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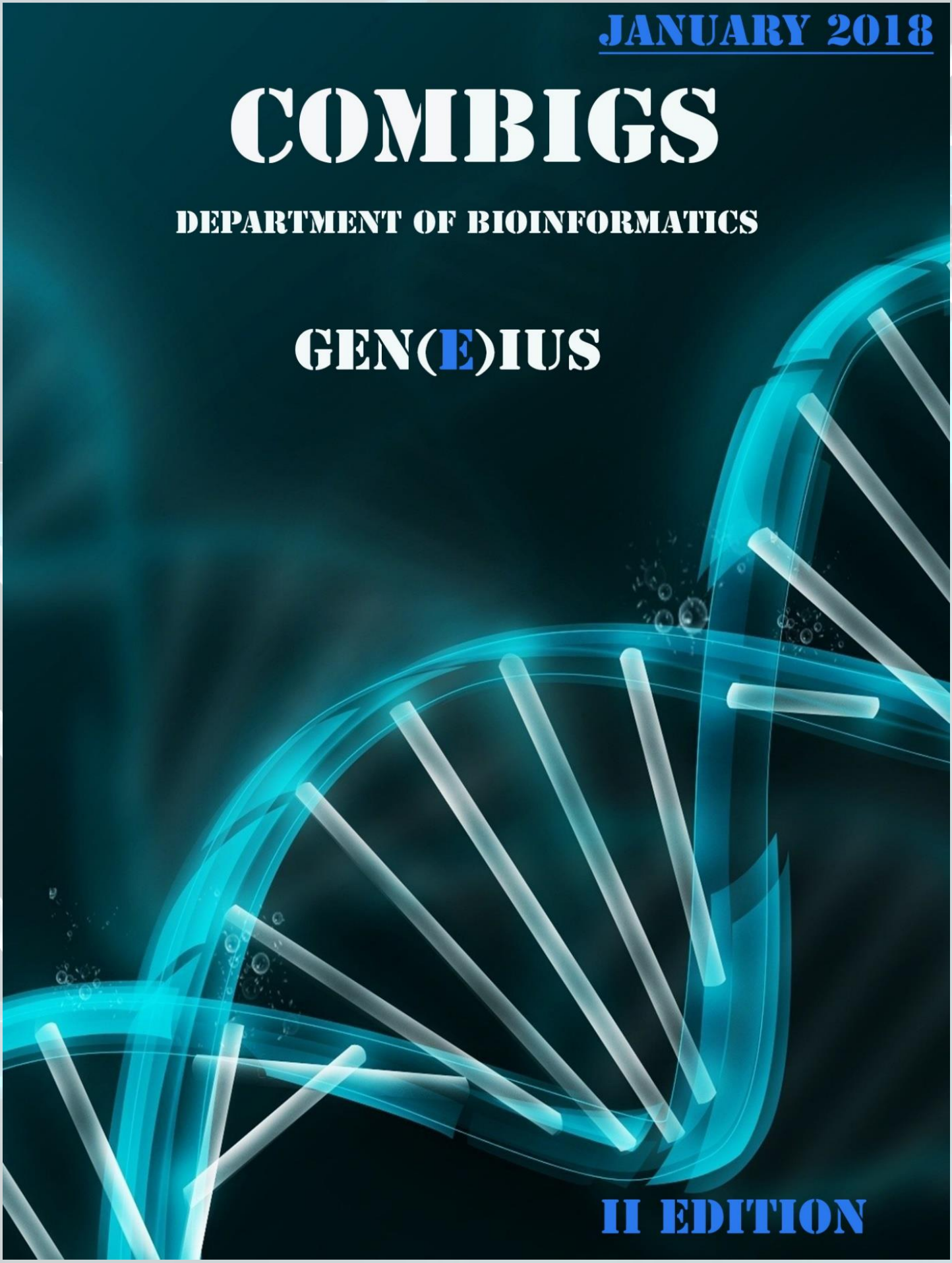
COMBIGS

DEPARTMENT OF BIOINFORMATICS

GEN(E)IUS

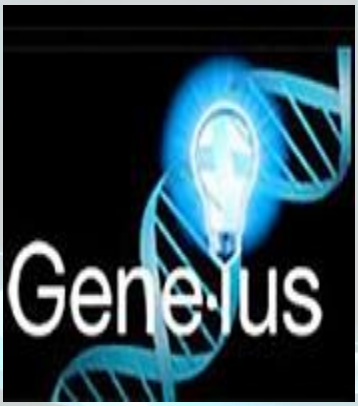


II EDITION

S.No	CONTENTS	Page no.
1.	FOREWARD	02
2.	WHAT AFTER BIOINFO?	03
3.	PLAYING GOD!!!	05
4.	ROYAL HEMOPHILIA AND THE FIRST COMMUNIST STATE	07
5.	CAN BIOLOGY BE UNDERSTOOD WITHOUT MATHEMATICS?	08
6.	CRISPR-CAS9 GENOME EDITING	09
7.	DISCOVERY OF NANO FOOT BALL IN GENES!	12
8.	IS PROTECTION FROM STROKE, NEURODEGENERATIVE DISEASES POSSIBLE?	13

GEN(E)IUS : THE COMBIGS MAGAZINE (ISSUE 2)

FOREWARD



COMBIGS is delighted to launch the second edition of GEN(E)IUS, the student-run magazine of the Bioinformatics department of SASTRA University. COMBIGS, Computational Biology Group @ SASTRA, a student chapter of Bioinformatics @ SASTRA began its journey on 01.09.2005 with just a handful of people as its members. This year COMBIGS has about 250 members, actively participating and enhancing the qualities of the association. Being a student-run group, we work on new themes for our fellow mates that would inculcate better taste of both life science and computer applications in their mentation. Our focus over the years has been fully on activities like technical forums, coding events and quizzes on a weekly basis that would keep the students engaged with departmental concepts in a different way. Also, we have introduced the Bioinformatics Library in JVC which consists of recent journals, magazines, reference books that help the students to explore the field of bioinformatics. In 2012, COMBIGS organized the "International conference on Structural and Functional Genomics" which had a huge number of participants from motley of departments. We believe in continuing the same and many other activities in the near future. Coming together is a beginning; keeping together is progress; working together is success.

WHAT AFTER BIOINFO?

Context is everything!

Bioinformatics is a discipline that addresses the need to manage and interpret the data that in the past decade was massively generated by genomic research. Bioinformatics is an umbrella term for the body of biological studies that use computer programming as part of their methodology. Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. Bioinformatics is the name given to these mathematical and computing approaches used to glean understanding of biological processes. It is the major outcome of the Human Genome Project (HGP) that aimed at elucidating the protein sequences of each chromosome of the humans. Among the numerous applications of Bioinformatics, let's explore the most the fascinating field- The field of Forensic Sciences. The word Forensics reminds all of us of one great person. Guess who?! Yes, he's Sherlock Holmes! He was a science based detective who was given life by Sir Aurthur Conan Doyle. It is evident from the series that he had employed many scientific methods to solve his cases. The word Forensic science means the application of scientific knowledge and methodology to legal problems and investigations.

To solve a legal problem the key is evidence, which can be of two types:

1.Testimonials or the statements from various people like the witnesses and victims of the crime.

2. Physical evidences, also called the real evidence, like blood, semen and other body fluids and fingerprints that actually connect a person to the crime.

When compared between the testimonials and physical evidences, physical evidence proves to be the indisputable one. The physical evidences need to be processed by scientific methods to derive the further information regarding it. The physical evidence collected at the crime scene is processed in a way to extract the DNA from it. As we know, DNA is unique to a person. DNA profiling, sometimes called as the DNA fingerprinting, is a forensic technique that is used to identify individuals based on the characteristics of their DNA. The DNA extracted from the crime scene is sequenced or profiled by various techniques:-

1 .RFLP analysis- Restriction Fragment Length Polymorphism.

2. PCR analysis - Polymerase Chain Reaction.

3. STR analysis- Short Tandem Repeats.

4. Amp analysis- Amplified Fragment length polymorphism.
5. DNA family relationship analysis.
6. Y-chromosome analysis.
7. Mitochondrial analysis.

This is where Bioinformatics comes into play. The DNA that is processed by the above techniques is then matched with the DNA database, CODIS- Combined DNA Index System which was developed by FBI. It uses two indices to provide the investigative lead from the biological evidence, namely the Convicted Offender Index and Forensic Index. Apart from DNA, fingerprint may also be helpful in identifying individuals. The fingerprints collected at the scene are matched with the fingerprint database, AFIS-Automated Fingerprint Identification System which was also developed by the FBI. Another area of forensics where Bioinformatics plays an important role is Computer forensics. Computer forensics is a branch of digital forensics pertaining to evidences found in computers and digital storage media. Evidence from computer forensics investigations is usually subjected to the same guidelines and practices of other digital evidence. It has been used in a number of high-profile cases and is becoming widely accepted as a reliable one. Forensics is the most challenging and interesting field with not many takers. In many Countries there are a lot of forensics organizations that actually look out for people with knowledge in Bioinformatics. For instance in Germany, the Federal Criminal Police Office (Bundeskriminalamt, abbreviated as BKA) is the federal investigative police agency of Germany, directly subordinated to the Federal Ministry of the Interiors, offer jobs to candidates with a degree in Forensics. In the US there are a lot of organizations that work for the government's crime lab. These private organizations are ready to recruit candidates, who hold a degree in Forensics Sciences too.

Some organizations in the US include:

1. North California Office of State Human Resources- North California.
2. Dept of Forensic Sciences- Washington, DC
3. Idaho Division of Human Resources- Pocatello, ID
4. LabCorp- Burlington, NC
5. Dept of Health/Mental Hygiene- Manhattan, NY

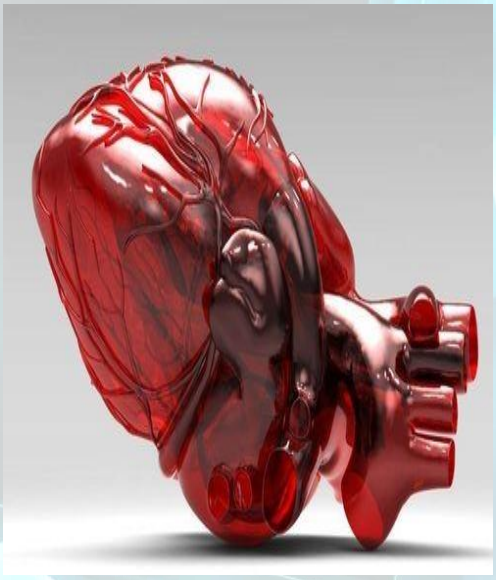
In UK, Forensic scientists are employed in commercial companies which specialize in providing forensic services to the police department such as:

1. Environmental Scientific Group
2. Orchid Cellmark.

In Scotland, a national forensic service is provided by the Scotland Police Authority. On looking into the crime rates across the world, it is certain that the forensic experts will be busy. This field is a great pick for Bioinformaticians. So, just "Keep Calm and Study Bioinformatics!!"

- Subathra Vijayakumar
(Class of '18)

PLAYING GOD!!!



The latest technique of medical field and biotechnology is the most frequent term in surgical world "3D Printing". Organ transplant have become simpler with a slogan "Print on, why wait long?" So let's have a brief look into what this actually is and how this works. 3D printing also known as Additive Manufacturing (AM) is a processes used to create 3D object from computer-aided design (CAD) model or another electronic data source such as an Additive Manufacturing File (AMF) by successively adding material layer by layer. STereoLithography (STL) is one of the most common file types that 3D printers can read. The technology used by most 3D printers to date—especially hobbyist and consumer-oriented models—is fused deposition modeling, a special application of plastic extrusion, developed in 1988 by S. Scott Crump and commercialized by his company Stratasys, which marketed its first Fused Deposition Modeling (FDM) machine in 1992.

GENERAL PRINCIPLES

The three main general principles involving 3D printing are

i. Modeling
ii. Printing
iii. Finishing

Modeling:

3D printable models may be created with a CAD package, via a 3D scanner, or by a plain digital camera and photogrammetric software. 3D printed models created with CAD result in reduced errors and can be corrected before printing, allowing verification in the design of the object before it is printed.

Printing:

At this step the model must be first examined for errors which are corrected using STL generation known as "repair". Once completed, the STL file needs to be processed by a piece of software called a "slicer," which converts the model into a series of thin layers and produces a G-code file containing instructions tailored to a specific type of 3D printer (FDM printers). This G-code file can then be printed with 3D printing client software (which loads the G-code, and uses it to instruct the 3D printer during the 3D printing process).

Finishing:

Though the printer-produced resolution is sufficient for many applications, a higher-resolution subtractive process is used to achieve greater precision. Some printable polymers such as ABS, allow the surface finish to be smoothed.

Applications:

• Biologists print 'biobots', viz., miniaturized bio-robots capable of finding their way through a human body to carry out repair jobs on a target organ or deposit medicinal drugs.

• At Harvard's Wyss Institute, clam-shell-shaped nano-robots containing DNA strands have been printed – capable of opening up selectively whenever they meet cancer cells, releasing specially calibrated antibodies to destroy these target cells.

3D PRINTED HEART REPLICA SAVES THE LIFE OF 9 MONTH OLD BABY

Another major application is the transplantation of heart where the each minute of waiting may even lead to fatal end. With the help of 3D printers this situation has been changed. On 26th September 2017, Chinese doctors have successfully performed a dangerous open heart surgery on a nine-month-old baby suffering from a severe heart defect using 3D printed heart model to plan the surgery. Despite the baby born healthy, doctors discovered that the baby had a severe congenital heart defect called a Total Pulmonary Venous Anomalous Drainage. This was the first time that a full 'sized 3D printed model of patient's heart was used to pre-plan a complicated surgery. Even though this is a rare case the heart replica operation was completed and the baby is safe and sound.

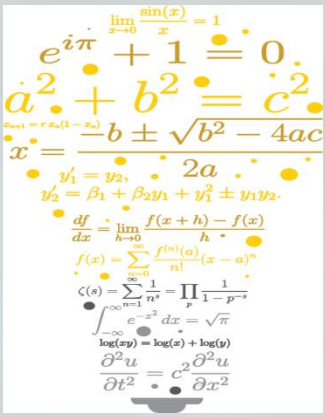
-Swetha R
(Class of '19)

ROYAL HEMOPHILIA AND THE FIRST COMMUNIST STATE

On August 12, 1904, Tsar Nicholas Romanov II of Russia wrote in his diary: "A great never-to-be forgotten day when the mercy of God has visited us so clearly." That day Alexis, Nicholas's first son and heir to the Russian throne, had been born. At birth, Alexis was a large and vigorous baby with yellow curls and blue eyes, but at 6 weeks of age he began spontaneously hemorrhaging from the navel. The bleeding persisted for several days and caused great alarm. As he grew and began to walk, Alexis often stumbled and fell, as all children do. Even his small scrapes bled profusely, and minor bruises led to significant internal bleeding. It soon became clear that Alexis had hemophilia. Hemophilia results from a genetic deficiency of blood clotting. When a blood vessel is severed, a complex cascade of reactions swings into action, eventually producing a protein called fibrin. Fibrin molecules stick together to form a clot, which stems the flow of blood. Hemophilia, marked by slow clotting and excessive bleeding, is the result if any one of the factors in the clotting cascade is missing or faulty. In those with hemophilia, life-threatening blood loss can occur with minor injuries, and spontaneous bleeding into joints erodes the bone with crippling consequences. Alexis suffered from classic hemophilia, which is caused by a defective copy of a gene on the X chromosome. Females possess two X chromosomes per cell and may be unaffected carriers of the gene for hemophilia. A carrier has one normal version and one defective version of the gene; the normal version produces enough of the clotting factor to prevent hemophilia. Because males have a single X chromosome per cell, if they inherit a defective copy of the gene, they develop hemophilia. Consequently, hemophilia is more common in males than in females. Alexis inherited the hemophilia gene from his mother, Alexandra, who was a carrier. The gene appears to have originated with Queen Victoria of England (1819 – 1901). One of her sons, Leopold, had hemophilia and died at the age of 31 from brain hemorrhage following a minor fall. At least two of Victoria's daughters were carriers; through marriage, they spread the hemophilia gene to the royal families of Prussia, Spain, and Russia. In all, 10 of Queen Victoria's male descendants suffered from hemophilia. Six female descendants, including her granddaughter Alexandra (Alexis's mother), were carriers. At this moment in history, the Russian Revolution broke out. Bolsheviks captured the tsar and his family and held them captive in the city of Ekaterinburg. On the night of July 16, 1918, a firing squad executed the royal family and their attendants, including Alexis and his four sisters. Although army investigators searched vigorously for the bodies of Nicholas and his family, they found only a few personal effects and a single finger. The Bolsheviks eventually won the revolution and instituted the world's first communist state.

-Anantha Krishnan
(Class of '19)

CAN BIOLOGY BE UNDERSTOOD WITHOUT MATHEMATICS?

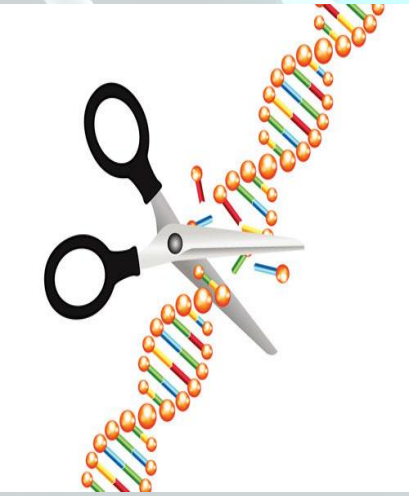


Living organisms are immensely complex. Every move, response, mechanism and action is the result of a dynamic, beautifully orchestrated process that involves more than a million at work. In some sense, they are akin to living machines that are driven by thousands of molecules that are all involved in some intricate biological pathway. A machine as complex as this is most certainly difficult to comprehend. The study of these living machines, biology, is primarily concerned with their topology, morphology, constitution, structure, composition and functioning. It is a vast ocean of information that must be processed by some mechanism or tool that converts this information into more comprehendible data. One such popular and widely used tool is mathematics, which deals with numbers and quantities as abstract concepts or in application in other sciences. Science has been rapidly advancing, with new discoveries being made each day in the vast arenas of biology, such as genetics, medicine, genomics etc. With the volume of biological data constantly increasing, the need for mathematics as a tool to process and analyze the information is being realized. Bio statistical data and methods were instrumental in determining the proportion of phenotypes obtained in Gregor Mendel's 19th century pea plant experiment. This essentially led to the birth of Genetics. Once the significance of mathematics in biology was more widely understood by biologists, massive discoveries and innovations have been possible. Recent revolutions in fields such as protein and genome studies are, in fact, largely attributable to the development and use of various analytical tools and equipment, all of which rely primarily on mathematical and computer algorithms. These developments have significantly reduced the time and effort required to analyze the enormous volumes of biological data resulting from experiments. In terms of protein studies, the use of visualization tools (such as PyMOL, Rasmol, etc.), secondary structure prediction methods, alignment algorithms, validation methods (such as Ramachandran Plot) and evolutionary studies that use phylogenetic trees has greatly simplified the understanding of these molecules. Mathematical simulations and models facilitate the understanding of protein folding, tertiary structure formation, their binding sites and interactions with other small molecules and compounds. Function determination, prediction of structure from sequence, identification of interacting forces and other structural bioinformatics studies are all fundamentally based on mathematics. Genome projects that generate a large amount of data and usually require much effort and time, now with the use of latest technologies such as microarrays, next generation sequencing methods and other tools, are made simpler. These methods use mathematics to statistically analyze and interpret results of the experiment. Computational Genomics approach is now popular to perform studies on genes and thereby identify gene function, location, evolution, etc. Sequence alignment algorithms, such as Needleman Wunch, BLAST, PAM, etc. are all privy to the understanding of the evolution of protein and DNA sequences and mutations of the same, use highly sophisticated mathematical algorithms to perform the alignment and generate scores.

Technology used in spectrometers, microscopes, sequencers, and other complex equipment fundamentally use mathematical formulae and equations to calculate a number of parameters such as optical density, signal strength, generation and output, in confocal microscopes, that use Fourier's series, etc. of the sample or data set being analyzed. As the data set of biological data to be analyzed is ever-increasing, the methods and technology used for the analysis of data require a high level of sophistication that is brought about by the extensive use of mathematics. Any biological problem is highly complex and requires a high level of accuracy when addressed. Humans in their own minds tend to be biased and allow a significant margin of error and this can be detrimental to the development of science. Such high levels of accuracy may be achieved only through the use of highly efficient mathematical algorithms or simulation as explained above. From analyzing highly complex biological data to the simple counting of leaves on a plant, mathematics seems to play an instrumental role. In fact, fundamentally in nature, there exists no such distinction between these two fields, or any field as such. They are all basically sciences that meander their way around each other, intersecting paths multiple times. Therefore there exists, if at all, a very fine hazy line on the basis of which they may be distinguished. This fine line has been used as the basis for laying the strong foundation for a boundary of distinction built over years, by humans. This boundary has been created for the sole purpose of better understanding of the world and phenomena around us. In conclusion, it is important to understand that while we may speak of biology and mathematics as being two separate fields, fundamentally, they are one science and cannot be separated from each other. It is without question therefore, that biology cannot be understood without mathematics.

- Rachita K Kumar
(Class of '19)

CRISPR-Cas9 GENOME EDITING



This technique is currently, the simplest and precise method of Genetic Manipulation and it is therefore causing a buzz in the science world. The development of efficient and reliable ways to make precise, targeted changes to the genome of living cells is a long-standing goal for biomedical researchers and also to elucidate the functional organization of the genome at the systems level and establish causal linkages between genetic variations and biological phenotypes. In this article, we describe the development and application of CRISPR-Cas9 while highlighting challenges as well as future directions.

Genome editing is the insertion, deletion or replacement of

DNA at a specific site in the genome of an organism or cell. Several approaches to genome editing have been developed. A recent one is known as CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein9. An enzyme called Cas9, this acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome.so that bits of DNA can then be added or removed. And then a piece of DNA called guide RNA (gRNA), this consist of a small piece of pre-designed RNA sequence (about 20 bases long) located within a longer RNA scaffold. The Scaffold parts binds to DNA and the pre-designed sequence guides Cas9 to the right part of the genome. This makes sure that the Cas9 enzyme cuts at the right point in the genome. However, want to highlight some of the challenges that the field has faced and look forward to what may come.

THE BIOLOGY OF Cas9:

The functions of CRISPR and CRISPR-associated (Cas) genes are essential in adaptive immunity to select bacteria and archea, enabling the organism to respond to and eliminate invading genetic material. These repeats were initially discovered in the 1980s in E.coli, but their function wasn't confirmed until 2007 by Barrangou and colleagues, who demonstrated that S.thermophilus can acquire resistance against a bacteriophage by integrating a genome fragment of an infectious virus into its CRISPR locus. Three Types of mechanism have been identified, of which type II is the most studied. In this case, invading DNA from viruses or plasmids is cut into small fragments and incorporated into a CRISPR locus amidst a series of short repeats 9 around 20 bps. The loci are transcribed, and then processed to generate small RNAs (crRNA-CRISPR RNA),which are used to guide effector endonucleases that target invading DNA based on sequence complementarity one Cas protein ,Cas9 (also known as Csn10), in these specifically type II CRISPR mechanism is unique compared to other CRISPR system because one Cas protein(Cas9) is required for gene silencing. In the type II system, Cas9 participates in the processing of crRNAs and it is responsible for the destruction of the target DNA. Cas9's function in both of these steps relies on the presence of two nuclease domain (a Ruvc-like nuclease domain located at the amino terminus and a HNH-like nuclease domain that residues in the mid-region of the protein).

To achieve site-specific DNA recognition and cleavage, Cas9 must be complexed with both a crRNA and a separate trans-activating crRNA (tracrRNA) that is partially complementary to the crRNA. The tracrRNA is required for crRNA maturation from a primary transcript encoding multiple pre-crRNAs. This occurs in the presence of RNase III and Cas9. During the destruction of target DNA, the HNH and RuvC-like nuclease domains cut both strands, generating double-stranded breaks (DSBs) at sites defined by a 20-nucleotide target sequence within an associated crRNA transcript. The HNH domain cleaves the complementary strand, while the RuvC domain cleaves the non-complementary strand. The double-stranded endonuclease activity of Cas9 requires a short conserved sequence (2-5 nts) known as protospacer-associated motif (PAM). In fact, even fully complementary sequences are ignored by Cas9-RNA in the absence of a PAM sequence.

Cas and CRISPR as a new tool for molecular biology:

Based on the type II CRISPR system described previously, a simplified two component system by combining trRNA and crRNA into a single synthetic single guide RNA (sgRNA). sgRNA programmed Cas9 was shown to be as effective as Cas9 programmed with separate trRNA. To date, three different variants of the Cas9 nuclease have been adopted in genome-editing protocols. The first is wild type Cas9, which can Site-specifically cleave double-stranded DNA, resulting in the activation of the double strand break (DSB) repair machinery. The second is, increasing the precision by the development of mutant form, known as Cas9D10A, with only nickase activity. The third variant is a nuclease-deficient Cas9 .Mutations H840A in the HNH domain and D10A in the Ruvc domain inactivate cleavage activity, but do not prevent DNA binding. Therefore, this variant can be used to sequence-specifically target any region of the genome without cleavage.

APPLICATION

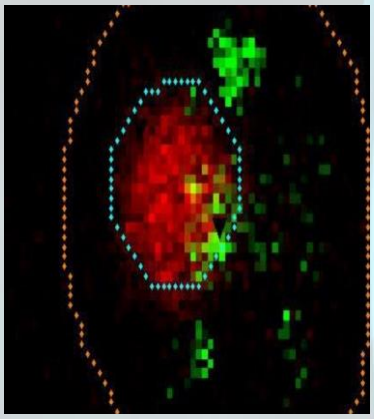
CRISPR-enabled genome editing has been used in controlling transcription, modifying epigenomes, conducting genome-wide screens and imaging chromosomes. CRISPR systems are already being used to cure genetic disorders in animals and are likely to be employed soon in the clinic to treat human diseases of the eye and blood. Many of the applications involve editing the genomes of somatic cells. Two clinical trials using CRISPR-Cas9 for targeted cancer therapies have been approved in China and the United States. Beyond biomedical applications, these tools are now being used to expedite crop and livestock breeding, engineer new antimicrobials and control disease-carrying insects with gene drives.

FUTURE OF CRISPR-Cas9:

It is likely to be many years before CRISPR-Cas9 is used routinely in humans. Much research is still focusing on its use in animal models or isolated human cells, with the aim to eventually use the technology to routinely treat disease in humans and also for altering human embryos.

- Vidya Lakshmi
(Class of ’19)

DISCOVERY OF NANO FOOT BALL IN GENES!



Genes are controlled by 'nano footballs', structures that look like footballs but 10 million times smaller than the average ball. By placing tiny glowing probes on transcription factors special chemicals inside cells which control whether a gene is switched 'on' or 'off' -- researchers gained a remarkable new insight into the way in which genes are controlled.

Crucially, they discovered that transcription factors operate not as single molecules as was previously thought, but as a spherical football-like cluster of around seven to ten molecules of roughly 30 nanometers in diameter. The discovery of these nano footballs will not only help researchers understand more about the basic ways in which genes operate, but may also provide important insights into human health problems associated with a range of different genetic disorders, including cancer. The research, supported by the Biotechnology and Biological Sciences Research Council (BBSRC) and published in eLife was carried out by scientists from the University of York, and the University Of Gothenburg and Chalmers University of Technology, Sweden.

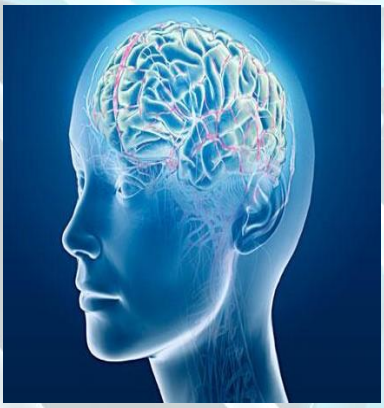
Transcription is regulated through binding factors to gene promoters to activate or repress expression, however, the mechanisms by which factors find targets remain unclear. Using single-molecule fluorescence microscopy, we determined in vivo stoichiometry and spatiotemporal dynamics of a GFP tagged repressor, Mig1, from a paradigm signaling pathway of Saccharomyces cerevisiae. We find the repressor operates in clusters, which upon extracellular signal detection, translocate from the cytoplasm, bind to nuclear targets and turnover. Simulations of Mig1 configuration within a 3D yeast genome model combined with a promoter-specific, fluorescent translation reporter confirmed clusters are the functional unit of gene regulation. In vitro and structural analysis on reconstituted Mig1 suggests that clusters are stabilized by depletion forces between intrinsically disordered sequences. We observed similar clusters of a co-regulatory activator from a different pathway, supporting a generalized cluster model for transcription factors that reduces promoter search times through intersegment transfer while stabilizing gene expression. The researchers employed advanced super-resolution microscopy to look at the nano footballs in real time, using the same type of yeast cells utilized in baking and brewing beer.

Professor Leake said: "We found out that the size of these nano footballs is a remarkably close match to the gaps between DNA when it is scrunched up inside a cell. As the DNA inside a nucleus is really squeezed in, you get little gaps between separate strands of DNA which are like the mesh in a fishing net. If a gene is switched on, specialized molecular machinery in the cell reads off its genetic code and converts it into a single protein molecule. Thousands of different types of protein molecules can then be made, and when they interact that can drive the building of

all of the remarkable structures found inside living cells. The process of controlling which genes are switched on or off at any particular point in time is fundamental to all life. When it goes wrong, this can lead to serious health problems. In particular, dysfunctional switching of genes can result in cells which grow and divide uncontrollably, which can ultimately lead to cancer. This new research may help provide insights into human health problems associated with a range of different genetic disorders. The next stages will be to extend this research into more complicated types of cells than yeast and ultimately into human cells.

-Shwetha Srinivasan
(Class of '20)

IS PROTECTION FROM STROKE, NEURODEGENERATIVE DISEASES POSSIBLE?



Scientists have discovered a new class of molecules in the brain that synchronize cell-to-cell communication and neuro inflammation/ immune activity in response to injury or diseases. Elovanoids (ELVs) are bioactive chemical messengers made from omega-3 very long chain polyunsaturated fatty acids (VLC-PUFAs, n-3). They are released on demand when cells are damaged or stress. Elovanoids might play a central role as synaptic organizers, especially important in conditions resulting from synaptic dysfunction such as autism or amyotrophic lateral sclerosis, for which we have no therapeutic answers. Although the occurrence of very long chain polyunsaturated fatty acids has been well documented, what has not been known is their significance and potential to be converted into biochemical triggers to resolve injury, inflammation and other threats to neuronal communication and cell survival. The researchers discovered the structure and characteristics of two elovanoids - ELV-N32 and ELV-N34 - in the brain. Starting with neuron cell cultures and then an experimental model of stroke, they found that elovanoids were activated when cells underwent either oxygen/glucose deprivation or excitotoxicity - early events associated with stroke, epilepsy, Parkinson's, traumatic brain injury and other neurodegenerative diseases. They determined the concentrations and therapeutic windows at which elovanoids conferred neuroprotection. The team found that elovanoids overcame the damaging effects and toxicity of these early events. In the stroke model, elovanoids reduced the size of the damaged brain area, initiated repair mechanisms and improved neurological/behavioral recovery. In the near future, we hope to apply this

knowledge to prevent traumatic brain injury, chronic traumatic encephalopathy, stroke and neurodegenerative diseases. Elovanoids may offer an answer to be tested as a potential therapy.

-Shwetha Srinivasan
(Class of ’20)