He and I complement each other in that he is the business side, and I'm the science side. We have also recruited Kwame Ohene as our Chief Product Development Engineer, Anani Sawadogo as our Chief Software Engineer, and Drew Matter as our Vice President of Manufacturing. Kwame and Anani are 14's who graduated from the Thayer School of Engineering, and Drew is a former NASA engineer and a Master of Engineering Management (MEM) graduate of Thayer.

Your sensors use imprinted polymer technology to detect nicotine and marijuana in the air. Could you elaborate on the chemistry and mechanisms that make the sensors work?

What happens is that we make the polymer, in



Faculty Spotlight: Joseph J. BelBruno

this case polyaniline, in the presence of the molecule we are trying to detect, the target molecule such as nicotine. The polymer will form around the molecule. We try to use non-covalent bonding such as hydrogen bonding or electrostatic bonding between the polymer and the target molecule. Then, we remove the target molecule from the polymer and leave a cavity in the polymer. The cavity formed not only has the same shape as the molecule, but it also has a chemical attraction towards it. The process is similar to making antibodies match with specific antigens. In the end, we make a film out of this porous polymer and put it in our sensors. When the target molecule like nicotine is in the air, it will bond with the cavity in the film and alert the sensor.

How long did it take you to perfect the design?

It was a project that we were working on in our lab at the Dartmouth Regional Technology Center in Centerra Resource Park for about two years. However, lab work and commercial use are different. In the lab, it is academic science. If you can detect nicotine with your device, you have made your point. Having a sensor that you can sell is a different scheme. Now your sensor has to be stable. It has to survive changes in temperature and changes in humidity. It is another whole operation. Optimizing the sensor to prove it works is one thing; optimizing it to become a commercial product is a



tough and different experience that I am learning about, so we have been working on moving the sensor from a laboratory project into a commercial product for almost two years.

What is your company's target demographic?

We are currently selling to hotels where guests may not smoke in certain rooms. We are also looking towards public housing and buildings for the same reason, as cities do not want people smoking in public spaces. Colleges, usually public and state, prisons, and nursing homes are also interested in our sensors because, again, authorities do not want people smoking in these state buildings. Another group is people with rental properties. Our biggest market, even bigger than hotels, will probably be multifamily housing.

What are some other uses for the imprinted polymer technology?

Instead of making the polymers into films, you can make them into powders and pack them into a column. You can then use the column to extract the target of your choice from a sample you are testing. For example, you could use an imprinted polymer to extract side products from a drug and purify it. You could even use it to deliver drugs! You can make the polymer into a powder and design it so that the medicinal chemicals come out under the right conditions. Imprinted polymers are also used in chromatography analysis setups. There are certainly many different uses.

Could you elaborate more about your other research projects?

We are interested in the nanoparticles of semiconductors. Specifically, we want the doping or introduction of impurities into these particles to make them useful and modulate their electrical properties. We want to look at the doping of a bulk material such as zinc sulfide and compare that to

the doping of a nanoparticle of zinc sulfide. That way, we can see if we can change the properties of a nanoparticle in a way that is more tunable than changing the bulk properties of the semiconductor. We can change the size of the nanoparticle, which gives us a better handle than just doping bulk zinc sulfide.

We are also interested in bringing molecules onto a surface and observing their interactions with the chemistry of the surface. We looked at bringing molecules containing nitrogen onto gold surfaces and how they might bind to the gold surface and react.

What can you expect to come from this kind of research?

With semiconductors, you can control one of their properties, such as their band gap, which determines the energy required to be conductive. You can use light to promote an electron and make the semiconductor conductive. You can use it on photovoltaic cells on solar panels to harvest energy. With surface interactions, you can study the chemistry on catalysts to increase reaction rates.

What are your future plans and expectations for the company?

We have a small research grant from the National Institutes of Health to build a formaldehyde sensor. Formaldehyde has recently been declared a carcinogen. It is present in glues and various construction materials, so people are worrying about formaldehyde levels in their newly-built homes.

We are also aiming towards sensors for other industrial uses. These sensors could be used for industries that must utilize toxic chemicals but also need to protect employees from overexposure: those chemicals must be kept below a certain limit. We envision having a whole repertoire of sensors for various molecules that are threats to health. **D**

From left to right: Jack O'Toole, Kwame Ohene, Professor BelBruno, Drew Matter, and Anani Sawadogo.



Psychological and Genetic Conflicts in Pregnancy

Image courtesy of Tips Times. Available at <https://www.flickr.com/photos/tiptimesadmin/11557918553>

BY MELVIN KING '16

It is often said that one of the tightest bonds among humans is that between a mother and child. Pregnancy exemplifies this relationship. A mother and her fetus share the same nutrients, as well as the same risks from pathogenic and physiological threats. Their physical connection, coupled with the fact that a healthy delivery is in the best interest of both individuals, suggests that pregnancy is a fully cooperative effort – one in which the mother and the fetus work together to ensure that the potential child receives as much nutrition as possible. This is called the “harmony argument” and is often supported by the fact that both individuals share the same genes (1). As per Darwin’s theory of kin selection, individuals who share a high degree of genetic relation favor interactions that promote the survival of the genes carried by the child, even at the cost of the mother’s health.

While there is a necessarily large degree of cooperation required to bring a healthy fetus to term, the harmony argument fails to describe pregnancy because a mammalian mother and her child are not genetically identical. Half of the child’s genome comes from the father, which leads to a noticeable degree of genetic and physiological conflict. The genes behind these conflicts have been implicated in a host of pregnancy-related disorders in humans, including placental abruption, gestational diabetes, preeclampsia, and a variety of autoimmune diseases (2). Even with the advances provided by modern medicine, pregnancy still kills roughly 800 women per day (3).

The underlying cause is that most female primates breed more than once, often with more than one male (4). A mother is related to all of her current and future children. To maximize their survivability, her genes evolve to give each child only as many nutrients as is healthy. By contrast, the father may not have another child with her. As

he is only guaranteed one offspring, his genes—expressed in the fetus—will evolve to coerce the mother into giving that particular child as many nutrients as possible. This conflict is further complicated by genomic imprinting, the silencing of a small subset (<1 percent) of these genes on a parent-of-origin basis (5).

In diploid organisms, a fetus receives one copy of each gene from each parent. Depending on the gene itself, expression is said to be maternally imprinted if only the father’s copy is active and paternally imprinted if only the mother’s copy is active. In primate and rodent pregnancies in particular, imprinting results in a mixture of antagonistic and cooperative interactions between three sets of genes: maternal genes in the mother and each of the two sets of maternally- and paternally-derived genes in the fetus.

Conflict at the Placental/Uterine Lining

In placental mammals, the developing fetus is connected to the mother’s blood supply by the placenta, allowing gas exchange, waste elimination, and nutrient uptake to occur. The outermost layer of the placenta, the surface in contact with the maternal tissue, is called the chorion. Rodents, monkeys, apes, and humans have hemochorial placentas, which involve direct contact between the chorion and the mother’s blood supply. In these species, the uterus undergoes a process called decidualization. Decidualization has the dual functions of providing nutrition for the embryo before the placenta is fully developed and protecting the mother from excessive chorionic invasion. Not only does the lumen of the uterus fill with nutritious glycoproteins, but vessels that supply the uterus with blood become coiled and develop a tough coating made of collagen,



laminin, and fibronectin. Decidualization takes place towards the end of the menstrual cycle. If a fertilized egg does not implant, either due to a lack of fertilization or because the immature fetus is unable to penetrate the uterine lining, then the innermost layer of decidualized uterus is expelled during menstruation. The endometrial surface is tough enough that roughly half of conceptions end here, often before the mother realizes she is pregnant (6).

Embryos healthy enough to penetrate the endometrium face the task of obtaining as many nutrients as possible from maternal tissue. In the early 20th century, physiologists noted that the interactions between the layer of trophoblasts, the outermost cells of the chorion, and the uterine lining were mutually antagonistic. In 1914, biologist R.W. Johnstone described the maternal/fetal interface as a “fighting line where the conflict between maternal cells and the invading trophoderm takes place... that is... strewn with such of the dead on both sides” (7). In particular, German gynecologist Ernst Gräfenberg noticed in 1910 that the embryo produces proteolytic enzymes, which break down proteins (8). These proteases are responsible for degrading the pericellular capsule around maternal blood cells to gain greater access to the blood supply.

For her part, the mother relies on protease inhibitors, notably those triggered by TGF- β 1, or transforming growth factor. TGF is secreted when the pericellular matrix begins to break down and has two functions. First, TGF promotes the conversion of invasive trophoblasts at the chorion

Figure 1: The placenta, connected to the fetus through the umbilical cord, is the primary medium through which the fetus interacts with the maternal blood supply.

into noninvasive cells. It also targets fetal cells and promotes production of a protease inhibitor called tissue inhibitor of metalloproteinases (TIMP). TIMP inhibits proteases that break down collagen, preventing further matrix degradation. The question as to why fetal tissue should respond to maternal manipulation by upregulating TIMP is prompted by its curious genetic behavior. While not imprinted, the gene still behaves as though it is maternally derived. The gene is X-linked, and the X chromosome in males must come from the mother. In females, Barr-body studies have shown that the paternal X chromosome is preferentially deactivated in trophoblast cells (9).

One protein that appears to have the opposite effect is IGF-2 (insulin-like growth factor). IGF-2 is paternally imprinted, and evidence of its importance for fetal growth comes from a variety of sources. The concentration of its inhibitor, the maternally produced binding IGF binding protein (IGFBP), is negatively correlated with birth weight (10). Similarly, in rats, inactivation of IGF-2 results in newborns that are well proportioned but small (11). Furthermore, the gene comes from a region of DNA implicated in Beckwith-Wiedemann syndrome, a fetal overgrowth disorder (12). In terms of mechanisms, IGF-2 mRNA is found in high concentration in invasive cytotrophoblasts and is scarce in their noninvasive neighbors (13). Some researchers hypothesize that the protein furthers growth by maintaining the invasive phenotype of chorionic cells.

Conflict in the Circulatory System—Quality and Quantity

The mother’s systemic circulation system supplies blood that travels to the uterus to feed the fetus. When analyzing blood distribution during pregnancy, the mother’s circulatory system can be considered as two parallel subcirculations: the uteroplacental circulation, from which the fetus gets its nutrients, and the nonplacental remainder.

The total blood volume in these two circulations is called the cardiac output. An increase in blood flow to one subcirculation is synonymous with an increase in the portion of cardiac output to that particular cycle and is matched by a corresponding decrease in blood flow to its competitor. Hemodynamics gives the relationship between cardiac output, mean arterial pressure, and vascular resistance as:

$$\text{Cardiac Output} = \frac{\text{Mean Arterial Pressure}}{\text{Vascular Resistance}}$$

Because the pressure difference between the aorta and the venae cavae is common to all subcirculations, the mean arterial pressure is taken to be constant in the above equation. Thus, for any subcirculation, the portion of cardiac

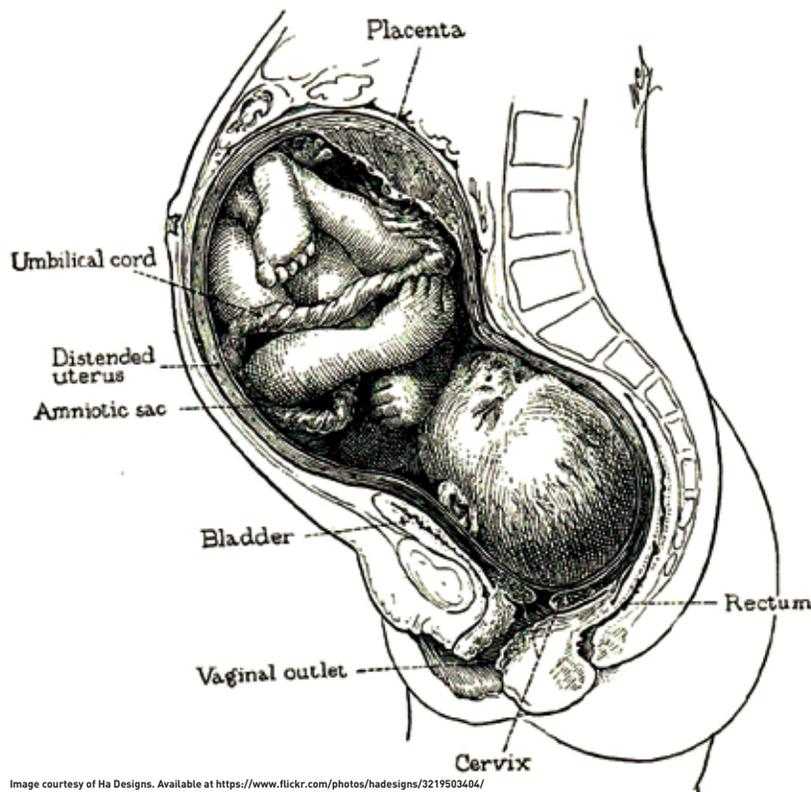


Image courtesy of Ha Designs. Available at <https://www.flickr.com/photos/hadesigns/3219503404/>

output received depends entirely on the vascular resistance of its tissues. In practice, this means the fetus can increase its share of blood flow by decreasing resistance in the uteroplacental circulation or by increasing resistance in the nonplacental remainder. The mother can oppose fetal actions by doing the opposite.

One of the most common biological methods of changing resistance in a blood vessel is altering the radius. According to Poiseuille's law, resistance in a cylinder is inversely proportional to the radius to the fourth power, which allows for enormous changes in resistance with relatively small changes to the radius. Consequently, changing blood vessel radii is the main process by which the fetus alters maternal blood flow. Fetal trophoblast cells turn the spiral arteries of the decidua into wide, low resistance channels. The process can be monitored through Doppler ultrasound, which demonstrates that resistance in the decidua drops until week 24, at which point trophoblast invasion of the uterine lining is generally complete (14). The mother inherently opposes these actions when she begins decidualization. Resistance in a cylinder is also directly proportional to its length, and the spiral arteries lengthen and become slightly entangled during the early stages of decidualization (15).

Not content with quantity alone, a healthy fetus will also try to take more blood sugar than the mother is willing to give. Evidence that the mother restricts fetal access to glucose comes from the fact that the mother's baseline blood sugar steadily decreases from the start of pregnancy until week 12, at which point it remains at the lowered value (16). This steady drop cannot be attributed to the fetus, as not only are fetal demands almost negligible in early pregnancy when blood sugar is decreasing, but they also increase rapidly during the period in which blood sugar stabilizes.

The abnormal behavior of insulin, the protein hormone responsible for reducing blood sugar, provides further evidence of conflict. Insulin levels remain close to normal until the third trimester but then increase in conjunction with fetal growth. Insulin's ability to lower blood sugar also declines, a condition called partial insulin resistance. Furthermore, blood glucose levels usually increase after a carbohydrate meal and then decrease as a result of insulin secretion by the pancreas. In pregnant individuals, blood sugar levels remain high for an extended period of time after a meal, even as they are matched by abnormally high insulin levels (17).

One view considered by researchers is that the longer the mother takes to lower her blood sugar, the more nutrients the fetus can acquire. Thus, it is in the best interest of the fetus to induce insulin resistance in the mother. The mother responds by increasing her insulin

output, resulting in the enlargement of many of her pancreatic cells by the end of pregnancy (18). Two pieces of evidence point to human placental lactogen (hPL) as the primary suspect for fetal manipulation. First, doses of hPL cause insulin resistance in non-pregnant individuals (19). Second, deletions of the hPL gene do not severely affect birth weight (20). These phenomena are consistent with the idea of allocrine/endocrine conflict, as the hPL secretions are met with an increased output of insulin production. The net result is a minimally positive effect on growth.

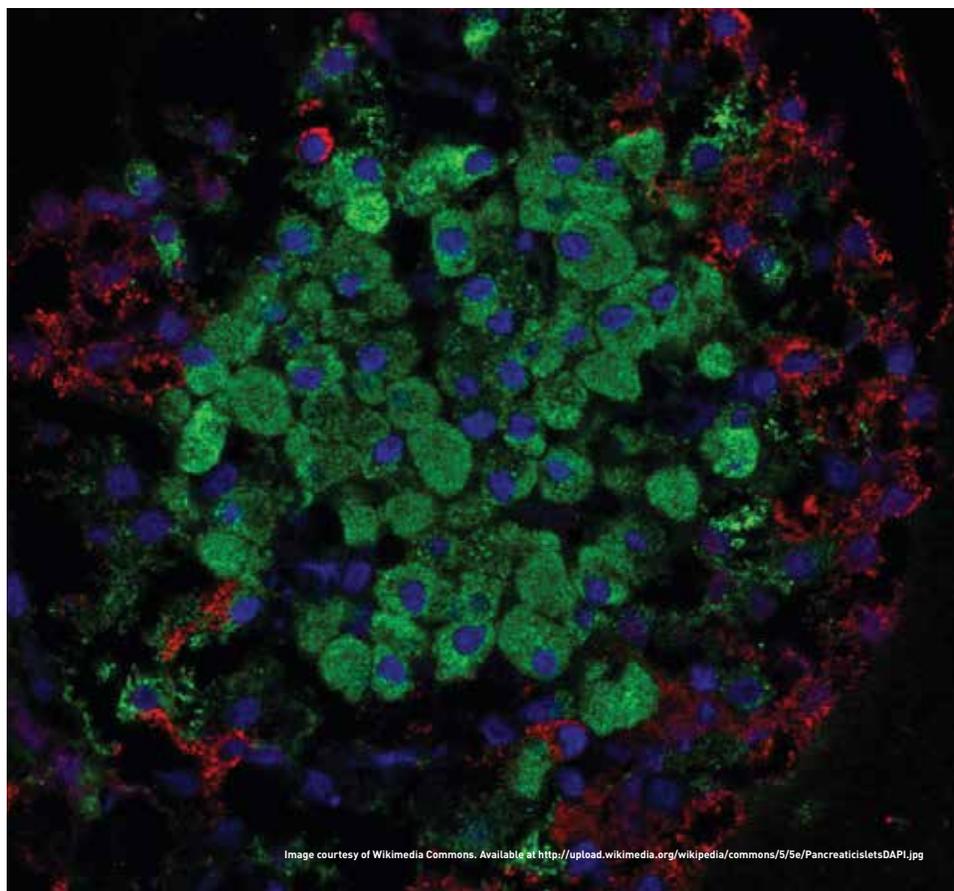
Implications — Diseases and our Evolutionary Background

The conflict between maternal and fetal genetic forces underlies many disorders that plague human development. One notable example is preeclampsia. If the fetus does not get sufficient blood flow, as evidenced by relatively poor trophoblastic invasion of the decidua, it can release toxins that constrict maternal blood vessels (21). This constriction drives up maternal blood pressure to the point of damaging the mother's glomerulus, the main filter between incoming blood vessels and the tubules of the kidney. The result is the primary symptom of preeclampsia: proteinuria, which is characterized by high levels of protein in the urine. Preeclampsia can lead to blood cell breakdown, liver and kidney impairment, and seizures if the condition is allowed to worsen.

Pregnancy can also complicate or cause a variety of other diseases, including gestational diabetes, cholestasis, and hyperemesis



Figure 2: Pancreatic Islet cells (stained green) produce large amounts of insulin during pregnancy to combat the effects of fetal hPL. By the end of pregnancy, these cells are hypertrophied (enlarged) from their constant secretions.



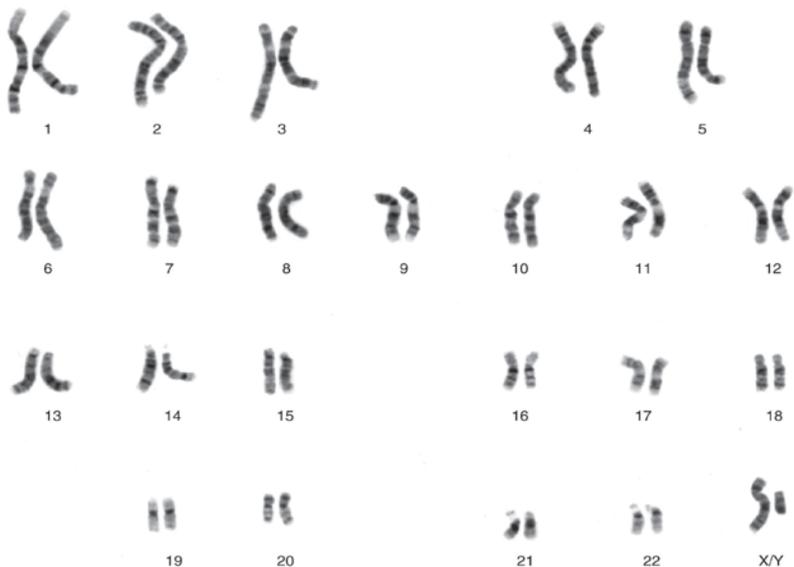


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Figure 3: Although scientists have mapped the physical and functional elements of the human genome, piecing together how these elements interact remains a difficult puzzle.

gravidarum. However, its interaction with autoimmune diseases in particular offers an interesting evolutionary perspective. Since the late 20th century, it has been shown that the degree of chorionic invasion in primate pregnancy is high enough that a small amount of fetal cells remain in the mother decades after delivery in a condition called microchimerism. While these cells are thought to provide a certain degree of pathological immunity, more recent studies have shown that they are also likely to play a role in the significant spike in autoimmune diagnoses, particularly lupus and rheumatoid arthritis, for women in the years immediately after delivery (22). One proposed purpose of this mechanism is to punish—and thereby prevent—malnourished mothers for potentially taking advantage of microchimerism and terminating pregnancy early in order to gain access to paternal resistances (23).

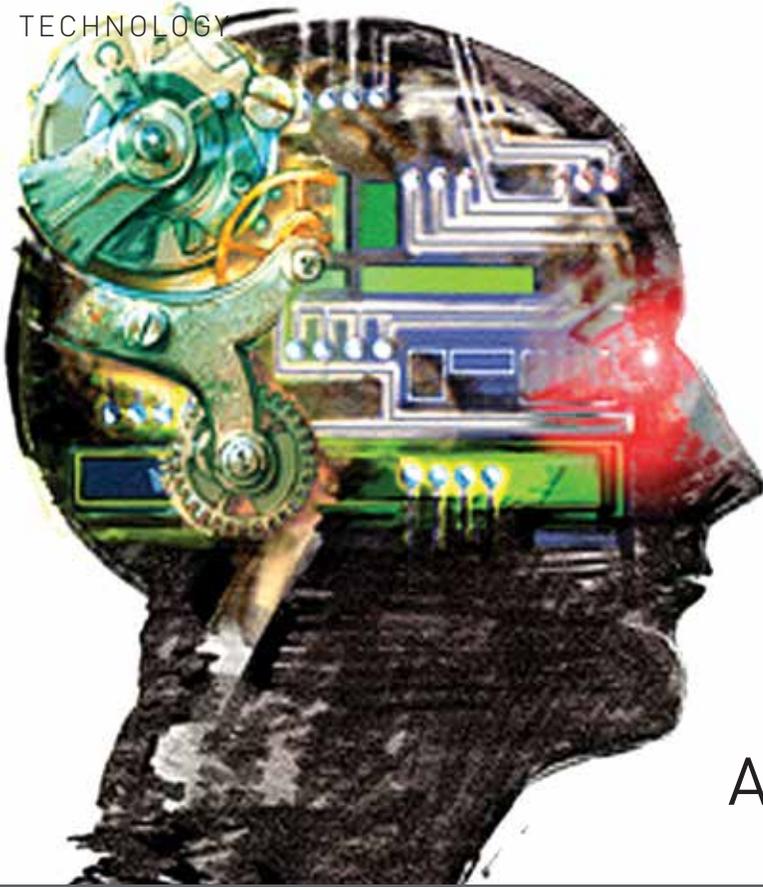
With the completion of the Human Genome Project in 1990, scientists have access to the physical and functional information that comprises every human gene. Nevertheless, developmental biology remains one of the most poorly understood topics in the life sciences. Determining how these genes interact to build and maintain functional organisms is an ad hoc practice, with advances being made only as individual suspicions are confirmed in the laboratory. As the scientific community continues to form and test these predictions, the genetic mechanisms behind critical processes such as pregnancy, limb development, organ development, and others will hopefully be clarified. In doing so, they may give a closer look at the nature of our evolutionary background and validate current predictions about the competitive nature of pregnancy. **D**

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TECHNOLOGY



Artificial Intelligence:

A Story of Expectations

BY NAN HU '18

People have long been fascinated by the idea of machines that can imitate human intelligence and skills. Even before the creation of the first digital computer or the onset of the industrial era, humans told stories about artificial, intelligent beings. Greek mythology has the tale of Talos, a giant bronze man created by Hephaestus assigned the task of protecting Europa. The Liezi, a Daoist text from the 5th century BC, tells the story of a mechanical humanoid made completely from wood, leather, and adhesives. Given the context of these stories, they can be regarded as nothing more than fantastical tales stemming from human imagination. There is, however, something in these stories worthy of noting: people expected these machines to have human intelligence. Talos was expected to be a warrior. The humanoid from Liezi acted exactly like a human being, with the same behavioral characteristics expected of a person at that time. Since these early tales, the abilities of artificial intelligence have been hypothesized by many.

With the advent of the digital computer in the 1940s and 1950s, exploration and development in the field of artificial intelligence (AI) turned from fantasy into reality. Because the field was unexplored, scientists made many predictions and tests for the abilities of AI.

In 1950, in his paper “Computing Machinery and Intelligence,” Alan Turing proposed the now widely known Turing test, one of the first tests of computer intelligence. In the latter half of the 20th century, scientists theorized about the rate of AI development and the tasks AI could perform, such as language processing. Present-day projections of AI concern two main areas: the likelihood of a machine takeover—a Terminator-like scenario of machine dominance—and the economic impacts of increasingly smarter technology.

The Turing Test

The Turing test is a test of a machine’s ability to exhibit intelligence comparable to or indistinguishable from that of a human. For context, Turing describes a game he calls the “imitation game,” which involves a man (A), a woman (B), and an interrogator (C) who may be of either gender. The game is set up as follows: C sits in a room separate from A and B, and the goal of C is to determine which individual is the man and which is the woman. C knows A and B by the labels X and Y, and C has the ability to ask A and B questions. At the end of the game, C says either, “X is A and Y is B,” or, “X is B and Y is A.” A’s goal is to convince C to make the wrong identification,





Image courtesy of Kraus-Maffei Automation. Available at http://www.kraussmaffei.com/media/files/kmnews/de/PM_AUT_2012-002.JPG

Figure 1: An automated injection molding machine can be seen in operation.

and B's goal is to help C to make the correct identification. To ensure that tone of voice does not affect the interrogator's reasoning, questions and answers are either printed or communicated by a third party (1).

Turing then proposes that a machine takes A's role. Instead of asking whether the machine can think or not, he asks, "will the interrogator decide wrongly as often when the game is played like this as he does when the game is played between a man and a woman?" (1)

Passing the Turing test, as this game has become known, is regarded as a standard in the field of artificial intelligence. There have been many attempts to create software that mimics human speech and behavior, many of them chat bots. For example, Cleverbot, an online chat bot that can carry out fairly intelligent but somewhat dry conversations with a human user, seeks out keywords in the user's input and gives a response based on the keywords. These responses make sense, but they are ultimately uninteresting (2).

During a 2014 event organized by the University of Reading, a chat bot named Eugene Gootsman passed the Turing test, successfully convincing 33 percent of judges that it is human, exceeding the 30 percent threshold for passing. Some scientists have called this event "historic," but others are not as convinced (3). It is worth noting that Eugene posed as a 13 year-old Ukrainian teenager who spoke English as a second language, and that the test lasted only five minutes.

The Dartmouth Conferences

In August of 1955, John McCarthy, then a professor of mathematics at Dartmouth College, and colleagues organized the Dartmouth Summer Research Project on Artificial Intelligence for the summer of 1956. This event was a "two-month, 10 man study of artificial intelligence," with the underlying assumption that, "every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it" (4).

The event's proposal covered many aspects of what McCarthy and his colleagues called "the artificial intelligence problem," including programming computers to use human language, calculation size, neuron nets, self improvement, and making computers that can deal with randomness. In addition to a description of the topic itself, the proposal included several possible paths of investigation. Overall, the topics considered were relevant to developing the AI field, and the discourse suggested that solutions would be found soon (4).

McCarthy and his colleagues vastly underestimated the complexity of the topics they sought to cover, however, especially language. The proposal recognized that human thought largely consists of word manipulation according to rules of grammar and syntax, and they thought they could apply this method to computers (4). In hindsight, human languages are very complex, but this may not have been obvious at the time. In the 1950s, computers could already solve complicated mathematical

problems that few humans could. Intuitively, there was no reason to suspect that interpreting English would be much harder than the mathematics computers were already capable of solving (5).

The tasks set out in the proposal have not all been achieved. Natural language processing is still a developing area, but there has been great progress in the past decades. Recent products include Dragon, a speech recognition software, and digital personal assistants such as Siri and Google Now (6, 7, 8). Currently, companies such as Google and Microsoft are investigating this area, with a focus on developing more efficient algorithms for language processing (9, 10).

Technology and the Economy

As a society, it cannot be denied that advancements in technology, including the field of AI, has increased quality of life. With the advent of the Internet and wireless technology, we can use devices that fit into our pockets to access a wide array of human knowledge. Many jobs have been made both easier and more efficient: what once took rows of file cabinets to store can be contained in flash drives the size of a thumb. Services based on AI, like Siri and Google Now, can act as our own personal assistants that can understand and answer our questions.

Nevertheless, in some ways, technology has been detrimental to society. The increased use of robots in factories has decreased the need for human laborers. Even though technology creates jobs and opportunities, it also inadvertently removes them. This phenomenon raises an obvious question: as technologies become smarter and more efficient, will AI-based applications displace more jobs than they create?

A Pew Research Center survey from 2014 asked the question, “Will networked, automated, artificial intelligence (AI) applications and robotic devices have displaced more jobs than they have created by 2025?” This survey collected the opinions of over 1800 experts ranging from entrepreneurs in the technology industry to university professors. Opinions were divided roughly evenly – about 48 percent of people believed that robots and other digital agents will displace more jobs than they create, and approximately 52 percent expect that technology will not replace more jobs than it creates (11).

AI is still a developing field, so many of the opinions collected were based on extrapolations from historical trends. Those who believed that AI applications would not replace more jobs than they create cited the historic trend that

technology has always been a net creator of jobs. Technology may change the types of jobs that are available, but it increases opportunity and productivity. Some extrapolated further and claimed that technology frees society from the day-to-day drudgery of work and can help us find a more meaningful definition of “work.” Those who believed the opposite cited that, while technology has historically encroached on blue-collar jobs, further technological innovation would threaten white-collar jobs as well. Automation in various industries has already displaced many jobs, and, in the future, a great variety of industries will be affected. In addition, they agree that the current education system does not adequately prepare students for a technological future (11).

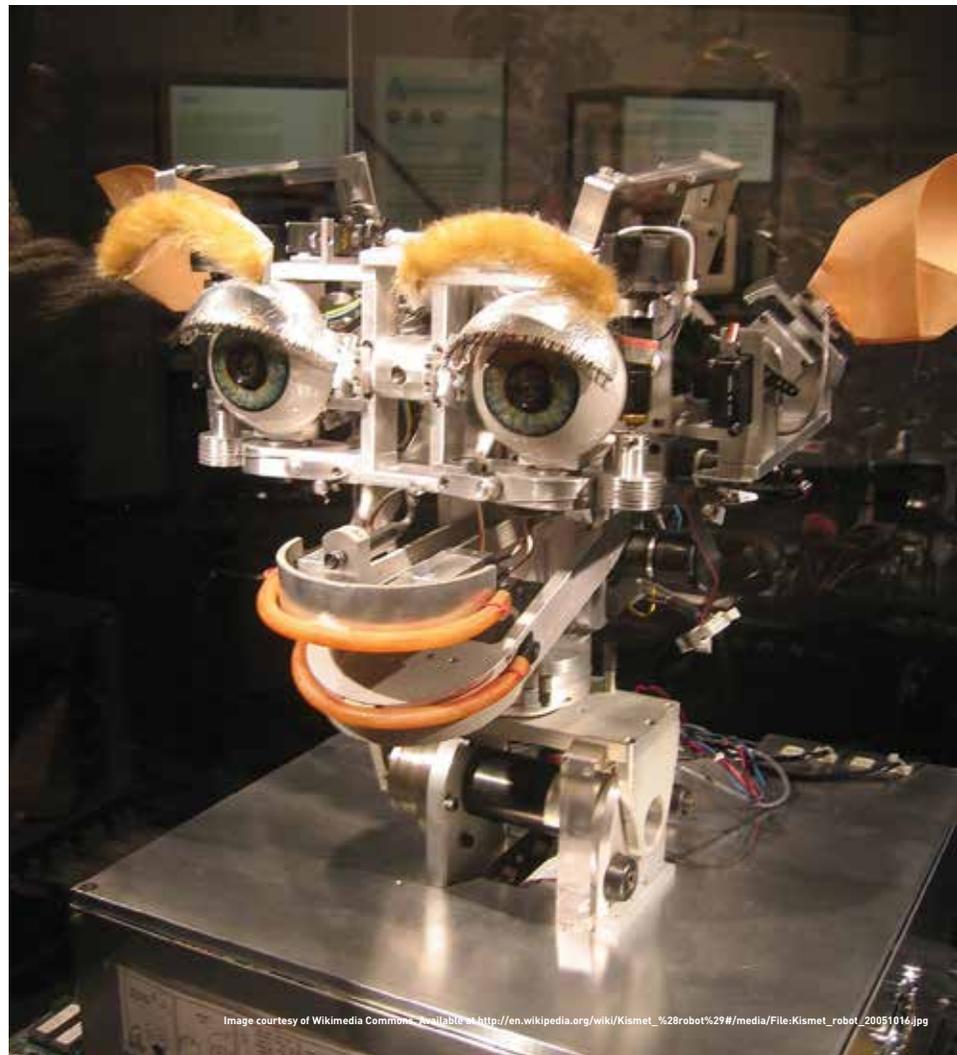
As the above results indicate, there is clear contention regarding the effects of AI development on the economy and the job market. Predictions based on history may prove accurate, but the development of AI is an unprecedented endeavor, and the results may very well be a surprise.

AI Takeover?

Science fiction has a lot to offer regarding the possible succession, destruction, or takeover



Figure 2: The Kismet robot head, an example of artificial social intelligence, can recognize and simulate human emotions.



“As a society, it cannot be denied that advancements in technology, including the field of AI, has increased quality of life.”

of human society by super-intelligent machines. The idea of a robot takeover may seem contained within the realm of fiction, but the possibility of takeover by super-intelligent machines is a subject explored by scientists and science fiction writers alike.

With recent breakthroughs in AI development, such as cheaper parallel computers, access to big data, and more efficient algorithms, scientists have become concerned about advanced AI superseding humans (12). Stephen Hawking, theoretical physicist and director of research at the University of Cambridge, has warned that the development of true superhuman artificial intelligence could mean the end of the human race. Hawking says current forms of AI have been beneficial, and he personally uses some forms of AI for communication, but he fears what may happen when humans create AI that can match or surpass us. Hawking hypothesizes that such an intelligent being could re-design and improve itself, eventually bettering humans, who are limited by biological evolution (13).

Hawking is not the only one concerned about AI. Elon Musk, the CEO of rocket maker SpaceX, has expressed similar views, claiming that AI is our biggest existential threat (13). Indeed, the University of Cambridge's Centre for the Study of Existential Risk (CSER) lists artificial intelligence as a major technological risk, citing the unpredictability and uncertainty of future advancements in the field. CSER sees the biggest risk of AI as the difficulty of designing safe goals and controls that prevent unexpected, potentially devastating errors (14).

It is more likely that our dependence on AI may do more damage to society. With components of life becoming increasingly automated, it is increasingly preferred to avoid memorization of information that may be stored on phones or computers. Even some cars can drive themselves, albeit in a very limited fashion. But what happens when this technology fails? So many things that society takes for granted, ranging from cellular connectivity to national security, are dependent on technology that could fail without notice. As a result, AI development may also focus more on creating reliable technology. Otherwise, the risk of system failure may yield wide-ranging negative effects.

Conclusion

Artificial intelligence is a new field experiencing unprecedented growth, which

makes setting accurate, well-grounded expectations for AI a challenging task. Turing's imitation game set a standard for AI, but achieving that standard has only been somewhat successful. The participants of the Dartmouth Conferences thought they had broken down the challenges of AI development into readily solvable problems, but they vastly underestimated their complexity.

Keeping this in mind, it may be pragmatic to view current predictions of the future of AI with a grain of salt. The questions of an increasing amount of technology in our workforce or the development of superhuman intelligence cannot be answered with current information. When it comes to artificial intelligence, expectations have been historically belied by the realities of the field. **D**

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Fad Diets in Modern America



BY KEVIN KANG '18

With one-third of American adults considered obese and about two-thirds considered either overweight or obese, obesity is a pervasive and concerning issue in the modern United States (1). Medical professionals often prescribe simple advice to their overweight patients: burn more calories than you consume (2). Despite these directions, many Americans fail to start or sustain weight loss, turning to fad diets, which promote quick weight loss by cutting out or selectively decreasing some specific food groups, instead. The number of fad diets continues to rise as Americans look for more creative ways to shed pounds.

Conventional medical wisdom prescribes low-fat diets as the most effective way to lose weight. Indeed, the deposition of fat, not proteins or carbohydrates, is the main indicator of obesity. Moreover, fats, or lipids, form plaques in arteries that lead to heart attacks. Although studies show that most Americans understand that high caloric intake and lack of exercise cause obesity, the conventional prescription for low-fat, low-calorie diets continues to go unheeded (3).

Paradoxically, fad diets such as the Atkins Diet claim that dieters can eat more fat to lose fat. The Atkins Diet strictly limits carbohydrate intake and mandates that virtually all calories come from fat or protein. This diet is particularly perplexing because a gram of fat contains nine calories, while a gram of either carbohydrate or protein contains only four calories. Common sense dictates that eating fat over carbohydrates or protein should lead to

weight gain. The Atkins diet works in practice because eating fats instead of carbohydrates satiates the dieter more quickly, so individuals eat less and ultimately lose weight.

Like the Atkins Diet, other fad diets compel dieters to completely change their eating habits. For example, the Japanese Diet, as described by a WebMD reviewer, instructs dieters to only eat Japanese food. WebMD maintains that followers of the Japanese diet eat 800 fewer calories per day after starting the diet. Such diets are effective because they compel dieters to make significant changes to their eating habits, ultimately leading to a calorie deficit.

In large, randomized studies, many popular fad diets have been compared to conventional low-calorie, low-fat diets in reputable medical journals like *The New England Journal of Medicine* (4). The studies' results indicated that dieters lost weight if they burned more calories than they consumed, regardless of the type of diet followed.

The principle that weight loss can only occur if the individual burns more calories than he or she consumes is consistent with the first law of thermodynamics—energy cannot be created or destroyed. It is important to recognize that even if a diet promotes weight loss, it may not necessarily be safe. Some fad diets eliminate foods that are essential to a balanced diet, meaning dieters should be careful not to develop nutritional deficiencies when following diets that exclude or cut down on essential nutrients.

Figure 1: Fad diets in the U.S. include those such as the raw food diet, where only uncooked and unprocessed foods are eaten.



Modern Fad Diets

The Atkins Diet

In 1972, Dr. Robert Atkins published the first edition of his book, *Dr. Atkins' Diet Revolution*. The newest edition, *Dr. Atkins' New Diet Revolution*, has swept the nation since its publication in 1992, selling more than 10 million copies worldwide and becoming one of the top 50 best-selling books of all time. When first introduced, the Atkins Diet was especially controversial because it was the first diet that placed no restrictions on caloric intake. The first phase of the Atkins Diet prescribes a maximum of 20 grams of carbohydrates and as many grams of protein or fat necessary to satisfy hunger. This phase is called the "Induction" phase, with the goal of shifting the body from primarily burning carbohydrates for energy to primarily burning fats for energy. The process of burning fats, lipolysis, leads to accumulation of ketones, an organic compound, in the body. Ketones can cause loss of appetite, assisting in weight loss, but they can also cause dehydration, so the Atkins Diet encourages aggressive hydration. As dieters move into subsequent stages of the diet, more carbohydrate consumption is permitted, yet many critics of the diet claim that the lack of fiber found in carbs causes constipation. The uncertainty regarding the long-term side effects of high-fat intake on the heart poses

Figure 2: The Zone Food Pyramid has fruits and vegetables near the bottom, meaning they comprise the majority of the diet, as compared to the traditional food pyramid with grains and starches at the base.

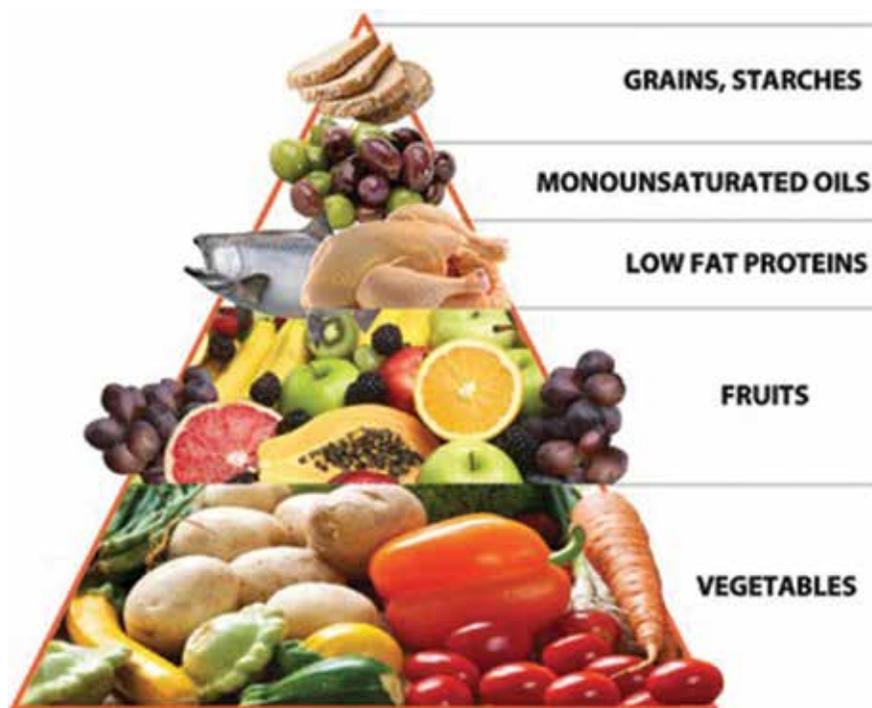


Image courtesy of Hammer Crossfit. Available at <http://hammercrossfit.com/wp-content/uploads/2013/06/image-food-pyramid.jpg>

another concern about the Atkins Diet (5, 6). Nevertheless, several randomized studies demonstrate that the Atkins Diet is as effective in weight loss as conventional low-fat diets (5).

The South Beach Diet

Miami-based cardiologist Arthur Agatston proposed the South Beach Diet. Although both the South Beach Diet and the Atkins Diet restrict carbohydrate intake, only the Atkins Diet mandates complete carbohydrate restriction. The South Beach Diet, on the other hand, allows for consumption of fiber-loaded carbohydrates like fruits and vegetables. So far, no research has shown significant weight-loss differences after six months of following a low-carb diet versus six months of following a conventional low-calorie or low-fat diet.

Paleo Diet

The rationale behind the Paleo Diet is that our ancestors were very healthy and fit, so if you eat like a caveman, you will lose weight. Since cavemen ate foods like fresh meat, fresh fruits and vegetables, eggs, fish, nuts, seeds, coconut oil, and olive oil instead of grain, milk products, peanuts, legumes, or beans, Paleo dieters follow suit. The Paleo Diet effectively leads to weight loss because the diet inherently consists of low-calorie foods. However, this diet can also lead to vitamin D or calcium deficiencies because it excludes dairy products.

Dietary approaches to stop hypertension (DASH) and Mediterranean Diets

United States dietary guidelines recommend DASH and Mediterranean diets because these diets follow overall healthy dietary patterns without excluding any large food groups. The Mediterranean diet consists of fruits, vegetables, whole grains, low fat dairy, fish, poultry, legumes, and nuts. The DASH diet prescribes foods commonly considered "healthy," such as fruits, vegetables, low-fat dairy products, whole grains, fish, poultry, and nuts, recommends less saturated fat, trans fat, and cholesterol rich foods, and limits sodium, sweets, sugary drinks, and red meats. DASH and Mediterranean diets consist of low-calorie foods, promoting weight loss when combined with a calorie-restricted regimen. In these diets, 20 to 25 percent of calories come from fat, 50 percent come from carbohydrates, and about 25 percent come from protein; these

percentages align closely with government-recommended dietary guidelines.

Low-fat diets without calorie restriction

Generally, any dieter who does not count calories and consumes less than 20 percent of his or her total calories from fat follows this type of diet. For example, vegan dieters do not count calories and consume 10 percent to 25 percent of their total calories from fat. As long as dieters adhere to these guidelines, low-fat diets without calorie restrictions usually result in calorie deficits and weight loss (2).

The Zone diet

The high-protein Zone diet is similar to the Atkins Diet, as it does not impose a calorie restriction but still leads to a calorie deficit. Zone dieters eat five meals per day and consume 40 percent of their total calories from carbohydrates, 30 percent from proteins, and 30 percent from fats. Proponents of high protein diets claim that these diets build muscle and lead to greater fat loss through mechanisms similar to ketosis. However, in order to build muscle, resistance training and exercise are required in addition to protein consumption. Moreover, people with poor kidney function should be cautious about high-protein diets because the by-products of protein digestion are difficult to eliminate from the body and can stress the kidneys.

Conclusion

Generally, the diets listed above are effective weight loss strategies. For both conventional and fad diets, maximal weight loss occurs during the first six months of dieting. Studies show that gradual, moderate weight gain tends to occur over the subsequent two-year period. On average, dieters lose 10 to 25 pounds in the first six months, but the average net weight loss is about seven to 10 pounds after two years.

For diets that specify calorie restrictions, the American Heart Association recommends reduced calorie targets of 1200 to 1500 calories per day for women and 1500 to 1800 calories per day for men (2). Several fad diets that eliminate easily accessible foods achieve similar daily caloric intakes without mandating any formal calorie restriction.

No study has shown that a specific diet is superior to another. If dieters can adhere to them, the above diets tend to promote healthy weight loss as long as they do not cause nutritional deficiencies or side effects like constipation. Although many fad diets



Image courtesy of DIY Health. Available at <http://diyhealth.com/high-five-reasons-increase-protein-intake.html>

cite a variety of reasons for their success, the achievement of a calorie deficit remains the key to weight loss. Weight loss will only occur if dieters burn more calories than they consume, and, as the many examples of fad diets demonstrate, there is more than one way to achieve this kind of calorie deficit. Any diet that compels dieters to make a conscious, significant change in their eating habits to promote a calorie deficit appears to cause weight loss. **D**

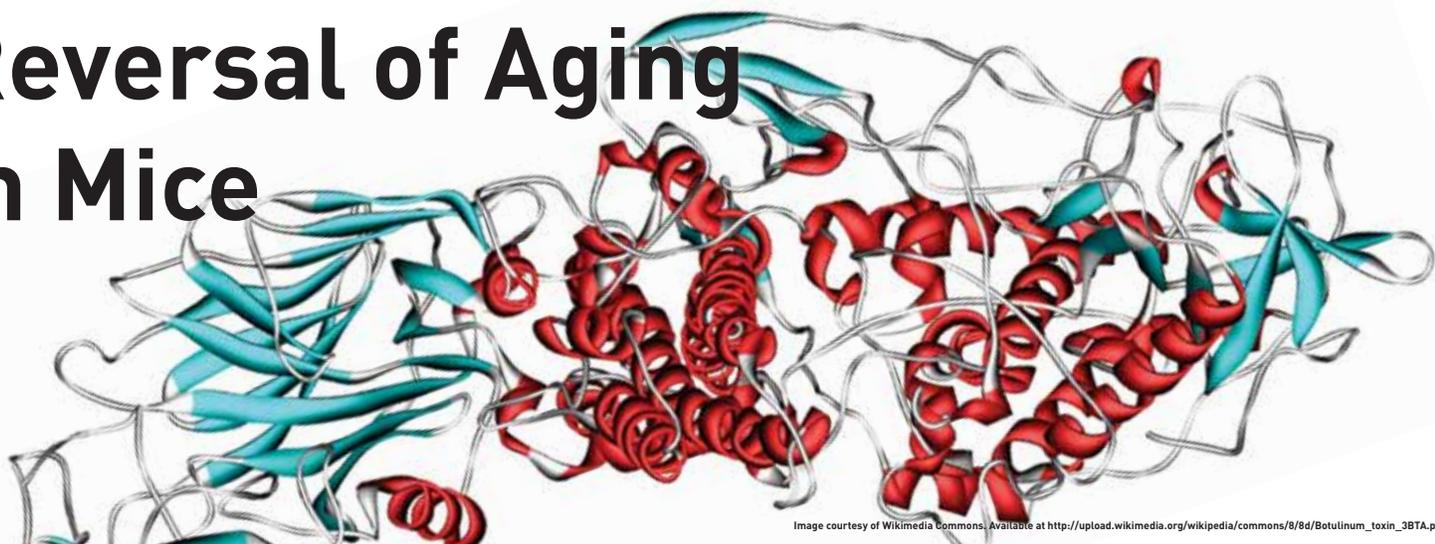
Figure 3: High protein diets limit dieters to foods like poultry, fish, red meat, beans, and nuts. However, protein digestion leads to by-products that are difficult to eliminate from the body and can stress the kidneys.

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Reversal of Aging in Mice



BY HEERUK BHATT '18

Figure 1: Botulinum toxin is a neurotoxic protein marketed under the name Botox for cosmetic use in preventing wrinkle development.

Aging is often associated with a general decline in the functions of the body. As individuals age, their muscles reduce in size, their bones become more fragile, and their heart pumps blood at a slower rate (1). Although all organisms must grow old, mankind seems to have an obsession with reversing the aging process. From a global perspective, the value of the anti-aging market has increased by nearly \$100 billion in the past five years. Plastic surgeries involving botulinum toxin, commonly referred to as Botox, that can remove facial wrinkles and restore a youthful look increased by 680 percent from 2000 to 2012 and continue to gain media attention (2).

In the past two years, several scientific breakthroughs have emerged in anti-aging. In December 2013, Dr. David Sinclair of Harvard Medical School published a study in which he established a functional link between aging and the loss of a coenzyme in the bodies of mice as they age (3). Complementing this study, in May 2014, research from the Harvard Stem Cell Institute showed that injection of a certain protein in aging mice could strengthen their hearts, muscles, and brains so that they more closely resembled those of younger mice (4). And, very recently, on March 9th, 2015, scientists from the Scripps Research Institute found that an anti-cancer drug and an antihistamine may be the key in reversing the aging process (5). Although significant, none of these studies have garnered much attention from the media.

The Biology of Aging

Several explanations exist for the cause of aging, although a single reason has not yet been clearly identified. When the major molecules in cells, such as DNA and proteins, become damaged,

cells lose their ability to divide and subsequently undergo apoptosis, or programmed cell death. Apoptosis often leads to the destruction of surrounding stem cells, resulting in inhibition of regeneration (6). This “damage” theory also seems to account for increased susceptibility to cancer (7).

The shortening of telomeres is also often associated with aging. These repetitive DNA sequences are found at the ends of sister chromatids that make up chromosomes in human cells. Every time a cell divides, its telomeres shorten. When these telomeres reach a certain minimum size after around fifty rounds of division, known as the Hayflick limit, the cell loses its capacity to divide and becomes a senescent cell (6). Senescent cells are unique in that apoptosis cannot target them. When too many senescent cells accumulate in the body, they secrete harmful substances that can affect other, “healthier” cells that have not reached their division limit, accelerating the aging process (5).

Other processes in the cell contribute to aging. Normally, when oxygen enters the body, it aids in the process of cellular respiration in the mitochondria by acting as the final electron receptor in the electron transport chain. Under ideal conditions, molecular oxygen accepts four electrons and is converted to water. Oxygen may accept fewer electrons, however, and, when this occurs, the molecule becomes a highly unstable and reactive species that can exit the mitochondria and damage other parts of the cell. This “oxidative stress” can damage multiple components of the cell, including proteins and the cell membrane, and can lead to widespread apoptosis, triggering the aging process.

Some scientists believe that aging coincides with a reduction in sex hormones in the body,

tying the theory to evolutionary mechanisms. When sex hormone levels are high, the organism is likely at a critical stage in its development where it can reproduce and continue the species; the body responds through massive cell regeneration (8). When sex hormone levels are low, as seen in the elderly, the organism no longer has the same reproductive capacity, and cell signaling leads to cell death. The reduction of other critical compounds and proteins in the cell along with damage to these substances may lead to aging in the cell. Still, other scientists believe in an autoimmune theory, which states that, as organisms age, they produce more antibodies that recognize their own cells as “foreign.” These antibodies then mount an attack on normal cells, which can lead to the effects of aging (6).

Of these explanations, it seems that the articles detailed in this study follow the cellular senescence theory, which states that, as cells age, levels of critical compounds may fall, either naturally or as a result of damage. The scientists featured in these articles hope to target anti-aging by increasing levels of reduced substances and keeping senescent cells in check.

A Tale of Three Studies

Dr. Sinclair’s lab at Harvard Medical School found that administering a coenzyme, nicotinamide adenine dinucleotide (NAD+), to mice could drastically improve muscle function (3). NAD+ is found in the mitochondria of cells and is necessary for cellular respiration. Also, NAD+ facilitates the cooperation between mitochondrial DNA and the nuclear genome, strengthening the function of the mitochondria (9). As individuals grow old, they lose the NAD+ in their mitochondria, which leads to a general reduction in the mitochondria’s ability to form ATP, the energy fuel source of the cell. In turn, muscles lose their tone. When the members of Dr. Sinclair’s lab injected NAD+ into old mice, they noticed that the coenzyme completely reversed the aging process. The skeletal muscles of the mice were significantly strengthened and increased in muscle tone. If this same result could be replicated in humans, it could lead a 60-year old to have the same strength as a 20-year old. In response to these findings, early human trials are underway. When interviewed, Sinclair remarked that his therapy may make it “natural for people to live until they’re 90, and in a healthy way.” He believes that, in the future, his therapy may be as widely used as antibiotics (3).

Following Sinclair, a research lab under the direction of Dr. Amy Wagers and Lee Rubin of Harvard’s Stem Cell Institute showed that injecting GDF11 protein into mice that is equivalent to that of a 70-year old human drastically reversed the aging process in their hearts, muscles, and brains (4).

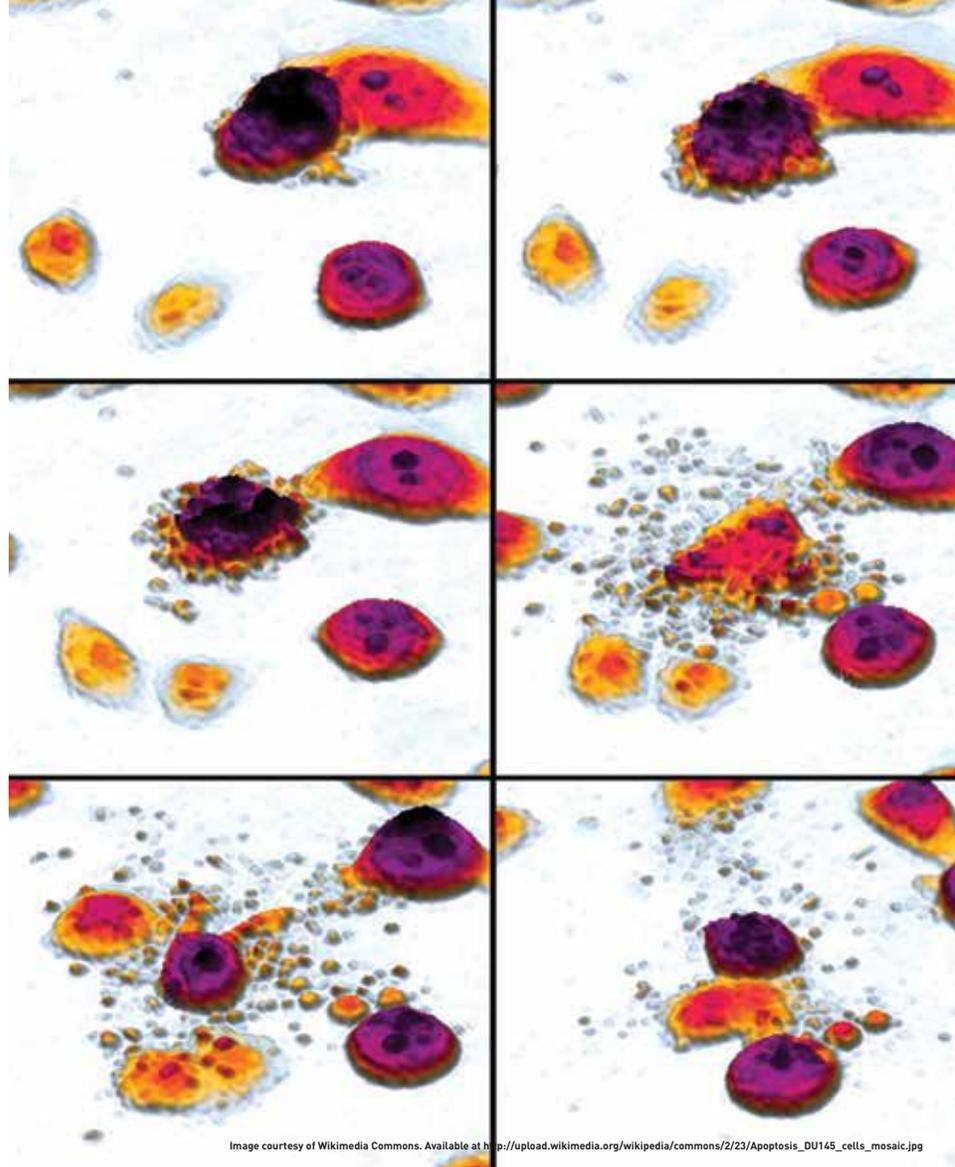


Image courtesy of Wikimedia Commons. Available at https://upload.wikimedia.org/wikipedia/commons/2/23/Apoptosis_DU145_cells_mosaic.jpg

The catalyst for this study was a previous study conducted by Dr. Amy Wagers that exploited the properties of a parabiotic system, which involves surgical fusion of a young mouse to an older mouse. Using this method, young blood can circulate in the older mouse. From the parabiotic system, Wagers noticed that the oversized, weaker hearts of the older mice changed in size to resemble those of the younger mice. She hypothesized that the GDF11 protein, found much more abundantly in younger mice than in older mice, seemed to have regenerative properties (4).

After this discovery, she began work with Dr. Lee Rubin and replicated the results of her previous study by injecting GDF11 into older mice. In this study, she noticed that GDF11 was not specific to the heart and had a much higher restorative capacity than previously thought. She and Dr. Rubin noted that the muscles of the older mice had been significantly strengthened, enabling the mice to exercise much more. The two researchers found for the first time that GDF11 had repaired DNA damage in muscle stem cells, which accumulates as a result of aging and often prevents these cells from dividing and repairing

Figure 2: Aging can result in apoptosis, also known as programmed cell death, where the cell breaks down.



mechanical damage in muscles. By repairing the DNA of muscle stem cells, GDF11 facilitated muscle repair. Importantly, however, GDF11 was shown to have effects on more than muscles (4).

MRI and 3-D imaging of the brains of the older GDF11 treated mice showed an increase in neurogenesis. Researchers saw a clear increase in the density of neural stem cells and blood vessels, a trademark of younger and healthier brains. An increase in vascularity and blood vessels also suggested neurogenesis. To find evidence for an increase in brain capacity, the researchers tested the ability of old mice treated with GDF11 to discriminate a very subtle scent of mint. The older control mice that had not been treated with GDF11 could not smell the mint, but the experimental group consisting of the treated GDF11 mice could discriminate the scent as well as the younger mice could. These findings suggest that the olfactory cortices in the brains of the older mice treated with GDF11 improved in function. Older mice that had been fused to younger mice also detected the scent, further verifying that GDF11 is the blood-borne link crucial to uncovering the anti-aging puzzle (4).

Both Dr. Amy Wagers and Dr. Lee Rubin feel that GDF11 therapy is particularly useful in treating age-related conditions such as Alzheimer's disease. Particularly, GDF11 could improve the cognitive faculties of those suffering from Alzheimer's disease. According to Dr. Wagers, "I would wager that the results of this work, together with the other work, will translate into a clinical trial and a treatment, but of course that's a wager" (4).

The most recent research uses the senescent cell theory as a foundation to target anti-aging. A collaborative effort by the Scripps Research Institute and the Mayo Clinic, led by Dr. Zhu and Dr. Tchkonina, showed that the use of senolytics, drugs that destroy senescent cells, could significantly alter the aging process. As mentioned earlier, senescent cells secrete substances that can harm surrounding cells, such as stem cells, which are crucial to the regenerative capacity of a tissue. Destruction of senescent cells may lead to an increase in function of stem cells and other crucial cells. Two senolytics already available to humans are dasatinib, an anti-cancer drug, and quercetin, a supplement that behaves as an antihistamine and an anti-inflammatory drug. To test their hypothesis, researchers involved in this study treated two-year old mice with senolytics and dasatinib and found that the amount of blood pumped by the hearts of these mice increased by 10 percent. These mice also had markedly high endurance compared to control mice, as evidenced by their ability to run on the treadmill for longer periods of time (5).

In addition to naturally old mice, scientists in the study used mice that age at six times the normal rate, mimicking humans with progeria.

These mice typically die after six months. When treated with the two senolytics, the healthy life spans of the rapidly aging mice increased by nearly 10 percent, and their bone densities increased by 15 percent (5).

Dr. Laura Niedernhofer, another member of the study, remarked, "Probably, these secreted factors from senescent cells inhibit regeneration, so just getting rid of the bad players, these senescent cells, is sufficient to have a positive impact." Kang Zhang, a professor of genetics at the University of California, San Diego, finds the study very "exciting" and would like to see the results in the mice replicated in humans. Because these two drugs are already FDA-approved, further clinical trials can be arranged relatively quickly (5).

Conclusions

The reversal of aging continues to be a very important topic in the modern world, not only for cosmetic purposes, but also as a result of the association between aging and disease. With the innovations detailed in the above studies, scientists may be able to find more effective therapies for age-related ailments such as Alzheimer's disease or arthritis. These therapies may displace more expensive treatments used currently, making relief more accessible to individuals across the socioeconomic spectrum. **D**

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From Where Will the Next Pandemic Emerge?

BY ALI SIDDIQUI '17

Every few years, an infectious outbreak catches the attention of both the public and the media. Epidemics ranging from the Ebola outbreak in the last year to various flu strains have emerged over the past fifteen years. Given the frequency of these events, as well as the deeper history of pandemics like the Black Death, smallpox, and the Spanish flu, speculation regarding the next big pandemic is justified. With every recent scare, massive worldwide casualties have been averted.

Granted, modern epidemics take different shapes in different nations. Epidemics and outbreaks currently ravaging the developing world include malaria, tuberculosis, and HIV/AIDS. Epidemic outbreaks are far more common and deadly in developing nations.

Examples include measles, typhoid fever, and the cholera outbreak in Haiti in the aftermath of the 2010 earthquake (1, 2). The Ebola epidemic displays this disparity quite well. While over 10,000 deaths have been reported or suspected in West Africa, most of those infected outside of Africa have recovered (3).

Ebola is known for its deadliness, with an average fatality rate of 50 percent among various strains (4). Such statistics induce fear, but, without any context, the fatality rate is an inaccurate measure of danger. Many factors must be considered in assessing the risk of a widespread epidemic or pandemic that affects both developed and developing nations. While history has seen several deadly pathogens, a closer analysis reveals that, more likely than not, the next pandemic will not be a repeat of a past pandemic.

The Black Death

The Black Death is arguably the most infamous pandemic. Caused by the *Yersinia pestis* bacterium, the Black Death wiped out

about a third of Europe's population and a twelfth of the entire human population in the 1300s (5). Its lethality was based on biological and cultural circumstances, as Europeans had little exposure and no immunity to *Y. pestis* (5, 6). Endemic to rodents in China and East Asia, the fleas carrying the bacterium came to Europe through trade routes that connected the East and the West. Dead animals in the streets provided food for rats, and, once these rats died, their fleas sought new hosts. More often than not, the next host was another rat, but, on occasion, it was a human. Once infected, the plague bacteria spread to the lymph nodes and blood stream. Infection of the lungs caused pneumonia-like symptoms, and the bacteria could then spread to new hosts when infected individuals coughed-up these pathogens. In the medieval era, the spread of disease was both quick and easy. Not only did up to a dozen people live in each home, which often consisted of a single room, but many medieval cities were also walled in, making city-wide outbreaks even more devastating (7).

The medieval era was a long one, and trade had been long established, so why did the Black Plague strike around 1350? Rainy conditions at the time rotted many crops, which may have caused a rodent population boom (6, 7). Famine and malnutrition resulting from food scarcity likely led to disease and susceptibility to the plague. Another hypothesis suggested that the bacterium itself became more potent as a result of critical changes in its DNA. Taken from the teeth of corpses, the *Y. pestis* genome from the 1350s showed little change when compared to modern strains. Of the 4.6 million base pairs, only 97 have changed, and only 12 of those changes were in expressible genes (6, 8). Further analysis revealed that these changes probably

Figure 1: The 1918 influenza pandemic, also known as the "Spanish Flu," killed over 20 million people worldwide.

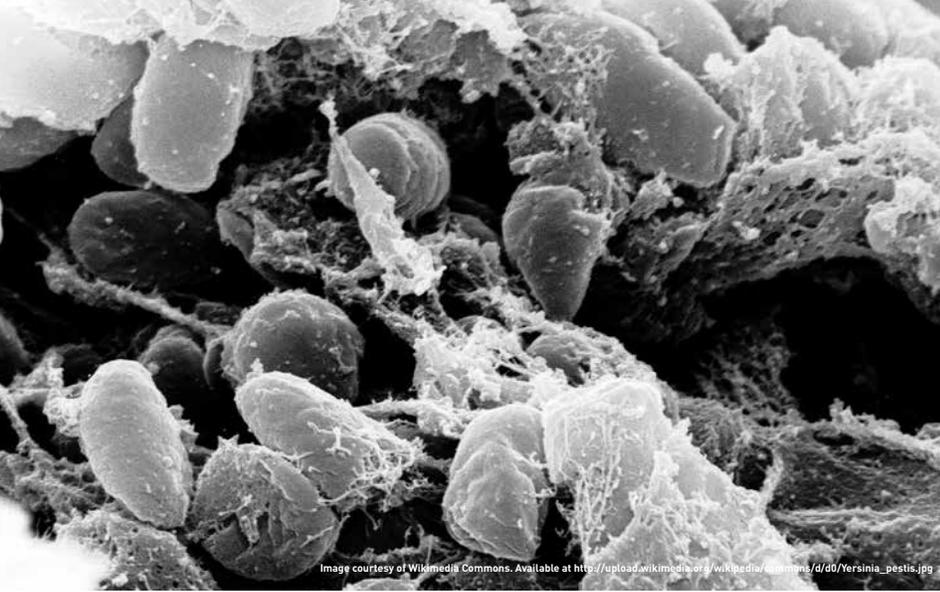


Image courtesy of Wikimedia Commons. Available at https://upload.wikimedia.org/wikipedia/commons/d/d0/Yersinia_pestis.jpg

Figure 2: *Yersinia pestis*, shown in this scanning electron micrograph, is the gram-negative bacterium responsible for causing the Black Death.

did not increase pathogenicity (8).

Regardless of whether genetics influenced the spread of the Black Death, a modern worldwide plague outbreak is very unlikely. Public health awareness and quarantines can now limit the spread of illness, and most strains, including the Black Death, are susceptible to modern antibiotics, such as tetracyclines (8, 9). The Black Death was not the only plague outbreak in the past, which may have allowed many human populations to develop a degree of immunity to the bacterium. Smaller, isolated outbreaks, like the one in Madagascar in the 1990s, are still possible, though (6).

The Spanish Flu

The Spanish flu, a strain of avian influenza, ravaged the world at the end of World War I. It is estimated to have infected about 30 percent of the world population and killed 40-50 million people (10, 11). The Spanish flu often presented as a lung infection followed by a severe immune response that damaged the lungs of victims, ultimately killing them. Oddly enough, the Spanish flu severely hit young adults in addition to typically at risk elderly individuals and children (12). A larger release of chemicals and fluids into the lungs to combat the virus in individuals with stronger immune systems may explain the large numbers of young adults affected by the Spanish flu (13).

The flu struck in three waves. In the spring of 1918, a few cases of severe flu were reported. During the summer, a second, more deadly wave spread across the world (13). A likely theory is that the virus found its way to the trenches of World War I, where it mutated to a more deadly strain that then spread when soldiers returned home from war (13, 14). The pandemic came to an end after a less severe third wave in the summer of 1919, at which point most of those infected either died or were now immune (15, 16). In one year, the average life expectancy in

the United States dropped by 12 years (12).

The Spanish flu has genetics similar to those of other avian flus. Two proteins, hemagglutinin (H) and neuraminidase (N), vary from virus to virus. There are 16 variants of hemagglutinin and nine of neuraminidase (17). The numbering helps classify the virus. For example, H1N1 caused the swine flu epidemic of 2009. Incidentally, the Spanish flu was also a variant of H1N1. Though the two viruses share these H1 and N1 proteins, they differ elsewhere genetically. Like the Spanish flu, the swine flu disproportionately affected young adults, but there are many reasons the swine flu epidemic was less deadly than the Spanish flu (18, 19). Much of the elderly population probably had some immunity to the swine flu as a result of exposure to the Spanish flu and other H1N1 variants that have come and gone with the seasonal flu. Some researchers worry that the elderly, as well as the general population, may not have immunity against future strains. Most flu outbreaks have been of the H1, H2, or H3 types, but there are 16 variants of the hemagglutinin protein. Like the Spanish flu and all avian flu strains, the swine flu arose randomly from the animal population and happened to be a more lethal strain, and such a random occurrence could happen with any combination of the H and N proteins. An additional concern with intermediate hosts, like pigs, is antigenic shift, where the virus might exchange some of its genes with other flu-like viruses in the host. This new strain may end up being more transmittable or potent (20).

Vaccines are constantly being developed for the annual flu and can be made for future outbreaks, however (18). Antiviral drugs can also be used by those already infected with new and old flu viruses, such as the H1N1 or H5N1 (21, 22, 23). Although the viruses mutate from year to year, researchers now know that most severe flu infections result in similar, intense immune responses. They also know that the H and N proteins play key roles in viral transmission, regardless of antigenic shift. Both of these facts can help researchers direct their efforts towards better antiviral drugs as well as a universal vaccine that should, in theory, apply to all H and N combinations (11, 18).

The tradeoffs involved in evolving to a new host should also be considered. Avian flu viruses exist among bird populations. They can mutate to reside in another host, such as humans and other mammals. Due to the initial lack of immunity, however, the mammalian host is likely to die. Should it survive, the virus has a chance to mutate once more. The goal of a virus is to spread, so mutations for transmission from mammal to mammal are favored. However, as a study with ferrets suggests, as the virus

evolves for easier transmission, it loses some of its lethality (24). Recent outbreaks of H5N1 in Egypt, India, and other nations provide examples among humans. H5N1 seems to infect the lower respiratory tract, making it both deadly and hard to transmit. More common strains of the flu affect the upper respiratory tract, making them less likely to damage the inner portions of the lungs and easier to expel by coughing or sneezing. Some speculate that the Spanish flu killed so many people due to the sheer number of people it infected, despite having a relatively low fatality rate. With new flu types, mutations can increase the risk for pandemics, but isolation techniques are now well known and employed to prevent the virus from spreading to the general population (24).

What about Ebola?

Ebola presents a unique study with regards to lethality. Since the first outbreak in 1976, Ebola outbreaks have had fatality rates ranging from 25 to 90 percent (4). Most of these have been in remote, forested areas, but the most recent outbreak spread to urban areas (4). Unlike the avian flu or the plague, the Ebola virus is transmitted through contact with bodily fluids (25). In theory, this should make the virus harder to transmit, but, during the most recent outbreak, cultural practices involving touch aided in transmission. Initial infection resulted from contact with bats, which often harbor the Ebola virus and related filoviruses, or with animals that have been infected through direct contact with bats (26). Once a human is infected, the virus blocks interferons, a compound that alerts the immune system (25, 27). When allowed to replicate freely, the virus damages the spleen and kidneys, which maintain the body's equilibrium, and can spread to the liver and lungs (26). While the immune system begins to respond to such an infection, blood vessels become weak and start to leak, which can result in deadly hemorrhaging (26, 27).

Like the Black Death, circumstances and cultural practices have helped spread the Ebola virus throughout Africa. Many West and Central African nations have weak public health systems and infrastructure that limit their ability combat such an outbreak (4). Many of these countries also have large native bat populations that could host Ebola viruses. To further complicate matters, some of these countries' populations have tripled since 1976, making it more likely that humans will come into contact with bats and the virus. As the need for land increases, people will inevitably cross into lands where these bats live, which could explain the increase in outbreaks and why the most recent outbreak has been more severe, as it has affected nations

with large urban populations (27). Additionally, physical contact is a key component of religious activities in these areas. In Liberia and Sierra Leone, hugging is a part of religious worship, and burial of the dead involves washing and kissing the bodies. Those who die of Ebola often have virus-containing blood coming out of their orifices and onto their skin, so transmission is quite likely if the dead are touched by relatives (28). While many viruses are deactivated when they dry out, the presence of the Ebola virus in blood and other bodily fluids allows it to remain active even weeks after a victim has passed away (4, 29).

Unlike the Black Death the Ebola virus seems to have a genetic basis for its potency. The virus is endemic to bats, so it has adapted to survive in the bat population. Bats, in turn, have probably evolved to survive such viruses because, had the virus killed bats efficiently, it would have lost its means of replication. Although humans have different immune systems, they are still similar enough for the virus to attack (29).

Why the virus is so deadly after transitioning from a bat to a human host is a matter of speculation. In stark contrast to the ferret experiment with H5N1, experiments in guinea pigs have shown that with each successive transmission from guinea pig to guinea pig, the virus becomes more virulent (30, 31). Like avian flu, the Ebola virus is an RNA virus, so it often makes errors while replicating, resulting in mutations (32). Some believe that this may explain the current Ebola outbreak, where the virus mutates to increase transmission, while others contend that the strain in question, Zaire ebolavirus, has mutated a hundred times over the last decade, with no clear indication that these changes have affected its properties (26). This does not explain why the Ebola virus does not lose its virulence as it becomes better at transmission.



Figure 2: The Ebola virus virion is shown here in a colored transmission electron micrograph.



Other researchers have looked into the biology of bats, the original hosts. As a result of the stresses and heat caused by flying, bats may have evolved hardy immune systems that constantly express antitumor and antiviral genes. Such expression may have forced viruses that remain in the bat population to evolve accordingly and keep viruses at bay in the bat population. In contrast to bats, human genes are expressed only when needed. Viruses that survive in bats would thus be quite potent to less adapted immune systems, such as those of humans (33).

Large contact-driven outbreaks can be prevented with proper education about avoiding disease transmission, as has occurred in many parts of Central Africa (28). Increased health infrastructure, use of isolation centers, and the development of new vaccines could also help prevent an outbreak from reaching epidemic proportions. A major issue with vaccines is that a new one would be needed for every type of filovirus. Moreover, The total number of filoviruses is unknown, but they have been found in pigs and primates in addition to bats. Not all of filoviruses are harmful, however; the Reston Ebola virus found in pigs in China and the Philippines did not seem to harm the farmers that were exposed to them (26).

Other Threats and the Potential for Our Own Undoing

With increased awareness, vaccines, and antibiotics, many known pandemic threats can be fought effectively. The above infections all fall under the class of disease known as zoonotic diseases, which are transmitted from vertebrate

animals to humans. Other recent outbreaks, like the severe acute respiratory syndrome coronavirus (SARS), the Middle East respiratory syndrome virus (MERS), Hendra virus, and Nipah virus, are examples of highly pathogenic viruses originally derived from bats. Despite their lethality, these viruses are not yet adept at human-to-human transmission. That said, many could mutate, and, like the Ebola virus, there is no guarantee that they will become less virulent over time. These viruses have probably been among bat populations for many years, so the threat was always present, just unexposed (34). One study of the Indian flying fox bat found 55 viruses among the sample, 50 of which were previously unknown (33). The increasing emergence of these bat-hosted zoonotic viruses over the last 30 years or so is due in part to modern farming practices and habitat destruction, bringing both livestock and humans closer to bats. Climate change is also changing how and where bats will live (34).

While many experts believe that the next big pandemic will be of zoonotic origin, other human practices may give rise to the next pandemic. Antibiotic resistant bacteria are on the rise, with some resistant to most antibiotics. MRSA alone kills about 11,000 Americans annually (35). Despite this fact, there is much room for hope. For one, there is the method of transmission. MRSA bacteria need physical contact to spread, so it is easy to isolate and identify the sources of infection (36). Education could also change our current over-prescription culture. For example, although antibiotics cannot be used to treat acute bronchitis, they are still prescribed in 70 percent of cases. Ensuring that patients and physicians know what treatments to expect could lower the number of unnecessary prescriptions, hasten recovery, and prevent bacteria from being exposed to other bacteria. While pharmaceuticals stopped making antibiotics due to a lack of profit, since 2000, they have joined public-private ventures with the goal of making 10 new antibiotics by 2020. Antibiotics in livestock feed have been banned in Europe, but not yet in the United States. Many European countries have started tracking the prescription of antibiotics and resistance development in their hospital wards, with dramatic results. Less than 5 percent of staph infections in the Netherlands and Denmark are resistant to methicillin, while 50 percent of such infections in the U.S. are resistant. The U.S. has implemented better hospital practices, decreasing the overall rate of MRSA infections by a third from 2005 to 2011 (35). While some argue that progress is too slow, perhaps human ingenuity will come through with enough pressure (37).

Preventing an outbreak from becoming

Figure 4: In emergency drills for pandemic infection control, workers must wear appropriate personal protective equipment, including air-purifying respirators.



Image courtesy of NBC. Available at http://media2.s-nbcnews.com//newscoms/2014_37/659306/140910-ebola-training-nebraska-1142_e8de2ba6d8b597b092b5de6f2b7c3fe.jpg

a pandemic adheres to a standard formula. Increased awareness of what works and what does not prevents any situation from getting out of hand. With increasingly advanced knowledge of diseases, the development of vaccines and drugs can only become more efficient. Governments and healthcare agencies are always on the lookout for new threats, and isolation of suspect cases for any disease will limit, if not stop, the spread of diseases. These tactics helped combat the swine flu, the most recent pandemic. While infrastructure improvements in less developed nations will take time, habitats and climates will continue to change, and new threats will continue to emerge, there is little reason to expect that new viruses will result in the devastations of the past. **D**

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“While many experts believe that the next big pandemic will be of zoonotic origin, other human practices may give rise to the next pandemic.”

Rituximab: The Journey of Immune-based Therapeutics



Image courtesy of Wikimedia Commons. Available at <http://upload.wikimedia.org/wikipedia/commons/d/d0/Rituximab.png>

BY HAE-LIN CHO '17

Figure 1: Rituximab, a chimeric, anti-CD20 antibody, recognizes all mature healthy and cancerous B cells, but not developing B cells or memory B cells, which lack the CD20 protein marker. The drug is primarily used to treat non-Hodgkin's lymphoma, a blood cancer resulting in high B cells counts in the sera.

Immunotherapy for Cancer

Although cancer remains a threat to millions of people worldwide, researchers and healthcare professionals approach the disease from different angles, hoping to get the upper hand over cancer.

Common cancer treatments include radiation therapy, chemotherapy, and surgical excisions when possible. Although the efficacy of these treatments has increased with technological advances, cancer still affects millions of lives annually in the form of both fatalities and new diagnoses.

At the turn of the 21st century, cancer immunotherapy emerged as a promising new treatment option. The success of this rapidly growing field, which uses a patient's own immune system to combat cancer, can be credited to the 1997 development of Rituximab (Rituxin), a chimeric, in this case part-human, part-mouse, antibody drug used primarily to treat non-Hodgkin's lymphoma (NHL) (2, 3). In 2013, Science named cancer immunotherapy the breakthrough discovery of the year (1).

Rituximab's effectiveness in drastically increasing survival rates of NHL patients made it a huge commercial success and catalyzed the booming market for antibody-based drugs in pharmacy (2). The unexpected value of Rituximab in treating cancer and other autoimmune diseases improved understanding of the various roles of the immune system and may lead to more efficacious treatments. In the future, scientists hope that this research may lead to cures for some of the current leading causes of death.

What are monoclonal antibodies?

The human immune system produces two major types of lymphocytes, or white blood cells: B cells and T cells. The former produce

immunoglobulin proteins called antibodies, which bind to immune-stimulators called antigens, preventing foreign pathogens from harming the host. Due to the need for recognition of various antigens, each B cell produces a single, unique antibody that recognizes a single, unique portion of the antigen termed an epitope. In this way, the immune system can respond to various and specific threats from bacteria, viruses, and parasites (4).

Although antibodies have been used throughout history, with some of the earliest documented usage in vaccinations in China, contemporary use of antibody therapeutics did not take off until the 1880s when German physiologist Emil von Behring used antibodies in animal serum to treat diphtheria patients. Despite von Behring's success, several barriers halted further developments in the promising field of antibody therapeutics, including hypersensitivities due to use of animal rather than human antibodies, as well as low amounts of desired antibody in the serum, with levels as low as one percent. As a result, antibiotics superseded sera-based therapies (2).

In the 1970s, the emergence of monoclonal antibodies (mAbs), or antibody copies generated in mass amounts from a single B cell, changed this pattern. Hybridoma technology, which combines an antibody-producing B cell with a tumor cell line to create a B cell hybridoma that mass-produces a specific antibody, allowed for the use of antibodies as treatments (2).

A Case Study: Rituximab

As discussed, prior to the 1990s pharmaceuticals did not focus on antibody-based drugs, although a couple of mAbs were FDA-approved in the late 1980s and early 1990s for non-cancer-related conditions. The emergence

of Rituximab in 1997 reversed this paradigm, changing the field of commercial pharmacy and oncology in several ways (2, 4).

The FDA approved Rituximab in 1997 for treatment of NHL, a cancer of the B cells that actually produce antibodies and is also the most common form of blood cancer in adults in the United States (4). As a chimeric mAb, Rituximab targets a protein called CD20, which is found on mature B cells and plasma cells. However, CD20 does not target memory B cells, which remain in the body after an antigen is cleared and produce antibodies in large quantities upon re-exposure to the antigen. Thus, Rituximab, an anti-CD20 antibody, recognizes, binds to, and eventually depletes virtually all B cells, including the cancerous ones, but leaves memory cells intact so they can continue to protect the patient from previously encountered pathogens. In addition, CD20 is not present on immature or developing B cells, so patients retain the ability to rebuild their B cell population after treatment (5).

More effective than traditional chemotherapy, Rituximab combined with chemotherapy became the “first-line” of defense against many types of NHL. Since its introduction, both mortality rates and incidence of NHL have decreased, the latter around three percent each year. The drug became the first mAb commercial success and generated over one billion dollars in revenue annually (4). Its success garnered the interest of large pharmaceutical companies like Biogen, Amgen, and UCB Pharma, which went on to produce several more successful mAbs (2). Although antibody-based treatments were ignored previously, they are now one of the fastest growing markets in pharmacy.

With the success of Rituximab in treating NHL, the market for mAbs soared and scientists gained interest in the role of the immune system in cancer. Rituximab opened the field of cancer immunotherapy, using the immune system to target oncogenic cells and cell components in cancers other than lymphomas. Some significant mAbs include ipilimumab (Yervoy) for skin cancer, bevacizumab (Avastin) for colon cancers, and trastuzumab (Herceptin) for breast cancer (2, 5). Antibody-based vaccines for cancers have also emerged – namely, Gardasil, a vaccine that protects against cervical cancer. In its mechanism, Gardasil uses an antibody to target a protein used by the cervical-cancer inducing human papilloma virus (6). Beyond the huge array of mAbs under development, researchers have developed T cell therapies for cancer (7).

As a result of the immune system’s natural role in fighting cancer, researchers hope to make cancer therapies more natural and specific to an individual patient by using cancer immunotherapy. Dr. William B. Coley elucidated the immune system’s role in fighting cancer

in the 1890s, after showing that injections of *streptococci* bacteria into the site of a tumor could boost the immune system enough to cause tumor regression (7).

In fact, researchers now speculate that more conventional cancer therapies like radiation and chemotherapy, most commonly known for suppressing the immune system, may actually stimulate the immune system in other ways (8, 9, 10). For instance, researchers in Japan found that gemcitabine, a chemotherapeutic drug used to treat pancreatic cancer, actually stimulates dendritic cells (DCs), critical components of the immune system (9). The end result of this stimulation may help the immune system recognize and attack tumor cells. Similarly, radiation therapy can cause the “abscopal effect,” an adaptive immune response at a site other than that of the actual tumor. The immune system responds to the tumor damage caused by radiation by releasing potential antigens for recognition by B cells and T cells (10). Scientists hope to use this information and newfound understanding to develop better combination therapies for cancer treatment (8, 9, 10).

Rituximab beyond cancer

Although initially only approved for NHL, Rituximab demonstrated the ability to treat various other diseases including autoimmune disorders like multiple sclerosis (MS) and rheumatoid arthritis (RA).

Based on various clinical trials, researchers found that Rituximab greatly reduces inflammation. Inflammation is a defining symptom of both MS and RA, which develop when a patient’s immune system attacks his or her own cells, the myeloid sheath in MS and the synovial joints in RA. Researchers discovered antibodies that specifically attack the myeloid sheath and contribute to the demyelination that defines MS (11). In clinical trials, Rituximab decreased lesions associated with MS by 74 percent, compared to 26 percent at baseline, and significantly lowered the number of MS relapses by depleting B cells (11). In RA patients, Rituximab decreased symptoms for 54-55 percent of patients in a clinical trial, compared to 28 percent of those who received a placebo (12). Clinical trials are also being run to investigate Rituximab’s effects on patients with systemic lupus erythematosus, another autoimmune disorder (4).

Rituximab has attained positive results for diseases related to the vascular system and kidney like Wegener’s Granulomatosis (GPA), Microscopic Polyangiitis (MPA), and nephrotic syndromes of minimal change disease (MCNS). In MCNS, only patients receiving Rituximab without other conventional MCNS medications



Figure 2: Both New York physician William B. Coley (top) and German physiologist Emil von Behring (bottom) made important contributions to the development of immunotherapies in the late 19th century. Von Behring used antibodies found in animal sera to treat diphtheria patients, and Coley injected streptococci bacteria into tumors to induce a stronger immune response.



“The unprecedented success of Rituximab in treating not only lymphomas, but also diseases beyond its intended scope, demonstrates the exciting potential of antibody-based therapies.”

achieved long-term remission (3, 13).

Although Rituximab's mechanism of action in these various autoimmune disorders is not completely understood, these findings prompted further studies that illuminated the role of the immune system, specifically B cells and their products, in these diseases. Lowering the levels of antibodies associated with disease progression may be a possible factor. Since 1997, the FDA has also approved Rituximab for treatment of RA, Wegener's granulomatosis (GPA), and microscopic polyangiitis (MPA) (3).

Similarly, Rituximab efficacy in ameliorating symptoms in conditions with unknown etiology, such as chronic fatigue syndrome (CFS), suggests possible mechanisms for the disease. Based on the findings of a study published in 2011, subjects with CFS reported improvements in their fatigue two to seven months after Rituximab treatment, causing scientists to postulate a potential autoimmune component of CFS progression (14).

Hundreds of clinical trials for mAbs are being conducted worldwide. Researchers have progressed beyond the chimeric Rituximab and developed both humanized and fully human mAbs, which decrease the likelihood of hypersensitivity. These techniques involve either splicing only the necessary components of the animal antibody onto a human antibody or genetically replacing the animal's immune system with that of a human. Many researchers hope to use a fully humanized version of Rituximab, such as Ofatumumab, to treat these autoimmune diseases. This technology would avoid concerns regarding the development of human antibodies against the animal portion of Rituximab (11, 13).

Challenges moving forward

Despite huge strides made in mAb therapy, there are still critical challenges to overcome. One of the main difficulties posed by mAb is price. A single treatment with Rituximab via intravenous infusion currently costs \$3,976 to \$5,680, and multiple infusions are required to meet the 650 mg dose necessary to treat an average person (5).

In addition, the relatively large size of mAbs presents structural challenges that prevent their effective use on solid tumors. These challenges prompted the development of domain antibodies called dAbs, which started clinical trials in 2011. These dAbs are much smaller than conventional mAbs, approximately 12-15 kDa versus 150 kDa, respectively. Researchers hope that this may expand the range of potential uses of antibodies in HIV and enable penetration of the blood-brain barrier (2).

Conclusion

A major shift has occurred in the fields of oncology and pharmacy since the success of Rituximab. The unprecedented success of Rituximab in treating not only lymphomas, but also diseases beyond its intended scope, demonstrates the exciting potential of antibody-based therapies. Researchers and pharmaceutical companies have created a burgeoning market for immunotherapies to capitalize on this potential.

In spite of recent advancements, the fight against cancer is in no way close to over. mAbs represent potential treatments for various cancers, but researchers must work further to improve existing treatments and find other potential therapies. Regardless of future advancements, Rituximab will continue to be unique in enabling scientists to explore the complicated and important role of the immune system against cancer, pioneering a new angle of attack. **D**

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A Background on MSG

BY SAM LEE '18

A Background on MSG

Monosodium glutamate (MSG), commonly known as the umami flavor, is tasteless on its own but intensely savory with other foods. MSG is naturally present in tomatoes, asparagus, cheese, and soy sauce, among other products. To create powdered MSG, the natural MSG from these foods is extracted and then sprinkled on food to impart the umami flavor (1).

In the past 50 years, however, MSG has gained a stigma as an unnatural food additive that causes migraine headaches, numbness, chest pains, and weakness. Although the FDA deemed it generally safe in 1959, studies that trace the ill effects of Chinese food to MSG have made many health professionals unsure of the negative health implications associated with MSG.

However, many of the studies that initially sparked public fear of MSG used faulty methods. These include injecting MSG into subjects, feeding individuals MSG on an empty stomach, and administering up to 45 times the typical daily MSG consumption. These studies also failed to consistently show that normal consumption of MSG, about 0.55 grams per day, by the general public negatively affects health. Competing studies with more realistic parameters have shown that moderate MSG consumption is harmless. When consumed with food in reasonable amounts, MSG does not have negative health effects. Through its association with Chinese food and America's long standing fears of the oriental in the late 1960s, however, the additive was stigmatized as dangerous.

Origins of MSG Sickness — Chinese Restaurant Syndrome

In a letter to *The New England Journal of Medicine* in 1968, Dr. Robert Ho Man Kwok made the first report associating MSG with negative health effects, which included numbness along the neck, arms, and back, weakness, and sweating (2). He hypothesized that the symptoms resulted from MSG added to the Chinese food he ate, coining the term "Chinese restaurant syndrome" (CRS) (2). Ten additional letters followed this report to the journal, each with anecdotal accounts of similar symptoms resulting from consumption of Chinese food. One letter reported that 69 percent of 80 women felt symptoms similar to Kwok's after eating a Polynesian luncheon (3, 4, 5, 6, 7, 8, 9, 10, 11,12).

Studies

Early studies conducted in response to Kwok's letter supported the theory that MSG could cause immediate negative side effects. In response to Kwok's letter, doctors at the Albert Einstein College of Medicine investigated the possible health effects of MSG and found that it could cause burning sensations, facial pressure, and chest pain (13). In the study, six subjects were given up to 25 grams of MSG orally, 45 times the amount consumed in an average restaurant meal (13). Subjects that did not react after receiving 25 grams of oral MSG were injected intravenously with MSG until they exhibited symptoms (13). Another study found that direct injection of high doses of MSG into

Figure 1: The natural MSG from foods is extracted to create powdered MSG.



the brains of baby mice led to the formation of brain lesions. As the mice grew into adults, they showed signs of stunted skeletal development, obesity, and female sterility (14). These findings not only supported Kwok's hypothesis but also convinced the public that MSG could significantly damage one's health. Despite the fact these studies were later considered insignificant due to their small sample size, high dose injections of MSG, and, in Schaumburg's case, flawed methodology, the public's negative opinion of MSG persisted (15). People shied away from MSG as a food additive. Anecdotal reports of health complications and the results of the aforementioned studies created a culture that viewed MSG as a harmful chemical rather than a seasoning, notwithstanding the lack of comprehensive research surrounding its effects (16).

MSG's health outcomes remained ambiguous from the 1970s to the 1990s as studies emerged that both supported and opposed the proposed relationship between MSG and CRS. These studies employed a double-blind placebo controlled method (DBPC) and were much more rigorous than both Schaumburg and Olney's studies. In the early 1970s, three DBPC studies found that there was no difference in symptoms experienced after ingesting MSG or a placebo (15, 17, 18, 19). In Morselli's study, subjects were given three grams of MSG mixed with a beef broth along with other food, similar to

Figure 2: Only a small percentage of the population may develop symptoms of monosodium glutamate symptom complex/CRS when consuming large amounts of MSG (>3 grams).



Image courtesy of Sasha Wolf. Available at http://commons.wikimedia.org/wiki/File:Throbbing_migraine_headache.gif

the DBPC experiment performed by Tarasoff where subjects received 1.5-3.75 grams of MSG or placebo after breakfast (15, 19). Both studies found that neither the placebo nor the MSG groups experienced any CRS symptoms. The results of these two studies directly opposed the findings of Kenny and Tidball, who found that subjects who ingested three to five grams of MSG experienced symptoms of CRS (20). Kenny's subjects were forbidden from eating for at least two hours prior to MSG administration, however, suggesting that food is a major factor in determining whether or not a subject experiences the symptoms of CRS (20).

Studies, such as that conducted by Kenny et al. (1972), in which subjects were given MSG or placebo on an empty stomach at high doses, created an unrealistic environment for the subjects. Given that MSG is a food additive, it is reasonable to assume it is only consumed with food (1).

The effects of MSG remained uncertain until a large-scale comprehensive study was conducted by Geha et al. in 2000. This study used a published list of 10 symptoms associated with monosodium glutamate symptom complex, the more inclusive term for CRS. One hundred and thirty self-identified MSG-sensitive subjects were placed in a four-step consecutive DBPC study. Subjects that exhibited two of the 10 documented symptoms of monosodium glutamate symptom complex after a single dosage of MSG or placebo without food would move on to the next round of testing, where they would receive a second dose. On the fourth dosage, food was given in addition to either MSG or placebo. Only 1.8 percent of the subjects who received only MSG showed symptoms for all four rounds of testing. Researchers noted a lack of consistent responses to either the MSG or placebo in the first two rounds of testing, and, when patients were retested, those that had reacted to MSG/placebo in prior rounds had no reaction to MSG/placebo in subsequent testing. Researchers also concluded that there was a higher rate of response in subjects that did not have a meal prior to administration (16).

These studies, when examined together, suggest that only a small percentage of the population may develop symptoms of monosodium glutamate symptom complex or CRS when consuming large amounts of MSG, defined as more than three grams. Others may develop CRS symptoms upon consuming large amounts MSG on an empty stomach, but such a situation is unlikely (1).

MSG and Obesity

More recent studies have suggested a correlation between added MSG and health

issues other than CRS, including obesity and metabolic issues. A 2005 study of rats found that a supplemental 100 grams of MSG per kilogram of body weight increased food intake as well as levels of glucose, triacylglycerol, insulin, and leptin (21). Two studies in 2008 followed-up on these findings, with one showing a correlation between BMI and MSG intake in middle-age Chinese adults, and the other uncovering a relationship between MSG intake and both nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in rats (22, 23).

MSG, a flavor enhancer, makes food more appealing and tasteful, thus increasing appetite (24). This increased appetite promotes overconsumption, which can cause metabolic syndrome (21). MSG may not directly cause metabolic syndromes and liver disease as suggested by these studies, but may instead be an indirect cause, increasing appetite and causing overeating. Furthermore, the amount of MSG administered to the rats in both studies was incomparably higher than any previously conducted studies. Nakanishi's study used two milligrams of MSG per gram of body weight, and Yeda used 100 grams of MSG per kilogram of body weight. Adjusted for a 170-pound person, Nakanishi's study would have injected 154 grams of MSG, and Yeda's study would have administered 7,711 grams of MSG. Even if MSG were directly responsible for the health issues in these studies, the amount of MSG administered renders the studies inapplicable to the general population.

MSG Sickness as a Psychological Issue

The Geha et al. (2000) study demonstrated that, although there are numerous self-identified MSG-sensitive people, only a small fraction of them are actually MSG-sensitive. The other "MSG-sensitive" subjects, those who inconsistently reacted to doses of both MSG and placebo, do not have a physiological problem with MSG, but may instead have purely psychological reactions.

While MSG has existed since 1909, reports of CRS and other reactions to MSG only gained traction as an issue following Kwok's letter in 1968. Kikunae Ikeda invented powdered MSG by extracting it from seaweed, and it saw wide distribution throughout China and eastern Asia in the 1920s. By the 1930s, it was heavily used throughout the American food industry as well. When the first study examining the health effects of MSG was published in 1969, 58 million pounds of MSG were being used in the American food industry (13, 25). In spite of the use of MSG in both Asia and America,



CRS seemed to be a distinctly American issue. Kwok, born in China, stressed that he only experienced CRS in America (26). Several others who wrote to *The New England Journal of Medicine* mentioned that they only experienced CRS symptoms when eating at Chinese restaurants in America (7, 13). In East Asian countries such as Japan and China that have used MSG for much longer periods, CRS is an unknown phenomenon (27).

Chinese food in America seemed to be the issue, not MSG. Americans already consumed substantial amounts of MSG prior to Kwok's 1968 letter through mass-produced foods such as Campbell's Soup and Doritos, but a majority of anecdotal cases involving CRS revolved around ethnic foods such as Chinese or Polynesian cuisines. People felt sick after eating Chinese food more often than after eating American foods that contained MSG, such as KFC, suggesting a psychological correlation between Chinese foods and CRS-like symptoms (28). After Kwok's letter was published, another doctor stated that he only experienced CRS symptoms when eating at Chinese restaurants, although that he used MSG in his own home cooking (13). CRS symptoms and Chinese food seem inseparable, with MSG taking a background role.

Some medical and scientific journals proposed alternative names for CRS, such as monosodium glutamate syndrome (28, 29), but the alleged symptoms associated with MSG remained known as Chinese restaurant syndrome. The "Chinese" aspect of the syndrome was key to the American public. Kenney et al. investigated this phenomenon, examining why CRS was associated with Chinese food rather than American foods that contained MSG (20). He suggested that Chinese cooking practices

Figure 3: MSG Sickness is often known as "Chinese restaurant syndrome."



were to blame, concluding that CRS did not occur when MSG was used in appropriate quantities. He posited that MSG quantities used in Chinese food were “bizarre” and wildly liberal (20). These conclusions, when picked up by the media, stigmatized Chinese food as filled with MSG, while other foods contained appropriate amounts. However, no studies compared the MSG content of Chinese food to that of industrial American food.

Beyond the allegedly high MSG content of Chinese food, the public viewed Chinese food as foreign and strange. The 1969 *New York Times* article titled “In Hong Kong it’s Dog or Snake at Lunch Now” encapsulates the sentiment felt at the time. The article focused on the Chinese tendency to eat exotic animals such as dogs and snakes, hiding such meats on menus at Chinese restaurants. These practices fascinated some and repulsed others (29). This scared the public, possibly leading them to believe that the food they were eating at Chinese restaurants was not what it seemed. Compounded with the preexisting notion that Chinese food contains unhealthily large amounts of MSG, this fear led many to perceive sickness or symptoms of CRS after eating meals at Chinese restaurants.

Conclusion

The debate over CRS’s relationship with MSG was put to rest after the large scale study conducted by Geha et al. in 2000. They concluded that MSG, when taken with food and in reasonable quantities, is harmless to the general population. However, many people who are not allergic to MSG still perceive CRS symptoms, possibly as a result of psychological factors associated with consuming Chinese food. In reality, MSG is utilized in a variety of foods, including American foods such as canned soups, chips, and instant meals. As a result, the reported CRS symptoms may be psychological symptoms linked to American consumers’ distrust of exotic foods. **D**

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“MSG, when taken with food and in reasonable quantities, is harmless to the general population.”

Accelerated Repetitive Transcranial Magnetic Stimulation:

The Future of Brain Stimulation Treatments for Depression

BY KATIE BILLINGS '16

Last year, nearly seven percent of Americans suffered from major depression (1). Unfortunately, pharmacotherapy is effective for only two-thirds of depressed patients (2). Patients with treatment-resistant depression (TRD) who are unresponsive to pharmacotherapy may try a clinically proven brain stimulation treatment. While repetitive transcranial magnetic stimulation (rTMS), one of the most common brain stimulation treatments, has proven effective in alleviating symptoms of TRD, numerous obstacles like expense of treatment, extensive time commitment, and remoteness of treatment centers limit the availability of rTMS for potential patients. To overcome the many limitations of brain stimulation treatments, Paul Holtzheimer III, MD, created a condensed rTMS schedule called accelerated transcranial magnetic stimulation (aTMS), which may prove to be an effective alternative to traditional rTMS treatment (3).

Repetitive Transcranial Magnetic Stimulation (rTMS)

How rTMS Works

Transcranial magnetic stimulation (rTMS) is a noninvasive treatment used to modulate cortical and subcortical functions using electromagnetic fields. In rTMS, a metal coil that generates rapidly changing electromagnetic fields is placed over the patient's scalp, and, depending on the parameters of treatment, the electromagnetic fields have either excitatory or inhibitory effects in the stimulated cortical regions (8). One brain region that serves as a target for rTMS is the left dorsolateral prefrontal cortex. rTMS of the left dorsolateral prefrontal cortex decreased in symptom severity by more than 50 percent in 20-30 percent of patients (1).

The specific mechanisms behind rTMS's effectiveness remain unknown. Neuroscientists hypothesize that the electromagnetic stimulation

of depression-specific regions of the brain is analogous to hitting a reset button for the neurochemicals in the brain. Though the reason rTMS works is unknown, the treatment has been successful in alleviating depression and reducing remission rates in patients with TRD, with limited side effects and safety concerns (4).

Limitations

Typically, rTMS treatment involves 40-60 minutes of active treatment, five days per week, for three to six weeks, and most patients complete rTMS treatment after 20-30 sessions (3). The daily administration schedule of rTMS may make it less viable as a treatment option for patients with TRD. Additionally, patients must travel significant distances to the nearest treatment site, so patients who work or have other commitments may not be able to follow the required rTMS treatment schedule. An alternative rTMS treatment with a condensed schedule could increase the availability of rTMS treatments to TRD patients in desperate need of a brain stimulation treatment.

Accelerated Transcranial Magnetic Stimulation

Origin and Subjects

In order to increase the accessibility of rTMS to patients, Dr. Holtzheimer and his team of researchers at Dartmouth-Hitchcock Medical Center designed an accelerated rTMS (aTMS) protocol for the treatment of TRD. aTMS allows patients to receive the same amount and intensity of traditional rTMS treatment in a condensed, two-day period. The pilot study addressed the safety and efficacy of open-label aTMS for patients who had failed at least one traditionally sufficient antidepressant treatment. The researchers hypothesized that aTMS would prove safe and effective. They also posited that aTMS would be accompanied by a decrease

Figure 1: The neural pathways in the brain, depicted using diffusion tensor imaging.



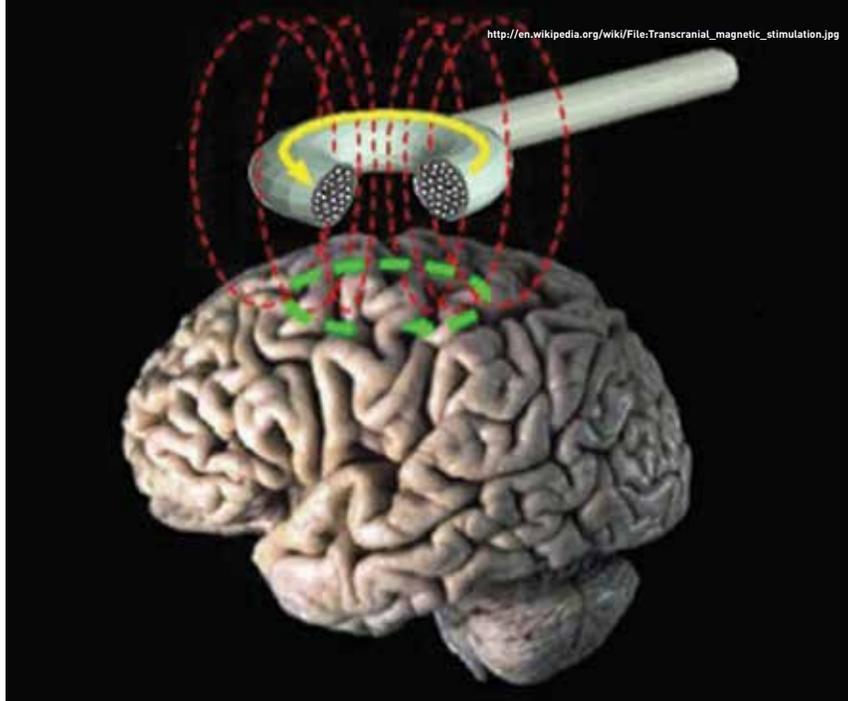


Figure 2: A schematic diagram depicting the process of transcranial magnetic stimulation.

in depressive symptoms at all post-treatment evaluations, including same-day, three weeks, and six weeks post-treatment, and would be associated with response rates equivalent to daily rTMS treatments for three to six weeks (3).

Subjects were recruited through physician referral. Participants met the following criteria: 1) experiencing a major depressive episode, 2) 24-item Hamilton Depression Rating Scale ≥ 20 at screening, 3) at most three sufficient antidepressant medication failures in the current episode, 4) willingness to continue taking current antidepressant medications with unchanged doses for at least two weeks prior to and six weeks following treatment, 5) no previous exposure to rTMS or TMS, 6) no clinically significant medical or psychiatric comorbidities, and 7) no increased risk of seizure.

Methods

The Cadwell high-speed magnetic stimulator and a custom iron-core coil were used for all aTMS treatments. The aTMS pulses were biphasic, and the current distributions were comparable to those produced by the rTMS figure-8 coil. Baseline ratings were obtained when patients were admitted to an inpatient research unit on the first day of the study. For each patient, scalp position of the lowest motor threshold was determined using single pulse TMS. The scalp position was either the right first dorsal interosseous or the abductor pollicis brevis muscles (5). The resting motor threshold (MT) for each patient was determined by the lowest power setting that produced a visible muscle contraction in at least five of the 10 trials. The left dorsolateral prefrontal cortex (DLPFC) treatment site was located 5.5 cm anterior in a mid-sagittal plane from the MT site (3).

Using 10 Hz rTMS, 15 rTMS sessions were administered to TRD patients. On day one of treatment, five consecutive hourly sessions were

administered. On day two, 10 consecutive hourly sessions were administered. The rTMS was delivered in five second trains with a 35 second intertrain interval at 100 percent of the MT intensity. Each hourly session of rTMS included 20 rTMS trains over 10 minute intervals. Over the complete two-day treatment, each patient received 15,000 rTMS pulses. Post-treatment, patients remained in the hospital for safety monitoring and follow-up testing. Patients were released from the hospital the morning after aTMS treatment.

During all aTMS treatments, patients were monitored for seizure activity and questioned about adverse effects following each of the treatment sessions. Following aTMS treatment, patients were clinically evaluated on day three (the first day post-aTMS treatment), week three and week six. The following scales were used as screening/evaluation measures: 24-item Hamilton Depression Rating Scale, Hamilton Rating Scale for Anxiety, Beck Depression Inventory-2, and the Repeatable Battery for the Assessment of Neuropsychological Status. Response to treatment was defined as an at least 50 percent decrease in the 24-item Hamilton Depression Rating Scale from baseline. Additionally, remission was defined as a 24-item Hamilton Depression Rating Scale of ≤ 10 (3).

Results

Patients included nine men and five women with a median age of 51 years (range 20-74 years). Thirteen patients were white/non-Hispanic, and one was African American. Patients reported a median of four depressive episodes, with a range of two to eight, and the median episode duration was nine months, with a range of three to 96 months. One patient was diagnosed with bipolar 2 disorder. Four patients had a prior psychiatric hospitalization, and five patients had a prior suicide attempt. 10 patients had failed one adequate antidepressant medication in the current episode, and four patients had failed two traditionally adequate antidepressant medications in the current episode. None of the 14 patients had failed electroconvulsive therapy. All patients were on at least one psychotropic medication and remained on a stable dose of their medications for at least two weeks. Two patients discontinued the study prior to completion of treatments: one due to increased suicidal ideation and a second due to the necessity of lowering the stimulation intensity for tolerability, which led to a concern that aTMS would not be effective at this lower dose. No seizures occurred. Including the two patients who did not complete the full treatment schedule, four patients, or 29 percent of the subjects, did not return for the week three evaluation, and five patients, or 36 percent of the subjects, did not return for the week six evaluation.

Significant treatment effects were achieved

by day three and maintained through week six of treatment. The mean 24-item Hamilton Depression Rating Scale decreased by 47 percent by day three, 45 percent by week three, and 55 percent by week six. Neuropsychological functioning did not decline with treatment and demonstrated improvement at the week six evaluation. Demographic and clinical variables like gender, age, age of onset, duration of current episode, number of lifetime episodes, or number of treatment failures in a current episode were associated with percent change in the 24-item Depression Rating Scale or response rate (3).

Limitations

The aTMS pilot study was limited by small sample size, with only 15 patients, open-label treatment, duration of follow-ups, and dropouts following completion of treatment. Additionally, the requirement that patients remain on a stable antidepressant medication for only two weeks prior to treatment may have served as a confounding variable. Consequently, a delayed effect of antidepressant medication may be responsible for the alleviation of depressive symptoms. Further research will require a randomized, sham-controlled, experimental treatment paradigm (3).

Discussion

Though limited, the findings support the safety and efficacy of accelerated rTMS treatment in TRD patients. The response and remission rates are equivalent to rTMS treatment protocols delivered over four to six weeks in two large, randomized, sham-controlled trials (6, 7). These rTMS controlled trials used treatment parameters, which were significantly more aggressive than the parameters of the aTMS pilot study. Consequently, it is possible that a similarly aggressive treatment of rTMS in the aTMS schedule could be a more effective treatment alternative to traditional rTMS. However, a more aggressive treatment schedule administered in the aTMS schedule could increase adverse effects, including decreased safety and tolerability.

Overall, in this initial study, patients tolerated the aTMS treatment with minimal side effects. However, it is possible that the aTMS treatment increased suicidal ideation in the patients who discontinued treatment. Increased monitoring and testing concerning suicidal ideation will be required in larger aTMS studies.

The Future of aTMS for the Treatment of Depression

The aTMS pilot study demonstrated safety and efficacy of a condensed rTMS treatment schedule. Researchers observed a significant, sustained antidepressant response both directly following and six weeks after treatment. Though side effects, including increased suicidal ideation,

may be adverse effects of a condensed treatment schedule, the response and remission rates of aTMS strongly support additional testing of this treatment paradigm (3). Paul Holtzheimer III, M.D., the creator of aTMS, explains,

“The field of brain stimulation for psychiatric and neurological disorders is rapidly developing, but also somewhat in its infancy. Although transcranial magnetic stimulation has been under investigation as a therapy for more than 20 years and is FDA-approved for the treatment of depression, we are still learning how to optimize its use and understand its mechanisms of action. Other interventions, like deep brain stimulation, have shown clear promise as treatments for severe psychiatric illness (e.g., OCD and depression). But, we are years away from knowing whether these treatments are clinically useful. At this stage, the focus is on continuing to collect clinical data on safety and efficacy, as well as learning more about how these interventions affect the brain and its functions.”

With research, validation of the aTMS schedule could provide a treatment alternative with greater accessibility compared to the current rTMS schedules. In addition, aTMS could become a standard inpatient treatment for a more rapid reduction of depressive symptoms. If aTMS is validated and proves safe and effective, brain stimulation could become a first-line treatment for depression. **D**

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“The response and remission rates of aTMS strongly support additional testing of this treatment paradigm.”



Women in STEM: Raising Expectations and Involvement

BY SUMITA STRANDER '18

Figure 1: John F. Kennedy signing the Equal Pay Act (EPA) of 1963, which aimed to eliminate sex-based wage disparity.

The Problem

Both in college and the workforce, women in the United States are significantly underrepresented in the fields of science, technology, engineering and mathematics (STEM). The disparity between male and female participation in STEM fields has widely debated roots and consequences. It remains clear, however, that society, and academia, more narrowly, has had trouble setting expectations for women and itself.

Based on predictions made by the National Science Foundation in 2006, over four percent of America's workforce was directly employed in a STEM field (1). Additionally, the United States Department of Labor estimated that, by 2018, 90 percent of the "fastest-growing occupations that require at least a bachelor's degree will require significant scientific or mathematical training" (1). Thus, STEM fields have a presence in society that is only expected to grow in years to come. For example, "engineering- and computer-related fields – fields in which women currently hold one-quarter or fewer positions" are expected to experience some of the highest growth rates (1). What remains less certain is how the role of women in these fields will change over time.

This article explores the current place

of women in STEM fields using case studies and reports approaching the problem from multiple perspectives. Additionally, it analyzes the broad topic of women in STEM and explores the narrower focus of women in specific STEM disciplines. It concludes by assessing methods that have been used in the effort to reduce this gender gap.

The Path to the Present

The gender gap in STEM fields first becomes prominent during college, but it is also evident in the workforce, making it important to examine possible factors that lead to disparities in both places. In its report "Why So Few? Women in Science, Technology, Engineering, and Mathematics," the American Association of University Women (AAUW) analyzes several causes that have been proposed over the years. In order to understand these causes, however, it is best to become familiar with how a woman's role in STEM fields changes over her lifetime.

The AAUW aids in this analysis by providing information, collected in 2005, regarding high-school performance in math and science based on gender. For example, while males appeared to take more Advanced Placement (AP) classes in STEM areas in high school and perform better in these courses,

females actually earned more math and science high school credits and higher math and science grade point averages (GPAs) (1). Thus, any gender-based difference in high school performance is inconclusive.

Based on data collected in 2006, however, gender-based differences become more evident in college, such as students' intent to major in STEM fields. According to this data, approximately 29 percent of male first-year college students — as opposed to only 15 percent of female first-year college students — expressed intent to major in a STEM field (1). When excluding biological sciences from this analysis¹, the gap becomes even more apparent, as roughly 20 percent of male first-years intended to major in engineering, computer science, or the physical sciences, as opposed to only around five percent of female first-years (1).

A similar lack of women in these latter areas is seen in the distribution of bachelor's degrees awarded to males and females, based on the same 2006 data. While women earned over half of the bachelor's degrees awarded in biology, as well as roughly half of those in chemistry and math, a notably lower percentage earned degrees in engineering, computer science, and physics² (1). In fact, a 2008 study concluded that even though “across all fields, 58 percent of undergraduate degree recipients in the United States are women... disparity persists particularly in computer and information science, where women receive 21 percent of the undergraduate degrees, and in engineering, where women receive only 19 percent of the degrees” (2).

This unequal gender representation is particularly drastic in areas like engineering, where women represent only 11 percent of the total workforce (1). While it may be less severe than in other disciplines, a gender pay gap still exists in STEM fields, as do gaps in career retention and promotion (1). As found in a 2008 study, “female scientists, engineers, and technologists” are better well represented at “the lower rungs on corporate ladders,” but by roughly a decade into their careers, 52 percent leave their jobs (1).

¹ The basis for this exclusion will be discussed later in this article.

² According to this same study, “women's representation in computer science is actually declining...in the mid-1980s women earned slightly more than one-third (36 percent) of the bachelor's degrees in computer science; by 2006 that number had dropped to 20 percent” (1).

Proposed Explanations

Now that an accurate trajectory for women's involvement in STEM fields has been mapped, it is possible to address proposed explanations for the observed gender gap. The AAUW report identifies three potential causes: that men are innately better at math, that women are naturally less interested in STEM topics, and that women experience conflicts in STEM careers related to environment, bias, and family roles.

In addressing the first cause, the AAUW concluded that, “a difference in average math performance between girls and boys no longer exists in the general school population” (1). It does acknowledge that males and females have distinct cognitive strengths, with males having an advantage in spatial orientation and visualization skills and females having an advantage in verbal, written, and perceptual skills (1). Although spatial skills are used in some STEM fields, such as engineering, “the connection between spatial abilities and success in STEM careers is not definitive” (1).

When responding to the claim that women are less interested than men in STEM fields, the AAUW claims that even girls who perform well in mathematics do not express interest in STEM fields (1). Therefore, lack of interest does seem to be a cause, but that interest itself is based on many factors, including self-confidence, self-assessment, and preconceived gender roles (1).

Studies by the AAUW also indicated that implicit bias is still very prevalent in the workforce and can make a large difference in processes such as peer reviewing, which is integral for publishing, and writing letters of recommendation (1). Finally, the AAUW highlighted the importance of familial roles in its claim that “married women in STEM appear to have a disadvantage compared with married men in relation to tenure and promotion decisions only if the married women have children” (1).

A Closer Look Inside STEM: Biology versus Physics

In their article “Gender Segregation in Elite Academic Science,” Ecklund, Lincoln, & Tansey (2012) further dissect the concept of women in STEM by differentiating between women scientists' involvement in biology and physics. To carry out this study, the researchers surveyed and interviewed male and female scientists in departments of the leading 20 graduate schools for physics and biology, asking them to explain the difference between female scientists' participation in biology and physics. The scientists were graduate students,

“Approximately 29 percent of male first-year college students — as opposed to only 15 percent of female first-year college students — expressed intent to major in a STEM field.”



“They found that self-confidence ranked as the most critical individual obstacle, and that ‘classroom climate’ ranked as the most critical structural obstacle.”

postdoctoral students, assistant professors, associate professors, or full professors. The researchers attempted to categorize the scientists’ explanations of women’s participation in STEM as either supply-side, due to innate differences in aptitude and preference, or demand-side, due to the structure of STEM fields and discrimination.

The results of the written survey indicate that most people provided a single reason, as opposed to a mixture of several reasons, for this difference in participation in biology and physics (3). Overall, more women than men scientists thought that discrimination was a critical factor, while more men than women thought a woman’s preference was key. Additionally, the researchers observed a trend based on career level, with more graduate students mentioning the importance of natural abilities, and more professors mentioning the impact of discrimination (3).

The verbal interviews, conversely, showed that most scientists cited a mixture of reasons for the gender difference in biology and physics participation (3). While both men and women interviewees mentioned the importance of innate preferences, men also mentioned innate abilities. Women also mentioned pragmatism and “emotional affinity” as reasons for this preference (3). When interviewees discussed structural obstacles, men mainly noted discouragement that comes from the primary and secondary education system. In contrast, women were significantly more likely to cite problems with the current model of physics departments as influential in deterring women from committing to physics (3). Both men and women scientists mentioned a dearth of role models and tradition as factors to consider. Finally, they contended that it was harder for women to have families and careers in physics than it was in biology. However, the researchers’ “data demonstrate that women scientists in both disciplines work approximately the same number of hours per week” (3).

The researchers concluded that, while gender and career level of the scientists correlated with certain types of responses, field of study was largely irrelevant. Scientists with less experience relied on supply-side explanations more frequently, while scientists with more experience relied more on demand-side explanations (3). This same comparison could be made between men and women scientists, respectively, but only to a small degree.

Assessing Current Efforts

In their 2011 study, Fox, Sonnert, and

Nikiforova describe different programs in universities across the country aimed to address the unequal representation of women in STEM fields. In fact, the researchers describe this study as containing the first concept-based analysis of current undergraduate efforts to promote women participation in science and engineering (2).

In order to do this, they made a clear distinction between “individual” concerns and “structural/institutional” concerns (2). Individual concerns, like supply-side explanations, deal with “the ways individual women’s attitudes, values, aptitudes, experiences, and/or behaviors may operate as deficiencies (or as facilitators) of their participation and performance,” with an example being low self-confidence in a STEM subject (2). In contrast, like demand-side explanations, structural concerns involve “potential deficiencies in the characteristics of settings in which women are educated (and work) in science and engineering,” with an example being exclusive or negative classroom or research environments (2).

To conduct this analysis, the researchers surveyed 48 programs at universities across the United States, attempting to obtain information in four main areas: 1) the program director’s ranking of obstacles, both individual and structural, to women majoring in STEM fields, 2) the activities utilized by the specific university program for women in STEM, 3) the goals of these programs, and 4) the relationship between the individual program and the university as a whole (2).

The researchers found a number of interesting results. First, they found that self-confidence ranked as the most critical individual obstacle, and that “classroom climate” ranked as the most critical structural obstacle. When these two were compared, program directors ranked “women’s self-confidence” above “supportive classroom climate” in importance. Overall, however, program directors tended to cite structural obstacles as more important than individual obstacles (2).

Second, they found that the activities included in the various programs, which were meant to increase women’s participation in STEM, were more individual than structural (2). Career seminars were the most used, followed by peer mentoring and social activities. Conversely, “faculty-centered activities” were most often cited as being “less than minor” in implementation (2). This directly contradicts the opinions of the directors of the same programs. The researchers comment on this disparity, noting,

“The reported program activities largely leave untouched key structural obstacles reported” and “do not [necessarily] align with their typical definitions of the program of women in science and engineering” (2).

Third, when identifying goals and impacts of programs, they did find the goals of “improving classroom climate” and “changing faculty attitudes toward undergraduate women” to be reasonably important. However, they also discovered that “among all goals specified, the disparity between mean importance of the goal and the mean impact is greatest for three goals that pertain to faculty” (2).

Lastly, they assessed faculty participation to be “low” in 36.8 percent and “high” in 10.5 percent of the programs (2). Based on aggregate data, the researchers were able to determine that “it is programs with ‘almost no’ faculty participation that have a clearly individual orientation...and programs with ‘high’ faculty participation that have the strongest structural orientation” (2).

From this study, the scientists concluded that structural activities, specifically faculty participation, are the most effective institutional elements, as they address structural obstacles cited by program directors. Although the data indicated that current programming activities and goals do not always align with these obstacles, they also indicate a potential to bridge this gap.

Moving Toward Solutions

Two main points can be drawn from this article. First, that society, not biology, is primarily responsible for both the difference in participation between men and women in STEM fields and the gender disparity that exists between distinct STEM fields. The second conclusion is that existing undergraduate programs designed to address these problems successfully increase women’s participation in STEM when program directors focus on the structure of the program, specifically the degree to which faculty are involved. **D**

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Notable Women in STEM

Marie Curie

(1867–1934)

Chemist and first female recipient of the Nobel Prize



Rachel Carson

(1907–1964)

Influential marine biologist and author



Gertrude Elion

(1918–1999)

Prominent biochemist

Images courtesy of Wikimedia Commons

Molecular Dynamics and Drug Discovery

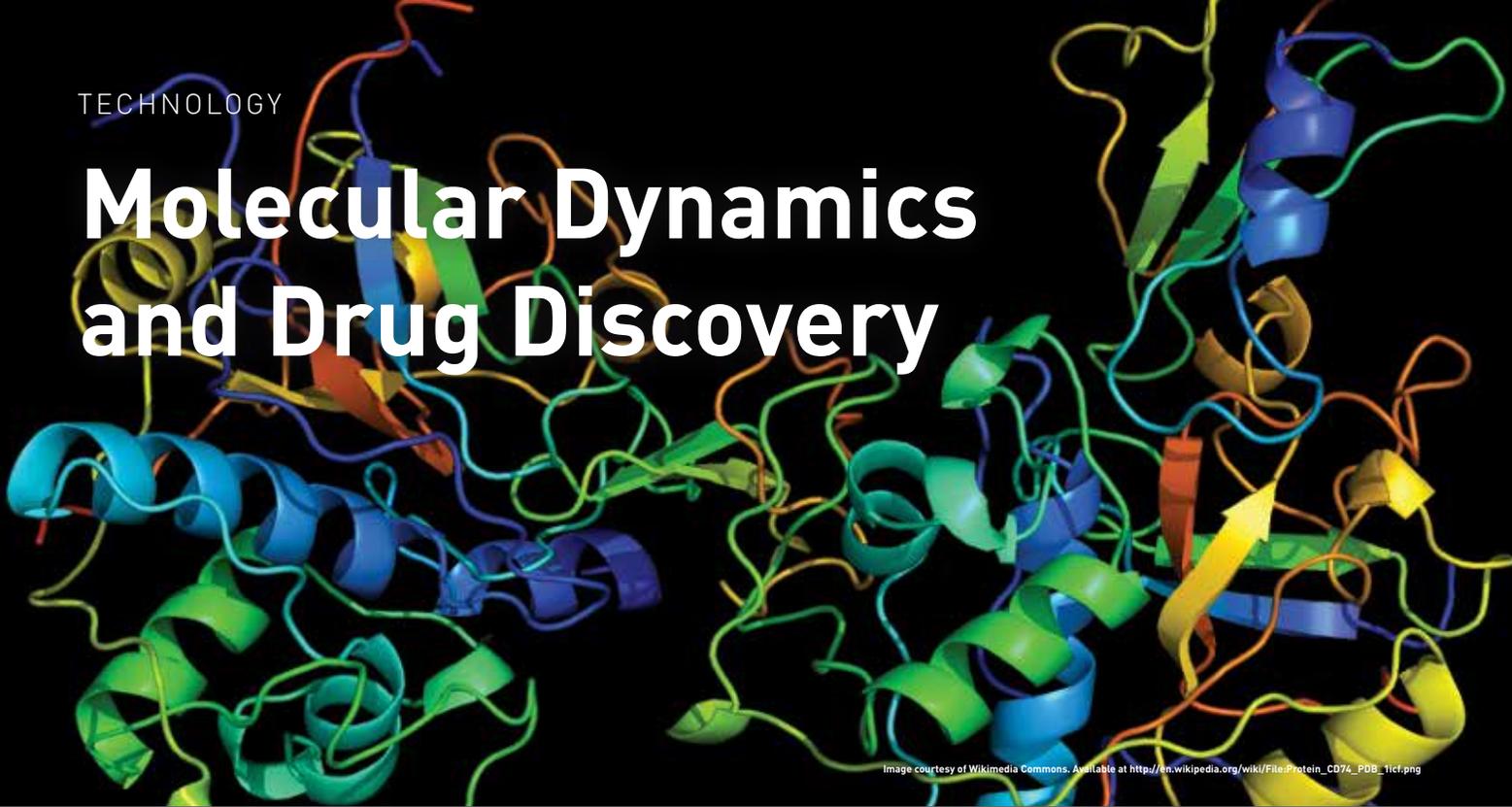


Image courtesy of Wikimedia Commons. Available at http://en.wikipedia.org/wiki/File:Protein_CD74_PDB_1icf.png

BY ALEXANDRA DALTON '16

Figure 1: CD74, a protein in humans encoded by the CD74 gene.

At its most basic molecular level, life is distinguished from non-life by its structure. Structural distinctions between non-living and living entities such as human beings are often based on an arbitrary distinctions regarding relative complexity and perceived function of micro- and macromolecular structure.

These comparisons between non-life and life with regard to form and function take on an entirely non-arbitrary nature when made in the context of proteins, and especially in the context of enzymes. Every moiety and individual amino acid of an enzyme is crucial to its function (1). These complex structures are unrivaled in complexity and diversity among other macromolecular structures, and there are on-going efforts to unlock the potential therapeutic benefits of these systems (2).

Real-world laboratory techniques often cannot provide sufficient insight into the structure, function, and interaction of proteins due to their tiny size and dynamic nature. Changes may occur at a microscale level in fractions of a second. In order to make and justify predictions about the effectiveness and possible side effects of drug therapies involving protein structures, alternative computational methods must be employed. Molecular Dynamics (MD) simulations are one such computational method that have the potential to, through the use of *in silico* models, elucidate the true function and interaction of compounds *in vivo*.

What is MD?

Protein and enzyme structure are created and maintained by an array of inter- and intramolecular relationships intended to produce a final three-dimensional product via self-arrangement, often with the help of chaperone proteins or other factors. All protein formations seek a minimum free energy and an entropic high point (3). On a biological level, this process begins with the assembly of a linear polypeptide chain composed of 23 proteinogenic amino acids, which is known as the protein's primary structure (2). This chain then folds into a secondary structure according to the physical and chemical principles alluded to above, which allows for the formation of common motifs, such as beta pleated sheets and alpha-helices, via local interactions between amino acids in relative proximity. Finally, the formation of tertiary, and sometimes quaternary, structures signifies the polypeptide's final three-dimensional superstructure, and its association with additional polypeptide chains.

Through physical analytic techniques such as X-ray diffraction or nuclear magnetic resonance (NMR), scientists can observe the protein formation process and the functions of proteins and other macromolecules at a high level, but these techniques yield only discrete portraits of structure and fail to depict the true dynamic nature of proteins. It is difficult to deeply understand this process through experimental techniques because protein folding involves interactions and movements on

a microscopic time scale. Computational models examine the structure, function, and interaction of biological macromolecules without direct experimentation by simulating the physical principles that govern the interactions and motions of the atoms within a dynamic system (1). MD simulation provides information regarding the system dynamics of protein folding and function by modeling the motion and interaction of atoms under the constraints of an analytical force model. This force model or “force field” is parameterized to fit quantum and statistical mechanics calculations and experimental data. Applications of quantum mechanics dictate how the atoms interact, while statistical mechanics calculations describe the ensemble of states in which a macromolecular system can reside. The use of a partition function provides the probability of the system occupying one of the vast populations of potential states at a certain time point. To make a realistic simulation, “Parameterization of the force field involves the definition of chemical bonding, atomic angles and dihedral angles, along with the determination of partial atomic charges for calculation of the electrostatic-interaction energies, and identification of appropriate van der Waals atomic radii (4)”. One of the most commonly used force models, Chemistry at Harvard Molecular Mechanics, CHARMM, “made it possible to build the system of interest, optimize the configuration using energy minimization techniques, perform a normal mode or molecular dynamics simulation, and analyze the simulation results to determine structural, equilibrium, and dynamic properties” (5). CHARMM considers numerous conformational and path sampling models that describe this ensemble of states and the transition between states (5). This force-field “tool-box” allows for manipulation of free energy estimates on the system being studied and molecular energy minimization in order to build a realistic and insightful model (5).

Abandoned Expectations, Antiquated Models

Embracing insights into true understanding of protein structure, interaction, and function involves abandoning certain expectations of existing models of these complicated systems. While the lock and key model, first proposed by the chemist Emil Fischer, is meant to describe the precision of the fit required for an enzyme and its substrate to bind, its usefulness is deposed by the “wiggle-jiggle” model that describes the necessity of fit but more accurately depicts the true, dynamic nature of a protein system (6).

The “lock and key” model misleads analysis of protein-protein interaction and

perpetuates inaccurate notions of rigidity in the process of site binding. Despite this common misconception, this dynamic formation never attains a final, definitive shape. Proteins are constantly in motion, and the term “structure” does not imply that the macromolecule is “structured” or “stiff.” Rather, the structure of a protein describes an ensemble of states occupied for varying amounts of time. Computational methods such as MD simulation provide models that depict protein conformation and protein-protein interaction on a biologically relevant timescale.

Post-Paradigm Shift: Expectations surrounding Applications of MD

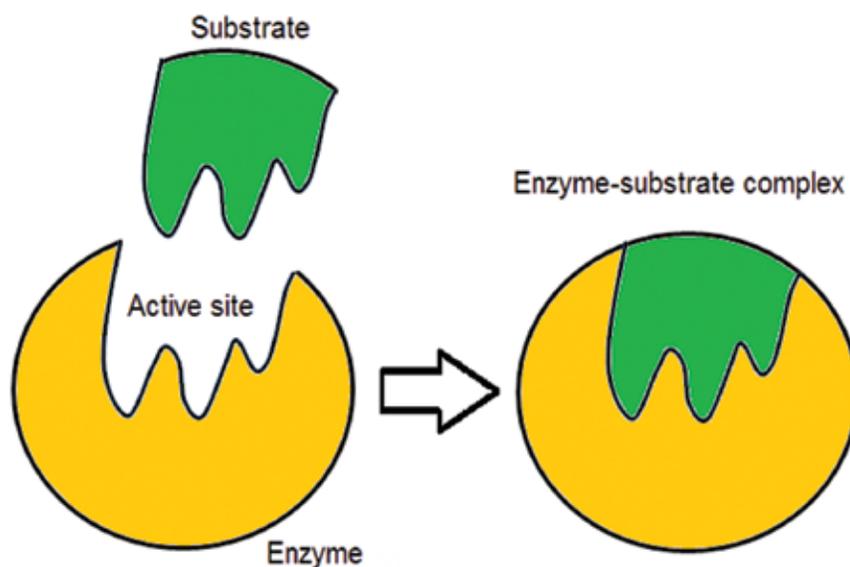
Though advances in and applications of MD trace back to the late 1950s, the use of these computational methods has only really started to accelerate the development of targeted drugs in the last 25 years (7). A lack of concrete understanding of the target, potency, efficacy, selectivity, and toxicity of trial compounds causes the majority of drug discovery projects to fail. Applications of MD include remedying this plague of uncertainty that thwarts the majority of drug discovery products. According to Borhani et al., “the bottom line is this: All experimental drugs enter human clinical trials based on extensive preclinical data indicating that they should work; most nonetheless do not, defying our well-grounded expectations” (7). The implications of this statement are manifold.

Among the many elements of a dynamic system that can be modeled through MD simulation, such as molecular self-assembly, dimerization, and adaptive conformational changes on ligand binding, simulations of drug



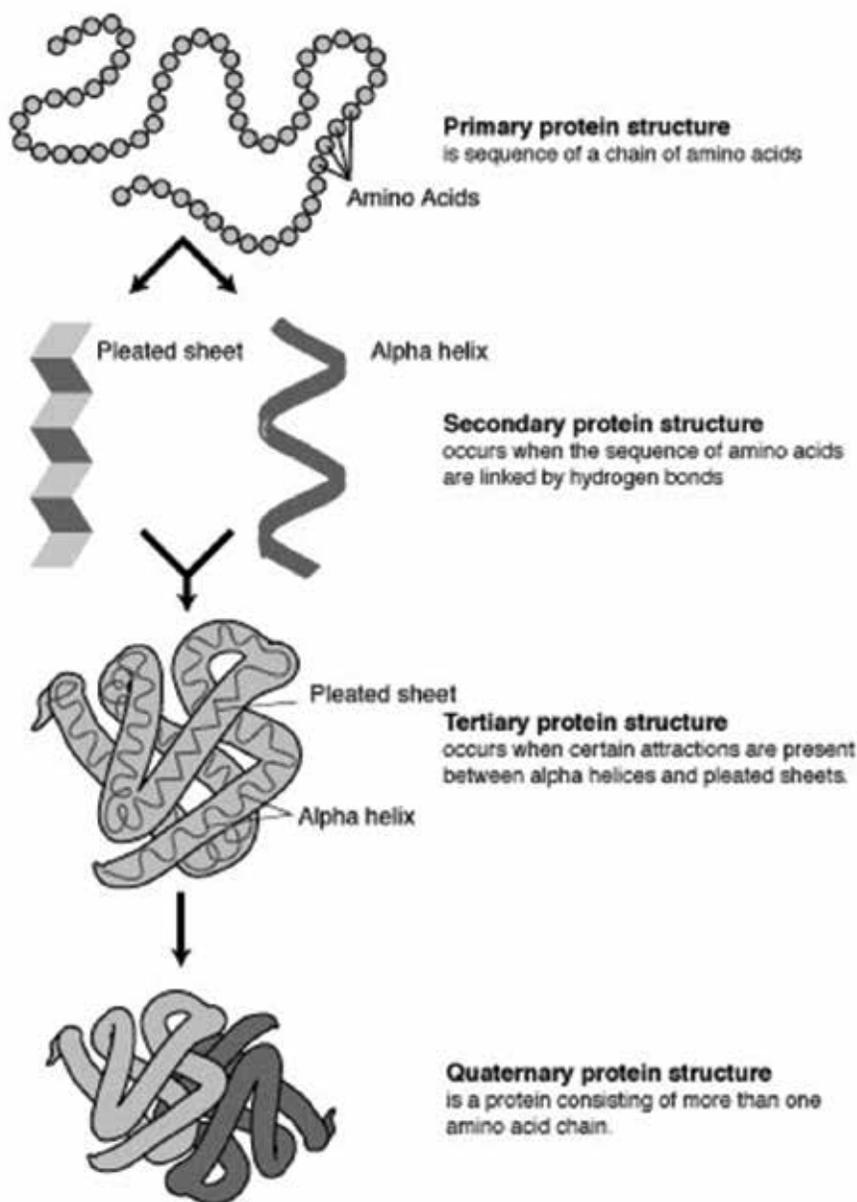
Figure 2: A graphic depiction of the “lock and key” model.

Image courtesy of Wikimedia Commons. Available at http://en.wikipedia.org/wiki/File:Protein_CD74_PDB_1tcf.png



and ion transport across cellular channels and membranes is a crucial application of MD in pharmacology (4). Molecular recognition and drug binding are dynamic processes, and, as discussed, when a small molecule or ligand encounters a receptor, it in no way resembles a frozen key fitting into a lock. Rather, the small molecules meet, and the receptors interact in constant motion in a vast collection of states. Only in rare cases are protein motions limited such that the lock and key model would paint a somewhat accurate picture. A protein seeks a state of lowest energy, creating the potential for ligand binding to restrict a larger probability distribution of states to a smaller subset to facilitate binding. This subset of states may not occur, or the sampling of this subset may be far less frequent in the absence of the ligand, highlighting another important potential for MD simulation to reveal structure

Figure 3: A diagram showing various protein structures.



and interaction on a representative timescale (8). In other words, the dynamic nature of receptor movement and ligand-receptor interaction are crucial to the binding of small molecule drugs, and several techniques have been developed to interpret information about the dynamic motions of proteins derived from MD simulations (9).

MD simulations are not limited to the particular structure and interaction of one receptor and its ligand. In some cases, MD simulation successfully revealed the potential drug target sites hidden in the limited “snapshots” generated by discrete data collecting techniques like NMR and X-ray diffraction (9). Perhaps one of the best examples of this phenomenon is HIV integrase. Initial experimental models had cast HIV integrase as an unsuitable target for structure-based drug design; however, in 2004 Schames et al. performed MD simulation of HIV integrase that revealed “a previously unidentified trench that was not evident from any of the available crystal structures” (9, 10). Its candidacy for structure-based drug design was later confirmed by X-ray diffraction, which revealed that known inhibitors do in fact bind to this dynamically hidden “trench.” The additional data gathered by MD simulation led to the development of the antiretroviral drug raltegravir, the first FDA approved HIV integrase inhibitor, by Merck & Co. (9). MD simulation accelerated the discovery of this drug by discovering structural details that real-world techniques failed to find, leading to an effective therapy that benefitted countless individuals.

Challenges to the success of MD

MD simulation is a dynamic tool whose success tool hinges on the accuracy and scale of both the time and size of the system studied (1, 8) The force field, a critical component to MD models, is one of the greatest hindrances to the advancement of MD. This particular limitation is twofold. In order for MD to provide greater insight into real-world systems and biochemical processes, the force field and its numerous parameters that attempt to model real-world systems must be refined continually (11). The accuracy of a simulation is measured by how well the parameters of the computer model reflect the complicated relationship of the forces acting on the system in the real world. Force fields are the most computationally intensive part of the simulations and tend to limit MD by constraints on time and computability. The billions of computations on every single atom in the system cannot be run accurately on a typical computer in a realistic time frame. Rather, computer clusters and supercomputers with immense parallel computing power are required to accomplish this daunting task (9).

Future Potential

MD simulations have potential beyond the discovery of new structure-based drug targets. New supercomputers have allowed for enormous advances in MD. One machine capable of accomplishing this task is the ANTON supercomputer, designed and constructed by D.E. Shaw Research in New York City, New York. This massive parallel supercomputer is capable of executing millisecond-scale MD simulations designed to use both parallel algorithms and special purpose logic to accelerate the calculations that dominate the time complexity for a typical MD simulation (12). Researchers hope that future progress in supercomputing and parallel processing will strip away the constraints in MD simulations described above (7).

Conclusion

The human walk is a common analogy in many discussions of molecular dynamics. Just as it is impossible to understand the motion of walking by observing a single stride, it is impossible to understand protein dynamics through a single protein conformation (9). This analogy can be extended to proteins and MD simulations and their importance in pharmacology: modeling a walk as freestanding movements in an isolated vacuum fails to describe the structural movements and interactions that occur with each step. In order to understand the nature of biological systems, it is crucial to examine processes on a microscopic level and timescale, and this feat is becoming increasingly possible through computer experimentation.

Although conventional laboratories have aided in our macroscopic understanding of molecules, computational methods and simulations have become increasingly important to our microscopic understanding and allowed for the interpretation of data generated by physical techniques. Physical techniques such as X-ray diffraction and NMR have been invaluable in understanding the chemical machinery that drives a protein's role in biological processes.

Experimental computer science deserves proper recognition for its central role for the incredible insight these methods provide to our growing understanding of macromolecule, however. The breakthroughs enabled by MD simulation and other computational methods helped validate expectations regarding drug design in terms of efficacy and effects of a pharmaceutical compound. Through the advent of technology that will allow MD simulations to be even more reflective *in silico* models of *in vivo* processes, MD simulation has the potential to meet high expectations for the future of macromolecular technology (1, 7). **D**

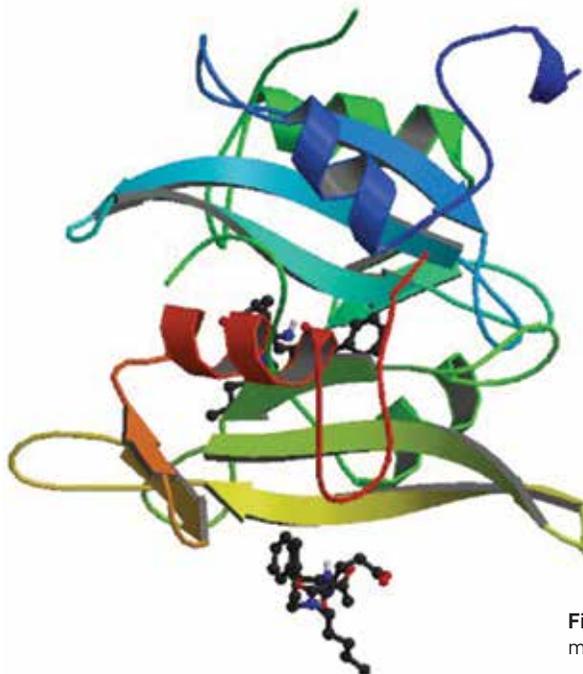


Figure 4: A protein folding model.

Image courtesy of Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3APBB_Protein_SRC_image.jpg

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A Probabilistic Bound on the Average Cumulative Regret for Bayesian Optimization

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Abstract

Bayesian optimization is a powerful technique for minimizing noisy and expensive functions. To characterize the theoretical behavior of Bayesian optimization techniques, we exploit certain properties of self-normalized martingales and derive a probabilistic bound on the average cumulative regret with respect to iteration size. We validate these results and discuss their significance in the context of line search optimization algorithms.

1. Introduction

Gaussian process regression is useful as a method of interpolating noisy data in order to predict the underlying function from which the data was sampled. Using the interpolation often provides computational efficiency over sampling the function itself. This interpolation is in turn useful for finding the minimum of a particular function f via a process known as Bayesian optimization.

Gaussian processes can be thought of as the generalization of a multivariate Gaussian distribution extended to infinite dimensions. It is a distribution over functions f where f is a map from some input space X to R , such that the marginal distribution over any finite subset of X is distributed according to a multivariate Gaussian distribution. We write,

$$f \sim \mathcal{GP}(\mu, k) \tag{1.1}$$

which means that the function f is distributed as a Gaussian process with mean function μ and covariance function k .

Using a Gaussian process to interpolate data, or Gaussian process regression, is a more flexible method of fitting data than for instance, linear, cubic, or even nonpolynomial fitting. Unlike these methods, it does not assume that the data follow a specific model.

The Bayesian optimization procedure used to find the minimum of a particular function f begins by sampling f with

zero-mean Gaussian noise at several points. From these points, a prior belief on the associated Gaussian process is established. We observe that the data is noisy and therefore wish to find the minimum of the function $E[f]$. The resulting Gaussian process has lower uncertainty at locations that have been sampled and higher uncertainty at unexplored regions. All subsequent points are then sampled based on some selection criterion, such as the location of maximum uncertainty or the location of maximum expected improvement for minimization. As new points are sampled, the Gaussian process is updated accordingly, producing an increasingly accurate interpolation. See Figure 1 for a pictorial illustration of the Bayesian optimization process.

This naturally raises the question: how close to the true minimum of $E[f]$ does the optimization get on a particular iteration n ? This is quantified by the difference between the true minimum value $E(f(t^*))$ and the value believed to be the minimum after iteration n , $f(t_n)$. This difference is the regret r_n which is written as

$$r_n = f(t_n) - f(t^*) \mid D_n \tag{1.2}$$

Note that we condition on the set of existing data D_n by the n iteration. For N total iterations, the cumulative regret and augmented cumulative regret are given respectively by,

$$R_N = \sum_{n=1}^N r_n \quad \text{and} \quad M_N = \sum_{n=1}^N r_n - (\mu(t_n) - \mu(t^*)) \mid D_n \tag{1.3}$$

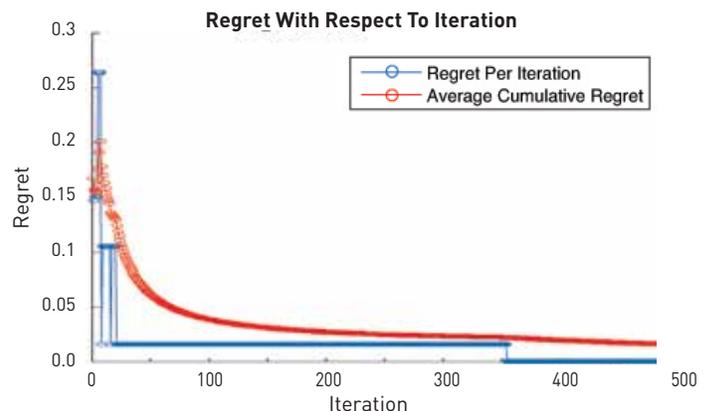
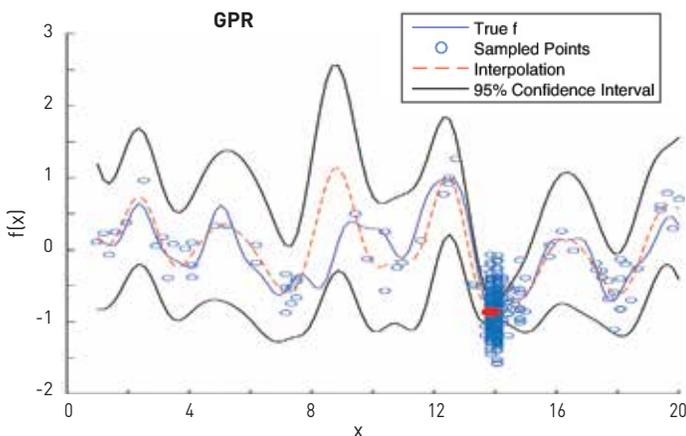


Figure 1: Notice that the interpolation is particularly accurate near the minimum of the function, where the majority of the points were generated.

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This paper will prove a probabilistic bound on the average cumulative regret of Bayesian optimization with respect to the number of iterations that have occurred:

$$\mathbb{P}\left[\frac{1}{N}R_N > \epsilon\right] = \exp(-\Omega(N)) \quad (1.4)$$

2. Proof of the Main Result

The proof relies on demonstrating that $(M_{N \setminus \text{NEIN}})$ is a particular type of martingale with properties that are crucial to the derivation of (1.4). We begin by presenting two relevant lemmas: that $(M_{N \setminus \text{NEIN}})$ is a martingale, and that $(M_{N \setminus \text{NEIN}})$ is both heavy on left and sub-Gaussian.

Lemma 2.1

$(M_{N \setminus \text{NEIN}})$ is a martingale with respect to its difference sequence:

$$Y_N = M_N - M_{N-1} = |r_N - (\mu_N(t_N) - \mu_N(t^*))| D_N \quad (2.1)$$

PROOF: Recall that the function f is distributed as the Gaussian process with some mean function μ and covariance function k : $f \sim \mathcal{GP}(\mu, k)$. Realizations of $(M_{N \setminus \text{NEIN}})$ are contingent on the Bayesian optimization procedure used to find the minimum of f . The key insight to understanding the GP update process is recognizing that f , conditioned on the presence of data by the N^{th} iteration D_N is a new Gaussian process: $f|D_N \sim \mathcal{GP}(\mu_N, k_N)$. It is easy, then, to see that $\mathbb{E}[Y_N | \{Y_n\}_{n=1}^{N-1}]$ can simply be written as:

$$\begin{aligned} \mathbb{E}[Y_N | \{Y_n\}_{n=1}^{N-1}] &= \mathbb{E}[r_N - (\mu_N(t_N) - \mu_N(t^*)) | \{Y_n\}_{n=1}^{N-1}, D_N] \\ &= \mu_N(t_N) - \mu_N(t^*) - (\mu_N(t_N) - \mu_N(t^*)) \\ &= 0. \end{aligned} \quad (2.2)$$

Crucially, we note that the conditioning on the existing data, D_N , causes the expectation of f to be μ_N . The variance can also be demonstrated to be:

$$\mathbb{V}[Y_N | \{Y_n\}_{n=1}^{N-1}] = k_N(t_N, t_N) + k_N(t^*, t^*) - 2k_N(t_N, t^*), \quad (2.3)$$

simply by computing the variance of $f(t_N) - f(t^*)|D_N$ which is the difference of two normally distributed random variables. Together, this shows that $Y_N | \{Y_n\}_{n=1}^{N-1}$ is zero-mean and normally distributed. Because this random variable has zero-mean, it can now be shown that $(M_{N \setminus \text{NEIN}})$ is, in fact a martingale:

$$\begin{aligned} \mathbb{E}[M_{N+1} | \{Y_n\}_{n=1}^N] &= \mathbb{E}[M_N + Y_{N+1} | \{Y_n\}_{n=1}^N] \\ &= M_N. \end{aligned} \quad (2.4) \quad (2.5)$$

This completes the proof.

Lemma 2.2

$(M_{N \setminus \text{NEIN}})$ is heavy on left, and sub-Gaussian.

PROOF: We say that a martingale is heavy on left if all its increments are conditionally heavy on left. The increments are heavy on left if it can be shown that

$$\mathbb{E}[Y_N | \{Y_n\}_{n=1}^{N-1}] = 0. \quad (2.6)$$

And furthermore,

$$\mathbb{E}\left[\min(|Y_N | \{Y_n\}_{n=1}^{N-1}|, a) \text{sign}(Y_N | \{Y_n\}_{n=1}^{N-1})\right] \leq 0, \quad (2.7)$$

for all $a > 0$. Because $Y_N | \{Y_n\}_{n=1}^{N-1}$ is a zero-mean Gaussian random variable, the above conditions are trivially true. The second condition (2.7) in particular can be shown by exploiting the symmetry of a zero-mean Gaussian distribution.

Additionally, we say that the martingale is sub-Gaussian if there exists some $\alpha > 0$ such that for all $n \geq 1$ and $t \in \mathbb{R}$:

$$\mathbb{E}\left[\exp\{t \cdot Y_N | \{Y_n\}_{n=1}^{N-1}\}\right] \leq \exp\left\{\frac{\alpha^2 t^2}{2} \mathbb{V}[Y_N | \{Y_n\}_{n=1}^{N-1}]\right\} \quad (2.8)$$

Since $Y_n | \{Y_i\}_{i=1}^{n-1}$ is zero-mean Gaussian, it has a well-defined moment-generating function that can be used to show that (2.8) is true when we take $\alpha = 1$, thus demonstrating that the martingale $(M_{N \setminus \text{NEIN}})$ is sub-Gaussian.

Theorem 2.1

We now prove the main result, demonstrating the rapid convergence of the average cumulative regret to zero:

$$\mathbb{P}\left[\frac{1}{N}R_N > \epsilon\right] = \exp(-\Omega(N)) \quad (2.9)$$

PROOF: There are many existing inequalities known for martingales which are self-normalized with respect to their quadratic variation. For sub-Gaussian, heavy on left martingale such as (M_N) , it is known that, for all values $x > 0$, $a \geq 0$, $b > 0$,

$$\begin{aligned} \mathbb{P}\left[\frac{M_N}{a + b \langle M \rangle_N} \geq x\right] & \\ &\leq \inf_{p>1} \left\{ \mathbb{E}\left[\exp\left(-\frac{x^2}{\alpha^2} \left(ab + \frac{b^2}{2} \langle M \rangle_N\right)\right)\right] \right\}^{\frac{1}{p}}, \end{aligned} \quad (2.10)$$

where α (in the case of $(M_{N \setminus \text{NEIN}})$, $\alpha = 1$) is the value used to satisfy the condition in (2.8) and $\langle M \rangle_N$ is the predictable quadratic variation, given by,

$$\langle M \rangle_N = \sum_{n=1}^N \mathbb{E}\left[\Delta M_n^2 | \{Y_i\}_{i=1}^{n-1}\right] = \sum_{n=1}^N \mathbb{V}[Y_n | \{Y_i\}_{i=1}^{n-1}]. \quad (2.11)$$

For notational convenience, we shall re-express $\sum_{n=1}^N \mathbb{V}[Y_n | \{Y_i\}_{i=1}^{n-1}]$ as $\sum_{n=1}^N \mathbb{V}_n$. To attain a form more amenable to our main result, we set the parameters to be $a = 0$, $b = N$, $\alpha = 1$:

$$\mathbb{P}\left[\frac{M_N}{N \langle M \rangle_N} \geq x\right] \leq \inf_{p>1} \left\{ \mathbb{E}\left[\exp\left(-\frac{x^2 N^2}{2} \langle M \rangle_N\right)\right] \right\}^{\frac{1}{p}}. \quad (2.12)$$

The internal expectation expression can quickly be reduced:

$$\mathbb{E}\left[\exp\left(-\frac{x^2 N^2}{2} \langle M \rangle_N\right)\right] = \exp\left(\frac{x^2 N^2}{2} \sum_{i=1}^N \mathbb{V}_n\right)^{1-p}. \quad (2.13)$$

Thus far, we have dealt purely with the augmented cumulative regret, (M_N) , exploiting the known properties of a self-normalized, heavy on left, sub-Gaussian martingale to arrive at the inequality demonstrated in (2.12). To derive an inequality with respect to the cumulative regret, we reduce the augmented cumulative regret into its components, $M_N = R_N - S_N$, where $S_N = \sum_{n=1}^N \mu_n(t_n) - \mu_n(t^*)$. It can now be stated that,

$$\mathbb{P}\left[\frac{R_N}{N} \geq x \sum_{n=1}^N \mathbb{V}_n + \frac{S_N}{N}\right] \leq \inf_{p>1} \exp\left(\frac{x^2 N^2}{2} \sum_{n=1}^N \mathbb{V}_n\right)^{\frac{1}{1-p}} \quad (2.14)$$

$$\leq \exp\left(\frac{x^2 N^2}{2} \sum_{n=1}^N \mathbb{V}_n\right)^{-\frac{1}{2}}. \quad (2.15)$$

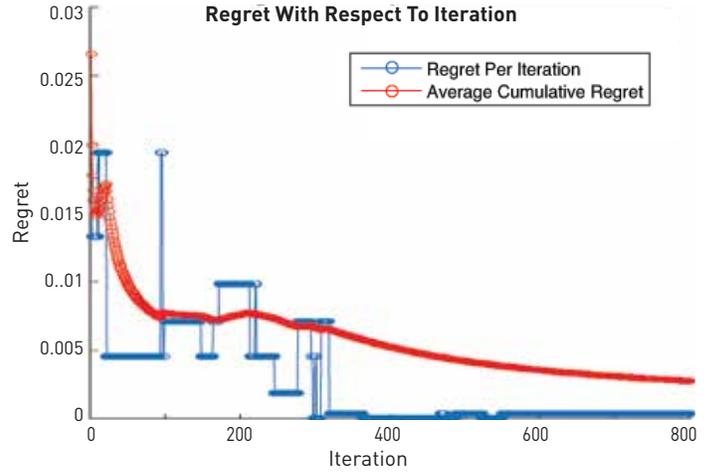
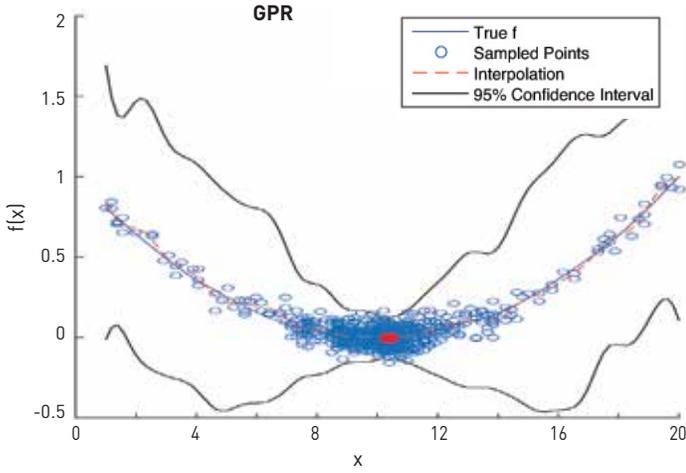


Figure 2: 800 iterations of the Bayesian optimization for a function drawn from a Gaussian process with mean $2(x-10)^2$ and squared exponential kernel.

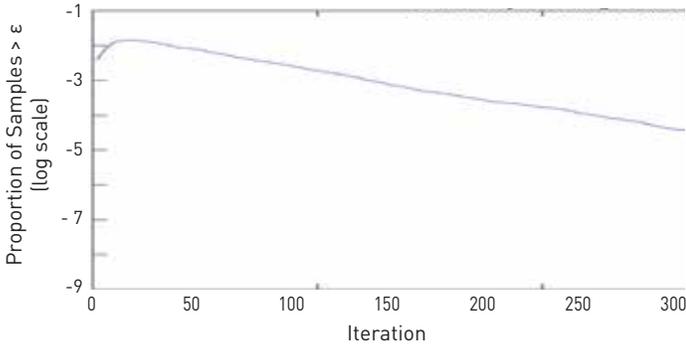


Figure 3: The linearity of the log-scale plot illustrates that the probability of the average cumulative regret being greater than some small ϵ indeed shrinks exponentially.

Setting $\epsilon = x \sum_{n=1}^N \mathbb{V}_n + \frac{S_N}{N}$, the derivation of the main result is completed:

$$\mathbb{P} \left[\frac{R_N}{N} \geq \epsilon \right] \leq \exp \left(\frac{(N\epsilon - S_N)^2 N^2}{2N^2 (\sum_{n=1}^N \mathbb{V}_n)^2} \sum_{n=1}^N \mathbb{V}_n \right)^{-\frac{1}{2}} \quad (2.16)$$

$$\leq \exp \left(\frac{S_N^2 - 2S_N N\epsilon + N^2 \epsilon^2}{2 \sum_{n=1}^N \mathbb{V}_n} \right)^{-\frac{1}{2}} \quad (2.17)$$

$$= \exp(-\Omega(N)). \quad (2.18)$$

This shows the desired result.

3. Empirical Results

To validate the theoretical results, we implemented a Bayesian optimization architecture and simulated the optimization process for 15,000 realizations of a Gaussian process with fixed prior mean and kernel function. The kernel function used was the squared exponential kernel,

$$k(x_i, x_j) = \sigma_y^2 \exp\left(-\frac{(x_i - x_j)^2}{2l^2}\right) + \sigma_n^2 \delta_{ij}, \quad (3.1)$$

where the hyperparameters $\theta = \sigma_n, \sigma_y, l$, were fixed to be the true parameters throughout the process. Notice that this condition would not affect the asymptotic behavior of the optimization and is therefore acceptable in this case.

Intuitively, the variable l describes the distance along the x -axis before which points become uncorrelated, σ_y controls the strength of correlation between data points, and σ_n illustrates the

belief of the amount of noise with which the data was sampled.

With 10% probability at any particular iteration, a random index was selected to sample, in order to prevent problems with being stuck at local minima. The prior mean selected for the trials was $2(x-10)^2$. The optimization procedure is illustrated in Figure 2.

We calculated the fraction of experiments at a particular iteration for which the average cumulative regret was larger than $\epsilon = 6e-3$. The result is illustrated in Figure 3, and empirically validates the main result. Bayesian optimization is able to fit many functions and converge on a value close to the minimum in relatively few iterations, which reflects its strength as an optimization method.

4. Conclusion

Our main result demonstrates the asymptotic behavior of the averaged cumulative regret with respect to iteration size. In particular, for any $\epsilon > 0$, the probability that the averaged cumulative regret is greater than ϵ decays exponentially. The fact that this probabilistic statement deals with the averaged cumulative regret suggests that the current cumulative regret converges even faster to zero. Thus, within a Bayesian optimization framework, our results demonstrate that the probability of finding the incorrect minimum goes to zero at a rate at or faster than exponential decay with respect to iteration (and thus sampling) size.

Bayesian optimization is particularly useful in line search, which is an iterative approach for finding the minimum of an objective function. It operates by first identifying a direction along which to reduce the objective function, and then determines step size for traversal along that direction. Bayesian optimization is a particularly useful technique for determining the step size. Our results demonstrate the theoretical asymptotic behavior of Bayesian optimization, validated by empirical evidence.

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TeamHEAL Fitness Challenge: A Pilot Study of Aerobic and Resistance Training Among Overweight High School Students in South Los Angeles

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Abstract

Sedentary behaviors among adolescents are leading to an increase in the prevalence of obesity. Adolescents that reside in urban environments are often at greater risk of developing obesity and obesity-related chronic conditions, because of limited opportunities to safely engage in physical activity. In response to these challenges, the TeamHEAL Foundation developed an after-school program to engage in moderate intensity exercise. The primary goal of the Fitness Challenge was to reduce obesity among adolescents in an urban high school in South Los Angeles, California using an exercise prescription for aerobic and resistance training. After 6-weeks of training, changes in body composition were observed, which supports the administrative feasibility and physiological effectiveness of aerobic and resistance training in a low resource setting with non-athletes.

Introduction

The high prevalence of obesity in adolescents shows no signs of decreasing and is a public health priority in the United States (1). Sedentary behaviors including high amounts of television watching, computer usage, and video gaming may be contributing to the high rates of obesity when such behaviors displace physical activity (2). The high levels of obesity in the adolescent population are driving rising levels of type 2 diabetes mellitus (T2DM) in this age group. Obesity and T2DM have been linked to vascular changes that increase the risk of cardiovascular disease and stroke (3). Certain racial groups, including African Americans and Hispanic Americans, have higher risk for developing T2DM as adolescents (4). Furthermore, obesity is also linked to adolescent hypertension (5). It is important to note that even if adolescent obesity doesn't cause these conditions in adolescence for an individual, it will dramatically increase their risk of obesity related diseases in midlife (6).

Given this increasing prevalence of obesity, T2DM, and hypertension among adolescents in the United States, the TeamHEAL Foundation developed the Fitness Challenge program to provide after-school opportunities to engage in moderate intensity exercise. The primary goal of the Fitness Challenge was to reduce obesity among adolescents in an

urban high school in South Los Angeles, California. A second short-term goal was to educate students on the importance of strength training exercises and proper nutrition.

Methods

Participant Recruitment and Informed Consent

The study design and instruments were reviewed and approved by the Loyola Marymount University Institutional Review Board (IRB #2013 SP 29) and by the Los Angeles Unified School District (LAUSD). The intervention was held during the spring at an urban high school within the LAUSD in South Los Angeles, California. The school provides free or reduced lunch to 93% of its students and the student body was 67% African-American and 32% Hispanic American at the time of the intervention. Students were recruited by announcements made using the school's public announcement system with an advertised incentive of an opportunity to visit the Los Angeles Lakers' training camp. Interested students were instructed to attend an information session, where the program was described by a Certified Athletic Trainer (ATC). Informed assent of the study participants was obtained in writing by the ATC after students were briefed on the physical activity intervention and the purpose of the study. Parental informed consent was obtained in writing via a form sent home with prospective student participants. Study participants did not receive academic credit or financial compensation for their participation.

Exercise Prescription

The exercise prescription was designed for implementation under the supervision of an ATC. Exercise sessions were offered three times a week and after school as 60-minutes of aerobic and resistance training. Each session began with an aerobic

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Table 1: Fitness Challenge exercise prescription for aerobic and resistance training

Aerobic Exercise		Progression for Non-Timed Exercises	
<i>Dynamic Warm-up</i>	<i>Track Program</i>	Week 1	3 sets of 8
Knee-chest for 10 yds	200m Warm-Up Walk	Week 2	3 sets of 10
Windmills for 10 yds	Stretching Series	Week 3	3 sets of 12
Walking hip rotation for 10 yds	Timed Walk	Weeks 4-6	3 sets of 15
	Competitive play: dodgeball, sack races, capture the flag		
Resistance Training			
	<i>Phase 1</i>	<i>Phase 2</i>	<i>Phase 3</i>
<i>Upper Extremity</i>	Dynamic Hugs with red Thera-band	Dynamic Hugs with green Thera-band	Dynamic Hugs with blue Thera-band
	Wall Push Ups	Knee push ups	Full push ups
	Rows with green Thera-band	Rows with blue Thera-band	Rows with black Thera-band
	Bicep Curls	Bicep Curls	Bicep Curls
<i>Lower Extremity</i>	Wall sits 3 x 15 seconds with Thera-band at knees	Wall sits 3 x 25 seconds with Thera-band at knees	Wall sits 3 x 35 seconds w Thera-band at knees
	Quadruped with hip abduction	Quadruped with hip abduction	Quadruped with hip abduction
	Bridges	Bridges with swiss ball	Bridges with swiss ball, alternating legs
	Side steps with red Thera-band at knees	Side steps with red Thera-band at ankles	Side steps with green Thera-band at ankles
<i>Core</i>	Superman's	Alternating Superman's	Alternating Superman's with 10 sec holds
	1/2 Planks 3 x 15 seconds	1/2 Planks 3 x 25 seconds	Full Planks 3 x 15 seconds
	Kick backs in quadruped	Alternating reaches quadruped	Alternating reaches with 5 sec hold

warm up followed by alternating bouts of aerobic exercise and resistance training. Aerobic exercise was prescribed to raise participant heart rates to a target zone of 70-85%. Resistance training included upper extremity, lower extremity, and core components (Table 1). The exercise difficulty and intensity increased weekly for 6 weeks through the use of higher repetitions, more strenuous anaerobic techniques, and more intense speed demands during the aerobic components.

Data Collection and Analysis

Demographic data was collected by survey. Surveys were mailed to parents of participants to assess race/ethnicity, occupation, education, presence of chronic medical conditions among the parent, and presence of chronic medical conditions among the participant. Students also completed a survey detailing demographic information, their method of transit to school, nutritional habits, and current physical activity levels. Body composition of participants was evaluated at baseline and post-intervention time points manually with a digital scale and stadiometer, and also with a Biospace InBody720 analyzer (Biospace, Cerritos, CA). Each week, the ATC documented

attendance and measured each participant's weight using a digital scale and blood pressure using a stethoscope and sphygmomanometer.

To assess dietary intake, each participant was asked to register and utilize My Fitness Pal. This is an online system with a database of over three million foods that will calculate and track caloric intake based on user input of food type and quantity. It allows for syncing real-time food diaries across phone and computer applications. My Fitness Pal allows both the participant and the study team to track types of food consumed, consumption itemized by time, total caloric intake, and trends in food consumption.

Results

Recruitment and Participation

Initially, 20 students provided assent forms and completed initial surveys. However, an unexpected administrative delay in receiving study approval led to a large decrease in willingness to participate. Ultimately, ten students participated in baseline data collection, seven participated regularly in the activity intervention, and five were present for both baseline and post-

Table 2: Demographics and behaviors of survey respondents and participants

All Initial Survey Respondents (n=21)				Participants (n=7)			
	<i>n</i>	<i>%</i>			<i>n</i>	<i>%</i>	
% Female	13	62%		% Female	2	29%	
Age				Age			
19	3	14%		19	0	0%	
18	5	24%		18	1	14%	
17	5	24%		17	1	14%	
16	7	33%		16	5	71%	
15	1	5%		15	0	0%	
Grade Level				Grade Level			
12	6	29%		12	0	0%	
11	5	24%		11	1	14%	
10	5	24%		10	5	71%	
9	5	24%		9	1	14%	
Race/Ethnicity				Race/Ethnicity			
African American	17	81%		African American	6	86%	
Hispanic	2	10%		Hispanic	1	14%	
Other (non-Caucasian, non-Hispanic)	2	10%		Other (non-Caucasian, non-Hispanic)	0	0%	
Report athletic participation	13	62%		Report athletic participation	4	57%	

All Initial Survey Respondents (n=21)					Participants (n=7)			
	<i>n</i>	<i>Average</i>	<i>SD</i>	<i>% report</i>		<i>n</i>	<i>Average</i>	<i>SD</i>
Physical Activity [min/day]	16	155	112	0%	Physical Activity [min/day]	6	202	161
TV Watching [min/day]	13	107	77	5%	TV Watching [min/day]	4	78	53
Computer Usage [min/day]	15	92	87	5%	Computer Usage [min/day]	4	90	73
Lunches [meals/week]	18	4	2	20%	Lunches [meals/week]	6	5	3
Breakfast [meal/week]	21	3	3	25%	Breakfast [meal/week]	7	2	3

intervention body composition analysis.

Initial Survey Data: Comparison of Survey Respondents and Intervention Participants

There was poor response from parents with regard to completion of surveys. Therefore, no results are available on parental occupation, education, or presence of chronic medical conditions among the parents or students. Twenty-one pre-intervention surveys were completed by students. During the two-month delay that separated recruitment and survey completion from the beginning of the intervention, the proportion of female students willing to participate declined dramatically (Table 2). Less than 20% of the female students that initially expressed interest in participating remained in the study. However, over 50% of the male students initially interested in participating were retained. Retention was 100% among sophomores but less than one percent of freshman, juniors, and seniors remained interested in participating. There were no noticeable differences in the percentages of African American and Hispanic American students in the survey group as compared to the intervention group.

The self-reported values of time spent in physical activity, watching television, and using a computer varied widely (Table 2). The participant group reported higher, although not statistically significant, levels of daily physical activity, lower levels of television watching time, and comparable computer usage. Participants reported slightly higher lunch consumption frequency but slightly lower breakfast consumption frequency.

Body Weight

No statistically significant changes were observed among the intervention participants; however, a majority of the participants did experience weight loss. The average weight loss was 2.4 pounds (SD = 4.86 pounds).

Body Composition Analysis

After the intervention, all participants with baseline and post-assessment body composition data experienced increases in percent lean muscle mass (average increase = 1.27%) and decreases in percent body fat (average decrease = 1.46%). Moreover, a majority of these participants had an increase in basal metabolic rate. Of those participants who experienced an

increase in basal metabolic rate, the average increase was 57 kcal/day (SD=32 kcal/day).

Blood Pressure

The Centers for Disease Control and Prevention (CDC) Task Force on Blood Pressure Control in Children's has put forth diagnostic criterion for pre-hypertension or hypertension in Children and Adolescents (7). Of the seven participants with baseline and post-intervention blood pressure readings, six participants (85%) met the CDC's diagnostic criterion for pre-hypertension or hypertension at the beginning of the intervention. One participant was pre-hypertensive, one participant was stage I hypertensive, and four participants were Stage II hypertensive. One participant experienced a resolution of Stage II hypertension to a normal blood pressure over the course of the intervention.

Discussion

It is very encouraging that measurable decreases in percent body fat and increases in lean muscle mass were observed in a small, 6-week pilot study. Moreover, the relative lack of change in participants' weight is consistent with the inadequacy of weight as a marker of body composition. The inclusion of such a high proportion of hypertensive students was not intentional but likely reflects the high co-prevalence of adolescent hypertension and obesity. This study's small size and short duration limit the opportunity to evaluate the effect of exercise on adolescent blood pressure. However, it can be inferred that improvements in cardiovascular health would accompany decreases in obesity.

It is not possible to determine whether the students who choose to fully participate were abnormally unhealthy relative to their classmates. It is possible that there was selection bias and that a particularly unhealthy group of students self-selected to participate. However, if this is the case, then it is likely that the benefits of the study were optimized by the inclusion of those adolescents most in need of an activity intervention.

Reported unhealthy habits of the participants and the initial survey group include daily television watching of an average of 90 minutes and high frequencies of meal skipping including very low numbers of breakfasts consumed per week. These habits could directly contribute to the observed rates of obesity and hypertension. Additionally, reported levels of computer usage, television watching, and extracurricular involvement might be a proxy indicator for low sleep levels. Sleep contributes dramatically to appropriate weight control, mental wellness, and adequate appetite regulation. It might be useful in future studies to ask participants to report their average daily sleep.

The differences between the intervention participants and the originally recruited survey group are difficult to explain. The markedly lower female student retention could perhaps

be related to higher social stigmatization of weight among female adolescents. It could also be a group social effect, if the large group of females who did not return are all in the same social group. One person's decision to not participate could have influenced the other participants. The high retention of sophomores might be a reflection of increasing extracurricular commitment of upper classmen. Students who had competing extracurricular activities immediately after school would have difficulty attending the activity intervention.

The self-reported levels of daily physical activity are intriguing. Few of the reported daily values are realistic time quantities to engage in vigorous exercise. It is likely that the students' understanding of what constitutes physical activity differs markedly from the level of activity necessary to promote metabolic and cardiovascular health. The unrealistically high reported levels of activity might also be related to the difficulty of accurate recall and generalization of weekly routines to average daily quantities. More specific questions that ask students to recall specific episodes of activity and the corresponding length of activity might help students accurately communicate their daily activity level.

In summary, this study suggests that a return to a school-based focus on physical fitness attributes, such as cardiovascular endurance and muscle strength, may be effective in addressing the prevalence of obesity among adolescents in a short period of time. Although some school-based programs promote increased movement, we would suggest that schools consider structured programs that strategically include aerobic exercise and resistance training for non-athletes.

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