Volume 25 Spring 2013

Massachusetts Institute of Technology Undergraduate Research Journal

Metakaryotic biology: the study of stem cellsp. 16Biomechanical properties of the corneap. 22Global warming and conflict in Sudanp. 35



We wish to thank MIT Research Scientist Felice Frankel, from the Center for Materials Science and Engineering, for giving us permission to use our cover image.



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UROP Summaries

Exploring molecular physics and quantum chemistry with 23Na6Li molecules Derek Kita



In the past few decades, advancements in atom cooling technology have allowed for the study of atoms. Forming low energy 23Na6Li molecules opens up the possibility to study rich systems of many interacting molecules. Such techniques can be applied to chemically reactive systems to study quantum chemistry in its purest, simplest form.

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Reviews

Biomechanical properties of the cornea and their use to detect and treat keratoconus



Ebaa Al-Obeidi, Colleen Meehl, Clara Park

One in every 2000 Americans suffers from keratoconus, the most common corneal disorder in the United States. In keratoconus, the cornea becomes thinner and protrudes outward in the shape of a cone, causing severe astigmatism and blurriness. The detection of this disorder is extremely difficult because there are no biochemical markers that can be used to diagnose it before it worsens. It is known, however, that the cornea possesses unique biomechanical properties due to its dual function as the eye's transparent window and tough mechanical shield, providing rigidity and protection from infection. Thus, the critical questions we are trying to answer include: How can the biomechanical properties of the cornea be used to distinguish between a keratoconus and a healthy cornea? What tools will be needed to measure these properties? How can these properties be used to develop a tissue-engineered treatment?

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Reports

E. coli growth phase distinction via three-dimensional insulatorbased dielectropheresis Brian Djaja, Camille Richman, Cullen R. Buie



In three-dimensional insulator-based dielectrophoresis (3D-iDEP), an electric field is applied across a microchannel through platinum electrodes. A constriction in the channel induces a field gradient, which causes trapping of particles or cells, in this case E. coli, based on differences in cell. This method is employed to observe differences in trapping behavior of E. coli at various growth phases. Preliminary data have shown that bacteria experience contrasting dielectrophoretic responses according to growth phase, demonstrating the potential to distinguish between growth phases or even sort bacteria accordingly.

Link between global warming and conflict in Sudan: from sea surface temperature to regional variation in rainfall to conflict Roshan Ardhasseril

There are correlations between global warming and rainfall in Sudan and between rainfall in Sudan and conflict. Studies of the effects of drought on population indicate a resulting increase in the scope and variability of internal migration patterns. With the past and current evidence of migration, combined with the expected average global temperature rise, an increase in both incidence and intensity of conflict is probable. Where fertile and arable land is marginal at best, these factors can combine and result in conflict; the past conflict in Sudan can be linked to a changing climate and future conflict is highly probable due to the very same. In other words, global warming may become one of the triggers for conflict in Sudan.

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Letters

Massachusetts Institute of Technology

UNDERGRADUATE RESEARCH JOURNAL Volume 25, Spring 2013

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MURJ Staff MIT Undergraduate Research Journal

1117

Massachusetts Institute of Technology murj.mit.edu

May, 2013

We are thrilled to present to you the 25th issue of the MIT Undergraduate Research Journal. It has been a pleasure to work alongside hard-working staff to be able to present this issue to you today. The outstanding work of the undergraduate researchers in this issue is evident in their numerous findings that will no doubt make a positive impact on the MIT community and the scientific community at large.

The feature articles in this issue include <J-Pal>, <Science for everyone>, both written by outstanding MURJ staff. Research presented in this issue ranges from considering the biomechanics of the cornea to examining the link between global warming and the conflict in Sudan.

We would like to thank all of the student researchers, authors and editors for their tireless work on this issue and hope you enjoy.

Best,

Ebaa Al-Obeidi (Co-Editor-in-Chief)

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Science News In Review

MEDICINE

Is it True? A Baby Believed to Be Cured of H.I.V.

standard cure for the H.I.V. Avirus has been thus far elusive to researchers and doctors, though reports have indicated some progress towards a possible solution. The first major milestone came with the Berlin patient, Timothy Brown, who was the first person to be cured of H.I.V. after he received a bone-marrow transplant from a donor genetically resistant to the H.I.V. infection. The second major milestone may have come from the work of Dr. Hannah B. Gay, an associate professor of pediatrics at the University of Mississippi Medical Center, Dr. Deborah Persaud, an associate professor at the Johns Hopkins Children's Center, and other researchers who have deemed to cure a baby of the H.I.V virus.

ies per milliliter, fairly low for a baby. Dr. Gay immediately started treatment without waiting for test results to confirm infection. The drug treatment continued until the baby was 18 months old, by which time virus levels had quickly declined and were almost undetectable. At 2 ¹/₂ years old, the child has no sign of the lethal virus.

While these results appear promising, many outside researchers are skeptical because there is no definite evidence that the virus had established a hidden reservoir in the baby, meaning that there is no way to tell if the baby was actually infected. Dr. Persaud, however, remains hopeful that further studies to replicate this case can provide the needed boost to research aimed at finding a cure for H.I.V, something that was thought be almost impossible only a few years ago.

—L. Subbaraj

Source: http://www.nytimes. com/2013/03/04/health/for-firsttime-baby-cured-of-hiv-doctors-say. html

Breakthrough Prize in Life Sciences

Two MIT Professors, Dr. Eric Lander and Dr. Robert Weinberg, have been awarded the Breakthrough Prize in Life Sciences in February. The award was founded this year by Google co-founder Sergey Brin, '23andme' co-founder Anne Wojcicki, Facebook founder

and CEO Mark Zuckerberg, and Russian entrepreneur and philanthropist Yuri Brin. Dr. Lander and Dr. Weinberg were one of 11 life scientists to be honored for their research and were awarded \$3 million each, a sum that is double that of the Nobel Prize.

Both life scientists and MIT Professors have contributed to significant research in biology, and notably, they have together taught 7.012 Introduction to Biology to MIT undergraduates for many vears. Dr. Lander is a leader of the Human Genome Project and founding director of the Broad Institute of MIT and Harvard. Dr. Weinberg is a founding member of the Whitehead Institute and was the first scientist to discover the human oncogene, a gene that can cause cancer. In a New York Times interview, Dr. Lander stated that he hopes to use the prize to help pay for methods to teach biology online the prize grabs "society's attention, to send a message that science is exciting, important, cool, our future."

—J. Kang

Source: http://news.sciencemag.org/scienceinsider/2013/02/new-breakthrough-prize-awardsmi.html

The Sobering Pill

The sobering pill may provide an easy way to become sober in a short period of time. It is a tiny capsule with two complementary enzymes that speed up the elimi-



Scientists have developed a new pill which may provide an easy way to become sober in a short period of time.

Credit: http://pazoo.com/blog/wp-content/ uploads/2013/03/pills.png



Researchers believe that they may have cured, for the first time, a baby of HIV. Credit: http://www.popsci.com/files/imagecache/article_image_large/ articles/HIV.jpeg

In this report, a baby born in rural Mississippi was treated with a three-step antiretroviral drug regimen about 30 hours after birth in response to a test that showed a level of virus at about 20,000 cop-

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IPS Skin Cells to Brain Cells: Road to Treat Parkinson's With Personalized Medicine

Each year, the movement disorder Parkinson's disease is diagnosed in about 60,000 patients and afflicts up to 1 million Americans. With the need for treatment and personalized medicine growing, the Parkinson's Disease Foundation funded a study held at the University of Wisconsin-Madison, where scientists transplanted neural cells grown from a monkey's skin cells into its brain.

In this study, rhesus monkeys with a lesion in the brain that causes movement disorder in Parkinson's were used. The transplanted neural cells were derived from induced pluripotent stem cells (iPS cells), which can develop into almost any type of cell in the body. Su-Chun Zhang, a professor of neuroscience at UW-Madison, was the first in the world to derive neural cells from iPS cells and says the success is based on the control over the whole development process.

Six months after these neural cells were implanted in the monkey's brain, the brain graft could not be seen by the naked eye and the cells looked entirely normal. In addition, no signs of cancer appeared, which is always a potential effect of stem cell transplants. Because the skin cells did not come from foreign tissue, no negative immune response was triggered, leading to possibility

nation of alcohol from the body, thus processing alcohol with essentially the same mechanisms the liver employs. This allows the body to temporarily function as though it had multiple livers.

The pill is meant to function as a preventative measure, as well as an antidote for alcohol intoxication. The primary enzyme is alcohol oxidase, which oxidizes alcohol and



The generation of brain cells from induced pluripotent stem cells hold great promise for treatments for Parkinson's disease. Image courtesy Yan Liu and Su-Chun Zhang, Waisman Center, University of Wisconsin–Madison)

of personalized medicine to treat specific diseases like Parkinson's with this method.

Although this study represents a step forward in the direction for treatment of diseases, the transplant technique is far from clinical trials. Researchers are optimistic about conducting further studies to determine if this transplant will improve symptoms, if there are any side effects, and if the treatment will last. Even with more work in the future, this study by itself kindles a hope for personalized regenerative medicine. —L. Subbaraj

Sources: hhttp://www.sciencedaily.com/ releases/2013/03/130314124605.htmfat/254087/; http://www.ajcn.org/content/early/2012/01/17/ ajcn.111.026328

produces hydrogen peroxide which is very reactive and can have toxic effects to the host's body. The secondary enzyme is catalase, which decomposes the toxic hydrogen peroxide into water and oxygen, effectively removing alcohol.

These enzymes are placed in a polymer capsule with a diameter of approximately ten nanometers, the wall of the polymer capsule being only one nanometer thick. To put this size into perspective, this is about 100,000 times thinner than a strand of human hair. The capsule protects the enzymes and allows them to freely enter an alcohol molecule, mimicking an organelle.

These capsules have been tested on mice, and the blood alcohol levels of those that received the enzyme packages fell much more rapidly than those that did not, regardless of whether it was taken with or after alcohol consumption.

Once the barrier of localization has been surmounted, this technology may be implemented for a much greater range of applications, because of the existence of numerous enzymes and their many effects that can really impact illnesses and other complications in a positive way.

-R. Park

Source: http://www.sciencedaily.com/ releases/2013/02/130220114337.htm

NEUROSCIENCE

Real-time Transfer of Sensorimotor Information via a Novel Brain-to-Brain Interphase

Researchers at Duke University Medical Center have developed a novel brain-to-brain interface (BTBI) that allows for the real-time transfer of behavioral sensorimotor information between the brains of two rats. In a study published in Nature this past February, intercortical microstimulation (ICMS) was used to transmit certain cortical activity of an "encoder rat" to a "decoder rat", allowing the decoder rat to learn to make similar behavioral choices using only these ICMS, and without any training. This study was significant in that not only was communication established only using brain activity signals, but also

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www.nytimes.

com/2013/03/01/sci-

ence/new-research-

suggests-two-ratbrains-can-be-linked.

html?ref=science&

tant future.

Sources:

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computers",

"organic

suspects

-D. Penny

http://

human



Brain signals in one rat are transferred to another using BTBI technology.

Credit: http://www.awaken.com/wp-content/uploads/2013/03/btbi.jpg

in that this BTBI allowed for a feedback loop between the rats.

Electrodes were placed in the encoder rat's primary motor cortex, and stimulating electrodes were then placed in corresponding areas in the decoder rat. The encoder rat then went through thorough reward training to learn to press certain levers in response to light. As the decoder rat learned only from the encoder rat's signals, the BTBI creating a feedback loop between the rats. Because the encoder rat was also rewarded if the decoder rat correctly pressed the lever, the encoder rat became increasingly accurate, and its brain activity patterns became clearer. Although how exactly the decoder rat applied these neural stimuli is not clear. the study has potential to be applicable to rehabilitation from stroke, Parkinson's, motor neuron disease, and more. These BTBIs can be further studied to allow for the development of more complex networks of information sharing between animals. Additionally, they show great promise in the development of biological computing mechanisms and in the study of social interactions. Senior author Miguel Nicholelis projects that this technology can lead to "brain nets", which may lay

ENERGY

Little Tubes, Big Current

team of scientists in Paris has Arecently developed a new nanotube-based system that may lead one day to the generation of electricity using only water and salt. The process relies on the difference in salt concentration between a reservoir of fresh water and a reservoir of salt water connected by boronnitride nanotubes embedded in a membrane. Charged particles from the salt water move through the nanotubes to equalize the salt concentration in the reservoirs, creating a current that can be converted into useful electrical energy. The current produced by the newly-designed



Scientists in Paris have developed a new nanotube-based system for generating electricity. Credit: http://images.sciencedaily. com/2013/02/130228093509.jpg

boron-nitride nanotube membrane far surpasses results generated by other types of membranes, giving new hope to renewable energy researchers attempting to develop osmotic power generators. Osmotic power generation, which harnesses the energy stored in concentration gradients, can potentially harness the energy stored in the differences in salt concentration among naturally-occurring bodies of water. Scientists estimate that approximately 1 terawatt, or 1 million megawatts, of energy is stored in osmotic potential on the Earth's surface. These new nanotubes have the capacity to capture and use some of this vast energy source, and could become part of a green energy device in the future.

—D. Van Egeren

Sources: http://www.sciencedaily.com/ releases/2013/02/130228093509.htm

HEALTH

Genetic Test More Accessible to Patients and Families

The newest advances in genome sequencing have already begun to directly impact the lives of individuals and families affected by rare genetic diseases. The cost of sequencing all the genes in a patient and searching through the sequence for disease-causing mutations has plummeted over the past decade. An analysis of this type now costs between \$7000 and \$9000, and is now accessible to many families struggling with an undiagnosed genetic disease. The test can determine whether there are mutations in a person's DNA that explain the symptoms the person is experiencing, allowing doctors the chance to treat the patient's specific disorder properly. Genetic sequencing can even detect diseases that are so rare and difficult to diagnose that only a handful of confirmed cases are documented. However, not all patients

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who turn to genetic sequencing are found to have a known genetic disorder; only about 25 to 30 percent of patients who choose to be tested receive a diagnosis. Even after a successful diagnosis, many of the most severe and least common genetic diseases lack effective treatments, and managing complex and debilitating symptoms is often a lifelong challenge for these patients. Despite these limitations, this progress in genetic sequencing still holds promise for many families and will no doubt stimulate future study of genetic disorders.



Is the obesity epidemic easing up? Credit: http://yourpureinvention.com/wp-content/ uploads/2012/07/Apple.jpg

-D. Van Egeren

Sources: http://www.nytimes.com/2013/02/19/ health/dna-analysis-more-accessible-than-everopens-new-doors.html?ref=science&_r=0



Genetic tests are now more accessible to patients and families.

Credit: http://www.genomesunzipped.org/wp-content/uploads/2011/01/ iStock_000002259918XSmall.jpg

Is the Obesity Epidemic Easing Up?

A new federal study has found that children in the U.S. consumed fewer calories in 2010 than in the previous decade. In recent years, the national obesity rates for children have been stable, though the obesity rates for children in several cities have declined. Among the evidence is the amount of carbohydrates, protein, and fats that children consumed. Many attribute carbs – which include the sugars added to sodas and cereals - to the childhood obesity epidemic. This new study revealed that there was a slight drop in carbohydrate consumption among children.

Conversely, protein consumption increased. Fat consumption remained stable. The evidence that children now consume fewer calories overall may suggest that there is a general national trend.

As for adults, their calorie intake hasn't changed considerably in recent years, but studies show that they are eating less fast food. Obesity rates for adults have leveled off after increases for many years; currently, one-third of adults are obese.

According to health experts, the results suggest that the obesity epidemic may be easing, though, currently, the magnitude of the downward trend is too small in comparison to the general prevalence of obesity. More years of data would be required to determine if this downward trend is long-term and significant.

—L. Jiang

Sources: http://www.nytimes.com/2013/02/21/ us/children-in-us-are-eating-fewer-calories-studyfinds.html?ref=science

MEDICAL TECHNOLOGY

Demand for Ear Implants May Be Effectively Met by 3D Printing

ricrotia is a birth defect in which the external ear is underdeveloped, affecting 1 in 6,000 to 12,000 births. Current forms of treatment include surgical reformation of the semblance of an ear by harvesting the child's rib, implantation of a polyethylene implant that is covered with a skin graft, and attachment of an ear prosthetic that is taken off every night during sleep for the rest of the child's life. These options are invasive and painful for the child, but their options may soon increase for the better. Bioengineers have begun molding ear implants using 3-D printers. Dr. Lawrence Bonassar from Cornell University describes the process as designing a digital 3-D image of a human subject's ear, and assembling a mold with a 3-D printer which is injected with collagen derived from rat tails. 250 million cartilage cells derived from cow ears are added to the mold with the collagen serving as a scaffold upon which the cartilage can grow.

"The process is also fast," Bonassar added, "It takes half a day to design the mold, a day or so to print it, 30 minutes to inject the gel, and we can remove the ear 15 minutes later. We trim the ear and then let it culture for several days in nourish-



Scientists can now use a 3D printer to mold and create ear implants. Credit: http://www.microtia.net/surgical-options.htm

Discount Drug Program Dispute

The idea of requiring pharmaceutical companies to give hefty discounts to hospitals and clinics that treat low-income and uninsured patients seems marvelous. It has the potential to transform healthcare in many regions of the United States. This idea, which led to creation of the federal program 340B in 1992, however, is great in theory. In reality, the program has stirred up controversy and is now the focal point of a battle between the pharmaceutical industry and the hospitals.

The 340B is a federally mandated program that requires most drug companies to provide discounts from 20 to 50% usually to hospitals and clinics that treat low-income and uninsured patients. This also means that hospitals can treat patients with Medicare or private insurance. In fact, hospitals can pocket the difference between the reduced price they pay for the drug and the money that they are reimbursed by the insurance companies. The hospitals are essentially profiting from the 340B program, contradicting their nonprofit nature.

The program now includes about one-third of the nation's hospitals, which is three times as many as the number of hospitals in 2005. Through the program, approxi-mately 2% of the nation's total drugs, roughly worth \$6.9 billion, are sold. This significantly reduces the profit of pharmaceutical companies by hundreds of millions of dollars each year. Sales are projected to reach approximately \$12 billion by 2016 due to the new healthcare laws. which increase the number of eligible hospitals for the discounts by increasing the number of Medicaid patients they treat. This is somewhat counterintuitive as the laws are meant to reduce the number of uninsured patients in the nation.

Some hospitals are defending 340B; for them, this helps treat more patients, not just provide

cheap medication. The revenue they gain aids in keeping the hospitals operating sufficiently and that in turn helps hospitals address and treat a greater number of needy patients. With the 340B program, the Columbus Regional Healthcare System in western Georgia was able to establish and sustain their outpatient cancer center, a feat that would not have been possible without the extra federal resources. However, Safety Net Hospitals for Pharmaceutical Access, which is the organization representing 340B hospitals, have warned companies helping hospitals run the discount programs against using terms such as "increasing profits" and "revenue enhancement."

At the core of the issue is the fact that federal oversight of this program in ensuring that both the hospitals and the drug companies were following the rules and regulations has been inadequate, as indicated by a 2011 report released by the Government Accountability Office.

After the question was raised, the Health and Services Administration responded by auditing 51 hospitals last year, the first time since the inception of the program. It also asked hospitals to reconfirm their eligibility for the program. As a result of the review, 271 treatment sites from 85 different hospitals were disqualified from the program. Drug companies such as Genentech are also either auditing or considering auditing in order to maintain their profit. However, no drug companies are being audited, even though some have been found to not be providing the full discounts.

There is a lot of money at stake for drugs and pharmaceutical companies. As a result, a niche has opened up for certain companies that have capitalized on this fact. These com-



Many claim that the 340B, despite its admirable goals, is being abused by hospitals profiting from the new program. Credit: http://consumernews.com/wp-content/uploads/2012/08/ money-and-drugs-426x2821.jpeg

panies are now creating programs that aim to help hospitals optimize their savings.

In 2010, the use of 340B rose significantly. The government permitted hospitals to use any neighborhood pharmacies to fill the 340B prescriptions. Prior to that, patients were restricted to the hospital pharmacy, which was inconvenient. Since then, according to Health Resources and Services Administration, about 25,000 arrangements between treatment sites and pharmacies have been established.

Patients can now receive drugs at little or no cost. However, if the patients are insured, the hospital pockets the difference between the discounted price it pays for the drugs and the higher price paid by the insurer and pays the local pharmacies a fee for dispensing the drugs, thereby instigating a "revenue-capture game." However, the actions that Congress will take to tackle this problem are still unclear. These actions will not only impact the hospitals and drug companies, but more importantly, will also affect the patients who are in need of the treatments.

-S. Islam

Sources: http://www.nytimes.com/2013/02/13/ business/dispute-develops-over-340b-discountdrug-program.html

ing cell culture media before it is implanted."

The implication of this research not only affects ear replacements, but the replacement of any human structure primarily composed of cartilage, such as joints, trachea, spine, and nose, because cartilage does not need to be vascularized with a blood supply in order to survive, meaning this method may work flawlessly.

-R. Park Sources: http://www.sciencedaily.com/ releases/2013/02/130220184728.htm

Artificial Retina Offers Limited Sight for the Blind

In early February, the FDA approved the first ever treatment that could bring partial vision to the blind with the use of technology called the artificial retina, marking a milestone in vision research. Called Argus II, the device is a visual system that consists of a sheet of electrodes that is implanted in the eye, as well as glasses that have an attached camera and portable video processor. The eveglass camera captures images that the video processor converts into pixilated patterns of light, which are transmitted through the electrodes to the brain. With the retinal prosthesis, patients with a particular type of blindness are able to perceive outlines and contours of people and objects – even large numbers and letters - especially if there is a contrast between light and dark.

Argus II was specifically targeted for patients with severe retinitis pigmentosa, a disease in which patients' photoreceptor cells deteriorate, rendering the eye unable to process light. However, experts say the technology holds great potential for treating other patients who are blind, especially patients suffering from advanced macular degeneration, an age-related disorder that is the major cause of vision loss among the elderly. About 100,000 Americans suffer from retinitis pigmentosa, while macular degeneration affects around 2 million Americans.

Argus II was developed by Dr. Humayun of the University of Southern California, with funding from the National Eye Institute and organizations such as the Foundation Fighting Blindness, and produced by Second Sight Medical Products. According to the scientists and organizations that helped develop this technology, Argus II is only the beginning. They one day hope to treat blindness from all causes by implanting electrodes directly into the cortex of the brain. —L. Jiang

Sources: http://www.nytimes.com/2013/02/15/ health/fda-approves-technology-to-give-limitedvision-to-blind-people.html



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NURJ Features

Science for Everyone

Research and current science is important for everyone to have access to. Reaching out to the public and explaining intricate scientific topics is crucial. Dr. Tal Danino at the Koch Institute is working on ways to providing "science for everyone".

BY ETA ATOLIA

A sensing array of radically coupled genetic 'biopixels'. In-silico pattern formation of vascular mesenchymal stem cells in threedimensions. Entrainment of a population of synthetic genetic oscillators. These are the titles of some papers authored by **Dr. Tal** Danino, Laboratory for Multiscale Regenerative Technologies. The titles are impressive as most names for research articles are. Looking at key words, such as "genetic biopixels" and "pattern formation", people get intrigued by what the papers have to offer. But who really is able to understand the intricate concepts in the paper? Some undergraduate students, graduate students, post-doctorates, and professors in the same field? What about everyone else?

In the scientific field today, there remains a large hole in being able to transmit the knowledge gained through novel research to the public. There is a lack of easy access to the most recent developments in key science fields, and the tools that are available for gaining this information are most often too difficult for the common person to understand. The question thus

"In the scientific field today, there remains a large hole in being able to transmit the knowledge gained through novel research to the public"



Figure 1. This is an agar plate of synthetically engineered light-sensitive bacteria. Using stencils and light, the light sensitive bacteria can be used to create this beautiful photographs. This is an easy way to illustrate the ways of engineering bacteria.

arises, how should we go about addressing this issue?

Dr. Tal Danino is one scientist

who is concerned with dealing with this problem. He has really sought to make his research available to the public. Dr. Danino does cancer research in Dr. Sangeeta Bhatia's lab in the Koch Institute. His research centers on bacteria and synthetic biology. Dr. Danino is looking at using bacteria as drug delivery systems into tumors and as possible early stage cancerdetecting agents. On April 14, 13, this research was presented to the public at the Cambridge Science Festival. Dr. Danino along with Andrea Sachdeva (Art and Science Prize), Neelkanth Bardhan (Graduate student in Angela Belcher Lab), and Eta



Figure 2. This is the homepage of the new website, coolsciencevideos.com. It is devoted to collecting interesting and informative videos that everyone can easily access.

"Cool Science Videos focuses on curating and creating the spark, wonder, and excitement about the world that we ware inherently born with"

Atolia (Undergraduate) prepared an interactive demonstration for everyone who stopped by. Included in the demonstration were colorful bacterial plates and bacterial photographs (Figure 1). Everyone was able to take a bacterial culture kit home. These demos provided an easy transition into explaining what is synthetic biology, why are bacteria useful, and what the current research is. It was a very easy connection that all the kids, teenagers, and adults were able to follow. Along with these activities there were interesting

videos playing on the background screen. Laptops were available to access a new site that this group has created: coolsciencevideos. com (Figure 2). This is a key way that this team, headed by Dr. Danino, is working

to make scientific information accessible to the public. In an interview with Dr. Danino, we were able to find out more about this endeavor.

MURJ: What is the main reason for your interest in science and the public?

Danino: I think we do fascinating and exciting things in lab that I think the public would be excited about if they knew more about what we do. MURJ: What is the main issue regarding the dissemination of scientific knowledge to the general population?

Danino: I think the way in which we communicate science is often times the issue. Scientists often times overcomplicate research and tend to focus on the details rather than the bigger picture when communicating with the media and the general public.

MURJ: Why Cool Science Videos?

Danino: Well, I think video is an extraordinarily effective way to communicate science. The ways you can display your data and summary visually

is one thing, but there is also the stylistic ways you can overlay sound, music, artwork, etc. to engage the viewer. I think videos & movies can often times creates a "moment" that can be quite memorable and open people up to learning. While video is great way to learn new things (see Khan Academy), Cool Science Videos focuses on curating and creating the spark, wonder, and excitement about the world that we are inherently born with.

MURJ: How will this help?

Danino: There are lots of amazing videos out there on YouTube, however, YouTube get 72 hour of video uploaded every minute. This makes it really difficult to find high-quality videos about scientific topics to watch. Searching for the most popular videos on YouTube often gives

videos that are sensationalistic, i.e. exploding things, but CSV focuses on videos that we think are high quality and span a broad range audience. In addition, there are lots of great videos out there, but they are often times at many different websites (university, blogs, and news channels) with their own interests in mind when promoting their videos. CSV curates the best videos we find from all over the Internet in many different formats.

MURJ: What are further goals or ideas?

We want CSV to integrate with school curriculum and build an educational program that helps students at different levels learn about science and communicating science. At the high school+ levels, students can form groups and get hands on experience in storytelling, writing, artwork, and videography to convey a relevant scientific topic from class. For younger ages, we envision students browsing the "Kids Activities" page by themselves or with parents and attempting to recreate some of the at-home science experiments (though these are fun for everyone). We are currently looking for educators and students to help with aspect.

MURJ: What is the best way to approach explaining a scientific topic to people with little background in the area?

Danino: I think there are a lot of approaches depending on the situation. In small groups, I think "showing" people what you do is the best approach. This includes lab tours, one-on-one communication with non-technical language, and relating your science back to everyday things. In terms of reaching large and broader audiences, I think video is one of the most effective ways to teach people about scientific topics with little background in the area.

To read more about Dr. Tal Danino's work, please visit http://tal.mit.edu/ ■



J-PAL and the Experimental Revolution in Development Economics

Development economics has a poor record of predictive success. However, researchers at MIT are quickly changing this by testing theories with rigorous experimentation. Results are helping policymakers choose more effective policies to combat global poverty.

BY MAX TIMMONS

Development economics has a troubled history. Grand theories have offered sweeping mandates and correspondingly grandiose predictions. However, widespread global poverty and continued underdevelopment of much of the world demonstrates the inadequacy of such theories. The repeated failure of growth rates to match the predictions of developmental economists proves the inability of such theories to make realworld forecasts. In many cases, development economists made very strong assumptions about how people decide to invest or how labor markets work in their models which turned out to not closely reflect empirical behavior.

The former MIT professor Paul Rosenstein-Rodan advocated one such grand theory, a "Big Push" that would develop a country's entire economy at once (1). In 1961, professor Rosenstein-Rodan boldly published growth forecasts based on his theory (Table 1) (2). Unfortunately, his predictions were completely incorrect. He missed the rapid growth South Korea, Taiwan, Singapore, and Hong Kong, the so-called East Asian Tigers, even as he overestimated the growth rates of many other developing countries. [see accompanying chart for details]. Development economists continuously argued whether foreign aid helped (Jeffrey

	Rosenstein-Rodan's forecasts			Actual average growth rates			
	1961-66	1966-71	1971-76	1961-66	1966-71	1971-76	1961-2009
Asia							
Afghansitan	1.5	2.2	1.7	na	na	-0.13	0.8
India	3	3	3.4	0.9	3.5	1.2	3.2
Pakistan	2	2.4	3	4.2	3.8	1.9	2.3
Singapore	1.1	1.3	1.5	2.6	8.8	7.4	5.1
South Korea	1	1.5	1.7	4.6	7.2	6.3	5.6
Taiwan	0.4	1	1.5	6.8	8.1	7.1	5.8
Thailand	0.8	1.3	1.7	5.3	5.6	3.6	4.4
Americas							
Argentina	2	2.5	3.2	1.3	3.3	0.5	1.3
Costa Rica	-0.3	0.2	0.8	3.5	3.1	2.7	1.8
Dominican Republic	0.3	0.1	0	2.7	4	4.6	3.2
Haiti	1.3	1	0.7	-0.2	-0.8	3.2	-0.4
Panama	0.1	0	0.5	4.5	4.1	2	3.1
Africa							
Angola	1.5	1.9	2.3	na	na	-0.7	1.7
Ghana	1.5	1.6	2.2	4.2	10.2	-6.4	1.7
Kenya	1.5	1.6	2.2	-1.7	3.6	-1.7	0.5
Liberia	1.1	1.5	1.4	na	na	-1	-3.9
Mauritius	0.2	1.1	1.6	-1.1	-2.8	11.3	3
Nigeria	1.4	1.75	2.2	-1.8	2.7	3.3	0.7
Uganda	1.7	2.2	2.7	3.8	1.1	-1.9	1.3

Table 1.

Sachs and others) or hurt (William Easterly among others) but no consensus was ever reached.

Hoping to reverse this trend of failure and disappointment, some economists decided to approach the problem of development like actual scientists. Instead of proclaiming grand theories, they would run rigorous experiments in the field and establish theories inductively. In 2003, MIT professors Abhijit Banerjee, Esther Duflo (PhD '99), and then-MIT professor Sendhil Mullainathan started the Poverty Action Lab to further such work. In 2005, the Poverty Action Lab was renamed the Abdul Latif Jameel Poverty Action Lab (J-PAL) after Mohammed Abdul Latif Jameel ('78) made a significant donation (3). Professors Duflo and

Banerjee also wrote a book, Poor Economics, which outlines some of their major findings on which interventions actually worked. Instead of theorizing from an office at some university they went into field and implemented some change for one random group while not implementing the change for another random group. Both groups were rigorously measured to detect effects of the change. This allowed them to establish causality to a much greater degree than previous statistical work.

In their essay "The Economic Lives of the Poor", Duflo and Banerjee examined a very large dataset of surveys to gain insight into how the poor live and make economic decisions (4). They found that food was the largest expense for the global poor. Interestingly, they observed that most people living in poverty could consume more calories, but instead spent their limited funds on higher quality food or festivals such as weddings, funerals, or religious ceremonies. They also reported that lack of capital led to many poor people working in low productivity unspecialized sectors. A Potential solution to this problem, , is microfinance pioneered by Nobel Laureate Muhammad Yunus, where banks give very small loans to the very poor. To test this hypothesis, Duflo, Banerjee, and their colleagues Rachel Glennerester and Cynthia Kinnan, increased the availability of microfinance loans in a random sample of slums in Hyderabad, India (5). They found that the increased availability of loans had a positive effect on purchase of durable goods and the creation of new businesses.

In "Inequality and Growth: What Can the Data Say?", Duflo and Banerjee examined previous work on the relationship between income inequality and economic growth (6). Earlier analyses typically used linear regression modeling, to disputed effect: some researchers found a positive relationship between the two, while others found that inequality inhibited growth. Duflo and Banerjee, in contrast, found that the data did not support a linear relationship at all. The different results in previous works, they found, were due to misconceived attempts to fit nonlinear data to a linear model.

Duflo and Baneriee also examined education in developing countries (9). Earlier studies lacked clear data on the results of various educational and pedagogical strategies. In "Remedying Education: Evidence from Two Randomized Experiments in India," however, Duflo, Banerjee, and their graduate students Shawn Cole and Leigh Linden reported the results from their rigorous experimental testing of education improvement strategies. They found that targeted interventions for struggled students had large short-term effects and smaller but still significant long-term effects on the academic and career success.

Duflo and Banerjee have been widely recognized for their work. In 2010, Duflo won the John Bates Clark Medal, typically considered the second most prestigious award in economics (8). She has also won a MacArthur "genius" grant and was named a top 100 global thinker by Foreign Policy in 2008, 2010, and 2012. Duflo and Banerjee's book Poor Economics was the 2011 Financial Times and Goldman Sachs Business Book of the Year.

Duflo and Banerjee have not offered simple answers to the question of how countries develop. However, their research has many clear policy implications. Their research on microfinance demonstrates developmentspurring effects of microloans. Their educational research suggests that targeted interventions for struggling students are both cheap and reasonably effective. They have also shown that an offering of a bag of lentils along with a shot dramatically raises vaccination rates in rural India (9). Their research might not answer every question, but their results are much more robust than robust than previous theorizing; they make policy recommendations based on their empirical data, not faulty conclusions from grand theories. These rigorous conclusions have tremendous potential to help developing countries, international aid agencies, and philanthropists utilize resources more effectively and reduce the number of global poor.

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^{2.} Ibid.

METAKARYOTIC BIOLOGY: the study of stem cells in development and pathology

A brief summary of the discovery of non-eukaryotic, amitotic, metakaryotic stem cells that appear to shape our organs, heal our wounds and give rise to the tumors and atherosclerotic plaques that account for about ³/₄ of the deaths in our country.

Way back before 1907, a University of Chicago professor, C.M. Child, went to the stockvards and collected specimens of the sheep tapeworm Monieza expansa. He found that in the female reproductive tract "after a long period of amitotic division the nuclei pass through the characteristic mitotic maturation divisions and the cells form typical ova". Biolog. Bull. (1907) 12:89-114. Amitotic division means cell division without condensation of chromosomes and mitosis. Amitosis was then pretty much ignored for about a century (brevity!).

Then in 2003, Dr. Elena Gostjeva focused on samples of human tissues and tumors (surgical discards from anonymous donors). Samples came from Chernobyl where she led studies of radiation induced genetic damage and some from the Massachusetts General Hospital. A former UROP student, Dan Haber, '77, had just become the director of the Cancer Center and he introduced us to pathologists Drs. Daniel Chung and Lawrence Zukerberg with whom we have a warm and productive collaboration. Funds came in 2007, when MIT Corporation Member, Ray Kurzweil, '69, introduced our work to the CEO of United Therapeutics



Figure 1. Feulgen stain for DNA (purple) shows symmetrical amitosis of metakaryotic nuclei. DNA doubles as the two separate bell shaped nuclei are formed and separated in both fetal organs and tumors.

Corporation. Ray represents UTC in monthly research discussions.

What Gostjeva found was a bizarre form of nucleus that first arose at about 4-5 wks of gestation when organ buds first appear. These bell shaped nuclei were hollow and were enclosed in long tubes containing many such nuclei (syncytia). Their nuclear fissions had no chromosomes evident and resembled the separation of two paper cups (Fig. 1). These syncytia disappeared (~12 wks) leaving the bell shaped nuclei in mononuclear forms in which the nucleus is appended to rather than enclosed in a large, mucinous cytoplasmic organelle (Gostjeva and Thilly,

BY PROFESSOR BILL THILLY,

FACULTY RESEARCH SPOTLIGHT

2005; Gostjeva et al., 2006). We called these amitotic forms "metakaryotes" as they arose with the meta-organs and were clearly not eukaryotes.

The idea that these things were stem cells came from Gostjeva's observations that a veritable zoological garden of solid, nuclear



Figure 2. Asymmetrical amitosis of a bell shaped metakaryotic nucleus forming an ~ 40 micron "sausage-shaped" nucleus that subsequently resides in eukaryotic cells dividing by mitoses in both fetal organs and tumors.

forms emerged from the hollow, bell shaped nuclei by asymmetrical amitoses (Fig. 2). The cells with solid nuclei subsequently divided by mitosis and became the numerically dominant cell forms of the various tissues of organs (animals and plants!) and tumors (Gostjeva et al., 2009).

Metakaryotes double their genomic DNA in coordination with amitosis rather than in a separate S-phase as in eukaryotes (Gostjeva et al., 2008). They use enzymes associated with "error-prone DNA repair" in yeasts and human cells (Muniappan and Thilly, 2002)). Perhaps not coincidentally, they seem to have prodigiously high point mutation rates during normal human development (Sudo et al., 2008) and are relatively impervious to x-rays and chemical agents commonly

used to treat cancers (unpublished observations). They organize their chromosomal material in what appear to be homologously paired, end-joined circles, i.e. they do not have "telomeres" (Gruhl et al., 2010).

Two freshmen UROP students. a graduate student and two senior researchers are working with Dr. Gostieva and me on the 7th floor of Bldg. 16. Together we have found a series drugs that kill metakaryotic human cancer stem cells in cell cultures and will test these metakaryocides in clinical trials against pancreatic cancer. We also do a fair amount of thinking about how mutations in metakaryotic stem cells drive agespecific death rates from cancer and atherosclerosis using algebraic models (http://mortalityanalysis. mit.edu). Interested students can

enroll in 20.102 (Fall), 20.104 (Spring), the seminar version, 20.002 (Fall) or just drop by to talk.

Interested students can contact: Prof. Bill Thilly, '67. 16-771 thilly@mit.edu ■





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MURJ UROP Summaries

Exploring molecular physics and quantum chemistry with ²³Na⁶Li molecules¹

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Introduction

In the past few decades, advancements in atom cooling technology have allowed for the study of atoms and molecules at very low nanoKelvin temperatures. These experiments have demonstrated a high level of control over individual quantum states and have been useful in studying fundamental aspects of quantum mechanics. Ultracold atoms have proven to be especially valuable for studying interacting many-body quantum systems[1]. At MIT, these types of experiments are commonly performed with sodium and lithium atoms. Forming low energy 23Na6Li molecules opens up the possibility to study rich systems of many interacting molecules[2]. Ultracold atom experiments take place in an isolated ultrahigh vacuum, and have demonstrated amazing precision and control over the atom's motional and internal states. Such techniques can be applied to chemically reactive systems, such as 23Na6Li molecules, to study quantum chemistry in its purest, simplest form.

Cooling to quantum degeneracy

The first step in cooling atoms is to slow them down using radiation pressure. A hot collimated beam of sodium and lithium atoms is brought to near standstill by counter-propagating lasers resonantly tuned to the atomic transitions. Under high vacuum, a magnetooptic trap is used to contain and laser-cool atoms to a few mK. At this point the magneto-optic trap is turned off and a purely magnetic trap is used to both contain the atom cloud and release the most energetic particles in a process called evaporative cooling[3]. As the kinetic energy of the atoms decreases, the position uncertainty increases from Heisenberg relations. At a low enough energy, the thermal deBroglie wavelength is on the order of the interatomic spacing - the sodium gas forms a Bose-Einstein condensate and lithium forms a degenerate Fermi-gas.

Forming ²³Na⁶Li molecules



Figure 1. Imaging of (a) an atomic cloud of 23 Na and 6 Li, (b) 23 Na and 6 Li atoms on the right and weakly bound 23 Na 6 Li Feshbach molecules on the top left, and (c) a cloud of weakly bound Feshbach molecules after removing unbound 23 Na and 6 Li atoms.

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When ultracold atoms of sodium and lithium are individually prepared and cooled, it is possible to form weakly bound molecules from resonant collisions of the two species. Careful tuning of a magnetic field allows the coupling of a weakly bound molecular state with the atomic scattering state through what is called a Feshbach resonance[4] (Figure 1). However, these highly vibrationally excited Feshbach molecules decay unpredictably and rapidly so it is useful to transition the atoms to a stable ground state of 23Na6Li that decays over a longer period of time. To form these states, two carefully tuned lasers simultaneously transfer the weakly bound molecule to the molecular ground state via two-photon transition[5].

Reaction dynamics

Upon collision, two 23Na6Li molecules in low-energy states exothermically react to form Na2 and Li2. The products of these reactions typically have kinetic energy greater than the trapping potential, so it is possible to extrapolate reaction rates by observing atom loss, which is done via imaging with resonant light. A similar reaction occurs for 87K40Rb molecules[6][7][8] and has been well studied in recent years. However, 23Na6Li molecules have the advantage of slower reaction rates, making them ideal candidates for studying quantum chemistry. With this in mind, it is possible to design interesting systems that use properties of the molecules, like dipole moments, to alter collision energies[5]. Highly precise tunable electric and magnetic fields can be used to manipulate dipole interactions and the result will be an observable change in the reaction rate and atom loss. Thus, because of the confinement of the system and high level of control over the collisions we will be able to observe reactions at a fundamental level and discover new paradigms of molecular physics.

Conclusion

Future work in this experiment will allow for the close study of molecular dynamics in a very isolated environment with a high degree of control over individual particle states. Future work in creating and manipulating 23Na6Li dipole molecules promises to reveal deep physics behind quantum chemistry and molecular reaction dynamics.

Acknowledgments

Special thanks to my UROP advisors Timur Rvachov and Professor Ketterle and labmates Tout Wang and Chen Chen Luo for supporting my research and teaching me about atomic and molecular physics.

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NURJ Reviews

Biomechanical properties of the cornea and their use in detecting and treating keratoconus

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Supplemental information is available online for this review article.

Introduction

One in every 2000 Americans suffers from keratoconus, the most common corneal disorder in the United States [1]. In keratoconus, the cornea becomes thinner and protrudes outward in the shape of a cone, causing severe astigmatism and blurriness (Fig. 1) [2]. The precise cause of keratoconus is unknown, but it may be attributed to inherited corneal abnormalities or mechanical trauma due to excessive eye rubbing or hard contact lenses [7]. The detection of this disorder is extremely difficult because there are no biochemical markers that can be used to diagnose it before it worsens [3]. It is known, however, that the cornea possesses unique biomechanical properties due to its dual function as the eve's transparent window and tough mechanical shield, providing rigidity and protection from infection. Thus, the critical questions we are trying to answer include: How can the biomechanical properties of the cornea be used to distinguish between a keratoconus and a healthy cornea? What tools will be needed to measure these properties? How can these properties be used to develop a tissue-engineered treatment?

Background

Structure and function of the cornea

The cornea is a fascinating feat of engineering. It is as smooth and clear as glass, yet also strong and durable providing rigidity to the eye and deriving its name from



Figure 1. In (a), an artist's rendition of the corneal deformation that results in keratoconus [1]. In (b), a keratoconic patient gazes downward, showing the protrusion of the cornea against the lower eyelid [7]. In (c), the left image is an eve chart viewed with 20/20 vision. The right image is how the chart appears to a keratoconic patient, revealing the severe blurriness that results from corneal deformation[2].

Latin for "hard as a horn". It performs three primary roles: acting as a shield, a window and a filter. As the outer sheath of the eye, it protects the sensitive inner tissue from germs and dust, and represents the eye's first line of defense against infection (Fig. 2) [5]. It is responsible for 65 to 75 percent of the eye's focusing power because the interface between air and the cornea is where light bends most [4]. The cornea also acts as a filter by screening out some of the most harmful ultraviolet rays in sunlight and



protecting the lens retina and from UV radiation [4]. In order for the cornea to properly focus light the

Figure 2. Anatomy of the eye [1].

into the eye, it must maintain perfect

transparency. This is in part achieved by the lack of blood vessels in the cornea; nutrients and oxygen are supplied directly by the tears and the aqueous humor located in the chamber beneath the cornea [5].Furthermore, the absence of blood vessels contributes to the tissue's incredibly high rate of healing since there are no ruptured blood vessels to repair [4]. This unique feature is what makes laser eye surgery so successful [7].

The cornea is approximately 520 μ m thick in the center, and increases to 650 μ m in the periphery [6]. Morphologically, it consists of five distinct layers: the epithelium, basal lamina, stroma, Descemet's membrane, and endothelium as illustrated in Figure 3. Functionally, however, the epithelium, stroma, and endothelium play the most critical roles. The epithelium is comprised of 5-7 layers of cells which are continually shed to prevent the progress of pathogens into the stromal tissue [7]. The stroma is thick (500 μ m), representing about 85% of the cornea's thickness, and is densely packed with highly oriented collagen fibers [6]. Bound to the fibers are proteoglycans (principally decorin and lumican), and these collagen/proteoglycan aggregates



Figure 3. Layers of the cornea with types of collagen labeled [11].

are arranged into lamella 500 layers thick [7], with a unique architecture discussed below. Between each laver of collagen, keratocytes can be found and are responsible for healing wounds and synthesizing collagen fibers. Loss of keratocytes has been observed in keratoconus corneas [4]. By weight, the stroma is 80% water, 15% collagen and 5% non-collagenous proteins and proteoglycans [7]. Biomechanically, the collagen provides tensile load resistance, and the proteoglycans provide an internal swelling pressure on the order of 60 mmHg [8]. The endothelium consists of flattened, hexagonally arranged cells one layer thick $(5 - 6 \mu m)$ [7]. These cells are responsible for pumping fluid out of the stroma, thereby preventing excessive hydration of the extracellular matrix [6]. This is critical to maintaining a stable hydrostatic pressure for stromal keratocytes [4].



Figure 4. Cartoon illustrating the perpendicular arrangement of subsequent stromal lamella; keratocytes are embedded between each layer [11].

Collagen Architecture

The microscopic organization of the collagen in the stromal lamellae defines the transparency of the cornea and has significant implications for its biomechanical behavior. Through X-ray diffraction studies, it has been determined that the lamellas of the stroma are oriented orthogonally to each other, as illustrated in Figure 4 [10]. In order to be transparent, the collagen fibers of the lamella form a three dimensional array of diffraction gratings, allowing for scattered light to be eliminated by destructive interference [6]. Further, the fibrils are separated from each other by less than half of a wavelength of light in order for the cornea to remain transparent [6]. In keratoconus, however, the arrangement of the collagen fibrils becomes highly irregular, as illustrated by the polar plots in Figure 5. These plots were produced from the scattering patterns obtained from X-ray diffraction studies [10]. The important trait to note is the orientation of the cross-shaped symbols in the control, or normal, cornea versus the keratoconus cornea (the color in the

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Figure 5. Polar plots of normal (a) and keratoconus (b) corneas. The important difference is that the lamella of the keratoconus cornea exhibits less perpendicular orientation, causing severe blurriness [10].

plots only defines how much the plots were scaled down in order to fit into the montage). The symbols represent the orientation of the lamella at the corresponding point in the cornea. In Fig.5(a), most of the symbols are perpendicular, while in Fig.5(b) there is much more irregularity. Also in Fig.5(b), there are no symbols in the center of the plot because that section represents the protruding cone of the keratoconus cornea where the collagen is so thin no data could be collected [10]. What these plots reveal is that the collagen fiber network of keratoconus corneas is mostly disorganized and lacks the preferred directions of the native tissue, which results in the deformation and blurriness that occurs in keratoconus.



Figure 6. Air pressure is applied on the surface of the cornea by Ocular Response Analyzer (ORA) [26]

Tools of study

Ocular response analyzer (ORA)

The ORA is a non-invasive device that is capable of analyzing biomechanical properties in vivo (Fig. 6). It determines the corneal hysteresis (CH) which is a measure of viscous damping. The ORA applies an air puff to the cornea and measures two applanation, or flattening, pressures: one while the cornea is moving inward, and the other while the cornea returns [26]. In a purely elastic material, the two values should be identical, but since the cornea is viscoelastic, the inward and outward applanation

Table 1: Biomechanical properties of diseased and healthy corneas.						
	Normal Cornea	Keratoconic Cornea	Citation			
Young's Modulus	0.29 ± 0.06 MPa	0.21 ± 0.04 MPa	Hamilton et al. 2008/ Alio, Azar et al.			
Shear Modulus	9.48 ± 2.92 kPa	Not currently available	Petsche et al. 2012			
Hysteresis	10.7 ± 2.0 mmHg	9.6 ± 2.2 mmHg	Shah et al. 2007			
Central Corneal Thickness (CCT)	545.0 ± 36.4 μm	491.8 ± 54.7 μm	Shah et al. 2007			
Poisson's Ratio	0.45	Not currently available	Gefen et al. 2009			
Viscosity	9.02 <u>KPa</u> -s	Not currently available				
Intraocular Pressure	15.6 ± 2.7 mmHg	9.95 ± 3.01 mmHg	Ruberti et al. 2011/ Kymionis et al. 2010			
Radius of Curvature	7.8 mm (anterior), 6.6 mm (posterior)	No quantifiable data available, but should be smaller than radius of curvature of normal cornea	Gefen et al. 2009			

pressures are different. The ORA measures this difference, which is the corneal hysteresis (Fig. 7).

It has been found that the CH is significantly higher in normal corneas compared to keratoconic corneas, with a mean CH of 10.7 \pm 2.0 mm Hg in





Figure 7. Standard ORA graph of pressure in time domain. The difference between applanation pressure 1 and applanation pressure 2 is corneal hysteresis (CH) [26]



Figure 8. Typical signal for keratoconic eye



Figure 9. Typical signal for normal eye

eyes (Figs. 8, 9). Due to its in vivo nature, the ORA is a valuable tool for measuring the CH for normal and keratoconus corneas, and may enable detection of keratoconus from the CH value.



Figure 10. Strip extensiometry device [28].



Figure 11. Stress versus strain measured by strip extensiometry. The curve on the top is from a normal cornea and the bottom curve is for a keratoconic cornea [28].

Strip Extensiometry

Strip extensiometry be used may to measure the elasticity the of cornea, and thus has potential as a tool for keratoconus characterization. It entails dissecting a strip of corneal tissue with a constant width monitoring and its behavior as it is attached to the grips of a slow rate tension machine [27].

From plotting the stress-strain relationship, Young's modulus, which is stress over

strain, can be determined from the slope. Corneas with a low elastic modulus stretch to a greater amount under the same force as corneas with a high modulus. In Figure 11, it is evident that keratoconic corneas have a lower Young's modulus than normal corneas. This means that keratoconic eyes will deform more under the same intraocular pressure (IOP) than a normal cornea, and that the overall mechanical strength of the keratoconic cornea is reduced [28].

It should also be noted that the precise value of Young's modulus cannot be measured due to the nonlinear stress-strain relationship that exists in the cornea (see Fig. 11). This nonlinearity is due to stress stiffening, where the cornea resists further strain as more stress is applied [27].

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Figure 12. Voigt spring and dashpot model in series with a spring. $\epsilon \sigma$ represents the total strain on the system, and $\epsilon 1$ represents the strain across the viscoelastic component only. σ is the applied stress on the system. E1 is the Young's modulus of the viscoelastic component, and E2 is the purely elastic component's Young's modulus. $\eta 1$ is the viscosity of the viscoelastic component. [23]



Figure 13. Viscoelastic model behavior in the time domain.

Models

Because the cornea's stroma is composed of 80% water, the cornea exhibits viscoelastic behavior. When subjected to a force, the cornea responds with some initial, instantaneous deformation followed by progressive deformation. This behavior can be modeled by a Voigt model (spring and dashpot in parallel) in series with a spring, as illustrated in Figure 12. The Voigt component of the model represents the viscoelastic component of the cornea, whereas the single spring represents its elastic part.

This viscoelastic model can be represented by the following differential equation:

$$E_{2}(\varepsilon_{0} - \varepsilon_{1}) = E_{1}\varepsilon_{1} + \eta_{1}\frac{d\varepsilon_{1}}{dt} = \sigma$$
(Eq. 1)

Figure 13, which is a plot of Eq. 1, demonstrates how the single spring, the purely elastic component of the model, experienced instantaneous strain when subjected to a stress, followed by more gradual deformation caused by the viscoelastic portion of the model. This second strain increased over time at a decreasing rate until it reached steady state. Despite the instantaneous deformation caused by the purely elastic component, the viscoelastic behavior dominates in the long term. This behavior is displayed in Figure 13, where the total model strain asymptotically approaches a value of ~0.6 as time approaches infinity.

The pure Voigt model was not chosen by Glass et al to represent the cornea's viscoelastic properties because it does not show the instantaneous deformation that defines actual corneal behavior. The Maxwell model (spring and dashpot in series) was also deemed insufficient, due to the asymptotic behavior of the corneal creep response to a finite value for stress. In addition, the Maxwell model doesn't fully recover from deformations caused by the time-dependent component, but the actual cornea can be restored to its original shape.

One limitation of this spring and dashpot viscoelastic model is that it assumes that the cornea is perfectly spherical and that both the thickness of the cornea and the stress applied are uniform. On these premises, there are some inaccuracies in the calculation of stress in some regions of the cornea. Another limitation of this model is the assumption that bending forces in the cornea are negligible, which could result in values for the tensile stress acting in the plane of the cornea that are too large. Additionally, this model examines the bulk corneal properties, when in reality the cornea exhibits regional variance in biomechanical properties.

Another limitation of the viscoelastic model is its failure to take into account the swelling pressure of the cornea, which can be incorporated into the stress tensor as a hydrostatic pressure. It also neglects to capture the poroelastic behavior of the aqueous proteoglycan cellular matrix and fiber network.

Animal models

Animal models are critical for testing various treatments for corneal diseases such as keratoconus, but it is necessary to understand how the biomechanical properties compare across species. In an experiment by Hoeltzel et al, the biomechanical responses of bovine, rabbit, and human corneas were compared over a series of three cycles of applied stress. Between the first and second cycles, the bovine and rabbit corneas developed

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more elastic behavior, becoming increasingly similar to the human cornea, which remained essentially constant in elasticity between the first two cycles (Supplementary: Figs. A and B). Between the second and third cycles, all three types of corneas exhibited little variation in elasticity (Supplementary: Figs. B and C).

This evidence suggests that bovine and rabbit corneas may be considered acceptable models for human corneas, given that the bovine and rabbit corneas can be preconditioned with one cycle of applied stress, after which they respond to biomechanical changes in a similar way as human corneas.

Biomechanics of treatments

Keratoconus can be understood as a cycle of biomechanical decompensation, which leads to disparities in the biomechanical properties of diseased and normal corneas (Fig. 14). This cycle is initiated by a decrease in elastic properties, which results in thinning as the weaker area strains more than the surrounding stronger areas [11]. Thus, to reverse the cycle and decrease the amount of strain on the eye and restore the even distribution of stress, the Young's modulus must be increased.

Recently, a treatment has been developed in which this is achieved by cross-linking the corneal fibers [12]. The treatment is performed by removing the epithelium then saturating the stroma with riboflavin. When exposed to type A ultraviolet light (which is the least harmful), the riboflavin initiates the formation of new molecular bonds between the collagen fibrils via a free radical reaction [13]. Through strip extensiometry, Wollensak et al. determined that after a half-hour of UV-A treatment, human keratoconus corneas exhibited a 328% (4.5 fold) increase in the Young's modulus [12]. This increase is a function of the depth of penetration of the chemical agent and UV light, and it is possible that longer exposure may further improve the results [14]. By raising the value of the elastic modulus, the tissue is made stiffer by the relationship Kb = EI, where Kb is bending stiffness, E is Young's modulus, and I is area moment of inertia. The stiffer tissue is more resistant to strain, which decreases

Figure 15. In (c) a silicon template with 650 nm pattern. In (d), a 650 nm nanopatterned collagen film from [30]. This technique allows for the creation of linearly oriented collagen fibers spaced according to the template.

the deformation of the keratoconus cornea and reduces the stress gradient across the tissue, thereby reversing the cycle of biomechanical decompensation.

It was further found that after initial treatment, the cornea continues to improve even years after due to the viscoelastic nature of the cornea, which supports this time-dependent response [11].

Future direction: tissue engineering

Cross-linking may be effective in mild cases where the cornea has not thinned excessively. For more advanced cases, the gold standard for treatment has been corneal transplant from a donor eye [1]. However, this solution is riddled with complications due to repeated rejections [3]. Therefore, the development of a synthetic cornea which mimics the native corneal tissue may be effective in avoiding these complications. The major challenge is to gain control of collagen organization, which may be possible through nanopattern scaffolding (see Figure 15). In this technique, silicon templates are used on which collagen fibers can be arranged and then cells seeded [30]. It may be possible to seed the fibers with keratinocytes, which are the fibroblasts responsible for synthesizing the collagen in the corneal stroma. That



Figure 16. Graph of stress versus strain in different nanopatterned tissues measured after 45 and 75 days of growth [30].

would allow for the construction of a tissue which is similar in composition to the natural stroma. An advantage to this tissue engineering method is that it allows for the manipulation of biomechanical properties (Young's modulus and ultimate tensile strength) by adjusting pattern spacing [30]. In Figure 16, different stress-strain relationships were obtained by varying the pattern spacing and growth time (during which the seeded cells secrete their own extra-cellular matrix and strengthen the newly synthesized tissue). Thus, a range of elastic moduli can be achieved, and the pattern spacing may be tuned to give a value for Young's modulus which approaches that of the natural tissue (normal cornea: 0.29 ± 0.06 MPa).

Unanswered questions

There are significantly fewer cross-links between keratoconic corneal fibrils compared to the normal cornea [7]. This suggests that there may be an abnormal adhesion mechanism between the collagen fibrils and the non-collagenous matrix, which results in slippage. Normally, the active interactions between the corneal fibrils and matrix proteins are stabilized by keratocytes. Since keratoconus corneas appear to be lacking such interactions, a critical question arises about how the interactions between adhesion molecules are disrupted. Are they due exclusively to mechanical traumas such as eve rubbing, or physical properties such as intraocular pressure? Also, are the lack of interactions a response of the keratocytes to mechanical forces? These questions can be investigated from the standpoint of molecular mechanics, and may be quantified by measuring the shear stresses and strains in response to the mechanical forces. The information gathered will grant insights into the causes of keratoconus, and will allow for additional treatments to be developed.

Conclusion

An integrated understanding of corneal anatomy, biomechanics, and viscoelastic properties will enable diagnosis and treatment of disorders such as keratoconus. By using tools such as the Ocular Response Analyzer, in vivo measurements of biomechanical properties such as corneal hysteresis can be made, which allow for the detection of keratoconus. Since keratoconus is the result of thinning and structural weakening of the cornea, successful treatments have been developed which focus on cross-linking the collagen network in order to increase the Young's modulus. This reverses the cycle of biomechanical decompensation which describes the progression of keratoconus by stiffening the tissue and evening the distribution of stress across the cornea [7]. In addition, time-dependent improvements have been reported due to the viscoelastic nature of the cornea. For more severe cases, however, corneal transplants may be necessary. In order to avoid complications due to rejection, a synthetic cornea may be tissue engineered with desired biomechanical properties through nanopattern scaffolding. Although details regarding the causes of keratoconus are not clear, it is evident that the unique biomechanical properties of the cornea may be applied to diagnose and treat this debilitating and widespread disorder.

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MURJ Reports

E. coli Growth Phase Distinction Via Three-Dimensional Insulator-Based Dielectrophoresis¹

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In three-dimensional insulator-based dielectrophoresis (3D-iDEP), an electric field is applied across a microchannel through platinum electrodes. A constriction in the channel induces a field gradient, which causes trapping of particles or cells, in this case E. coli, based on differences in cell envelope and medium polarizabilities. The channel walls and medium are prepared such that the bacteria are more polarizable and thus experience positive dielectrophoresis, trapping in areas of high electric field intensity, around the channel constriction. This method is employed to observe differences in trapping behavior of *E. coli* at various growth phases. Preliminary data have shown that bacteria experience contrasting dielectrophoretic responses according to growth phase, demonstrating the potential to distinguish between growth phases or even sort bacteria accordingly. Additionally, these data validate the importance of ensuring growth phase equivalency between samples when conducting DEP experiments on a single strain of bacteria.

Introduction

Dielectrophoresis (DEP) is the movement of polarizable, but not necessarily charged, particles in a non-uniform electric field that causes the particle to polarize and experience a force along the field lines. The DEP force is governed by several factors: particle volume, medium permittivity, the magnitude of the field gradient, and the Claudius-Mossotti factor. The Claudius-Mossotti factor contains a frequency dependence, but since a DC electric field is utilized in these DEP experiments, the Claudius-Mossotti is a constant (Braff, 2011). DEP can be used for a multitude of applications on the micro and nanoscale levels (Braff and Pignier, 2012).

A well-studied method of DEP, three-dimensional insulator-based dielectrophoresis (3D-iDEP), was used to

study the behavior of *E. coli* at various growth phases. In 3D-iDEP, the field gradient is established by the existence of a microchannel constriction, with the Poly(methyl methacrylate) (PMMA) which the microfluidic devices are made from acting as the insulation around the constriction. Bacteria suspended in a buffer medium are inserted into the microchannel and, based on the difference in cell envelope and medium polarizabilities, exhibit positive DEP, trapping near the constriction in the region of highest electric field intensity as demonstrated in Figure 1.

E. coli in the lag phase, log phase, and stationary phase were tested, with a total of five points in the growth curve being represented in the data. Preliminary data have shown that bacteria experience contrasting DEP responses according to growth phase, demonstrating



Figure 1. 2D abstraction of electric field lines inside the 3D-iDEP microfluidic chip. The red lines indicate the general field, running from positive on the right, to negative on the left. The field is constricted by the insulating material that the chip is made of, PMMA. Positive DEP trapping occurs in the region labeled, to the left of the constriction.

the potential to distinguish between growth phases or even sort bacteria accordingly. Additionally, these data validate the importance of ensuring growth phase equivalency between samples when conducting DEP experiments on a single strain of bacteria.

Background

Dielectrophoresis arises when a non-uniform electric field polarizes a particle. Many factors affect the DEP force which, for a spherical particle or cell, can be modeled by the following:

$$E_2(\varepsilon_0 - \varepsilon_1) = E_1\varepsilon_1 + \eta_1 \frac{d\varepsilon_1}{dt} = \sigma$$

Where ε_m is the dielectric constant of the buffer, V is the volume of the particle, κ_{CM} is the complex Claudius-Mossotti factor, (which is dependent on the dielectric constants of the particle, buffer, and the dimensions of the particle), and E is the electric field.

Methods

Microfluidic Device

Each device is constructed from two laser-cut rectangular chips of PMMA. Seven microchannels are CNC micromilled onto one of these chips, complete with drilled microchannel inlets and outlets. The channels are 500 μ m wide by 500 μ m deep and have 50 μ m by 50 μ m constrictions. The milled chip is bonded to a blank chip using a combination of heat and a solvent composed of



Figure 2. Progression of chip evolution, beginning with a blank chip and ending with a fully assembled device complete with fluid reservoirs.

dimethyl sulfoxide, methanol, and deionized water, and fluid reservoirs are attached to the chip with epoxy. The manufacturing sequence is shown in Figure 2.

Channel Preparation

The channels are sequentially flushed with 0.1M potassium hydroxide, DI water, and a neutral pH buffer with a conductivity of 100 μ S which is made with potassium hydroxide and potassium chloride.

Bacteria Culturing and Preparation

Green Fluorescent Protein (GFP) expressing E. coli are cultured in LB media according to standard procedures. The bacteria are then transferred to the buffer and fluorescently stained with SYTO BC (Life Technologies/Invitrogen, Carlsbad CA). Sample concentrations are



Figure 3. The experimental set-up: microfluidic device prepared, secured on microscope stage, electrodes in place.

normalized to an OD600 of 0.1 prior to injecting them into the fluid reservoirs for experimentation.

3DiDEP Experimental Procedure

Platinum electrodes are placed in each fluid reservoir on both ends of the microchannel, and 75 volts is applied across the channel. To monitor, an inverted microscope with an epifluorescence feature and a 4x objective lens was focused on the microchannel constriction. Images were captured using a CCD camera. The experimental setup can be seen in Figure 3.

Data analysis

Each 3D-iDEP experiment yields a stack of 120 images centered around the constriction of the microfluidic channel which documents the positive DEP trapping of the bacteria. These image stacks are analyzed using a MATLAB code which tracks fluorescence intensity in the trapping region due to the bacteria. The median fluorescence intensity of the first ten images, which are captured while voltage is not yet applied, is subtracted from the rest to reduce background noise in the data.



Figure 3. In the top image, the voltage source is turned off, but bacteria are present, indicated by the white specs. In the middle, the 75V is applied across the electrodes, and consequently bacteria begin to concentrate near the constriction, in the center. Finally, in the bottom image, the voltage is turned off, and the bacteria begin to disperse.



Figure 5. The bacterial growth curve for *E. coli*. The three phases that we are most interested in are the lag phase, log phase, and stationary phase. (Source: Qiagen) DEP experiments were performed on bacterial samples at 6, 12, 14, 17, and 23 hours after culturing.



GFP SYTO BC E. coli Trapping at Different Growth Phases at 75 Volts

Figure 6. Fluorescence intensities for different bacteria growth times plotted versus time. The applied voltage was 75V in all experiments.

The code focuses on the boxed area to the left of the constriction, as shown in Figure 4. By graphing the fluorescence intensity over time, it can be seen that the intensity increases as more bacteria are trapped.

Experimental data for *E. coli* samples from the lag, log and stationary phases were collected based on the Qiagen growth curve shown in Figure 5: a six hour sample from the late-lag or early-log phase, twelve and fourteen hour samples for the log phase, and seventeen and twenty-three hour samples for the stationary phase. DEP trapping was performed three times in different microchannels, and the fluorescent intensities were averaged between the three trials for the data shown in Figure 6.



Figure 7. The GFP E. coli growth curve, in which the lag phase ends at approximately six hours, and the stationary phase spans a larger number of hours than previously expected.

Upon examining the data in Figure 6 and noticing the abrupt difference between the six-hour sample and the rest, the *E. coli* growth curve was re-mapped using the GFP strain in order to see whether the strain follows a slightly different growth curve than the generic non-GFP E. coli growth curve in Figure 5. Figure 5 was used to determine growth phase when pulling samples from culture. As the new growth curve shown in Figure 7 demonstrates, the GFP strain appears to leave the lag phase around six hours, and concentration levels out considerably earlier than previously thought. The phase transitions for GFP are more ambiguous, as the log phase constitutes a steeper concentration increase while the stationary phase appears to be more drawn out.

Conclusions

Our data indicate that growth phase does affect DEP trapping response and therefore polarizability. Plotting the fluorescence response over time shows that the magnitude of trapping abruptly decreases as bacterial growth proceeds along the growth curve into the log phase. These measurements do not reveal a noticeable difference between log and stationary phases, however, which elicits the question whether the samples taken at various hours in bacteria growth are in fact in the growth stage suspected. For example, the twelve, fourteen, seventeen, and twenty-three hour samples, which were assumed to be in the log and stationary phases, may in fact all have already reached stationary phase. Further experimentation according to the new growth curve in Figure 7 will be necessary to confirm or reject this hypothesis. Additionally, further testing is warranted for specific growth phases such as early lag phase and late log phase. This research serves as an important reference to those conducting DEP experiments with bacteria, encouraging researchers to be conscientious of growth phase when sampling cultures to keep the maximum number of variables controlled. Voltage ramping experiments on growth phases may shed light on the minimum voltage necessary for trapping, which would be very valuable data for future sorting experiments in which multiple samples reside in the channels simultaneously and only one exhibits positive DEP trapping at a certain voltage. This would allow the rest of the bacteria to be removed, leaving the aggregated sample of interest purified.

Potential applications of these research findings include: sorting bacteria in real-time, sorting bacteria based on phenotypes, sorting based on viability, and applications in lab-on-chip biomedical devices. The device in its current state is not a continuous-flow device, but with some redesign, it could be tailored to perform sorting of bacteria, as different species of bacteria exhibit different DEP responses. Similarly, bacteria within the same species but exhibiting different phenotypes may also exhibit different DEP responses, allowing for continuous sorting. It is anticipated that these principles can be used in practical devices as they have great potential as tools for the biomedical device industry.

Acknowledgements

We would like to thank the MIT Laboratory for Energy and Microsystems Innovation (LEMI) for hosting us and the MIT Undergraduate Research Opportunities Program (UROP) for funding us and giving us the opportunity to do this research. Many extend thanks to our PI, Professor Cullen R. Buie for his superb ideas and advice and William A. Braff for his training and guidance on the 3D-iDEP process, which he perfected in his thesis work. And finally, thank you to Zhifei Ge for his expertise in *E. coli* culturing and Andrew Jones III for taking us under his wing throughout this work.

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Reports

Link between global warming and conflict in Sudan: from sea surface temperature to regional variation in rainfall to conflict

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There are correlations between global warming and rainfall in Sudan and between rainfall in Sudan and conflict. There is a direct link between sea surface temperature variabilities and the intertropical front, the El Nino Southern Oscillation, and the rainfall patterns in the Sudan-Sahel zone. Furthermore, increase in land surface temperatures has an effect on precipitation patterns and vice versa, a feedback loop mechanism that causes increasing temperature and decreasing rainfall annually. Studies of the effects of drought on population indicate a resulting increase in the scope and variability of internal migration patterns. With the past and current evidence of migration, combined with the expected average global temperature rise, an increase in both incidence and intensity of conflict is probable. Where fertile and arable land is marginal at best, these factors can combine and result in conflict; the past conflict in Sudan can be linked to a changing climate and future conflict is highly probable due to the very same. In other words, global warming may become one of the triggers for conflict in Sudan.

Introduction: Sudan, climate, and conflict

Background on Sudan and climate

Over 60% of Sudan has faced conflict over the past 50 years. Tribal and small-scale conflicts fought with small arms have been common throughout the history of Sudan. Mostly concentrated in the south, west, and east of the country for the past 30 years, these conflicts included disputes over cattle theft, access to water and grazing, and local politics. Many of the large-scale conflicts in Sudan have connections to tribal friction. The majority of the local conflicts have been long-term confrontations between forces that were either aligned with the central Sudanese government based in Khartoum or aligned with an array of antigovernment forces. The government generally used the conventional army, the air force, or allied local militias while the opposition mainly used local militias (that later evolved into a united resistance with parallel governments and administrative structure). The various conflicts involved about 6 million people in Darfur alone and 15 million in the rest of Sudan; there were a total of 2 to 3 million casualties (UNEP report, 2007).

For the past at least 30 years until 2003, there had been intermittent fighting consisting of partially connected tribal and local conflicts. In 2003 this resulted in a full scale military conflict which spilled over into Chad and the Central African Republic. This "scorched earth campaign," a campaign in which militias roamed over large areas intentionally destroying all resources that may be useful to the opposition, caused high civilian deaths, widespread destruction, many internally displaced persons [IDPs], and a general lack of food and water. Casualties numbered between 200,000 and 500,000. (UNEP report, 2007) Of the 50 years that the nation of Sudan has been independent, southern Sudan has had only 11 years of peace. Since then, there has been civil war where the Sudanese Armed Forces [SAF] held major towns and launched ground offensives, while the Sudan People's Liberation Army [SPLA] used guerrilla attacks to seize towns in both wet and dry seasons. The 1990s constituted the fiercest fighting, with the front lines changing almost constantly and high casualty rates. Most of the fighting took place in the Abyei district, Blue Nile, and the Nuba Mountains in South Kordofan. (UNEP report, 2007)

Environment and climate overview

I suggest that there is a direct link between global warming and rainfall in Sudan and also that there is a correlation between rainfall in Sudan and conflict. Global warming is, therefore, one of the triggers for conflict in Sudan.

There are strong linkages between environmental conditions and conflict. They are believed to be key issues in the Darfur crisis. Environmental and economic problems go hand-in-hand for developing nations due to livelihoods based on competition over limited resources. This is demonstrated by confrontations over rangeland and rain fed agricultural land in the drier parts of the country. Increasing population combined with environmental stress has resulted in a situation that is ripe for conflicts to be triggered and maintained by political, tribal, and ethnic differences. Since the 1930s, for example, there has been a southward shift of boundary between desert and semi desert of about 50 km to 200 km. The remaining semi-desert and low rainfall savannah constitute 25% of Sudan's agricultural land and is at risk of further desertification, which would cause a 20% drop in food production. Note that there is a lack of deep boreholes that can be relied upon during even short dry spells in these areas. In addition to drought and desertification, agriculture is negatively affected by severe land degradation due to demographic pressure and poorly managed development. Furthermore, the declining precipitation due to regional climate change has been a significant stress factor for pastoralist societies in Darfur and Kordofan. The long and devastating droughts have been exacerbated by a tendency to maximize livestock herd sizes rather than herd quality as an insurance against starvation. Livestock has increased from 29 million in 1961 to 135 million in 2004, an increase of 400% and an unprecedented strain on water resources. (UNEP report, 2007)

Desertification, soil erosion, and soil exhaustion, due to compaction and combined with the depletion of nutrients, lower the productivity of land, sometimes removing it from use altogether. Deforestation, for example, causes a near permanent loss of resources, such as seasonal forage for pastoralists, and prevents soil recovery through natural fertilization. The current forecast for climate change implies a further reduction in productivity of the land due to both declining rainfall and an increased variability in rainfall. (UNEP report, 2007)

To further exacerbate an already delicate situation, the population of Sudan is expected to increase in conjunction with livestock growth rate. The increase in livestock will occur concurrently with a decrease in rangeland from agricultural expansion. Furthermore, the agricultural expansion blocks the migratory routes of nomadic pastoralists and reduces the land available for grazing their cattle. Therefore, available lands will be overgrazed, causing a higher rate of degradation. The loss of livelihood and subsequent poverty for pastoralist societies are probable. (UNEP report, 2007)

Data and analysis

The evidence supporting the argument shall be presented in three parts. The first section will confirm the link between global warming, especially with respect to sea surface temperature anomalies, and the connection to rainfall in the Sahel region. The second section shall form a link between rainfall and conflict. The third section shall attempt to look at the specifics of the tribes in relation to each other, especially with respect to how the changing climate has shifted the land use and migration dynamics.

Section 1: Linking global warming to rainfall in the Sahel

First, we will look at the intertropical front and its effect on rainfall over the Sudan-Sahel zone. Note that this and other weather patterns are in turn affected by global sea surface temperature. We shall address global sea surface temperature variations and their regional and local effects on Sudan in the latter part of the section.

The intertropical front is a fundamental feature of the atmospheric circulation over West Africa. It separates the wedge of warm, moist, southwesterly air and the hot, dry, northeasterly air from the Sahara desert. From April to early August, the northward advance of the intertropical front across the region is relatively slow, especially compared to the rapid southward retreat between mid-August and mid-November that is almost twice as fast. In other words, the monsoon-rain-belt migrates northward and intensifies. There is a linear correlation between the front latitude and the total rainfall in the Sahel zone. Lele` et al found a linear correlation between decadal average intertropical front latitude and the decadal mean Sudan-Sahel rainfall. This means that adequate

rainfall generally occurs more than 400 km south of the front- a front which has gradually been retreating. The association between the intertropical front and rainfall in the Sudan Sahel zone is strongest during the early April to June and late October rainy season months. (Lele'et al., 2010)

Furthermore, the temperature, humidity, and rainfall data for 1974 to 2003 were gathered by Lele` et al in order to understand the role of the intertropical front in the Sudan Sahel rainfall patterns. We can conclude from the Lele` et al paper that there were significant rainfall changes in the Sudan Sahel zone since the mid-1950s, with the additional input of prior studies. In addition to the specifics, the Lele` study identified the links between global and basin scale sea surface temperature anomalies and the Sudan Sahel seasonal rainfall totals. (Lele'et al., 2010)

The studies by Palmer have shown that the persistently dry and wet periods of several years in the Sahel zone have been accompanied by global scale patterns of sea surface temperature anomalies. The Indian Ocean has a dominant role in reducing rainfall, particularly over Sudan. Palmer showed that an increase in rainfall over the Indian Ocean might indicate a decrease over Sudan. He found that, over a larger scale, the Atlantic, Pacific, and the Indian Ocean have all shown an effect on the degree on rainfall in the Sahel zone to a varying degree. The north to south gradient indicates that the anomalous non-divergent wind in the tropics had a westerly component strongest over the East Pacific but extending over the Atlantic Ocean and Africa. This component produces the southwest monsoon flow into the Western Sahel region. This is further indication that the model results are in agreement with the observed correlations between worldwide sea surface temperature and the Sahel rainfall as discussed by Foland et al. Note that ground reflectivity and soil moisture capacity were not built into the model and, had they been, there might be a stronger response to sea surface temperature anomalies shown. (Palmer, 1986)

Elagib found that there has been an unequivocal and dramatic decline of rainfall amounts since the mid-1960s, peaking in the 1980s, and resulting in the existence of a distinct wet and dry sequence. This includes the areas of the Nile Congo watershed, the Highlands of Darfur, and the lands to the east of the Ethiopian plateau. The Nuba Mountains are located within this area. Two areas of Sudan, El Gedaref and Kosti, were included in the study by Elagib due to their importance as productive agricultural regions, using data from the Sudanese Meteorological Authority from 1941 to 2006. Changes in large-scale atmospheric circulation that are triggered by multidecadal variations in global sea surface temperature have been proposed by Elagib as one of the modulators of rainfall over most of the African continent. Among these is the El Niño Southern Oscillation also known as ENSO. (Elagib, 2009)

The potential connection of rainfall events to the El Niño Southern Oscillation was investigated over the period of 1952 to 2006. The rainfall series was standardized based on the 1971 to 2000 anomalies data. The question that remains is whether rainfall variability is connected to the variability of increased rainfall events. In other words, do the changes in trace events have any other importance or would they explain an underlying phenomenon? Despite the inter-annual variability and the existence of peaks, the trend lines for most of the series show decline, and they are steeper for the arid station of Kosti than for the semi-arid station of El Gedaref. Except for the early wet season, Kosti shows significant downward trends, especially for the first three rainy day classes: trace, weak, and moderate rainy days. (Elagib, 2009)

The pace of drying conditions is faster in the arid regions of central Sudan compared to the semiarid ones. Interestingly, there is a significant trend toward the concentration of trace events into a few months within the year. The factors influencing the production of rain may include the stability of the atmosphere, the column water content as determined by the lifting condensation of the cloud, and the type of cloud. Also, drier conditions create more dust, which in turn is a positive feedback for drier conditions, as it affects cloud formation, rainfall, and albedo. The Sahel drying suggests that anthropogenic forcing of the northern hemisphere sulfate aerosols force a meridional gradient in the Atlantic sea surface temperature, hence producing moisture flux by anomalous winds. (Elagib, 2009)

Note that heavy rain falls are more likely to diminish in drought years and increase in wet years, while light and medium events tend to vary independently of either wet or drought years. The number of rainfall days in all classes except weak rainfall tends to decline in drought periods and vice versa. The warm El Niño Southern Oscillation episodes enhance the drought conditions in many regions in Africa. (Elagib, 2009) This means that warm tropical ocean waters could result in a drought in Africa. Earlier studies have shown connections between the El Niño Southern Oscillation and the Atlantic Congolese Southwest monsoon flow (Diro et al.). The warm El Niño southern oscillation episodes inhibit rainfall; however, it may be noted that this factor does not explain all the variation. The more frequent aerosol emissions from soil, dust, haze, storms, and smoke may have contributed to or exacerbated the suppression of rainfall processes. (Elagib, 2009)

There is mounting evidence of daytime and nighttime warming in Sudan since the 1940s until at least 2005. when Elagib conducted the study of temperature variabilities across Sudan. The progressive drought across inland locations has raised the maximum temperature and, to a lesser extent, the minimum temperature of the wet season. The warmer climate in Sudan is associated with higher interannual temperature variability and a decrease in the diurnal temperature range, especially in the hot and dry annual series. An increasing cloud cover could be the cause of the decreasing diurnal temperature range. (Elagib, 2010) Though this has not resulted in an increase in strong rainfall, it has resulted in an increase in trace rainfall events. These trace events may be caused by elevated cloud formations that, in conjunction with an increase in mean temperature, causes most of the water in rainfall to evaporate before it reaches the ground. (Elagib, 2009)

Climate models indicate that temperature changes are sufficiently large to cause corresponding changes in the frequency of extreme events. Simulations show that the temperature variability tends to decrease in warmer climates, as observed in the decreased diurnal temperature range. The results of projected climate change indicate that all of Africa is very likely to be warmer in all seasons through this century. By taking Elagib's results of the mean maximum and minimum temperatures for several recording stations across Sudan and superimposing a linear trend line, one can see an annual temperature increase of 1 to 2°C since 1941 in many places in Sudan, particularly the central parts. Elagib also found that there has also been an increase in average mean temperature in Sudan. By examining a spatial distribution of interannual temperature trends, particularly in central to northern Sudan, one can see that the diurnal temperature range has shown a decrease throughout Sudan, meaning that temperatures are reaching an average which, when considered with the maximum, minimum, and average temperatures, show an overall increase in the temperature of Sudan. Moreover, these results show that, in addition to increasing temperature, there is greater overall instability in the climate of Sudan. (Elagib, 2010)

As stated by Elagib, "The region has become generally drier at significant rates in the areas designated with hyper arid and arid climates. The conditions of extreme drought have become recurrent and widespread during the recent 35 years." (Elagib, 2010) Less rainfall results in depletion of the soil moisture. The summertime maximum temperature days have become hotter as the soil dries. With enhanced radiation received, the release of sensible heat fluxes at the surface, in lieu of latent heat of vaporization, limits the evaporative cooling agent making it hotter still – a positive feedback effect. The statistical significance in the Elagib study is displayed by an 86% upward trend, compared to a 46% downward trend in temperature data. Regionally, the extreme eastern and western parts of the central region were more frequently affected by increased warming in Sudan, followed closely by the northern region. This has resulted in migrations south from northern Sudan. The trends in the data indicate that not only does temperature have an effect on rainfall in the Sahel region, but also rainfall has a principal effect on temperature as well, particularly with respect to localities, creating a positive feedback loop. (Elagib, 2010)

Section 2: Linking rainfall to conflict

There are strong historical linkages between civil war and temperature in Africa. The historical response to temperature, combined with climate model projections of future temperature trends, suggest a 54% increase in conflict incidence by 2030. Since 1960, about two thirds of sub-Saharan Africa have experienced civil conflict. There is quantitative evidence linking historical internal armed conflict incidence to variation in temperature, with significant increases in conflict during the warmer years. Burke conducted a study that combined historical responses of conflicts to climate projections from over 20 models. The effects propagate mainly from the dependence of the majority of poor African households on agriculture or grazing. Agriculture in Africa is heavily dependent on rainfall. The role of temperature and precipitation and their effect on the spatial and temporal variation in agriculture is an important factor in the analysis of conflict. Both higher temperature and lower precipitation have direct negative effects on agricultural productivity, upon which both livelihood and economy depend. If future conflicts are as deadly as today's conflicts, and we assume a linear increase in temperature up to 2030, then the warming-induced increase in conflict risk would result in an additional 393,000 battle deaths by 2030. The total loss of life - the human cost of conflict - would be much higher. (Burke, 2009)

In Sudan, decades of drought have preceded conflict. As reported by Giles, Marc Levy found that when rainfall is significantly below normal, the risk of a low-level conflict escalating into a full-scale civil war approximately doubles in the following year. An international crisis group in Brussels, Belgium, which monitors regions for conflict, has recently started discussing whether to include another variable in its analyses - climate change. An example of where this would be useful is Nepal, which witnessed fighting during the 2002 Maoist insurgency and suffered worse droughts in preceding years than in regions that were conflict free. In the Ivory Coast, the 2003 peace accord ended years of violence but many have not surrendered their weapons; ongoing drought in the north might destabilize the country and trigger a return to violence. In addition, drought can cause food shortages, generating anger against governments. Levy uses rainfall measurements and forecasts to calculate the impact of weather on conflict risk. Droughts and floods add to the pressure on governments and need to be monitored. While climate change will not be the sole issue causing conflict, it will exacerbate issues known to be linked to conflict and could act as a threat multiplier. (Giles)

There are several studies that indicate that climate has a direct link to conflict. Another example is the study by Hsiang, which has shown that the El Niño Southern Oscillation and its effects have had a role in 21% of all civil conflicts since 1950. The Hsiang study was one of the first to demonstrate how global climate change was strongly linked to the stability of modern societies. Specifics can be found in Hsiang's paper. (Hsiang, 2011)

Migration is a commonly adopted response strategy used by populations to adapt to livelihood stress. The extent of climate change related migration is likely to be highly nonlinear, and the extent of this nonlinearity is dependent on population growth. Migration behavior is determined by a host of microlevel factors including: access to the right capitals necessary to migrate, viability of alternative livelihood strategies, the extent of institutional barriers to migration, and the access to migration networks. In the Kniveton study, the focus is on migration that tends toward the adaptive end of the migration spectrum, with individuals migrating seasonally. Migration, by Kniveton, is defined as restricted to annual seasonal migration for the duration of the dry season, October to May. These factors were identified in an analysis of Burkina Faso, the inhabitants of which largely depend on rain fed agriculture and cattle raising - a situation and migration pattern very similar to that of the Misseriva. Models show that the drier scenarios depict periods of enhanced migration, particularly when separated by destination. The results show that when population growth is nonzero, a climate change signal in migration seems to emerge; as population growth increases, the impact of climate change on migration is enhanced. The low-level influences of demography. combined with the impact of climate on individual behavior, produce nonlinear and emerging changes in total migration that are not apparent when considering climate change alone. (Kniveton, 2012)

Evidence of abandonment of rural land can be found all along the northern edge of the Sahel, due to the encroachment of the desert. The UNEP reports that the long-term regional climate change in several parts of the country include an irregular but marked decline in rainfall, especially in Kordofan and Darfur, with the greatest decrease on the northern edge of the Sahel. In Darfur, for example, millions of hectares of marginal land have become desert due to rainfall decline. This has created a stress on the livelihood of pastoralist societies and has forced them south. The final results of the studies examined by the UNEP report are alarming in light of the conflict in Darfur. Recent data shows that a 2°C warming is guaranteed, and higher average warming is probable. The stresses created by this warming will be proportional. (UNEP report, 2007)

Migration, resulting from a net loss in agriculture, grazing land, etc., is an adaptation response, a livelihood strategy composed of different types of movement: permanent, temporary, or seasonal. Often, it consists of movement into, outside, and within arid lands due to increasing water shortages, poverty, food insecurity, and frequency of drought. Migration has a role in both increasing and reducing risks to societies. Net negative migration generally occurs over large areas due to migration's inherent rural character. In developing nations, migration occurs out of marginal dryland, mountain ecosystems and drought prone areas. Increasingly, environmental factors influence migration and therefore affect population distribution and movement. A minimum of 2 to 4°C warming is expected this century, changing temperature and precipitation pattern norms. This in turn can prompt migration and lead to civil and intrastate conflicts, which are a precursor to population displacements. Environmental displacements take place mostly within national boundaries, such as the seasonal migration patterns of the pastoralists. (Sherbinin and Levy et al, Nov 2012)

Section 3: A brief look at tribes, migration, and conflict

The conflict between tribes comes from competition over limited resources and land. Furthermore, these separate groups often have widely disparate livelihood strategies, which they aim to implement on the concurrent plots of land, causing conflict. Such is the case with the Misseriya and the Nuba and with the Misseriya and the Dinka.

The UNEP report designated three major groups with varying livelihood strategies within Sudan. The first is composed of predominantly sedentary crop rearing societies and tribes, such as the Nuba. The second are the predominantly nomadic livestock rearing tribes, for example, the Misseriya, who migrate seasonally and use land primarily for grazing. Third are the owners of and the workers on mechanized agricultural schemes. The mechanized agriculture farmers have increased the stress by their unrestrained land grab from the first two groups, escalating conflict. The three groups identified by the UNEP report are competing for the same land and depend on rainfall for their livelihood. The most recorded local conflict occurs between the pastoralists such as the Misseriya and the agriculturalists such as the Nuba and the Dinka. In Darfur and Kordofan, there has been a long history of clashes due to competition over agricultural and grazing rights. Many studies indicate that between 1930 and 2000 the driving force behind the majority of local confrontations was competition for pastoral land and water. In fact, only 16 out of 41 local conflicts near Darfur in the last 70 years were not water related. (UNEP report, 2007)

The disappearing livelihoods for dryland pastoralist societies resulted in shifting annual herd movements. Misseriya began to have conflicts with tribes en route to their seasonal destination after the British aggravated the situation between tribes. Prior to this, the pastoralists recognized and negotiated with the Nuba chieftains; this was far more successful than attempted negotiations with the involvement of the established Sudanese government. Factors such as water, land availability or allocation, and migration routes all played a role in triggering conflict. (Suliman, 1998)

As pastoralists that depend on cattle for their livelihood, the Misseriya need to migrate in order to survive. They have been doing this for thousands of years, but lately their habits are changing. The likely reaction of the pastoralists to these environmental stressors are as follows: abandonment of livelihood in favor of farming or cities; increasing and varying extent of annual herd movements with a general interannual southern trend; maximization of herd sizes; change of herd composition due to curtailment of long-distance migration, such as replacing camels with sheep; movements through or grazing on cropland without consent; attempted reduction of competition by forcing others off previously shared land. The southward trend in migration in particular is a harbinger of renewed conflict in the Nuba Mountains.

The Misseriya have had a history of conflict with both the Nuba tribes in the plains near the Nuba Mountains and the Dinka tribes around Abvei. The Misseriva moved into the plains that belonged to the Nuba and have forced them out, and have even taken them for slaves, starting from 200 years ago. While there were eventually treaties between the two tribes, the agreements were asymmetric and the Nuba still had to endure being taken for the slave trade. Today, not much has changed for the Nuba. They are still kept from farming their lands and their options for survival are few. More recently, the Dinka were in conflict with the Misseriya due to the migration route that the Misseriva took. The Misseriva are still in conflict with the Nuba and the Dinka. Even as recently as 2011, the Misseriva helped in transposing the Dinka from their lands near Abvei.

Fertile land is scarce, especially in South Kordofan. In recent decades, land was given by the Sudanese government to mechanized farmers; this created further conflict with indigenous farmers. Furthermore, since the mid-1970s, the delicate balance of soil, climate, water, and flora have been disrupted, particularly in the northern semi-arid regions, caused by persistent drought, unsustainable methods of land use, and overgrazing of marginal lands. There has been unprecedented extraction of renewable resources by members of the northern Sudanese traditional merchant class. In addition, bond conditions by the World Bank and the IMF caused a shift away from local needs towards international needs. This caused a collapse of prices and resulted in peasants and pastoralists having to produce more goods from a shrinking resource base. The expanding population, mechanized farming, and political and ethnic tensions have required movement to other ecozones, which further exacerbates tensions. This was especially prevalent in Darfur and South Kordofan. In Darfur, drought was followed by a flaring of skirmishes. The destruction of the Sudan-Sahel ecozone affected 70% of the total Sudanese population. (Suliman, 1998)

Conclusion

The historical, ongoing, and forecasted shrinkage and degradation of remaining range lands in the northern part of the Sudan-Sahel belt is due to a changing climate. Sea surface temperatures are rising and their effects are devastating to more than just the coastal cities in the US. It has been established that there is a direct link between sea surface temperature variabilities and the intertropical front, the El Nino Southern Oscillation, and rainfall patterns in the Sudan-Sahel zone. Furthermore, the increase in land surface temperatures has an effect on precipitation patterns and vice versa in a feedback loop mechanism. The connection between drought and conflict has been established in many varied scenarios.

Studies of the effects of drought on population indicate a resulting increase in variable internal migration patterns. This becomes another trigger for conflict. Direct correlations have been established between temperature, drought, rainfall variabilities and the incidence of small scale conflicts escalating to civil wars. Combining the past and current evidence of migration with the expected average temperature increase of about 2 to 4 degrees Celsius reveals that an increase in both conflict incidence and intensity is probable. The availability of fertile land in Sudan, which is dependent on annual rainfall variability, is likely to cause an increase and shift in established migration patterns, raising the likelihood of increased conflict in the region.

While this paper has attempted to establish the correlation between global warming and conflict in Sudan, it has not addressed the resultant consequences or policy impacts. It does, however, raise questions about the unbalanced nature of the effects of global warming. It is impossible not to acknowledge that the nations that face the highest risk of conflict as a result of changing climate are the developing nations, which are unable to mitigate the effects of a rapidly changing world. The populations facing risk are those that did not generally contribute to the cause. The question then is whether this increased risk of conflict due to unviable livelihood strategies can be mitigated by monetary contributions or even guidance in adaptation strategies. Moreover, who, if anyone, has the right or obligation to involve themselves in the highly probable upcoming crisis these developing nations face?

Acknowledgements

It is a pleasure to acknowledge the guidance that I received from Professor Ted Postol at the Massachusetts Institute of Technology and for the ideas, encouragement, and support that I received from the very beginning from Nathaniel Raymond, Benjamin Davies, Isaac Baker, Brittany Card, and Ziad Achkar at the Harvard Humanitarian Initiative's Signal Program. This paper would not have been written without them.

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