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# THE GENETIC UNDERPINNINGS OF SLEEP DURATION

#### Individual fruit flies similar to the type used in Harbison's study. https://naturligtliv.dk/category/hus-og-hobby/naturlig-rengoering/

## by LILY DING '20

At Choate, many students compare how much sleep they get each night as a measure of academic prowess. It is not uncommon to hear students telling others about how they only got five hours of sleep and still managed two tests the next day. There are numerous factors that contribute to the length of a person's sleep time and in the case of students that includes homework, upcoming major assessments, extracurricular commitments, and stress. However, there is another factor that most have not considered: genes!

Recently, a relationship between a specific group of genes and sleep duration was discovered. Led by Susan Harbison, Ph.D., an investigator in the Laboratory of Systems

and Blood Institute (NHLBI), this study could possibly lead to better approaches for treating sleep disorders such as insomnia and narcolepsy.

For а long time, scientists have recognized that genes

play a key role in sleep patterns and durations, but the exact genes that control these biological processes are unclear. In the study, published December 14, 2017, scientists used a population of fruit flies (Drosophila melanogaster) chosen because of the similarities between their circadian internal clock and the human one to collect data that could be used to model natural variations in sleep be-

Genetics at the National Heart, Lung havior applicable to humans.

This study is an important step toward solving one of the biggest mysteries in biology: the need to sleep."

In the NHLBI study, individuals from a population of wild type fruit flies were artificially bred over the course of thirteen generations to create two types of fruit - Susan Harbison fly populations: long sleepers who slept

> for eighteen hours per day, and short sleepers who slept for only three hours each day. The genetic data between the short and long sleepers were then compared.

> Harbison and fellow researchers then identified 126 differences among 80 genes that were associated with sleep duration. These gene deviations contribute to how much sleep each type of fruit fly needs

without compromising patterns of function during waking periods. This is similar to humans, as each person seems to need different minimum hours of sleep to function well. In addition, the scientists determined that these genetic differences are linked to several important developmental and cell signaling pathways, while some of the identified genes are known to have functions related to brain development and memory.

Harbison says, "This study is an important step toward solving one of the biggest mysteries in biology: the need to sleep...The involvement of highly diverse biological processes in sleep duration may help to explain why the purpose of sleep has been so elusive."

In addition to sleep duration, the researchers also discovered that the lifespan of long and short sleepers did not differ significantly from that of normal-length sleepers, thus indicating that there are few physiological consequences of sleeping for an extended or a limited period of time.

This NHLBI study is unique relative to other research labs doing similar experiments because the fruit flies with varying sleep patterns were created using the preexisting genetic material in the founder population. The fruit flies were not engineered to have different genotypes, nor were they the result of inserting DNA from a different organism. The latter process is transgenesis and is frequently used to create populations that generate data for animal modeling systems. Transgenesis involves injecting foreign DNA directly into the nucleus of embryonic cells or by using a retroviral vector to insert the transgene into the fruit fly's DNA.



Over the course of thirteen generations, individuals from a population of wild type fruit flies were selectively bred to generate populations of long sleepers, normal sleepers, and short sleepers. *https://www.nhlbi.nih. gov/news/2017/sleep-or-not-researchers-explore-complex-genetic-net-work-behind-sleep-duration* 

However, transgenic flies usually only contain genetic fragments and are not dependably comparable to the endogenous genes. This means that transgenic genes do not always perform the same way that naturally occurring genes do. Because Harbison's team was able to create short and long sleepers from a population of normal sleepers without modification of the DNA, the results are more applicable. The naturally-occurring genes in humans that contribute to sleep patterns correlate more closely with the bred fruit fly populations compared to genetically engineered ones.

In the future, Harbison hopes to identify which gene networks contribute the most to sleep duration and to determine if the information gained by studying those genes in fruit flies is transferrable to humans. If so, it raises the possibility of this type of research leading to better treatments for sleep-related disorders.•

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# STOPPING TRANSPORTERS TO STOP TUMORS

## by KATE SPENCER '20

Decades of research have been devoted to uncovering the molecular basis of gliomas, tumors that originate in the glial cells of the brain or spinal cord and grow from this supportive brain tissue. A recent discovery regarding the relationship between protein RanBP6 and epidermal growth factor receptor (EGFR) may help to understand a possible origin of the malignant brain cancer glioblastoma.

Glioblastomas represent approximately 70 percent of all astrocytoma, or tumors that occur within the cerebral hemispheres of the brain. As highly malignant tumors, glioblastomas produce a large number of tumor cells and are nourished by a heavy blood supply, but they rarely spread through the body. The treatment of the cancer, however, is difficult as the tumors contain a variety of cells that respond differently to treatments. Combined with the limited understanding of the genetic causes of this type of cancer, glioblastoma has remained largely elusive for patients, doctors, and researchers.

Epidermal growth factor receptor is a transmembrane protein to which epidermal growth factor binds. In a healthy cell, when the growth factor binds to EGFR, it causes the cell to grow and divide in a controlled manner. A mutation that causes the accumulation of an abnormally high number of receptors on the cell surface is correlated with excessive cell growth even in the presence of normal levels of epidermal growth factor. This induced level of cell division is correlated with the formation of cancer. It had been supposed that blocking the binding sites would interrupt the EGFR signaling and prevent the growth of EGFR-expressing tumors.

Co-lead authors Barbara



# 5-Year survival rates of brain tumor types

Oldrini and Wan-Ying Hsieh recently uncovered an additional layer of complexity in the expression and regulation of EGFR. They identified a previously uncharacterized protein, RanBP6, as a modulator of EGFR expression. RanBP6 is a member of the family of proteins involved in the transport of macromolecules through the pores of the nuclear membrane. Specifically, RanBP6 controls the nuclear import of STAT3, a signal transducer which activates transcription. The silencing or elimination of RanBP6 impairs the nuclear translocation of STAT3 and results in transcriptional depression of EGFR.

Head researcher Massimo Squatrito noted, "Our studies showed for the first time that STAT3 is a direct inhibitor of EGFR expression. I believe that this has important clinical implications: STAT3 inhibitors are currently being investigated for the treatment of glioblastoma and other tumor types."

The impact of this experiment is expected to accelerate not only glioblastoma studies but also to advance the understanding of the genetic alterations that are at the root of many types of cancer. Oldrini concludes that "Our results provide an example of EGFR deregulation in cancer through silencing of components of the nuclear import pathway. We have identified a new link...which warrant[s] further study as inhibitors targeting nuclear transporters enter clinical evaluation as cancer therapeutics." •

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# HOW VIRTUAL REALITY IS RESHAPING MEDICINE

by ARIEL KIM '20

Virtual reality (VR) refers to the newly developed technology that simulates or emulates reality through a computer generated environment. Until recently, virtual reality had been a futuristic invention. According to Stuart Dredge, however, when American teenager Palmer Luckey created the first prototype of a VR headset in 2010, then went on to create Oculus Rift, the age of virtual reality began.

Since then, virtual reality has been applied in many industries, such as entertainment, education, sports, and even medicine, because of its ability to realistically simulate environments and situations. In fact, VR is reshaping medicine by revolutionizing surgical training, creating methods for pre-operative planning, and helping to reduce stressful or painful patient experiences.

Surgical training through VR simulation programs is gaining more popularity recently as more companies develop high-quality simulation programs. Traditional surgical simulation methods are complex and difficult to use as well as incredibly expensive with high maintenance costs. Full or partial replacement with VR is an attractive option.

One virtual reality training platform that has gained fame recently is Osso VR. This company

utilizes VR to enable surgeons to perform orthopedic surgery virtually and to measure their performance instead of using the 3D plastic models of bones created by Sawbones Corp. According to Forbes Magazine, surgeons who train with Osso VR achieve results twice as good as those trained using traditional methods.

Another company, ImmersiveTouch, uses Vive and Rift Head Mounted Displays (HMDs), patient-specific anatomy, and haptic (tactile) feedback to train surgeons and conduct patient demonstrations. This company provides simulation programs in neurosurgery, orthopedic surgery, ophthalmology, as well as ear, nose, and throat procedures, and has reduced the average number of surgical errors by 54 percent. Fink (2017) reports that because of this outcome, many elite medical institutions and hospitals, such as Johns Hopkins and the University of Chicago, use ImmersiveTouch's simulation programs to train their surgeons.

Moreover, some surgeons are live streaming their operations through VR cameras so that residents, medical students, and even interested civilians can experience the entire operation from the perspective of a surgeon. Thus, VR can not only provide simulations for training, but can also provide easier access into the actual surgical operation experience. According to Dr. Shafi Ahmed, a surgeon and co-founder of Medical Realities, "It's ... important that people who are training in medicine see problems. There is not a perfect operation, ever. If we have some complications, you have to see how to deal with them." In 2013, Ahmed used Google Glass to livestream the removal of a cancerous liver while 13,000 students from 113 countries watched it.

In addition to helping medical students and medical residents, VR can benefit veteran surgeons. A startup named Surgical Theater created a technology called SuRgical Planning (SRP) that allows for neurosurgical pre-operative planning. This technology utilizes the patient's CT and MRI to create a realistic and dynamic three dimensional model. Fink



http://medicalfuturist.com/5-ways-medical-vr-is-changing-healthcare/

# Technology | 6

(2017) reports that surgeons can then "mentally rehearse the entire operation ahead of time" by reviewing the complex anatomical structures and surgical procedures prior to the actual surgery.

According to Sergio Agirre, chief technology officer of EchoPixel, "X-rays, CT scans, and MRI scans can now be turned into high-resolution 3D images in under a minute" with new VR technology. Complicated surgical procedures that require surgeons to do meticulous pre-operative planning can now be performed more smoothly. For instance, at Masonic Children's Hospital in Minneapolis, three-month-old twins were conjoined quite extensively, having intricate connections between their hearts and livers. This interconnection of critical organs made the surgery complex and potentially life-threatening. Prior to the procedure, the surgical team created a meticulous virtual model of the twins using CT, ultrasound, and MRI scans. With this model, the team identified potential pitfalls that could be encountered during the surgery and planned how to avoid them. The operation was successful.

VR is also being used to calm patients and to take their minds off their painful medical problems and situations. Anesthesia and sedation can be risky for certain patients, particularly for the elderly. In these cases, some surgeons offer VR headsets during minimally invasive procedures to help the patient control pain without medication. Results have shown that VR is successful in reducing anxiety and discomfort during procedures. DiGiulio (2017) notes that it can be useful for making injections and frightening procedures less painful or traumatic for children.

Overall, the impact of VR on surgical training, pre-operative planning, and the reduction of pain and stress in medical patients is tremendous. Doctors and researchers are hopeful that VR will continue to revolutionize the understanding and treatment of disease in even more ways in the future. •

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In the middle of winter, cold weather and heavy snows are to be expected. Though not surprising, and often very exciting when first experienced, snow can become difficult to deal with as the season progresses. Road safety during harsh weather involving precipitation and cold temperatures becomes a significant concern. The snow must be cleared and roads must be kept as free of ice as possible so accidents can be prevented.

Ever since experimentation began in 1938, road salt has been considered a viable solution to ensure safer roads. Also known as rock salt or sodium chloride (NaCl), it is a substance made of the same chemicals as table salt. Its ability to lower the melting point of snow seemed to be the ideal method for clearing roads. Only three years after road salt was introduced in the winter of 1942, five thousand tons of salt were spread on roads and highways throughout the nation. Now, it is commonly spread on roads everywhere with over 24 million tons of salt used every winter on roads across the United States. The salt that makes regular appearances on the Choate campus is a combination of sodium chloride and magnesium chloride.

Given this volume, it is relevant to ask where does road salt go after it does the job of melting snow on streets and sidewalks? What many people do not realize is that after the salt interacts with snow, there is actually nothing done to get rid of it. As the snow or ice turn to water, the salt is washed away, ultimately entering bodies of freshwater or the ocean. It comes as no surprise that neither of those is good for the environment.

Over time, the problem has grown in magnitude and measurable changes in salinity levels exist. In streams near areas with a high concentration of paved roads, salt levels are high enough to alter aquatic ecosystems. Even levels not considered lethal impact organisms and their ability to function. Relatively moderate salt levels in freshwater pools can cause a decrease in the reproductive capacity of amphibians. In terrestrial ecosystems, road salt run-



Model projection of annual deicing salt deposition around highways I-55 and I-355 and small surface roads with the spacing of some test sites shown. *Illinois Department of Transportation (DOT) in collaboration with Argonne National Laboratory (ANL) and the U.S. National Atmospheric Deposition Program/National Trends Network (NADP/NTN)* 

off changes soil chemistry and causes browning in plants or leads to a decrease in nutrient uptake. Even in larger bodies of water, accumulation of salt has a discernible effect. Salty water sinks, affecting organisms living in the deeper levels of freshwater ponds.

The use of road salt not only negatively impacts ecosystems, but also human health and wellness. Road salt can collect near or in sources of groundwater which provide well water for many communities. The United States Environmental Protection Agency suggests that up to 20mg/L of sodium in drinking water is a safe concentration. Despite the limit for sodium in drinking water, highly problematic because salt contamination can persist for years in reservoirs and aquifers.

To no surprise, alternative solutions to slippery road conditions have been pursued. But all of the possible materials used to mitigate icy road and sidewalk conditions have varying degrees of negative consequences. Sand is seen as a possible option and is often used on surfaces directly over water ways. However, sand does not lower the freezing point of water and can cause increased sedimentation along roads. Potassium acetate, on the other hand, is more effective in terms of how quickly it melts snow but in aquatic systems it severely re-

a 2008 study in Dutchess Countv. New York found the water of 125 wells had an average sodium concentration of 48 ma/L and that almost half of the wells had a concentration significantly greater than 20mg/L. In 2015 drinking water supplies in regions of New Jersey with a high density of roads reached 108 mg/L, five times the recommended level. Water authorities had to dilute the supply with cleaner water from other sources. This is

duces oxygen availability. Beet juice has been tested on a small scale, but it has an odor and is not easy to apply. Oftentimes, the alternative products either are not sufficiently effective or also produce unwanted consequences. So, what really can be done? While no specific material is deemed better, something that could actually help is proper salt management. By setting goals with a targeted reduction amount and limiting the broadcast application of salt, the excessive use of salt on roads, parking areas, and walkways could be greatly reduced.

Salt is such a common substance that it can be difficult to see its invisible but negative effects. At the moment, there is no perfect solution for keeping the balance between road safety and healthy ecosystems. It is clear, however, that current levels of sodium chloride in the environment have become extremely detrimental to many non-human and human lives. •

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Donald Trump is a president in American history like no other. Anyone who has scrolled through Trump's Twitter account or even been exposed to a few of his tweets can feel his distinct style of interacting with the public. His characteristic use of the exclamation mark and that hyperbolic tone clearly set him apart from other politicians. Even simple phrases like "so sad!" and "wrong!" have become Trumpian icons. His revolutionary approach to public communication gives rise to numerous discussions; however, there is a great amount of evidence that the account @realDonaldTrump is not solely manipulated by Trump. Instead, a portion of his tweets come from his staff. The natural question arises: how is it possible to further determine whether a particular tweet comes from Trump's very own mind? Computational linguistic approaches happen to offer some unique insights on Trump's style and the true authorship of Trump's posts.

Natural language processing (NLP) is an interdisciplinary field of computer science, artificial intelligence, and linguistics that is concerned with using statistical methods and machine learning to process and analyze natural language data. The field is tasked with analysis problems such as part-of-speech tagging and sentence/word boundary breaking, or even text summarization and natural language generation. Some important everyday applications of NLP include machine translation and speech recognition. NLP may also be used in emergency situations such as natural disasters to quickly identify regions in dire need of aid through analyzing thousands of social media posts.

In order to analyze textbased data, some preprocessing of the data set needs to be done. The nature and degree of the data cleaning depend on the specific task at hand. Some simple techniques that are useful in text analysis include punctuation removal and decapitalization. When counting word frequencies, stemming, i.e. reducing inflected words to their stems ("wrote", "writes", "writing" -> "write"), may also come in handy. Getting rid of escape sequences and recovering HTML characters ("&" -> "&") are necessary steps as well if the data are stripped from the web. To take care of Trump's tweets, we might also want to delete retweets from the data set since they do not represent Trump's (or Trump's staff's) writing and replace various pictures, urls, and usernames with a single string corresponding to each type of item.

After we obtain a relatively clean data set, we can focus on specific features we want to analyze. Dr. Patrick Juola, an expert in text analysis, forensic linguistics, and stylometry, provided an excellent example of authorship analysis when he was requested to assess J.K. Rowling's novel The Cuckoo's Calling under the pen name Robert Galbraith before it was confirmed to be written by Rowling. The central idea of authorship analysis relies on the fact that all languages have some degree of free variation, be it different forms of the same word ("burned" vs "burnt"; "while" vs "whilst"), or different function words denoting the same relationship ("to" vs "at" the right of). Writers make subconscious but con-



A comparison of tweets emanating from Android and iPhone for the Twitter account @realDonalTrump. The morning tweets primarily originate from Trump on the Android while the campaign posts the majority of tweets from the iPhone in the afternoon. *Source: http://varianceexplained.org/r/trump-tweets/* 

sistent choices and fall into a habitual pattern, which can be statistically analyzed. Juola ran tests on *Cuckoo* and four other comparable novels written by Rowling and three other authors to compare their similarities. As one of the tests, he compared the distribution of word length using normalized cosine distance and found the top common words of each text. What's more, he computed the distribution of character 4-grams and word bigrams which are proven to be reliable indicators of authorship. An n-gram is simply a co-occurrence of n linguistic units such as characters, syllables, or words in a given text. For example, "appl" and "neap" are character 4-grams from the word "pineapple," while "I like" and "like fish" are word bigrams from the sentence "I like fish." These statistics are simple and efficient to compute, yet they can be great indicators when run over a large set of textual data.

So, what did linguists and data scientists find about tweets under Trump's account using various methods of statistical and linguistic analysis?

Ben Sugerman's site "Did Trump Tweet It" uses a trained machine learning model to determine the possibility of a certain tweet being posted by Trump himself. The training and testing data comes from the well-established assumption that the tweets posted by an Android device were written by Trump while the ones posted by an iPhone were by his staff. This assumption was confirmed by data scientist David Robinson. He found that the posts from Android were mostly only text and used a manual retweeting mechanism by copy-pasting the tweet and surrounding it with quotation marks, while the iPhone posts were much more likely to contain pictures and links and were mostly announcements and holiday greetings.

Using this tagged data set, Sugerman explored multiple features of the tweets and incorporated them in his machine learning model. First, each tweet went through a sentiment analysis algorithm and was associated with a sentiment measure. Sentiment analysis is commonly used for analyzing product reviews and customer surveys, which requires a quantification of the writer's attitude. Roughly speaking, the algorithm classifies texts into "positive," "neutral," or "negative." It is no surprise that tweets attributed to Trump are analyzed to be a lot more negative in sentiment, which agrees with the fact that he often appears to be angry and irritable on Twitter. Moreover, plenty of other features including word choice and grammatical structure were analyzed. Combining the predictions from models with different feature sets, the site suggests the probability of new tweets from @realDonaldTrump and @POTUS

being written by Trump.

Unfortunately, due to the limited size and length of social media textual data, linguistics alone cannot provide a full and definitive answer to the question of whether a certain tweet was posted by Trump, as it can more confidently identify authors of literature and legal documents. Trump's controversial post concerning his former national security advisor, Michael Flynn, stirred the public due to the speculation that Trump interfered with the FBI investigation of Flynn. "I had to fire General Flynn because he lied to the Vice President and the FBI. He has pled quilty to those lies. It is a shame because his actions during the transition were lawful. There was nothing to hide!" the post goes. However, it is also claimed that this tweet was actually the work of Trump's lawyer, John Dowd. Some people see the use of "pled" instead of "pleaded" as a dead giveaway that Dowd indeed wrote the tweet, but the real situation is much more complicated, as a single word usage is never a reliable indicator of authorship, especially given that "pled" and "pleaded" are both accepted use even in legal literature. Sugerman's site claims a high probability of 96.2% that this post comes from Trump. This seems to be a reasonable conclusion, since the exclamation mark at the end and the sentence structure looks typically Trumpian. However, it does not exclude the possibility that the writer behind the post is deliberately imitating Trump's style. A tweet with the 140-character limit is just not enough data to reach a conclusive result.

Certainly, analyzing Trump's tweets is not the only thing text analysis is capable of doing, but the field of natural language processing does indeed provide a fresh way of looking into political behaviors through scientific and quantitative lenses. The models we currently have for analyzing internet language and social media texts are nowhere near perfect: new challenges await for computational linguists to tackle. •

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by SE RI LEE '19

Imagine ordering a 10 oz New York strip at your favorite steakhouse. Your mouth waters as you watch the browning flesh sizzle and you inhale the nutty aroma infusing the room. You are witnessing one of the most complicated chemical reactions in the world: the Maillard reaction.

The Maillard reaction is a type of non-enzymatic browning that occurs with the presence of a reducing sugar and an amine group of an amino acid, the building block of proteins. This is one of three types of browning, the others of which are enzymatic browning (such as the spontaneous browning of fruits) and caramelization (a type of non-enzymatic browning that requires only the presence of sugars). Most foods that are cooked at temperatures around 250-300 °F undergo the Maillard reaction, caramelization, or often a combination of the two. Cooked onions, toasted bread, roasted coffee beans with added sugar - all foods that undergo this reaction - are nuttier and richer in taste as well as browner in appearance due to melanoidin, a nonvolatile compound produced in the reaction.

French chemist Louis Camille Maillard discovered this reaction not in his kitchen, surprisingly, but in his laboratory while studying the effects of glycerin and sugar on the amino acids of kidneys. In 1913, Maillard published his thesis on the complex, multi-step reaction mechanism to propose a viable cure for kidney diseases. Maillard's thesis drew wide attention in World War II, when the desire to industrialize food production grew in the military. Scientists soon discovered that Maillard's proposed mechanisms created products accountable for the smell of certain types of food and often for undesirable products that are formed in stored or canned foods.

In 1953, John E. Hodge, a chemist working at the U.S. Department of Agriculture in Peoria, simplified this complex mechanism into three steps. In the first step, a reducing sugar, such as glucose or fructose, reacts with an amino acid to form water and glycosylamine. (A reducing sugar is any type of saccharide that can give away electrons. It usually contains an aldehyde or ketone functional group. A Schiff base is also formed during the process.) Because of its instability, the glycosylamine then forms an Amadori or Heyns compound, depending on whether the initial sugar molecule was an aldehyde or ketone. Finally, the Amadori or Heyns compounds collide with each other to form numerous different products that give foods their nuttiness and brownness. Hodge's abridged version clarifies the complicated reaction, but it is important to note that the actual mechanism entails far more chemicals than the molecules mentioned above.

There are certain conditions that make the Maillard Reaction highly favorable. The most obvious one is temperature. As in the cooking of steak or onions and the toasting of bread, the Maillard reaction occurs rapidly at high temperatures. Lack of water and higher pH also contribute to the faster proceeding of the reaction. A piece of dry bread toasts faster than a piece of water-infused bread does. Cooked onions turn brown more rapidly with the addition of baking soda, an alkaline substance.

Though many Maillard products enhance the flavor and aroma of foods, some give foods an unappetizing flavor and are extremely hazardous to our health. For example, 2-acetyl-1-pyrroline, a compound that can be formed in Hodge's "third" step, adds a desirable flavor to foods like bread and popcorn. However, this same compound tastes unpleasant in pasteurized milk at high temperatures. The Maillard reaction can also yield acrylamide, a carcinogenic substance, found in french fries and chips.

Researchers are continuing to find ways to control this mechanism, varying the initial conditions at times to obtain the desirable products only. This multistep mechanism, however complex and magical it may be, continues to fascinate scientists and food-lovers. •

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# MAILLARD REAC





