

— BLUE MOON —

ANDOVER'S STEM-BASED MAGAZINE

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NO MORE SEX? THE
ADVANCEMENT AND ETHICS
OF IN VITRO
GAMETOGENESIS

IF NOT FOUR... HOW
ABOUT FIVE? THE FOUR
COLOR THEOREM

GRAVITATIONAL
WAVES AND THE
TECHNOLOGY USED TO
DISCOVER THEM



ISSUE II.

Blue Moon was created as a platform for STEM research, as a means by which students can exercise the final step of the scientific method: communication. It aims to foster curiosity and cooperation in both its writers and its readers. Bi-annual print publications are made possible by a grant from the Abbot Academy Association, continuing Abbot's tradition of boldness, innovation, and caring. Issue II of Blue Moon spotlights the diversity of student interests within the sciences, topics ranging from THC to gravitational waves to combinatorics.

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SCIENCE

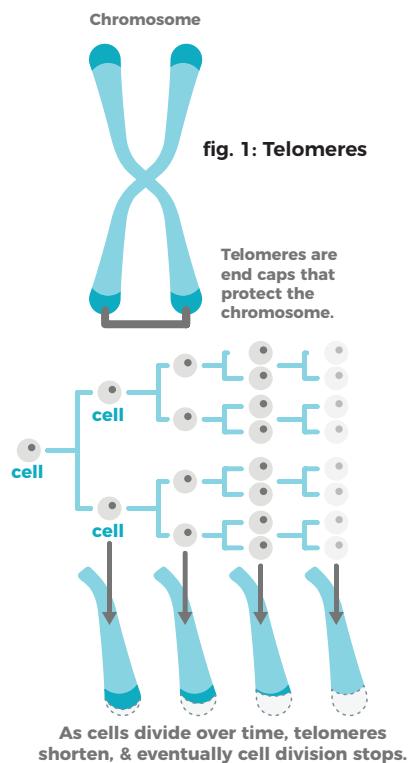
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WHY WE AGE AND CAN WE STOP IT?

DAVID MOON

For thousands of years, humans have tried to understand aging and death. What sets the limits on our lifespan? What can be done to slow down aging? The dream of cheating death has lead to a scientific quest to extend our lifespan. Scientists and doctors are looking for ways to maximize the number of years that we live free of cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Before we can intervene, however, we have to understand the cellular and molecular mechanisms that drive aging. Our telomeres (fig. 1), the tips of our chromosomes that shrink with age, might provide some clues. Other clues may lie in our stem cells, which cannot repair our tissues forever. The mitochondrial dysfunction and changes in the gut microbiota too may hold some answers to prolonging our lives.

Aging is an inevitable biological process characterized by a progressive decrease in physiological function (Gems, 2013). Transition through the aging process is associated with numerous molecular changes, such



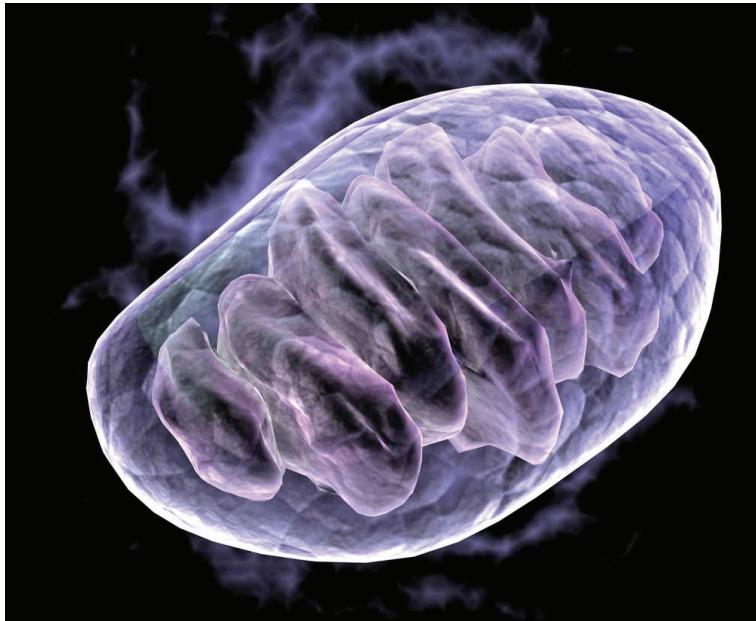


fig. 2: The strands within/around the inner membrane space are mitochondrial DNA.
Source: biodiverseperspectives

as altered gene expression and metabolite levels, somatic mutations and epimutations, and accumulated molecular damage. The age-dependent accumulation of damage has long been considered a general cause of aging. Many previous studies focused on particular forms of damage, such as oxidative damage, mutations, errors in transcription or translation, and damage to metabolites, as well as on cumulative damage. However, it has been difficult to prove the specific role of each in aging (Lee, 2017). Nevertheless, most researchers agree that molecular damages, including particular types of damage and the accumulation of damage, contribute significantly to the aging process.

Some scientists, however, proposed models that argue against the idea of molecular damages as essential contributors to aging. While acknowledging that damage does accumulate as a function of age, these models predict that this damage has no direct impact on the aging process. Instead, it is proposed that aging may be caused by hyperfunction or continued development because of excessive biological activities, leading to organ pathologies, before the damage can exert its deleterious effects (Blagosklonny, 2006). Hyperfunction and continued development are, in part, reflected in altered gene expression and metabolite levels. These models further expose the fact that the impact of either damage or other molecular changes on the aging process is difficult to characterize and quantify. Be-

cause the forms of damage are so numerous, and because they vary depending on factors such as genotype, environment, and diet, it is nearly impossible to prove the specific role of molecular damage to aging. At the current state of knowledge, there are nine tentative hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín, 2013).

Out of the nine groups, I will focus on the mitochondrial dysfunction. Mutations and deletions in aged mitochondrial DNA (mtDNA) may contribute to aging (Park, 2011). The mtDNA has been considered a major target for aging-associated somatic mutations due to the oxidative microenvironment of the mitochondria, the lack of protective histones in the mtDNA, and the limited efficiency of the mtDNA repair mechanisms compared to those of nuclear DNA (Linnane, 1989). Single-cell analyses have revealed that the mutational load of individual aging cells accumulates and may attain a state of homoplasm in which one mutant genome prevails (Khrapko et al., 1999).

The first evidence that mtDNA damage might be important for aging and age-related diseases derived from the identification of human multisystem disorders caused by mtDNA mutations that partially phenocopy

aging (Wallace, 2005). Further, causative evidence comes from studies on mice that are deficient in mitochondrial DNA polymerase γ , which is the only known DNA polymerase in human mitochondria and is essential for mitochondrial DNA replication and repair. These mutant mice exhibit aspects of premature aging and reduced lifespan in association with the accumulation of random point mutations and deletions in mtDNA. Stem cells from these progeroid mice are particularly sensitive to the accumulation of mtDNA mutations (Ahlgqvist et al., 2012). Future studies and research are necessary to determine whether decreasing the load of mtDNA mutations are able to extend lifespan.

Recent studies have shown that a great variety of factors and pathways can modulate aging, including genetic, pharmacological, or nutritional factors. In particular, previous studies identified two canonical nutrient-sensing pathways: mammalian target of rapamycin (mTOR) and insulin/insulin-like growth factor signaling. During aging, continuous stimulation of these pathways leads to a higher risk of aging-related diseases and a decreased lifespan due to reduced autophagy, increased protein aggregation and proteotoxicity, inflammation, reduced expression of antioxidant proteins, mitochondrial dysfunction, and other mechanisms (Kenyon, 2010). Modulation of these pathways is thought to affect the rate of aging and postpone the advent of aging-related diseases. One of the most significant aspects of these pathways is that they are regulated by nutrients. This nutritional relationship suggests the possibility that these pathways directly or indirectly regulate the patterns of age-related gene expression and molecular damage, suggesting that even our diet can affect molecular pathways that modulate aging.

Overall, more research and studies are necessary to fully understand the biological mechanism behind aging. While we have pinpointed several major mechanisms that are correlated with aging, they cannot be proven to have causal relationship to aging due to innumerable number of factors that need to be considered. Through these ongoing research in aging of our body, we might one day be able to achieve humanity's long desire to escape death. ■

See Appendix 1.1 for references.

BYPASS THE BYPASS

GABIJA SAGINAITE

Just like all muscles, heart muscle requires a supply of oxygen-rich blood in order to function. It receives blood from two major coronary arteries (CAs) that branch off from the aorta. In the case of coronary heart disease, CAs narrow or are blocked usually due to atherosclerosis—buildup of cholesterol or fatty deposits (plaques) on the inner walls of the arteries (“Coronary Artery Disease”, n.d.). Plaques clog the arteries, restricting the blood flow, which usually leads to a heart attack, as the heart muscle dies without sufficient amount of oxygen.

The bypass surgery is the most prominent surgical solution to coronary heart diseases at the moment. It helps to lower the risk of a heart attack, as surgeons takes blood vessels from another

part of the body and attaches one end to the aorta and the other end to the area on the other side of the blockage in order to create a path of blood flow around the blocked artery (James Beckerman, n.d.). Although these surgeries have a success rate of 95 to 98 percent, scientists believe that regenerating CAs would be more effective - instead of taking a part of already existing vessel, we could grow new arteries that could replace the blocked ones. So far people have been able to regenerate damaged heart muscle by inserting stem cells taken from the bone marrow into the heart using a catheter. Once in place, stem cells differentiate and develop into a new heart tissue. Yet the body may reject the stem cells if they are taken from an unrelated donor. This field still requires more long-term trials to

identify the stem cells' potential role in treating heart disease (“Bypass Surgery”, n.d.).

The obstacle to a similar treatment in regenerating the CAs has been the lack of understanding of how the coronary arteries form—which heart cells form the smooth muscle sheaths (caSMCs) are needed to form CAs, and whether they exist in adults at all (Ian Sample, 2015).

In 2015, a team of scientists at Stanford University tracked the development and differentiation of arterial muscle cells in adult mice by immunofluorescence of the epicardium, the tissue layer that covers the heart. They then traced the epicardial cell and all the cells it gave rise to, some of which became arterial muscle cells (Christopher Vaughan, 2015). It allowed the scientists to identify the originating cells for arterial muscle—pericytes, branched cells embedded within the basement membrane of capillaries (D. Ribatti Et Al., n.d.).

To be able to form new arteries on the heart's surface with pericytes, scientists needed to elucidate the molecular signals that induce pericyte differentiation into arterial muscle cells. The Stanford team characterized the expression of mural cell markers—a protein in the membrane of a mural cell that is unique to this one type of cell and helps to identify it—at the arterial remodeling zone—the area where the structure and arrangement of blood vessels is altered through cell growth, death, and migration—to identify molecular regulators of the differentiation from pericyte to caSMC. It was observed that a protein called Notch 3 was upregulated at the region where the expression of smooth muscle-myosin heavy chain (SM-MHC) protein, one of the most specific markers for mature smooth cell, was initiated (Katharina S. Volz Et Al., 2015) (Figure

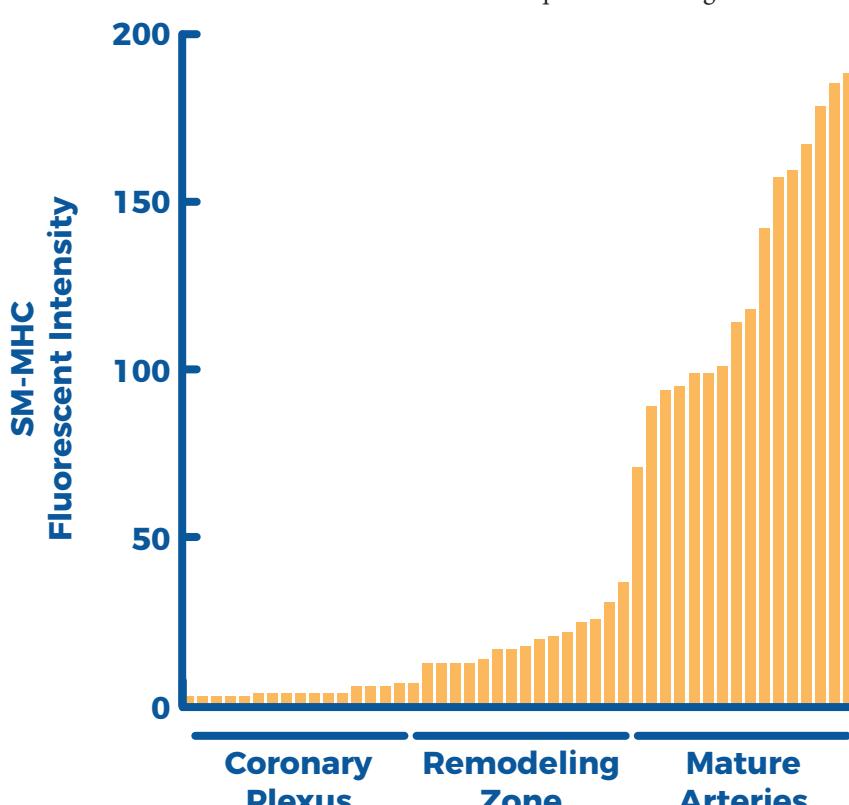


fig. 1: SM-MHC Levels in Individual Mural Cells at Different Regions of the Vasculature

1).

Jagged-1, a major ligand for Notch 3, is expressed in arterial endothelium and stimulates smooth muscle differentiation as well as the expression of SM-MHC by binding to Notch 3: while Notch 3 is upregulated in pericytes at the arterial remodeling zone, Jagged-1 binds to it, and it induces Notch 3 signalling pathway in endothelial cells in the same region after the initiation of blood flow (Figure 2).

As Notch 3 is upregulated in regions where SM-MHC is initiated, and Jagged-1 binding to Notch 3 is what induces Notch 3 signalling pathway, it can be hypothesized that the Notch 3/Jagged-1

receptor-ligand pair could trigger caSMC differentiation in coronary pericytes.

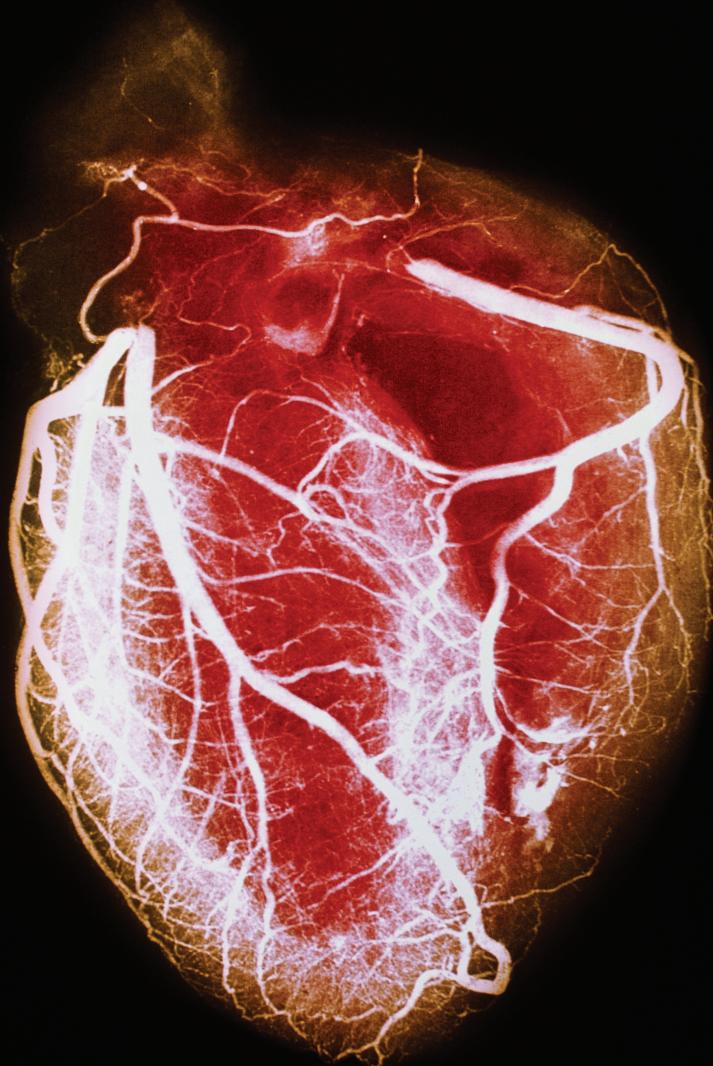
Yet it remains unknown whether diverted arterial blood flow due to CA narrowing or blockage causes Notch 3 signaling and differentiation of pericytes into caSMCs as a part of the formation process of collateral vessels—a smaller network of neighboring vessels that reroute blood around the diseased artery (Ian Sample, 2015). If so, perhaps the collateral formation could be made more efficient by stimulating Notch activity. If Notch 3 activity or its signals could be mimicked by a drug, the heart cells could potentially form

fresh arteries on the heart's surface, through which the blood could flow (Katharina S. Volz Et Al., 2015). Further research building on the discovery of pericytes could potentially lead to the development of a new, more effective treatment for heart diseases. ■

See Appendix 1.2 for references.

Source: Science Photo Library

fig. 2: coronary arteries



NO MORE SEX?

The Advancement and Ethics of
In Vitro Gametogenesis

JASMINE HARRIS

What do biological same-sex parents' babies, children of postmenopausal women, and single-sex parents with genetically related children have in common? With advances in science, all of these former figments of imagination are becoming possible.

In vitro gametogenesis (IVG) is the engineering of gametes, eggs and sperm, in laboratories instead of in the body. IVG can potentially become a form of assisted fertilization, or aid people and couples who are unable to biologically have children. The key to human IVG is embryonic stem cells (ESCs), also known as induced pluripotent stem cells (iPSCs) (Cohen et al., 2017). ESCs are a type of pluripotent, or unspecified cells that can eventually become specified or made into specialized cells such as that of bone marrow and originate from the inner parts of blastocysts, or a fertilized eggs that become embryos. ESCs are intended to be randomly made into specific cells, however scientists are finding ways to induce the creation of gametes with ESCs (Suter, 2016).

Another key component in IVG is gametogenesis. The traditional formation of an embryo involves the fusion of gametes during fertilization. Gametes are the cellular basis of reproduction and each hold genetic information that is passed down to a zygote, or a fertilized egg. Gamete production or gametogenesis naturally occurs in the gonads, the testes and ovaries of males and females, respectively. As females naturally produce eggs and males produce sperm, there are many difficulties in the conversion of one into the other. The lack of a Y chromosome makes the change from female gametes to male gametes more complex. The only way



Source: infertilityalabama
fig. 2: In Vitro Fertilization



fig. 1: two mothers and their children

Source: 4thtrimesterbodiesproject

that oocytes, or eggs, can become sperm cells is if the testes send hormonal signals (Suter, 2016).

Despite being unable to form eggs from sperm, in 2016 Chinese researchers were able to create primitive germ cells from ESCs and then use testosterone to form sperm (Cohen et al., 2017). Unfortunately, researchers have been unable to create eggs from sperm and are unsure whether this will be a possibility, as induced pluripotent stem cells have yet to transform into haploid gametogenic cells (Rettner, 2017). Another difficulty in gamete-formation from stem cells is that they must be able to undergo meiosis, a form of cell division, to produce more sex cells.

Imprinting patterns are also a potential obstacle in the progress of IVG. Imprinting patterns are the action of genes being tagged which ultimately determines how genes are expressed in offspring. Gametes have imprinting patterns that indicate maternal or parental origin. In zygotes, these patterns determine whether an allele is recessive or dominant. However, only a set amount of genes are expressed via imprinting patterns and the rest of the genes are expressed with both sets of maternal and paternal genes. To have IVG occur properly, imprinting patterns in ESCs must be temporarily erased, changed to that of a matured gamete with maternal or paternal patterns, and then must be translated to *in vitro* (Suter, 2016).

Recent breakthroughs in science include the creation of viable offspring from the ESCs of mice. Along with the leaps and bounds scientists are making in proving if IVG is possibility for human reproduction, a questioning of the ethics of IVG rises. Embryo farming presents itself as a potential issue, as people will be able to pick the most genetically fit characteristics for their child, down to the last detail (Rettner, 2017). A variety of embryos can be created via *in vitro* fertilization (IVF), or the fertilization of eggs with sperm outside the body, increasing the chances of conception. IVF has been in use for over twenty five years. The female who

wished to conceive is given a follicle-stimulating hormone (FSH) that increases the amount of eggs produced by the ovaries thus resulting in a higher chance of fertilization. Then, the eggs are surgically removed and mixed in a dish with male sperm. After a few days, fertilized eggs are able to be reinserted into the uterus. Unlike IVG, IVF uses gametes that originate from their respective sex instead of engineering them in a lab ("In Vitro Fertilization Today", 2016). IVG and IVF combined could allow multiple offspring to be created with the genes that the parents wish to be expressed. IVG can likely devalue human life with its methods. The advancement of IVG will also be hindered by multiple safety trials, as eggs created by IVG will be considered as "cellular and gene therapy products" by the Public Health Service Act and Federal Food, Drug, and Cosmetic Act. IVG involves the construction and destruction of embryos. Some laws have revoked funding for research that involves the use of embryos, as it is seen as unethical which further obstructs the progress of IVG research, including the U.S. with the Dickey-Wicker Amendment (Cohen et al., 2017). The Dickey-Wicker Amendment states that the use of embryos that could be potentially damaged or killed should be prevented (Adashi et al., 2011). Single-parent offspring suggests risks as scientists are unaware if the chance of health risks are similar to if there are closely related parents (Rettner, 2017). The more looming and pressing ethical issue with *in vitro* gametogenesis is the decomposition of traditional notions of parentage (Rettner, 2017). IVG questions the necessity for physical intercourse when progeny may no longer need to be created by the fusion of male-originated sperm and female-originated eggs. Although IVG will allow for people who are biologically unable to conceive to have children, ethical concerns with the practice may thwart future research and prevent IVG from becoming a common form of conception.

See Appendix 1.3 for references.

THC: A PROMISING TREATMENT FOR ACUTE LEUKEMIA

JESSICA YUJIA WANG

Despite its harmful physiological and psychological effects, THC has been proven to be a promising treatment for acute leukemia. This antitumor efficacy has been demonstrated *in vitro*, *ex vivo*, and *in vivo*.

Background Information of THC and Acute Leukemia

THC is the principal active constituent of cannabis (marijuana), which was introduced into New England in 1629 and remained a major crop in North America until after Civil War (Boyce, 1900, p. 35). However, because of the harmful physiological and psychological effects, cannabis has then been banned globally: by 2016, medical cannabis is legal in only 28 states in the U.S. and around 15 countries in the world, with most cannabis trades still taking place in black markets ("Legal Medical", 2016). While the exploration of THC's medical effects is highly limited, however, cultivation of cannabis for therapeutic use is not at all new ("History of", 2015). History of THC's medical values are documented across many cultures in many forms, such as written reports in a Chinese medical reference dating from 2737 B.C. ("History of", 2015). Additionally, it has been previously suggested by several cancer

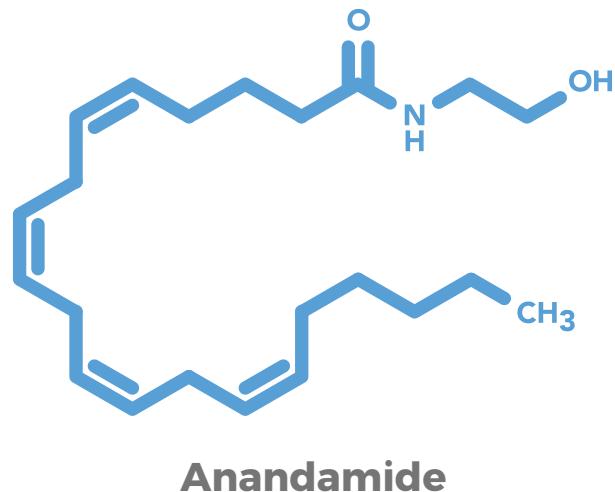
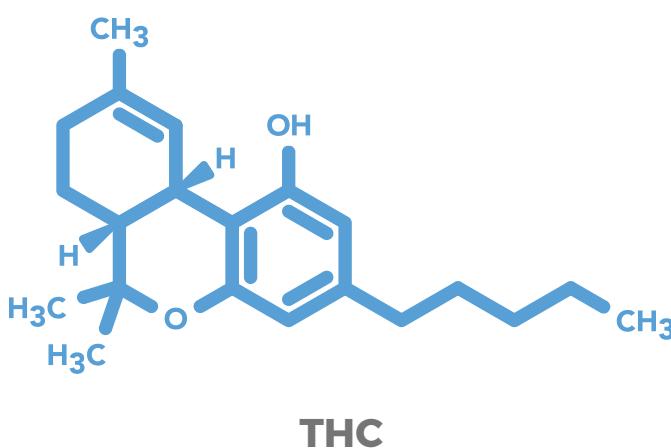
models that THC – more precisely, its main isomer (*-trans*- Δ^9 -tetrahydrocannabinol (also known as dronabinol) – have antitumor efficacy (Rieder et al., 2010). Being interested by these discoveries, scientists and doctors have recently examined the effects of THC on acute leukemia (Kampa-Schittner et al., 2016).

Leukemia is cancer of the blood cells, and different types of leukemia vary in the type of blood cell that becomes cancer. The treatment for leukemia generally depends on whether it is acute or chronic – acute leukemia undergoes malignant transformation quickly and requires immediate treatment, whereas chronic leukemia develops slowly over time. Leukemia is also classified as lymphocytic or myelogenous – lymphocytic leukemia is characterized by abnormal cell growth in the marrow cells crucial to the immune system, while myelogenous leukemia occurs on marrow cells that mature into blood cells and platelets ("Leuke-

mia", n.d.). Therefore, the four broad classifications of leukemia are acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia, with many subtypes under each category.

Interest in medicinal use of THC against acute leukemia grows recently with the discovery of cannabinoid receptors, protein molecules that are located throughout the body and receive chemical signals that affect various physiological processes such as mood and memory (Makie, 2008). There are two known types of cannabinoid receptors, CB1 and CB2. Normally, these cannabinoid receptors bind to endocannabinoids, or cannabinoid chemicals that naturally occur in the body (McKallip et al. 2002). These endocannabinoids send chemical messages along the nervous system like neurotransmitters and influence its regular function (Volkow, 2017). It has been suggested that through acting with these canna-

fig. 1: Skeletal formulas of THC (left) and Anandamide (right). Both molecules contain hydroxyl and methyl groups, and their three-dimensional shapes are very similar. But anandamide is more fragile than THC and breaks down quickly in the body, which explains why it doesn't produce a psychoactive effect like THC (Tetrahydrocannabinol, n.d.; Anandamide, n.d.).



binoid receptors (discussed more in depth later), THC can lead to apoptosis (cell death) in acute leukemia cells and thereby may be used to treat the cancer (Powles et al. 2005). As some laboratory and clinical evidence demonstrates positive results, this paper will attempt to investigate whether THC is a promising treatment that should be further studied and administrated more commonly on acute leukemia patients.

How THC Induces Apoptosis

THC is similar in molecular structure to the naturally occurred endocannabinoids such as anandamide [Fig. 1]. Therefore, THC is able to bind to the cannabinoid receptors, CB1 and CB2, as a competitive inhibitor and disrupt the body's normal mental and physical functions (Yamamoto et al., 1998). Despite the side effects, such as impaired memory and reduced learning abilities, that this competitive inhibition may cause, THC is proved to induce apoptosis of acute leukemia cells through the ligation (the binding of a molecule to a site on its target protein) of cannabinoid receptors (Bifulco et al., 2006; Powles et al. 2005). As apoptosis eliminates harmful or unwanted cells from the body, it plays a crucial role in biological development and health maintaining (Rieder et al., 2010). Thus, understanding the precise receptors and pathways of THC induction of apoptosis could contribute to the development of a more promising THC treatment against acute leukemia.

In general, effects of THC can be mediated by the aforementioned cannabinoid receptors, CB1 and CB2 (Lombard et al. 2005). These two receptors appear in different locations in the body: CB1 receptors are found extensively in several influential brain regions, while CB2 receptors are present mainly in immune cells and only a few neurons (Makie, 2008). Theoretically, because of the areas affected, high toxicity may be caused by over-activating CB1 receptors, but triggering CB2 receptors can avoid the harmful psychoactive effects of THC on the body to a large extent (Jia et al., 2006). In order to determine the specific receptor responsible for the pro-apoptosis

efficacy of THC, McKallip et al. (2002) examined these two types of receptors in an experiment where THC induced apoptosis in human acute leukemia lines *in vitro*. The result was that only CB2 receptors were expressed according to the screening of these cell lines (McKallip et al., 2002). Consequently, it can be concluded that THC leads to apoptosis of acute leukemia cells mainly via the ligation of CB2 receptors.

Condie et al. (1996) further illustrated the mechanism of THC induction of apoptosis on many acute leukemia cell lines. For example, in T cell leukemia cell line, THC binds to CB2 receptors and influences the T cell through inhibiting the activity of adenylyl cyclase, an enzyme that normally acts on adenosine triphosphate (ATP) (Condie et al., 1996). As a result, this inhibition blocks the ATP stimulation of cAMP, a second messenger used for intracellular signal transduction (Condie et al., 1996). Therefore, the activation of several proteins regulated by cAMP, such as protein kinase A and CRE, is decreased (Condie et al., 1996). This process also disrupts the function of the cAMP-regulated proteins that contribute to the growth of white blood cells, especially one of its subtypes, T cell (Condie et al., 1996). Thus, by blocking the normal function of the regulatory proteins of T cell, THC can lead to T cell apoptosis and thereby alleviates acute T cell leukemia (Condie et al., 1996). Even though the particular proteins affected vary from different types of acute leukemia, the overall mechanisms are similar; likewise, THC may induce apoptosis in other types of acute leukemia (Condie et al., 1996).

The molecular changes on acute leukemia cells caused by THC make up two different pathways of apoptosis: the extrinsic pathway through death receptors, and the intrinsic pathway via mitochondria (Lombard et al., 2005). The intrinsic pathway is triggered by an imbalance of anti-apoptotic and pro-apoptotic proteins that controls the permeability of the mitochondrial membrane, causing leakage of certain enzymes from the electron transport chain of mitochondria into the cytosol (Kroemer and Reed, 2000). This leakage

leads to reaction among enzymes that breaks down proteins and peptides and results in apoptosis (Kroemer and Reed, 2000). As for the extrinsic pathway, it is initiated by the ligation of death receptors, forming Death Inducing Signaling Complex that eventually leads to cell death (Kroemer and Reed, 2000). Both pathways play a role in THC induction of apoptosis on acute leukemia cells.

Evidence of THC's Pro-apoptotic Efficacy

Proof-of-principle data from experiments and researches confirm the pro-apoptotic efficacy of THC in a broad range of acute leukemia cell lines and blast cells cultured *ex vivo* and *in vitro*. In one study, Kampa-Schittenhelm et al. (2016) proved that THC was able to induce apoptosis in all acute leukemia cell lines, including but not limited to acute T cell leukemia, acute myeloid leukemia, and acute monocytic leukemia. In addition, the efficacy of THC was exhibited in a dose dependent manner, meaning the quantity of THC doses applied shows a direct relationship to the biological response [Fig. 2] (Kampa-Schittenhelm et al., 2016).

It has also been demonstrated that THC was capable of reducing viable native blast cells (a primitive blood cell often found in the blood of patients with leukemia) cultured *ex vivo*. (Kampa-Schittenhelm et al., 2016). Samples of blast cells were extracted from patients with acute lymphatic leukemia, acute myeloid leukemia, and acute lymphoblastic leukemia; and a considerable reduction of viable blast cells was observed after a 48-hour exposure to THC (Kampa et al., 2012; Kampa-Schittenhelm et al., 2016). The result also showed THC has a more significant effect on patients with acute lymphatic leukemia than those with acute myeloid leukemia [insert Fig. 3] (Kampa-Schittenhelm et al., 2016). The outcomes of these experiments and researches further prove that THC is capable of mediating antileukemic activity.

Anecdotal results of a clinical case further validated THC's antitumor efficacy *in vivo*. This case study was on a 14-year-old patient who was diagnosed

with a very aggressive form of acute lymphoblastic leukemia (Singh & Bali, 2013). The attempts to treat this patient with standard bone marrow transplant, aggressive chemotherapy, and radiation therapy all failed after 34 months (Singh & Bali, 2013). Without any other solutions, the family decided to administer THC extracts orally to the patient, which proved to be an effective treatment with further indications of the aforementioned positive dose-dependent correlation (Singh & Bali, 2013). The clinical observation of this case suggests that THC is able to effectively control the disease, as long as the dose is determined correctly depending on various factors (Singh & Bali, 2013).

The Future of THC Treatment for Acute Leukemia

Kampa-Schittenhelm et al. (2016) demonstrated that a more systematic and widely accepted THC treatment against acute leukemia *in vivo* was achievable. With detailed drug information provided by the safety profile of THC (drug information of

Marinol® - FDA), Kampa-Schittenhelm et al. (2016) extracted blood plasma from an acute leukemia patient treated with THC and showed signs of apoptosis of cancer cells. This patient was not going through any other antitumor therapies (Kampa-Schittenhelm et al., 2016). His blood plasma was immediately used to culture other acute leukemia cells *in vitro*, and apoptosis was observed (Kampa-Schittenhelm et al., 2016). Therefore, this experiment supports that a pro-apoptotic efficacy of THC is obtainable *in vivo*.

When it comes to the psychoactive side effects of THC, they may be minimized by slowly increasing the dose over time, which would build up the patient's tolerance, as shown in previous anecdotal cases (Singh & Bali, 2013). Meanwhile, the demonstrated

pro-apoptotic efficacy of THC may suggest an alternative approach to treating acute leukemia: although mainly examined *ex vivo*, the fact that the ligation of CB2 receptors induces apoptosis in acute leukemia cells indicates that targeting CB2 may be another method

of treating the cancer. In other words, if the concerns of legalizing medical THC widely still hinder its exploration, future studies could focus on the possibility of upregulating the patient's endocannabinoids or administrating non-psychoactive cannabis that has similar molecular structure as THC, in order to achieve the same medicinal effects through the ligation of CB2 receptors (Palazuelos et al., 2006). Therefore, treating acute leukemia while bypassing THC's psychoactive effects can be made feasible.

It goes without saying, however, that no matter the future therapies involves THC, endocannabinoids, or other types of cannabis; much more research and clinical trials need to be completed in order to ascertain the benefits of such treatments. Promising rationale has been provided for the medical use of THC in various entities of acute leukemia, thereby this approach should be further evaluated. ■

See Appendix 1.4 for references.

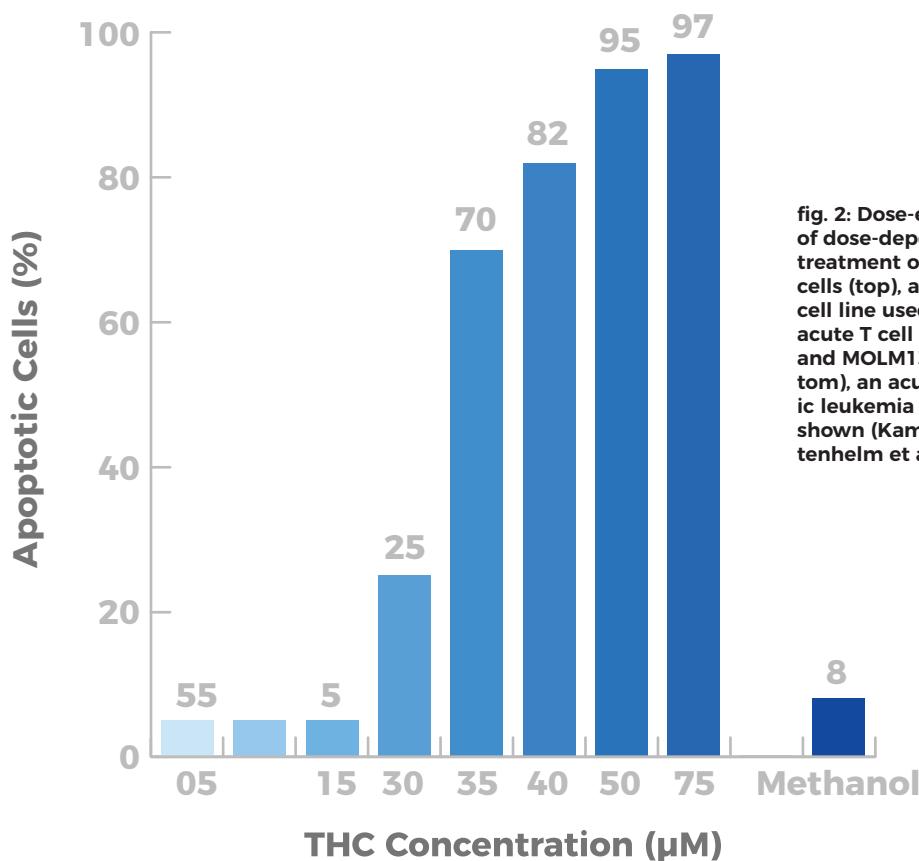


fig. 2: Dose-effect curves of dose-dependent THC treatment on Jurkat cells (top), a human T cell line used to study acute T cell leukemia, and MOLM13 cells (bottom), an acute monocytic leukemia cell line, are shown (Kampa-Schittenhelm et al., 2016).

MATH

i. If Not Four... How About Five? The Four Color Theorem

ii. Calculating Expected Value of Second Gonality and Beyond on Erdős-Rényi Random Graphs

iii. Enumerative Combinatorics

iv. Modeling Traffic Flow

v. RSA Cryptography

IF NOT FOUR... HOW ABOUT FIVE?

The Four Color Theorem

SHU SAKAMOTO

The Most Beautiful/Ugly Theorem

The four color theorem, which states that any map can be colored with four colors such that no two adjacent regions have the same color (Fig. 1), is known for the beautiful simplicity of its statement yet ugly brute-force proof. The theorem has never been proven mathematically — it has only been verified by an exhausting number of computational analyses. Some mathematicians do not accept this proof, but a counterexample has yet to be found.

In spite of this sad reality, there exists a simple mathematical proof for the related “five color theorem” that any high school student can understand.

Some Preparations

1. We can translate a map into a **graph** (Fig. 2). A graph is a set of unique vertices (states/countries) connected with several edges (borders). If a map has no enclaves or exclaves (like Alaska or the peninsulas of Michigan), which is in fact a prerequisite for the four color theorem, its graph will be a **planar graph**, which means that edges only intersect at vertices. In a complete graph, every possible pair of vertices is connected by a unique edge. A **complete graph** with n vertices is noted as K_n .

2. A planar graph can be treated as a polyhedron if we count every space bounded by edges, as well as the “outer bound” of the graph, as a face. It may help to think of the graph as a polyhedron for which all but one face is visible from one side. Then the graph must follow Euler’s formula for polyhedra, which states that $v - e + f = 2$, where v is the number of vertices, e is the

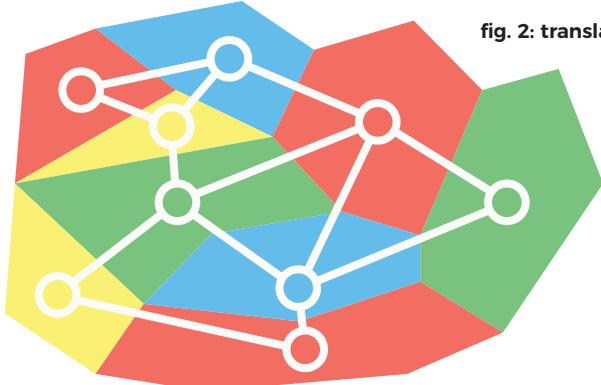


fig. 1: example of four color theorem

number of edges, and f is the number of faces.

3. For a planar graph, $e \leq 3v - 6$. To prove this, notice that each edge lies between two faces, so the “total” number of faces is $2e$ without adjusting for overcounting. When f_n represents the number of n sided polygons in the figure, f_{total} must be equal to $f_3 + f_4 + f_5 + \dots$. The number of faces based on the number of edges must be equal to $3f_3 + 4f_4 + 5f_5 + \dots$. Thus, $2e = 3f_3 + 4f_4 + 5f_5 + \dots \geq 3f_3 + 3f_4 + 3f_5 + \dots = 3f_{\text{total}}$. From $3f \leq 2e$ and $v - e + f = 2$, we get $e \leq 3v - 6$.

4. K_5 is not a planar graph. For the sake of our proof, let us assume that K_5 is a complete graph, which means that $v = 5$ and $e = (5 \text{ choose } 2) = 10$. This contradicts with $e \leq 3v - 6$, and therefore K_5 cannot be planar.

5. A planar graph has at least one vertex that is connected to less than 6

fig. 2: translation of map to graph

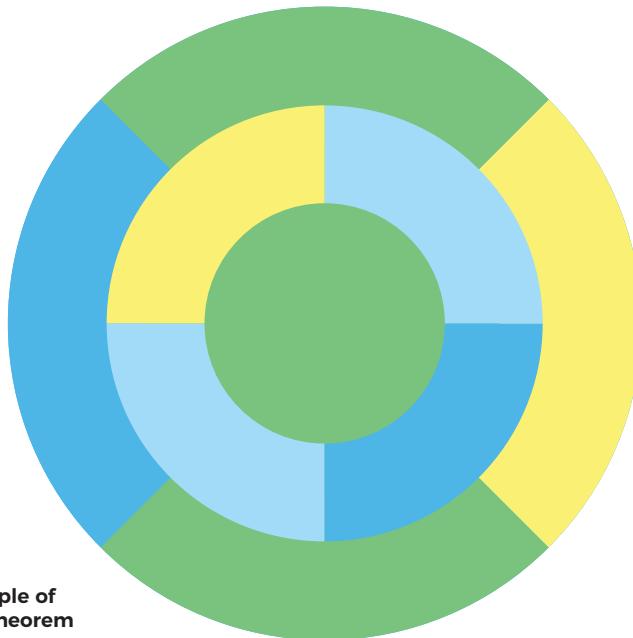
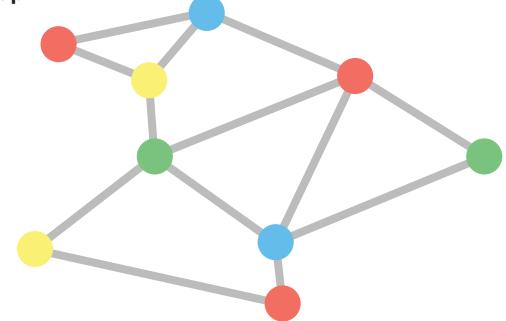


fig. 3: A circular map divided into four regions (green, blue, yellow, red) with a different internal structure than Figure 1, illustrating a more complex case for the four color theorem.

edges. For the sake of contradiction, let us assume that each vertex is connected to at least 6 edges, so $6v \leq e$. This contradicts our previous result that $e \leq 3v - 6$, so such a configuration is not possible for a planar graph.

The Real Proof

With all these statements, now we are ready to prove the “five color theorem.” The proof is fairly simple in contrast to the brute-force proof of the four color theorem.

We will prove the theorem using induction, i.e. assuming that the statement is true when $v = k$ and using that to prove it for a graph G with $v = k + 1$. From statement 6 above, the graph G has a vertex with less than 6 vertices connected to it. Let this vertex be noted as v , and G' be the graph of G where v is omitted. G' has k vertices, and since we

have assumed the theorem to be true for any graph with k vertices, we can color G' with five colors.

There are two possible cases:

1. When there are less than 5 vertices around v , we can color v with the remaining color.

2. When there are 5 vertices around v and all of them have different colors, let the vertices noted as v_1, v_2, \dots, v_5 and the colors as c_1, c_2, \dots, c_5 . Let the set of vertices that we can reach from v_1 by using only c_1 and c_3 be denoted by V_{13} .

- If $v_3 \notin V_{13}$, we can flip the color used for V_{13} between c_1 and c_3 and thus the color at v_1 to c_1 . We can now color v_3 with c_1 .
- If $v_3 \in V_{13}$, there exists a path from v_1 to v_3 that can be colored only with c_1 and c_3 . Since the map is a planar graph, there does not exist a path from v_2 to v_4 that can be colored only with c_2 and c_4 . Therefore, if we do the same with V_{24} with c_2 and c_4 , we can color v_2 with c_4 and thus v with c_2 .

Although the proof may seem complicated at first, it is very logical and elegant solution compared to the brute-force methods that mathematicians have used to prove the four-color theorem. Try coloring some maps yourself — a world map or a random one from your own imagination — and really prove to yourself that you can always color a map with just with five or even four colors. Or better yet, develop a mathematical proof that is just as rigorous as the one described above but for the four color theorem instead, and you could be on your way to winning a Nobel Prize! ■

ENUMERATIVE COMBINATORICS

NHAT PHAM

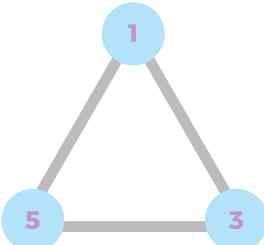


fig. 1: Graph representation of the permutation $w=325614$



I. Concept: Imagine you have 3 friends: James, John, and Jonathan. They all go to the commons and wait in line for the stir fry. How many ways can they form a line? One way to find the answer is to list all possible arrangements. There are only 6 possible ways to arrange them, so it should be manageable. However, what if another friend, Jocelyn, comes in? What if another friend, Jake comes in? The number of ways to arrange these friends in a line grows pretty fast, and soon you find yourself unable to exhaustively list all possible arrangements. What a bummer!

This is where math comes in! Instead of writing down arrangements, let's consider the problem in a more abstract way. Think of each arrangement as a series of choices. Suppose there are n people, then there are n ways to choose the first person in the line, $n-1$ ways to choose the second person in the line (as there are only $n-1$ people remaining), etc. This goes on and on, and finally we're left with only one (unlucky?) person for the final position in the line. This gives us $n \times (n-1) \times (n-2) \times \dots \times 1$ ways to arrange n people in a line. As this interesting product appears again and again in combinatorics problems, we usually call it n factorial and denote it as $n!$.

The above situation is an example of **permutation**, a very important concept in enumerative combinatorics. To put simply, a permutation is a way to rearrange objects in a specific order. Rigorously speaking, a permutation is a bijection from $[n]$ to $[n]$, where $[n]$ is the set containing the first n positive integers. As we have proved in the first example, the number of permutations of n objects is $n!$.

II. Permutation Representation: The simplest way to represent a permutation is to write it

out explicitly. For instance, if the permutation w sends 1 to 2, 2 to 3 and 3 to 1, we write $w=231$. More generally, if w sends i to w_i for i from 1 to n , we can write $w=w_1 w_2 \dots w_n$.

One interesting way to represent and visualize permutation is through a **directed graph**. A graph is a structure with a set of vertices and edges connecting those vertices. If the edges of a graph have direction, we say that the graph is **directed**. Given a permutation of $[n]$, we can create a directed graph with n vertices and n edges going from the vertex i to the vertex w_i . This representation gives us much more information and intuition about the structure of the permutation in general, as we will see above (fig. 1).

III. Cycle: If we look at the graph of a permutation, we can see that there are two types of structures: either a point is connected to itself, or it is part of a **cycle**. This means that if we start from one vertex and travels along the edges, eventually we will get back to the original point. It is the case that every permutation can be decomposed (uniquely) into a finite number of disjoint cycles.

IV. Type: Now let's look at what the cycle structure of a permutation implies. Suppose w is a permutation from $[n]$ to $[n]$. Then a cycle of w can have length from 1 to n . Suppose c_i is the number of cycles of length i . Then the sequence (c_1, c_2, \dots, c_n) is called the **type** of w , or w is a permutation of type (c_1, c_2, \dots, c_n) . A question then arises: Can we count the number of permutation of type (c_1, c_2, \dots, c_n) ? We have the following proposition:

Proposition: The number of permutation of type (c_1, c_2, \dots, c_n) is equal to

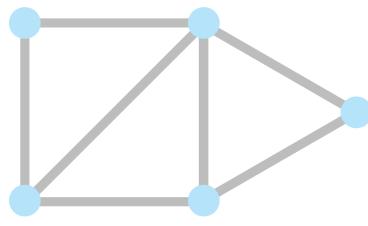
$$\frac{n!}{\prod_{i=1}^n i \cdot (c_i!)}$$

Proof: Suppose $w=w_1 w_2 \dots w_n$ is any

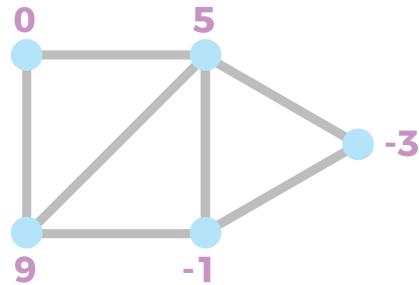
permutation from $[n]$ to $[n]$. Put brackets around w_i so that the first c_1 pairs of brackets has 1 element, the next c_2 pairs of brackets has 2 elements, etc. If all elements of each pair of brackets form a cycle, we then obtain a new permutation w' of type (c_1, c_2, \dots, c_n) and an injection f that maps from the set of all permutations of length n to the set of permutation of type (c_1, c_2, \dots, c_n) . Given a permutation of type (c_1, c_2, \dots, c_n) , we now claim that there is $\prod_{i=1}^n i \cdot (c_i!)$ ways to write it in disjoint cycle notation so that the cycle lengths are weakly increasing from left to right. Namely, order the cycles of length i in $c_i!$ different ways, and choose the first elements of these cycles in i^{c_i} ways. These choices are all independent, so the claim is proved. Hence for each permutation u of type (c_1, c_2, \dots, c_n) , the number of elements w such that $f(w)=u$ is $\prod_{i=1}^n i \cdot (c_i!)$, and this gives us the desired result.

V. Standard Representation: The notion of cycle decomposition gives us another way to represent a permutation. Instead of listing the elements of $[n]$ in order, we can group them based on the cycles they belong in. However, there is one problem with this idea: there is no unique representation of a permutation, as there are many ways to list the cycles and many ways to list the numbers within a cycle. We can work around this by following a set of rules: first, in each cycle, we start from the highest number, then the number that it is mapped to, all the way until the final number of the cycle. The order that we list the cycle is determined by the largest number of each cycle. This representation is called the **standard representation** of the permutation. Note that in standard representation, brackets are not necessary. We can recover the cycles by looking at the left-to-right maxima, which is elements a_i such that $a_i > a_j$ for $i < j$, and insert a right parenthesis so that it closes off the elements from one left-to-right maximum to right before the next one. Naturally, the number of left-to-right maxima is equal to the number of cycles of the permutation. ■

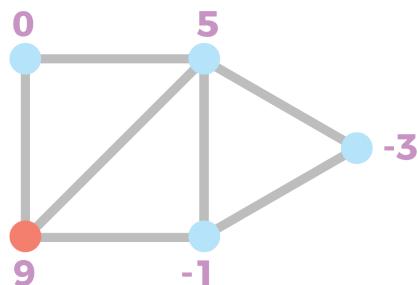
graph



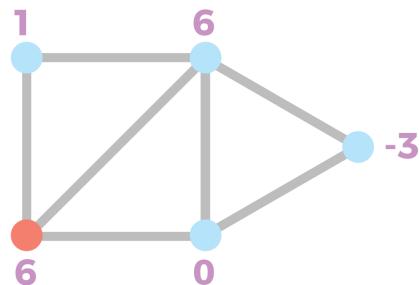
divisor on a graph



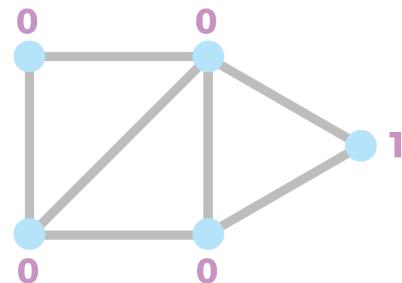
chip-firing before firing vertex



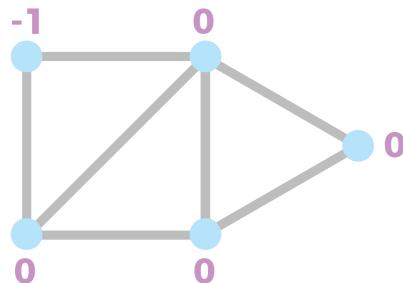
after firing vertex



effective



not effective



CALCULATING EXPECTED VALUE OF SECOND GONALITY AND BEYOND ON ERDŐS-RÉNYI RANDOM GRAPHS

WENDY WU

Sometimes mathematics gets extremely complicated. We've all had our moments where we look at some notation or theorem and wonder how it is even possible for anyone to understand. Mathematicians try to simplify math as much as possible to make it easier to deal with, and, ultimately, easier to attain results. Consider algebraic geometry, most generally defined as the study of geometric structures with an algebraic definition, such as a linear equation graphed on the coordinate plane. One specific field of algebraic

geometry deals with so-called divisors on an algebraic curve, where an integer is assigned to each one of the infinite points on a curve. A finite number of these integers are nonzero, and they are the primary points considered in this field. Attempting to calculate certain important and useful characteristics of such divisors using this definition is very difficult. Fortunately, divisors on graphs in graph theory form an analogy to such divisors on curves.

In graph theory, a graph is a set of points called vertices potentially connected by edges. A **divisor** on a graph is an assignment of an integer value, possibly negative, to each vertex. This is widely compared to placing piles of chips at each vertex. Each integer value assigned to each vertex on the graph corresponds with an integer value assigned to a point on the corresponding curve.

In this configuration of chips, an action can be taken, called “chip firing,” where firing a vertex consists of moving a chip along each edge emanating from that vertex to each adjacent vertex connected by such an edge. After firing a vertex, the number of chips in its pile decreases by the number of edges it is connected to, and the number of chips in each vertex connected to the original by an edge increases by one. Two divisors on the same graph, such that one vertex fired transforms the first divisor into the second, are regarded as linearly equivalent, or equal. Addition and subtraction between two divisors on the same graph is using the operation on the chip piles at corresponding vertices.

Another useful classification of divisors on graphs is if it is **effective**. A divisor is effective if it is equivalent to a divisor, through a (possibly empty) sequence of chip firings, with a nonnegative integer number of chips at each vertex of the graph.

Characteristics of divisors on graphs useful to gathering information on their corresponding divisors on algebraic curves include degree, Baker-Norine rank, and gonality. **Degree** is simply the total number of chips on a graph. The **rank** of a divisor is a concept introduced by Baker and Norine, mathematicians who studied chip firing games.

The rank of a divisor D is the maximum integer r such that for each divisor E with degree r , $D - E$ is effective. Rank is defined to be -1 if the divisor is not effective. The “ r -th” **gonality** of a graph is the minimum degree d such that a divisor exists on that graph with degree d and rank r .

This project studies gonality of one of the two Erdős-Rényi models for random graphs. We will consider the random graphs generated by $G(n, p)$, which will have n vertices and an edge existing between any two distinct vertices with probability p . Note that any graph G generated this way has no loops and at most one edge between any two vertices. The purpose of this project is to determine asymptotic behavior of the expected value of gonality of Erdős-Rényi random graphs in relation to number of vertices. As such asymptotic behavior of first gonality of random graphs has already been calculated and higher gonality are difficult, the current focus of this project is calculating asymptotic behavior of second gonality.

It has been determined that first gonality of random graphs approaches the number of vertices as that number gets large, and second gonality should approach a value between the number of vertices and 2 times that number as it gets large. Potential methods of determining this value are finding an expression equivalent to both an upper and lower bound for it based on known information, which is the approach that was used to determine asymptotic behavior of first gonality, or finding a algebraic expression describing second gonality of random graphs dependent on number of vertices and probability.

A computer program was written to approximate second gonality of random graphs given n and p , by generating many graphs using the aforementioned model and calculating second gonality for each. The output of this program, run in Mathematica, was the average of these values, providing an accurate estimation after being run on a large number of test graphs. Note that these test graphs are from the subset of graphs with exactly n vertices, with distribution of repeats close to the

probability the specific graph is formed, for accuracy. This program gave data beneficial to searching for patterns. Unfortunately, the extremely slow running speed of the program made it impractical to compute data for the random graph with any number of vertices above approximately 30. As well, it could only calculate second gonality for graphs generated to be connected, thus was set to discard any non-connected graph to avoid skewing the probability, and, consequently, the expected value calculated.

Overall, any potential results from this project will aid in study of certain divisors on algebraic curves. Current work on finding the asymptotic behavior of expected value of second gonality of random graphs will help with studying asymptotic behavior of expected value of higher gonality of random graphs. ■

See Appendix 2.2 for references.

MODELING TRAFFIC FLOW

KAIYING HOU

Introduction

The large population density of many cities puts much stress on their traffic systems. A well-designed traffic system can greatly increase the overall efficiency of the citizens. The main way to understand traffic is by building models that describe actual traffic flow. If the models are accurate enough, the models will exhibit important qualities of real traffic, which allows us to gain insights on areas such as urban planning and programming for autonomous vehicles. This article will explain how we can build a traffic flow model for a simple one-lane road.

Let's consider a one-lane road with numerous cars going at the same direction. x represents the position on the road and t represents time. There are two important dependent variables. The first is ρ , which represents the density of cars at a given location on the road. The second is the flux J , which represent the amount of cars that pass through a certain location on the road. Both ρ and

J depend on time and the location. Thus, we have two functions $\rho(x, t)$ and $J(x, t)$. Because there are numerous cars on the road and we are looking at the road from a macroscopic perspective, the discrete nature of the cars is negligible, and we can consider ρ and J as continuous functions.

Conservation Law

In a specific segment $(x_0, x_0 + dx)$ of the road, there are $\int_{x_0}^{x_0+dx} \rho(x, t) dx$ cars on that segment on the given time. Therefore, $\frac{d}{dt} \int_{x_0}^{x_0+dx} \rho(x, t) dx$ represents the instantaneous rate of change of the amount of cars on that segment. This change in the amount of cars can also be expressed by the flux. The change equals the cars entering the segment minus the cars exiting the segment, which is $J(x_0, t) - J(x_0 + dx, t)$ because cars enter from the left side at x_0 and exit through the right side at $x_0 + dx$. These two expressions describe the instantaneous change of the amount of cars on the segment $(x_0,$

$x_0 + dx)$, and we set them equal to each other to obtain the equation below:

$$\begin{aligned}\frac{d}{dt} \int_{x_0}^{x_0+dx} \rho(x, t) dx &= J(x_0, t) - J(x_0 + dx, t) \\ \frac{d}{dt} \int_{x_0}^{x_0+dx} \rho(x, t) dx + J(x_0 + dx, t) - J(x_0, t) &= 0\end{aligned}$$

Then, if we take the spatial derivative $\frac{d}{dt}$ of both sides, we get a nice simple equation:

$$\rho_t + J_x = 0$$

This equation is called the **conservation equation**. It is an essential equation for building traffic models. Then, because the amount of cars equal to density times length, the flux equals to density times velocity or $J = \rho v$. The speed is related to the density of the cars because people tend to drive slower when there are more cars. Therefore, $J = v(\rho)\rho$. Plugging this value into the conservation equation and applying the product rule, we get:

$$\rho_t + c(\rho)\rho_x = 0$$

Where $c(\rho)$ is $v(\rho) + \rho v'(\rho)$. A simple linear model for the relationship between v and ρ is shown in figure 1. Here, the $v = v_m(1 - \frac{\rho}{\rho_m})$ where ρ_m and v_m indicate the maximum density and velocity. This correspondence between v and ρ is called the **Greenshield Law**. Our conservation equation for the Greenshield Law therefore becomes:

$$\rho_t + v_m(1 - \frac{2\rho}{\rho_m})\rho_x = 0$$

Solving this equation for ρ will then yield a simple model for one lane traffic.

Method of Characteristics

The method of characteristics is a way to solve this equation. Lets consider the following equation:

$$\rho_t + a\rho_x = 0$$

This implies that when t increases by 1 unit and x increases by a units, their effect on ρ will cancel out and ρ will stay

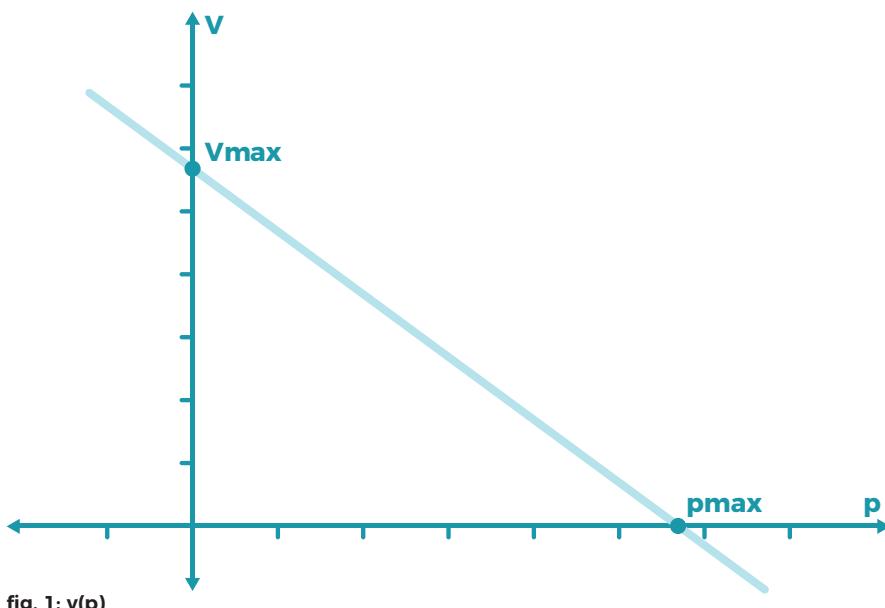


fig. 1: $v(\rho)$

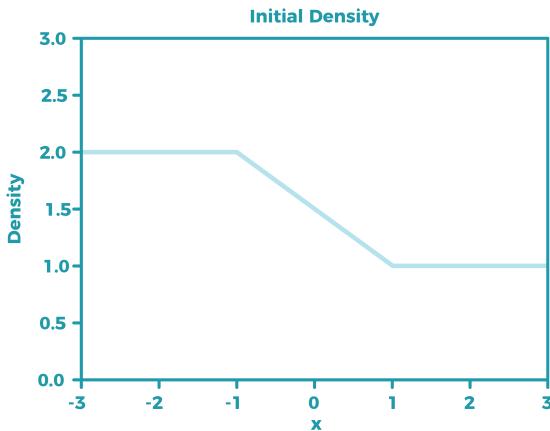


fig. 2: $\rho(x,0)$

the same. Another way to put this is that on the curve $\frac{d}{dt}t = a$, ρ will not change. Thus, on the line $x = x_0 + at$ the density will stay the same. Now, if we look at the conservation equation, we get that on the curve $\frac{d}{dt}t = c(\rho)$, ρ will not change. Note that because ρ is constant on the curve, $c(\rho)$ is also constant. Therefore, the slope of the curve does not change and the curve is in fact a line. These lines on which the density stays the same are called characteristic.

Lets look at a example. The initial density on a given road is given by $\rho(x, 0)$ in figure 2 and we want to know what the density distribution on the road in a future time. Because the slope of the characteristic $c(\rho)$ is based on ρ , the different initial density will result in different slopes for the characteristic. If we use the Greenshield Law, which makes the slope $c(\rho) = v_m(1 - \frac{2\rho}{\rho_m})$, we can draw the characteristics shown in figure 3.

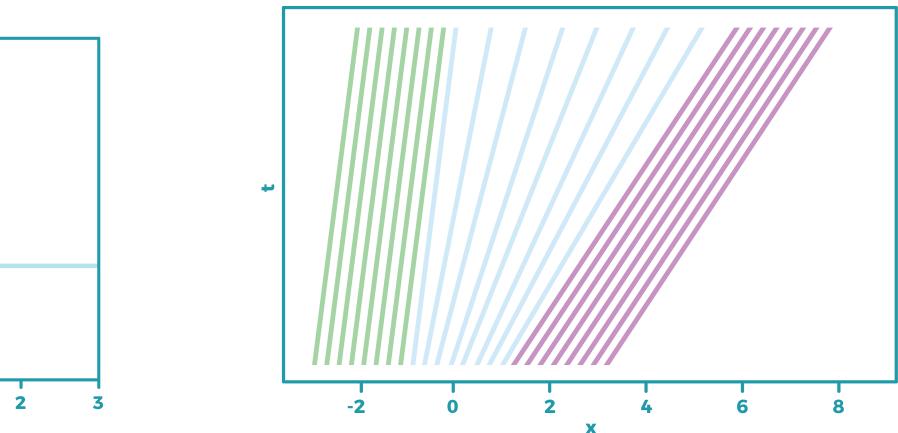


fig. 3: characteristics

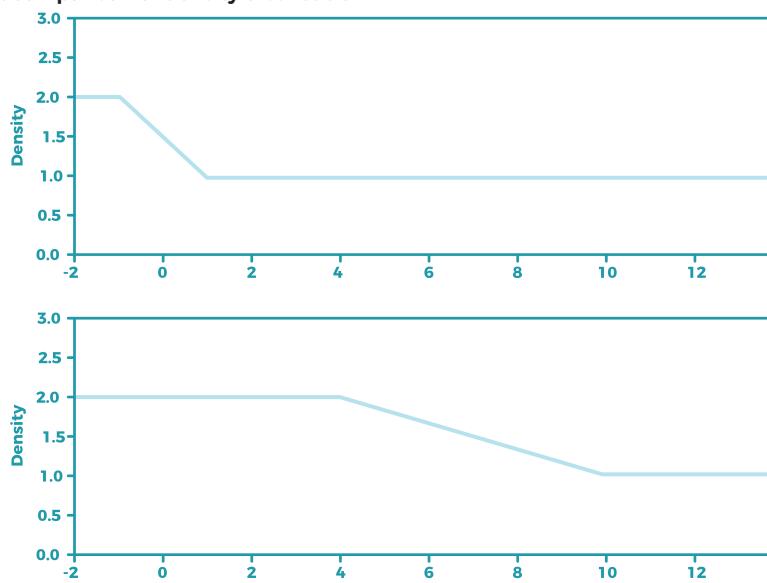
Now, how do we make sense of this figure? The green characteristics on the left represent the high density region of $x_0 < -1$. On those characteristics, t increases quickly while x increases slowly, indicating that these cars in high density regions tend to have low velocity. Because of the uniform initial density at $x_0 < -1$, the cars have the same velocity and move forward in the same speed. The purple characteristics on the right represent the cars in the initial low density regions of $x_0 > 1$. From the characteristics, we can see how these cars travel at a much higher velocity. Then the blue characteristics in the middle represent the region with $-1 \leq x_0 \leq 1$. Because the initial density was decreasing from 2 to 1, we can see how this decrease results in a gradual change for the slope of the characteristics. Thus, we learn from the model that after $t = 0$, the cars in low density region of the right rush forward while the cars stuck

in high density of the left go with a much slower velocity. The gap between these two groups will widen. The cars in the gap move with varying velocity. Figure 4 compare the initial density distribution with that of a later time. In fact, for any point (x, t) , we can find the characteristics that pass through it and trace back to a initial x_0 that has $\rho(x, t) = \rho(x_0, 0)$. This way, we can find the density of any location at anytime in the future.

An Open Field for Research

In the above example, we build a simple model to predict the future behavior of a one lane road with a specific initial density of cars. We also assumed that the velocity of a car corresponds linearly to the density around it. In reality, many other factors may affect the speed at which they drive. For instance, they can be affected by the speed of the cars around them. Thus, our model may not be completely accurate. As we take multiple lanes, turning and traffic lights into account, the complexity for the models increases quickly. There is always room for proposing more complicated models and testing how accurately these models describe real traffic. Currently, as self-driving vehicles attract more attention, there are also research on traffic models that takes autonomous vehicles into account. Many people think that incorporating autonomous vehicles into traffic flows may lessen the likelihood of traffic jam and improve the overall efficiency. Therefore, traffic modeling is a developing field that is relevant to our daily life. ■

fig. 4: comparison of density distribution



RSA CRYPTOGRAPHY

ERIC YOU

Say Alice wants to send a message to a friend, Bob. Well, Alice could just write down the message and send it to Bob. But what if it contained sensitive information, say the time of a secret meeting, and Alice didn't want anyone to read it?

Well Alice would probably encrypt the message (known as a ciphertext) using some sort of private key that only she knows. Yet, in order to decrypt the ciphertext, Alice would also have to send the same key that she used to Bob. This is known as symmetric cryptography, the method of using the same key to both encrypt and decrypt.

However, keys can easily get lost or become stolen on something like the Internet, so this method is not

very practical to implement just by itself. Furthermore, what if Alice had a friend Carly to whom she wanted to send a secret message? Well then, she would need to make another, different key. Quickly, the keys would grow exponentially, and such a system would be impossible to implement again. Instead, what if Alice only needed one key, and so did everyone else who wanted to communicate with her? What if anyone could send a message to Alice, but only Alice could read such a message? This is the basis of asymmetric key cryptography, and RSA cryptography. But, before we get into that, we need to go into a little bit of modular arithmetic.

1. In modular arithmetic, we are

only concerned with the remainders of numbers, of a certain modulus. For example,

$$14 \equiv 4 \pmod{5}$$

Here, 14 is equivalent to 4 modulo 5, which is denoted by the special \equiv .

That means in modulus 5, the only numbers that "exist" are 0, 1, 2, 3, and 4. This also means that negative numbers wrap around the opposite direction: $-1 \equiv 4 \pmod{5}$

2. Most arithmetic operations are also well defined, such as addition, subtraction, multiplication, and even exponentiation.

$$2^2 \equiv 4 \pmod{5}$$

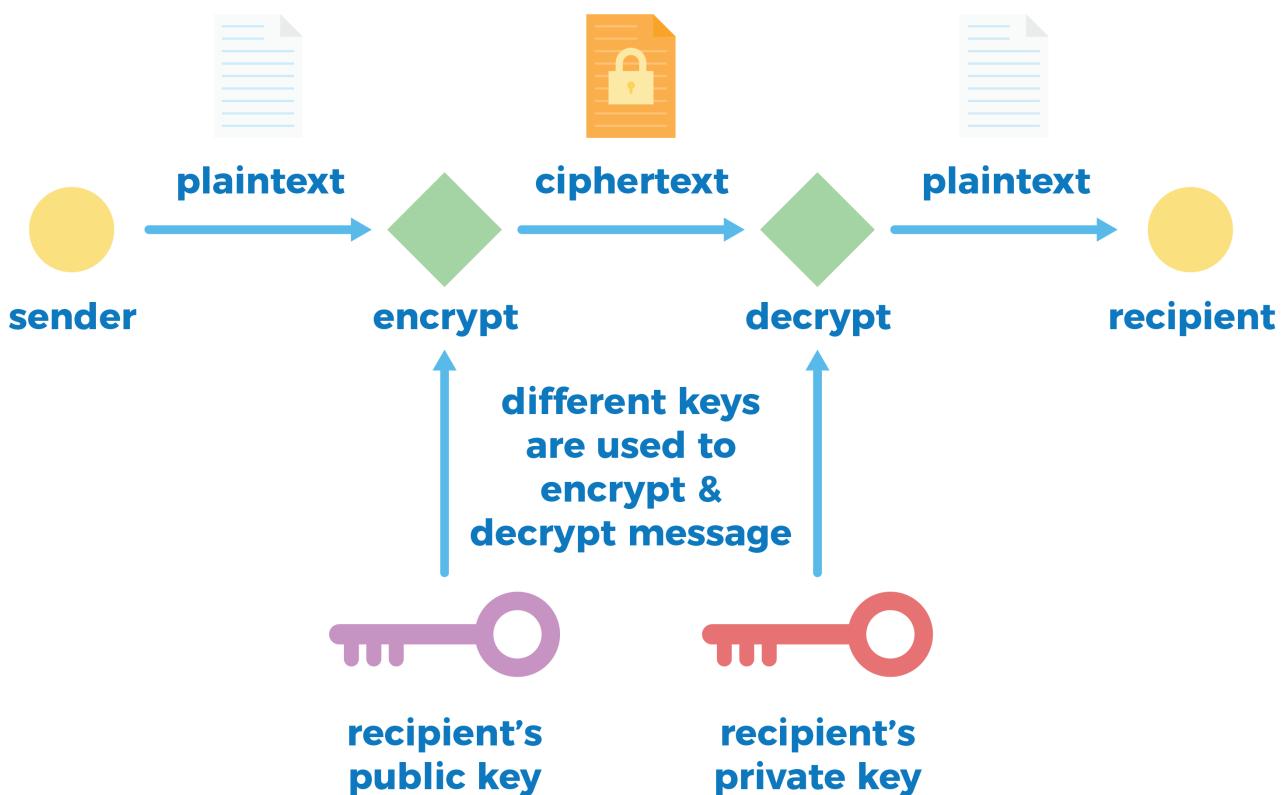
$$2+4 \equiv 6 \equiv 1 \pmod{5}$$

$$2-4 \equiv -2 \equiv 3 \pmod{5}$$

$2^4 \equiv 16 \equiv 1 \pmod{5}$ which implies stuff like $16^4 \equiv 1^4 \pmod{5}$

Source: Tutorials Point

fig. 1: outline of encryption process.



However, division is much more complicated. Division is only defined if the dividend, the divisor, and the modulus are relatively prime (that is, they do not share any common factors except 1).

$$2 \div 4 \equiv ? \pmod{5}$$

Since 2, 4 and 5 are relatively prime, division is defined for 2 and 4. But that still does not help us solve our equation. Instead, if we think of division as multiplying by the reciprocal, known as the modular inverse, we can find a different way of calculating our answer. Here, we denote modular inverse with the negative exponent 1, and solve the following modular equation $4x \equiv 1 \pmod{5}$, which gives us $x=4$ as one possible solution. Therefore,

$$4^{-1} \equiv 4 \pmod{5}$$

$$\text{Thus, } 2 \div 4 \equiv 2 \cdot 4^{-1} \equiv 2 \cdot 4 = 8 \equiv 3 \pmod{5}$$

With that out of the way, Alice now has all the tools she needs to use RSA cryptography.

So how does RSA work?

In the default RSA scheme, Alice begins by picking two large prime numbers p and q (each on the order of 155 digits or 309 digits, aka 512 bits or 1024 bits) and multiplies them to get a larger number n (on the order of 1024 bits or 2048 bits). Next, Alice randomly chooses a number d that is coprime to n (that is, it shares no factors with our large number). Together p , q and d make up the private key in an RSA cryptosystem.

With our private key, Alice can then encrypt our original message m by modular exponentiation to get our encrypted ciphertext c .

$$c \equiv m^d \pmod{n}$$

In order to decrypt the message, Alice can give others a public key which comprises of e , the modular inverse of d modulo $\varphi(n)=(p-1)(q-1)$.

This is where the magic happens:

All a person needs to do to get the message back is to do modular exponentiation with c and e (that is, raising the encrypted message c to the e th power, and finding the remainder when divided by n).

$$c^d \equiv (m^e)^d \equiv m \pmod{n}$$

(For those interested in the math behind RSA, Euler's totient theorem proves $a^{e \cdot d} \equiv a \pmod{n}$, because $e \cdot d \equiv 1 \pmod{\varphi(n)}$)

So why is RSA so secure then? Well, it is easy for anyone else to read Alice's messages, but extremely difficult to find out what in encrypted message sent to Alice is.

First of all, the encrypted message would have used the public key, such that

$$c^d \equiv (m^e)^d \equiv m \pmod{n}$$

$$c \equiv m^e \pmod{n}$$

However, here we have hit a road bump: we do not know the private key exponent d in order to decrypt it. That means, the only way to find the original message is to find d , and to find d , the modular inverse of e , modulo $\varphi(n)$ we need to know $\varphi(n)=(p-1)(q-1)$. This turns out to be virtually as difficult as factoring n , as finding p or q allows to calculate $\varphi(n)$ easily.

So how hard is it to factor a number? Take, for example, 2016. Well, it's divisible by 2, so $2016 = 2 \times 1008$. How about 1008? It's still divisible by 2, so $2016 = 2^2 \times 504$. In fact, if we continue to factor out twos, we get $2^5 \times 63$, and from there it is easy to see $2^5 \times 7 \times 9 = 2016$.

But, how about 2017? Well, 2017 is a little bit harder to factor. In fact, it's not divisible by 2, 3, 4, 5, 6, 7, 8, 9, or 10. And if we were to check every number less than 2017, we'd find that 2017 is not divisible by any number except 1 and itself. In other words, it's a prime number.

Yet, to verify that 2017 was a prime number, we had to check every number less than 2017. Even if we checked every number less than its square root (each possible pair of factors of 2017 must have one factor less than $\sqrt{2017}$), we would still have to check an exponential amount of possible factors.

This means that as our number grows larger and larger, to say 310 digits, the size of n in 1024 bit RSA, we would be checking a number of at least 155 digits. Suddenly, factoring a

number becomes hard.

Even with modern algorithms, such as the General Number Field Sieve, the Quadratic Sieve, and Pollard's rho, and the task is extremely time consuming and when our numbers grow to be 309 digits long (1024 bits), it becomes infeasible.

In fact, the largest RSA modulus that has been cracked so far is only 768 bits, in 2009. Even then, it took the computing power of hundreds of machines over the course of two years—equivalent to around 1500 years of CPU time.

Still, when RSA was first formulated by Ron Rivest, Adi Shamir, and Leonard Adleman, it was not meant to be used as is. Today, RSA is still an essential part of secure communication in our world today, but it is not used to directly encrypt messages. Instead, it is used to send the keys used in symmetric-key cryptography, so that faster and safer communication may result. In fact, a 128-bit symmetric key can be just as safe as a 3000-bit asymmetric key, but take much less time to encrypt and decrypt messages. ■

DIY DRONE

ALEX REICHENBACH

I am an enthusiastic advocate of the maker movement, where creative individuals are encouraged to build things from the ground up. Though building from raw materials and components may not always be practical, it is through the making process (rather than simply by studying projects completed by others) that true learning can occur. Practicing the ground-up process on previously implemented ideas, such as drones, helps makers develop the skills for designing new products, where designing from the ground up is a necessity, not simply a mental exercise. For this reason, I am currently designing and building a drone from scratch. It has been a rough path with a number of setbacks, which I will share so that others may avoid them.

When attacking any new project, the first step should be to research similar products or projects. My strong inclination is to jump into a project prior to doing any research, and though tempting, it is rarely the best path. Even if your design is unavailable in the current market, research the field. Products are designed the way they are for good reasons! When I started my drone project, I wanted to use a single rotary design. The propellor would be on a central gimbal with flaps below directing airflow. Unfortunately, this design had a fatal flaw, which had I researched the market, I would have discovered. It turns out that quadcopters dominate the market due to their optimal cost to performance ratio, stability, and number of propellers. Why might an even number of propellers be important? Because of the torque produced by the propeller's inertia. This is why a helicopter needs the second, smaller propellor acting as a lever away from the body. It prevents the helicopter from reacting equally and opposite to the propeller's rotational acceleration. My first drone, though able to lift off the ground, spun completely out of control, at least until the propellor caught on the frame and tore it apart.

TECH + ENGINEERING

- i. DIY Drone
- ii. Gravitational Waves and the Technology Used to Discover Them
- iii. The Future of Transportation is Self-Driving Cars
- iv. A Stance on Chimera Research
- v. LM11A-31: A Novel Method of Treating Alzheimer's Disease

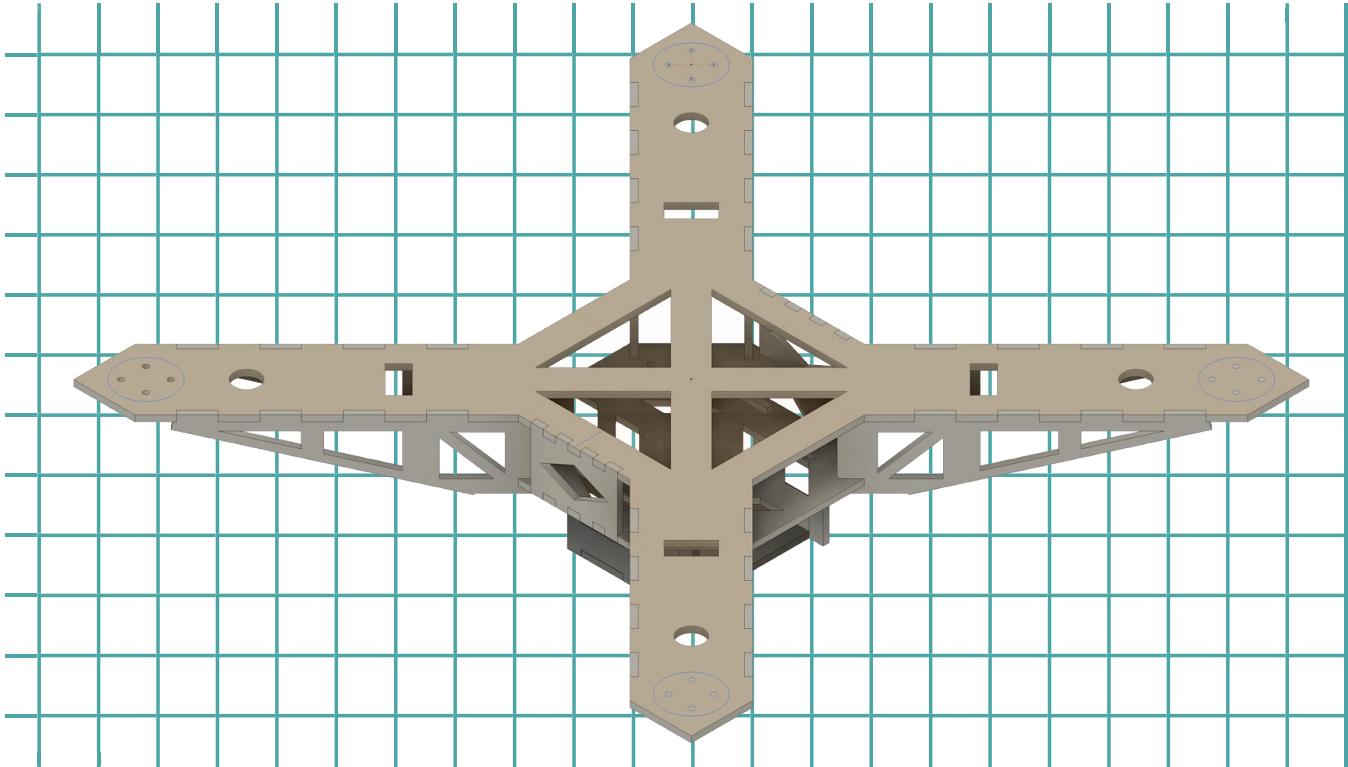


fig. 1: Initial CAD model of drone

On my second drone attempt, I briefly considered adding two counter-rotating propellers, so that their forces would cancel. But this brings me to another important lesson I have learned through making: do not overcomplicate things! You are already doing something difficult, so don't make it any harder than it needs to be. Keeping this mantra in mind, I decided to go with the conventional quadcopter design. However, I didn't give up all creativity and buy a prebuilt frame. Instead, I designed a drone that could be entirely laser-cut. This would be helpful following the inevitable, numerous crashes during the testing phase because any part of the frame could be cheaply replaced in minutes.

I designed the entire drone on Fusion360, an application free to students (link to designs at bottom). I had never used this app or any other engineering CAD software before, but I threw myself into mastering it. My third piece of advice to aspiring makers is just that: never be afraid to throw yourself into something entirely new. With tutorials a few clicks away and Andover's incredible resources readily available, nearly any

topic can be conquered.

Now that you know something of my basic approach to making, read on to learn about some of the more specific problems I encountered and troubleshooting I did in making my drone.

The most frustrating problem I grappled with was that of a common ground. On an electronic speed controller (ESC), there are generally five wires: motor power positive, motor power negative, signal, signal power positive, and signal power negative. When testing the drone, I used an Arduino as my microprocessor, and it was powered through a USB cable. The motors, however, could not be. Each motor maxed at 20 amps and 14.8 volts, for a total of 80 amps when wired in parallel. The output of an Arduino pin is 50mA. Due to this fact, I wired the motor power positive and negative to the battery, but the signal positive and negative to the USB. Unfortunately, despite working in circuit diagrams that assume a common ground, this design didn't work in reality. When debugging, it is usually possible to hypothesize what the error is by the output. I couldn't in this case, however, because there was no output. Without a common ground between signal and motor supply power,

nothing happened. I soldered and checked each connection, but for naught. Only after checking the current through my signal wire and seeing nothing at all did I realize that a common ground was necessary.

A clearer, but equally frustrating, problem I encountered with the drone was that of drifting data. Inertial measurement units (IMUs) measure movement and rotation in the XYZ axis. Though the measurements of my IMU at any specified update were accurate to the spec-sheet's $\pm 1\%$, the data wasn't accurate for long. The IMU I was using, the MPU6050, updated two-hundred times a second. This led the gyroscopic data to drift overtime to the point that it became useless to any measurement other than acceleration. In order to prevent this drift, I switched to solely accelerometer data. Accelerometer velocity data doesn't have any built-up error.

The final major error I encountered with the drone was that I assumed a constant resistance. Lithium Ion batteries (LiPos) aren't very good at quick discharge without battery degradation. The ones that are good at quick discharge tend to be significantly more expensive. Since I had a limited budget for this

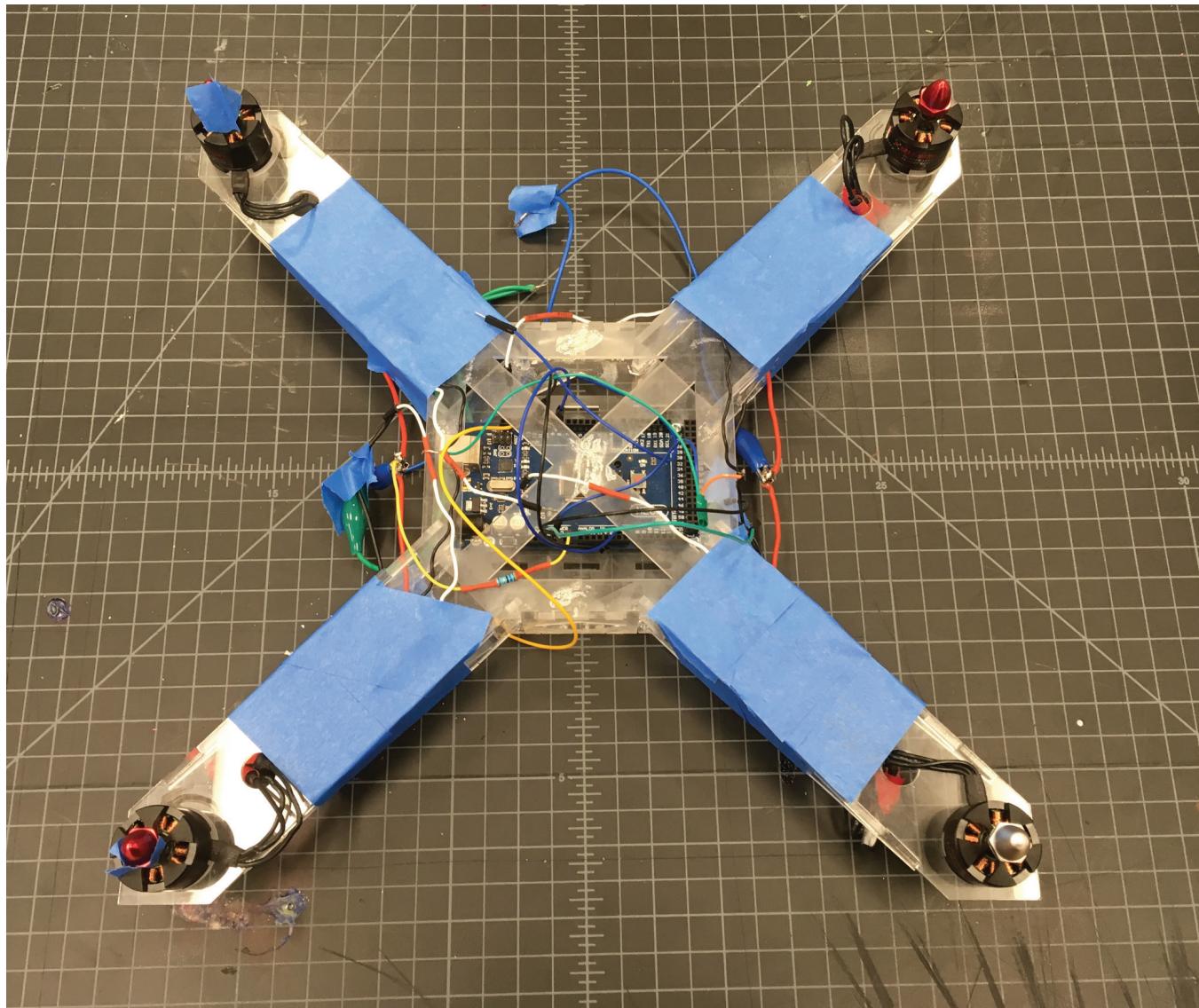
project, I cut costs whenever possible. I decided to double the battery's voltage and half its maximum output amperage. I used a common circuit design: the voltage divider. Using two equal resistors in series in a circuit creates an equal voltage drop over each, so I put two motors in series in parallel with two other motors in series. The motors usually require 4s ($4s \approx 14.8V$), so I supplied the series 8s ($8s \approx 29.6V$) hoping that the normal voltage divider circuit would work. It didn't. It turned out that, though the motors have consistent resistance, the ESCs constantly change their internal resistance. This was a fairly easy problem to debug, as the symptoms were clear. When starting the motors up, only two spun. They were the two that encoun-

tered the voltage first. I measured the voltage drop across them, and it was the entire 14.8 volts. The other two had no voltage drop. This error forced me to buy a new battery and wire all four motors in parallel. My original cost savings measure ended up costing me more money, rather than less.

Making things from the ground up isn't easy. It requires an elastic attitude that will snap back no matter how hard the punch. When making something new, most of your time will be spent either debugging or redesigning around flaws in your design. But don't give up. My first ground-up project (a 3D printer) took me two years to complete. I redesigned it three times, and the week after I finally finished it, my family

moved overseas, and the printer was destroyed. But that moment when I saw the mechanics and software moving in perfect synchrony was transcendental. All my blood, sweat, and tears (I almost lost a fingertip) were entirely worth it. I hope that you will find your efforts worth it too when you view your first successful project. ■

fig. 2: Building, in progress



GRAVITATIONAL WAVES AND THE TECHNOLOGY USED TO DISCOVER THEM

ALEX EL ADL

1 .3 Billion years ago in a galaxy far, far away, a black hole 29 times the mass of our sun collided with another black hole 36 times the mass of our sun. In the last fraction of a second of this spectacularly massive cosmic event, ripples in space-time known as gravitational waves were released. This merger emitted 50 times as much energy as the rest of the observable universe combined. These never before observed waves travelled through our universe and reached earth on September

14, 2015. Thanks to massive technological advances, scientists at the LIGO (Laser Interferometer Gravitational-Wave Observatory) facilities in Louisiana and Washington USA detected gravitational waves for the first time in human history with ultra sensitive machinery. This has been proclaimed as one of the greatest scientific discoveries within the last century as humanity has now definitively observed a major prediction made by Albert Einstein over 100 years ago in his General Theory

of Relativity. Einstein referred to gravity as the distortion of the fabric of space and time created by matter. The waves he described are what emanate from a disturbance in this fabric, caused by gravity. Gravitational waves will change astronomy and our understanding of the universe. The incredible technology that is being utilized to measure such ancient, remote, and eventually almost unmeasurable discrepancies in space is just as fascinating.

We must first understand these tiny rip-

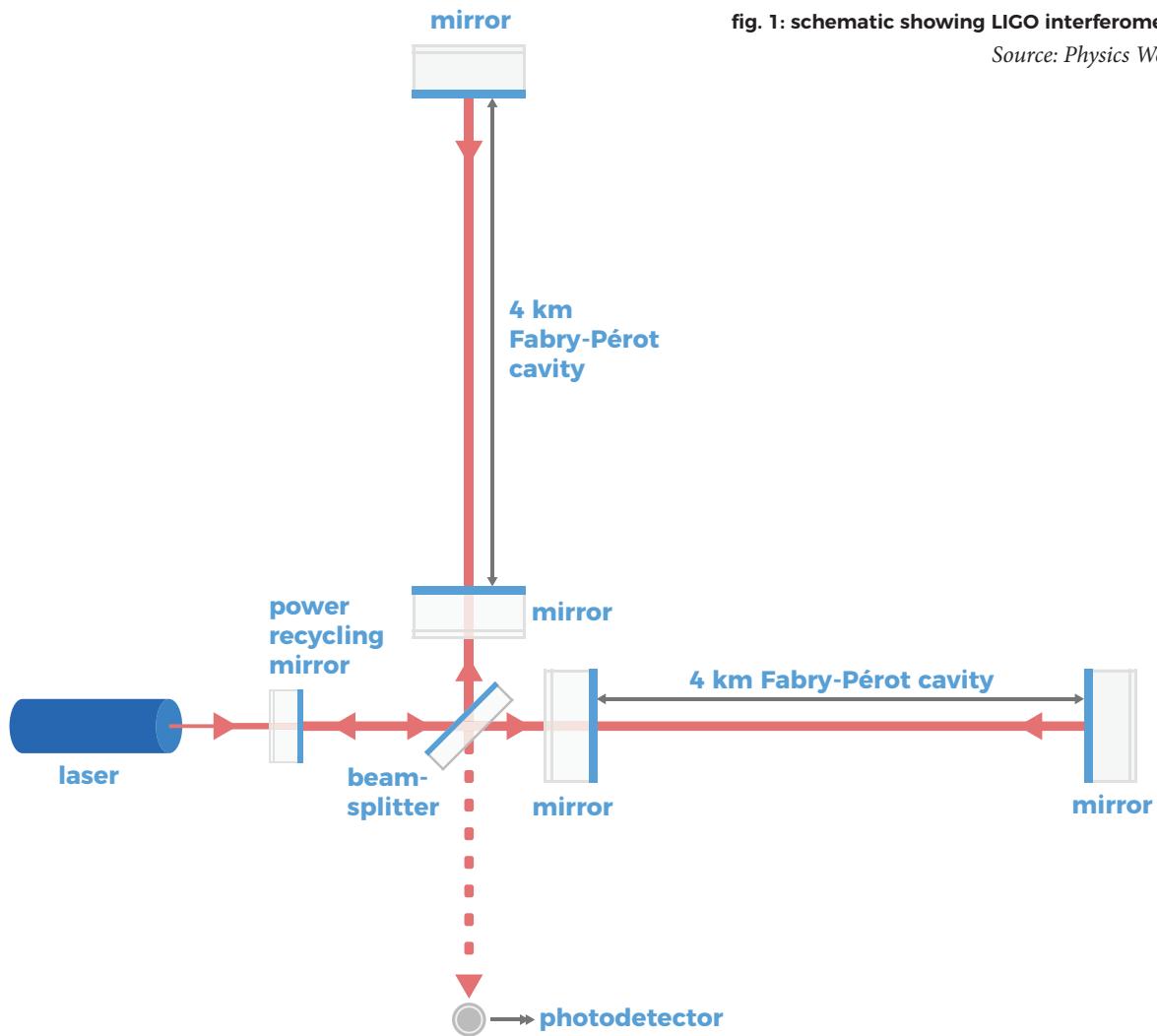


fig. 1: schematic showing LIGO interferometer

Source: Physics World

ples in spacetime and gravity itself. Gravity is a force that attracts all objects with mass or energy towards each other. While sound waves are created by moving air molecules, gravitational waves are created by moving objects that have gravity. They carry gravitational radiation and move at light speed as they progress through space. They bend and stretch space to compress matter in one direction and lengthen distances in another as they travel. For example, shaking this journal causes gravitational waves. However, they are undetectable and so minute that they have almost no effect on matter. Because the force that warps matter is so minute, we can only measure the gravitational waves that stem from the most violent and energetic processes in our universe. The disturbance, in our case the merger of two huge black holes, can be thought of as a stone being dropped in a pool of water that represents the fabric of space. Ripples in the pool are the gravitational waves that move points on the surface of the water closer together or farther apart.

To really understand how remarkable the technology behind this discovery is, we must analyse the two LIGO observatories. Since gravitational waves stretch matter in one direction and squeeze it in another direction, we should be able to check for the change in distances between objects. However, we cannot simply employ a precise ruler to see if an object in the path of a gravitational wave gets bigger or smaller because all space is altered by gravitational waves, meaning that the ruler will change size too and there will be no relative change. However, light travels at a constant speed and if a laser beam is constantly shot at a sensor while being timed, a change in the distance the light travels will alter the timing. Since the laser in the LIGO observatories is constantly on, stretched photons at the beginning of a ripple in space will be replaced and a difference in timing can be recorded. This difference will be tiny and the rig must be ultra exact because gravitational waves only stretch or compress space by 1 part in 10^{21} . This is why the LIGO labs have two perpendicular 4 km long arms containing the smoothest mirrors ever constructed and 1

megawatt infrared lasers in vacuum tubes that ensure that the lasers are not even impacted by any air molecules. If a ripple passes through the observatory, one arm gets longer and one gets shorter. The 4 km distance the light must travel makes the minute ripples in space even measurable. In 2015 the calculated ripple caused by the collision of two black holes only stretched and compressed space by 10^{-18} meters which is equivalent to 1/10000 the width of a single proton. The LIGO experiments performed the most precise measurements in the history of science. The scale of the gravitational alterations present countless problems including the effect of the vibrations of someone's voice. Talking will cause a bigger discrepancy in the data than a supernova. Environmental noise is why the observatories are highly insulated by hanging equipment on silica threads twice the thickness of a human hair, on top of isolation tables on top of more super precise stabilization and insulation equipment. There are still two observatories because gravitational waves will hit Washington and Louisiana almost simultaneously but earthquakes and sound will only happen in one of the extremely remote locations.

In conclusion, we know very little about these gravitational waves, but as LIGO executive director David Reitze said, "Up until now, we've been deaf to gravitational waves. What's going to come now is we're going to hear more things, and no doubt we'll hear things that we expected to hear but we will also hear things that we never expected." Through human ingenuity and insanely precise as well as rapidly advancing technology, we have discovered only a small clue our universe has in store for us. For thousands of years we have explored and looked at the universe with waves of light. The discovery of gravitational waves will allow us to see our universe in a whole new way. Every Time humanity has created a new way to look at nature we have made countless groundbreaking discoveries. With gravitational waves now added to our toolbelt, astronomers and physicists will find a side of the universe we have been deaf to for all these years. This discovery will alter astronomy forever. ■

See Appendix 3.1 for references.

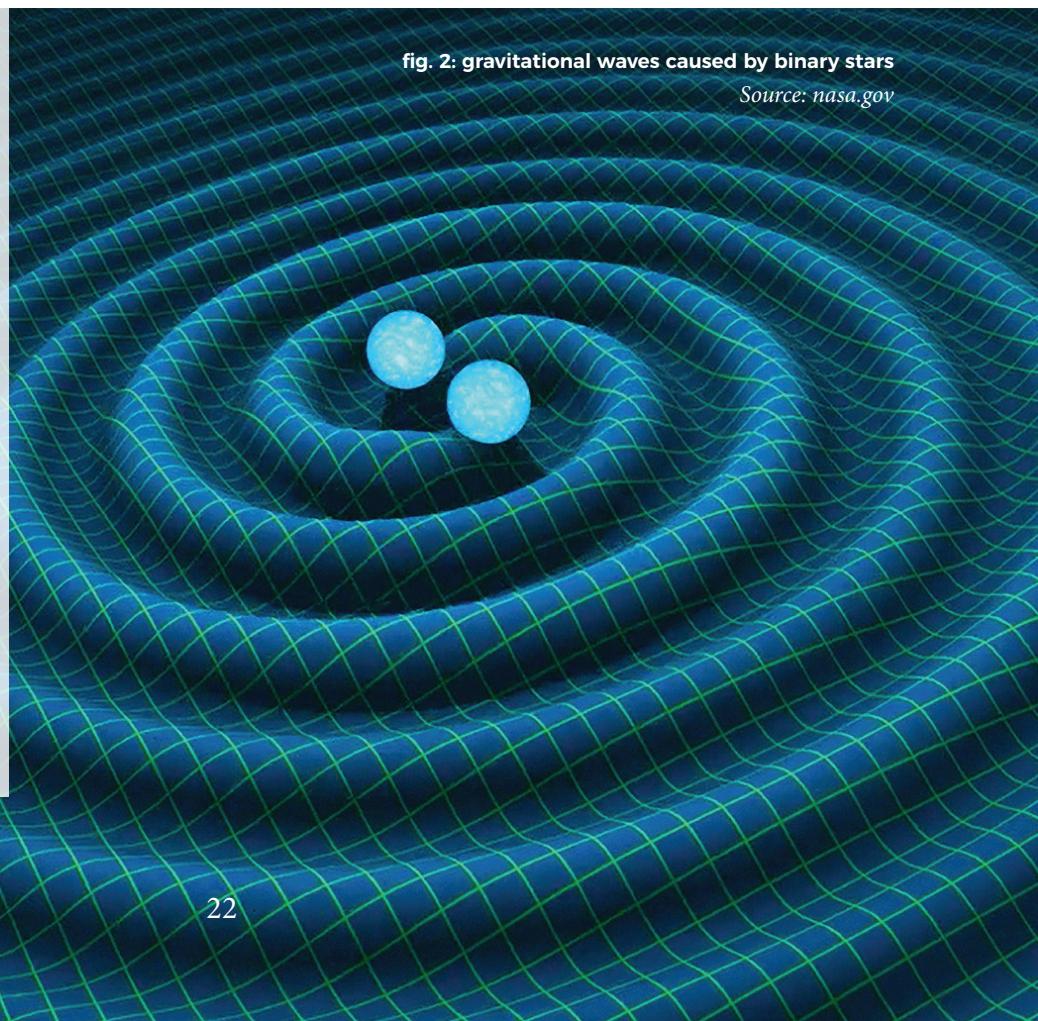


fig. 2: Google self-driving car

THE FUTURE OF TRANSPORTATION IS SELF-DRIVING CARS

ANDIE PINCA

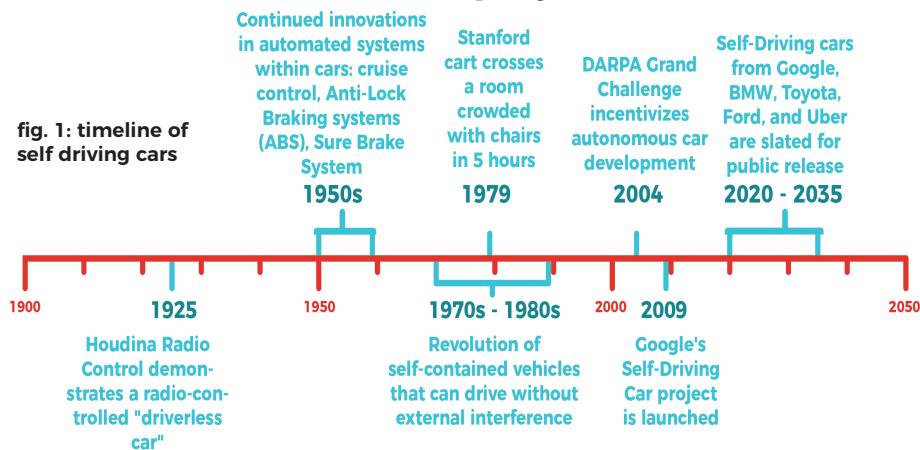
Dreaming of the future usually entails an image of sprawling futuristic metropolitan cities with flying cars zooming in and out of the towering glass skyscrapers. This city only seen in movies may seem far into the future, but innovations in technology are reaching new heights everyday. At this rate of technological progress, this future is attainable within the next century. Although they won't fly (yet), autonomous cars have already become a reality. The Google initiative for self-driving cars, "Waymo," plans to debut their fleet on public roads by 2020. (Levin, 2017) The Google company is arguably the most well-known and the most advanced institution creating self-driving cars, but other major companies such as Toyota, GM, Ford, BMW, Uber, and Lyft also plan to launch their autonomous vehicles in the next five to ten years. There is no question that self-driving cars are the vehicles of the future (Adams, 2015).

Contrary to popular belief, driverless cars aren't a recent innovation. In 1925, Houdina Radio Control navigated a radio-controlled "driverless car" up Broadway. This vehicle was controlled by a second car from behind, but still marks the first movement towards creating an autonomous vehicle. Since then, there has only been rapid progress on creating a self-driving car throughout the

19th century. Automated systems, such as cruise control, the Anti-Lock Braking System (ABS), and the Sure Brake System, were implemented in the 1950s, and the 1970s to 1980s marked a revolution of vehicles that were able to drive without any external interference. The first self-contained vehicle was built in 1979 by Stanford University; the "Stanford Cart" used video processing technology to analyze images for ten to fifteen meters for one meter of movement, crossing a room filled with chairs in five hours. About twenty years later, the DARPA (Defence Advanced Research Projects Agency) Grand Challenge was founded in 2004 by the US Government to incentivize autonomous car development. Google ended up recruiting the leading members of winning DARPA challenge teams to start their famous self-driving car project in 2009 (Engineering.com, 2016).

Google has created functioning autonomous cars suitable for everyday life by using a combination of Google Maps and Laser Illuminating Detection and Ranging (LIDAR) and Radar technology. LIDAR builds a 3D Map of the car's surroundings, allowing the car to "see" potential immediate hazards by using a laser beam to determine the distance of profiles of objects. Because LIDAR can't monitor real-time speeds of passing cars, a radar is used to monitor this

fig. 1: timeline of self driving cars



information and prevent collisions. The car is also equipped with high-powered cameras that function like LIDAR, which is a fallback in case of malfunctions. These technologies work with Google Maps to position and drive the car. The GPS data from Google Maps includes real-time information and can determine the position of each vehicle to the last centimeter. Additionally, Google's technology allows the car to learn from each mile logged on the dashboard, as human behavior is logged and analyzed to address potential situations the car may encounter. For example, the car can deduct that other vehicles usually swerve to avoid potholes from previous experiences. Google's self-driving car is programmed to be the "ideal human driver" transforming driving and safety on the roads (Clark, 2015).

People are not great at driving – 30,000 people die in car accidents every year (Clark, 2015), and the leading cause of car accidents is distracted driving (King, 2016). Replacing the human element of driving is predicted to reduce traffic fatalities by up to 90% in 2050. This prevents 300,000 motor-related fatalities in a decade and 1.5 million fatalities in 50 years (Lafrance, 2015). Self-driving cars will provide simple transportation for the disabled and elderly who can't manually drive a regular car. They will also be more energy efficient, as they will be most likely powered by electricity (Clark, 2015).

There are still a few problems left in the technology, such as driving in rough weather, but the hurdles that self-driving cars face is more cultural than technological. Only 39% of surveyed people in The Guardian would ever consider buying a driverless car, and the most cited reason for distrust in automated vehicles are their potential for malfunction (Adams, 2015). Placing the wheel in the hands of a machine will most likely destroy driving services and create legal issues in terms of the responsibility when a car accident occurs. However, these cultural shifts are important to create a safer population and is an important realization of the growing presence of machines in our everyday lives. Although the widespread usage of automated cars will most likely take decades to become cultural norm, their implementation will ultimately transform safety in transportation worldwide and will also provide a major step towards the inevitable era of human dependence upon machines.

See Appendix 3.2 for references.

A STANCE ON CHIMERA RESEARCH

ARNO MIN

In recent years, many advancements have been made that allow researchers to manipulate the biological development of organisms. One such advancement is the creation of genetic hybrids between animals, called chimeras. As with most forms of genetic experimentation, ethical objections have been made for the creation of chimeras, and many consider further experimentation morally problematic. However, because of the many potential benefits chimera research holds for the field of medicine, it is important to carefully consider both the possible ethical issues and possible benefits of this burgeoning application of biological science.

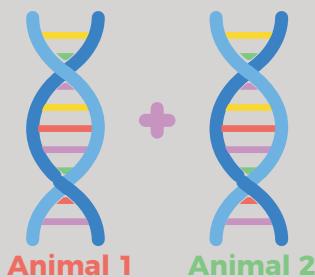
What are chimeras?

Before discussing the ethical considerations involved in chimera research, it is important to have a basic understanding of what exactly chimeras are. The term 'chimera' refers to any organism that has cells from at least two different zygotes (Behringer, 2007). The creation of these cellular hybrids has already been used in a multitude of experiments, such as when a team of researchers created mice with pancreas made of rat cells (Kobayashi et al., 2010). This experiment implied the possibility of growing entirely human organs in host animals.

Potential benefits of chimeras

The creation of animals with developed human physiological traits could be applied in the field of medicine for a wide variety of benefits for human patients. The most direct application would be organ transplantation. According to statistics from the United Network for Organ Sharing, there are around 2,500 current organ donors. To put that into perspective, there are currently more than 118,000 patients who require lifesaving organ transplants (Data, n.d.). The experiment involving the creation of rat organs in mice hosts in 2019 has already proven that it is possible to grow the organs of one species in the body of another. Now, researchers are attempting to do the same for human organs in larger hosts (Rashid, Kobayashi, & Nakauchi, 2014). Animal hosts could be harvested for multiple organs, allowing many more

fig. 2: chimeras are genetic hybrids between different animals, created through the splicing of their DNAs.



patients to get organs in time. Additionally, by transplanting cells from a specific patient into an animal host, the organs harvested would have virtually no chance of rejection when transplanted into patient, as they would be made of their own cells.

Outside of direct organ transplantation, chimeras would offer a new avenue for medical experimentation. Chimeras with human physiological characteristics would be much more analogous to human bodies, providing better subjects to perform experiments on than normal animals. Attempts to test or optimize lifesaving drugs and treatments for human patients could be made more accurate by using chimera test subjects. Additionally, in-depth research could be conducted on the human body's systems. Such research into the endocrine system, for example, could lead to hormonally-targeted treatments for cancer, reducing the need for harmful radiotherapy and chemotherapy procedures. Treatments for genetic disease could also be developed with the assistance of chimeric experimentation. In essence, human organs and their related functions could be studied and experimented with to a high degree without actually experimenting on a human being.

Arguments against chimeras

The main concern with chimera research is that the implantation of human stem cells into animal embryos could cause chimeras to develop in an unprecedented manner (Hyun 2016). Though researchers hope to create chimeras with isolated human organs, they could instead take on an unexpected or even undesirable degree of human similarity. There is evidence to suggest that the implanted human cells could develop human-like brain functions within the chimera host. When adult mice hosts had human glial cells (cells that aid brain function by protecting neurons and creating myelin) grafted into their brains, significantly increased learning ability was observed in the mice (Han et al., 2013).

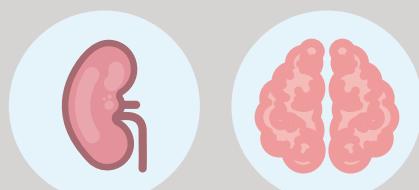


fig. 1: kidney and brain, potential areas of application.

Clearly, the possibility of animals developing human-level cognition is concerning (if not altogether frightening). If chimeras with human or near-human mental capacity were accidentally created, what would be the necessary treatment of the subject? Would they deserve rights? If so, how would the treatment of the chimera in question compare to the treatment of humans? These are necessary questions when considering chimeras that have been humanized to an unexpected degree, and force researchers to confront complex ethical issues.

However, it is possible to continue chimera research in a safe, regulated manner. Currently, the National Institute of Health has instituted a moratorium on all public funding for chimera research involving the creation of human organs in animal hosts. I believe that this measure is both extreme and unnecessary. To simply continue chimera research without caution and learn from mistakes would be irresponsible, but completely stopping research dashes all hopes of being able to use chimeras for medicine in the future. Carefully regulating research by instating mandatory limits on several variables in experiments (such as the number of human cells implanted, the type of host animal used, the location of the cell implants, the age of the host at the time of implantation, etc.) would allow researchers to make the necessary breakthroughs and discoveries to use chimeras for medical purposes without violating the aforementioned ethical issues. ■

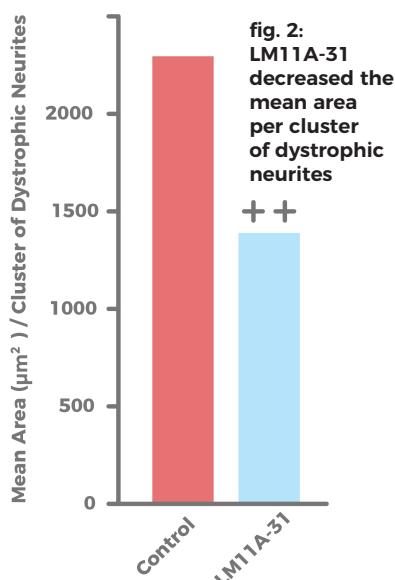
See Appendix 3.3 for references.

LM11A-31: A NOVEL METHOD OF TREATING ALZHEIMER'S DISEASE

KAITLIN LIM

In 2016, the World Health Organization cited dementia as a disease affects 47.5 million people worldwide. These numbers are slightly larger than the population of Spain. Alzheimer's Disease (AD), a genetic disorder, burdens approximately 60-70% of these cases, making it an issue of high priority. Scientists are working to find treatment that can cure AD, preventing consequences that can affect families of all demographics. Dr. Frank Longo, a neurobiology professor from Stanford, worked with a team of scientists to create a drug called LM11A-31 that can change the way doctors treat AD.

Neurobiologists have discovered similar characteristics in brains afflicted with AD. Scientists found protein β -amyloid 1-42 in plaques that overrun the brain. While standard amyloid proteins are harmless to the brain, AD morphs the structure of the protein to generate a specific variation of the amyloid protein. This variation of the protein increases the toxicity of amyloid plaques. These amyloid plaques ravage the brain's neurons. These cells are responsible for sending signals to other parts of the body. More specifically, amyloid plaques attack the neurons of the hippocampus, or the portion of the brain that controls memory and spatial navigation. Amyloid plaques work in tandem with neurofibrillary tangles (NFT).



NFTs are made of a protein called tau. Tau proteins normally stabilize the microtubules that maintain the structure of neurons. However, the genetic mutations that characterize Alzheimer's Disease hyperphosphorylate the tau proteins at abnormal rates. Hyperphosphorylation throws tau proteins into overdrive, prompting the tau protein to aggregate and cause NFTs. These NFTs do not promote microtubule production, but instead interrupt the process, disrupting the microtubules and destroying neurons. The amyloid plaques and NFTs work in tandem to destroy neurons, causing deterioration of the brain and producing symptoms indicative of Alzheimer's Disease such as difficulty completing everyday tasks, inability to keep track of the passage of time and, of course, memory loss.

AD can be sorted into early-onset AD and late-onset AD. Geneticists have yet to find the definitive gene mutations that can be attributed to both variants of AD. However, scientists have found conclusive results for the genes that cause early-onset AD. The hypothesis states that in early-onset AD, mutations in the APP, PS1, and PS2 genes generate amyloid plaques while mutations in the MAPT gene creates NFTs. A different gene mutation is attributed to late-onset AD—the APOE gene with the $\epsilon 4$ allele accounts for many cases of late-onset AD. Geneticists have yet to find the definitive gene for late-onset AD, so it is difficult to track the inheritance pattern of late-onset AD. Early-onset AD is autosomal dominant, so a cell only needs one copy of the mutated gene to cause the disorder. Late-onset AD is much more confusing. Bearing the APOE $\epsilon 4$ allele increases risk of contracting AD, but there is no certain way of knowing.

Despite this difference, both early-onset AD and late-onset AD affect people similarly—someone infected with one or the other experiences the same symptoms. Patients suffer from different neuropsychiatric symptoms such as aggression, depression, apathy, anxiety, and hallucinations. As the amyloid plaques and NFTs work their way

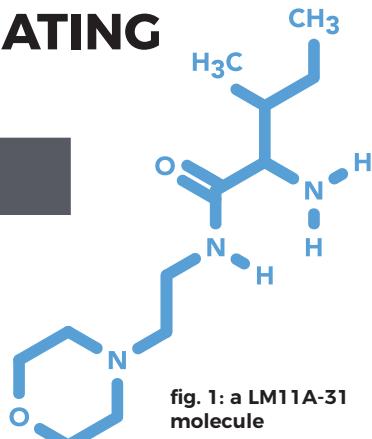


fig. 1: a LM11A-31 molecule

throughout the brain, the patient begins to lose memory and is unable to control speech, motor skills, and bowel movements. In the late stages of AD, patients cannot react to their environment and cannot control any form of movement.

To help find a cure for Alzheimer's, neurobiologist Dr. Frank Longo, with his team, synthesized a drug called LM11A-31. This drug consists of p75NTR ligands, or molecules that bind to a larger molecule. Neurotrophin receptor p75, or p75NTR, normally acts as a receptor of proteins called neurotrophins that are essential for the survival, development, and function of neurons. However, in the brain of someone with AD, aberrant signaling through p75NTR promotes amyloid-induced degenerative signaling and destroys neurons. Longo and his lab worked with mice afflicted with different stages of AD. In all experiments, LM11A-31 reversed the degeneration of neurons while normalizing levels of p75NTR. Moreover, LM11A-31 reduced the excessive phosphorylation of tau proteins and their anomalous clumping. This new study has put a spotlight on p75NTR as a potential mode of therapy for those affected with AD.

Before being approved by the Federal Drug Administration, LM11A-31 underwent and was approved during the first phase of clinical trials. The drug is currently in the second phase, where it is administered to people who are affected by AD to prove or disprove its usefulness. With this novel way of approaching AD, Longo and his team have the potential to mitigate the harmful effects of AD. LM11A-31 can save lives and keep families united. Alzheimer's Disease no longer has to burden millions of families. ■

See Appendix 3.4 for references.

APPENDIX

1.1

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