Current Studies in Basic Sciences, Engineering and Technology 2021

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ISRES Publishing

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Cover Design and Layout
Davut ALAN

This book was typeset in 10/12 pt. Calibri, Italic, Bold and Bold Italic.

Current Studies in Basic Sciences, Engineering and Technology 2021
Published by ISRES Publishing, International Society for Research in Education and Science (ISRES)

Includes bibliographical references and index.

ISBN
978-605-73797-0-2

Date of Issue
December, 2021

Address
Istanbul C. Cengaver S. No 2 Karatay/Konya/TURKEY

E-mail
isresoffice@gmail.com

www.isres.org

PREFACE

Current Studies in Basic Sciences, Engineering and Technology 2021 is published annually from the selected papers invited by the editors. This edition includes 6 sections and 21 papers from the field of Technology, Engineering, Mathematics, Chemistry, Physics, Biology & life sciences. All submissions are reviewed by at least two international reviewers. The purpose of the book is to provide the readers with the opportunity of a scholarly refereed publication in the field of basic sciences, engineering and technology. Current Studies in Basic Sciences, Engineering and Technology 2021 is published by ISRES Publishing

This book is intended for the all fundemental aspects of the science such as enviromental, zoological, botanical, microbiological and molecular subjects or new idea for life sciences.

We wish the book will present curiosity about the LIFE, we wish the book will be usefull for new scientists, science readers and anyone who intented to learn about the mystery of the science.

November 2021

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SECTION 1: TECHNOLOGY

SECTION 2: ENGINEERING

SECTION 3: MATHEMATICS

SECTION 4: CHEMISTRY

SECTION 5: PHYSICS

SECTION 6: BIOLOGY & LIFE SCIENCES

SECTION 1
TECHNOLOGY

Augmented Reality and Application Areas

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Augmented Reality

Augmented Reality (AR) technology dates back to the 1960s, but its adoption has been limited to existing technologies. The idea of how to represent two-dimensional objects in three dimensions in the real world has been tested on a limited number of computers (Sutherland et al., 1968).

AR technologies draw attention in the field of rapidly developing information technologies. In recent years, AR; It has made a name for itself in fields such as education, medicine, digital advertising, technical service, robotic technologies, entertainment and navigation. AR is a technology in which simultaneous interaction between real and virtual objects was provided by placing computer-generated models and data on the real world (Azuma, 1997). Azuma identifies three basic components of AR systems.

These are respectively;

1. merging virtual images with real world
2. three-dimensional recording of digital data
3. is the interaction in real time.

Azuma also states that AR is an advanced derivative of Virtual Reality (VR). VR applications have similar basic components to AR. These key components are virtual objects, real-time response, and visual equipment, respectively. In addition, there are some differences from each other. While VR technologies offer the user a virtual environment completely independent of the real world, AR technologies allow the user to see virtual objects in the real world. The most important factor that distinguishes AR from VR is to provide interaction between the real world and the virtual world by allowing 3D images produced on computers to be displayed on a real world environment (Sin et al., 2010). The virtual, augmented and hybrid reality process was shown in Figure 1.

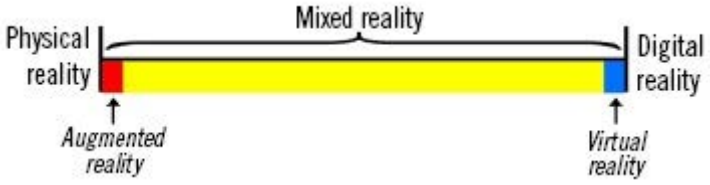

Figure 1. Virtual, Augmented and Mixed Reality Process

Many of the basic concepts of AR have been used in the movie industry. It has been used extensively, especially in science fiction movies such as Terminator and RoboCop. These movies feature cyborg characters rendered on the real world with 3D graphical overlays.

The term AR was coined by Tom Caudell in 1990 for the development of directional diagrams and marking plates used on the ground for guidance purposes at the Boeing aircraft factory (Caudel et al., 1992). Many researchers talk about the use of head-mounted displays (HDM) for AR technology (Janin et al., 1993). While this statement provides the accepted basic components for AR, it also aims to enable some advanced technologies such as mobile technology (Azuma et al., 2001). 2D images can be rendered in interactive proportions on top of a live image from the camera, but 3D images cannot be combined in the real world.

Today, the rapid spread of mobile devices and wireless network technologies brings with it a number of opportunities for the use of technologies such as AR and VR. These innovative technologies, which have been developed, bring two-dimensional or three-dimensional content produced on computers to the realms of reality, sensory immersion and interaction. Thanks to the unique interaction features of AR and VR technologies, a number of special skills and applications that cannot be realized with traditional methods can be developed.

Technologies for AR

AR systems basically contain three elements. These are respectively; monitoring and recording, imaging technology and real-time processing. AR is a real-time interactive three-dimensional recording technology. Virtual data (audio dec video, 3D animation, images, etc.) is added to this information by collecting real-world information experienced in AR technologies and using it as a tool.b.) occurs when it is integrated (Butuner & Toraman,2018)

Correct viewing and recording is essential to obtaining a quality enhanced image. While presenting a realistic image to the user, the camera must be mapped to real-world space and virtual data, taking into account perspectives. Especially for a camera system in motion, the user's position in the real environment where the virtual object is located must be

determined continuously. The aim here is to display the object created on the computer in a real environment (Bimber et al., 2005). In the future, both imaging technology and real-time imaging seem to be the fundamental building block and challenge for AR. The first of these are limitations such as the optical system of limited value (ie field of view), technical capability (resolution etc.) and user factor (eg human height and weight). The other, real-time image processing, depends on the AR devices' ability to quickly, reliably and realistically position a virtual object layer on top of the real-world environment. The aim here is to integrate the virtual object created on the computer in a way that users cannot distinguish between the real environment and the virtual object.

Hardware Technologies

We can list the hardware components that are frequently used for AR as processor, screen, sensors and input devices. Mobile devices such as smartphones and tablets can run AR applications due to the MEMS sensors they have such as camera, GPS, accelerometer and solid state compass.

Display devices

A number of technological devices such as monitors, optical projection systems, manually controllable devices and body-worn imaging systems were used to develop AR applications (Pair et al., 2002).

- Head-Mounted: A head-mounted display (HMD) is an AR display device paired with a headset. HMDs transfer images of both the real world and virtual objects into the user's field of view. The most popular HMDs today use six degrees of freedom sensors that allow virtual objects to be positioned in accordance with the real world and adjusted by taking into account the user's head movements.

- Glasses: AR applications can also be shown in glasses-like devices. AR glasses contain technology that uses cameras in which the AR image was projected from the surfaces of the lens parts of the glasses to display the virtual object image over the real world image.

- HUD (Head-Up Display): These AR devices can be defined as portable head-up displays that enable users to see data, information and a number of virtual images while watching real-world images. As an example, we can give the HoloLens manufactured by Microsoft.

- Contact Lenses: Bionic contact lenses under development are an embedded imaging system consisting of LEDs, electronic integrated circuit and a Wi-Fi antenna to provide wireless communication.

- Virtual Retina Display: Developed at the University of Washington's Human Interface Technology Laboratory. In this technology, the image was transferred directly to the retina of the eye of the user.
- EyeTap: Also known as 2nd generation glasses, it captures rays passing through the center point of the wearer's eyepiece and replaces computer-controlled light for each beam.
- Portable Displays: Handheld AR displays used MEMS sensors such as GPS, digital compass and six degrees of freedom accelerometer-gyroscope.
- Spatial Augmented Reality: This technology uses digital projectors to display graphical information over the real world. The difference of this device from others is that the screen is separate from the user.

Some of the headsets produced for virtual, augmented and hybrid reality were shown in Figure 2.

Figure 2. Headsets for Virtual, Augmented and Hybrid Reality.

Tracing

Modern mobile AR systems consist of digital cameras, accelerometers, GPS, optical sensors, solid-state compasses, gyroscopes, RFID and wireless sensors. These mobile AR technologies offer varying levels of accuracy and precision. The most important of these is the location and direction information of the user's head.

Input Devices

There are also wearable AR technologies, which include voice recognition systems that convert the user's voice into computer instructions, systems that can detect body movements or interpret from sensors placed on devices such as pointers, stylus, and gloves. Two types of AR platforms, beacon-based and unsigned, were used for input devices to detect AR applications. Example applications of marker-based and markerless

AR were shown in Figure 3.

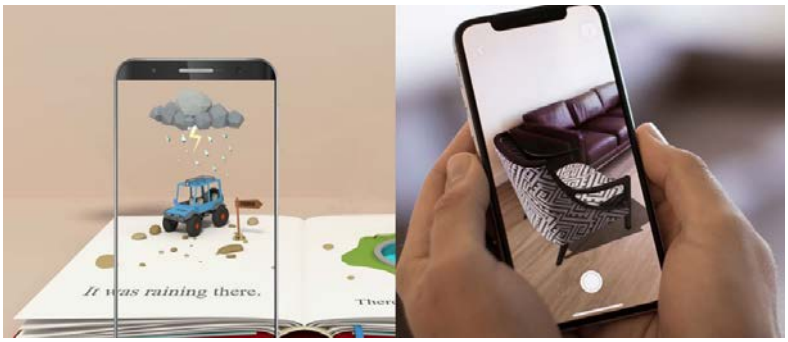

Figure 3. Marker-Mased and Markerless AR.

Computer

The computer analyzes the perceived visual and other data to synthesize and position virtual objects.

Software Technologies

In AR systems, the software should be capable of deriving real world coordinates from camera images using computer vision methods and recording the image. Many computer vision methods used in AR were derived from visual odometry. These methods consist of two stages. First, reference marks or optical flow are detected from the camera images. In the first step, some feature detection methods such as edge detection, blob detection, corner detection, or thresholding and other image processing methods can be used. The second stage restores the real world coordinate system from the data obtained as a result of the first stage (Segura et al., 2005).

Some methods used in AR accept objects with known reference pointers in the scene. Here, the 3D structure of the scene must be calculated prior to processing. If there are unknown parts of the scene, the simultaneous localization and mapping (SLAM) method can map on relative positions. If no information about the geometry of the scene is available, the structure can be determined from motion algorithms such as beam tuning. The mathematical methods used at this stage include geometric algebra, exponential map and rotation representation, projective (epipolar) geometry, nonlinear optimization, robust statistics, Kalman and particle filters.

A number of software development kits (SDKs) have been produced in order to enable easy and fast development of AR applications. Vuforia, CloudRidAR, Catchoom CraftAR ARToolKit, AR, Layar, Blippar, Wikitude, and Mobinett offer some of the AR SDKs available in the market.

Application Areas of AR

AR has many applications such as education, military, arts, industrial, medical, commercial and entertainment.

Archaeology

AR was used to assist research in the archaeological field by incorporating a number of archaeological features into modern landscape techniques. It is especially useful for archaeologists to draw some conclusions about the layout and configuration of research areas. Another important benefit is that it helps archaeologists to rebuild ruins, historical buildings and historical sites in accordance with the original. An example of the use of AR in archeology was shown in Figure 4.

Figure 4. AR in Archeology (AR in archeology, 2021).

Architectural

With the AR method, 3D images of a building can be placed on the physical real area where the building will be built. With AR, an architect's 2D drawings can be transferred to an animated 3D visual view. Users can virtually see the exterior and interior of a building, as well as make virtual object layouts. An example of using AR in architectural projects was shown in Figure 5.

Figure 5. AR in Archeology (AR in architecture, 2021).

Build

Today, with AR construction applications, underground construction components such as sewage and water and electrical wiring installations on a construction site can be easily visualized with the help of GPS technology. As an example of such applications, we can give the AR supported Daqri Smart Helmet helmet such as visual instructions, warnings and 3D mapping for employees. Especially in disasters such as earthquakes, these applications provide great benefits. An example of AR application in the construction industry was shown in Figure 6.

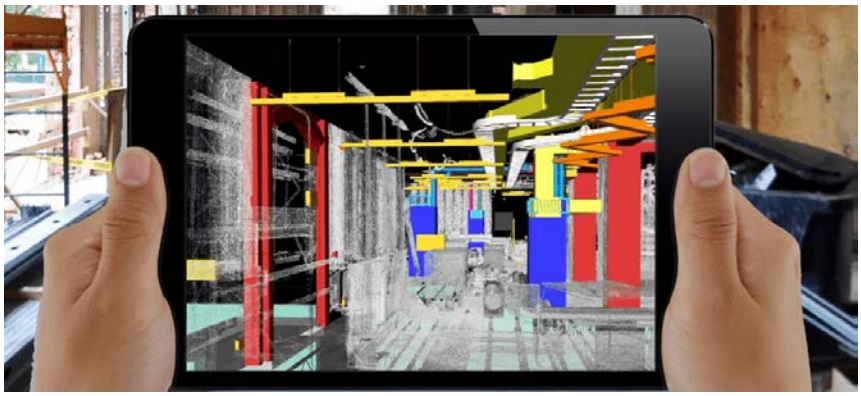

Figure 6. AR in Construction (AR in construction, 2021)

Industrial Design

AR offers industrial designers the opportunity to virtually experience the design and manufacture of any product in the real world, before realizing it. Volkswagen, one of the leading companies in the automotive industry, uses AR technology to compare theoretically calculated values with actual crash test data. With AR applications, experimental calculations can be made by visualizing the structure of a car body, engine system and other materials before production. An example of pre-production use of AR technologies in industrial design applications was shown in Figure 7.

Figure 7. AR in Industrial Design (AR in industry, 2021)

Education

A real-time training application can be developed by using materials such as text, graphics, video and audio in AR applications. Using the AR mobile device, interaction can be made through markers placed on textbooks, flashcards and other materials. With the AR applications developed, students provide an interactive participation in the lessons by discovering and learning. Construct3D application, a Studierstube system used in higher education, enables students to actively learn the basic concepts of mechanical engineering, mathematics or geometry with virtual experiments and applications. AR applications can also help students understand the course topics in courses that require laboratory studies such as chemistry, physics and biology.

It can also enable medical education to visualize the anatomical structure of the human body in 3D. Especially in surgical applications, cadaveric problems are experienced. AR human models were used instead of cadavers. AR technology gives students the opportunity to experience an educational experience without being in a certain physical space. Considering that distance education was used extensively, especially during the pandemic process, we cannot ignore the positive contributions of AR systems to education. An example of the use of AR application in the education sector was shown in Figure 8.

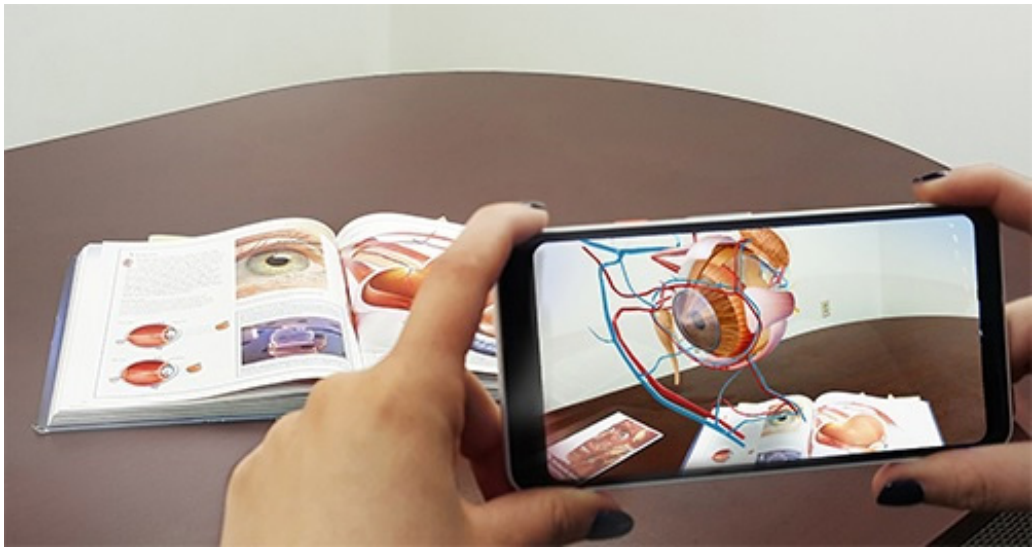

Figure 8. AR in education applications (AR in education, 2021)

Art

AR technology has also started to make a name for itself in the field of art. Many applications have been developed in order to increase the interest of the disadvantaged groups in art. By adapting eye tracking systems to physically disabled people, the experience of drawing pictures was provided. An example of the use of AR application in the field of art was shown in Figure 9.

Figure 9. AR in Art Practices (AR in art, 2021)

Card Apps

One of the interesting and innovative application areas of AR technology is the development of interactive applications such as digital content, 3D animation, video and sound on cards such as business cards, greetings, weddings and invitations. An example of the use of the commercial card AR application was shown in Figure 10.

Figure 10. AR in Commercial Card Applications (AR in cards, 2021)

Tourism and Travel

AR applications try to engage customers by providing real-time informative data and images about the location and features of the venue on a tourism and travel website. It allows users to experience historical events, places and objects in 3D simulations of the real world by using AR applications about places in sightseeing trips. An example of the use of AR application in the tourism and travel sector was shown in Figure 11.

Figure 11. AR in Tourism and Travel Applications (AR in tourism, 2021)

Translation

AR systems can translate foreign language texts on signboards and menus into the user's language and display the text again in an augmented view. A foreign person's spoken language can be translated and displayed with subtitles on the user's AR display device. AR translation applications provide great convenience, especially in travels to different countries. An example of using the translation application in AR was shown in Figure 12.

Figure 12. AR translation application (AR in translation, 2021)

Business

Today, AR also makes a name for itself in the field of trade. Mobile AR applications, which enable customers to get detailed information about the contents of product packages on the shelves in shopping malls, make the daily lives of the visually impaired significantly easier. In the e-commerce sector, customers were provided with the opportunity to try products interactively. Especially jewelry and watch companies offer such opportunities to their customers. The customers were provided with the opportunity to experience AR with a mobile camera through the sign-based cardboard watches and jewelry apparatuses they send. The AR clock application developed by Tissot was shown in Figure 13.

Figure 13. LV clock application of Tissot (Tissot, 2021)

Military

By using AR glasses, AR applications in which war scenarios are processed on the real world environment can be developed to enable soldiers to experience how they can act in the face of potential dangers interactively. Rockwell International has developed an AR application for video map layers of satellite and orbital debris traces to aid in space observations of an Air Force Maui Optical System. This application allowed telescope users to identify satellites in outer space, as well as identify and catalog threatening space debris. AR applications have been developed to increase the flight skills of pilots in aircraft simulations in the aviation system. An example of the use of AR application in the military field was shown in Figure 14.

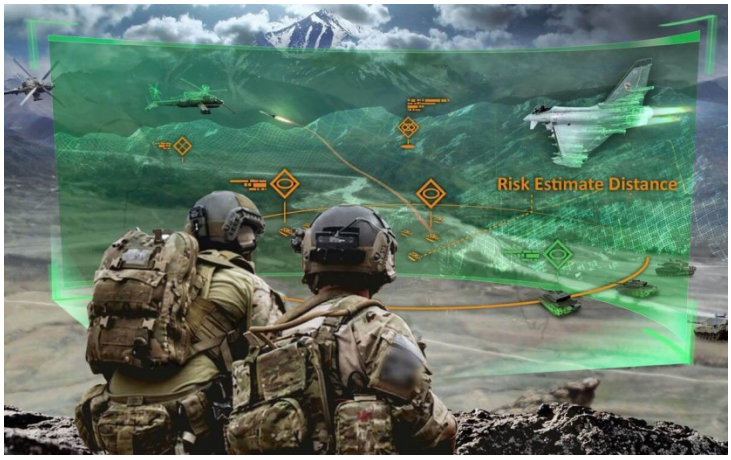

Figure 14. AR Application in the Military Field (AR in the military, 2021)

Medical

In medicine, a vein imaging device is used that films the subcutaneous veins, processes the image of the veins and reflects them on the skin to detect the location of the veins in

the human body. AR applications can provide the surgeon with some useful information such as the patient's heart rate, blood pressure, and the instantaneous state of the organ in surgical procedures.

Examples of AR applications include an AR system in which real data was virtualized on real-time images taken from tomography or ultrasound devices. AR systems have been used extensively in many disciplines such as anatomy, neurosurgery, general surgery and biochemistry in the medical field. An example of the use of AR application in medicine was shown in Figure 15.

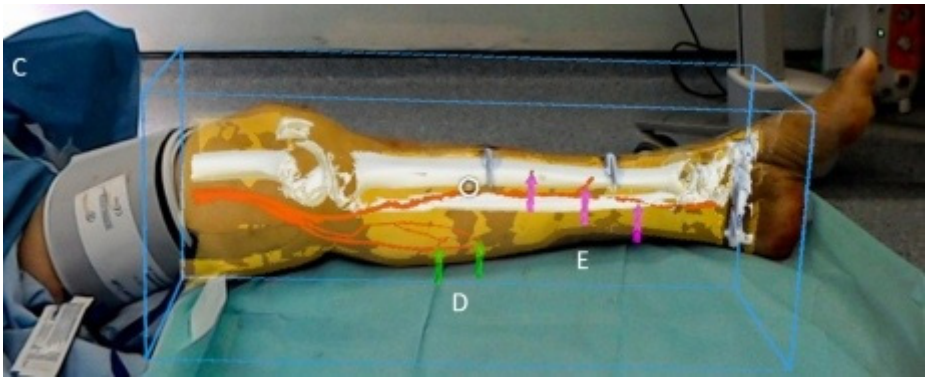

Figure 15. AR Medicine Application (AR in medicine, 2021)

Technical Maintenance and Support

It is a great advantage for technical personnel to display AR images of assembly and operating instructions on the parts of a system using pointer labels or unmarked methods during the repair, maintenance and repair processes. In addition to Boeing, many automotive industries such as BMW and Volkswagen have incorporated AR technology into their assembly lines to improve the production and assembly processes in factories. With the use of AR, employees can immediately intervene in problems and problems on the machines. An example of AR use in technical maintenance services was shown in Figure 16.

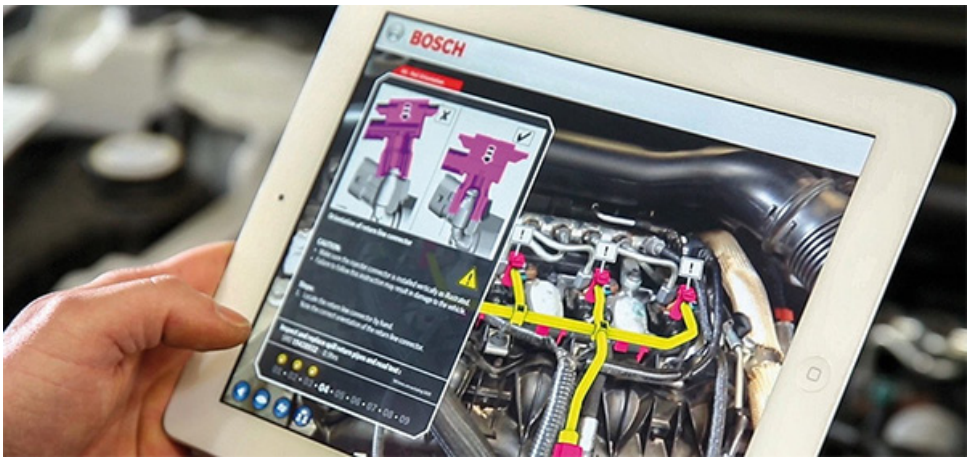

Figure 16. AR Application in Technical Maintenance Services (AR in technical, 2021)

Television

Almost many television channels have started to use AR applications in their programs such as weather, news programs and sports events. AR is also used in football and other sports competitions to display a number of sports details such as commercial advertisements placed on the view of the sports field, information about the team, technical information about the game. AR technology allows TV viewers to interact visually with the programs they watch, such as TV series, movies and documentaries. Day by day, we started to see AR applications more frequently in TV programs. One of them was shown in Figure 17.

Figure 17. AR Application in Television Programs (TV AR, 2021)

Navigation Systems

AR applications help increase the efficiency and effectiveness of navigation devices used in automobiles. Target direction and distance, terrain and road conditions, weather and traffic flow information projected on the windshield of the cars provide drivers with a safer and more comfortable travel opportunity. It also contains some useful information that warns drivers of potential hazards on their roads. AR navigation systems were used in the maritime and aviation industries as well as in the automotive industry. An example of AR application used in automotive navigation was shown in Figure 18.

Figure 18. AR Application in Navigations (Nav AR, 2021)

Game

AR-based computer and mobile games developed today allow players to experience playing games using digital objects in the real world. At the same time, the comfort of playing an interactive game by perceiving the movements of the player was provided. In this regard, many game developers have started to adapt new technologies to their games. An AR game application developed on the real world was shown in Figure 19.

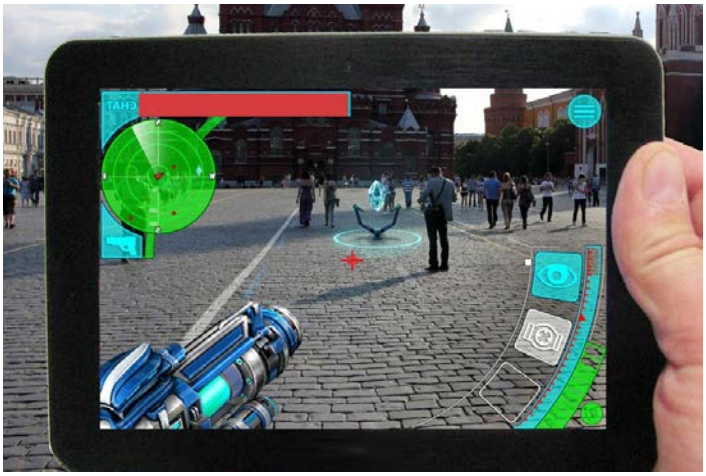

Figure 19. AR Game Application (Game AR, 2021)

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To Cite This Chapter

Uzun, Y., Calp, M. H., & Butuner, R. (2021). Augmented reality and application areas. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 2–18). ISRES Publishing

Wearable Technology

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Tuba BABAOGLU
Cankiri Karatekin University

Introduction

Humans have always needed to improve themselves and their environment since the early ages. With this quest and the development of various products, technology has moved to a very important point today. The initial aim was to serve the basic needs of people, but in recent years, increasing the comfort of these basic needs has become a priority. Wearable technology is one of the technologies that has an important place for comfort. Wearable technology generally includes devices that the user can wear for various purposes or place on any object in different ways.

Wearable technology first came into our lives in the 13th century with the glasses invented by Roger Bacon (Rosen, 1956). While these designed glasses are a fact of life today, smart glasses have started to enter our lives now. It can be said that the designed watch in the form of a necklace by Peter Henlein in 1504 is among the first designs used in wearable technology in history (Guler et al., 2016). This pocket watch evolved into different models in the 1900s and became a wrist watch, the most convenient design for users.

With the development of the cinema industry, people began to transfer the products of their dreams to movies. These products of imagination, which only appear in science fiction films, have become commonplace today. For instance, it is seen that the smart glasses used in the movie “Back to the Future”, which was screened in 1987, were produced by Google company, and the self-drying smart jacket used in the same movie was produced by Kickstarter company. The used smart shoes in the movie “Back to the Future” came also into our lives with Nike company.

With the development of wearable technology, products have begun to be developed in many different sectors. In Figure 1, wearable technology products for many needs of users from different sectors are given. They are frequently used in the sports and entertainment sectors, especially in health.

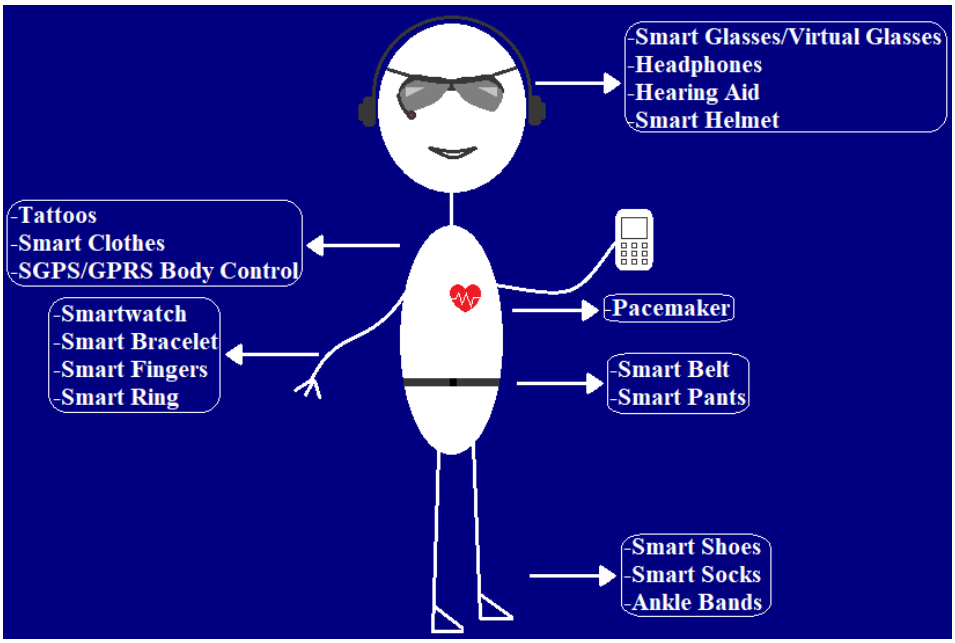

Figure 1. Wearable Technology Devices

Today, studies continue for new wearable technology devices and the development of existing technology devices. For example, in a study that outlines the future, motion recognition was aimed with an accelerometer and microphone placed on the arms of users such as workers (Ward et al., 2016). The health sector has had the biggest share in the growth of wearable technology. The bracelet, which was designed to track the movement of the user in 2008, is one of the essential studies carried out in the field of health (Ananthanarayan et al., 2010). With the progress of these studies, the production of wearable technology devices for more special cases has gained momentum. As an example, in the study carried out in 2021, the used wearable wrist sensor to observe the reach-to-grasp movement of the arms of individuals with stroke and to determine the treatment goals is mentioned (Yang et al., 2021).

In a different study using wearable technology devices, smart collars used to track the activities of dogs are mentioned (Yashari et al., 2015). With this study, it clearly shows that wearable technology is used in other living things besides humans and that the point it has reached today is very comprehensive. The improvement of wearable technology in many areas will increase its effects on our lives and will continue to change our lives.

Data Process of Wearable Technology

The data collection and processing process in wearable technologies generally has the same logic. Figure 2 shows the data process of wearable technology schematically. There are 5 data process steps, namely data collection, preprocessing data transfer, computation, data processing and data storage, respectively.

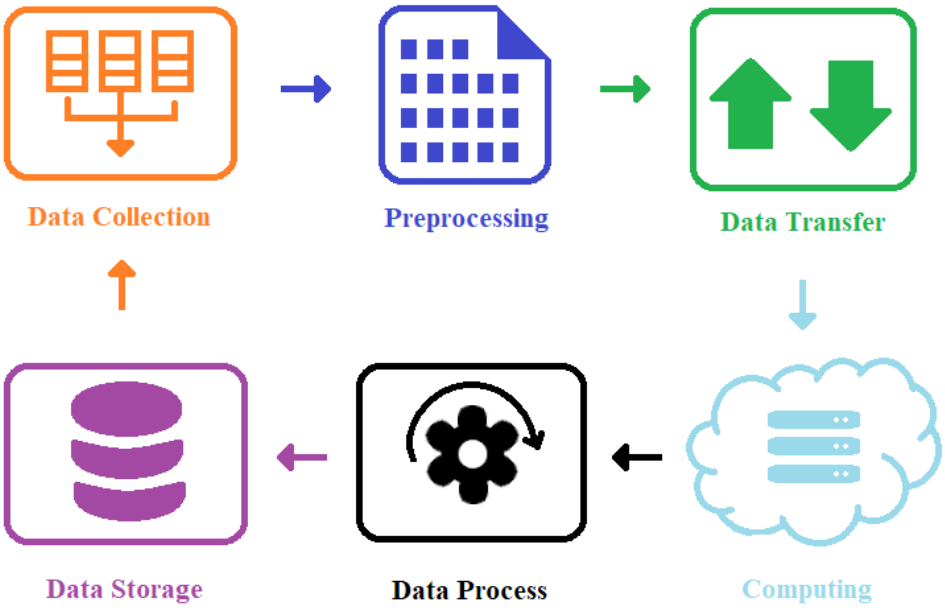

Figure 2. Data Process of Wearable Technology

Data Collection

User data is collected and processed on wearable technology devices. Crowdsourcing is used in collaborative retrieval of collected data, depending on its size. Crowdsourcing of data collected from wearable technology devices, in other words, crowdsensing, is used to activate the regular collection of data. Crowdsensing is carried out in forms such as participatory (active) sensing, where users actively report their movements or observations voluntarily, and opportunistic (passive) based on the automatic sensing, collection and sharing of data with certain applications running in the background. User involvement is almost nonexistent in opportunistic sensing (Delmastro et al., 2016).

Preprocessing

In wearable devices, as in many technologies (Crone et al., 2006), there is a data preprocessing. Unnecessary or bad data is passed through important stages such as filtering, structured, cleaning and validation so that the storage resource is not sufficient or the raw data is in an understandable format. It is aimed to improve the performance of wearable technology devices by improving the collected data as a result of these stages. In addition, in the preprocessing step, data is compressed to reduce the amount of consumed power during data transmission.

Data Transfer

One of the most significant steps in data process of wearable technology is the data

transfer between the device and the network. Considering various parameters such as distance, transmission rate and consumption of power for wearable devices, various technologies are used in data transfer. Various cellular networking such as Bluetooth Low Energy (BLE) (Bluetooth 4.0BLE), Wi-Fi and Zigbee can be given as examples of technologies that are widely used in wearable devices. These networking have advantages and disadvantages among themselves in terms of transmission distance, transmission rate, power consumption and security. It is possible to achieve a range of up to one hundred meters in all three networking. While the transmission rate is higher in Wi-Fi technology than others, consumption of power is higher than other technologies. Wi-Fi technology also has a wide range of application area. It is also known that BLE and Zigbee technologies have higher security compared to Wi-Fi technology. BLE technology has a small size and uses in many applications, but has limited capacity. Zigbee technology is a newer, low-cost wireless mesh network technology with features such as self-healing of the network structure compared to other technologies (Li et al., 2019). The fact that Zigbee is newer limits its application area. Each of these networking depending on the mentioned features has advantages and disadvantages compared to the other. In this context, the technology to be used will vary according to the priority of features such as transmission rate, security and power consumption, depending on the device and application.

Computing

The workload has increased as the user needs of wearable technology devices. Performing computations on these devices faster and more effectively has been a significant part of the process. Especially in the early development stages of wearable technology, it was necessary to collect data about the used devices and then transfer the data from these devices with a computer connection. With the development of technology, computing began to be carried out not locally, but by moving them to a closed network device. In this context, Multi-Access Edge Computing (MEC) was introduced (Ometov et al., 2021). MEC is a system that allows computing to be returned to the device after being made quickly and effectively.

Nowadays, cloud, edge and fog are the first computing that come to mind in wearable technology devices. Computing, storage and networking are aimed as a result of filling the gap between end-to-end devices in cloud computing. Edge computing is a more comprehensive version of cloud computing, but user data may be at risk. By removing a disk driver from the edge source or copying collected data from a memory stick in cloud computing, important information of user can be compromised. In edge computing, the data of the edge node that is in the nearest network is processed. In fog computing, this network is wider. But fog computing is a technology with a lack of knowledge. Therefore, it has not yet become a frequently used technology in wearable devices. In addition to

these technologies, computing such as mist, mobile, mobile cloud, and cloudlet are also included in the literature (Dolui et al., 2017).

Data Process

Various methods are used to obtain understandable results from data inputs of wearable devices that serve certain purposes. Machine learning techniques such as clustering, classification, and regression are among the commonly used techniques (Lown et al., 2020).

Time series of data are generally used for analysis in wearable technology devices (Sprint et al., 2017). These time series, which are recorded depending on the need, provide a pattern in which physical changes such as behaviors belong to the individual and deterioration of health can be observed in line with the purpose of use. In addition to machine learning, preprocessing steps such as Convolutional Neural Network (CNN), Multilayer Perceptron (MLP), Long Short-Term Memory (LSTM), Physical Activity Change Detection (PACD) are used to obtain the most efficient and accurate results (Janković et al., 2018). The obtained data as a result of the process is presented in formats such as reports and images in a way that is clearer for users.

Data Storage

After data process, the data is stored for later analysis. This process is crucial for the secure recording of personal data. Therefore, it can be necessary to use complex systems in the data storage. Besides, the fast performance and low energy consumption of equipment used for storage are important for devices such as used cell phones for communication. The energy efficiency of the equipment will decrease the workload on the cell phone, which is used for different purposes in daily life (Huang et al., 2015).

Wearable Technology Application Areas

The desire of people to access information quickly and reliably is increasing day by day. Various technologies are being developed for this purpose. Wearable devices are one of these technologies. In this section, the rapidly developing wearable technology sector is covered together with its application areas.

Use in Daily Life

Wearable technology is actively used in many areas of our lives. Smart watches, glasses, headphones, rings and wristbands are just a few of them. In this section, a few wearable technology products used in daily life are discussed.

Now, smart watches reach a wide range of users around the world as they accelerate

access to information, appeal to fashion and are one of the most affordable wearable technologies. The market share of smart watches produced by many companies in the sector is quite large. This technology, which is far beyond any watch, has many features such as measuring the oxygen level in the blood, heart rate monitoring, stress measurement, pedometer, calling for help in the event of a fall, wristband alarm, inactivity alerts, remote connection with mobile phones, making calls, etc. As seen in the image of Apple smart watches in Figure 3, these watches, which have very stylish designs in terms of compliance with fashion, also have models that offer the option to choose a compatible watch dial by taking a picture of the clothes worn (Turakhia et al., 2019).

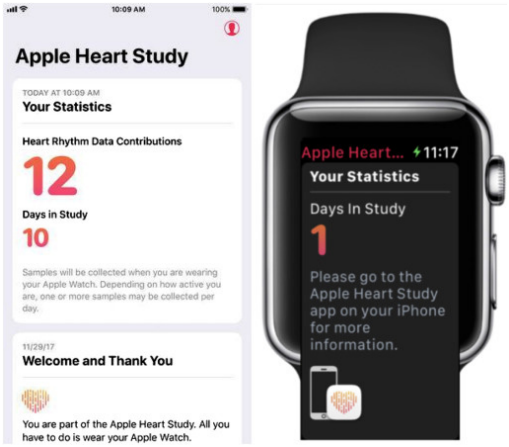

Figure 3. The Photograph of the Apple Application (left) and Smart Watch (right) (Turakhia et al., 2019)

One of the most used accessories in daily life is rings. These smart rings provide some of the key features that smart watches offer. These are basic features such as heart rate tracking, pedometer, remote connection with mobile phones, sleep tracking. As it is known, among the people, the ring is seen as a symbol of love rather than a jewelry. Based on this perception, the manufacturers added the feature of sending the heart rhythms of the couples to each other via radio frequencies. These rings, which are made in collaboration with Oura Health organization and Rezai, photographed in Figure 4, and attracting attention with their stylish designs, are expected to be as popular as smart watches in the future (Poongodi et al., 2021).

Figure 4. The Image of a Smart Ring (Poongodi et al., 2021)

Smart glasses, another wearable technology that is thought to be used frequently in the future, have many features such as recording videos, taking photos, making phone calls, sending messages, and searching on the internet. These glasses support the Global Positioning System (GPS), Wi-Fi and Bluetooth. In addition, some of them also include a face recognition system (Schweizer, 2014). Figure 5 shows the smart glasses produced by Google (Erbas & Demirer, 2014).

Figure 5. Google Glass (Erbas & Demirer, 2014)

Besides smart glasses, there are also glasses such as virtual reality and augmented reality. These glasses, seen in Figure 6, allow people to feel like they are in a virtual environment with their features such as high resolution, eye tracking sensors and game controllers (Ferhat, 2016). Thanks to these glasses, the doors of the virtual world are opened to the users. It is now mostly used in the game and entertainment industry.

Figure 6. Virtual Reality Glasses (Ferhat, 2016)

Bluetooth headphones, which are also wearable technology products, have a growth rate that will remove wired headphones from production and have reached a very wide audience in a very short time. These headphones, which eliminate the cable problem, provide the opportunity to access data remotely with the help of bluetooth feature. For example, it provides you with the ability to answer calls by connecting with your phone. It can also be connected to other devices such as computers and tablets. Bluetooth headphones released by Samsung in Figure 7 can be given as an example to these

headphones. These headphones are one step ahead in the industry by providing freedom of movement to the user and being more aesthetic (Yoo & Ju, 2018).

Figure 7. Released Headphones by Samsung (Yoo & Ju, 2018)

Smart clothes can be given as an example as another wearable technology product that is not used very often yet. Smart clothes, by connecting to mobile phone via bluetooth; with the help of motion sensors, accelerometers and gyroscopes, it provides ease of life for the user by following the movement during the day. Some clothes follow human health with features such as giving a postural warning, monitoring heart rhythm and helping to maintain body temperature. Other smart clothing, on the other hand, appeals to the daily life and entertainment industry and offers features that give a warning when away from the phone, prevent the phone from being lost, and allow instant status updates on social media.

Use in Sports

Smart shoes used today are generally described as computerized sports shoes. These shoes can collect statistics by tracking the sports activities of the wearer. In addition, there are smart shoe models that can automatically adjust the tightness of the shoe according to the foot of the wearer for those who are uncomfortable with the loosening of the shoelaces while doing sports.

Since smart watches can easily replace smart wristbands, smart wristbands are more commonly used during sports activities. These wristbands have features such as heart rate measurement, step counting, calorie calculation, sleep tracking, vibration alarm, reminder, phone notifications and distance measurement.

Golf gloves with motion sensors, produced for golf enthusiasts, offer the opportunity to follow the statistics of the angle and intensity of the athlete’s stroke, how many points she/he has collected, from a smartphone.

A company that produces warm trousers for athletes aimed to use less energy to warm up the athletes by providing the ideal heat for the leg muscles in cold weather. Another

company measures distance, pelvic rotation, jump, step and rhythm with the sports shorts it produces and transmits the data it collects to the smartphone via bluetooth.

Use in Healthcare

The new generation wearable devices used in the healthcare field allow the monitoring of the patient's condition and the remote notification to the doctor, thanks to the sensors and communication devices integrated into the suit. This technology provides great convenience for elderly or disabled citizens who have difficult access to the hospital, as well as for patients living in rural areas where there is no hospital.

Hearing aids are the most basic wearable technology product used in the field of health since ancient times. These devices amplify the sounds coming from the outside and send them to the ear of the hard-of-hearing patients in the form of vibration. In this way, the hearing problem of these patients is eliminated.

Sleep tracking devices used for patients with sleep problems are another product discussed in this field. This product analyzes a person's sleep quality, breathing patterns and sleep hours. In this way, the person can easily decide whether or not to go to the doctor.

Wearable electrocardiogram (ECG) monitors measure heart electro diagrams with the same precision as large hospital ECG devices. In this way, it can predict the risk of heart attack according to the heart rhythm and instantly transmit the data it receives from the patient to the doctor when necessary.

Military Use

Wearable technology appears in the military field, which is especially important in terms of security. As seen in Figure 8, there are many wearable technologies on the vests and helmets of the soldiers (Karamak, 2018).

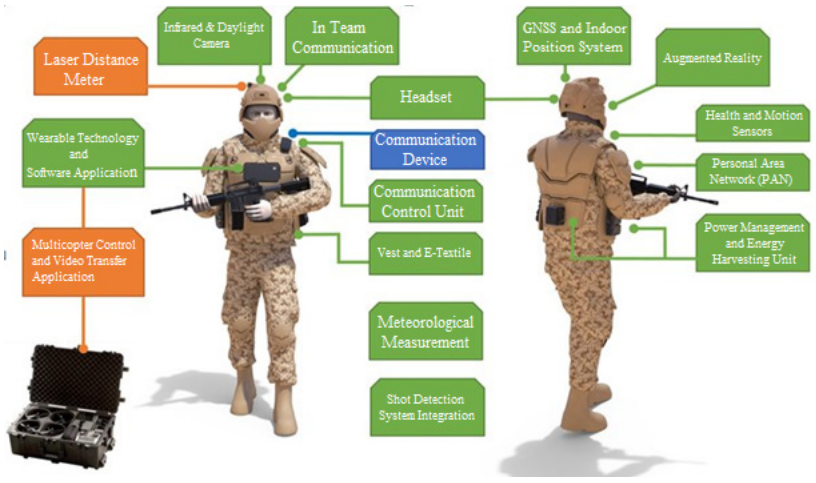

Figure 8. A Sample of Used Wearable Technology in the Military Applications (Karamak, 2018)

There is a military computer on each soldier as seen in Figure 8. Thanks to this computer, commanders and other soldiers can see each other's positions and health status. There are health and motion sensors on each team member. There are two cameras on the helmets which are infrared and daylight cameras. These cameras have the features of recording for educational purposes and monitoring the operation directly. If desired, the images obtained from the cameras can be transmitted to the higher command centers. There are also Global Navigation Satellite System (GNSS) and indoor positioning systems on the back of the helmets. Other technologies on the soldiers are laser distance meter, communication device, shot detection system integration, power management and energy harvesting units. By means of all these technologies, the soldiers can be in continuous contact with each other and with the command centers during the operation and increase their power in the battlefield.

Use for Animals

Smart collars designed for pets track the location and activity of animals and report the information they collect to our smartphones, thanks to their GPS features. This device, seen in Figure 9, is a beautiful wearable technology product against the risk of losing pet (Sagbas et al., 2016).

Figure 9. Smart Collar for Pets (Sağbaş et al., 2016)

In addition to pets, wearable technology devices are also used for cattle. An example of this is smart necklaces produced for cows. These necklaces can monitor cows' temperature, pulse, oxygen needs, birth and hunger times.

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To Cite This Chapter

Ince Keser, Y., & Babaoglu, T. (2021). Wearable technology. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 19–31). ISRES Publishing

Wireless Sensor Networks Technology

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Introduction

The process that started with the first social revolution, in which people formed the agricultural society by sedentary life, is followed by the industrial revolution. The industrial revolution emerged as three major changes (Bulut & Akcaci, 2017). With the first industrial revolution, steam, water power, and mechanization made a significant contribution to economic development. This situation has caused a series of radical changes in economic, cultural, political, and social fields all over the world, especially in Europe (Baser, 2011). With the Second Industrial Revolution, the widespread use of electricity and the increase in mass production resulted in a significant increase in productivity in production. With the beginning of the Third Technology Revolution, developments in fields such as computers, microelectronics, nuclear, genetics, and laser continued. In this period, the development of mechanical and electronic fields, along with digital technology, was followed by programmable devices and computer technologies. The rapid development of information and internet technology has made this period known as the information revolution (Bulut & Akcaci, 2017). Societies that can catch these revolutions early have turned into a structure based on the development and export of technology. In this way, modern societies have gained significant economic power (Karasekreter, 2020).

With the information technology revolution, all public institutions and private sectors entered the restructuring process, the technological transformation was experienced in every field and an information society was formed (Bulut & Akcaci, 2017). Since 2011, the stage of the information society has emerged as Industry 4.0. Industry 4.0, called the new industrial revolution, is a concept that was first introduced in 2011 at the Hannover Fair held in Germany. The concept of the “Internet of Things (IoT)” is one of the important definitions of this era. (Bulut & Akcaci, 2017). The concept of IoT was used for the first time by Kevin Ashton in the presentation made on behalf of Procter and Gamble (P&G) company in 1999. The concept of IoT was used for the first time by Kevin Ashton in the presentation made on behalf of Procter and Gamble (P&G) company in 1999. In the report published by the International Telecommunication Union (ITU) in

2005, the concept of IoT was officially announced (Bayuk & Oz, 2017). Machines have become coordinated thanks to new developments in computers, electronics, and internet technologies. IoT covers the systems that do not interact with humans and are connected to the internet through data sharing over the internet in order to meet the needs of people.

Today, thanks to the integration of devices with the internet, it perceives the needs of the users and communicates with smart devices over their systems, and meets the needs of the users. With the Internet of Things, objects with different ID addresses use the Internet infrastructure to process the data over the virtual platform. It consists of 5 basic layers: detection layer, network layer, middle layer, application layer, and business layer. IoT detection layer Radio Frequency Identification (RFID), ZigBee, QR code reader, etc. consists of different sensing devices. This layer generally performs the processes of obtaining and defining certain information through all kinds of sensors. The collected information includes temperature, humidity, location, vibration, and dust, etc. it could be. The information obtained by different sensors is transferred to the upper layer (Arslan & Kirbas, 2016).

The developments in robot technologies, big data, artificial intelligence, IoT, and sensors, which are the new terms of the industry, have led to the emergence of intelligent systems. The use of smart systems is increasing day by day with the technological developments, current applications, and opportunities offered by IoT. Smart home automation systems, smart factories, environment, and agriculture/livestock automation systems, security analysis systems, etc. There are many examples of IoT. Artificial intelligence, whose popularity is increasing with Industry 4.0, is increasing day by day due to technological developments. By combining the main elements of production such as monitoring, coordination, and control with sensing, computing, and communication technologies, the Cyber-Physical System has emerged as a whole system managed by wired or wireless combined technology, and Industry 4.0 is accepted as the most important technology (Uludag & Ucar, 2018).

Wireless Sensor Networks (WSN), one of the technologies that Industry 4.0 has brought, by placing sensors with sensing ability in different areas, in these areas temperature, humidity, light, sound, pressure, pollution, noise level, vibration, object movements, etc. It refers to wireless networks that contain independent tools to detect situations and monitor environmental conditions. WSN's have limited energy resources. Despite these disadvantages, they have advantages such as reliability, accuracy, flexibility, cost efficiency, and ease of installation. WSN has many application areas such as military systems, remote control systems, and medicine. For example, WSN's can be effective in disaster areas where they are placed in disaster situations. Accurate and timely location detection in WSN's is of vital importance in rescue operations (Bayuk & Oz, 2017).

One of the advantages of WSN's is that they operate unattended in harsh environments where monitoring by humans is risky, inefficient, and sometimes impossible. For this reason, it is expected that the sensors will be randomly placed by a relatively uncontrolled drop by a vehicle, eg helicopter, and temporarily form a collective network. Considering the short life of battery-operated sensors and the possibility of having damaged nodes during deployment, it is expected that there will be a large number of sensors consisting of hundreds or even thousands of sensor nodes in WSN's. Designing and operating such a large network requires architecture and management strategies. In these networks, since the energy of the sensors is limited and the batteries cannot be charged, it becomes important to design algorithms based on energy and to extend the lifetime of the sensors (Abbasi & Younis, 2007).

Wireless Sensor Networks

With the development of sensor technology, multifunctional sensor elements can be designed in small sizes, with low power consumption. These elements are; sensing, data processing, and communication among themselves. WSN's are composed of sensor nodes working with limited resources. Each sensor node has the ability to measure quantities such as temperature, humidity, pressure around it, perform simple calculations, and communicate with other nodes or base stations around it. As an example, the architecture of WSN's is shown in Figure 1.

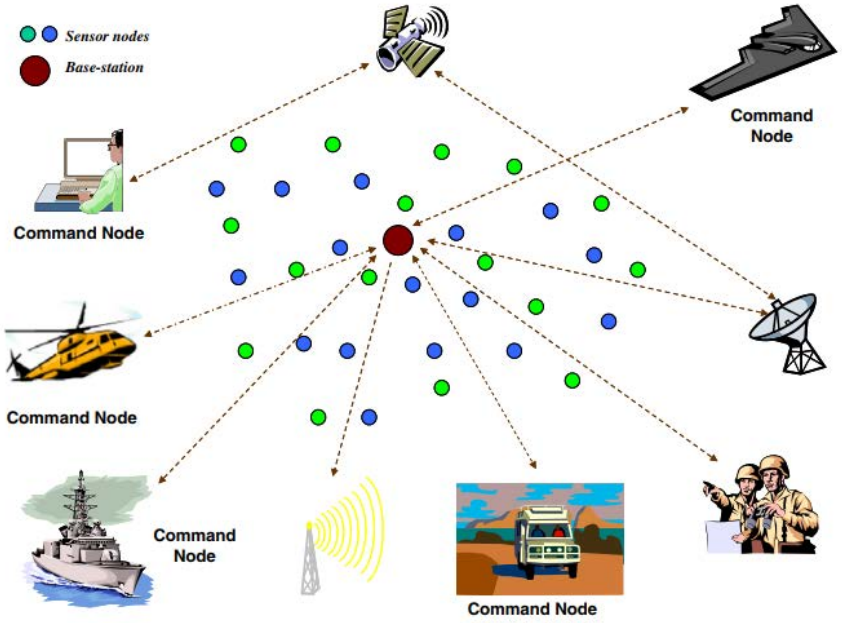

Figure 1. Wireless Sensor Network Example (Abbasi & Younis, 2007)

The overall architecture of WSN's can be explained at two main levels. The first is the sensor nodes equipped with sensing capabilities, and the second is the collection of sensing devices acting together to create the WSN. It is extremely important to understand the structure of the sensor node in WSN's (Alshahrani, 2018).

The Architecture of Detection Device: Sensing Node

WSN's, as mentioned earlier, consist of several independent small sensing units equipped with the necessary resources to measure current conditions. The basic sensing unit is called a node in WSN's. The task of the nodes, which are the basic building blocks of WSN's in general, are responsible for perceiving and measuring the characteristics of the current conditions, recording the measured values, and transmitting the recorded information to the base station. A node basically consists of a power supply, a processing unit or controller, sockets for connecting sensors, an analog-to-digital converter (ADC), onboard memory to store data, and a transceiver to communicate with other nodes. Figure 2 shows the basic block diagram of the sensor node (Alshahrani, 2018).

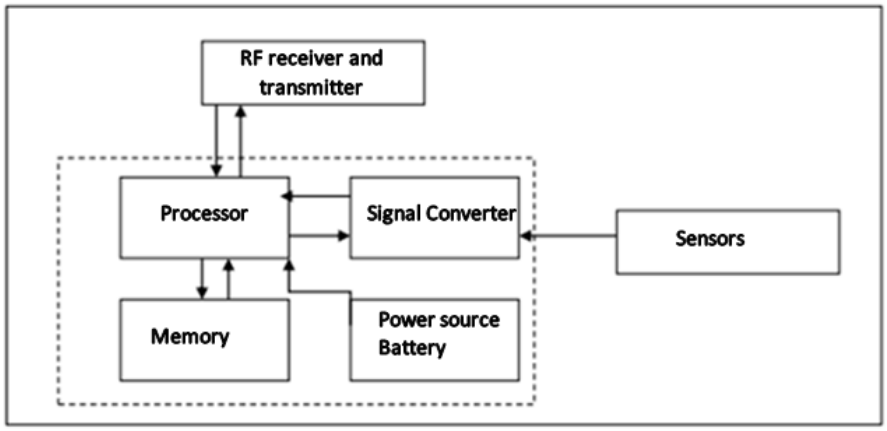

Figure 2. Block Diagram of the Sensor Node (Amin, 2016)

Controller/Processing Unit

It is the main processing unit of the node. It is responsible for the timely execution of all operations and transactions in the node. It performs various tasks such as data processing, checking the functionality of all components, reading/writing data to memory, and collecting data from the ADC. Since energy consumption control is important in node designs, the selection of the microprocessor/microcontroller to be used should be done meticulously. MSP 430 series and Atmel Atmega can be counted among frequently used processors/controllers (Karasekreter, 2020).

Receiver - Transmitter

Wireless connection of each node is important since the nodes are located in remote locations in SSAs. It is the unit that enables the wireless transmission of the detected data to another node or the signals from another node to be analyzed and transmitted to the control unit. Infra-red, wireless communication with radio frequencies is possible. Infrared technology operates in a rigid topology where two communication devices must be in the line of sight of each other. Due to this strict limitation, infrared communication is not used in WSN's. Radio frequency communication is preferred instead. Radio

frequency technologies such as ZigBee, Bluetooth, and Wi technology are used in CSA's. Figure 3 shows the ZigBee module that performs the data transfer process.

Figure 3. ZigBee Module

Sensors

Advances in microelectromechanical system technology have made it possible to develop various sensors to measure various physical properties of the environment in which they are placed. Sensors, mechanical, thermal, chemical, etc. in the external environment. It is the unit that detects the changes and sends them to the processing unit. Thanks to the ADC modules, the detected analog signal is converted into digital and transmitted to the processing unit. The temperature sensor produced to measure the ambient temperature is shown in Figure 4.

Figure 4. LM35 Temperature Sensor

Energy Source

In WSN's, nodes are randomly distributed to areas inaccessible to humans. Since it is not possible to operate the nodes continuously connected to an energy source, batteries are used. Batteries are the basic requirement for keeping a node operational. Since the nodes are placed randomly in a large number of geographically difficult regions, changing them frequently and in some cases impossible. That's why nodes need to have long-lasting batteries to get longer network life. Conserving the energy of the node is very important in WSN's. Strategies are being developed to reduce a node's duty cycle and prevent unnecessary data generation. Figure 5 shows the energy sources used in WSN's.

Figure 5. Energy Sources Used in Sensor Nodes

Wireless Sensor Networks Structure

WSN's may be released or deployed in an area to provide information on current conditions. The sensors form a network to communicate with each other and also to send information with the base station or base station in the network. The base station transmits the information to other systems where it is used for analysis. WSN's do not have a predetermined infrastructure. Therefore, the network needs to be set up specially. In WSN's, nodes may have limited mobility but are usually in a fixed position. Unlike wired networks, which have special hardware that directs network traffic, each node acts as a router in WSN's. In WSN's, each node communicates directly with other nodes within its transmission range and uses other nodes to transmit messages to nodes outside its transmission range.

In WSN, energy efficiency is one of the most important criteria that should be emphasized. There are two main factors affecting energy efficiency. The first of these is the determination of media access protocols between nodes. The other is the way the data is transmitted to the base station. Figure 6 shows the architecture of WSN's.

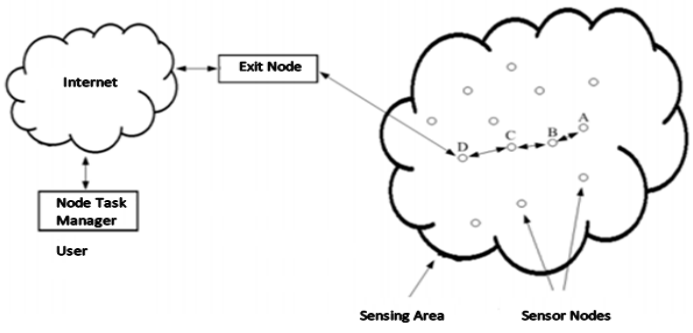

Figure 6. WSN's Architecture

WSN Structures

Network structures created in WSN applications can be examined in two parts as regular distributed networks and irregular distributed networks. This difference is

related to the type of application and the geographical conditions of the area to be applied (Karasekreter, 2020). WSN's are used in home automation for various purposes such as security, control, and speech. Temperature, light, and humidity, etc. in home automation. Networks established to measure values, agricultural practices, hospitals, networks established from sensors placed regularly in factories can be shown in a regular distributed network. An example of a smart home system consisting of sensors placed to detect different events is shown in Figure 7.

Figure 7. Smart Home System in Which Various Sensors are Placed

Sensor nodes form WSN by irregularly scattering by means of a vehicle in hard-to-reach areas for sensing and data collection. For military purposes, random distribution of sensor nodes is suitable for monitoring open-air mobility and forest fires. Such applications can be defined as WSN's with an irregularly distributed structure. An example of WSN in distributed structure is given in Figure 8.

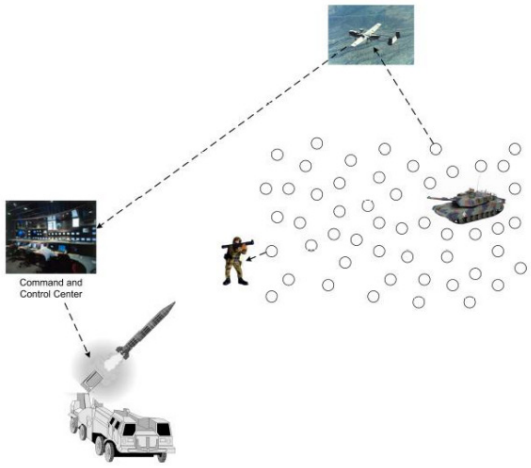

Figure 8. Distributed WSN's

WSN's can consist of thousands of sensor nodes over a wide geographical area or indoor area. Nodes are unevenly distributed across the region. The "D" variable shown in Figure

9 is the distance between any two nodes. Suppose R is theoretically the circular wireless range of a node. The maximum distance condition D<2R between any two nodes in the network should be sought.

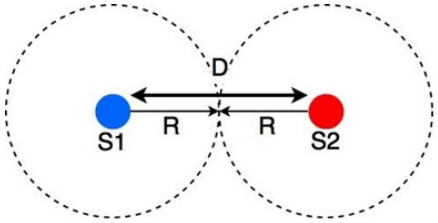

Figure 9. Distance Between any Two Nodes

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To Cite This Chapter

Unlu, T., Basciftci, F., & Karasekreter, N. (2021). Wireless sensor networks technology. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 32–41). ISRES Publishing

Agricultural Technologies

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Introduction

The concept of “agriculture”, known in its most general sense, means the production of vegetable and animal products. It is a branch of science that deals not only with their production, but also with improving their quality and efficiency, preserving products under appropriate conditions, processing and evaluating them efficiently, and marketing them. In other words, the care, cultivation, nutrition, protection of all plant and animal products that have nutritional and economic value for the benefit of people and the mechanization necessary for them are all activities. Agriculture even includes fishing activities carried out in private areas or in still waters.

We don’t stop and think about the stages at which any food we eat every day comes from the field or from the farm to our table. In fact, these foods come across as a result of a worldwide network of many people involved in the food business, such as farmers, merchants, food manufacturers and retailers. Humanity has faced many problems throughout its history. In addition to problems such as natural disasters, drought, global warming, the global food system is also one of the problems that will greatly affect humanity. Due to the rapid growth of the world’s population, the world population is expected to be 10 billion, up from 7.5 billion in 2050. Therefore, it is important that the worldwide food system in the world provides reliable and nutritious foods against this food demand. For this reason, it is estimated that global food production should increase by 70 percent to prevent a major famine that may occur in the future (Zhang & Kovacs, 2012).

Due to the fact that the need for food is increasing day by day, it is necessary for producers to learn how to deal with problems such as climate change, floods, droughts and resource depletion. It is necessary to overcome these great difficulties in order to meet the upcoming food demand (Lindblom et al., 2017).

Today, technologies are being developed to overcome these challenges and agriculture precision farming precision agriculture be sustainable for centuries to technological innovations to change the understanding of people the main aim of Agriculture is to offer their service. In this way, increase its productivity and hence profitability of precision agriculture, sustainable agriculture, improving the quality of the product with

the environment and the reduction of harmful effects to nature, agriculture dealing with individuals who are enhancing their quality of life, natural and safe the convenience of access to food, rural life and economy, such as the development of new agricultural innovations and related benefit that will provide many approaches have been developed (Liaghat & Balasundram, 2010). When we look at the rapid development of technology, we see that investments for research and technology development have increased rapidly in this regard significantly in the last decade (Schellberg et al., 2008).

Precision agricultural applications have continued to develop in a different way with the advent of GPS (GPS: Global Positioning System) and GNSS (GNSS: Global Navigation Satellite System). Researchers, farmers in a field by finding the precise location many measurable variable (e.g., crop yield, land features/topography, organic matter content, moisture levels, nitrogen levels, Ph, EC, Mg, K, and others) allows the creation of maps of the spatial variability (McBratney & Pringle, 1999). In addition to these measured variables, for example, GPS data can be collected thanks to a GPS-equipped harvester. In the same way, a series of real-time data can be obtained with sensors and multispectral images that can measure the water state of the plant and the water stress at the chlorophyll level. However, recent technological developments have enabled the use of real-time sensors directly in the ground with wireless data technology that eliminates the human factor (Reyns et al., 2002; Sophocleous, 2016).

The technologies used in the field of agriculture are increasing day by day and are aimed at providing the maximum benefit. Agriculture is currently undergoing a process of transition from low-tech mechanization to high-tech mechanization. Briefly, we can list the points of origin of these developments and the solution suggestions as follows (Technology Development Foundation of Turkey, 2020);

- Using sensors, cameras, IoT (IoT: Internet of Things), satellite and drone technologies for remote monitoring of garden and field products, it is able to detect risks such as plant health, irrigation needs, disease and pest detection.
- Blockchain technology stands out in providing technological integration at all stages of the supply chain to ensure food safety and traceability.
- Biotechnological developments should be used for quality and efficient products that will adapt to changing environmental conditions with climate change.
- Vertical farming should be encouraged in order to minimize space and input costs.
- Artificial intelligence, machine learning, autonomous and robotic systems should be brought to the forefront for low-cost and data-based agricultural production with optimal parameters.

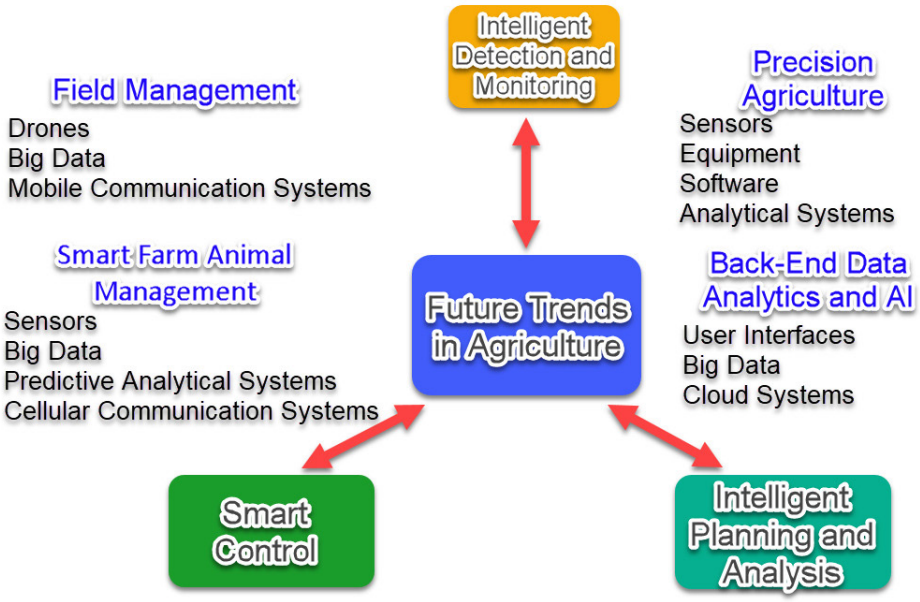

Figure 1. Future Trends in Agriculture

The emergence of this kind of technology in agriculture has been around for more than half a century, though today we have seen significant progress in this area, to facilitate sensor technology, computer vision, cost-effective computing power and recent development in the field of artificial intelligence, has made progress.

Looking at the world as a whole, countries that are advanced in technology for sustainable and efficient agricultural production are creating intelligent agriculture and agriculture 4.0 research centers. Venture capital and angel investors who want to invest in companies that want to enable farm applications of the developed technologies and develop technology in these areas have an accelerating role in the development of agricultural technologies.

The most basic goal of agricultural technologies is to improve crop production by understanding the soil. At the same time, it aims to reduce the impact of environmental pollution by enabling farmers to use fewer pesticides (pesticides) in their products. Monitoring soil and weather conditions is significantly effective for reducing water waste. Digital agriculture contributes to the economic development of farmers by obtaining maximum production from their land. The use of technology by farmers with digital agriculture allows them to work together as well as collect and share data.

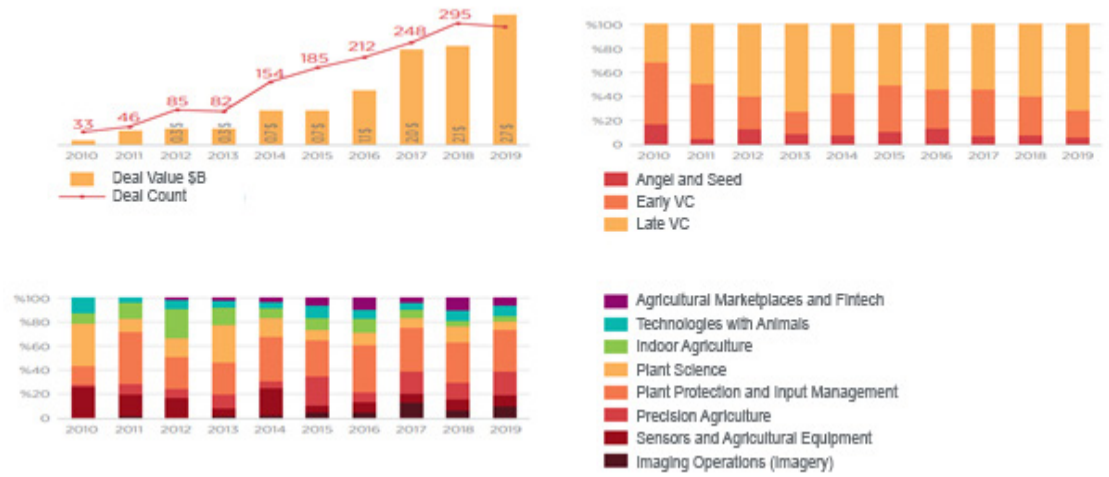

Figure 2. Global Investment in Agricultural Technologies (Source: PitchBook)

The Importance of Agricultural Technologies

Thanks to the rapid development and change of technology, sensors, autonomous devices, machines and information technologies, today's modern farms and agricultural operations work more efficiently than a decade ago. Robots, various sensors, ground imaging systems, GPS and related agriculture-facilitating systems are often used routinely in precision agriculture, which have replaced classical agriculture.

With the use of technological facilities, applications such as water, fertilizers and pesticides are applied not only to the entire area of the land, but also to the areas where they are needed. Thanks to such agricultural improvements, the agricultural operations performed by enterprises become profitable, efficient, safe and environmentally friendly. In parallel with technological developments, new methods applied in agriculture aim to provide maximum profit with minimum inputs. For example, the areas needed for fertilizer application are targeted, and only the plant that needs fertilizer can be detected. In this way, it can be applied to the required points to the required extent. If we look at the advantages in this way, we will:

- Increasing product efficiency
- Reducing the use of water, fertilizers and pesticides and reducing costs
- An approach that protects nature
- Fewer chemical mixtures to nature
- Protection of the health of working personnel

In addition, sensor technologies provide reliable monitoring and management of natural resources such as water.

It provides traceability and control in processes such as processing, distribution and storage of plant and animal production. This gives us the advantages that we will list below:

- Increasing productivity and, accordingly, reducing prices
- The cultivation process is reliable and healthy foods are produced
- Reduction of the negative impact on the environment

Vertical Farming

Vertical farming can be defined as the practice of growing crops stacked on top of each other in a closed and controlled environment. Vertically mounted racks, using layers, significantly reduce the amount of land required for growing crops compared to traditional farming methods (Saygin, 2017).

Vertical farming can be of different shapes and sizes - from simple two-level or wall-mounted systems to large areas with several floors. To provide plants with nutrients, one of three hydroponic systems is used (hydroponic, aeroponic or aquaponic).

Hydroponics (hydroponics): Hydroponics, the most common cultivation system used in vertical agriculture, is to grow plants growing in nutrient solutions in hydroponic water. The plant roots are located in a water whose correct mineral and necessary compositions are constantly in circulation (Velazquez et al., 2020).

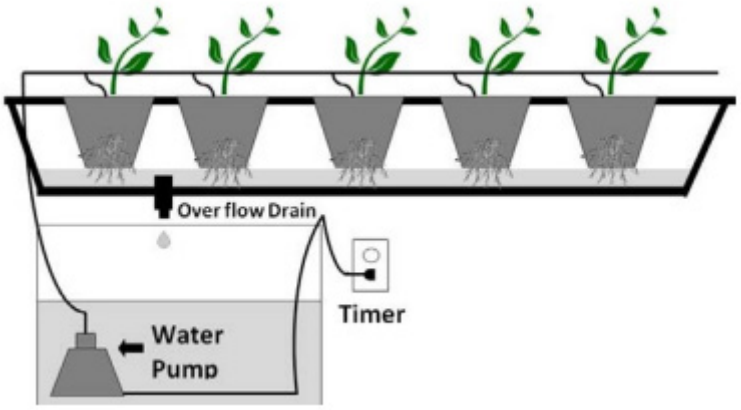

Figure 3. Hydroponic Plant Cultivation (Source:NCAT)

Aeroponics: Aeroponics is actually a subset of the hydroponic system. in the 1990s, he developed the concept of “aeroponics”, which was called “farming in an air/fog environment with a small amount of water without using soil” by NASA to farm in space. The aeroponic system is the most efficient agricultural system that can be used on vertical farms and uses close to 90% less water than the hydroponic systems known as the most efficient. It has been shown that plants grown in these aeroponic systems receive more minerals and vitamins, making plants healthier and potentially more nutritious (Eldridge et al., 2020).

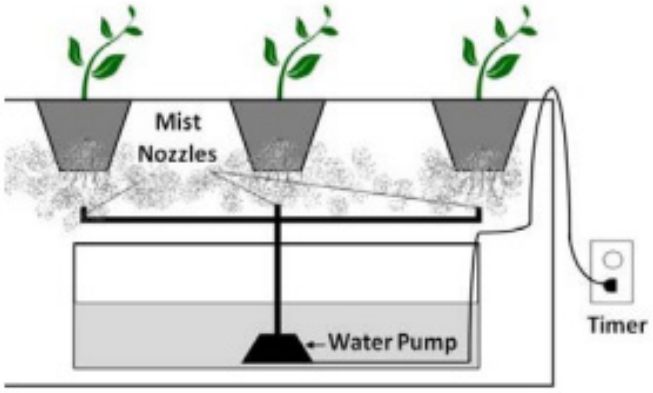

Figure 4. Aeroponic System (Source:NCAT)

Aquaponics: An aquaponic system takes the hydroponic system one step further, combining plants and fish in the same ecosystem. The fish are raised in closed systems (aquarium-style but in large waters) and produce nutrient-rich waste that is used as a feed source for vertical agricultural crops. On the other hand, plants reach the necessary vitamins and minerals by using these rich wastes (Nesterova, 2019).

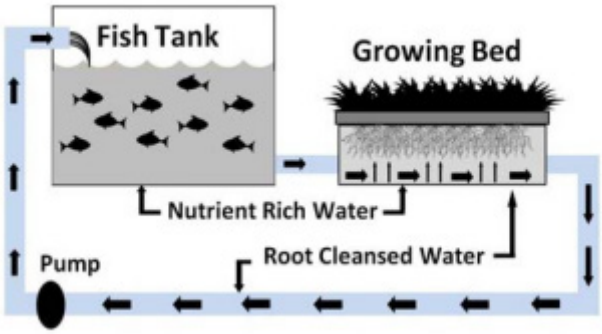

Figure 5. Aquaponic System (Source:NCAT)

These vertical farming variations that excite the world will increase the energy efficiency and profit margins of these farms in the near future with new technologies. Innovative vertical agricultural areas currently under construction or already under construction are closely monitored by urban planners and the sustainable agriculture community. It is considered to be available to people at certain points of cities (Birkby, 2016).

Figure 6. Example of Vertical Farming

Farm Automations

Farm automation includes intelligent systems with automatic systems that are associated with ”smart agriculture”, aimed at bringing the human factor to the least likes, which allows farms to be more efficient and transform the production of life. Today, companies working in the field of agriculture are working to develop many technologies, such as drones, autonomous tractors, robot harvesters, automatic irrigation and seeding robots. Despite the fact that the developed technologies are still new, it seems that agricultural companies that carry out their business with the help of incoming methods are being included in farm automation processes day by day.

IoT (internet of things) is a network-device technology that allows devices to communicate with each other using common communication protocols. Its most important feature is that it is the systems created by devices that provide data exchange over wireless networks without human intervention. In smart agricultural applications, the fact that it allows wireless data exchange and that different devices communicate with each other has allowed the development of technologies in this direction. For example, in an automatic irrigation system, thanks to modern technology, it makes it possible to find out the humidity and temperature values of the soil from different parts of the agricultural land using affordable and affordable wireless sensor network technology. The irrigation system can automatically turn on and off the pump system to ensure that the plant receives the optimal amount of water it needs (Abdurrahman et al., 2015; Maureira et al., 2011).

To say a few automation systems that we may encounter in agricultural fields;

- Automatic Harvesting Automation
- Autonomous Tractors
- Automatic Seed Sorting Systems
- Flying Drones

Figure 7. An Autonomous Spraying Machine (Source:Web)

Today's consumer habits indicate an increasing interest in organic and sustainable agricultural products. On the other hand, manufacturers incorporate developing automation systems into their production processes to ensure that the products demanded by consumers are faster, fresher and the products are sustainable. The positive effect of the use of automation on the manufacturer's side is that increasing productivity and reducing costs increase earnings. At the same time, automating the process helps to reduce costs by minimizing the labor force needed by doing the work that manpower routinely does with the help of autonomous systems (Ahmed et al., 2018).

Livestock Technology

Animal production, or animal husbandry as it is commonly called, is the branch of agriculture that covers the care, nutrition, production and breeding of domestic animals useful to humans with their products and powers. Livestock farming includes poultry farms, dairy farms, cattle farms or other agricultural enterprises related to livestock in general. Accurate financial records should be kept in animal husbandry, workers should be supervised, and animals should be properly cared for and fed. As technology has affected many areas, it has also been effective in changing the traditional understanding of livestock and livestock management issues. The developments over the last ten years have provided great improvements for data-oriented and quick decision-making systems on many livestock-related issues, such as livestock tracking and management (Annosi et al., 2019).

Livestock technology provides producers with various systems for increasing animal and animal productivity, facilitating the welfare and management of animals. Today, the concept of "Connected cow" is used for cows with sensors aimed at increasing productivity by monitoring the health of herds on large farms. Data-oriented tracking of each cattle in the herd is provided with the help of sensors that can be worn on the cattle, or worn on their bodies, as well as tracking data related to daily activity and health of the cattle. All the data obtained can be converted into meaningful and actionable information for manufacturers, from which they can make quick and healthy decisions at the same time (Zin et al., 2018).

Figure 8. Thanks to the Intelligent Sensor Installed on the Cows, the Condition of the Cows can be Monitored (Source:Tarnet)

Sensor and data technologies have great benefits for the current livestock industry. It can increase the productivity and well-being of livestock by detecting sick animals and taking measures against it early. The data collected by computer vision can be translated into action by making sense of it and allows us to have all kinds of unbiased data in the future. Data-driven decision-making systems enable better, more efficient and timely decision-making that will increase the productivity of animal herds.

In addition to the use of facial recognition in various systems, another area of use is the surveillance of livestock with the help of drones. This technology allows farmers to register their cattle's identities and information in a database. These counted features can then be easily accessed by facial recognition with the help of drones to recognize each animal, detect where it is located in the pasture and track vital health information such as weight, size, facial features and physical activity. This allows not only to identify the disease quickly, but also to reduce the work of farmers, in addition to the fact that the health of cattle can be constantly monitored as an example. It is possible to find out the location of any cattle outside in the pasture and manually monitor its health, which is done at that moment through the heart rate and GPS locators (Zin et al., 2018).

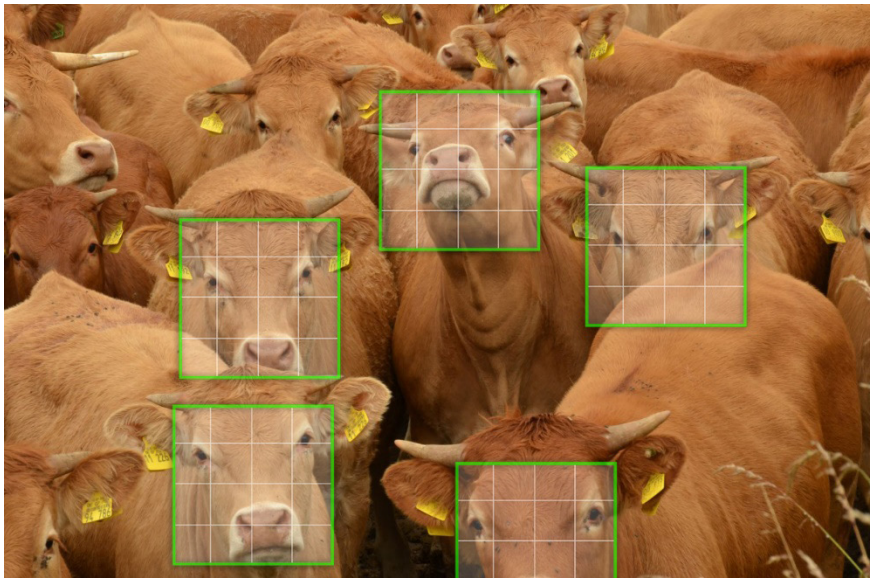

Figure 9. A System that can Receive Data from Cattle with the Help of Facial Recognition and Sensors (Source:Web)

Precision Agriculture

Agriculture is becoming an indispensable part of every farmer with a continuous process of change and development with the development of technology. New precision agricultural companies are developing technologies that allow maximizing yield by tracking all kinds of variables such as soil moisture level, pest stress of the plant, soil conditions and microclimates. Precision october provides more accurate techniques for october and growing crops, allowing farmers to increase productivity and manage costs (Kent Shannon et al., 2018).

The word “Precision” used in precision agriculture is used because it aims to make the right intervention possible at the right time, in the right place, at the right time by responding with superior levels of sensitivity to the special conditions and situations of crops and land areas thanks to the state-of-the-art tools used.

Nowadays, the term Agriculture 4.0, which is the evolution of the concept of precision agriculture, refers to: all tools and strategies that use the latest technologies, starting with the use of data to improve and optimize production.

Figure 10. Precision Agricultural System (Source: Agricultural Credit)

Soil Sampling with the Help of GPS**:** It is important to test the soil of an area, to know the pH level along with the available minerals and vitamins contained in the soil, to make informed and profitable decisions. At the core of this technology is soil sampling, which allows growers to take into account differences in productivity in an area and create a plan that takes these differences into account. As a result, it creates an infrastructure for variable rate applications to optimize seeding and fertilizer in the light of these data (Huuskonen & Oksanen, 2018).

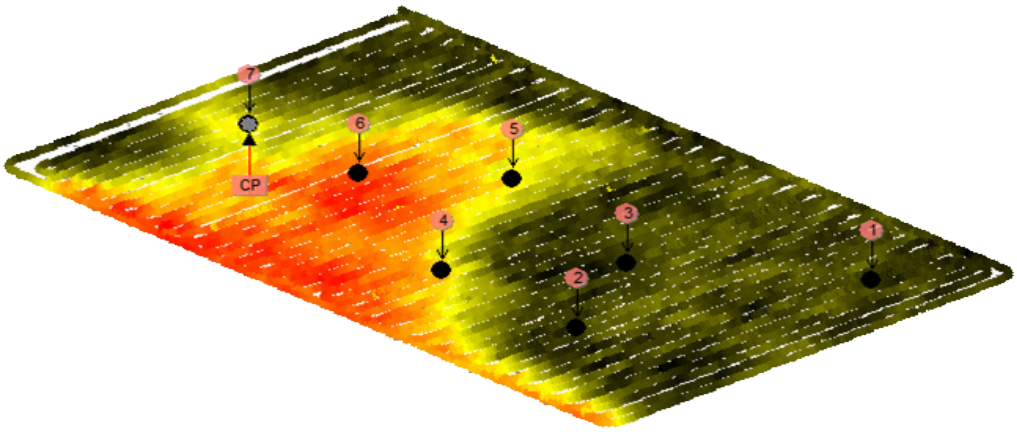

Figure 11. A Representative Picture of the Different Structure of the Land (Source: Web)

Computer-based Applications: Computer applications can be used to create precise farm plans, field maps, crop exploration and yield maps. This in turn allows for more

precise application of inputs such as pesticides, herbicides and fertilizers, so that it can help reduce expenses, produce higher yields and create more environmentally friendly work. The difficulty of these software systems is that they sometimes offer a narrow value, which does not allow using data to make larger farm decisions, especially with the support of a specialist. But many software applications are able to draw accurate results for farmers from large datasets using techniques such as deep learning, artificial intelligence, and machine learning (Razmjooy & Estrela, 2019).

Figure 12. Computer-Based Precision Agriculture Applications (Source: Web)

Remote Sensing Technology: It is a technology used in agriculture since the early 1970s. Remote sensing technology is a unique tool for monitoring, managing and using water and other resources depending on the current state of the land. This technology, which allows you to predict for what reason the crop will be stressed, up to the amount of water and moisture in the soil, helps determine the cause of many problems. This data can come from a variety of sources, including drones and satellites, making it easier for farmers to make decisions.

In addition to protecting the environment, critical issues such as sustainability of agriculture, profitability and productivity constitute the primary purpose of precision agriculture. The use of remote sensing technology ensures that the chemical drug, fertilizer and seed that will be used optimally at the best time will give results that will guide decisions both at that time and for years to come as a result of analyzing the large-scale data collected.

Although the principles of precision agriculture have been around for many years, they have become more widespread in the last decade with the contribution of technological advances and other technologies. The adoption of mobile devices, high-speed internet access, low cost and reliable satellite - positioning and images - optimized for precision agriculture and farm equipment by the manufacturer, are some of the important technologies that characterize the trend of precision agriculture (Pallavi et al., 2017).

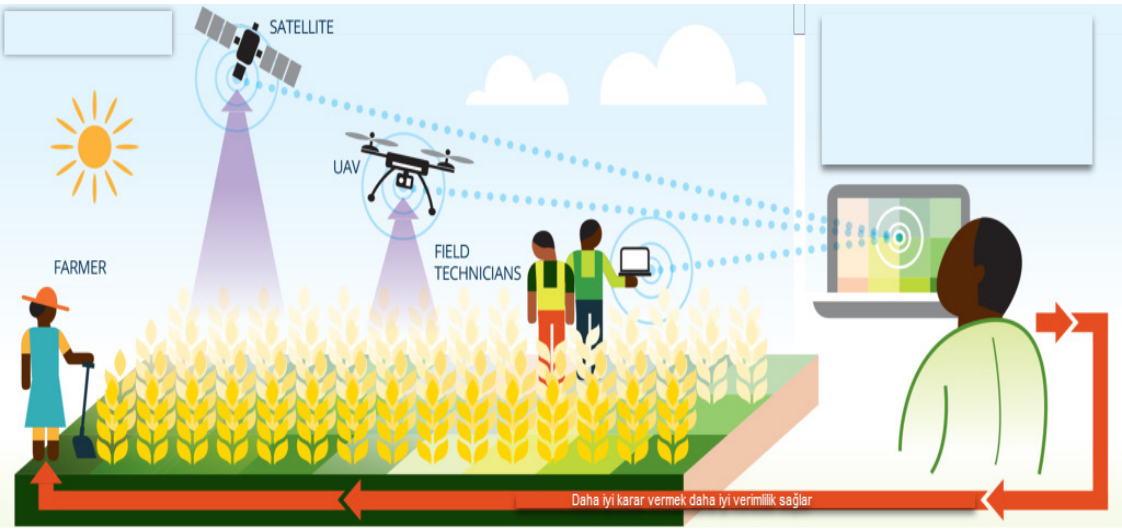

Figure 13. Use of Remote Sensing Technology (Popović et al., 2017)

Blockchain

A blockchain is a shared, immutable large registry for recording transactions, tracking assets, and building trust. For this reason, the blockchain infrastructure can be used in critical situations such as food fraud, food recall processes for security reasons, food supply chain disruptions, and traceability of food during the supply process. Sundays Decoy's unique decentralized structure ensures that these products create a reliable market in the entire process between the production and consumption stages, as well as the fact that high-quality products are real and verified (Bermeo-Almeida et al., 2018).

Food traceability is at the center of food safety discussions. Especially new developments in blockchain applications come across with different applications regarding food safety. The food industry remains extremely vulnerable in the processes of production, preservation, transportation and supply of perishable foods to the consumer against making mistakes that will affect human health. Therefore, when foodborne diseases threaten public health, there is no tolerance for uncertainty in the process of food, from farm to table, to find the source of the problem as the first step in the cause-and-effect analysis.

As a result, it is critically important to monitor this process until the food arrives from the farm to the table. Given the current communication used in the food ecosystem, the relevant people of the process cannot save the time-consuming and complex process of traceability on paper, which they use as a classic technique. In order to create an accountable and traceable system at every stage of the food chain, each recorded data point and the sharing of these points are required by the structure of the blockchain. Step by step with the help of well-known tags, each data point is saved instantly without modification. Thanks to the recorded data points, the journey of a food leaving the farm

until it reaches the consumer is made traceable in real time and without error.

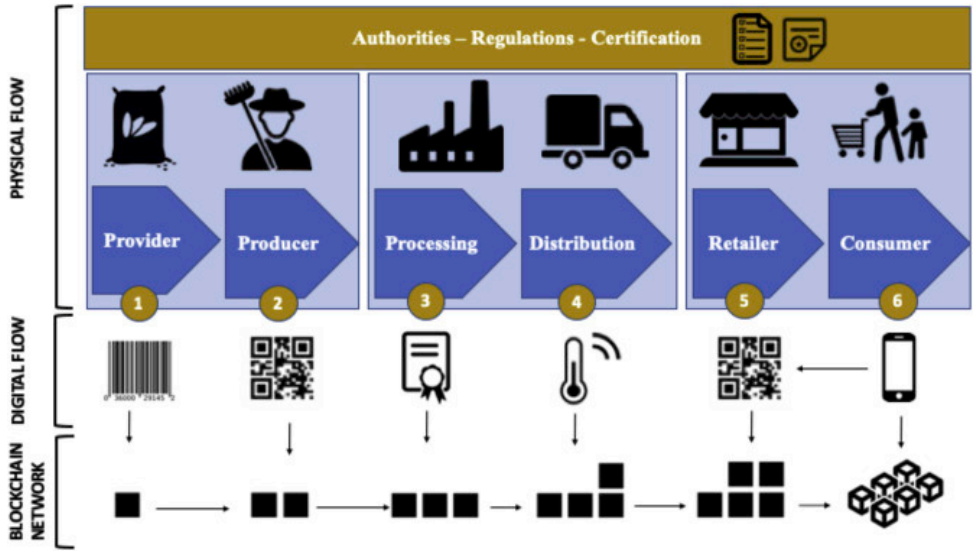

Figure 14. Application of Blockchain in Agriculture (Source: Web)

Artificial Intelligence

The rise of digital agriculture and its related technologies has opened up a lot of new data opportunities. It is possible to collect information 24/7 in all desired areas with remote sensors, satellites and drones. These data include plant health, soil condition, temperature, humidity, etc. it contains information. The analysis of the results of the collected data is much more than the human mind can make sense of.

Thanks to high-tech sensors that contain more data than the human eye can see, this data makes it easier to better understand the situation about the land or a farm. Thanks to technologies such as remote sensing, many situations can be detected until the lack of minerals and water in the soil is reached (Eli-Chukwu, 2019).

This collected data, thanks to software containing artificial intelligence algorithms, allows any environment to interpret its values as statistical data that can be understood and useful to farmers for making decisions. These developed algorithms process the data according to the received data, adapt it and learn it for later data. Making the right decision is the result of a multifaceted process. For this, a lot of input and statistical data will be processed thanks to a number of algorithms, which will be effective in making the right decision for the farmer. It is here that artificial intelligence allows farmers to make better decisions and achieve the goal of a better harvest through a series of data retrieval and processing processes (Ku, 2021).

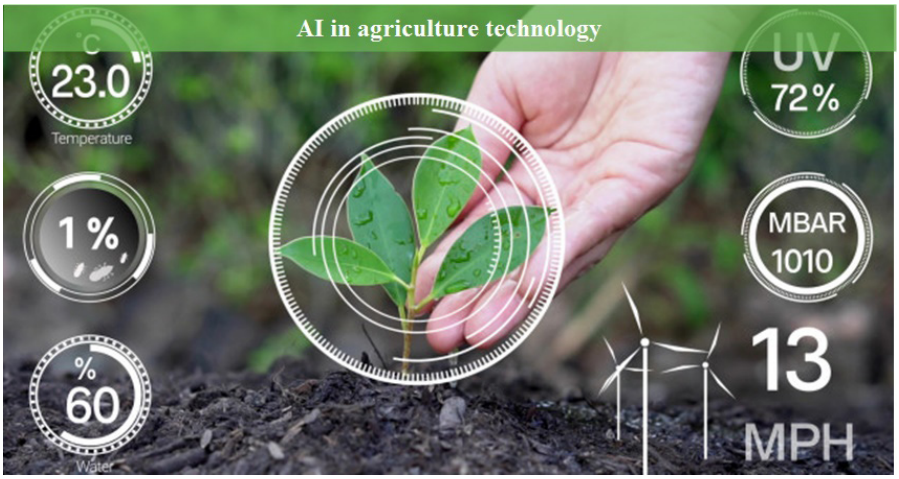

Figure 15. The use of Artificial Intelligence in the Agricultural Field (Source: Web)

Harvest Quality Detection

Image processing based systems developed for the detection of harvest quality are a new technology that simplifies the harvesting process of fruits and vegetables by eliminating the need for manual inspection (Tian et al., 2020).

At the heart of the system are a wide range of various and technological image acquisition tools for determining the quality and quantity of products. It ensures that high volumes of products harvested at once are graded before being placed in storage. Using a camera to rate products is superior to the selectivity of the human eye. Thanks to the developed software, growers can be informed about and take precautions against diseases, defects and lack of yield early in the period from the beginning to the end of the harvesting process. In this way, it helps farmers to produce the same type of products with high quality with the measures and improvements taken, which ensures that their income increases. Looking at the literature, although this technology is currently only available for grading and sorting apples, it is an example for its use in other agricultural products.

Figure 16. Harvest Detection System [(*Harvest Quality Vision*, 2021)]

Spectral Cameras

Remote sensing by unmanned aerial vehicles is a technology that disrupts memorization in precision agriculture. Spectral cameras, on the other hand, provide spatial and temporal resolution, as well as provide detailed vegetation height data and versatile observations. They are spectral cameras that provide a picture of the wavelength of light that the human eye cannot see. These images are processed and interpreted in special image processing programs. With the combination of both technologies, it can be used in drought stress, weed and pathogen detection, soil mineral status and growth viability assessment and yield estimation (Daponte et al., 2019).

Figure 17. Multispectral Camera Image (Source: Web)

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To Cite This Chapter

Kursun, R. & Buber, M. (2021). Agricultural technologies. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 42–59). ISRES Publishing

Blockchain Technology, Challenges and Current Developments

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Introduction

Knowledge and information is known as the most valuable resource today. Obtained data is transformed into information and information is transformed into knowledge. Thanks to the developing computer technologies, data can be collected in many areas. It is a necessity that the collected data can be easily and securely stored and managed effectively. Due to these needs, database management systems and approaches are developing rapidly (Onder, 2005). In this context, the topics of performance, success, security and query/audit in database systems come to the fore. Currently used database management systems have many advantages and disadvantages. Preventing the access of malicious third parties to data becomes the priority of everyone who stores and manages data, especially public institutions and private sector companies. Malicious third parties are also changing their attack methods day by day with the developing technology and making them more dangerous. All these developments turn today's known safe systems into tomorrow's weakest systems (Vural and Sagiroğlu, 2010).

At this point, the rapidly developing and spreading blockchain technology comes to the fore. This technology is defined as a decentralized distributed database. It is known to be a more consistent and secure database because it is a distributed database. Also finance, education, tourism etc. It is widely used in many different fields such as (Nakamoto, 2008). The innovations and advantages that come with blockchain technology are also important for public institutions and private sector seeking secure databases. Recently, the increasing popularity of blockchain technology and the new approach it has developed have led to an increase in the number of users of this system (Kakavand et al., 2017). Users do not need a third agent when transferring products or services, thanks to the decentralized distributed data structures feature of the blockchain. Thus, a more transparent, reliable and accountable opportunity is provided. As a result of the development of the internet and making communication effective, more and more interactive societies have emerged. As a result, new technologies such as smart phones, smart contracts and the internet of things have been widely used (Tapscott & Tapscott, 2016).

Definition and Features of the Blockchain

Blockchain has different definitions in the literature. According to Nakamoto, a blockchain is a distributed data structure that records every step/transaction information performed by users on the network and shares this information (Nakamoto, 2008). Zheng et al. have been defined the blockchain as a ledger that is stored in blocks as the nodes in the network approve the transactions and grows as new blocks are added (Zheng et al., 2017). According to Beck, the blockchain is a database that allows the transactions to be made consistently and securely by the nodes in the network (Beck, 2018). On the other hand, Glaser defined the blockchain as a ledger shared by all stakeholders, where the records of valuable assets (house, car, contract, etc.) are recorded publicly (without using real identity, if desired) with pseudonyms without the need for a central authority (Glaser, 2017). According to Reyna et al., the blockchain is a distributed, transparent and immutable data structure in which the reliability of every transaction is verified by the nodes in the network (Reyna, 2018). Tama et al. stated that the purpose of the blockchain is not to interfere with the data from the outside, there are blocks approved at every node in the network and it is a part of a distributed software system (Tama et al., 2017).

Technically, blockchain is defined as the integration of distributed ledger, decentralized contract and cryptographic algorithms. Transactions made on blockchain technology are stored in a list of data blocks that are cryptographically linked in a chain. The formation of blocks in the blockchain system is provided by the confirmation of the accuracy and validity of the transactions by the participants in a decentralized network in a distributed structure, and as a result of time-stamped algorithms (Hawlitschek et al., 2018). Zhao et al. revealed that the most important feature of the blockchain system is that it supports transparent and reliable transactions with network-based mathematical calculations instead of human control of transactions. With this feature, the blockchain can be thought of as an "operating system for interactions" (Zhao et al. 2016). Lewis stated that the blockchain is an improved database that provides solutions based on consensus rules for operations such as adding records, verifying and distributing information (Lewis, 2016).

Technical Concepts and Classification of the Blockchain

Basic Concepts

Distributed Ledger Technology (DLT)

DLT is a transparent database where important data or assets of public institutions and private sector companies can be viewed by all users in the network (Pinna & Ruttenberg, 2016). What is meant by distributed ledger is a ledger that can work with its own consensus standards without a central approval system (European Securities and Markets Authority, 2016). Another feature of DLTs is the use of cryptography as a

tool for storing assets and verifying transactions (Wessel, 2016). Transactions performed through DLTs can be cleared and finalized almost instantly, as all information or records will be distributed among all users (Digital Currencies, 2015).

Irreversibility of Records

Every transaction performed in blockchain technology is stored as an endless chain in block lists. Considering the irreversibility of these stored records, some calculation algorithms are used. It is not possible to change the information in a previously created block without breaking the structure of the chain. Therefore, if the data is corrupted, the records are visible to everyone in all the nodes created (Marco & Lakhani, 2017).

End-to-End Communication

Rather than using any centralized structure, individual nodes transmit and store data directly to each other in a peer-to-peer network (Nakamoto, 2008; Marco & Lakhani, 2017; Huumo et al., 2016). Due to the consensus among the nodes in the blockchain system, there is no need for a specific center and intermediaries (Pilkington, 2016). In the blockchain, information is stored by all participants (nodes) in the BitShares chain (Marco & Lakhani, 2017). Some authors argue that transactions created in the blockchain are not recorded by all nodes, but can be used (Nakamoto, 2008; Huumo et al., 2016).

Transparency

The concept of transparency in blockchain occurs when the participants in the network can see all transactions and blocks (Marco & Lakhani, 2017; Huumo et al., 2016). This suggests that the blockchain system is more transparent than a centralized system managed by a third party. Most of the sources state that the blockchain technology is open source, that is, it does not have a specific owner (Huumo et al., 2016; Tian, 2016).

Computational Logic

Since the BitShares chain is located in a digital environment, the computational logic can be realized according to the transactions in the blockchain. Nodes can use rules and algorithms to trigger transactions/processes automatically. BitShares transactions can be programmed to handle any type of information (Marco & Lakhani, 2017).

Classification of Blockchain Systems

Blockchain systems are classified under three headings (Buterin, 2015; Puthal et al., 2018; Zheng et al., 2017).

Public Blockchain

It provides an open permissionless platform that enables individuals affiliated or independent of various institutions or organizations to participate and mine. In this type of blockchain, there are no barriers or restrictions on entry to the blockchain. That's why the Public blockchain is also known as the permissionless blockchain. Public Blockchains are completely open and transparent and do not contain any private validator node, that is, a node that controls the transactions or that requires permission to enter the block.

They are blockchain structures that allow data exchange between individuals in the organization and are managed by a participant or group of participants in the network. Such blockchains are also known as permissioned blockchains. Because participants who do not have a special permission cannot join the chain. A node's access to and participation in the network is done by the group that manages the network according to the set rules. This situation reduces the level of compliance with the decentralized and transparent nature of blockchain technology.

Consortium Blockchain

It is defined as a private and permissioned blockchain technology in which a previously identified group of nodes is the authority/decision maker instead of a single transaction in the block verification and consensus process. These nodes identify the participants who can join the network and mine. Block validation is only valid if a block is signed by authorized nodes. A consortium decides that the network is public and that anyone on the network can read/write data. A comparison of all blockchains is given in Table 1.

Table 1. Comparison of the Blockchains

	Public Blockchain	Private Blockchain	Consortium Blockchain
Settlement Providers	All Miners	An Organization	Selected Nodes
Read Permissions	Open	Open or Allowed	Open or Allowed
Efficiency	Low	High	High
Centralization	No	Yes	Partially
Participation in Settlement Procedures	Without Permission	Permitted	Permitted

Challenges and Current Developments

Although blockchain technology has very important advantages and possibilities, it also has some limitations and difficulties. In this section, both these (difficulties) and possible solutions are given.

Scalability

With the number of transactions increasing day by day, the volume of blockchain systems is also increasing. Each node in the blockchain system must store all blockchain data. The purpose here is to perform verification and reconciliation transactions. However, this situation causes the blockchain structure to grow much more (Zheng et al., 2017). Due to some difficulties such as the capacity of the blocks and the speed of publishing, the number of confirmed transactions in the chain in a certain period of time is limited (Vukolić, 2015). The fact that miners prioritize large transfers and ignore small transactions causes delays in transaction time (VISA Fact Sheet, 2021).

Privacy

Users can transact with their own public and private keys without using their real identities. At the same time, data such as sender, receiver, time and transferred value are publicly published because transparency is essential (Meiklejohn, et al. 2013). Two concepts, namely anonymization and mixing, have been developed against privacy violations that may be encountered in the blockchain.

Anonymization

A zero-knowledge proof method is used, which allows verification with a one-sided password in order to hide (ensure privacy) of user information. This process is done instead of verification with digital signature and mining. Thus, the activities or relationships between the person and the transfer process remain confidential (Sasson et al., 2014).

Mixing

The scrambling service enables data to be collected from multiple sending addresses and forwarded to multiple receiving addresses. Recipient addresses are mixed by a central scrambling server to prevent theft. Thus, both encryption and address mixing methods are used (Bonneau et al., 2014; Van Wirdum, 2016; Ruffing et al. 2014).

Blocking Attack (Selfish Mining)

Malicious miners put the blocks they create on hold before releasing them and issue their private chain branches. They do this by using their own blocks after the necessary conditions are met. As a result, a bifurcation occurs in the chain. Malicious miners cause competitors to waste their power and time and can gain unfair advantage (Heilman, 2014).

Conclusion and Recommendations

In this chapter, blockchain technology, current developments and challenges are presented. Blockchain technology is a current technology and has a great development and transformation potential in many areas. First of all, when evaluated in terms of advantages and disadvantages of blockchain technology, it has been seen that it will replace traditional database systems. In addition, with these systems, very successful results can be obtained in terms of data security, consistency and data transfer. The privacy, transparency and distributed nature of blockchain technology provides advantages against central authorities. However, features of blockchain technology such as verification, system performance and querying can sometimes be a disadvantage. In addition, when we look at this technology from the perspective of the financial sector, it can be said that performance is a big handicap. In existing systems, thousands of transactions are performed instantaneously per second. It has been observed that these numbers are very low in the blockchain. The verification of transactions in the blockchain enables transactions to be made with big data. This has an impact on performance and productivity.

Along with blockchain technology, many innovations have entered our lives. In addition, it can be said that there is a great need for data analysis of the blockchain system. With the developments in blockchain technology, artificial intelligence creates new opportunities and approaches in applications. These technologies have superiority over traditional systems thanks to their secure and efficient data transfer features. As a result, projects and investments related to blockchain technologies should be made and this technology should be supported to develop and spread faster.

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To Cite This Chapter

Calp, M.H., Uzun, Y., & Butuner, R. (2021). Blockchain technology, challenges and current developments. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 60–69). ISRES Publishing

Data Resources and Machine Learning for Transcriptomics Data Analysis

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Introduction

Different types of omics data are analyzed individually or integratively to understand the cancer biology and for better decision-making on cancer patients' diagnosis and prognosis. The analyses include but are not limited to classification of tumor (sub)types, clustering of samples, predicting prognosis and drug response, and the understanding of the information flow between different data types.

The omics data types and the relevant fields are listed in Table 1. A genome is the entire DNA of an organism. Genomics relates to all genes in contrast to genetics which considers only a limited number of genes. Transcriptomics relates to mRNAs, non-coding RNAs, and small RNAs. It is a snapshot of the samples or cell's current situation. Although the active elements are proteins, transcriptomics data can be used as a proxy to protein expression. Proteomics is the omics approach that focuses on proteins' structure, location, quantity, modifications, and functions in tissue and cell. The Human Protein Atlas (Fernandes, 2004), which started with the end of the Human-Genome Project, and The Cancer Proteome Atlas of MD Anderson Cancer Center are the major data portals created for this concept (Li et al., 2017). RNA expression levels may not always correlate with protein expression levels, activity, and post-translational modifications for various reasons; therefore, it has an important place in the holistic approach. Lipidomics is an omics approach that aims to describe lipids and the functions of lipid-forming building blocks. Metabolomics shows the genomic and transcriptome makeup in practice. Phenomics emerges as a result of the system formed by all omics structures. The phenotype (external structure) describes the entirety of the observable characteristics of a living thing. It depends on the genes that govern enzyme and protein synthesis, namely its genotype (hereditary structure) and the effects of the environmental conditions in which it lives.

Table 1. Omics Data Types and Relevant Fields in Systems Biology.

Omics	Relevant field
Genomics	DNA
Transcriptomics	RNA
Proteomics	Protein
Lipidomics	Lipid
Metabolomics	Metabolite
Phenomics	Phenotype

In the rest of this chapter, we give a detailed description of the data resources and analyses in different types of transcriptomics data that is bulk (microarray and RNA sequencing) and single-cell RNA sequencing (scRNA-seq) data. We also mention drug and perturbation datasets.

Microarray Data Analysis

The expression of thousands of genes can be measured by microarray technology at a time. Known gene sequences are placed on a glass slide (chip) and a sample is placed in contact with this glass slide, complementary base pairings produce light that identifies gene expression in the sample (*Microarray Technology*, n.d.). Microarray data analysis starts with the biological question or hypothesis and is followed by experimental design. The data is collected, RNA is extracted, fluorescent labeling is performed. The image is acquired after microarray hybridization. Following the image analysis, data preprocessing and normalization, further statistical/machine learning analysis is performed to investigate the biological question (Leung & Cavalieri, 2003).

RNA sequencing (RNA-seq) Data Analysis

RNA sequencing is performed using next-generation sequencing and counts the discrete sequence reads (Hitzemann et al., 2013). The raw RNA-seq data is stored in FASTQ files and for each read the file has an ID, read sequence, and a quality score (Chu & Corey, 2012). The low-quality reads are filtered, and the rest of the reads are mapped to the reference genome (if the reference genome is available). After splice junction detection and gene/isoform expression quantification are done, further analysis can be performed to relate the transcriptomics data to relevant phenotype(s) and answer biological questions (Chen et al., 2011). RNA sequencing does not require a model organism unlike microarray platforms (Young et al., 2012).

Single Cell RNA Sequencing Data Analysis

scRNA-seq data enables researchers to understand the tumor heterogeneity and perform analyses at the cell level which provides higher resolution compared to bulk RNA sequencing (RNA seq) data analysis. In bulk RNA-seq data, each sample is an average

expression level of all cells in the sample and represented by an expression profile. In scRNA-seq data, each cell is represented by an expression profile and different cell types like immune and tumor cells can be analyzed individually or in their cluster. Clustering analysis can be performed on single-cell data to find different cell groupings and use the signature genes for each cluster to give a clue about the biological processes that are going on in the sample.

Publicly Available Data Resources

Gene-Expression Omnibus (GEO) (Edgar et al., 2002), was originally developed to host gene expression studies but now it also provides access to other types of high throughput data like protein expression, methylation, and copy number variation(CNV). Users can find the datasets by either entering GEO Accession ID or searching for keywords from the web interface. R Bioconductor GEOquery package (Davis & Meltzer, 2007) allows users to get data from GEO and parses it into R data structures.

The Cancer Genome Atlas (TCGA) (Tomczak et al., 2015) is a publicly available multi-omics data platform that consists of gene, exon, miRNA and protein expression, CNV, loss of heterozygosity (LOH) mutations, single nucleotide polymorphism (SNP), and DNA methylation data together with clinical features of over 20,000 samples from 33 cancer types. TCGA provides researchers to do multi-omics data analysis to characterize cancer types and subtypes, and find biomarkers for diagnosis and prognosis of cancer patients (Hoadley et al., 2014), (Zhou et al., 2020), (Liu et al., 2018), (Berger et al., 2018). The TCGA data can be retrieved from the GDC portal.

The Expression Atlas is located under European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI). It contains microarray, RNA-seq, proteomics data that meet various criteria.

In DDBJ (DNA Data Bank of Japan) center sequencing data is being collected in a joint consortium with GenBank at the NCBI and with the European Nucleotide Archive (ENA) at the EBI. Sequencing data is being collected in a joint consortium with GenBank at the NCBI and with the ENA at the EBI. The name of the common mechanism in this framework is International Nucleotide Sequence Database Collaboration (INSDC) (Fukuda et al., 2021).

Some example databases for publicly available transcriptomics data can be found in Table 2.

Table 2. Publicly Available Bulk Transcriptomics Databases

Bulk Transcriptome	Database description	Link
	ArrayExpress: Archive of Functional Genomics Data	www.ebi.ac.uk/arrayexpress
DDBJ	Biological database that collects DNA sequences	www.ddbj.nig.ac.jp
Expression Atlas	Gene expression pattern data	www.ebi.ac.uk/gxa
GEO	Public functional genomics data repository	www.ncbi.nlm.nih.gov/geo
HCMDB	Expression data of cancer metastasis	hcmdb.i-sanger.com
GDC Data Portal	TCGA - The Cancer Genome Atlas Program	portal.gdc.cancer.gov

Some of the R and Python libraries that can be used to retrieve data from Array Express, Expression Atlas, GDC Data portal - TCGA, and GEO are listed in Table 3.

Table 3. R and Python Package for Accessing Genomic Data Portal

Data Portal	R Package	Python Package
ArrayExpress	ArrayExpress	arrayexpress
Expression Atlas	ExpressionAtlas	Geneexpatlas
GDC Data Portal	TCGAbiolinks	Pytcga
GEO	GEOquery	GEOparse

Table 4 shows some of the databases that host single-cell RNA-sequencing data.

Table 4. Publicly Available Single-Cell Transcriptome Databases

Single-Cell Transcriptome	Database description	Link
GEO	Public functional genomics data repository	www.ncbi.nlm.nih.gov/geo
PanglaoDB	scRNA sequencing experiments from mouse and human	panglaodb.se
SC2disease	Single-cell transcriptome for human diseases database	easybioai.com/sc2disease
scRNASeqDB	Gene expression profiling scRNA-seq	bioinfo.uth.edu/scrnaseqdb
	Single-Cell Expression Atlas	www.ebi.ac.uk/gxa/sc
Tabula Sapiens	Human transcriptome reference at single-cell resolution	tabula-sapiens-portal.ds.czbiohub.org

Some of the R and Python environments that can be used to analyze scRNA-seq data are listed in Table 5.

Table 5. Single-Cell Data Analysis Packages

Package	Environment	Link
Bioconductor	R	www.bioconductor.org
SEURAT	R	satijalab.org/seurat
scanpy	Python	scanpy.readthedocs.io
scanpy	R	theislab.github.io/scanpy-in-R
scRNA-tools	R — Python	www.scrna-tools.org

The Drug Databases

Different types of drug databases keep drug-related information like targeted pathways/ genes or drug screening results. We mention some of the most up-to-date drug and cancer dependency databases.

The Dependency Map (DEPMAP) portal consists of CRISPR (Ledford, 2015) and RNA interference (RNAi) (Hannon, 2002) screens, Cancer Cell Line Encyclopedia (CCLE) (Ghandi et al., 2019) multi-omics data, and drug response screening datasets like profiling relative inhibition simultaneously in mixtures (PRISM) (Corsello et al., 2020), Cancer Therapeutics Response Portal (CTRP) (Rees et al., 2016) and the Genomics of Drug Sensitivity in Cancer (GDSC) (Yang et al., 2013) to detect cancer vulnerabilities. Using these datasets, researchers can relate mutation and/or gene expression to drug or gene intervention response, detect genes that are commonly essential for cell lines or specifically essential to a particular subset of cell lines (Copeland, 2012), (Shimada et al., 2021).

Connectivity Map (CMAP) (Lamb et al., 2006) (Subramanian et al., 2017) and the Library of Integrated Network-based Cellular Signatures (LINCs) (Keenan et al., 2018), provide gene expression after a chemical compound perturbation. These resources have been used for prioritizing drug candidates and detecting the drugs that can be repurposed (Dudley et al., 2011), (Gottlieb et al., 2011).

A list of drug databases can be found in Table 6.

Table 6. Drug-Related Resources

Drug Portals	Database Description	Link
DSEA	Drug Set Enrichment Analysis	dsea.tigem.it
Gene2drug	Pathway-based Rational Drug Repositioning	gene2drug.tigem.it
DRUGBANK	Database for Drug and Drug Target Info	go.drugbank.com
DGIdb	The drug-gene interaction database	www.dgidb.org
ChEMBL	Bioactive molecules with drug-like properties database	www.ebi.ac.uk/chembl
PubChem	Collection of chemical information	pubchem.ncbi.nlm.nih.gov
PharmGKB	Pharmacogenomics knowledge resource	www.pharmgkb.org
STITCH	Interaction networks of chemicals and proteins	stitch.embl.de
LINCS L1000	Gene expression profiles for small molecules and drugs	lincsproject.org/LINCS

Analyses Performed in Cancer Research

Gene IDs/Symbol Conversion

Gene ids (EntrezID, gene name, EnsembleID, etc.) obtained as a result of the analyzes may differ. Different gene enrichment tools may require different gene name inputs. That's why there are some packages and online tools for different notations. Tools such as DAVID and UCSC Gene ID Converter can be used online and bioMart, AnnotationDBi, and ClusterProfiler packages as R packages (Roy, 2020). Table 7 shows examples of Gene ID mapping tools.

Table 7. Some Examples of Gene ID Mapping Tools.

Gene ID mapping tools	Link
HGNC	www.genenames.org
AnnotationDbi	www.bioconductor.org/packages/release/bioc/html/AnnotationDbi.html
biomaRt	bioconductor.org/packages/release/bioc/html/biomaRt.html
org.Hs.eg.db	bioconductor.org/packages/release/data/annotation/html/org.Hs.eg.db.html
clusterProfiler	guangchuangyu.github.io/software/clusterProfiler

SYNGO DEFINING THE SYNAPSE	www.syngoportal.org/convert.html
DAVID Bioinformatics Database	david.ncifcrf.gov/conversion.jsp
g:Profiler	https://biit.cs.ut.ee/gprofiler/convert
UCSC Gene ID Converter	www.biotools.fr/human/ucsc_id_converter

Feature Selection/Reduction and Visualization

In transcriptomics data analysis, the number of genes (features) is very high (in thousands) compared to the number of samples causing the curse of dimensionality. There are also housekeeping genes that are almost equally expressed in every cell obscuring the difference among samples/cells.

Feature selection means picking a subset of informative genes for further analysis, and it is performed using statistical tests like t-test between two groups (for exp., cancer vs normal). Feature reduction is performed to map the features into a lower-dimensional space that can capture the variance in the dataset like Principal Component Analysis (PCA) or Multidimensional Scaling (MDS). After picking or forming 2 or 3 dimensions (features), we can visualize the data in a lower space.

Classification Analysis

Classification analysis can be performed to predict healthy versus cancer tissues and different subtypes of cancer. Different subtypes are treated differently, and the prognosis may also be different, so it is important to know/predict which subtype the sample/patient belongs to. The classification analysis algorithms like decision trees, logistic regression, k-nearest neighbor algorithm (KNN), support vector machines (SVM), random forest, and artificial neural networks can be used in transcriptomics data classification. Many classification algorithms internally have feature selection mechanisms that can detect discriminative genes between subclasses or the labels of interest.

Clustering Analysis

Clustering analysis shows which samples are similar in terms of their expression profile and which genes are grouped in terms of their expression pattern over samples. Different genes can be grouped and enriched with a biologically meaningful unit like a pathway or biological process term. Similarly, similar samples are clustered together according to the gene expression profiles implying that they have shared biological events and may show similar prognosis or drug response. The clustering algorithms like hierarchical clustering, k-means, self-organizing maps (SOM) can be used for clustering transcriptomics data.

Regression Analysis

In cancer research, regression analysis is performed to predict the numerical value of a relevant phenotype like drug response. Some of the regression analysis algorithms are linear regression, support vector regression (SVR), and random forest regression.

Differential Expression Analysis

Given two groups of samples (before and after drug treatment, healthy vs. cancer), differential expression analysis can be performed to get the differentially expressed genes between two conditions. T-test and Wilcoxon test are commonly used for microarray data. There are some frequently used methods baySeq, DESeq2, EBSeq, edgeR, limma-voom, NOISeq, sleuth, and TCC-GUI for RNA-seq data analysis.

After getting the differentially expressed, either each gene is searched individually, or gene set enrichment is performed to get biological differences between the two groups.

Gene Set Enrichment Analysis

Gene Set Variation Analysis-GSVA (Hänzelmann et al., 2013) and single-sample Gene Set Enrichment Analysis-ssGSEA (Sweet-Cordero et al., 2005) are methods which are used for gene set enrichment analysis within the gene expression data (without a comparison group) and map the gene expression profile into a functional annotation profile.

Gene Ontology (GO) (Harris et al., 2004) is a large human and machine-readable knowledge base, defined from different perspectives regarding the functions of genes. Gene ontology has been defined to cover three areas: biological processes (GO-BP), molecular function (GO-MF), and cellular components (GO-CC) (Ashburner et al., 2000; Gene Ontology Consortium, 2021).

Panther database, which is a part of the gene ontology database, is a biological database created to describe the functions of gene-protein families (Thomas et al., 2003).

Kyoto Encyclopedia of Genes and Genomes (KEGG) database maps genes, chemicals, and drugs to functional elements (pathways). The database is kept-up-to date and is a free online resource accessible to all researchers. It contains submodules such as genes, pathways, ligands, and drugs (Kanehisa & Goto, 2000).

Gene set enrichment tools are listed in Table 8.

Table 8. Functional Gene Set Enrichment Analysis Tools

Enrichment Tools	Description	Link
DAVID	Database for Annotation Visualization & Integrated Discovery	david.ncifcrf.gov
Enrichr	A suite of gene list enrichment analysis tools	maayanlab.cloud/Enrichr
KEGG	Kyoto Encyclopedia of Genes and Genomes	www.genome.jp/kegg
BIOCARTA	Online maps of metabolic and signaling pathways	www.biocarta.com
PANTHER Classification System	An ontology-based pathway database coupled with data analysis tools	www.pantherdb.org/pathway
GSEA	Gene Set Enrichment Analysis	www.gsea-msigdb.org/gsea/index.jsp
GENEONTOLOGY Unifying Biology	The Gene Ontology Resource	www.geneontology.org
Metascape	An annotation and analysis resource	metascape.org/gp
CPDB	ConsensusPathDB-human	cpdb.molgen.mpg.de
GeneSCF	Gene Set Clustering based on Functional annotation	github.com/genescf
MSigDB Molecular Signatures Database	The Molecular Signatures Database MSigDB	www.gsea-msigdb.org/gsea/msigdb
NCG7.0	Network of Cancer Genes & Healthy Drivers	ncg.kcl.ac.uk
g:Profiler	Web server for functional enrichment analysis	biit.cs.ut.ee/gprofiler/gost
ToppGene	Portal for gene list enrichment analysis	toppgene.cchmc.org
	GO enRIchment anaLysis and visuaLizAtion tool	cbl-gorilla.cs.technion.ac.il
ShinyGO	GO Enrichment Analysis	bioinformatics.sdstate.edu/go
iDEP.94	Integrated Differential Expression and Pathway analysis	bioinformatics.sdstate.edu/idep
KOBAS-intelligence	Intelligent prioritization and exploratory visualization of biological functions for GSEA	kobas.cbi.pku.edu.cn
WEGO 2.0 Web Gene Ontology Annotation Plotting	Web Gene Ontology Annotation Plot	wego.genomics.cn

	The functional Enrichment analysis tool	www.funrich.org
	Network augmented Gene Set Enrichment Analysis	www.inetbio.org/ngsea
	Collections of genes and variants associated with human diseases	www.disgenet.org
	Database of biological pathways	www.wikipathways.org/index.php/WikiPathways
	Enrichment Analysis Utilizing Active Subnetworks	github.com/egeulgen/pathfindR
	Visualization of Functional Enrichment Result	github.com/YuLab-SMU/enrichplot
	Protein-Protein Interaction Networks	string-db.org
	Network Data Integration Analysis and Visualization	cytoscape.org
	Visual web editor for cancer pathways and genomic data	www.pathwaymapper.org
	Collect and disseminate biological pathway and interaction data	www.pathwaycommons.org
	Visualization and analysis of cancer genomics data sets	www.cbioportal.org
	Gene Expression Profiling Interactive Analysis	gepia.cancer-pku.cn
	Network-Based Gene Enrichment Analysis	net-ge2.biocomp.unibo.it
	Gonet tool for interactive GO analysis	tools.dice-database.org/GOnet/
	An integrated data-mining platform for comprehensive analysis of cancer transcriptome	ualcan.path.uab.edu/home

Drug Response Data Analysis

To find the best treatment for an individual patient, the drug response can be predicted given patient gene expression data or other genetic attributes. The computational drug response analysis was performed for predicting the Area Under Curve (AUC), half-maximal inhibitory concentration (IC50), and half-maximal effective concentration (EC50) for cell line or patient sample to each drug and to relate the best possible drug

treatment to genetic characteristics like gene expression profiles and mutation status.

Chapter Summary

This chapter aims to provide introductory material to the researchers who are new to bioinformatics and computational cancer research domain and aim to work on transcriptomics data, particularly. We provide basic information about different types of omics data and more detailed explanations on transcriptomics data for cancer research. We mention the publicly available datasets and tools. We explain different analyses performed to analyze bulk and single-cell RNA sequencing transcriptomics data. We also touch upon the functional annotation tools and drug response databases that relate the analyses results to phenotypes.

Acknowledgments

Bahar Tercan has been supported by Personalized Cancer Models to Discover and Develop New Therapeutic Targets (NCI P01 CA077852) and Molecular Determinants of Cancer Therapeutic Response (NCI U01 CA217883) projects. Asim Leblebici has been supported by TUBITAK 2214-A International Research Fellowship Program for Ph.D. Students. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health and TUBITAK.

Declaration of Interest

The authors declare no competing interests.

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To Cite This Chapter

Tercan, B., & Leblebici, A. (2021). Data resources and machine learning for transcriptomics data analysis. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.70–85). ISRES Publishing

Video Adaptation Concept for Universal Access

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Universal Access

The phenomenal rise in the multimedia content available to an increasing number of users, who intend to consume it at different locations with different presentation preferences, using a plethora of devices and through heterogeneous networks, have resulted in a complex dilemma for universal access to the multimedia content.

Universal access is the vision of accessing multimedia content with a certain amount of user experience regardless of any constraints (e.g., terminal capabilities, network condition, etc.) (Mao et al., 2019; Calvalho et al., 2004). There exist two main concepts, namely Universal Multimedia Access (UMA) (Rong et al., 2006; Vetro et al., 2003) and Universal Multimedia Experience (UME) which follow this vision (Pereira et al., 2003).

UMA

Video content can be viewed on a variety of devices such as laptops, tablets, TVs, etc. These devices use ubiquitous network connections with different characteristics to obtain the content. Moreover, the owners of these devices have various preferences. The amount of video content is increasing enormously day by day. Interoperability problem occurs within this complex landscape comprised by rich multimedia content, diverse devices with varying capabilities, diverse user preferences, etc.

The notion of UMA concept relies on allowing users to seamlessly access any content, using any device, through any network, at any time, and from anywhere. Thus, UMA is mainly focused on the negotiation between the usage environment constraints (i.e., network and terminal capabilities) and the vast quantities of content meeting these constraints for allowing this seamless access (Mao et al., 2019; Waltl et al. 2009; Jain 2004). Figure 1 shows the concept of UMA.

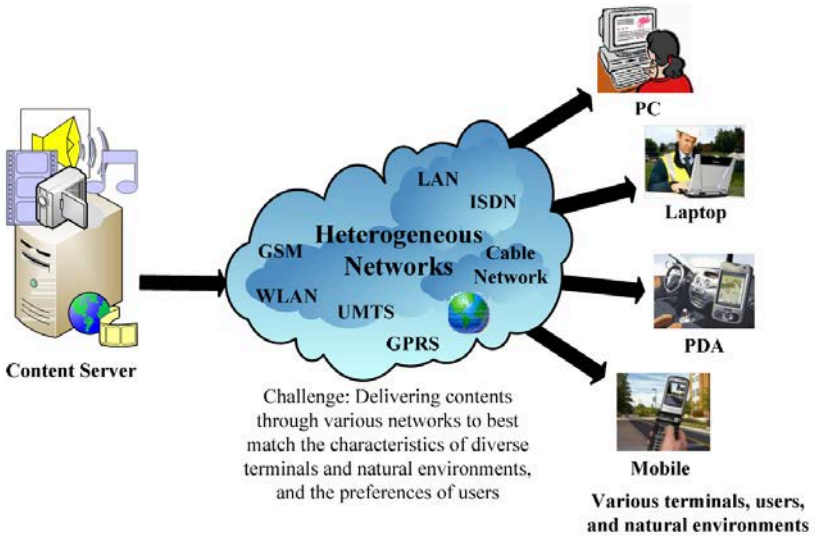

Figure 1. The Concept of UMA

UME

The context associated directly with the user her/himself (e.g., user's activities, habits, etc.) is the dominant driving force in the UME concept to provide the best possible multimedia experience to users. UME has been thought as the future of universal access to information since the theme of universal access has been shifted from a device-centric approach (i.e., the UMA concept) to a user-centric approach (Waltl et al., 2009).

Figure 2 presents the switch on the focus of universal access from UMA to UME. Adaptation is the most important process to provide the best possible video representations accommodating various constraints (e.g., terminal and network characteristics) as well as user preferences in both UMA and UME (Mao et al., 2019; Waltl et al. 2009; Jain 2004).

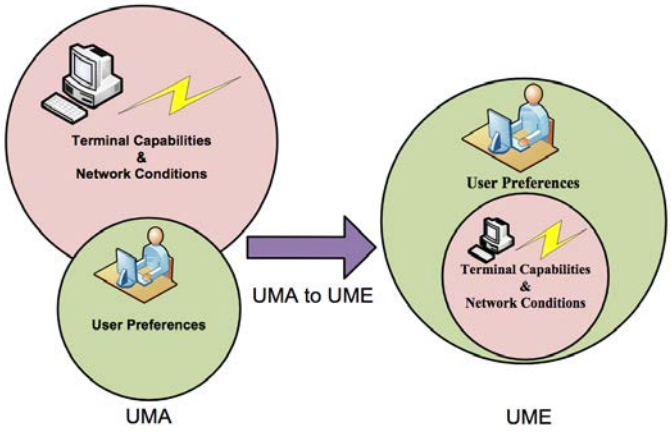

Figure 2. The Concept of UME

Video Adaptation Techniques

There are a number of video adaptation techniques which can be classified into three categories considering the processing technologies, the way the adaptation performed, and the level of adaptation operations executed (Mao et al., 2019; Waltl et al. 2009; Jain 2004).

Video Adaptation Techniques Based on Processing Technologies

Video adaptation techniques are split into three categories depending on the processing technologies used in the adaptation, namely: Scalable Video Coding (SVC) based adaptation, transcoding, and transmoding.

- SVC-Based Adaptation:

Adapting a compressed video stream into different spatial resolutions, temporal and quality levels using the support of SVC is offered by SVC based adaptation. This adaptation technology is performed by removing part(s) of a scalable video stream to satisfy a set of constraints (Nur Yilmaz, 2021; Kofler et al., 2008; Shen et al., 2006; Pan et al., 2008).

- Transcoding:

Transcoding is the process of manipulating or converting data from one format into another one. There are three major types of transcoding techniques existing in the literature: heterogeneous transcoding, which is based on format change (e.g., Motion Picture Experts Group-2 (MPEG-2) to MPEG-4), homogeneous transcoding, which relies on modification (e.g., temporal, spatial, quality etc.), and information insertion transcoding (e.g., editing, error resilience, etc.) (Kim et al. 2005).

- Transmoding:

Transforming multimedia content with one modality into another multimedia content having another modality (e.g., video to images, image to text, etc.) is called transmoding. Transmoding can also be identified as cross-modality transcoding (Baltazar et al. 2006).

Video Adaptation Techniques Based on the Way the Adaptation is Performed

The video adaptation techniques are divided into two categories when taking into account the way the adaptation is performed (Bijur et al., 2021; Martinez et al., 2005).

- Static (Off-line) Adaptation:

With the static adaptation technique, multiple versions of the same content are created at authoring time and the best variation satisfying a specific usage

constraint (e.g., terminal capabilities, user preferences, etc.) is selected at runtime. Static adaptation technique is quick since the adaptation is only performed by selecting content from a set of content versions and sending the adapted content to the receiver. However, it has a disadvantage that it requires high storage capacity because different content versions should be pre-prepared and stored at the server (Bijur et al. 2021; Sofolleous et al., 2008).

- Dynamic (On-line) Adaptation:

Due to the dynamic behaviors of the terminals and network, it is required to process and adapt the multimedia content dynamically. This way of adaptation technique can be identified as real time adaptation, and is needed for the cases where various devices exist, and require on-the-fly adaptation of the accessed content. Dynamic adaptation can be performed at any location that has enough processing power. The processing power required for the on-line adaptation is higher compared to that for the off-line adaptation because of the dynamic adaptation operations (Bijur et al., 2021; Hutter et al., 2005).

Adaptation Techniques Based on the Level of Adaptation Operations

According to the levels of adaptation operations, the adaptation techniques are divided into three categories, namely: signal level adaptation, semantic level adaptation, and structural level adaptation (Bijur et al., 2021;Valdes et al., 2006).

- Signal Level Adaptation:

Signal level adaptation technique relies on using media signals (e.g., video, audio, etc.) during adaptation operations. Bit rate transcoding and spatial resolution reduction are some examples for signal level adaptation (Bijur et al., 2021; Nur Yilmaz, 2021).

- Semantic Level Adaptation:

This technique is based on rendering important events (e.g., scoring points in basketball videos, breaking news in broadcast programs, etc.) in video contents by summarization. These important events are defined by the content providers or user preferences (Bijur et al., 2021; Chang et al., 2003).

- Structural Level Adaptation:

Structural level adaptation is based on utilizing the relations of structural elements in a video content, which arise due to event occurrence orders, camera control patterns, etc. Mosaicking, which is converting video sequences captured by continuous camera into panoramic views is an interesting technique utilized in

structural level adaptation. While mosaicking, the pixels in the background of different image frames are aligned together considering pixel correspondence and camera motions (e.g., pan, zoom, etc.). The pixels belong to the foreground moving objects are detected and they are placed on the top of the mosaicked background pixels (Bijur et al., 2021; Martinez et al., 2004).

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To Cite This Chapter

Yilmaz, G. N., & Cimtay, Y. (2021). Video adaptation concept for universal access. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.86–93). ISRES Publishing

SECTION 2
ENGINEERING

The Effects of Artificial Intelligence on Industry: Industry 4.0

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Cankiri Karatekin University

Introduction

For many, when the industry is mentioned, the first thing that comes to mind is Factories and Production. There is a term that has been heard frequently in the last decade: Industry 4.0. Although this term, which has been used for the last decade, connotes with words such as “factories” and “industry”, when it comes to the subject, a huge scope emerges. Before starting to explain this scope, it is necessary to mention the versions “1.0”, “2.0”, “3.0”.

Wars have been the factors determining the living spaces of nations and the borders of countries for centuries. However, the factors affecting the changes in living conditions and lifestyles and affecting the economies of societies have been agriculture and industry. The biggest factor affecting the transition from nomadic life to a settled life by hunting has been the revolutions and innovations in agriculture (Ozsoylu, 2017). The most important development of the industry was experienced in the 18th century. Although references are made to different dates of the 18th century in different sources, the most important development here has been the “steam engine”. Making different mechanical systems available depending on the power of the steam engine and here is Industry 1.0 (Bagcı, 2018; Pamuk & Soysal, 2018; Soylu, 2018). With this development, serious changes have begun to occur in people’s working life and economy. Thanks to the technological developments brought by the steam machines, the production in the factories have increased. While this increase increases the need for raw materials, on the other hand, it has started to enable countries with this technology to gain superiority over other countries.

The 19th century brought the birth of a second revolution in the field of production in human life. Industry 2.0, which came out with electricity and mass production lines. Railway transportation systems developed thanks to steam engines facilitated the transportation of raw materials from one place to another. Thus, it has also facilitated the delivery of the materials needed in the factories with increasing production speed to the factories. The widespread use of electrical energy and the use of oil as a fuel in the 20th century brought radical changes in human life (Alcin, 2016; Jänicke & Jacob, 2009). The era of mass production, which conformed to a certain standard, was begun, instead of personalized handmade products. Thus, the prices became cheaper and people’s living standards began to change.

The 20th century has been a century in which the rate of development of technology has increased exponentially. The World Wars are undoubtedly the catastrophes faced by humanity as the major factors that accelerate this development. Enemy states, trying to establish superiority over each other, made inventions one after another. The second half of the 20th century heralded the beginning of a new era in production with computers and programmable machines that started to be developed after the Second World War. Information and communication technologies (ICT), electronics, automation, and Industry 3.0. Automation has been achieved in the production sector with programmable microprocessors and robots have taken their place in the factories. In many parts of the factories in developed countries, automatic operations with robots have begun to be performed (Siemens, 2021). The robot industry will develop gradually and will take its place at more key points in the following periods.

In the 21st century, developments in ICT such as artificial intelligence (AI), the internet, and big data gave the production sector a completely different look. Industry 4.0. Digital technologies have become used in all areas of life. Production in the factories has become editable without the human factor. In this section, the relationship between AI and production/consumption, and even from where supply/demand relations bring societies and where they lead them are mentioned.

Industry 4.0

The term Industry 4.0 was first used at the Hannover Fair held in Germany in 2011. In a study prepared by Henning Kagermann, Wolf-Dieter Lukas, and Wolfgang Wahlster, it is stated that the world has entered a new era that can be called Industry 4.0 (Henning et al., 2011). Germany then started to carry out studies on this subject within the framework of a strategic plan, and thus the term Industry 4.0 began to be officially accepted in the world. In different countries of the world, the components specified as Industry 4.0 appear under different names. Although the term Industry 4.0 is widely accepted in Turkey, these components and this process are used in different countries as “Industrial Internet” (Bruner, 2013; Li et al., 2017), “Internet+” (Hong, 2017; Wang et al., 2016), and “Factories of the Future” (Herrmann et al., 2014; Jardim-Goncalves et al., 2017) etc. Since it is widely accepted in the world, the contribution of AI technologies to the production sector has been mentioned, especially by going through the term Industry 4.0. Development of the industrial revolution is shown in Figure 1.

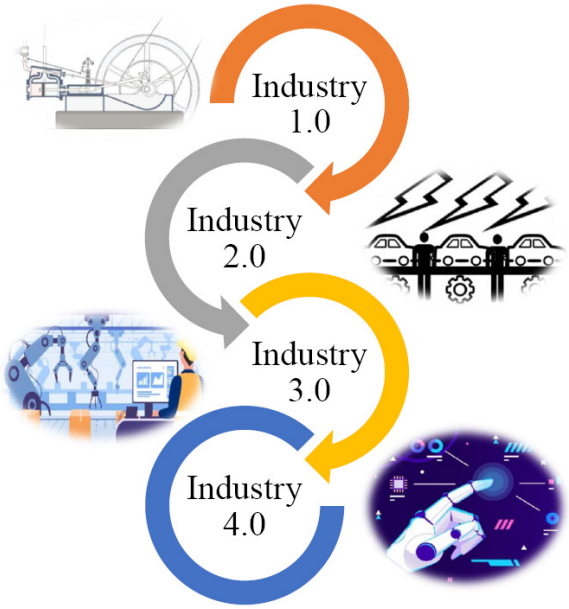

Figure 1. Development of the Industrial Revolution

Although Industry 4.0 has become a necessity rather than a choice for countries, many countries have not even completed the previous processes yet. According to a report prepared by TÜBİTAK for 2016, the digital maturity level of the industry in Turkey is between Industry 2.0 and Industry 3.0. Only 22% of companies have extensive knowledge and 50% have strategies to integrate relevant technologies within 3-5 years. 3 sectors with the highest maturity level; Materials (Rubber and Plastic), Computers, Electronics and Optical Products, Automotive and White Goods Sub-Industry. The 3 technologies that are considered to provide the most added value; Automation and Control Systems, Advanced Robotic Systems, and Additive Manufacturing (TUBITAK, 2016).

Demand is one of the important factors that direct production systems. Speed has become one of the most important factors in production, especially since the speed factor has become very decisive for people. With this new industrial revolution, the machines in automation systems were replaced by systems that enable instant tracking by communicating with data systems at the same time. Thus, the operators who managed the data were immediately informed about the malfunctions and problems on the production line and had the opportunity to solve the problem quickly.

Key Dynamics of Industry 4.0

One of the factors affecting the developments in the industry is the concept of big data. The entire cycle of the parts and products in production, from the production process on the band to the delivery to the customer, can be followed. This is how the production and consumption cycle can be personalized. Processes can be managed dynamically. Even the production data in the factory, product comments on social media and product

complaints on different sites can contribute to decisions about how the product should be made in the next stage. If these data are looked at from within the production facility, for example, the information that a cutting tip will wear from which product can be determined and faulty production can be prevented. New versions of the product can be shaped according to customer comments, taking into account the product follow-up and product comments after the sale.

Big data means storing, accessing, and processing information in a wide variety of high-volume and high-speed data. Processes such as analyzing this data, recognizing patterns, and revealing hidden connections mean big data analysis and are at the top of the agenda of technology companies in today's world, both because of their performance and management difficulties, and to create competitive advantage (Sagıroglu & Sinanc, 2013). The development of sensor technologies, the increase in mobility, the increase in the use of social networks, and the development of communication technologies have also brought about the birth of the concept of big data, increasing the variety, speed, and amount of data produced (Savas & Topaloglu, 2016). It is not possible to manage, process, and extract information with traditional database management systems of high-volume, complex, and high-speed data. Therefore, it requires different algorithms, techniques, and technologies, such as software running in parallel on server clusters (Jacobs, 2009). The solution to this requirement is found in AI. AI is not a new concept, in fact, its foundation dates back to seventy years ago and it is obvious that it will shape our future. With the contribution of sensor technologies, social media data, corporate data, and many more data, the need for AI technologies has increased during the evolution from data mining to big data (Savas, 2020). Big data processes are continuous processes and the example diagram is shown in Figure 2.

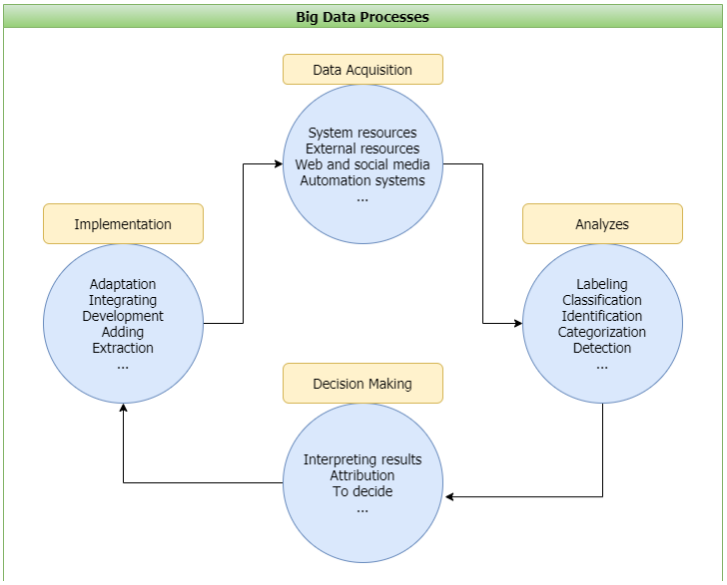

Figure 2. Big Data Processes

Another key dynamic is the Internet of Things (IoT), which makes it possible for machines on the production line to communicate with each other. This concept will probably be mentioned more frequently in the coming years. Because now, devices that use these technologies in daily life are used not only in industrial environments but also in homes. Today, televisions, refrigerators, ovens, heaters, and even smart vacuum cleaners have internet connections. The number of people using these devices will continue to increase. This is how the IoT is spreading. This technology is also used in factories. With AI technologies, this data is processed and improvements are made regarding the production-consumption cycle.

The IoT has been defined as "the ability of objects in our daily use to connect to the Internet and send and receive data" (Commission, 2017). The concept of the IoT has emerged with Radio-frequency identification (RFID) technology. The camera system installed by about 15 academics at Cambridge University in 1991 to see the coffee machine was an eye-opening application when evaluated under the conditions of the day. The system sent the image of the coffee machine to computer screens three times a minute. It took its place in history as the first example of the concept of the "IoT" because it is online and in real-time. In 1999, Kevin Ashton listed the benefits of RFID technology application and suggested its use. The proposed system; was a global system standard based on radio waves and sensors that gave rise to the concept of the "IoT". In today's internet, just as IPv4 network technology is used for human-to-human and human-to-machine communication via machines, IPv6 technology has special importance for IoT-based devices to work together. In IPv4, while a gateway converts between the protocols of different devices, it is aimed to remove this situation with IPv6 and to enable devices to work together without protocol problems (Geng, 2017; Ocal et al., 2021).

The fields of application for IoT technologies are as numerous as they are diverse, as IoT solutions are increasingly extending to virtually all areas of every day. The most prominent areas of application include the smart industry, where the development of intelligent production systems and connected production sites are often discussed under the heading of Industry 4.0. In addition; smart home applications with intelligent thermostats and security systems are receiving a lot of attention, while smart energy applications focus on smart electricity, gas, and water meters; smart transport solutions with vehicle fleet tracking and mobile ticketing; smart health areas with surveillance of patients and management of chronic diseases; and smart city projects with real-time monitoring of parking space availability and intelligent lighting of streets can be mentioned in IoT concept (Wortmann & Fluchter, 2015). The IoT components and processes are shown in Figure 3.

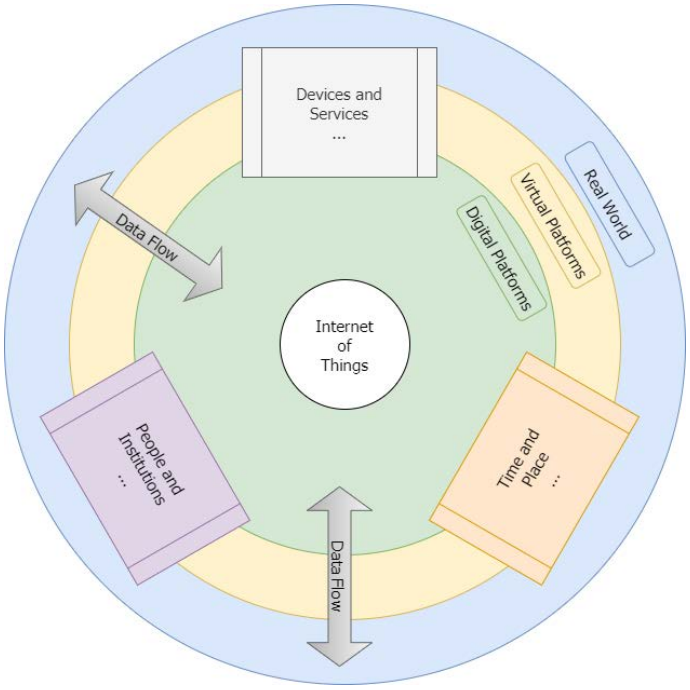

Figure 3. IoT Components and Processes

Another important element for Industry 4.0 is Cloud Computing (CC) technologies. Hardware-independent, flexible, expandable, and fast information infrastructure has been provided with these technologies. Thus, even the data of a factory in different countries were collected in a single-center, resulting in an enormous integration in production automation. This is only a sample for the production part of the business. It is also possible to benefit from CC on the consumption side.

CC can be defined as information services that are easy to manage, scalable according to needs, easily accessible from many different devices, and offered on common resources. CC, which offers the flexible structure of institutions is helping to manage ICT services. The cloud approach, reduce costs, although reducing the risks offers a safer work environment (Ersever et al., 2017).

Adopting and utilizing CC provide several major benefits. Some of these benefits can be mentioned like (Brian et al., 2008):

- Enables economies of scale for both the provider side and user side.
- Allows organizations to focus on their core competencies in a sustainable manner.
- Follows information technologies' evolutionary logic, or the achievement of ever-greater complexity and to continually improve information hiding or "transparency engineering."

CC has specific characteristics and realizations that, compared with other forms of outsourcing, have both advantages and disadvantages. On-demand self-service, Broad network access, resource pooling, rapid elasticity, and measured services can be can be counted among the characteristics of CC (Brian et al., 2008). The components of the CC are shown in Figure 4.

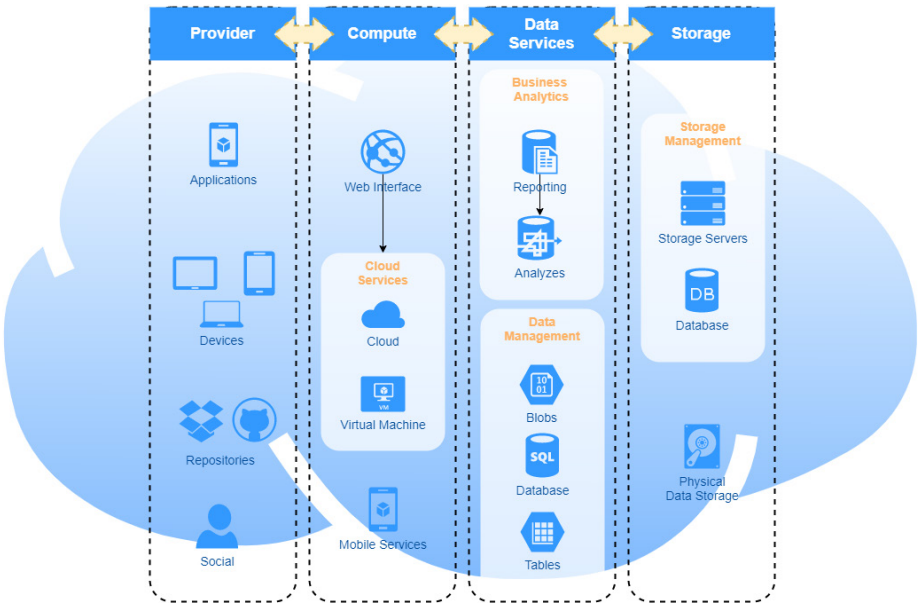

Figure 4. Components of CC

Cyber security (CS) is also one of the major issues of Industry 4.0. If ICT are involved, there are always cyber risks and threats. Especially in environments where there is such a large amount of data, which can be explained with big data, ensuring the security of the data is one of the problems that need to be dealt with.

CS can be defined as "the set of tools, policies, security concepts, security assurances, guidelines, risk management approaches, activities, pieces of training, best practices and technologies used to protect the assets of institutions, organizations, and users in the cyber environment" (Alkan, 2012). In the Industry 4.0 process, with the emergence of cyber-physical systems, these systems have become open to cyber threats. These vulnerabilities have made smart systems and Industry 4.0 systems a favorite of attackers. Although these systems make significant contributions to human life such as efficiency, speed, and operability, if cyber security vulnerabilities are not properly evaluated, the true potential of Industry 4.0 may never be reached (Yilmaz et al., 2021) defined information security elements in Industry 4.0 as "accessibility", "confidentiality", and "integrity" as seen in Figure 5.

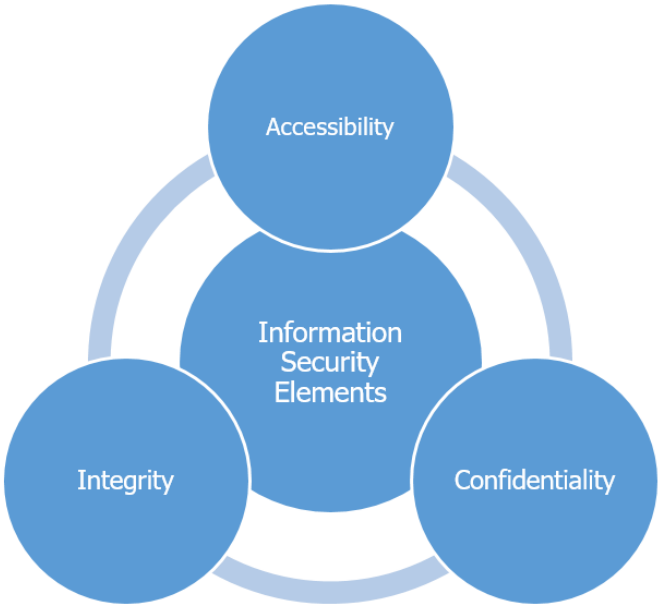

Figure 5. Information Security Elements in Industry 4.0

The developments in the production sector together with AI brought with it new factory applications called “Smart Factories”. In these factories, the production has been completely customized and the communication between the products and the machines as well as the communication between the operators and the machines has been made continuous and traceable. In fact, factories that are called dark factories and completely self-produced began to emerge. With the fourth revolution, robots began to be used both in the field of production and in the field of service. While the robots on the production line can perform tasks that require manpower, the robots on the service line are now able to perform smarter operations with AI technologies.

The main purpose of smart factories is to reduce the error rates in production, accelerate the production processes, and reduce the production costs by providing an automation system. Smart factories provide important benefits such as prototyping, ordering the first version of the product before it is produced, or the opportunity to make your own design. Thus, with the industrial revolutions, factories had to update their production processes and the role of the human factor in these processes changed with the coming of automation. At this point, with the emergence of smart factories and high-tech automation systems, the need for low-skilled labor has decreased considerably (Calp et al., 2018).

Apart from these, there are also different factors that can be counted as key dynamics for Industry 4.0 such as autonomous robots, simulation technologies, augmented reality, blockchain technology, and sensor technologies. The number of these components is increasing with the developing technology.

Discussion and Conclusion

Today, with the developments in ICT, consumers can easily access the product anywhere in the world. While this provides ease of consumption for individuals, it also creates a globally competitive environment for producers, not only on a country basis. It does not seem possible to remain indifferent to Industry 4.0 components in order to strengthen the country's economy, compete with global production power, and maintain the supply-demand balance. For this reason, it is necessary to understand these technologies as a whole and to evaluate their opportunities by creating a country strategy.

This new industrial revolution, which has been on the agenda for the last decade, continues as a process in which major countries carry out locomotive activities. However, especially with the progress of AI studies, the gap between countries will gradually increase and there will be a distinction between producing and consuming countries.

The industry 4.0 concept, which brings innovations listed as global interaction of storage systems and resources and machines, development of unique smart products with location information, implementation of smart factories that adapt to product features and optimize resources, the realization of new business models, new social infrastructure in the workplace for employees, work structure sensitive to individual differences, better work-life balance, responding to individual consumer requests, and instant engineering and smart software developed for instant response to problems, has features that will affect human life at every stage of life (Alcin, 2016; Calp & Dogan, 2018).

In order to realize all these, structures called cyber-physical systems need to be established. All machinery, equipment, and systems need to be integrated into this structure. When this is the case, there are significant differences between countries that have the opportunity to install these technologies and those that do not. For this reason, these technologies need to be put in place as soon as possible if it is desired to survive in the competitive system because the consumption habits will not end.

From all these mentioned, it is obvious that although a revolution focusing on products similar to the previous revolutions in the industry has been realized with AI, the situation will no longer be only in this field. The commitment to digital life, the inclusion of these technologies in daily lives and even being an indispensable part of them will affect all stages from production processes to consumption and marketing. Along with these, the growth of countries, their existence in global competition, business conditions, working styles, education levels and types, investment areas, and many other issues will be affected one after the other like a domino effect.

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To Cite This Chapter

Savas, S. (2021). The effects of artificial intelligence on industry: industry 4.0. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.95–106). ISRES Publishing

Artificial Intelligence Applications in Engineering

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Introduction

With the introduction of the computer and later the internet, we have experienced a digital transformation in our social life and we continue to live with advancing technologies. Nowadays, we have started to hear the name of artificial intelligence (AI) from computer science a lot and all of us that it has become a rapidly growing subject in many different fields know it.

The history of the concept of artificial intelligence dates back to ancient times. The idea father said, “Can machines think?” It is Alan Mathison Turing, who brought up the problem of machine intelligence and opened it up for discussion. Artificial intelligence terminology was first used in 1956 by John McCarthy et al. has revealed (McCarthy et al. 2006).

Although the definition of artificial intelligence cannot be fully revealed, it can be expressed as machines with human-like perception and cognition, since it initially refers to creating a “humanoid” machine. To clarify this expression, it can be said that artificial intelligence is a discipline that studies the computer simulation process of some human-specific behaviors such as reasoning, learning, perception and communication (Pannu 2015; Gabriel 2016; Li & Jiang 2017).

Looking at the literature, definitions have been made for artificial intelligence in 4 different perspectives. These definitions are given in Table 1.

Table 1. Definitions Made for Artificial Intelligence

	Definition	References
System that think like humans	"The automation of activities that we associate with human thinking, activities such as decision-making, problem solving, learning…"	(Bellman 1978)
	"The exciting new effort to make computers think …machines with minds, in the full and literal sense."	(Haugeland 1989)
Systems that act like humans	"The art of creating machines that perform functions that require intelligence when performed by people."	(Kurzweil et al. 1990)
	"The study of how to make computers do things at which, at the moment, people are better."	(Rich and Knight 1991)
System that think rationally	"The study of mental faculties through the use of computational models."	(Charniak and McDermott 1985)
	"The study of the computations that make it possible to perceive, reason, and act."	(Winston 1992)
Systems that act rationally	"A field of study that seeks to explain and emulate intelligent behaviour in terms of computational processes"	(Schalkoff 1990)
	"The branch of computer science that is concerned with the automation of intelligent behaviour"	(Luger and Stubblefield 1992)

Advantages and Disadvantages of Artificial Intelligence

The advantages of artificial intelligence applications are huge and can lead to revolutionary changes in professional industries. But looking at the other side of the coin, artificial intelligence also has some disadvantages (Khanzode & Sarode 2020; Bhbosale, Pujari, & Multani 2020).

Advantages of Artificial Intelligence

- *Elimination or minimization of the human error factor:* When systems such as violation detection with the help of weather forecast systems or video cameras are considered, the effects of human errors can be minimized with the help of artificial intelligence.

- *Reducing the risk factor that people may face in risky areas or areas:* Considering artificial intelligence-assisted robots, it can help eliminate the risk of death of people as a result of the detection or destruction of a bomb. In situations such as natural disasters, the risks that may be encountered in dangerous interventions can be minimized.

- *Effective and efficient working time:* When you think of human-assisted machines in an industry, these machines can be operated for as long as humans can

perform effectively. In addition, these periods can be shortened in repetitive jobs. Considering the machines working with artificial intelligence decision support system or artificial intelligence supported robots, it is possible to operate these machines 7/24 without a break and get efficiency. Another example is artificial intelligence supported customer support software. With the help of these systems, it is possible to respond to the requests and demands of the customers regardless of time.

- *Quick decision-making ability:* Systems using artificial intelligence technology offer faster and more practical solutions thanks to the algorithms they contain and due to the lack of emotional analysis as in humans.

- *Leading new solutions or inventions:* Artificial intelligence is also frequently used in the field of medicine. Thanks to artificial intelligence-based technological systems, more effective or different solutions can be offered than experts in terms of disease detection or diagnosis.

Disadvantages of Artificial Intelligence

- *Costs:* With the rapid development of technology, the field of artificial intelligence is also updating itself with different innovations every day. In order to keep up with these updates, making the necessary updates in the hardware and software area causes the costs to increase.

- *Lack of emotion:* Artificial intelligence systems, which lack human-specific emotions, cannot develop a bond with people in team management.

- *People getting lazy:* Thanks to systems or applications that are automated in many areas of life with artificial intelligence technologies, people get used to laziness.

- *Unemployment:* thanks to the innovations provided by artificial intelligence technology, automated machines replace the human factor. This may lead to a decrease in the demand for human labour.

Research Areas of Artificial Intelligence

The place of artificial intelligence in our lives is increasing day by day and continues to show itself in different fields. Areas of common use are given in the following sections.

Natural Language Processing

Natural language processing can be expressed as the ability of computers to perceive the language we speak, to process the perceived language, and then to produce sentences by making comments. In general, texts are used as input, as well as combined with speech

recognition. Today, it has many uses. Examples are translation programs, call services, or smartphone assistant applications (Nadkarni, Ohno-Machado, & Chapman , 2011; Maulud et al. 2021) & Chapman 2011; Maulud et al., 2021.

Computer Vision

In computer vision, a digitized input image is captured by the computer and converted for analysis and interpretation. Important aspects of computer vision can be expressed as pattern and object recognition, extraction of depth information, edge detection and motion detection. In addition to standard camera images, satellite images, medical images, as well as computer modelling of three-dimensional objects are also of interest to computer vision. Promising applications in computer vision can be given as examples of many uses such as autonomous vehicles (automobile, drone, etc.), humanoid robots, security systems for biometric verification (Zhang, 2010; Rybchak & Basystiuk, 2017).

Robotics

Traditionally, industrial robots are programmable machines to perform manual tasks automatically. However, unlike pre-programmed industrial robots, autonomous robots equipped with artificial intelligence often have the ability to make their own decisions to achieve a goal or perform a task.

Autonomous robots are equipped with texture and motion sensors, video/image input and various sensors specially designed for specific tasks. In this way, inputs from different sensors are coordinated to perform various actions with artificial intelligence algorithms and software. Autonomous robots are equipped with intelligence capabilities for sensing their environment and planning their movements by exhibiting independent behaviours with the developing artificial intelligence technology (Brady, 1984; Perez et al., 2018; Vrontis et al., 2021).

Games

The ability of computers to play certain games was demonstrated in the early days of artificial intelligence with games such as checkers, backgammon and chess. In such games, the probability of a large number of moves was systematically calculated and the calculations were repeated according to the position of the opposing player, aiming to reach the best solution. So much so that a computer specially designed for the game of chess defeated Gary Kasparov, the world champion in chess, in the late 90s.

Today, the game industry is perhaps one of the areas where artificial intelligence shows the most impact. For example, events such as the passing of a different character in the game, the fact that the game difficulty levels can be adjusted according to the current situation of the player, or the enemy soldiers seeing and shooting the opponent in a

war game are realized thanks to the learning, analysis and inferences of the computers (Schaeffer & Van den Herik, 2002; Mateas 2003).

Speech Recognition

Speech recognition is the process of recognizing speech sounds spoken by the speaker and converting them into text in a verbal form. By mapping the digitally represented acoustic signal to a string of words, it provides automatic and accurate conversion into text via keywords or phrases. The voice typing feature in the messaging applications of smartphones can be given as an example as one of the most used applications among the applications using speech recognition technology (Forsberg, 2003; Huang, Baker, & Reddy, 2014).

Knowledge Discovery and Data Mining

Knowledge discovery and data mining is an organized interdisciplinary field focused on methodologies for extracting useful information from data using large data pools, identifying new, useful and understandable patterns. While many of the techniques used for knowledge discovery and data mining are similar to machine learning or some types of neural networks, the goals here are different. The key here lies in identifying interesting bits of information in a large dataset, rather than finding a representation that specifies key aspects of the entire sample set (Mining, 1996; Maimon & Rokach, 2009).

Genetic Algorithm

The Genetic Algorithm is one of the first of the population-based stochastic algorithms. These algorithms work by encoding a potential solution to a particular problem on a simple chromosome-like data structure. It also applies recombination operators to these constructs to preserve critical information. Although the range of problems to which genetic algorithms are applied is quite wide, they are generally seen as function optimizers. It includes approaches such as inheritance, mutation, selection and crossover to look for a better alternative to the problem. Genetic algorithms have wide application areas in different research fields such as management, engineering, industrial design and so on (Mirjalili, 2019; Mathew, 2012; Wang 2003).

Expert Systems

They are computer programs developed to simulate human-specific design, planning, problem solving and reasoning abilities by designing intelligent models and algorithms. Expert systems can store human knowledge and experience within a limited area by including them in the artificial intelligence system and reach the solution of the problem by inferring from the results.

While expert systems were originally designed as separate systems for specific tasks, they can now be integrated into larger systems and have an advantage over traditional programs when it comes to dealing with incomplete, inconsistent or uncertain information (Jackson, 1986; Lucas & Van Der Gaag 1991; Gupta & Nagpal 2020).

Machine Learning

Machine learning is a technology designed to mimic human intelligence by learning from the surrounding environment, improving the performance of its system not only by following the program's instructions, but also depending on the data. The purpose of machine learning can be expressed as extracting useful information from a set of sample data and representing this information in a way that can be used in a reasoning system (Yao & Liu, 2014; El Naqa & Murphy, 2015).

It draws inspiration from work in a variety of disciplines, including machine learning, computer science, statistics, information theory, cognitive science, philosophy, and biology. Machine learning has a wide range of uses in areas such as manufacturing, sales and marketing, finance, defence, transportation and healthcare (Sarker, 2021).

Applications of Artificial Intelligence Technology in Engineering

Artificial intelligence is a collective of advanced computational techniques. In addition to the advantages of artificial intelligence technology such as reducing costs, increasing efficiency and ensuring safety, there are also effects such as reducing the labor intensity of workers. Engineering fields, business, medicine, defence etc. Artificial intelligence technology is frequently used in today's technologies to solve complex problems in the field.

Artificial Intelligence Applications in Medicine

With the development of technology, artificial intelligence supported medical technologies produce viable solutions for clinical applications. Artificial intelligence has uses in diagnosis, treatment and predicting outcome in many clinical scenarios. When the literature is examined, the use of artificial intelligence in drug development (Mak & Pichika, 2019), in health monitoring (Smarsly, Lehner, & Hartmann, 2007; Sun et al., 2020) in the management of medical data (Greengard, 2018), in the diagnosis of disease (Vashistha, Chhabra, and Shukla 2018), in personalized treatment (Schork, 2019), in the analysis of health plans (Mahmic) and surgical treatment (Loftus et al., 2020) such as it is frequently used in fields

Artificial Intelligence Applications in Defence Industry

Countries are closely following and developing artificial intelligence technology, which

has potentially important effects in the field of national security and is growing rapidly. Artificial intelligence is used to improve the features of critical systems in the field of defense, thanks to its integrated computing and decision-making capabilities (Hoadley & Lucas, 2018; Bistron & Piotrowski, 2021). Intelligence gathering and analysis (Hoppa et al., 2019; Xi, Lingyu, & Jiapeng, 2021), information operations (Telley, 2018; Paterson & Hanley, 2020), cyber security (Alhayani et al., 2021), logistics and transportation (Bujak, Smolarek, & Gębczyńska, 2011; Amir & Ahmad, 2019), target recognition (Min et al., 2019; d'Acremont et al., 2019), simulations and training (Ernest et al., 2016; Fawkes 2017), in command and control areas (Schubert et al., 2018; Wang 2019) and also in various semi-autonomous and autonomous vehicles (Gare 2016, Mori 2018; Amir & Ahmad 2019) work continues on the use of artificial intelligence.

Applications of Artificial Intelligence in the Field of Business

Computing systems with programmed intelligence can solve different real-world problems much more accurately and efficiently than deterministic and hard-coded computing systems. Artificial intelligence plays an important role in overcoming the problems in the business world, as many problems in business cannot be solved with deterministic systems (Bai, 2011; Ghimire et al., 2020). Looking at the usage areas of artificial intelligence, marketing (Martínez-López & Casillas, 2013; Vlačić et al., 2021) and product recommendation (Shahbazi & Byun, 2019; Sharma et al., 2021), fraud detection (Bao, Hilary & Ke, 2020; Yazici 2020), algorithmic trading (Hara et al., 2018; Li, Zheng,& Zheng, 2019), insurance (Riikkinen et al., 2018; Guimaraes, 2020), customer service (Ping, 2019; Li et al., 2020), such as it is seen that it is widely used to solve and optimize many problems in the business world.

Artificial Intelligence Applications in Agriculture

Interest in artificial intelligence technologies in the field of agriculture has been increasing recently. Examining this area, there are many challenges to maximizing yields, including improper tillage, underproduction, diseases, pest infestation, and the knowledge gap between producers and technology. At this point, the flexibility of artificial intelligence in solving agricultural problems, its high performance, accuracy and cost effectiveness come to the fore with its tight learning capabilities (Bannerjee et al., 2018; Eli-Chukwu, 2019).

When the areas where artificial intelligence technology is used in the field of agriculture are examined, the yield estimation (Raorane & Kulkarni 2012; Kuwata & Shibasaki, 2015; Chlingaryan, Sukkarieh, & Whelan, 2018), disease detection (Kothari, 2018; Patil & Kumar, 2020), weed detection (Sarvini et al., 2019; Sohail et al., 2021), and species recognition applications (Taner et al., 2018; Cinar & Koklu, 2019; Koklu, Cinar, & Taspinar, 2021; Kong et al., 2021), animal welfare and livestock management

(Mcloughlin, Stewart, & McElligott, 2019; Neethirajan, 2020; Neethirajan & Kemp ,2021), water management (Grundmann et al., 2012; M Sánchez Céspedes, Espinosa Romero, & P Rodríguez Miranda, 2019) with soil management (Prithviraj et al., 2020) it is seen that there are studies on these issues.

Artificial Intelligence Applications in the Field of Transportation

The developments in the field of artificial intelligence offer unprecedented opportunities in the transportation sector as well as in different fields and lead the way in finding solutions too many different challenges. Some of the difficulties encountered, capacity problems, safety problems, environmental pollution, noise pollution, wasted energy and economic losses due to all these are the first ones that come to mind. With the use of artificial intelligence, various studies are carried out such as eliminating possible congestion in transportation, making travel times more transparent and reliable for customers, reducing environmental and noise pollution, and improving productivity in transportation (Sadek, 2007; Abduljabbar et al., 2019).

When the literature is examined, the use of artificial intelligence in the field of transportation, traffic management (Chowdhury et al., 2006; Lendel et al., 2017; Astarita, Festa, & Giofrè, 2018), traffic safety (Zhang, 2020; Yao & Ye, 2020) and accident forecast (Yasin Codur & Tortum, 2015; Zhou ,2019; Yu et al., 2021), vehicle control (Korjagin and Klachek, 2017; Sambana & Ramesh, 2020), public transport (Heppe & Liebig, 2017; Minea, Dumitrescu, & Chiva, 2019) and urban mobility (Ceder, 2020; Smith, 2020; Cho & Kim, 2021) such as collected under the headings.

The Future of Artificial Intelligence

Today, artificial intelligence has found many different uses in many different fields. Research and development will continue in the future, new software techniques will be discovered and we will come up with different models. It will be possible to come up with professional software development tools that make it easier to develop expert systems and other artificial intelligence applications. These developments will occur not only in the field of software, but also in the field of hardware. Much larger capacity and faster microprocessors and memories will be offered; completely new and more advanced devices will be created in addition to the development of semiconductor technology. The new parallel processing with many processors working at the same time, and especially their architectures suitable for artificial neural networks processing will add a completely new dimension to artificial intelligence. Natural language interfaces will become a common feature in many application programs and intelligent databases will be developed. Symbolic language programs will increasingly use artificial intelligence technologies to make some performance improvements. Expert systems advising on many important issues will become much more common. In short, artificial intelligence

will continue to act as a technological innovator in the future (Haenlein & Kaplan, 2019; Bundy, 2017; Dhar, 2016; Floridi, 2020).

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To Cite This Chapter

Cinar, I., Taspinar, Y.S., & Koklu, M. (2021). Artificial intelligence applications in engineering. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 107–125). ISRES Publishing

SECTION 3
MATHEMATICS

Continued Fractions and Pell's Equation

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1.Introduction

The study of Diophantine equations is one of the most important topics in the history of number theory. Diophantine equation is an $n-$variable $(n\geq 2)$ polynomial equation $f(x_1,x_2,x_3,\ldots,x_n)=0$ whose coefficients are integers.

The studies related to Diophantine equations are based on three fundamental problems (Andreescu et al., 2010):

- The first one is whether the Diophantine equation is solvable.
- The second one if it is solvable, is the number of solutions to the Diophantine equation finite or infinite?
- The third problem is that if the Diophantine equation is solvable, determine all of its solutions.

The form $ax^2+bxy+cy^2+dx+ey+f=0$ where $a,b,c,d,e,f\in\mathbb{R}$ and $x,y\in\mathbb{Z}$ is called as quadratic Diophantine equation. Such an equation with integral coefficients is reduced in its main case to Pell-type equation. So, a Pell's equation is a kind of Diophantine equation.

Pell's equation has a long history. Many mathematicians have been fascinated by Pell's equations and have done a lot of work on it. The first important development regarding the solution of Pell's equations was in India. In AD 628, Brahmagupta explained how to use known solutions of Pell's equation to generate new solutions. After that in AD 1150 Bhaskaracharya gave a method for finding a minimal positive solution to Pell's equation. Brahmagupta explains a method for generating new solutions from old ones and gives an algorithm. After the years Bhaskaracharya extended Brahmagupta's work on Pell's equation via repeated reductions. Bhaskaracharya showed his method by solving the equation $x^2-61y^2=1$. In AD 1657, Fermat challenged his fellow mathematicians to solve the equation $x^2-61y^2=1$, and thus began the modern European history of the Pell equation. Brouncker gave a general method for solving Pell's equation and solved the equation $x^2-313y^2=1$ (Silverman, 2013). John Wallis described Brouncker's method in his book entitled Opera Mathematica. Euler mistakenly thought that the method in Wallis's book was created by John Pell and this name was given to the Pell's equation by

Euler. Therefore, the quadratic Diophantine equation of the form $x^2 - Dy^2 = 1$, where D is a positive non-square integer, unknowns x and y are positive integers, is called as *Pell's equation*, following an erroneous attribution of Euler. Brouncker and Wallis explained a method of solution that is the same as the solution by continued fractions (Coppel, 2006).

Many great mathematicians of the seventeenth and eighteenth centuries have been fascinated by continued fractions and have done work on it. Appearing in many areas of mathematics, continued fractions are interesting and useful in other areas of number theory. For instance, continued fractions are "the best" approximations of real numbers. Continued fractions, which also provide a way to learn about the decimal approximations of rational numbers, also appear in many other areas. Additionally, continued fractions provide a way to analyze solutions to Pell's equation $x^2 - Dy^2 = 1$. Since all integral solutions of Pell's equation come from convergents to $\sqrt{D}$.

2. Continued Fractions

Definition 2.1. (Olds, 1963) An expression of the following form

$$a_1 + \cfrac{b_1}{a_2 + \cfrac{b_2}{a_3 + \cfrac{b_3}{a_4 + \ddots}}}$$

is called as *continued fraction* where the $a_1, a_2, a_3, \ldots, b_1, b_2, b_3, \ldots$ are any real or complex numbers, and the number of terms is finite or infinite.

The purpose of the present section is to acquaint with the so-called regular continued fractions, that is, those of the form

$$a_0 + \cfrac{1}{a_1 + \cfrac{1}{a_2 + \cfrac{1}{a_3 + \ddots}}}$$

usually with the assumption that all the elements $a_1, a_2, a_3, \ldots$, are positive integers.

Definition 2.2. (Rosen, 1992) An expression of the form

$$a_0 + \cfrac{1}{a_1 + \cfrac{1}{a_2 + \cfrac{1}{a_3 + \ddots + \cfrac{1}{a_{n-1} + \cfrac{1}{a_n}}}}}$$

is called as a *finite continued fraction* where $a_0, a_1, a_2, \ldots, a_n$ are real numbers with $a_1, a_2, \ldots, a_n$ positive. A finite continued fraction is denoted by $[a_0; a_1, a_2, \ldots, a_n]$ where the real numbers $a_1, a_2, \ldots, a_n$ are called the partial quotients of the continued fraction. The continued fraction is called *simple* if the real numbers $a_0, a_1, a_2, \ldots, a_n$ are all integers.

A finite continued fraction can also be written as $[a_0; a_1, a_2, \ldots, a_n] = a_0 + \dfrac{1}{[a_1; a_2, \ldots, a_n]} = [a_0; [a_1, a_2, \ldots, a_n]]$ for $n > 0$.

Example 2.3. Express $[2;1,3,1,4]$ as a rational number.

$$[2;1,3,1,4] = 2 + \cfrac{1}{1 + \cfrac{1}{3 + \cfrac{1}{1 + \cfrac{1}{4}}}} = \frac{67}{24}$$

As can be seen, the value of any finite simple continued fraction is always a rational number and every rational number can be represented by a finite simple continued fraction (Rosen, 1992; Burton, 2010; Robbins, 1993).

Example 2.4. Express $\dfrac{67}{29}$ as a finite simple continued fraction.

By the Euclidean Algorithm, we have

$$67 = 2.29 + 9$$

$$29 = 3.9 + 2$$

$$9 = 4.2 + 1$$

$$2 = 2.1 + 0,$$

it follows that

$$\frac{67}{29} = 2 + \frac{9}{29} = 2 + \frac{1}{29/9} = 2 + \cfrac{1}{3 + \cfrac{2}{9}}$$

$$= 2 + \cfrac{1}{3 + \cfrac{1}{9/2}} = 2 + \cfrac{1}{3 + \cfrac{1}{4 + \cfrac{1}{2}}}$$

$$= [2;3,4,2].$$

Since $2 = 1 + 1$, it can be written

$$\frac{67}{29}=2+\cfrac{1}{3+\cfrac{1}{4+\cfrac{1}{1+\cfrac{1}{1}}}}$$

Therefore, it can also be denoted as $[2;3,4,1,1]$.

This explains the following theorem.

Theorem 2.5. (Long, 1987) If $a_n>1$, then $[a_0;a_1,a_2,\ldots,a_n]=[a_0;a_1,a_2,\ldots,a_n-1,1]$.

Definition 2.6. (Rosen, 1992) Let $A=[a_0;a_1,a_2,\ldots,a_n]$ where $\forall a_i\in\mathbb{R}$ with $a_1,a_2,\ldots,a_n$ positive. The continued fractions $C_k=[a_0;a_1,a_2,\ldots,a_k]$, where $k\in\mathbb{Z}$ with $0\le k\le n$, is defined as the *kth convergent of the continued fraction* $A=[a_0;a_1,a_2,\ldots,a_n]$ and it is denoted by C_k.

Theorem 2.7. (Stein, 2008) If real numbers p_k and q_k are defined as follows:

$$p_{-2}=0,\quad p_{-1}=1,\quad p_0=a_0,\quad p_1=a_1a_0+1,\quad \ldots\quad p_k=a_kp_{k-1}+p_{k-2}\quad \ldots,$$

$$q_{-2}=1,\quad q_{-1}=0,\quad q_0=1,\quad q_1=a_1,\quad \ldots\quad q_k=a_kq_{k-1}+q_{k-2},\quad \ldots,$$

then the *kth convergent* $C_k=[a_0;a_1,a_2,\ldots,a_k]$ is given by $C_k=\frac{p_k}{q_k}$ for $0\le k\le n$.

Theorem 2.8. (Burton, 2011)

a. The convergents with even subscripts form a strictly increasing sequence; that is, $C_0<C_2<C_4<\ldots$.

b. The convergents with odd subscripts form a strictly decreasing sequence; that is, $C_1>C_3>C_5>\ldots$.

c. Every convergent with an odd subscript is greater than every convergent with an even subscript.

In other words, this theorem briefly states that $C_0<C_2<C_4<\ldots<C_n<\ldots<C_5<C_3<C_1$.

Theorem 2.9. (Long, 1987) Let $\alpha=[a_0;a_1,a_2,\ldots,a_n]$ with $a_n>1$ so that α is the rational number $\frac{p_n}{q_n}$. Then, for $1\le i\le n$, we have that

$$\left|\alpha-\frac{p_i}{q_i}\right|<\left|\alpha-\frac{p_{i-1}}{q_{i-1}}\right|$$

and also

$$|\alpha q_i-p_i|<|\alpha q_{i-1}-p_{i-1}|.$$

Let's show what has been given so far on an example.

Example 2.10. Express $\frac{170}{39}$ as a finite simple continued fraction and compute the convergents for this simple continued fraction. Also, show that its continued fraction satisfies Theorem 2.5., Theorem 2.8. and Theorem 2.9.

By the Euclidean Algorithm, we have

$$170 = 4.39 + 14$$

$$39 = 2.14 + 11$$

$$14 = 1.11 + 3$$

$$11 = 3.3 + 2$$

$$3 = 1.2 + 1$$

$$2 = 2.1 + 0,$$

it follows that

$$\frac{170}{39} = 4 + \frac{14}{39} = 4 + \frac{1}{39/14} = 4 + \frac{1}{2 + \frac{11}{14}}$$

$$= 4 + \frac{1}{2 + \frac{1}{14/11}} = 4 + \frac{1}{2 + \frac{1}{1 + \frac{3}{11}}}$$

$$= 4 + \frac{1}{2 + \frac{1}{1 + \frac{1}{11/3}}} = 4 + \frac{1}{2 + \frac{1}{1 + \frac{1}{3 + \frac{2}{3}}}}$$

$$= 4 + \frac{1}{2 + \frac{1}{1 + \frac{1}{3 + \frac{1}{3/2}}}} = 4 + \frac{1}{2 + \frac{1}{1 + \frac{1}{3 + \frac{1}{1 + \frac{1}{2}}}}}$$

$$= [4; 2, 1, 3, 1, 2].$$

Since $2 = 1 + 1$, it can be written

$$\frac{170}{39}=4+\cfrac{1}{2+\cfrac{1}{1+\cfrac{1}{3+\cfrac{1}{1+\cfrac{1}{1+\frac{1}{1}}}}}}$$

Therefore, it can also be denoted as $[4;2,1,3,1,1,1]$. This satisfies Theorem 2.5.

The various convergents are

$C_0=[4]$ $\qquad C_0=\frac{p_0}{q_0}=\frac{4}{1}=4$

$C_1=[4;2]$ $\qquad C_1=\frac{p_1}{q_1}=\frac{9}{2}=4,5$

$C_2=[4;2,1]$ $\qquad C_2=\frac{p_2}{q_2}=\frac{13}{3}\approx 4,3333333333$

$C_3=[4;2,1,3]$ $\qquad C_3=\frac{p_3}{q_3}=\frac{48}{11}\approx 4,3636363636$

$C_4=[4;2,1,3,1]$ $\qquad C_4=\frac{p_4}{q_4}=\frac{61}{14}\approx 4,3571428571$

$C_5=[4;2,1,3,1,2]$ $\qquad C_5=\frac{p_5}{q_5}=\frac{170}{39}\approx 4,358974359.$

It is clear that $\frac{4}{1}<\frac{13}{3}<\frac{61}{14}<\frac{170}{39}<\frac{48}{11}<\frac{9}{2}$. Thus, $\frac{p_0}{q_0}<\frac{p_2}{q_2}<\frac{p_4}{q_4}<\frac{p_5}{q_5}<\frac{p_3}{q_3}<\frac{p_1}{q_1}$.

Therefore, $C_0<C_2<C_4<C_5<C_3<C_1$. This satisfies Theorem 2.8.

Let us check that if Theorem 2.9 is satisfied.

$$\left|\frac{170}{39}q_4-p_4\right|=\left|\frac{170}{39}14-61\right|=\left|\frac{1}{39}\right|\approx 0,0256410256$$

$$\left|\frac{170}{39}q_3-p_3\right|=\left|\frac{170}{39}11-48\right|=\left|\frac{-2}{39}\right|\approx 0,0512820513$$

From this we easily obtain $\left|\frac{170}{39}q_4-p_4\right|<\left|\frac{170}{39}q_3-p_3\right|$. It can be shown similarly for the others p_k and q_k $(1\le k\le 5)$.

Theorem 2.11. (Koshy, 2007) Let $C_k=\frac{p_k}{q_k}$ be the *kth convergent* of the simple continued fraction $[a_0;a_1,a_2,\ldots,a_n]$ where $1\le k\le n$. Then, $p_kq_{k-1}-q_kp_{k-1}=(-1)^{k-1}$ is valid.

The Procedure of Continued Fraction

The procedure of continued fraction can also be explained as follows.

Let $x \in \mathbb{R}$ and

$$x = \lfloor x \rfloor + \{x\} = a_0 + \{x\}$$

where $\lfloor x \rfloor \in \mathbb{Z}$ and $0 \le \{x\} < 1$.

If $x \in \mathbb{Z}$, then this is the end of the algorithm.

If $x \notin \mathbb{Z}$, i.e. $\{x\} \neq 0$, then we write $x_1 = \dfrac{1}{\{x\}}$. Therefore

$$x = \lfloor x \rfloor + \frac{1}{x_1} \text{ with } x_1 > 1.$$

If $x_1 \in \mathbb{Z}$, then this is the end of the algorithm.

If $x_1 \notin \mathbb{Z}$, then we write $x_2 = \dfrac{1}{\{x_1\}}$. Therefore,

$$x = \lfloor x \rfloor + \frac{1}{\lfloor x_1 \rfloor + \dfrac{1}{x_2}} \text{ with } x_2 > 1.$$

Set $a_0 = \lfloor x \rfloor$ and $a_i = \lfloor x_i \rfloor$ for $i \ge 1$.

$$x = \lfloor x \rfloor + \frac{1}{\lfloor x_1 \rfloor + \dfrac{1}{\lfloor x_2 \rfloor + \dfrac{1}{\ldots}}} = a_0 + \frac{1}{a_1 + \dfrac{1}{a_2 + \dfrac{1}{\ldots}}}$$

Consequently, $x = [a_0; a_1, a_2, \ldots]$. The algorithm finishes after finitely many steps if and only if x is rational.

Example 2.12. Let $x = \dfrac{24}{7}$. Then $x = 3 + \dfrac{3}{7}$ i.e. $a_0 = 3$ and $\{x\} = \dfrac{3}{7}$.

$x_1 = \dfrac{1}{\{x\}} = \dfrac{7}{3} = 2 + \dfrac{1}{3}$, so $a_1 = 2$ and $\{x_2\} = \dfrac{1}{3}$.

$x_3 = \dfrac{1}{\{x_2\}} = \dfrac{3}{1}$, so $a_2 = 3$ and $\{x_3\} = 0$.

Therefore, $x = \dfrac{24}{7} = [3; 2, 3]$.

Definition 2.13. (Burton, 1992) An *infinite continued fraction* is an expression of the following form

$$a_0 + \cfrac{1}{a_1 + \cfrac{1}{a_2 + \cfrac{1}{a_3 + \ddots}}}.$$

where $a_0, a_1, a_2, a_3, \ldots$ are real numbers with $a_1, a_2, \ldots, a_n$ positive and $a_0 \geq 0$ and it is denoted by $[a_0; a_1, a_2, \ldots, a_n, \ldots]$. If the real numbers $a_0, a_1, a_2, \ldots, a_n$ are all integers, then the continued fraction is called *simple*.

Theorem 2.14. (Rosen, 1992) Let $a_0, a_1, a_2, \ldots$ be an infinite sequence of integers with $a_1, a_2, \ldots$ positive, and let $C_k = [a_0; a_1, a_2, \ldots, a_k]$. Then, the convergents C_k tend to a limit α, i.e. $\lim_{k \to \infty} C_k = \alpha$.

Definition 2.15. (Stein, 2008) *A periodic continued fraction* is a continued fraction of the form $[a_0; a_1, a_2, \ldots, a_n, \ldots]$ such that $a_n = a_{n+t}$ for some fixed positive integer t and all sufficiently large n. Such a minimal t is called as the *period of the continued fraction*.

If the continued fraction contains no initial non-periodic terms, then it is called *purely periodic*.

Theorem 2.16. (Koshy, 2007) Let $\alpha = x_0$ be an irrational number. Define the sequence $\{a_k\}_{k=0}^{\infty}$ of integers a_k recursively as follows:

$$a_k = \lfloor x_k \rfloor, \qquad x_{k+1} = \frac{1}{x_k - a_k}$$

where $k \geq 0$. Then $\alpha = [a_0; a_1, a_2, \ldots]$.

Continued fraction expansion can also be found in the above form if α is an irrational number. Let's show this on an example.

Example 2.17. Express $\alpha = \sqrt{19}$ as an infinite simple continued fraction.

$$a_0 = \lfloor x_0 \rfloor = \lfloor \sqrt{19} \rfloor = 4, \qquad x_1 = \frac{1}{x_0 - a_0} = \frac{1}{\sqrt{19} - 4} = \frac{\sqrt{19} + 4}{3}$$

$$a_1 = \lfloor x_1 \rfloor = 2, \qquad x_2 = \frac{1}{x_1 - a_1} = \frac{1}{\frac{\sqrt{19} + 4}{3} - 2} = \frac{\sqrt{19} + 2}{5}$$

$$a_2 = \lfloor x_2 \rfloor = 1, \qquad x_3 = \frac{1}{x_2 - a_2} = \frac{1}{\frac{\sqrt{19} + 2}{5} - 1} = \frac{\sqrt{19} + 3}{2}$$

$$a_3 = \lfloor x_3 \rfloor = 3, \qquad x_4 = \frac{1}{x_3 - a_3} = \frac{1}{\frac{\sqrt{19} + 3}{2} - 3} = \frac{\sqrt{19} + 3}{5}$$

$$a_4 = \lfloor x_4 \rfloor = 1, \qquad x_5 = \frac{1}{x_4 - a_4} = \frac{1}{\frac{\sqrt{19} + 3}{5} - 1} = \frac{\sqrt{19} + 2}{3}$$

$$a_5 = \lfloor x_5 \rfloor = 2, \qquad x_6 = \frac{1}{x_5 - a_5} = \frac{1}{\frac{\sqrt{19}+2}{3} - 2} = \sqrt{19} + 4$$

$$a_6 = \lfloor x_6 \rfloor = 8, \qquad x_7 = \frac{1}{x_6 - a_6} = \frac{1}{\sqrt{19} + 4 - 8} = \frac{\sqrt{19}+4}{3} = x_1$$

As it can be seen that $x_7 = x_1$. So, the pattern continues. Thus,

$$\sqrt{19} = [4; 2,1,3,1,2,8,2,1,3,1,2,8,\ldots] = \left[4; \overline{2,1,3,1,2,8}\right].$$

As can be seen, every irrational number can be represented by an infinite simple continued fraction (Koshy, 2007; Robbins, 1993).

Example 2.18. Express the purely periodic continued fraction $\alpha = \left[\overline{2;1}\right]$ in the form $a + b\sqrt{d}$, where $a, b \in \mathbb{Q}$ and d is a square-free integer greater than 1.

$$\left[\overline{2;1}\right] = 2 + \cfrac{1}{1 + \cfrac{1}{2 + \cfrac{1}{1 + \cfrac{1}{2 + \cdots}}}}$$

Since $\alpha = \left[\overline{2;1}\right]$, it can be written

$$\alpha = 2 + \frac{1}{1 + \frac{1}{\alpha}} = \frac{3\alpha + 2}{\alpha + 1}.$$

That is, $\alpha^2 - 2\alpha - 2 = 0$, so $\alpha = 1 + \sqrt{3}$.

Every purely periodic continued fraction is an infinite continued fraction. As can be seen from the example, the value of an infinite continued fraction is an irrational number. This explains the following theorem.

Theorem 2.19. (Burton, 1992) The value of any infinite continued fraction is an irrational number.

Theorem 2.20. (Mollin, 2008) If $C_k = \frac{p_k}{q_k}$, for $k \in \mathbb{N}$, is the *kth convergent* of an irrational number α, then the following holds

$$\left| \alpha - \frac{p_k}{q_k} \right| < \frac{1}{q_k^2}.$$

For example, if $\sqrt{41} = \left[6; \overline{2,2,12}\right]$, it is obvious that $C_5 = \frac{p_5}{q_5} = \frac{2049}{320}$. So, $\left|\sqrt{41} - C_5\right| < \frac{1}{q_5^2}$, where C_5 is the *5th convergent* in the infinite continued fraction representation of $\sqrt{41}$.

3. Pell's Equation

In the literature, there are different methods for solving Pell's equation such as the Lagrange-Matthews-Mollin algorithm, the cyclic method, Lagrange's system of reductions, use of binary quadratic forms, etc. Here it will be explained how to solve Pell's equation using continued fractions.

Definition 3.1. (Robbins, 1993) The quadratic Diophantine equation of the form $x^2 - Dy^2 = N$, where D is a positive non-square integer and N is a non-zero integer, unknowns x and y are positive integers, is called as *generalized Pell's equation*. If $N = 1$, i.e. $x^2 - Dy^2 = 1$, then the form is called as *Pell's equation*. If $N = -1$, then the equation $x^2 - Dy^2 = -1$ is called as *associated Pell's equation (negative Pell's equation)*.

The *trivial solution* of Pell equation is $x = 1$, $y = 0$. There is a minimal solution to $x^2 - Dy^2 = \pm 1$ in positive integers which is greater than 1 is called as the *fundamental solution* of this equation.

Theorem 3.2. (Burton, 2011) If p, q is a positive solution of $x^2 - Dy^2 = 1$, then $\frac{p}{q}$ is a convergent of the continued fraction expansion of $\sqrt{D}$.

Theorem 3.3. (Rosen, 1992) Let (x_1, y_1) be the fundamental solution of the equation $x^2 - Dy^2 = 1$, where D is a positive integer that is not a perfect square. Then, all positive solutions (x_n, y_n) are given by

$$x_n + y_n\sqrt{D} = \left(x_1 + y_1\sqrt{D}\right)^n$$

for $n = 1, 2, 3, \ldots$.

The next theorem will present several important tools for solving the Pell's equation.

Theorem 3.4. (Robbins, 1993) Let D be a positive non-square integer. Let t be the length of the period of the continued fraction expansion of $\sqrt{D}$. Then, Pell's equation $x^2 - Dy^2 = 1$ has infinitely many solutions, all are given as follows:

a. If t is even, then $x_n = p_{nt-1}$, $y_n = q_{nt-1}$ for $n = 0, 1, 2, 3, \ldots$

b. If t is odd, then $x_n = p_{2nt-1}$, $y_n = q_{2nt-1}$ for $n = 0, 1, 2, 3, \ldots$.

If the negative Pell equation $x^2 - Dy^2 = -1$ is examined, the following holds:

c. If t is even, then the equation $x^2 - Dy^2 = -1$ has no solutions.

d. If t is odd, then the equation $x^2 - Dy^2 = -1$ has infinitely many solutions, all given by $x_n = p_{nt-1}$, $y_n = q_{nt-1}$, where $n = 1, 3, 5, \ldots$.

Theorem 3.5. (Andreescu & Andrica, 2015) Let $p \geq 3$ be a prime. The negative Pell's equation $x^2 - Dy^2 = -1$ is solvable in positive integers if and only if $p \equiv 1 \pmod 4$.

Example 3.6. Solve the Pell's equation $x^2 - 63y^2 = 1$.

The solution depends on the continued fraction expansion of $\sqrt{63}$.

$$a_0 = \lfloor x_0 \rfloor = \lfloor \sqrt{63} \rfloor = 7, \qquad x_1 = \frac{1}{x_0 - a_0} = \frac{1}{\sqrt{63} - 7} = \frac{\sqrt{63} + 7}{14}$$

$$a_1 = \lfloor x_1 \rfloor = 1, \qquad x_2 = \frac{1}{x_1 - a_1} = \frac{1}{\frac{\sqrt{63} + 7}{14} - 1} = \sqrt{63} + 7$$

$$a_2 = \lfloor x_2 \rfloor = 14, \qquad x_3 = \frac{1}{x_2 - a_2} = \frac{1}{\sqrt{63} + 7 - 14} = \frac{\sqrt{63} + 7}{14} = x_1$$

As it can be seen that $x_3 = x_1$. So, the pattern continues. Thus,

$$\sqrt{63} = [7; 1, 14, 1, 14, 1, 14, \ldots] = \left[7; \overline{1,14}\right].$$

The period length of the continued fraction $\sqrt{63}$ is 2, that is, even. $(p_1, q_1) = (8,1)$ i.e. fundamental solution of the Pell's Equation $x^2 - 63y^2 = 1$ is $(x_1, y_1) = (8,1)$.

All positive integer solutions of the Pell's Equation $x^2 - 63y^2 = 1$ are given by

$$x_n + y_n\sqrt{D} = \left(8 + \sqrt{63}\right)^n$$

for $n = 1, 2, 3, \ldots$.

Example 3.7. Solve the Pell's equation $x^2 - 98y^2 = 1$.

The solution depends on the continued fraction expansion of $\sqrt{98}$.

$$a_0 = \lfloor x_0 \rfloor = \lfloor \sqrt{98} \rfloor = 9, \qquad x_1 = \frac{1}{x_0 - a_0} = \frac{1}{\sqrt{98} - 9} = \frac{\sqrt{98} + 9}{17}$$

$$a_1 = \lfloor x_1 \rfloor = 1, \qquad x_2 = \frac{1}{x_1 - a_1} = \frac{1}{\frac{\sqrt{98} + 9}{17} - 1} = \frac{\sqrt{98} + 8}{2}$$

$$a_2 = \lfloor x_2 \rfloor = 8, \qquad x_3 = \frac{1}{x_2 - a_2} = \frac{1}{\frac{\sqrt{98} + 8}{2} - 8} = \frac{\sqrt{98} + 8}{17}$$

$$a_3 = \lfloor x_3 \rfloor = 1, \qquad x_4 = \frac{1}{x_3 - a_3} = \frac{1}{\frac{\sqrt{98} + 8}{17} - 1} = \sqrt{98} + 9$$

$$a_4 = \lfloor x_4 \rfloor = 18, \qquad x_5 = \frac{1}{x_4 - a_4} = \frac{1}{\sqrt{98} + 9 - 18} = \frac{\sqrt{98} + 9}{17} = x_1$$

As it can be seen that $x_5 = x_1$. So, the pattern continues. Therefore,

$$\sqrt{98} = [9;1,8,1,18,1,8,1,18,\ldots] = \left[9;\overline{1,8,1,18}\right] .$$

The period length of the continued fraction $\sqrt{98}$ is $t = 4$, that is, even. $(p_3, q_3) = (99,10)$

i.e. fundamental solution of the Pell's Equation $x^2 - 98y^2 = 1$ is $(x_1, y_1) = (99,10)$.

All positive integer solutions of the Pell's Equation $x^2 - 98y^2 = 1$ are given by

$$x_n + y_n\sqrt{D} = \left(99 + 10\sqrt{98}\right)^n$$

for $n = 1, 2, 3, \ldots .$

Let's continue with the more general Pell's equations.

Application 3.8. Let $a \in \mathbb{N}$. Solve the Pell's equation $x^2 - \left(a^2 + 1\right)y^2 = 1$ for $a \geq 1$.

Continued fractions crop up a way to analyze solutions to Pell's equation. In this equation, the solution depends on the continued fraction expansion of $\sqrt{a^2 + 1}$. It can be seen that the continued fraction expansion of $\sqrt{a^2 + 1}$ is $\left[a;\overline{2a}\right]$ (Robbins, 1993, p. 225).

Let's find the continued fraction expansion ourselves.

$$\begin{aligned}\sqrt{a^2 + 1} &= a + \left(\sqrt{a^2 + 1} - a\right) \\ &= a + \frac{1}{\sqrt{a^2 + 1} + a} \\ &= a + \frac{1}{2a + \left(\sqrt{a^2 + 1} - a\right)}.\end{aligned}$$

Therefore, $\sqrt{a^2 + 1}$ has continued fraction representation $\sqrt{a^2 + 1} = \left[a;\overline{2a}\right]$. So, $t = 1$.

That is, the length of the period of the continued fraction expansion of $\sqrt{a^2 + 1}$ is odd.

So $(x_1, y_1) = \dfrac{p_1}{q_1} = \dfrac{2a^2 + 1}{2a}$ is the fundamental solution to the Pell's equation

$x^2 - \left(a^2 + 1\right)y^2 = 1$. Moreover, the positive solution set S to Pell's equation is as follows:

$$S = \left\{(x_k, y_k) \in \mathbb{Z}^2 : \left(x_k + y_k\sqrt{a^2 + 1}\right) = \left(2a^2 + 1 + 2a\sqrt{a^2 + 1}\right)^k\right\}_{k=1}^{\infty} .$$

Application 3.9. Let $a \in \mathbb{N}$. Solve the Pell's equation $x^2 - \left(a^2 + 2\right)y^2 = 1$.

Since all small values of $x^2-\left(a^2+2\right)y^2$ arise from convergents, if $x^2-\left(a^2+2\right)y^2=1$ is to have a solution it must arise from a convergent to $\sqrt{a^2+2}$. Therefore, it should be found a continued fraction representation of $\sqrt{a^2+2}$. It can be seen that the continued fraction expansion of $\sqrt{a^2+2}$ is $\left[a;\overline{a,2a}\right]$ (Robbins, 1993, p. 225).

Let's find the continued fraction expansion ourselves.

$$\sqrt{a^2+2}=a+\left(\sqrt{a^2+2}-a\right)$$

$$=a+\frac{1}{\frac{\sqrt{a^2+2}+a}{2}}$$

$$=a+\frac{1}{a+\frac{\sqrt{a^2+2}-a}{2}}$$

$$=a+\frac{1}{a+\frac{1}{\sqrt{a^2+2}+a}}$$

$$=a+\frac{1}{a+\frac{1}{2a+\left(\sqrt{a^2+2}-a\right)}}$$

Therefore, the continued fraction expansion of $\sqrt{a^2+2}$ is $\left[a;\overline{a,2a}\right]$. So, the length of the period of the continued fraction expansion of $\sqrt{a^2+2}$ is $t=2$. Then, the fundamental solution of the equation $x^2-\left(a^2+2\right)y^2=1$ is $\left(x_1,y_1\right)=\frac{p_1}{q_1}=\frac{a^2+1}{a}$. Moreover, the positive solution set S to Pell's equation is

$$S=\left\{\left(x_k,y_k\right)\in\mathbb{Z}^2:\left(x_k+y_k\sqrt{a^2+2}\right)=\left(a^2+1+a\sqrt{a^2+2}\right)^k\right\}_{k=1}^{\infty}.$$

Application 3.10. Let $a\in\mathbb{N}$. Solve the equations $x^2-\left(9a^2+3\right)y^2=1$ and $x^2-\left(9a^2+3\right)y^2=-1$.

Continued fractions provide a way to analyze solutions to the Pell's equation $x^2-\left(9a^2+3\right)y^2=1$. In this equation, the solution depends on the continued fraction expansion of $\sqrt{9a^2+3}$. It can be seen that the continued fraction expansion of $\sqrt{9a^2+3}$ is $\left[3a;\overline{2a,6a}\right]$ (Robbins, 1993, p. 226).

Let's find the continued fraction expansion ourselves.

$$\sqrt{9a^2+3}=3a+\left(\sqrt{9a^2+3}-3a\right)$$

$$= 3a + \cfrac{1}{\cfrac{\sqrt{9a^2+3}+3a}{3}}$$

$$= 3a + \cfrac{1}{2a + \cfrac{\sqrt{9a^2+3}-3a}{3}}$$

$$= 3a + \cfrac{1}{2a + \cfrac{1}{\sqrt{9a^2+3}+3a}}$$

$$= 3a + \cfrac{1}{2a + \cfrac{1}{6a + \left(\sqrt{9a^2+3}-3a\right)}}.$$

Therefore, $\sqrt{9a^2+3} = \left[3a; \overline{2a, 6a}\right]$. So, $t = 2$. That is, the length of the period of the continued fraction expansion of $\sqrt{9a^2+3}$ is even. So $(x_1, y_1) = \dfrac{p_1}{q_1} = \dfrac{6a^2+1}{2a}$ is the fundamental solution to the Pell's equation $x^2 - \left(9a^2+3\right)y^2 = 1$. Moreover, the positive solution set S to Pell's equation is as follows:

$$S = \left\{ (x_k, y_k) \in \mathbb{Z}^2 : \left(x_k + y_k\sqrt{9a^2+3}\right) = \left(6a^2+1+2a\sqrt{9a^2+3}\right)^k \right\}_{k=1}^{\infty}.$$

The length of the period of the continued fraction expansion of $\sqrt{9a^2+3}$ is even. Therefore, the equation $x^2 - \left(9a^2+3\right)y^2 = -1$ has no solutions.

Solutions of different Pell's equations can be found in the literature. For example, Peker and Senay (2015), found continued fraction expansion of $\sqrt{D}$ when $D = a^2 + 2a$ where a is positive integer. They solved the Pell's equation $x^2 - \left(a^2+2a\right)y^2 = N$ when $N \in \{\pm 1, \pm 4\}$ and they formulated nth solution via the generalized Fibonacci and Lucas sequences. Keskin and Güney Duman (2019), considered continued fraction expansion of $\sqrt{D}$ when $D = k^2 \pm 4$ and $D = k^2 \pm 1$. They solved the Pell's equation $x^2 - Dy^2 = N$ when $N \in \{\pm 1, \pm 4\}$. Raza and Malik (2018) extended all the results of the various papers about the Pell's equation $x^2 - Dy^2 = N$ when $N \in \{\pm 1, \pm 4\}$.

4. Conclusion

It has been presented a brief introduction to the theory of continued fractions. Continued fraction types are mentioned. Continued fractions have been introduced and have been applied these properties to solve Pell's equation. The Continued Fraction Algorithm is explained. It is stated that the continued fraction algorithm finishes after finitely many

steps if and only if x is rational.

It was mentioned that how to determine rational and irrational numbers using continued fraction representations. Every nonzero rational number can be represented by a finite simple continued fraction and the value of any finite simple continued fraction $[a_0;a_1,a_2,\ldots,a_n]$ is always a rational number. Every irrational number can be represented by an infinite simple continued fraction and the value of any infinite simple continued fraction $[a_0;a_1,a_2,\ldots,a_n,\ldots]$ represents an irrational number.

The quadratic Diophantine equation of the form $x^2-Dy^2=1$, where D is a positive integer which is not a perfect square, unknowns x and y are positive integers, is called *Pell's equation*. In the literature, there are different methods for solving Pell's equation. Here, it was explained how to solve Pell's equation using continued fractions. The solution depends on the continued fraction expansion of $\sqrt{D}$. The fundamental solution of Pell's equation is found by using convergents of $\sqrt{D}$. All solutions of Pell's equation can be reached using the fundamental solution. The complete set of solutions to Pell's equation is the infinite cyclic group generated by the fundamental solution.

Finally, applications have been made on various Pell's equations by determining continued fractions for square roots of positive integers initially and after that applying their results to solve Pell's equation.

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To Cite This Chapter

Peker, B. (2021). Continued fractions and Pell's equation. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 127–142). ISRES Publishing

An Introduction to Pade Approximation

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The Pade approach has emerged based on continued fractions and the Euclidean algorithm, and its history dates back to ancient times. The Pade approach continues to attract the attention of researchers with the development of high-speed computers and the application of the Pade approach to numerical analysis, fluid mechanics, theoretical physics, signal processing, cryptography, engineering and other disciplines (Andrianov & Shatrov, 2020; Brezinski, 1990; Wuytack, 2006). That's why it's still popular.

Pade approximations are widely used in numerical solutions of differential equations, analytical continuation problems of power series, orthogonal polynomials, rational approximations, Gaussian quadrature, convergence acceleration, computation of special functions, finding singularity, zero points, roots and poles of power series (Andrianov & Shatrov, 2020; Brezinski, 1990; Wuytack, 2006).

Most solutions of ordinary or partial differential equations are of power series forms due the result of numerical solutions of the associated differential equations upon approximation or truncation. These power series are often approximated by polynomials, nevertheless, polynomials tend to exhibit oscillations that may produce error bounds, also, the singularities of polynomials cannot be observed clearly in a finite plane (Peker et al., 2011; Wazwaz, 2002; Wazwaz, 2009). Therefore, Pade approximants yield meromorphic continuations of functions defined by power series and can be used even in cases where analytic continuations are inapplicable. If a Pade approximation converges to the given function, then roots of the denominator tend to points of singularities. One-point Pade approximants give possibilities to improve convergence of series (Gonchar, 1986; Litvinov, 1994; Litvinov, 2003; Suetin, 2002; Suetin, 2004).

A Pade approximant of a function is a rational function of two polynomial functions where the coefficients of the numerator and the denominator depend on the coefficients of the concerned function (Baker & Graves-Moris, 1996; Boyd, 1979; Wazwaz, 2009).

Let f be a function analytic on a neighborhood of $x=0$ and let n and m be non-negative integers. In the literature (Baker & Graves-Moris, 1996; Brezinski, 1990), Pade approximant of f with order (n,m) where $n,m\in\mathbb{N}\cup\{0\}$, denoted by $f_{[n/m]}(x)$, is defined as the unique rational function

$$f_{[n/m]}(x)=\frac{P_n(x)}{Q_m(x)}$$

where $\deg P_n(x)\le n$, $\deg Q_m(x)\le m$ and $Q_m(x)\not\equiv 0$.

Suppose that the power series of f is given as

$$f(x)=\sum_{k=0}^{\infty}c_k x^k$$

where c_k's are non-negative. For simplicity, we assume that the power series is about zero. Now, the principle is that the formal series,

$$Q_m(x)f_{[n/m]}(x)-P_n(x)$$

coincides with f as far as possible. That is, our aim is to make the maximum error as small as possible (Mathews & Fink, 2004). In other words, it is required that

$$Q_m(x)f_{[n/m]}(x)-P_n(x)=O\left[x^{n+m+1}\right]$$

where $O\left[x^t\right]$ denotes for some power series of the form $\sum_{k=t}^{\infty}c_k x^k$.

Pade approximants can be written as the following expression (Baker & Graves-Morris, 1996)

$$f_{[n/m]}(x)=\frac{p_0+p_1x+p_2x^2+\ldots+p_nx^n}{q_0+q_1x+q_2x^2+\ldots+q_mx^m}$$

where q_0 can be taken 1 so that $Q_m(x)\not\equiv 0$. Additionally, numerator and denominator have no common factors (Wazwaz, 2002).

By using the last equation, the coefficients of polynomials $P_n(x)$ and $Q_m(x)$ can be determined as follows:

$$P_n(x)=p_0+p_1x+p_2x^2+\ldots+p_nx^n,$$

$$Q_m(x)=q_0+q_1x+q_2x^2+\ldots+q_mx^m.$$

There are $n+1$ numerator coefficients and $m+1$ denominator coefficients. Thus, $n+m+1$ unknown coefficients in all. Since $f(x)=\sum_{k=0}^{\infty}c_k x^k$, the series can be written as

$$f(x)=\sum_{k=0}^{\infty}c_k x^k=\frac{p_0+p_1x+p_2x^2+\ldots+p_nx^n}{1+q_1x+q_2x^2+\ldots+q_mx^m}+O\left(x^{n+m+1}\right).$$

By cross-multiplying last equation, one can find that

$$\left(c_0+c_1x+c_2x^2+c_3x^3+c_4x^4+\ldots\right)\left(1+q_1x+q_2x^2+\ldots+q_mx^m\right)$$

$$=\left(p_0+p_1x+p_2x^2+\ldots+p_nx^n\right)+O\left(x^{n+m+1}\right)$$

The following set of equations are deduced from this equation:

$$\begin{aligned} c_0 &= p_0 \\ c_1 + c_0 q_1 &= p_1 \\ c_2 + c_1 q_1 + c_0 q_2 &= p_2 \\ \vdots & \vdots \\ c_n + c_{n-1} q_1 + \ldots + c_0 q_m &= p_n \end{aligned}$$

and

$$\begin{aligned} c_{n+1} + c_n\, q_1 + \ldots + c_{n-m+1}\, q_m &= 0 \\ c_{n+2} + c_{n+1}\, q_1 + \ldots + c_{n-m+2}\, q_m &= 0 \\ \vdots & \vdots \\ c_{n+m} + c_{n+m-1}\, q_1 + \ldots + c_n\, q_m &= 0 \end{aligned}$$

where $c_n = 0$ for $n < 0$ and $q_j = 0$ for $j > m$.

The solution, that is $f_{[n/m]}(x)$, can be written in the following form

$$f_{[n/m]}(x) = \frac{\begin{vmatrix} c_{n-m+1} & c_{n-m+2} & \cdots & c_{n+1} \\ \vdots & \vdots & & \vdots \\ c_n & c_{n+1} & \cdots & c_{n+m} \\ \sum_{j=m}^{n} c_{j-m}\, x^j & \sum_{j=m-1}^{n} c_{j-m+1}\, x^j & \cdots & \sum_{j=0}^{n} c_j\, x^j \end{vmatrix}}{\begin{vmatrix} c_{n-m+1} & c_{n-m+2} & \cdots & c_{n+1} \\ \vdots & \vdots & & \vdots \\ c_n & c_{n+1} & \cdots & c_{n+m} \\ x^m & x^{m-1} & \cdots & 1 \end{vmatrix}},$$

(Baker & Graves - Moris, 1996; Boyd, 1979; Wazwaz, 2009**).**

Example 1: Find the Pade approximation $f_{[2/2]}(x)$ for $f(x) = e^x$.

Solution:

Maclaurin series expansion of the given function is as follows:

$$f(x) = 1 + x + \frac{x^2}{2} + \frac{x^3}{6} + \frac{x^4}{24} + O\left(x^5\right).$$

Since $m = n = 2$,

$$P_2(x) = p_0 + p_1 x + p_2 x^2 \quad \text{and} \quad Q_2(x) = q_0 + q_1 x + q_2 x^2 = 1 + q_1 x + q_2 x^2.$$

$$f(x) = \frac{P_2(x)}{Q_2(x)} \Rightarrow f(x)\, Q_2(x) - P_2(x) = 0$$

$$\Rightarrow \left(1 + x + \frac{x^2}{2} + \frac{x^3}{6} + \frac{x^4}{24} + O\left(x^5\right)\right)\left(1 + q_1 x + q_2 x^2\right) - \left(p_0 + p_1 x + p_2 x^2\right) = 0$$

$$\Rightarrow (1-p_0)+(1-p_1+q_1)x+\left(\frac{1}{2}-p_2+q_1+q_2\right)x^2+\left(\frac{1}{6}+\frac{q_1}{2}+q_2\right)x^3$$

$$+\left(\frac{1}{24}+\frac{q_1}{6}+\frac{q_2}{2}\right)x^4+O\left(x^5\right)=0$$

By equating to zero both sides of the last equation, the following equations find:

$1-p_0=0$,

$1-p_1+q_1=0$,

$\frac{1}{2}-p_2+q_1+q_2=0$,

$\frac{1}{6}+\frac{q_1}{2}+q_2=0$,

$\frac{1}{24}+\frac{q_1}{6}+\frac{q_2}{2}=0$.

Solving these equations simultaneously, coefficients of $P_2(x)$ and $Q_2(x)$ can be found as follows:

$p_0=1$,

$p_1=\frac{1}{2}$,

$p_2=\frac{1}{12}$,

$q_1=-\frac{1}{2}$,

$q_2=\frac{1}{12}$.

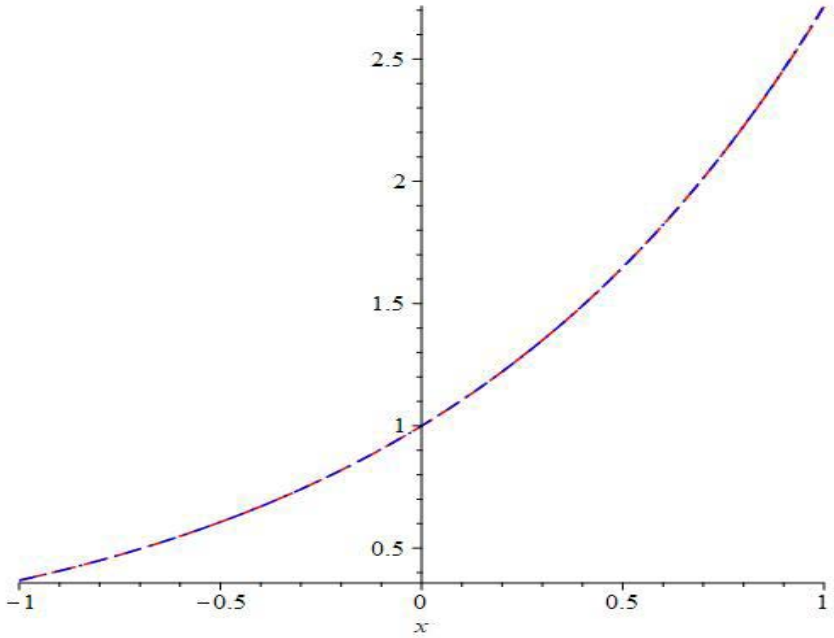
Therefore, $[2/2]$ Pade approximation of $f(x)=e^x$ is as follows:

$$f_{[2/2]}(x)=\frac{1+\frac{1}{2}x+\frac{1}{12}x^2}{1-\frac{1}{2}x+\frac{1}{12}x^2}=\frac{12+6x+x^2}{12-6x+x^2}.$$

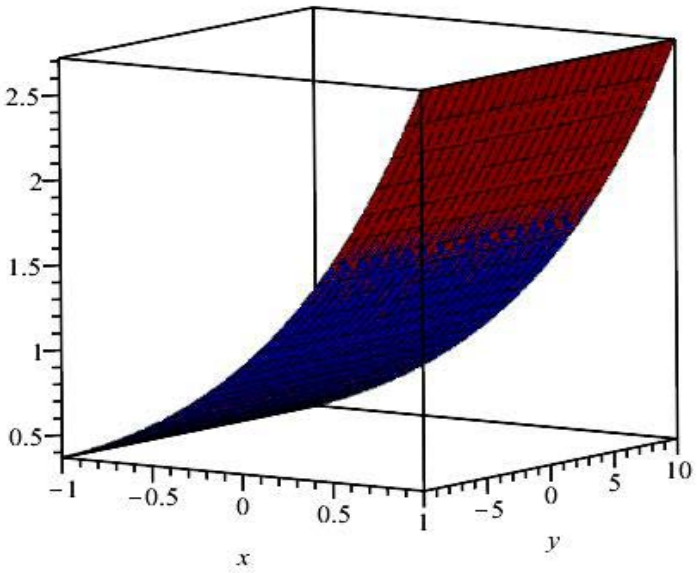
By a similar manner, one can easily find the following Pade approximation table of $f(x)=e^x$ when $m=0,1,2,3$ and $n=0,1,2,3$.

n/m	0	1	2	3
0	$\frac{1}{1}$	$\frac{1}{1-x}$	$\frac{1}{1-x+\frac{1}{2}x^2}$	$\frac{1}{1-x+\frac{1}{2}x^2-\frac{1}{6}x^3}$
1	$\frac{1+x}{1}$	$\frac{1+\frac{1}{2}x}{1-\frac{1}{2}x}$	$\frac{1+\frac{1}{3}x}{1-\frac{2}{3}x+\frac{1}{6}x^2}$	$\frac{1+\frac{1}{4}x}{1-\frac{3}{4}x+\frac{1}{4}x^2-\frac{1}{24}x^3}$
2	$\frac{1+x+\frac{1}{2}x^2}{1}$	$\frac{1+\frac{2}{3}x+\frac{1}{6}x^2}{1-\frac{1}{3}x}$	$\frac{1+\frac{1}{2}x+\frac{1}{12}x^2}{1-\frac{1}{2}x+\frac{1}{12}x^2}$	$\frac{1+\frac{2}{5}x+\frac{1}{20}x^2}{1-\frac{3}{5}x+\frac{3}{20}x^2-\frac{1}{60}x^3}$
3	$\frac{1+x+\frac{1}{2}x^2+\frac{1}{6}x^3}{1}$	$\frac{1+\frac{3}{4}x+\frac{1}{4}x^2+\frac{1}{24}x^3}{1-\frac{1}{4}x}$	$\frac{1+\frac{3}{5}x+\frac{3}{20}x^2+\frac{1}{60}x^3}{1-\frac{2}{5}x+\frac{1}{20}x^2}$	$\frac{1+\frac{1}{2}x+\frac{1}{10}x^2+\frac{1}{120}x^3}{1-\frac{1}{2}x+\frac{1}{10}x^2-\frac{1}{120}x^3}$

The graph of the given function and its Pade approximation over the interval $[-1,1]$ can be drawn by using MAPLE as below:



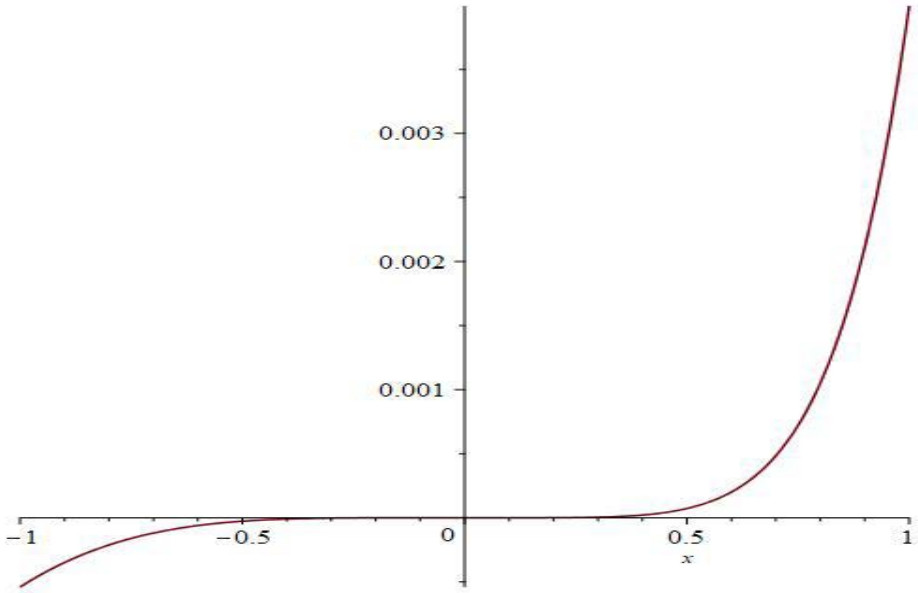
The three-dimensional graph of the given function and its Pade approximation over the interval $[-1,1]$ can be drawn by using MAPLE as follows:



The error between the given function and its Pade approximation is given by

$$f(x) - f_{[2/2]}(x) = e^x - \frac{12+6x+x^2}{12-6x+x^2} .$$

The graph of the error over the same interval can be plotted as follows:



The table given below shows the error over the same interval.

x	Error $\left(f(x)-f_{[2/2]}(x)\right)$
-1	-0.0005416114
-0.8	-0.0002123204
-0.6	-0.0000605444
-0.4	-0,0000096245
-0.2	-0.0000003649
0	0
0.2	0.000000544
0.4	0.000021420
0.6	0.000200992
0.8	0.001051132
1	0.003996114

It is easily seen from the table that the maximum error is

$$\left|f(x)-f_{[2/2]}(x)\right| \le 0.003996114\,.$$

Example 2: Find the Pade approximations $f_{[2/2]}(x)$, $f_{[3/3]}(x)$ and $f_{[4/4]}(x)$ for the function $f(x)=\tanh x$.

Solution:

Maclaurin series expansion of the given function is as follows:

$$f(x)=\tanh x = x-\frac{1}{3}x^3+\frac{2}{15}x^5-\frac{17}{315}x^7+O\left(x^8\right).$$

First of all, we will find $f_{[2/2]}(x)$. Since $m=n=2$,

$$P_2(x)=p_0+p_1x+p_2x^2 \quad \text{and} \quad Q_2(x)=q_0+q_1x+q_2x^2=1+q_1x+q_2x^2\,.$$

$$f(x)=\frac{P_2(x)}{Q_2(x)} \Rightarrow f(x)\,Q_2(x)-P_2(x)=0\,.$$

$$\Rightarrow\left(x-\frac{1}{3}x^3+\frac{2}{15}x^5-\frac{17}{315}x^7+O\left(x^8\right)\right)\left(1+q_1x+q_2x^2\right)-\left(p_0+p_1x+p_2x^2\right)=0$$

$$\Rightarrow(-p_0)+(1-p_1)x+(q_1-p_2)x^2+\left(q_2-\frac{1}{3}\right)x^3-\frac{q_1}{3}x^4+O\left(x^5\right)=0$$

By equating to zero both sides of the last equation, the following equations find:

$$-p_0=0$$

$$1-p_1=0$$

$$q_1-p_2=0$$

$$q_2 - \frac{1}{3} = 0$$

$$\frac{-q_1}{3} = 0$$

Solving these equations simultaneously, coefficients of $P_2(x)$ and $Q_2(x)$ can be found as follows:

$$p_0 = 0,\ p_1 = 1,\ p_2 = 0$$

$$q_1 = 0,\ q_2 = \frac{2}{5}.$$

Thus, $[2/2]$ Pade approximation of $f(x) = \tanh x$ is obtained as follows:

$$f_{[2/2]}(x) = \frac{x}{1+\frac{1}{3}x^2} = \frac{3x}{3+x^2} \quad .$$

Secondly, in order to find $f_{[3/3]}(x)$, since $m = n = 3$, we have $P_3(x) = p_0 + p_1x + p_2x^2 + p_3x^3$

and $Q_3(x) = q_0 + q_1x + q_2x^2 + q_3x^3 = 1 + q_1x + q_2x^2 + q_3x^3$.

$$f(x) = \frac{P_3(x)}{Q_3(x)} \Rightarrow f(x)\,Q_3(x) - P_3(x) = 0.$$

$$\Rightarrow \left(x - \frac{1}{3}x^3 + \frac{2}{15}x^5 - \frac{17}{315}x^7 + O\left(x^9\right)\right)\left(1 + q_1x + q_2x^2 + q_3x^3\right) - \left(p_0 + p_1x + p_2x^2 + p_3x^3\right) = 0$$

By a similar manner as above, coefficients of $P_3(x)$ and $Q_3(x)$ can be found as follows:

$$p_0 = 0,\ p_1 = 1,\ p_2 = 0,\ p_3 = \frac{1}{15}$$

$$q_1 = 0,\ q_2 = \frac{2}{5},\ q_3 = 0.$$

Thus, $[3/3]$ Pade approximation of $f(x) = \tanh x$ is obtained as follows:

$$f_{[3/3]}(x) = \frac{x + \frac{1}{15}x^3}{1+\frac{2}{5}x^2} = \frac{15x + x^3}{15 + 6x^2}.$$

Finally, $f_{[4/4]}(x)$ will be found as follows, since $m = n = 4$, we have

$$P_4(x) = p_0 + p_1x + p_2x^2 + p_3x^3 + p_4x^4$$

and $Q_3(x) = q_0 + q_1x + q_2x^2 + q_3x^3 + q_4x^4 = 1 + q_1x + q_2x^2 + q_3x^3 + q_4x^4$.

$$f(x) = \frac{P_4(x)}{Q_4(x)} \Rightarrow f(x)\,Q_4(x) - P_4(x) = 0.$$

$$\Rightarrow \left(x - \frac{1}{3}x^3 + \frac{2}{15}x^5 - \frac{17}{315}x^7 + O\left(x^9\right)\right)\left(1 + q_1x + q_2x^2 + q_3x^3 + q_4x^4\right) - \left(p_0 + p_1x + p_2x^2 + p_3x^3 + p_4x^4\right) = 0$$

By a similar manner as above two stages, coefficients of $P_4(x)$ and $Q_4(x)$ can be found as follows:

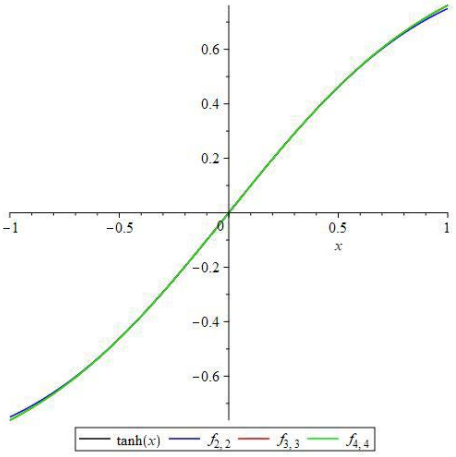
$$p_0 = 0,\ p_1 = 1,\ p_2 = 0,\ p_3 = \frac{2}{21},\ p_4 = 0$$

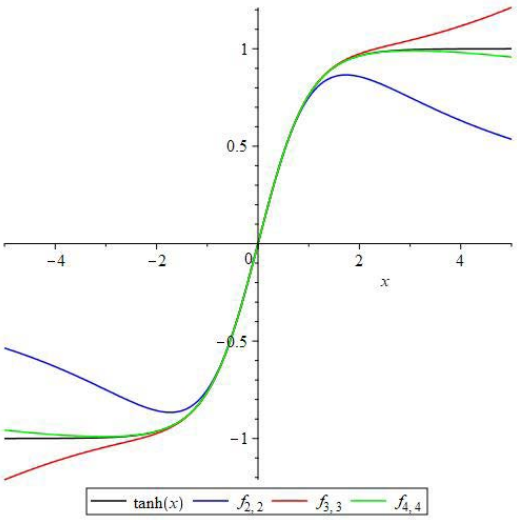
$$q_1 = 0,\ q_2 = \frac{3}{7},\ q_3 = 0,\ q_4 = \frac{1}{105}.$$

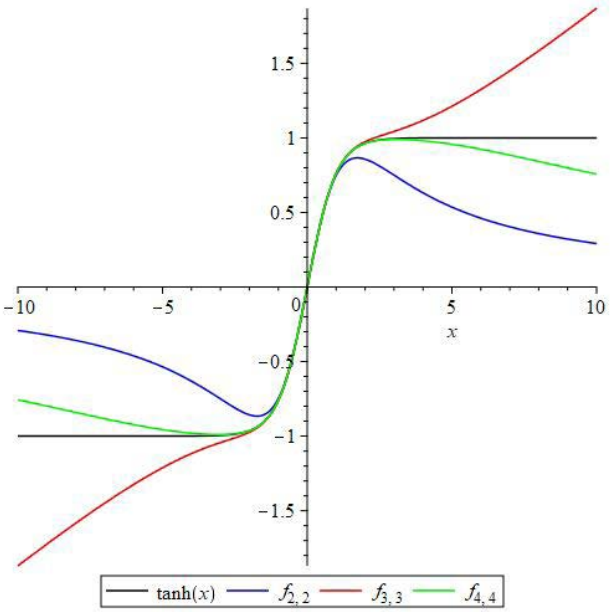
Hence, $[4/4]$ Pade approximation of $f(x) = \tanh x$ is obtained as follows:

$$f_{[4/4]}(x) = \frac{x + \frac{2}{21}x^3}{1 + \frac{3}{7}x^2 + \frac{1}{105}x^4} = \frac{105x + 10x^3}{105 + 45x^2 + x^4}.$$

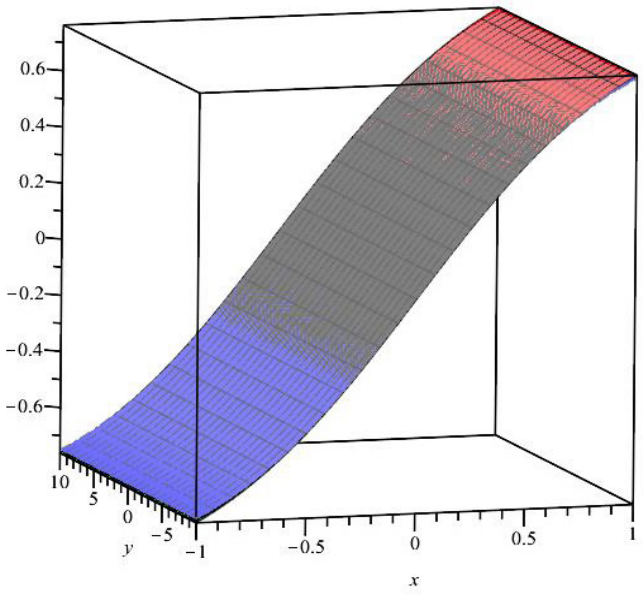
The graph of the given function and its Pade approximation over the intervals $[-1,1]$, $[-5,5]$ and $[-10,10]$ can be drawn by using MAPLE as below:

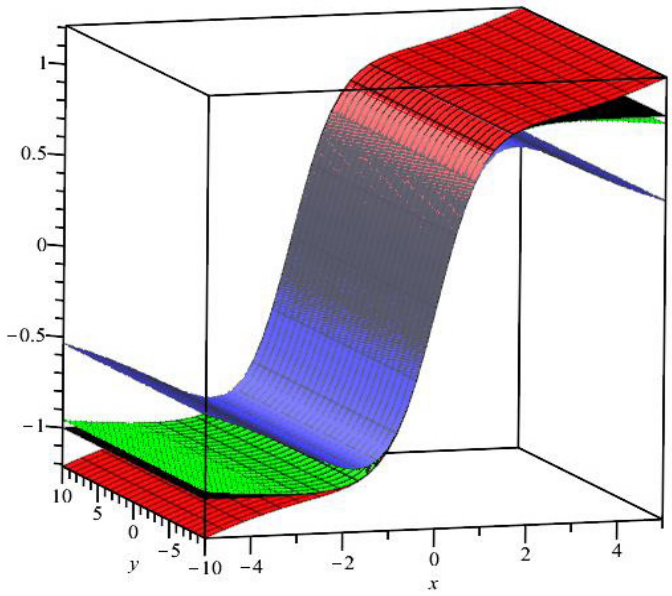


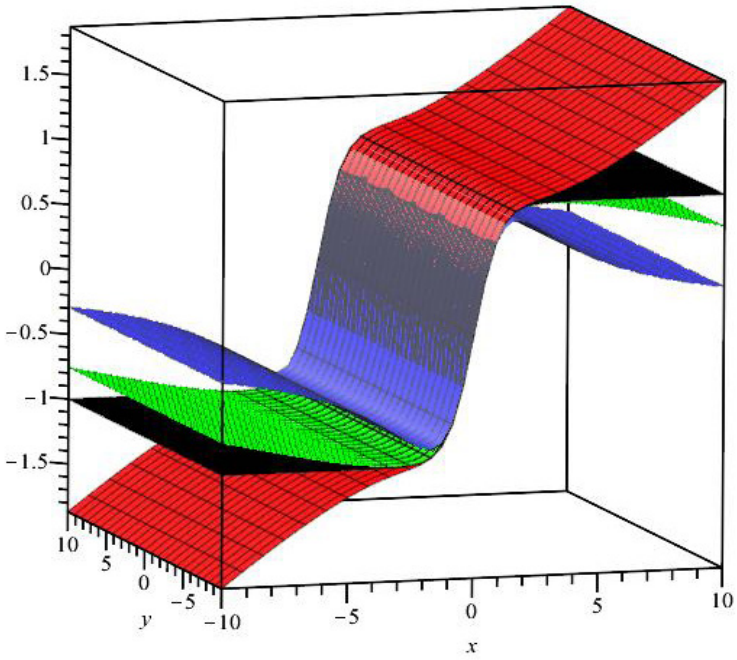




The three-dimensional graph of the given function and its Pade approximations over the intervals $[-1,1]$, $[-5,5]$ and $[-10,10]$ can be drawn by using MAPLE as follows:







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To Cite This Chapter

Peker, H. A. (2021). An introduction to Pade approximation . In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 143–155). ISRES Publishing

SECTION 4
CHEMISTRY

Synthesis of Triazole Compounds

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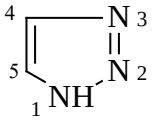
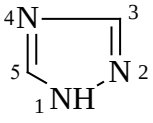
Synthesis of Triazole Compounds

Compounds containing three nitrogen atoms in a five-membered ring are called "Triazoles". Triazoles have two isomers. These are 1,2,3-triazole (v-triazole) and 1,2,4-triazole (sim-triazole) rings. Triazoles are generally resistant to reducers and oxidizers (Ikizler, 1996).



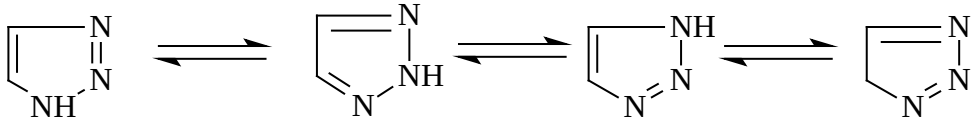
1,2,3-Triazole
(v-Trizole)



1,2,4-Triazole
(sim-Trizole)

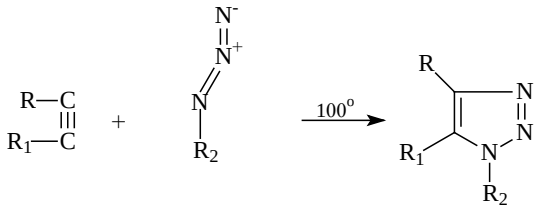
Synthesis of 1,2,3-Triazoles

The 1,2,3-triazole boiling point is 206°. The tautomeric forms of the 1,2,3-triazole ring are (Ikizler, 1996):



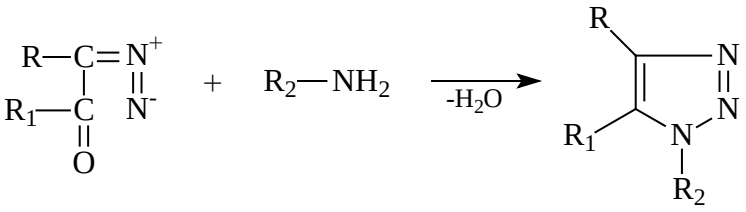
Some methods used to obtain 1,2,3-triazole and its derivatives (Aykut İkizler, 1996):

From Alkynes and Azides (Ikizler, 1996):

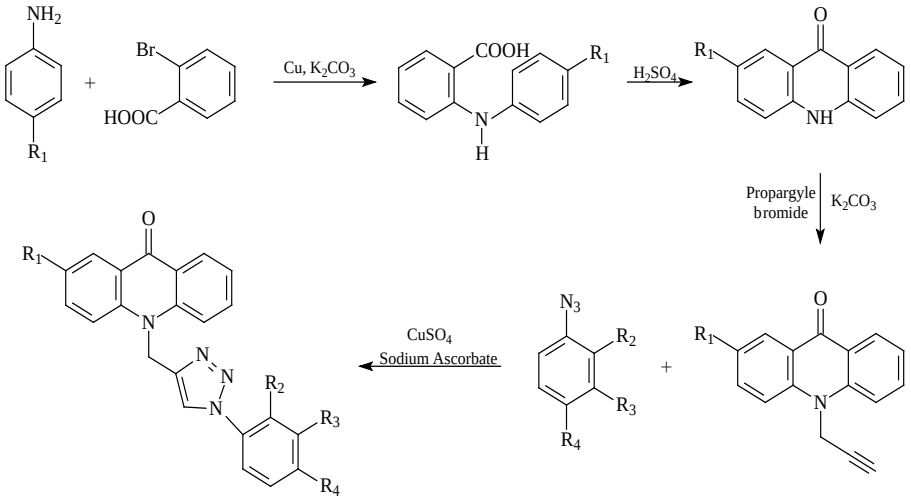


1,2,3-Triazole Derivative

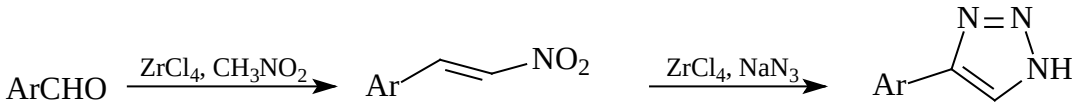
From Diazoketones (Ikizler, 1996):



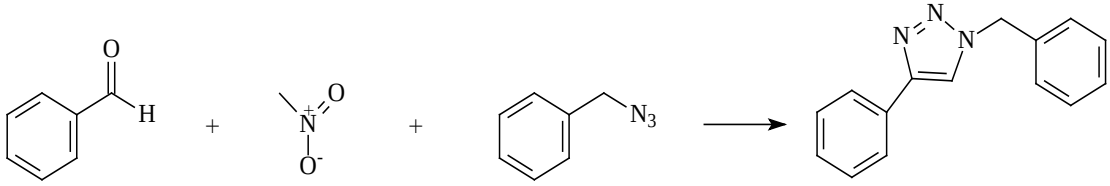
Synthesis of 1,2,3-triazole derivatives from acridone by the cycloaddition reaction between aromatic azides and *N*-propargyl acridones was obtained by the following reaction (Aarjane, Slassi, & Amine, 2021)



Vinyl nitrate is formed as a result of the reaction of the aldehyde compound with CH_3NO_2 in the presence of $ZrCl_4$. It was observed that this compound reacted with NaN_3 in the presence of $ZrCl_4$ at room temperature to form 1,2,3-triazole compound (Sridhar et al., 2017).

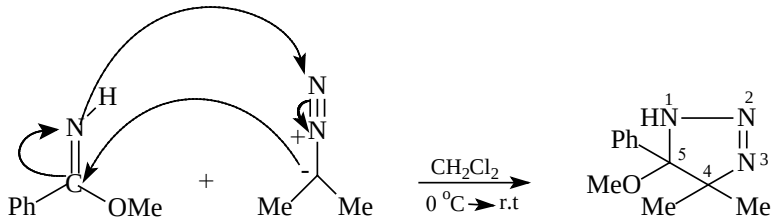


The 1,2,3-triazole triazole was obtained as a result of the reaction of aldehyde, nitromethane and benzyl azide under the catalysis of Fe_2O_3@MgO@ch.OAc in EtOH (Mohammadkhani & Heydari, 2021).

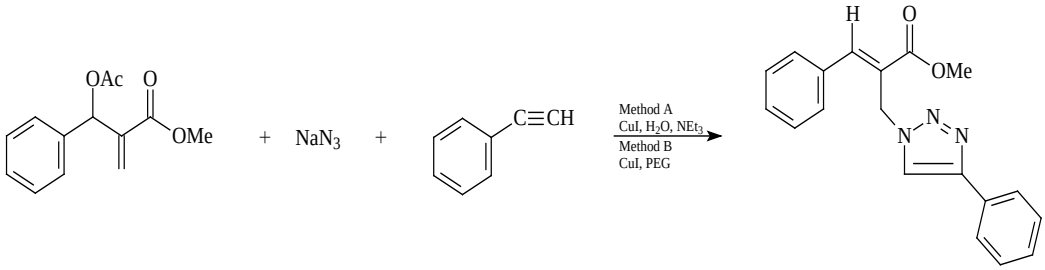


2-diazopropane reacts with methyl benzene carboximidoate in dichloromethane at

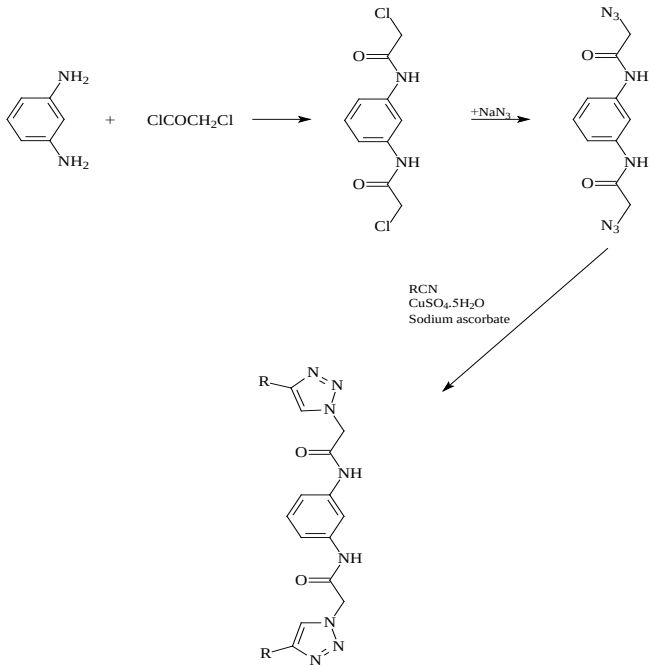
0°C, and after reaction 5-methoxy-4,4-dimethyl-5-phenyl-4,5-dihydro-1*H*-[1,2,3]-triazole occurs. This compound consists of regioselective 1,3-dipolar cycloaddition of 2-diazopropane to the imidate C=N bond (Hamdi et al., 2006).



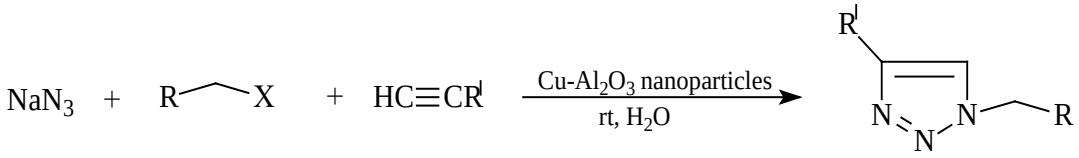
1,4-disubstituted 1,2,3-triazoles can be synthesized in one step by reacting Baylis-Hillman acetates, sodium azide, and terminal alkynes in water or poly(ethylene glycol) [PEG] (Sreedhar et al., 2006).



N,*N*'-(1,3-phenylene)bis(2-chloroacetamide) compound is formed as a result of the reaction of m-phenylenediamine with chloroacetyl chloride. As a result of the reaction of this compound with sodium azide, the compound *N*,*N*'-(1,3-phenylene)bis(2-azidoacetamide) is obtained. In the treatment of this compound with alkyne compounds and sodium ascorbate under the catalysis of $CuSO_4.5H_2O$ in DMF, bis-1,2,3-triazole compound is formed (Nural et al., 2021).

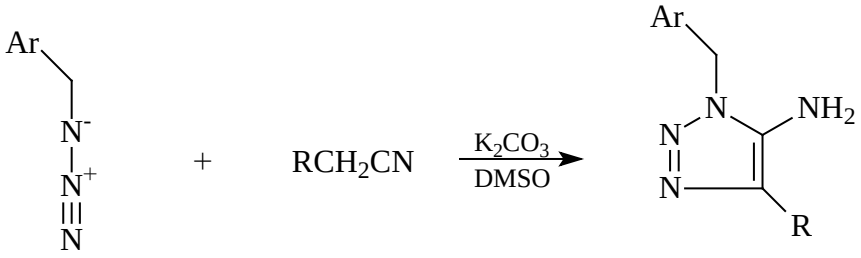


1,2,3-triazoles are produced in one-pot using Cu-Al_2O_3 nanoparticles at room temperature with sodium azide of aliphatic/aromatic alkynes of alkyl/allyl halides (Kantam et al., 2006).

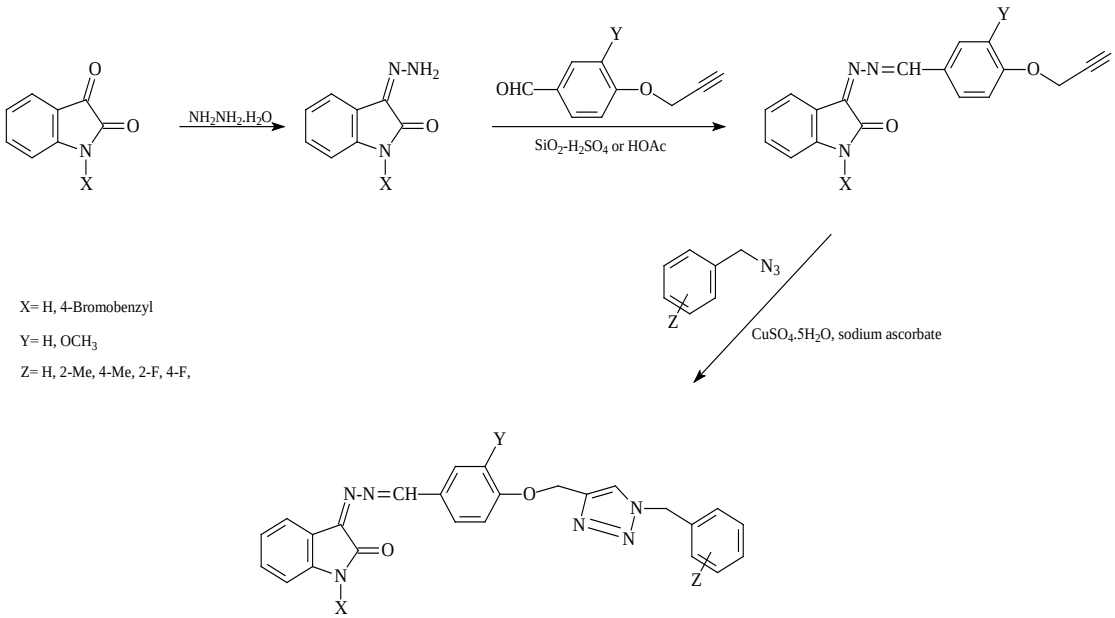


R= Alkyl, allyl
X= Cl, Br, I
R'= Aromatic, aliphatic

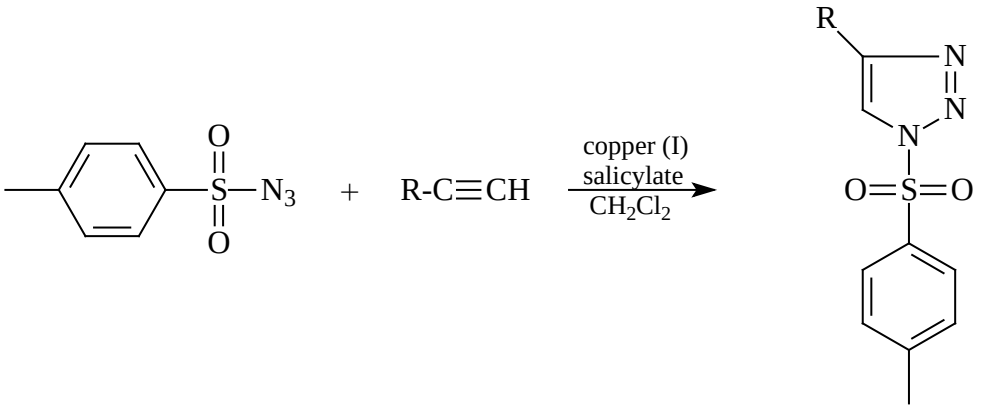
It has been shown that benzyl-1*H*-1,2,3-triazole compounds are formed by the reaction of benzyl azides and active methylene compounds with anhydrous potassium carbonate in DMSO under mild conditions (Cottrell et al., 1991).



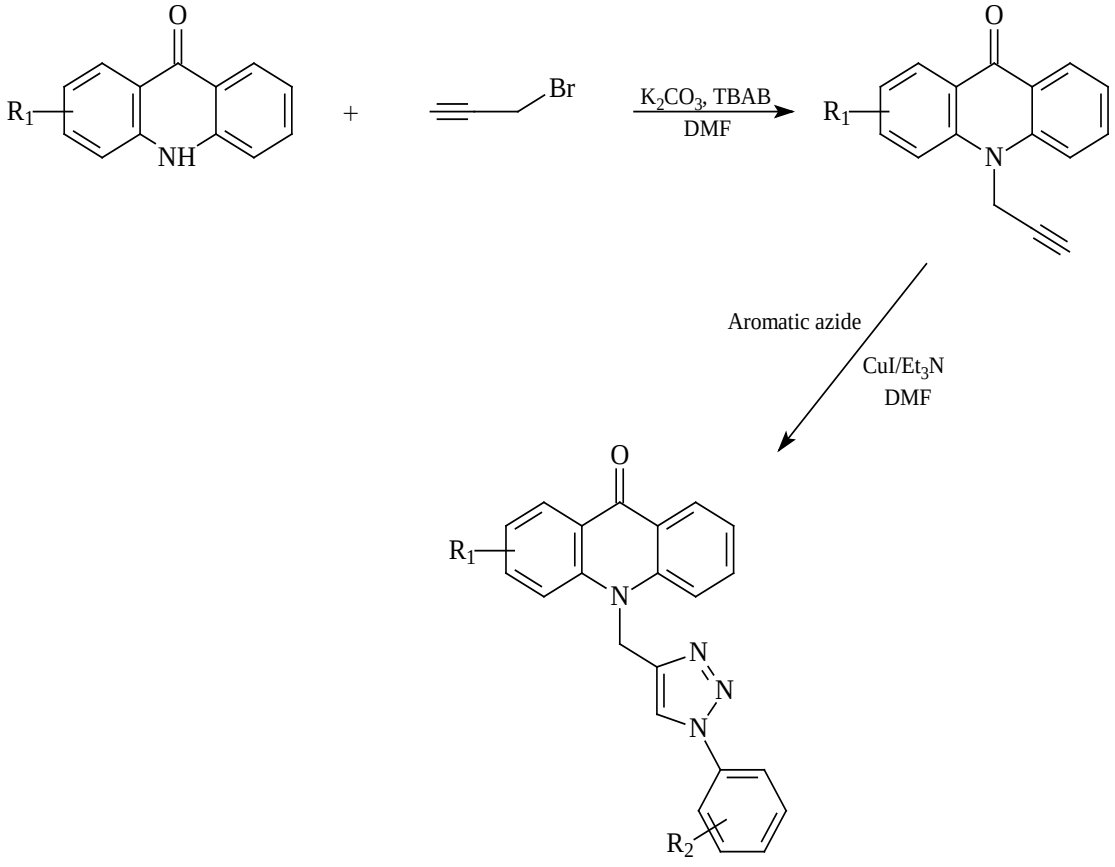
Isatin or its 4-bromobenzyl derivative reacts with hydrazine hydrate to form hydrazineylideneindolinone. Then, prop-2-yn-1-yloxybenzylidene-hydrazineylideneindolinone derivative is obtained by reaction of this compound with aldehyde in the presence of catalytic amount of SiO_2-H_2SO_4 or acetic acid under microwave irradiation. Finally, this compound leads to the formation of 1,2,3-triazole derived compound by click reaction with benzyl azide (Shareghi-Boroujeni et al., 2021).



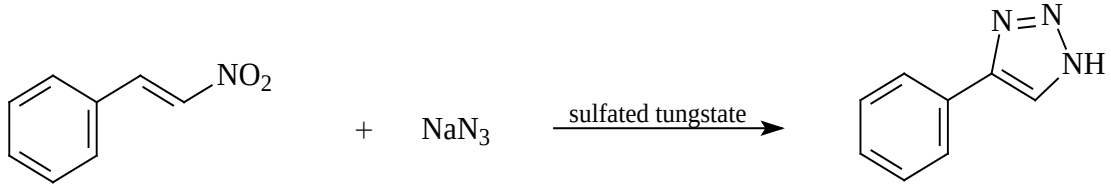
The copper-catalyzed azide-alkyne cycloaddition of *p*-toluenesulfonyl azide with an alkyne provides the appropriate compound 1-sulfonyl-1,2,3-triazole (Jose Garcia-Vanegas et al., 2021).



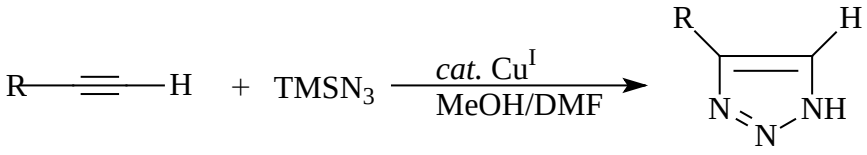
10-(prop-2-yn-1-yl)acridone derivatives were synthesized by reacting acridon and propargyl bromide in a mixture of tetra-n-butylammonium bromide (TBAB) in anhydrous potassium carbonate and DMF under microwave irradiation. It was determined that 1,2,3-triazole derivatives were obtained in the presence of CuI and triethylamine by using microwave assisted and conventional heating methods by 1,3-dipolar cycloaddition reaction between 10-(prop-2-yn-1-yl)acridone derivatives and aromatic azides (Aarjane, Slassi, Tazi, et al., 2021).



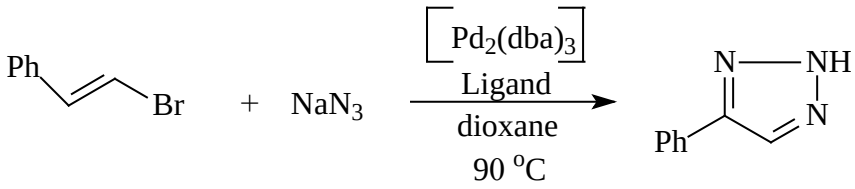
It was determined that 4-phenyl-NH-1,2,3-triazole compound was formed as a result of the reaction of a nitro styrene and sulfated tungstate with NaN_3 (Autade & Akamanchi, 2019).



N-unsubstituted 1,2,3-triazoles are obtained by the copper-catalyzed [3+2] cycloaddition reaction of nonactivated terminal alkynes and trimethylsilyl azide (Jin et al., 2004).



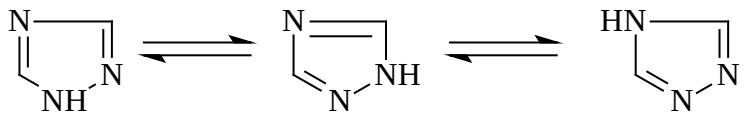
1*H*-1,2,3-triazoles were obtained from the reaction of an azide with an alkenyl halide under Pd^0 catalysis (Barluenga et al., 2006).



dba = trans, trans-dibenzylideneacetone

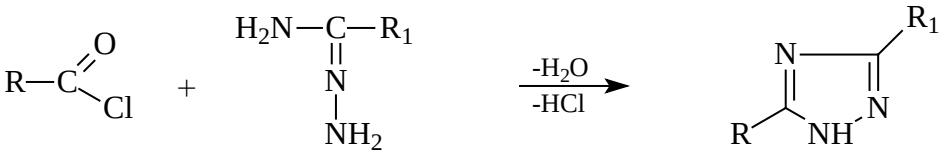
Synthesis of 1,2,4-Triazoles

1,2,4-triazole has a melting point of 121°. The tautomer shapes are as follows (Ikizler, 1996):

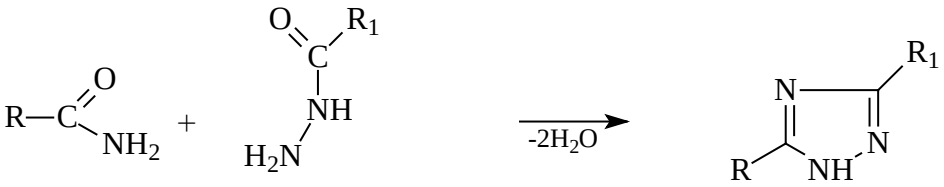


Methods used in the preparation of 1,2,4-triazole and its derivatives (Aykut İkizler, 1996):

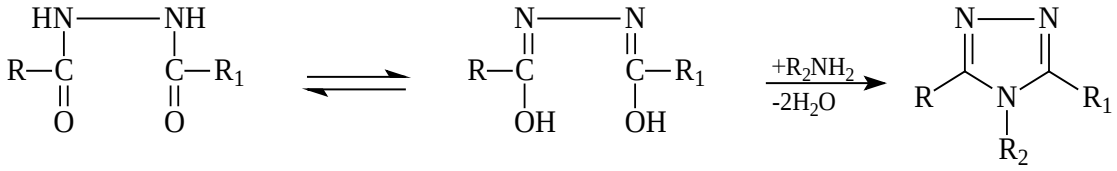
From Amidrazones (Ikizler, 1996):



From Heating of Acylhydrazines and Amides (Ikizler, 1996):

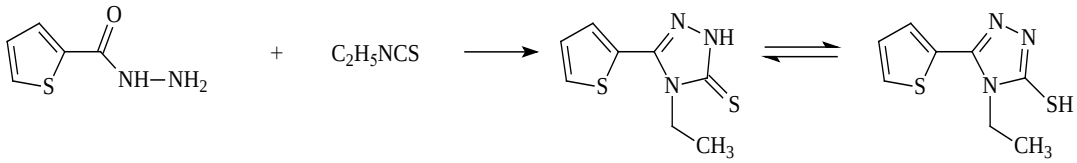


From Diacylhydrazines (Ikizler, 1996):

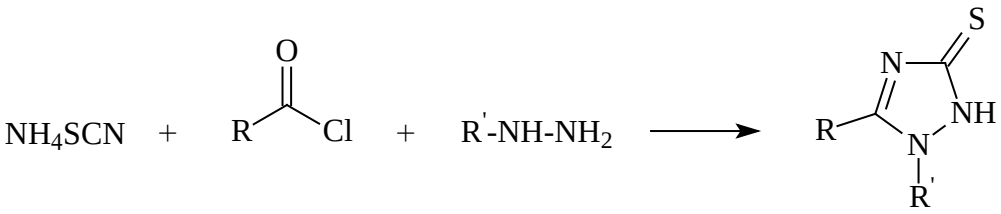


1,2,4-triazole derivatives are obtained from the reaction of diacylhydrazines with primary amines (Ikizler, 1996).

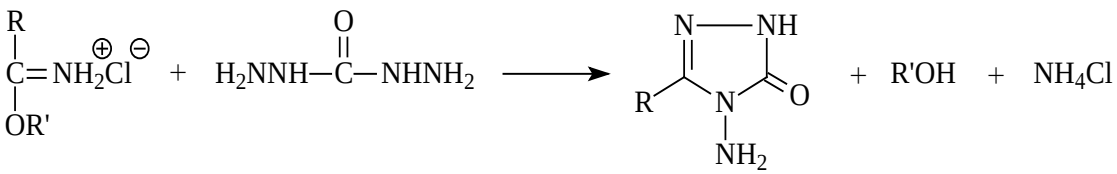
It has been shown that 4-ethyl-5-(thiophene-2-yl)-4*H*-1,2,4-triazole-3-thiol compound is synthesized as a result of the reaction of thiophene-2-carbohydrazide and ethyl isothiocyanate (Koparir et al., 2022).



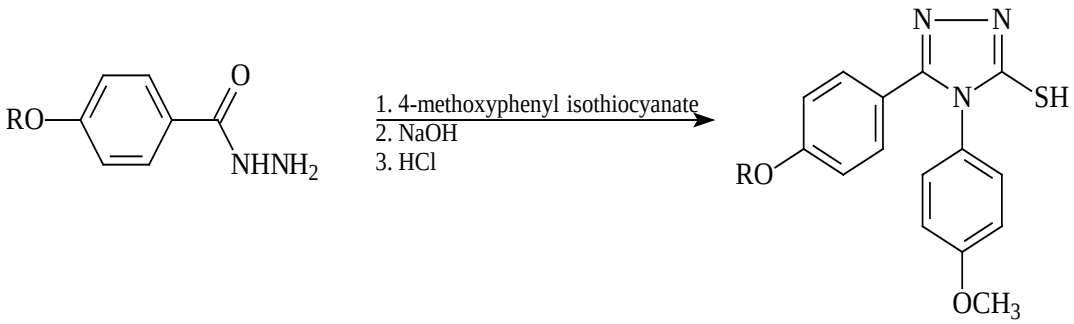
As a result of the reaction of ammonium thiocyanate, acyl chloride and arylhydrazine, 1,2,4-triazole derivative was synthesized (Yavari et al., 2010).



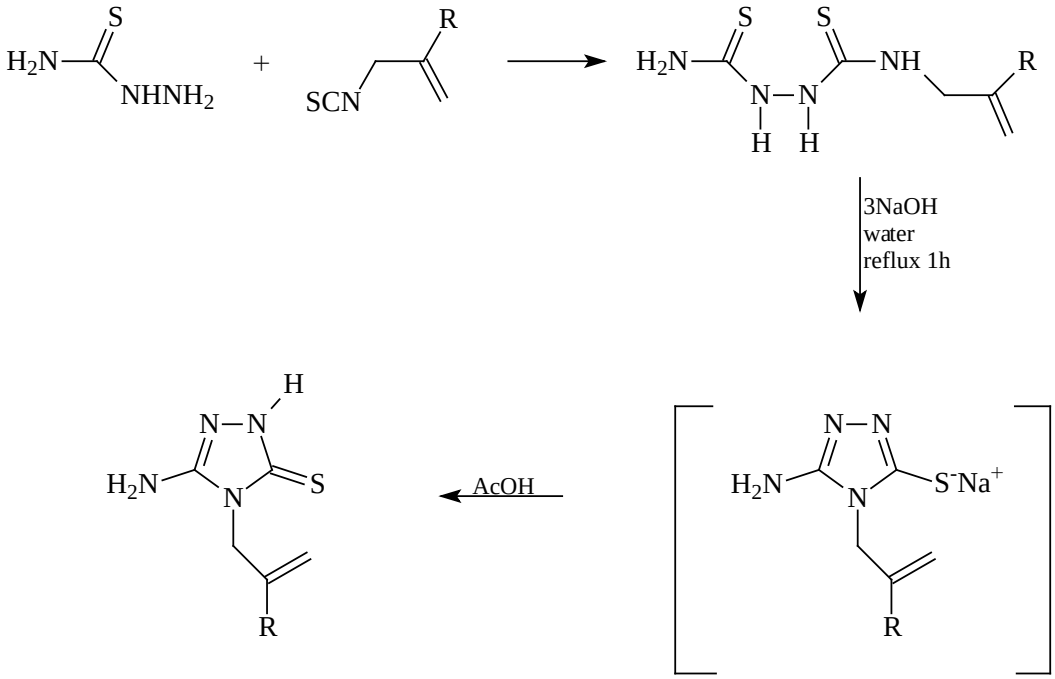
Some methods have been developed for the synthesis of 4-amino-derived 1,2,4-triazol-5-one compounds. In one of these methods, the reaction of iminoester hydrochlorides obtained from nitriles with carbohydrazide is predicted (Milcent & Redeuilh, 1979).



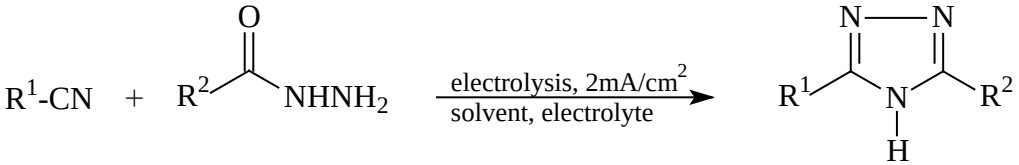
3-mercapto-1,2,4-triazole derivatives are obtained by the reaction of 4-alkyloxybenzohydrazides with 4-methoxyphenyl isothiocyanates (Al-Mansury et al., 2021).



1-alkenyl-2,5-dithiourea is formed by the reaction of thiosemicarbazide with allyl isothiocyanate or methallyl isothiocyanate. Heating this compound in sodium hydroxide solution forms 4-alkenyl-5-amino-1,2,4-triazole-3-thiolate sodium salts. Direct acidification of the reaction mixture yields 4-alkenyl-5-amino-1,2,4-triazol-3-thiones (Fizer et al., 2022).

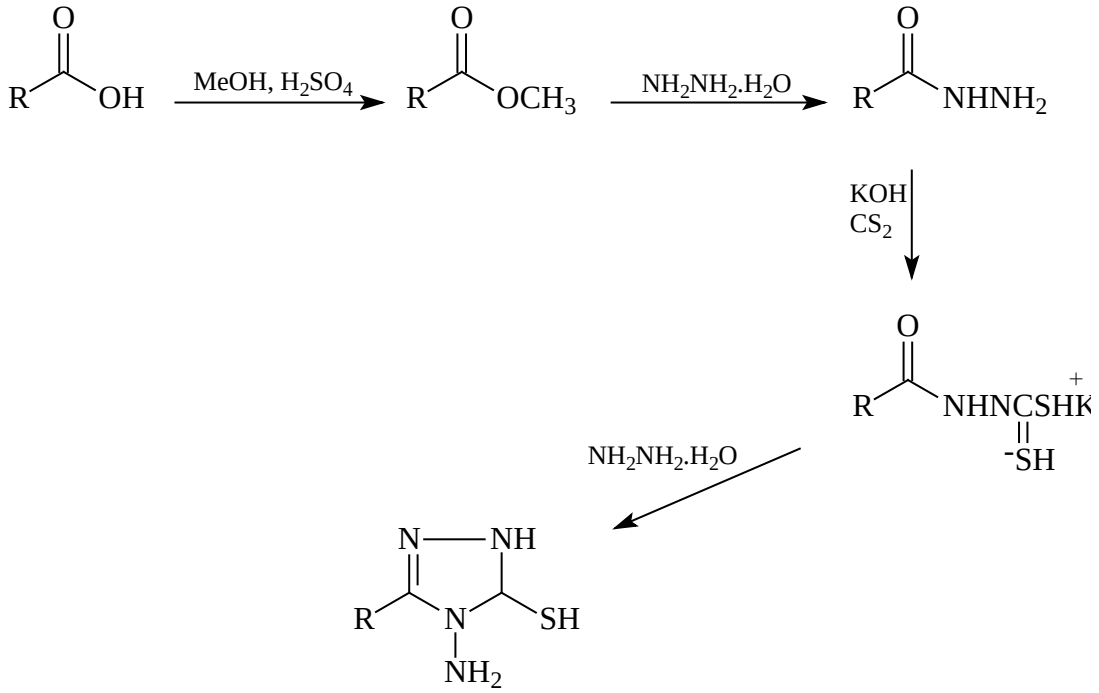


Electrochemically, one-pot direct synthesis of 3,5-disubstituted 1,2,4-triazoles from nitrile and hydrazide using KI as a redox catalyst was carried out (Singh et al., 2020).

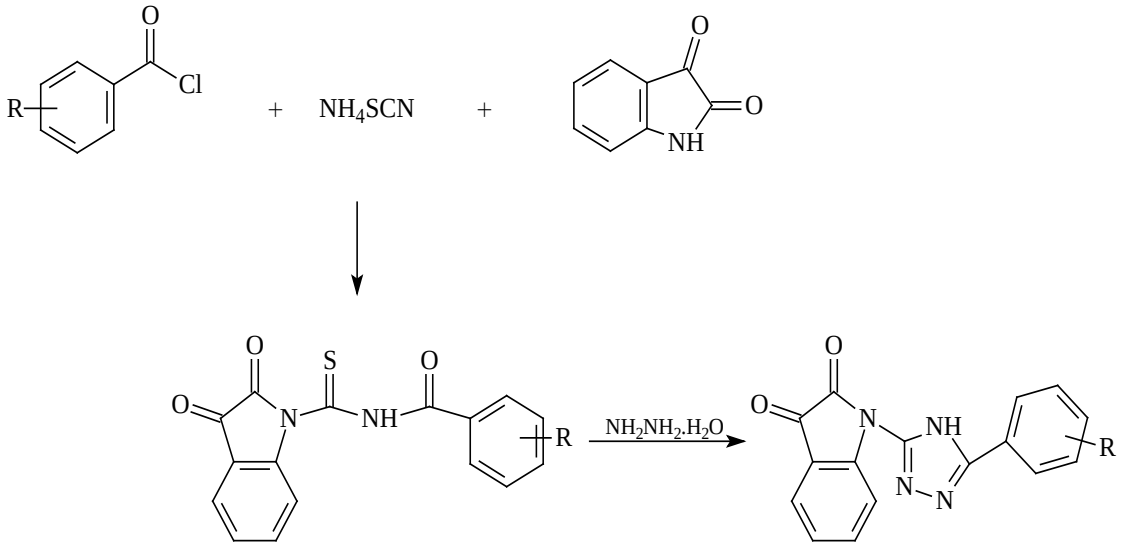


The following procedure has been followed for the synthesis of 1,2,4-triazole-derived compounds: The aromatic carboxylic acid is treated with methyl alcohol in the presence of sulfuric acid via Fischer esterification to form the aromatic acid ester. Subsequent treatment of this compound with hydrazine hydrate forms acid hydrazide. It gives dithiocarbazinic acid salts as a result of interaction with KOH and carbon disulfide. It

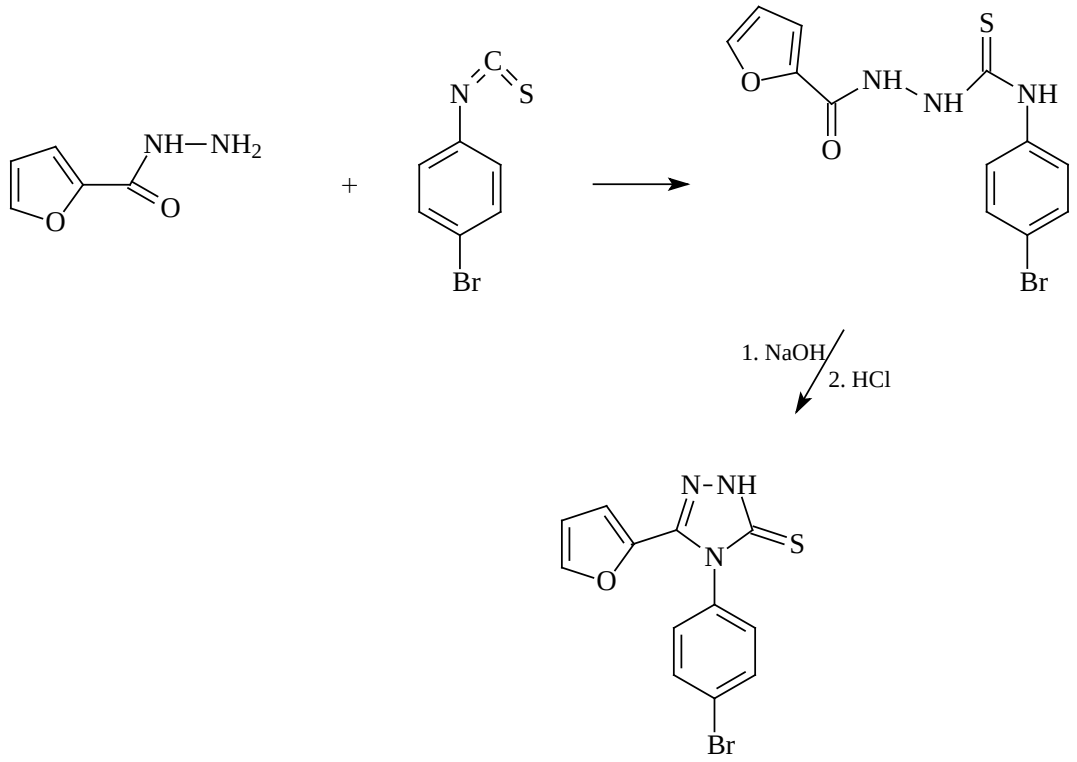
has been shown that 1,2,4-triazole-derived compound is formed in the interaction of this compound with hydrazine hydrate (Pathak et al., 2021).



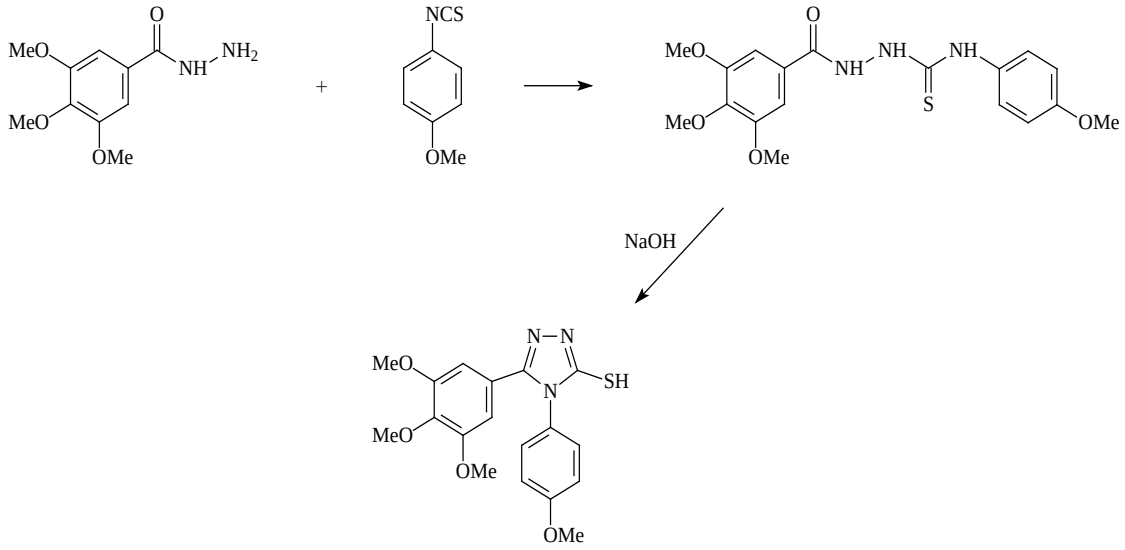
Benzoyl chloride, ammonium thiocyanate, and isatin react to form the thiourea-derived compound. As a result of the reaction of this compound with hydrazine hydrate, an indole-derived 1,2,4-triazole compound is obtained (Afshar et al., 2020).



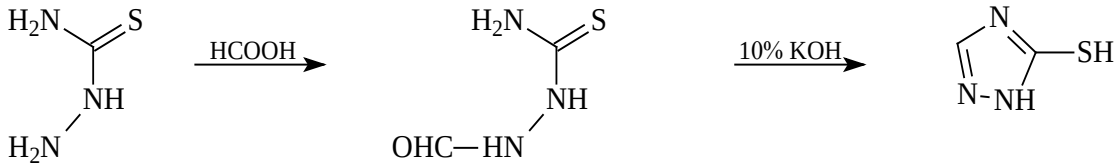
The following procedure was followed for the synthesis of the 1,2,4-triazole-derived compound: Furoic acid hydrazide and 4-bromophenyl isothiocyanate react to form *N*-(4-bromophenyl)-2-(furan-2-carbonyl)hydrazinecarbothioamide. This compound is reacted with NaOH. Then, the reaction mixture is acidified with HCl to give 4-(4-bromophenyl)-5-(furan-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (Dincel et al., 2021)



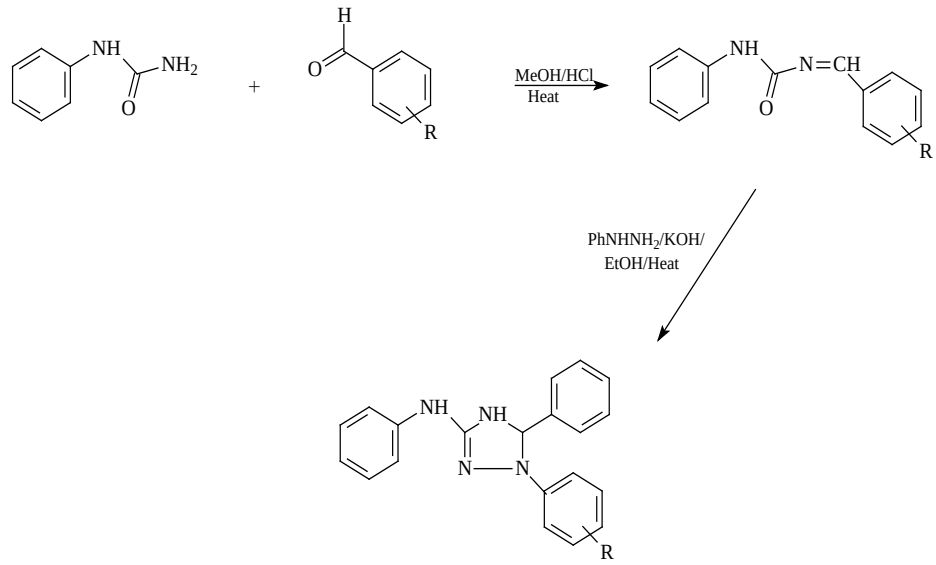
The intermediate product formed by the reaction of 3,4,5-trimethoxybenzohydrazide and 4-methoxyphenyl isothiocyanate is treated with NaOH to obtain 1,2,4-triazole derivative (Al-Mansury et al., 2019).



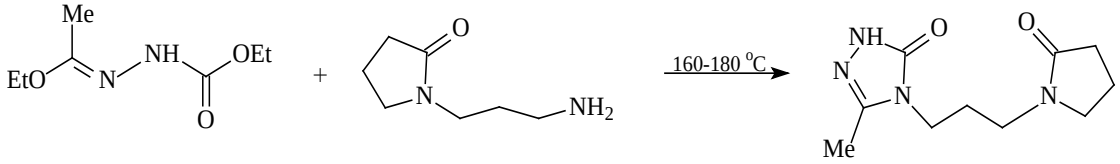
1-formylthiosemicarbazide is formed as a result of the reaction of thiosemicarbazide and formic acid. As a result of the reaction of this compound with 10% KOH, 2*H*-1,2,4-triazole-3-thiol compound is obtained (Khan et al., 2021).



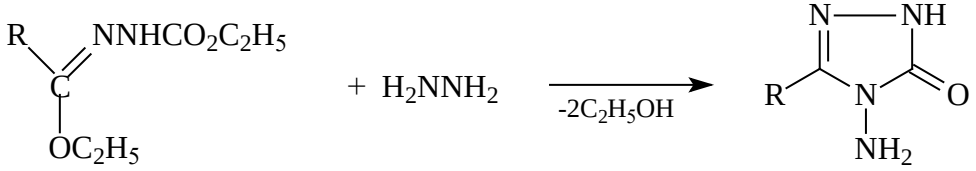
Dihydrotriazoles are synthesized from the cyclization reaction of 3-phenylurea-derived Schiff bases with phenylhydrazine under KOH/EtOH medium (Yusuf & Thakur, 2019).



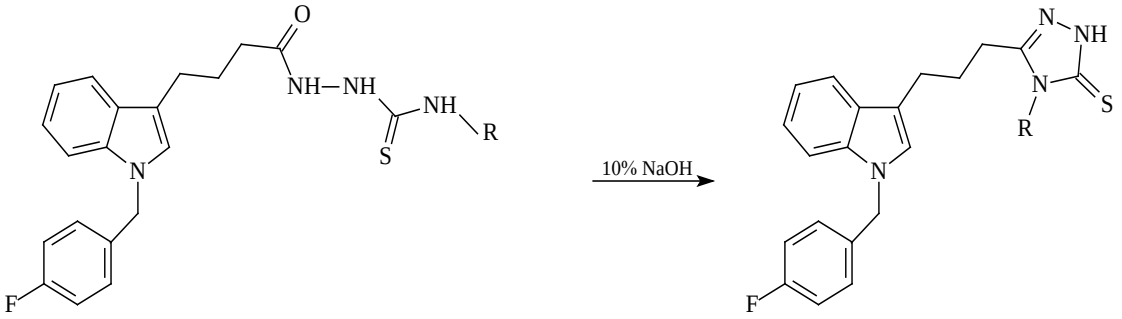
5-methyl-4-[3-(2-oxopyrrolidin-1-yl)propyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one are obtained by condensation of ethyl 2-(1-ethoxyethylidene)hydrazine-1-carboxylate with 1-(3-aminopropyl)pyrrolidin-2-one under solvent-free conditions at 160-180°C (Suleymanoglu et al., 2019).



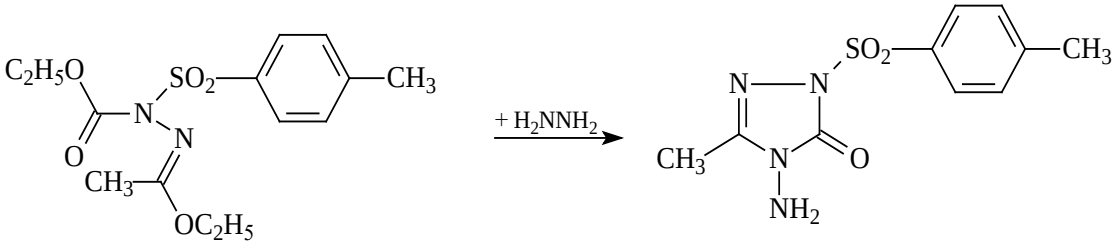
The compound 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-one is obtained from the reaction of the corresponding ester ethoxycarbonylhydrazone with an aqueous solution of hydrazine hydrate (Ikizler & Yuksek, 1993).



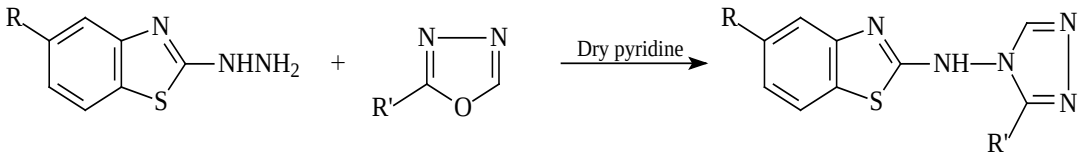
1,2,4-triazole-derived compounds are made by heating with 10% NaOH solution of corresponding thiosemicarbazides via cyclodehydration reaction (Ali et al., 2019).



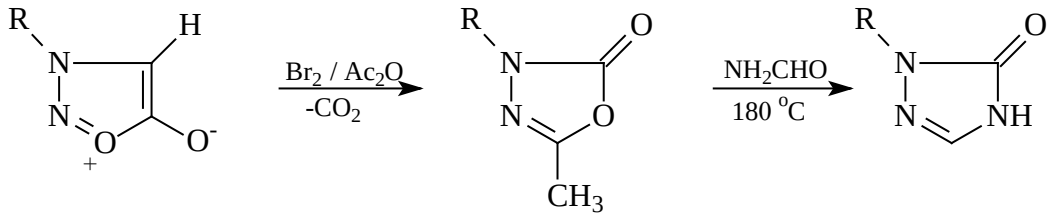
The compound 4-Amino-5-methyl-3-oxo-2-tosyl-1,2,4-triazol-3-one is obtained by the reaction of N^1-ethoxylcarbonyles N^1-tosylhydrazonates and hydrazine hydrate in ethanol containing a catalytic amount of glacial acetic acid (Saadaoui et al., 2019).



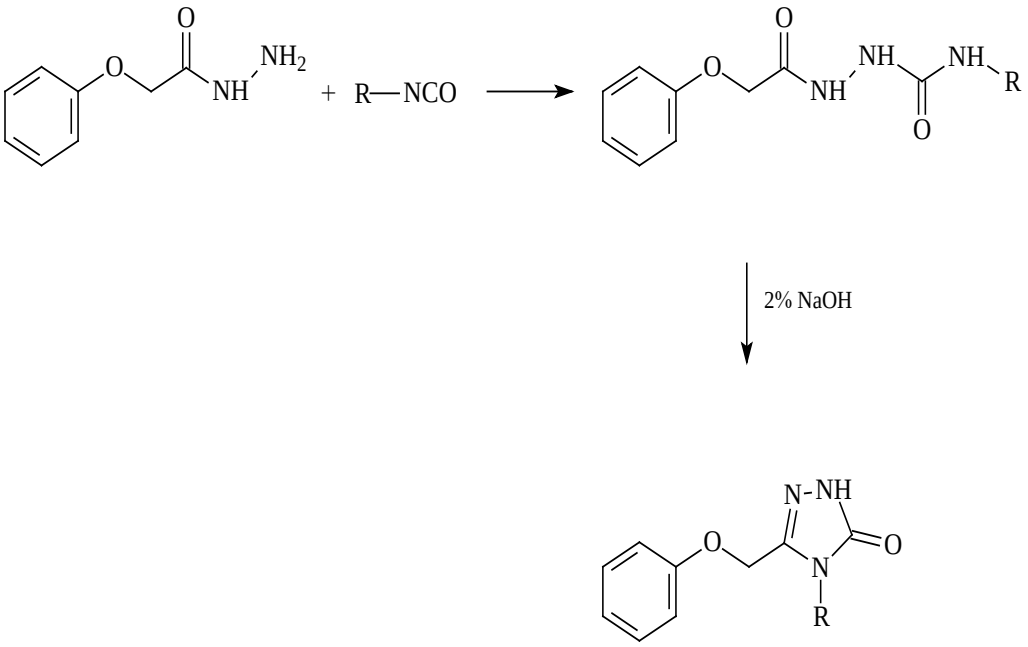
N-[3-(substituted-4*H*-1,2,4-triazol-4-yl)]benzo[d]thiazol-2-amines are formed as a result of condensation of oxadiazoles with hydrazinylbenzothiazoles (Tariq et al., 2018).



N-arylsydnone is converted to 3-aryl-5-methyl-1,3,4-oxadiazol-2(3*H*)-one by the [3 + 2] cycloaddition reaction with bromine in acetic anhydride followed by the release of CO_2. Then, this compound reacts with formamide at 180°C to synthesize 2-aryl-2*H*-1,2,4-triazol-3(4*H*)-one as a result of nitrogen addition to the ring and demethylation at C_5 (Somagond et al., 2018).



Semicarbazide derivatives are synthesized by the reaction of phenoxyacetic acid hydrazide with suitable isocyanates at room temperature. Heating the semicarbazide derivatives in 2% aqueous sodium hydroxide solution provides 5-phenoxymethyl-4-substituted-1,2,4-triazol-3-one (Pachuta-Stec et al., 2017).



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To Cite This Chapter

Akyildirim, O., & Beytur, M. (2021). Synthesis of triazole compounds. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 157–173). ISRES Publishing

Thiadiazoles and Their Properties

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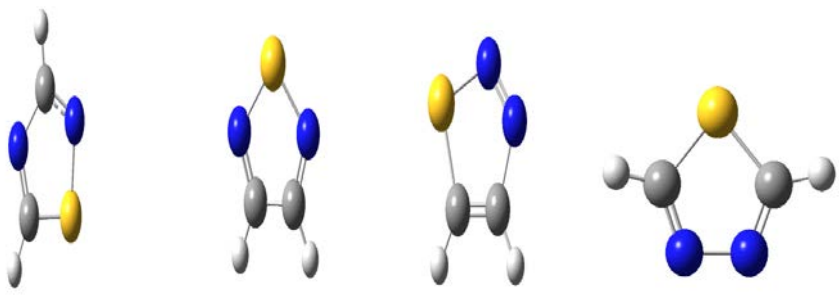
Thiadiazoles and Their Properties

Heterocyclic compounds containing structural parts specific to natural biologically active substances are being designed as a database to create new drugs over time. Thiadiazoles are biologically active five-membered aromatic heterocyclic compounds containing one sulfur and two nitrogen as heteroatoms at different positions of the ring bileşiklerdir (Boger, 1985; Jain et al., 2013; Li et al., 2013; Liu et al., 2007). The presence of these heteroatoms increases both the membrane permeability and the ability to act as versatile hydrogen bond acceptors. The inductive effect of the sulfur atom gives this structure a very weak base character with relatively high aromaticity. Thiadiazoles containing embedded sulfur atoms of vinyl groups can be considered as diazines (Meanwell, 2011; Morreira Lima & Barreira, 2005) isosteres due to their cyclic similarity, which adds to their potential to serve as fragments of bioactive structures (Aurelio et al., 2016). Thiadiazoles, which are multifunctional heterocyclic compounds, have wide applications in pharmaceutical, agricultural and materials chemistry (Haider et al., 2015; B. Hu et al., 2014). They also play an important role as versatile ligands in coordination chemistry (Frija et al., 2015). It has been widely reported that compounds bearing thiadiazole rings exhibit anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, anticonvulsant and antiparasitic activities (D. Kumar et al., 2010). Thiadiazoles used as pharmacophores are useful as thiol scavengers, pesticides and corrosion inhibitors (Bentiss et al., 2004; Castro et al., 2006; Tam et al., 2005). Thiadiazoles can occur in four different regioisomeric forms such as 1,3,4- thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,2,3-thiadiazole, which enrich their structural diversity according to local polarization (Figure 1). The most widely studied thiadiazoles are the 1,2,4-thiadiazole and 1,3,4-thiadiazole isomers.

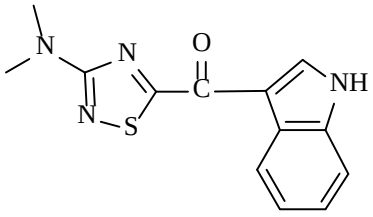


1,2,4-Thiadiazole 1,2,4-Thiadiazole 1,2,3-Thiadiazole 1,3,4-Thiadiazole

Figure 1. Regioisomer Forms of Thiadiazoles

Synthesis and Properties of 1,2,4-Thiadiazoles

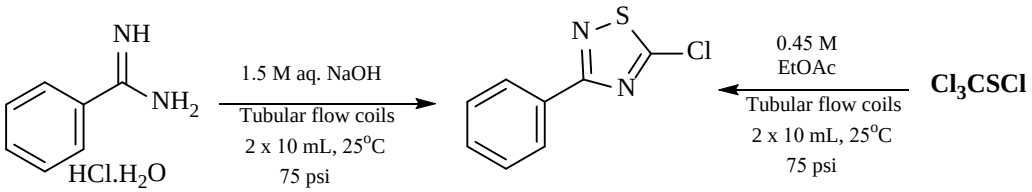
1,2,4-Thiadiazole was first described in 1821 and synthesized and characterized in 1955. Until 1980, the natural product containing the 1,2,4-thiadiazole core wasn't reported. Dendrodoin, the first natural product, is a cytotoxic product isolated from marine Tunicate Dendrodoa grass (Franz & Dhingra, 1984).



1,2,4-Thiadiazoles are generally stable due to the aromatic nature of the ring. Thiadiazoles react with acids, alkalis, oxidizing and reducing agents. Research on the reactivity of 1,2,4-thiadiazole has been done on 1,2,4-thiadiazoles with substituents in the 3- and 5-positions, which are more stable to acid, alkali, oxidizing agents and reducing agents. The 5-position in 1,2,4-thiadiazoles is the most reactive site in nucleophilic substitution reactions. The electrophilic reactions of 1,2,4-thiadiazoles are very low and limited (Kurzer, 1982).

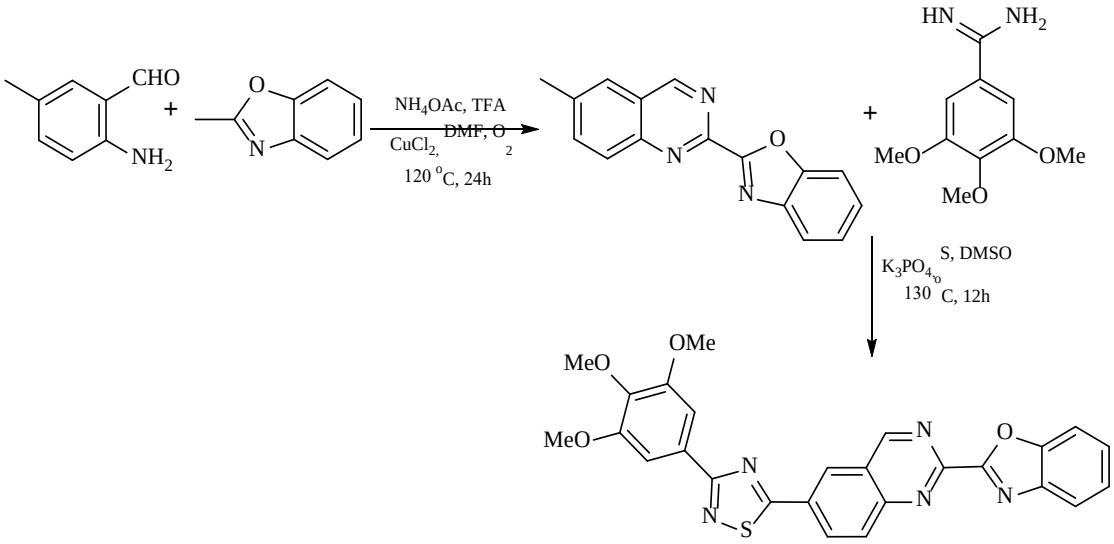
Among the thiadiazole isomers, the 1,2,4-thiadiazole structure is an important one as it resembles the ubiquitous pyrimidine moiety. 1,2,4-thiadiazole derivatives are widely used in the treatment of different pathologies, including Alzheimer's disease, in which neurodegenerative ones take an important place (Porcal et al., 2008). The synthesis of 1,2,4-thiadiazoles is achieved by various methods, including oxidative ring closure (Mariappan et al., 2016; Vanajatha & Reddy, 2016), multicomponent reactions (Xie et al., 2016) or [3+2]-cycloadditions (Aitha et al., 2016).

5-Chloro-3-phenyl-1,2,4-thiadiazole were efficiently prepared by reaction with different nitrogen, sulfur and oxygen-based nucleophiles, enabling efficient synthesis and derivatization of 1,2,4-thiadiazole heterocycles. This synthetic approach was then applied to produce a series of bromophenyl-5-chloro-1,2,4-thiadiazoles, providing a valuable introduction to further structural diversification on this important heterocyclic scaffold (Baumann & Baxendale, 2017)

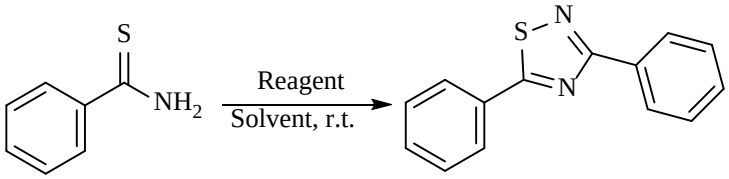


A new compound consisting of structurally modified 1,2,4-thiadiazole containing benzoxazole-quinazoline derivatives was synthesized. A series of 1,2,4-thiadiazole-containing benzoxazolequinazoline derivatives. designed and synthesized. It was

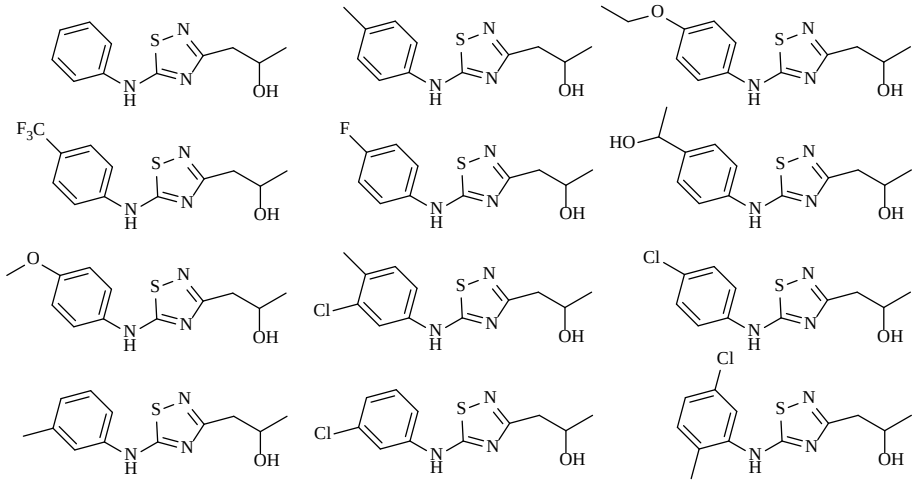
screened for its anticancer profile against human cancer cell lines, including lung cancer, breast cancer, colon cancer, and ovarian cancer, and the clinical agent as etoposide selected as positive control (Perupogu et al., 2020).



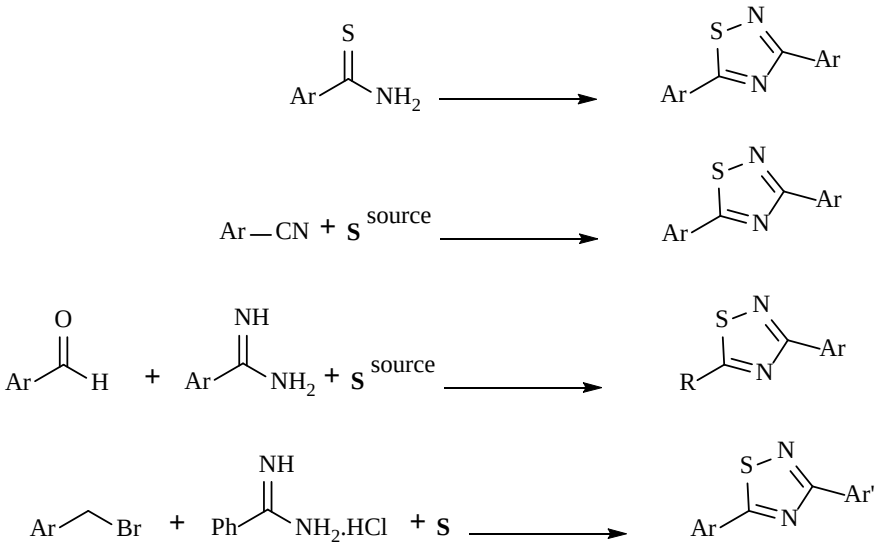
The classical methods used for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles can be expressed as intramolecular cyclization, intermolecular cyclization and oxidative dimerization of thioamides. 3,5 unsymmetrical disubstituted 1,2,4-thiadiazole was synthesized by intramolecular oxidative cyclization of amidinithioureas(Castro et al., 2006) and 1,3-dipolar cycloaddition of nitrile sulfides to nitriles (Howe & Franz, 1974). Ceric ammonium nitrate (CAN), a versatile reagent, effectively mediated the oxidative dimerization of primary thioamides in acetonitrile at room temperature, and thus the synthesis of symmetrically 3,5-disubstituted 1,2,4-thiadiazoles took place in high yield (Vanajatha & Reddy, 2016).



The effect of a structural modification on the solubility of 1,2,4-thiadiazole drug-like compounds in pharmaceutically relevant solvents n-hexane and 1-octanol and on thermodynamic aspects of solvation processes was investigated. The solubility of compounds in 1-octanol is largely independent of the nature and location of the substituent in the phenyl moiety. However, in n-hexane, the addition of any substituent to the phenyl ring of the 1,2,4-thiadiazole molecule reduces the solubility in the solvent (Surov et al., 2016)



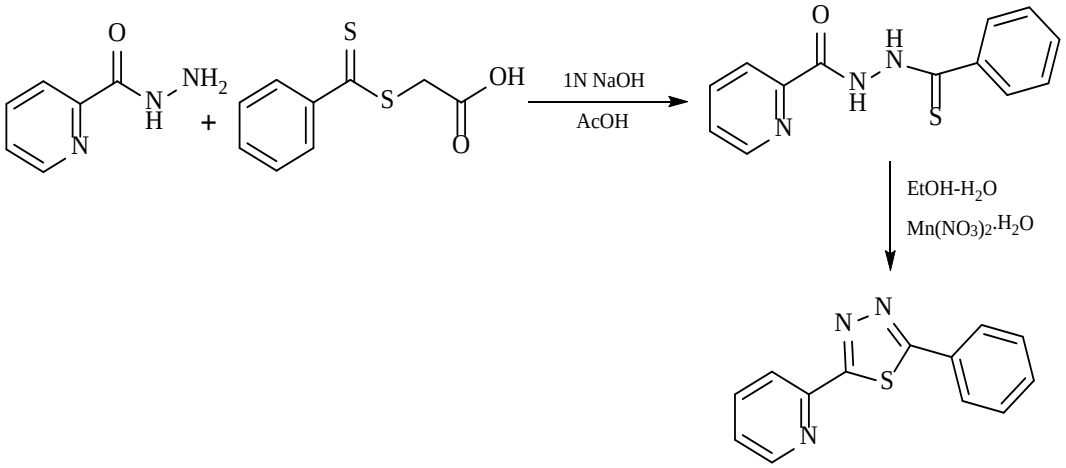
Both in terms of diversity and complexity, the development of new methods for the unsymmetrical 3,5-diaryl-1,2,4-thiadiazole or suitable substrate design has been synthesized although highly desirable but still challenging for organic chemists. Examples were not reported until Deng developed the ring between amidines, elemental sulfur and 2-methylquinolines (or aromatic aldehydes) under transition metal-free conditions (Xie et al., 2016; Zhou et al., 2017).



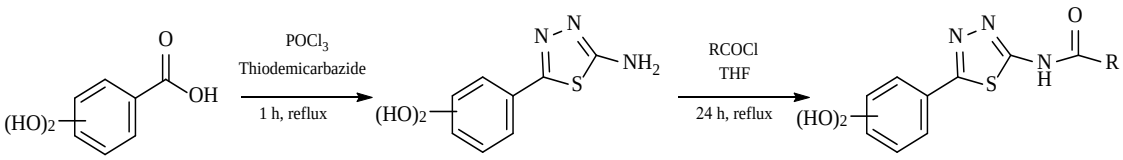
Synthesis and Properties of 1,3,4-Thiadiazoles

The synthesis of heterocyclic compounds is of great interest and various methods have been reported for their synthesis, such as oxidative cyclization of acyclic precursor such as NO-acyl hydrazine-carbodithioic acid alkyl ester (Jasinski et al., 2010; Jedlovská & Leško, 1994). It is used as a starting material in the synthesis of many chemical compounds, including 1,3,4-thiadiazoles, biocides, sulfa drugs, dyes, fungicides and chemical reaction accelerators (Jalhan et al., 2013). Thiadiazoles containing hydroxyl, amino and mercapto substituents can exist in their tautomeric form. Many industrial

applications and chemical properties such as their capacity to form complexes with metal ions have been reported (Barboiu et al., 1996). These results led to the synthesis of a new type of heterocyclic compound, assuming that the presence of phenyl and pyridine rings in the thiadiazole moiety would have much better solubility in anhydrous medium. Metal assisted cyclization of 4-phenyl-1-(2-phenylacetyl)thiosemicarbazide and N'-benzothioylpicolinohydrazide to 5-benzyl-N-phenyl-1,3,4-thiadiazol-2-amine and 2-(5-phenyl-1,3,4-thiadiazol-2-yl) pyridine attempted to prepare complexes with manganese (II) nitrate. Conversion of 5-methyl-1,3,4-thiadiazol-2-thiol to 2-(5-methyl-1,3,4-thiadiazole-2-ylthio)-5-methyl-1,3,4-thiadiazole provided using Manganeseacetate under mild conditions (Dani et al., 2013).

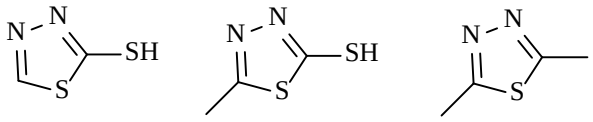


The 1,3,4-thiadiazole heterocyclic scaffold incorporated into many heterocyclic compounds with varying degrees of antiproliferative activity has the well-known pharmacophore property (Aliabadi, 2016; Haider et al., 2015). A series of 5-(2,5-dimethoxyphenyl)-1,3,4-thiadiazol-2-amino derivatives were synthesized and investigated for cytotoxic activity against HT-29 and MDA-MB-231 cancer cells. Heading molecules were synthesized in two steps (Jakovljević et al., 2017).



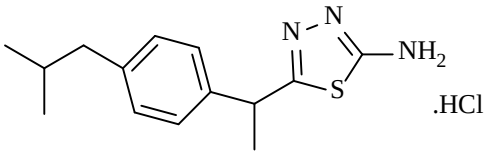
Mercapto-substituted thiadiazoles can have different tautomeric forms such as thiol or thione, which affects their reactivity. However, studies on the tautomeric stability of mercapto thiadiazoles have been reported recently(Enchev & Angelova, 2010; Esmaiel et al., 2020; Hipler et al., 2002; Ortega et al., 1996). The structural and energetic properties of heterocycles with a five-membered ring containing nitrogen and sulfur as heteroatoms can be determined to establish energy-structural correlations. These correlations are important in predicting thermochemical and thermophysical properties for other structurally related compounds. An experimental and computational thermochemical study of thiadiazoles such as 2-mercapto-1,3,4-thiadiazole, 2-mercapto-5-methyl-1,3,4-

thiadiazole and 2,5-dimethyl-1,3,4-thiadiazole has been reported (Silva et al., 2022).



1,3,4-Thiadiazoles with both electron accepting and donating groups have been reported to be potential compounds with optical, electronic, biological and chemical properties (Hu et al., 2014). Especially, 2-amino-1,3,4-thiadiazole derivatives have attracted a lot of attention due to their significant anticancer activities. 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole inhibits the proliferation of tumor cells, possibly through a mechanism that reduces cell division and decreases cell migration (Kumar et al., 2010; Remko et al., 2006).

Considering the individual pharmaceutical significance of ibuprofen and 1,3,4-thiadiazole compounds, the possibility of synthesizing chemical entities containing both ibuprofen and thiadiazole moieties was investigated. An optimized strategy was applied for a one-step acylation and cyclization reaction of the carboxylic acid group of ibuprofen with thiosemicarbazide in the presence of phosphorus oxychloride (Al-Omar et al., 2004). The target compound, 2-amino-5-ibuprofen substituted-1,3,4-thiadiazole as hydrochloride salt was synthesized and its structure was elucidated. The molecular structure and vibrational properties of the target compound are studied using experimental X-ray diffraction and spectroscopic techniques (FTIR and Raman) and complemented by quantum chemical calculations, including NBO population analysis (Channar et al., 2019).

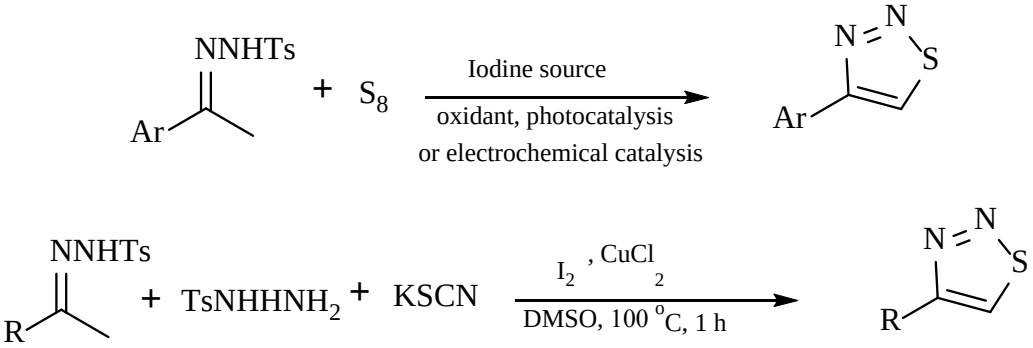


Synthesis and Properties of 1,2,3-Thiadiazoles

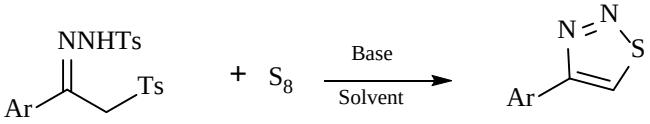
1,2,3-Thiadiazoles are widely used in pharmaceuticals, agrochemicals and organic synthesis as an important class of heterocyclic compounds. The structure of the molecular skeleton aroused great interest. Conventional methods for the synthesis of 1,2,3-thiadiazoles include Hurd-Mori synthesis (Hurd & Mori, 1955; A. Kumar et al., 2012), Wolff synthesis (Singh et al., 2013), Pechmann synthesis (May & Townsend, 1976), and the like. However, these approaches often have limitations such as diazo compounds or azides, substrates not readily available, air-sensitive sulfur sources, harsh reaction conditions, and narrow substrate coverage. Therefore, the development of a simple and effective method for accessing 1,2,3-thiadiazoles remains an active topic in organic synthesis (Feng et al., 2021).

N-tosylhydrazones are excellent agents for the synthesis of 4-aryl-1,2,3-thiadiazoles due

to their stable structure, easy availability and high reactivity. Various iodine-catalyzed cyclization reactions have been reported under the influence of oxidants, photocatalysis or electrochemical catalysis with different sulfur sources of N-tosylhydrazones (J. Chen et al., 2016; Zhang et al., 2020). $I_2/CuCl_2$ promoted one-pot three components of ketones, p-toluenesulfonyl hydrazide and KSCN have been reported to synthesize 1,2,3-thiadiazoles with aliphatic or aromatic substitutes (Feng et al., 2021; C. Wang et al., 2019).



Different derivatives of 2-(p-toluenesulfonyl)-N-tosylhydrazones were obtained with different sulfur sources. A series of 4-aryl-1,2,3-thiadiazoles and new 4-aryl-5-tosyl-1,2,3-thiadiazoles were synthesized by adjusting the reaction conditions (Feng et al., 2021).

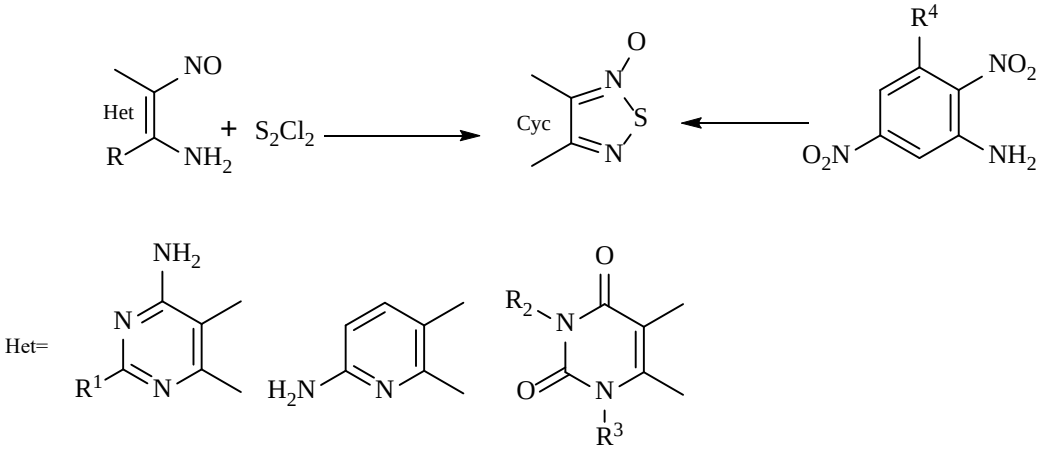


Synthesis and Properties of 1,2,5-Thiadiazoles

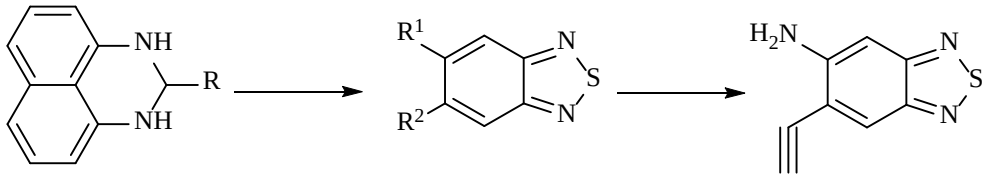
1,2,5-Thiadiazoles and their benzo-fusion derivatives have been known for many years and their synthesis, chemical and physical properties have been extensively reported (Neto et al., 2013) (Konstantinova et al., 2014). Besides their use in various branches of chemistry, medicine (Konstantinova et al., 2014), and agriculture (Gozzo, 2003) respectively. The latter is relevant when a cultivar resistant (R, they have been found to be efficient electron acceptors and used as building blocks of many real or potential molecule-based functional materials for organic electronics (Chen et al., 2014) and spintronics (Shuku et al., 2009). Recently, they have been used in the synthesis of thermally stable radical-anion salts, revealing antiferromagnetic Exchange interactions in spin systems (Gritsan & Zibarev, 2011), and also conducting charge transfer complexes with photoconductivity (Gritsan & Zibarev, 2011; Semenov et al., 2013).

Based on DFT calculations of electron affinity, N-oxides of the above-mentioned compounds, such as 1,2,5-thiadiazole 2-oxides and 2,1,3-benzothiadiazole 1-oxides, were also expected to be good precursors of stable RAs that can be isolated in salt form.

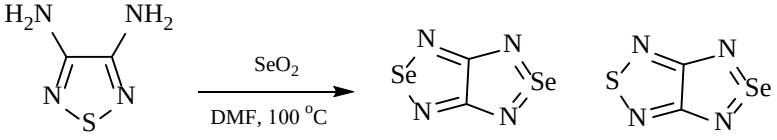
It should be emphasized that the well-studied chemistry of 1,2,5-thiadiazole, in contrast to S-oxides and S,S-oxides, including its potential applications in electrochemistry and materials science. 1,2,5-Thiadiazole 2-oxides and derivatives are rare compounds. Benzo- and heterocyclic fused derivatives were obtained in the reaction of sulfur monochloride with o-aminonitroso and o-aminonitro precursors (Konstantinova et al., 2014).



To investigate the structural diversity of 1H-2,3-dihydroperimidine derivatives, a scaffold-hopping strategy was used to replace the 1H-2,3-dihydroperimidine motif with the benzo[c][1,2,5]thiadiazole motif, designed and a series of benzo[c] [1,2,5]thiadiazole derivative was synthesized. The inhibitory activities of the synthesized compounds against protein tyrosine phosphatase 1B (PTP1B) and Src homology 2 (SH2) domain containing protein tyrosine phosphatase-2 (SHP2) were evaluated (Wang et al., 2017)



It has been reported that there are very important studies in various fields of 1,2,5-selenadiazole derived compounds, basic and applied chemistry, biomedicine and technology (Konstantinova et al., 2014). Similar to these studies, a concise and convenient synthesis of 1,2,5-thiadiazoles and fused 1,2,5-selenadiazoles from selenium dioxide has been developed (Konstantinova et al., 2015).



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To Cite This Chapter

Beytur, M., & Akyildirim, O. (2021). Thiadiazoles and their properties. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 174–189). ISRES Publishing

SECTION 5
PHYSICS

Direct Energy Convertion: Thermoelectricity

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Electric energy is produced in four ways: electrochemical, electromagnetic, electrostatic, and direct conversion. The product of electrochemical energy conversion is batteries. Electromagnetic conversion tools are generators called alternators or dynamos and are the most widely used electricity generation method today. Electrostatic electricity generation is of two types, friction generators, and triboelectric generators. Friction generators are useful when high voltage low current is needed. Triboelectric generators have become one of the wearable technologies and it is an issue on which a lot of work has been done today. The direct generation of electrical energy without any moving parts is called direct energy conversion. The tools that convert light energy into electrical energy are called photovoltaic cells. The conversion of heat energy into electrical energy is called the thermoelectric effect, and the conversion of sound and vibration energy into electrical energy is called the piezoelectric effect.

Thermoelectric Effect

Thermoelectricity is an environmentally friendly, low-cost, pollutant-free energy conversion technology that involves the conversion of heat energy directly into electrical energy or electrical energy into a heat pump through thermoelectric materials. Thermoelectric devices have no moving parts, so they provide noiseless, reliable and maintenance-free operation. These materials have various applications in temperature sensors, local cooling units, power generation designed for special purposes and waste heat recovery.

Although it is stated in many sources that it was discovered by Thomas Johann Seebeck in 1821, Alessandro Volta observed the thermoelectric phenomenon for the first time. While working on the phenomenon Luigi Galvani called animal electricity, he thought that electrical energy could be caused by temperature, but he did not investigate the effect of temperature because the work shifted to electrochemical interaction (Saini et al., 2021). Seebeck put a compass inside the closed system of copper and bismuth plates and observed that when he heated one of the connection points, the compass needle deviated and this was called the thermomagnetic effect. He mistakenly concluded that this interaction was a magnetic phenomenon and tried to relate the temperature difference between the equator and the poles to the earth's magnetic field.

Hans Christian Ørsted explained that the phenomenon Seebeck observed was not magnetic but electric, and he called this phenomenon the thermoelectric effect (Poudel,

2007). Later, Seebeck, who repeated this event using a large number of materials, some of which we know as semiconductors, arranged the "S.σ" products of these materials in his study and published them in 1823 (Poudel, 2007; Rowe, 1995). Here, "S" is the Seebeck coefficient and "σ" is the electrical conductivity coefficient. 12 years after Seebeck's discovery, Jean Charles Athanase Peltier discovered a complementary effect. Realizing that when current is passed through a circuit consisting of two dissimilar metals, there is a temperature change around the points where the metals join, Peltier tried to use the Seebeck effect as an electric generator that produces weak current, but failed to explain the basic nature of his observations or relate them to Seebeck's findings. The true nature of the Peltier effect was explained by Heinrich Friedrich Emil Lenz in 1838. Lenz concluded that this phenomenon was dependent on the direction of the current, and proved with a simple experiment that in an arrangement consisting of two conductive junctions, heat is absorbed at one of the junctions and produced at the other. In this experiment, he observed that after turning the water into ice at one of the intersections, the ice began to melt when the current changed its direction. In 1851, William Thomson (Lord Kelvin) established a relationship between the Seebeck and Peltier coefficients and revealed the existence of a third thermoelectric phenomenon. This phenomenon, called the Thomson effect, was later observed experimentally. In 1885, although John William Strutt Rayleigh calculated the efficiency of the thermoelectric generator incorrectly, he suggested the possibility of using the thermoelectric phenomenon for electricity generation (Rowe, 1995). Edmund Altenkirch presented a very satisfactory theory for the thermoelectric generator and refrigeration. In his work, he showed that a good thermoelectric material should have a low thermal conductivity (κ) and low electrical resistivity (ρ) together with a high Seebeck coefficient (S) to minimize Joule heating and retain heat at junctions (Polozine et al., 2014).

Seebeck Effect

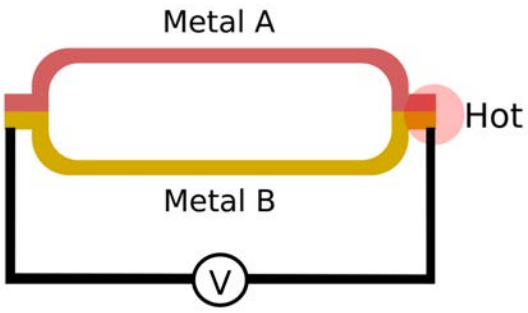

Figure 1. Seebeck Experiment

When two different metal sheets are joined as shown in the Figure 1 and one of the connection points is heated, a potential difference occurs between the junction points. The resulting voltage can be given by the following equation.

$V=S_{AB}.(T_{Hot}-T_{Cold})$

"S" is given as the Seebeck coefficient. Valence electrons in the hot region move towards the cold region with the effect of thermal energy. Electrons in the cold region slide towards the warm region. However, since the average momentum of the electrons in the hot region will be higher than in the cold region, a negative charge will occur in the cold region. S_{AB} is the relative Seebeck coefficient of metals with respect to each other.

$S_{AB}=S_B-S_A$

S_A and S_B are the Seebeck coefficients of each metal, with the platinum metal being the reference metal. The Seebeck coefficient is not a fixed value, but changes depending on the average temperature value. The average temperature is the arithmetic average of the temperature of the hot and cold zone. Seebeck coefficients for some metals at room temperature are given in the table below (Lasance, 2006).

Table 1. Seebeck Coefficient of Some Metals (Moffat, 1997).

Metals	Seebeck Coefficient (μV/K)	Metals	Seebeck Coefficient (μV/K)
Antimony	47	Aluminum	3,5
Molibdenum	10	Platinum	0
Tungsten, Cadmium	7,5	Sodium	-2
Copper, Gold, Silver	6,5	Potassium	-9
Rhodium	6,5	Nickel	-15
Tantalum	4,5	Bismuth	-72

Peltier Effect

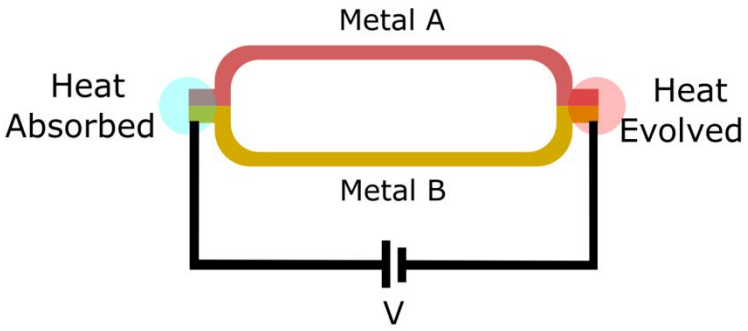

Figure 2. Peltier Circuit

When two different metal sheets are joined as shown in the Figure 2 and voltage is applied between the junctions of metal plates, as shown in the figure, heat is absorbed in one of the connections, while heat is released in the other. Depending on the direction of the current, heat is given or absorbed by the metal pairs. The heat transferred through the metal can be given by the following equation.

$Q=\pi_{AB}.I$

"Π" is given as the relative peltier coefficient of metal pairs. The Peltier effect is an inverse process of the Seebeck effect.

Thomson Effect

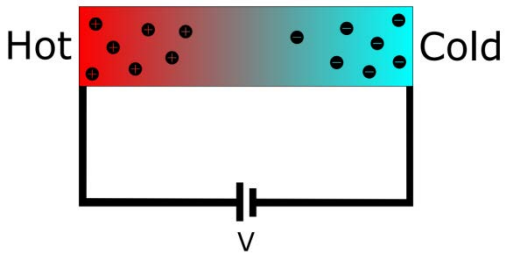

Figure 3. Thomson Experiment

Thomson found that when a current is passed through a wire consisting of a single homogeneous material in which there is a temperature gradient as shown in the figure, the heat must be exchanged with the environment so that the original temperature gradient can be maintained along the wire. As a result of this experiment, he proved that the Peltier effect and the Seebeck effect are interdependent processes. The reversible heat produced in a part of the conductor can be given by the following equation.

$$Q=\rho.I^2-\beta.\Delta T.I$$

Here, in order for ρ to be the resistivity of the material, is the Joule heat, Q is the Thomson heat, ΔT is the temperature difference between the ends of the conductor, I is the current through the conductor, and β is the Thomson coefficient. Interestingly, the total amount of heat produced varies depending on the direction of the current and the type of material. For lead the Thomson heat effect is zero, for copper the hot end exhibits high potential behavior, while for iron the hot end exhibits low potential behavior.

The relationship between the Seebeck coefficient and the Peltier coefficient is given by the following expression.

Figure of Merit and Conversion Efficiency

These desirable traits were represented by Z, which was defined as the quality factor (figure of merit), and was defined as

$$Z = \frac{S^2.\sigma}{k}$$

In this expression obtained by Altenkirch by doing experimental studies, "S" is Seebeck coefficient, "σ" is electrical conductivity and "κ" is thermal conductivity of thermoelectric element. expression is also called power factor. However, according to this definition,

the unit of the thermoelectric quality factor (Z) was K^{-1}. For ease of use, the expression was multiplied by the average temperature (T) to become dimensionless ZT (Becker et al., 2008; Bottner et al., 2004).

The maximum efficiency η_{max} for an energy production is given below.

$$\eta_{max} = \frac{\Delta T(\sqrt{ZT+1}-1}{T_H\sqrt{ZT+1}+T_C}$$

Thermoelectric energy conversion is a process that occurs through electron transport and this process accompanies Joule heat and is irreversible. Therefore, the η_{max} expressions in the equation can be reduced to the Carnot efficiency for (Paul, 2013).

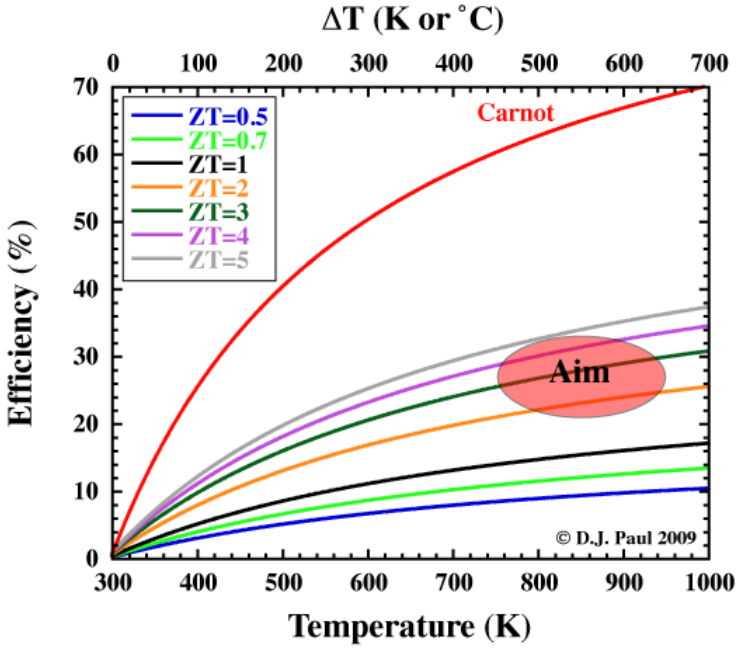

Figure 4. Energy Conversion Efficiency for Some ΔT Values of ZT (Paul, 2013).

According to the graph above, applications where the temperature difference is 600 degrees for a thermoelectric generator with ZT=2 can be commercially preferred.

Thermoelectric Modules

A modern thermoelectric module consists of ingot-shaped "n" and "p" type thermoelement semiconductors connected in series through conductors between two insulating ceramics (Figure 5). When the temperature difference is created between the surfaces of this module, the electrical power is transferred in an external way and the module works like a generator.

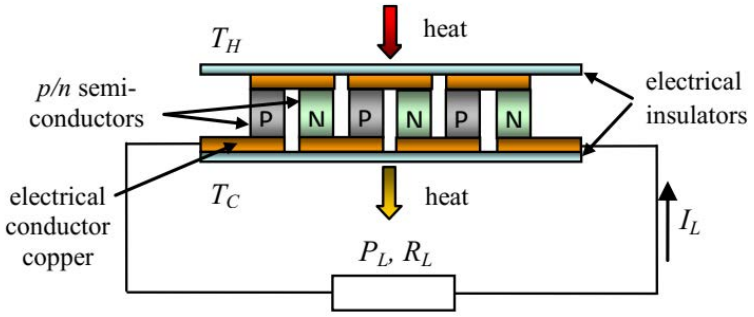

Figure 5. Thermoelectric Modules for Power Generation (Ahiska & Mamur, 2014).

The first commercial thermoelectric generators were produced in 1898 and it have a power of 21 watts. The longest-term use of thermoelectric generators is Radioisotope Thermoelectric Generators used in space probes sent by NASA away from the sun. These devices are closed systems surrounded by many modules with a thermonuclear core in the middle. Many countries continue their research and development activities on these devices, which have been operating for about 20 years without any maintenance and without any change in performance.

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To Cite This Chapter

Erdal, M. O. (2021). Direct energy convertion: thermoelectricity. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp. 191-197). ISRES Publishing

Summary Review on the Early History of the Semiconductor

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Since the middle of 20th century, semiconductors have been at the heart of technological progress. Early electronic devices made to solve simple equations. However, they were expensive and unreliable. Semiconductors changed all that doing the work of a basement full of vacuum tubes with one chip. In 1965, Gordon Moore predicted the number of transistors that could fit in one square inch of integrated circuits would double every two years. For half of century through competition and collaboration the semiconductor's history formed. Semiconductors powered the personal computing revolution, putting incredible capability in our homes and on our desks. They also make electronic devices of every kind smaller, more affordable and long-lasting. Moreover, Semiconductors engendered the emerging technologies literally that were almost science-fiction. Undoutedly, inventions of the transistor and the integrated circuit led to the emergence of the modern computers, telecommunications, and satellite technologies.

Through history of semiconductors, there are indisputable and essential works performed by scientists which led to advent of today's technology. In 1833, M. Faraday observed the properties of silver sulphide, and discovered a negative temperature coefficient in it. Later on, M.A. Rosenschold observed asymmetric conduction in solids in 1835. Afterwards, E. Becquerel realized the effect of the voltage on junction between a semiconductor and an electrolyte under illumination in 1839. M. Faraday also published a paper demonstrating on a temperature sensitive non-linear resistor in 1850. Soon after, Willoughby-Smith expressed the photoconductive effect in 1873, and distinguished the decreasing resistance of crystalline selenium under illumination which led to fabrication of photoconductive cells. Adams and Day discovered the photovoltaic effect existing at a contact between selenium and a metal in 1877. 17 years later, J.C. Bose applied non-linear rectifying properties of semiconductors for electromagnetic waves detection. Therafter, H. Dunwoody and G.W. Pierce discovered that rectification effects were electrical rather than being thermal in 1907-1909. In 1935, O. Heil patented a proposed field effect transistor device. However, transistor was successfully invented on December 23, 1947 by William Shockley, John Bardeen and Walter Brattain at Bell Laboratories. Later on, it was introduced to public by New York Times on July 1, 1948 (Morris, 1990).

Working on semiconductors have been intensified by the late thirties and researches continued until inevntion of integrated circuits at the end of the fifties. In 1947, Bell Lab

is recorded for invention of point-contact germanium transistor and growth of single crystals of germanium and silicon which led to fabrication of the "grown- junction" transistor by Morgan Sparks by introducing dopants directly into the melted germanium during crystal growing. Despite the all fundamental works done by Bell Lab, Texas Instruments fabricated the first grown- junction silicon transistor in May 1954, for military applications due to its various advantages. Photolithography is another transistor fabrication method originated at the Diamond Ordnance Fuze Laboratory (DOFL) and at Bell Labs (Li, 2011).

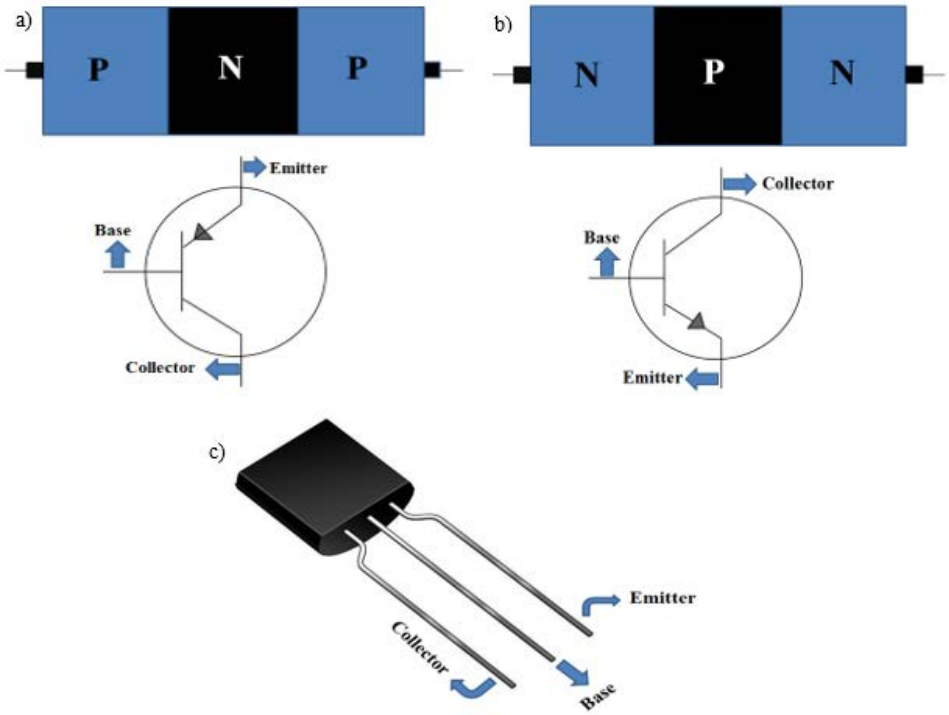

Figure 1. Images of a) PNP, b) NPN, and c) Typical Transistors.

Undoubtedly, Bell Laboratories can be considered as nucleus and origin of today's electronic and technology, which is established in New York city with huge numbers of scientists, researchers, and engineers. Among them, developing a solid-state switching device originated from Mervin Joseph Kelly, who has been director of research, president, and chairman between 1925-1959. During his career as research director, William Shockley was put in charge of the Solid State project. William Bradford Shockley Jr. was awarded the 1956 Nobel Prize in Physics for "his researches on semiconductors and discovery of the transistor effect". At the beginning, Shockley intended to investigate earlier works done by the Pohl group in Germany, and Davydov and Joffe in Russia. Moreover, they investigated the purification of semiconductor materials for microwave detector used in radar. Russell Shoemaker Ohl's researches on properties of crystal detectors for radar applications led him to discovery of the first p-n junction device. Ohl cut a section of sample across an boundary between p and n regions of a silicon ingot solidifying from a doped melt (Lojek, 2007).

Shockley stated a hypothesis that modulated the "field effect" using existing theories for Germanium and Silicon. He proposed that by inducing a surface charge using strong electric field, thin layers of semiconductors can gain conductivity. He also stated that contact potential between n and p type samples can be increased by doping. In November 1947, R. B. Gibney suggested that voltage be applied between the metal plate and semiconductor. Due to current flowed through the sample resistivity can be determined. When the potential of the electrolyte was modulated the current in the external circuit was accordingly modulated. Brattain and Gibney had fabricated amplifiers using the field effect with electrolyte to get the desired high electric field. John Bardeen held U.S. Patent 2,524,033 by modifying the suggested device by Brattain and Gibney, replacing liquid electrolyte with metal forming a rectifying contact with semiconductor. Gibney also held U.S. Patent 2, 560,792, by modifying the device which leads to transistor. Brattain also came up with a device known as "high back voltage" N-type germanium on December 8, 1947. The obtained device exhibited high resistivity. Then Brattain proposed to apply gold on a wedge and then separate the gold at the point of the wedge with a razor blade to make two closely spaced contacts (Lojek, 2007).

Shockley also invented the junction transistor highlighting on 3 significant concepts which are:

1. exponentially-increasing minority carrier injection across the base-emitter junction

2. reverse bias on the collector-base junction

3. appropriate device geometrical dimension and doping profil (Lojek, 2007).

Shockley put his signature on almost ninety U.S. patents due to his undeniable works on theory of vacuum tubes, solid state physics, semiconductor amplifier, electron microscope, nature of metallic state, band theory of solids, order in alloys, space charges and many others (Lojek, 2007).

On December 23, 1947 H. R. Moore had fabricated an oscillator by connecting the input and output of the transistor to a 1 kHz signal and an oscilloscope. In addition to this, Bell Laboratories held five patents in February 26, 1948 covering the basic principle of the transistor. Due to Gibney's contribution his name appears only on two patent applications (Lojek, 2007).

The term of minority carriers were known from the work of Boris Davydov a Soviet scientist. Davydov expanded previous work of Walter Schottky in Siemens & Halske Laboratories in Berlin. On the other hand, Shockley accomplished his theory of junction transistors in early 1948, and used the Davydov junction theory and expanded it for

transistors. Transistor, oscillator, pulse and TV amplifier were announced to public on June 30, 1948. Furthermore, W. G. Pfann and R. Ohl fabricated a "plug-point" contact transistor by modifying the structure of the 1N26 shielded microwave point contact rectifier (Lojek, 2007).

Helmar Frank and Jan Tauc have designed and fabricated successfully the first point-contact transistors outside Bell Laboratories in Prague due to high quality germanium crystals they possessed. In January 1950, Morgan Sparks succeeded in growing crystal rods with a thin-base layer. On April 12, 1950, Morgan Sparks entered into his laboratory notebook, data for a chemically-etched sample made by this grown-junction technique which was working as a large-area transistor (Lojek, 2007).

The two significant transistors developed in BTL were M-1752 and M-1852 transistor. The 1752 was encapsulated in plastic and violet-green-red. The M-1852 shown in Figure 2, was enclosed in a hermetically sealed can and the semiconductor body was covered by red-lead polyethylene-polyisubutylene to reduce some of the detrimental surface effects (Lojek, 2007).

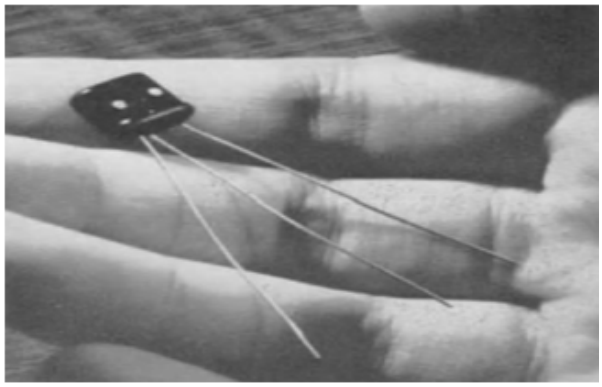

Figure 2. M-1852 Grown-Junction Transistor

John Moll and Ian Ross have developed a theory on diffused transistor impressing two factors that are the magnitude of the built-in fields and the distance over which the built-in field extends. M. Tannenbaum, D. E. Thomas, C. S. Fuller, J. A. Ditzenberger fabricated the double-diffused transistor which exhibited high speed, low saturation current, and satisfactory operation at high temperatures. Scientists from GE Research Laboratories developed the P-N junction produced by an "alloying process" in 1950 (Lojek, 2007).

Lew Miller designed the silicon NPN transistor with mesa "ring-dot" structure which was manufactured by Western Electric as the 2N560 for military logic applications (Lojek, 2007).

In 1955, Shockley decided to establish his own company (Shockley Semiconductor) and left Bell Telephone Laboratories. Bishop, Beckman and Shockley focused on four-

layer diode and Junction Field Effect Transistor. A revolutionary device, the four-layer diode was supported by military contracts in 1957. Unlike common rumor, Shockley Semiconductor Laboratory never developed a mesa transistor similar Bell Laboratories's device. There were two major innovations in Shockley Semiconductor Laboratory. Firstly, they have used photoresist for patterning of semiconductor structures. Secondly, they used silicon oxide to protect the semiconductor surface during diffusion. While, the obstacles on device development were associated to the diffusion and contacting the diffusion regions. It was well-known that poor junctions and worse contacts caused a large reverse leakage current (Lojek, 2007).

Jean Amédée Hoerni, who was a silicon transistor pioneer, developed the planar process. Later on, Shockley hired Hoerni to work with him at the Shockley Semiconductor Laboratory division of Beckman Instruments. Hoerni focused mainly on the diffusion and samples evaluation; Harry Sello developed the wax masking; Sheldon Roberts and Noyce worked on the ohmic contacts (Anonymous a, 2021).

Hoerni made the second big invention after the invention of the junction transistor by silicon planar device fabrication on Wednesday, March 4, 1959. He also developed a sophisticated oxidation method which was affecting the pinholes in oxide film. The significant advantage of the planar process is oxide passivation of the semiconductor substrate, which improved the electrical parameters such as reverse leakage current, breakdown voltage, noise figure, and low current hFE. Hopefully, the planar process eliminated the main disadvantage of the mesa transistor which was collector-base junction being vulnerable to contamination during contacting and assembling. Fairchild Semiconductor demonstrated the diffused planar transistor in March 1960 and the planar version of the 2N696 begun for sampling in August 1960. Regarding to 1000 hour test, the planar transistor challenged all mesa transistor by exhibiting less than one nA of leakage at VC = 60 V compared to other mesa transistor (10 nA at VC = 30 V). The novel device made Fairchild sales increasing to 80% and booking to 90% (Lojek, 2007). Side views of mesa and a planar transistor are shown in Figure 3.

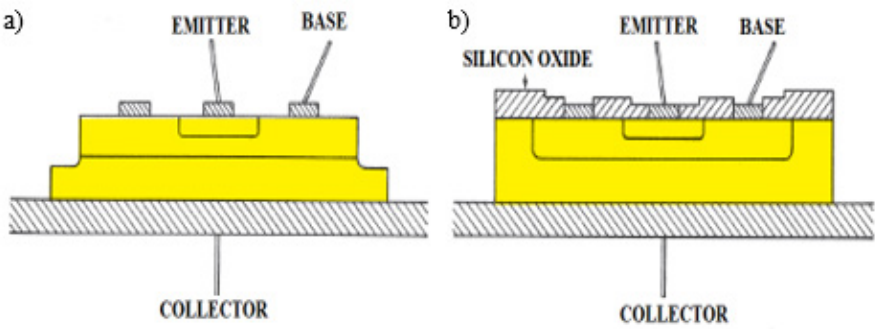

Figure 3. a) Side Views of a Mesa and b) a Planar Transistor, from a Report Hoerni Prepared in 1960 (Riordan, 2007).

Jay T. Last a silicon pioneer was born on October 18, 1929 and worked at the Shockley Semiconductor Laboratory from April 1956 to September 1957. Jay Last figured out the significance of linear integrated circuits and made Amelco the first major supplier of linear integrated circuits. Amelco's contributions were high-end weapons systems, submarines, space launchers, satellites, space stations, and many other applications (Anonymous b, 2021).

Fairchild Semiconductor International, Inc. was established in 1957 located in San Jose, California. The Fairchild's establishers were Gordon Moore, Jean Hoerni, Robert Noyce, C. Sheldon Roberts, Jay Last, Victor Grinich, Eugene Kleiner, and Julius Blank (Li, 2011). It became a pioneer in the manufacturing of transistors and of integrated circuits. By the end of 1957, Fairchild decided to continue the same approach as Shockley Laboratories with wax masking and patterning structure on mesa transistor fabrication. Moreover, they used photoresist developed by Eastman Kodak for patterning of printed circuits. Fairchild Semiconductor fabricated the first silicon transistors (2N696 and 2N697) in Silicon Valley, in 1958 (Lojek, 2007). Fairchild Semiconductor's paramount innovations were technology for diffused silicon devices, the planar process, and the planar integrated circuit (Li, 2011). Whereas, Fairchild Semiconductor applied combining diffusion, oxide masking, and photolithography methods.

Haas and Kattner modified the diffusion process and Lionel Kattner produced the very first integrated circuit in May 1960. Haas tested the circuit which suprisingly seemed functional with the maximum operating clock 1 megahertz and the delay 60 nanoseconds. Haas modified the transistor geometry by replacing the Carbon resistors with diffused resistors in August 1960. Unfortunately, the device passed tests at room temperature and failed at 70 ^{o}C (Lojek, 2007).

L. Kattner modified an integrated epitaxial transistor based on the Fairchild 2N914 device in March 1961, to simplify the isolation problem. Besides, Bob Norman designed the first Micrologic Flip-Flop circuit. Bob Norman and Bob Anderson designed and introduced Flip-Flop (4 transistors, 2 resistors), Half-shift register (9 transistors, 5 resistors), Gate (3 transistors, 1 resistor), Buffer (3 transistors, 3 resistors), Half Adder (4 transistors, 3 resistors), Counter Adapter (6 transistors, 5 resistors), and Shift Register (17 transistors, 9 resistors) in summer 1961 (Lojek, 2007).

National Semiconductor preserved patent notebooks carefully and donated materials and reports of Fairchild to Stanford University, after they took management of Fairchild in 1987. On the other hand, Sylvania introduced the world's ever fastest silicon switching transistor (2N2784) in August 1963, with high beta in the microamperes range, with gradual fall off beyond 10 mA, low saturation voltage, typically 0.2 V and switching speed of 12 nsec (Lojek, 2007).

Texas Instruments convinced Regency Radio to invest in TI for radio receiver fabrications and certainly made it a pioneer in the germanium transistors marketting. Haggerty was another investor in TL and put $3 million for silicon transistor fabrications during 1952–55. Eventually, in early 1954, they had fabricated a working silicon device similar to the germanium junction transistor designed at Bell Labs. Therafter, the effect of strong electric fields on the observed spreading resistance of metal-germanium point-contact rectifiers was investigated by Lark-Horovitz and R. Bray during 1949–1950, which somehow resembled to the work carried out at BTL (Lojek, 2007).

Lehovec equipped the laboratory and intended not to duplicate BTL devices. Additionally, he worked on the photo-voltaic effect, light-emitting diodes and lithium batteries, and successfullu came up with the concept of p-n junction isolation used in every circuit element. Furthermore, he realized and highlited the exhausting labor to manipulate under a microscope two tiny wires to the correct position and the possibility of sliding of the wires during the handling the device as 2 main hurdles being in BTL transistor which the Sprague Company licensed. Lehove's contributions were mainly to CV techniques, solar cells, solid-state batteries, and LED diodes (Lojek, 2007).

The Sprague Electric R&D group successfully introduced the first design of their first integrated circuit during 1961-1962. Sprague Company was also pioneer in the lead of ion implantation technology in the early sixties (Lojek, 2007).

The Signetics hired a former employee of Fairchild Orville Baker who developed the DTL series SE100. The Signetics DTL series contained a metal-overoxide capacitor, with a propagation delay of 25 nsec with a power consumption of 6 mW per gate (Lojek, 2007).

By early 1965, Sylvania was credited for the largest selection of compatible digital circuits production. The Sylvania company produced the best speed-power and the highest level of noise immunity devices. On ther hand, Fairchild did not produce any high quality memory devices before 1968. The only memory device available was an 8 bit Micrologic element with a cost of $2 per memory bit and a 256-bit static RAM 4100 designed by H. T. Chua (Lojek, 2007).

At the end of a semiconductor industry recession during 1970 and 1971, Longo's group introduced a new product line including low power Schottky logic (the 9600 series) and later ECL logic. The group started work on a 1k static RAM, which Longo offered to his old friend Seymour Cray who was developing the Cray-1 computer. Fairchild's 1k (and later 4k) static RAM was used in the Cray-1 as a main memory. The cost per bit dropped to 17 cents and other main-frame computer manufacturers such as Univac, CDC, Burroughs, Fujitsu, and Siemens also switched from core memory to semiconductor memory (Lojek, 2007).

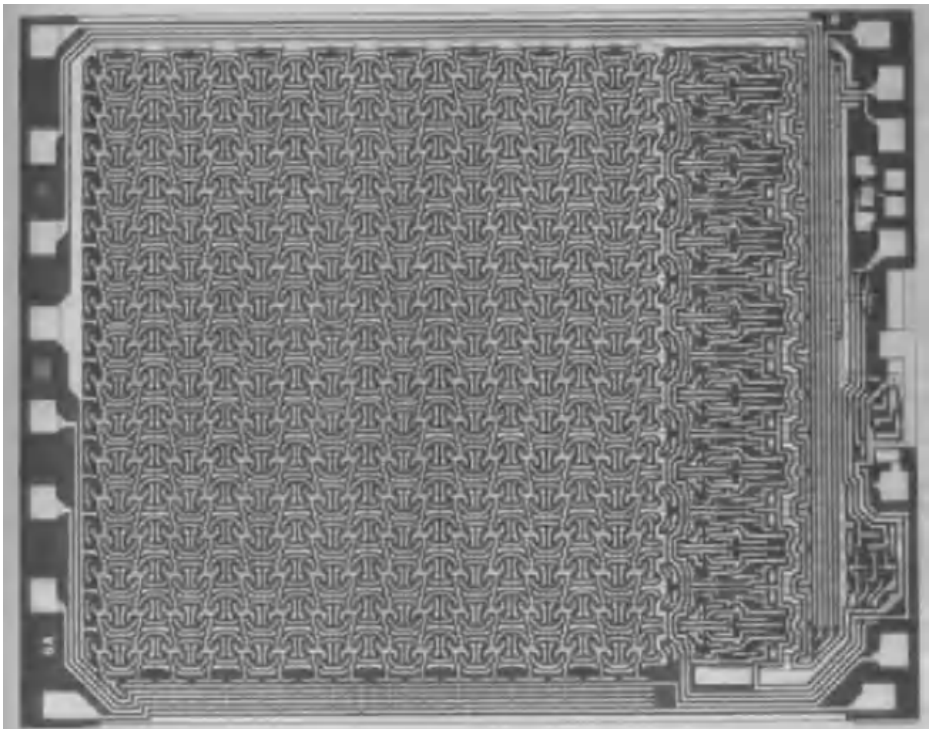

Figure 4. Fairchild's 256-bit Static RAM 93410 (2650×3400µm) (Lojek, 2007).

After Tom Longo left Fairchild in 1984, he established Performance Semiconductor Corporation to manufacture fast CMOS and static memory. Later on, the world's fastest 16 bit 40 MHz microprocessor 1750 was developed for airborn computers and weapons systems. The 1750 was mainly produced in radiation resistant forms for military applications. Tom Longo argued that BiCMOS will almost double the mask count and the bipolar part will not be scalable. Performance Semiconductor expanded business up to a $200 million annually. Unfortunately, after the fall of the Soviet Union military projects stopped (Lojek, 2007).

An eminent engineer of General Electric company, Dr. Robert N. Hall invented power rectifier device made of germanium and figured it out the recombination of the electrons and holes that it can produce. Somehow, rectifiers developed by silicon are widely used in power delivery, locomotives, power distribution system and dc transmission. He also invented the first semiconductor laser, intrinsic detectors and hyper pure germanium detectors. As a one of the pioneers in semiconductor history he held 43 U.S. patents (Anonymous c, 2021).

Hoerni established Intersil with $300,000 of his own budget, then investments on Intersil increased to $4.5 million. The first N-MOS memory technology was developed by Intersil, which had low voltage metal-gate CMOS technology for the quartz clock and EPROM (Lojek, 2007).

The Semiconductor Department of Westinghouse decided to fabricate high power semiconductor devices. Westinghouse applied the technology used at TI and introduced

the industry's first silicon power transistors, 2 and 5 amp units rated at a maximum collector current of 7.5 amps with the highest available power rating of 150 W. They also developed and delivered Molecular Receiver AN/ARC-63 to Air Force in 1961 (Lojek, 2007).

Within the history of microelectronics, Bob Widlar remains as inventive genius due to his various inventions such as linear integrated circuits, the Widlar bandgap voltage reference, µA702, µA709, LM100, LM105, super-beta transistors (LM108), and the first operational amplifiers (LM101). Bob and Dave Talbert developed brilliant manufacturing methods and process control to decrease the price of the planar process. Dave also worked on development of a process which included an epitaxial layer. Moreover, John Barrett determined probable performance of a differential amplifier using the Micrologic kit block on April 1, 1962 (Anonymous d, 2021). The µA709 operational amplifier is shown in Figure 5.

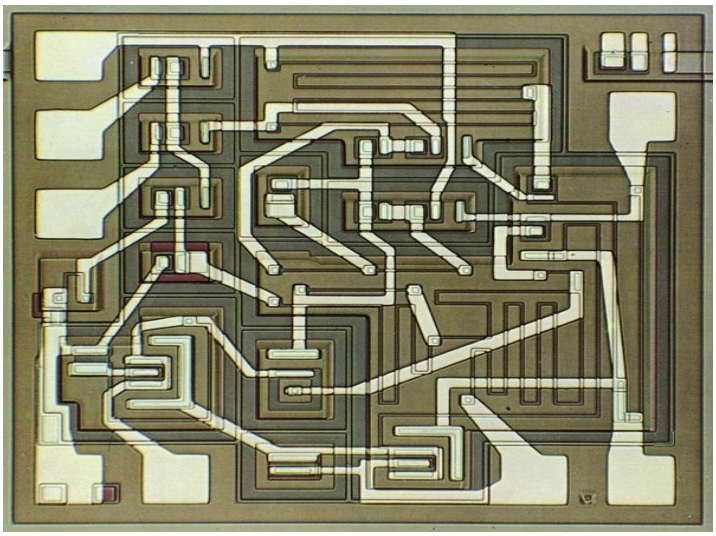

Figure 5. The µA709 Operational Amplifier Developed by Widlar (Anonymous e, 2021)

Computer components and calculator chips increased the demand for MOS technology in 1960s. In July 1970, AMI developed the 6-chip set that contained all the MOS circuitry for an arithmetic calculator. AMI was quickly followed by Texas Instruments and North American Rockwell (Lojek, 2007).

MOS technology and its advantages attracted engineers worldwide. Due to its huge demands 20 companies started developing MOS technology by 1969. MOS technology were used in calculator, electronic memories and electronic wristwatches fabrications which rose the MOS market to $80 million in 1970. However, a significant loss in global market share appeared between 1990-2000 (Lojek, 2007).

In conclusion, owing to the invention of transistor, the human race is more interwined to technology. Inspite of it's simple archietecture, it is absolutely the foundation of the modern technology and devices. Without the transistors, accessing to myriad

of informations would be time-consuming and troublesome. Moreover, in order to understand it's impact, we need to ponder over the science and history behind it.

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To Cite This Chapter

Hussaini, A. A., & Yıldırım, M. (2021). Summary review on the early history of the semiconductor. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.198-208). ISRES Publishing

SECTION 6
BIOLOGY & LIFE SCIENCES

Non-Coding RNAs in Autophagy Regulation

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Non-Coding RNAs

The human genome contains around 20,000 protein-coding genes, accounting for 2% of the genome. The rest of the genome was considered evolutionary junk until the last 20 years. With the publication of the first draft of the human genome project about 20 years ago, it was revealed that the sequences considered as junk in the genome constitute a large part of the genome. When these sequences, defined as garbage, were identified as Non-Coding RNAs (ncRNAs), they have attracted attention in the RNA world. The genome Tilling Array method revealed that non-coding sequences were at least four times more abundant than coding sequences (Consortium, 2004; Ezkurdia et al., 2014). Considering the great influence amount of ncRNAs in the organism on the complex molecular mechanisms of complex organisms, it is suggested that it might be directly proportional to the level of development of the organisms. Although the C-value paradox was largely unknown before the discovery of noncoding RNAs, it has been partially resolved with the completion of the human genome project (Gall, 1981; Kung et al., 2013).

Studies on ncRNAs have revealed many unknowns about the genome and brought new complications. It is sometimes difficult to distinguish between ncRNAs and protein-coding sequences. Although protein-coding sequences have an open reading frame (ORF) longer than 100 amino acids, they can be distinguished from non-coding RNAs. However, rarely some long ncRNAs (lncRNAs) may also contain ORFs longer than 100 amino acids. There is still no definition of ncRNA that can distinguish between coding and non-coding sequences with sharp lines (Chooniedass-Kothari et al., 2004; T. Kondo et al., 2007).

Various classifications have been made to partially facilitate the complex world of ncRNAs. However, ncRNAs are commonly classified according to their length. ncRNAs are classified as lncRNAs that are longer than 200 nucleotides and short ncRNAs (sncRNAs) that are shorter than 200 nucleotides. Ribosomal RNAs (rRNA), small nuclear RNAs (snRNA), carrier RNAs (tRNA) and small nuclear RNAs (snoRNA) are also members of sncRNAs and are classified as housekeeping ncRNAs. In addition, microRNA, piRNA, siRNA, CrasiRNA, snoRNA and tel-sRNAs are also members of

sncRNAs and have regulatory functions. (Katsarou et al., 2015).

LncRNAs

lncRNAs, a fairly broad subclass of ncRNAs, are generally non-protein-coding transcripts which are poorly conserved across species. Compared to sncRNAs, lncRNAs are more structurally and functionally diverse. Most of the transcripts identified in the literature as lncRNAs are transcribed by polymerase II, similar to mRNAs. LncRNAs can undergo 3' polyadenylation (poly(A)), 7-methyl-guanine cap insertion and cleavage, similar to mRNAs. Although lncRNAs are very similar in structure to mRNAs, the signals that direct them to their cellular localization are still enigmatic. In addition, lncRNAs have lower expression levels than protein-coding transcripts. However, many lncRNAs show tissue-specific expression profiles and function as regulatory specific to developmental processes (Katayama et al., 2005).

The functions of lncRNAs depend upon their localization in the cell. Cellular localization of lncRNAs can provide information about their functions. Some of the lncRNAs are localized in the cytoplasm and some in the nucleus. LncRNAs in the cytoplasm might be involved in expression regulation at the mRNA level. LncRNAs that are localized in the nucleus could bind directly to the target gene and inhibiting or activating gene expression (Taft et al., 2010).

LncRNAs could regulate gene expression in various ways and levels and also interact with RNA-binding proteins. LncRNAs could inhibit mRNA expression by binding to transcription factors which bind target mRNA, or they could act as decoys by mediating the degradation of target mRNA. Some LncRNAs that could interact with the PRC2 complex lead to histone modifications and play an important role in epigenetic regulation (Hajjari & Salavaty, 2015). LncRNAs contain several potential binding sites for miRNAs. Complementary base pairing between lncRNAs and miRNAs, RNA-RNA interaction causes lncRNAs functions as a sponge to miRNAs and inhibits miRNA expression. Another group of lncRNAs acts as a scaffold, facilitating the interaction of various proteins and playing a role in the regulation of cellular processes (Y. Kondo et al., 2017).

LncRNAs could be categorized according to their transcript length, their relationship to protein-coding genes, and their relationship to DNA elements (Laurent et al., 2015). The most widely used lncRNA categorization is based on their association with protein-coding genes. LncRNAs to their relationship with protein-coding genes; classified as intergenic lncRNAs, antisense lncRNAs, and intronic lncRNAs (Jarroux et al., 2017).

Intergenic lncRNAs (lincRNAs) are synthesized from the region that does not overlap with protein-coding genes. To date, 13,105 lincRNAs have been identified in the genome

(Cabili et al., 2011). While the distance of lincRNAs to protein-coding genes can be up to 3 Mb, their average distances is 40 kb (Hon et al., 2017).

Intronic lncRNAs are transcribed from the intronic regions of protein-coding genes. Circular RNA (circRNA), circular intronic RNA (ciRNA), exonic circRNA (ecircRNA), exon-intron circRNA (EIcircRNA) and switch RNA are the major types of intronic RNA (Jarroux et al., 2017). CircRNAs have a tissue-specific expression profile and the vast majority are ecircRNAs. While ecircRNAs are mostly located in the cytoplasm, ciRNAs are localized in the nucleus and may play a role in gene regulation at the transcriptional level (Jeck et al., 2013; Memczak et al., 2013).

Antisense lncRNAs are transcribed from the opposite strand of protein-coding genes. Antisense lncRNAs are common in the genome and have complementary sequences with other transcripts. Antisense lncRNAs can be divided into two subgroups, cis and trans. Trans-antisense lncRNAs are transcribed from different genomic regions, while cis-antisense lncRNAs are transcribed from the opposite strand in the same genomic region. Cis-antisense lncRNA pairs contain exactly overlapping regions. Antisense lncRNAs could regulate gene expression at the pre-transcriptional, transcriptional, and post-transcriptional levels (Villegas & Zaphiropoulos, 2015).

LncRNAs are classified as long intergenic RNA (lincRNA), very long intergenic RNA (vlincRNA), macro RNA and promoter-associated long RNA (PALR) according to their transcript length. ANRIL, H19, HOTAIR, HOTTIP, lincRNA-p21 and XIST are well-studied lincRNAs. vlincRNAs are RNAs encoded from an intergenic space with transcript lengths ranging from 50 kb to 1 Mb (Laurent et al., 2015). Over 2000 vlincRNAs have been identified, accounting for approximately 10% of the genome in humans (Laurent et al., 2015; St Laurent et al., 2013). Macro RNAs are also quite large like vlincRNAs, they are transcripts larger than approximately 10 kb. Airn, Nespas, KCNQOT1, Gtl2lt, Lncat transcripts are examples of macroRNAs (Laurent et al., 2015).

MicroRNAs

MicroRNAs (miRNAs) are single-stranded sncRNAs about 22 nucleotides in length. miRNAs interact with target sequences through complementary base pairing. Target sequences of miRNAs could be ncRNAs or protein-coding transcripts. miRNAs can shorten the poly(A) tails of target mRNAs, thus destabilizing the mRNA leading to degradation of the target mRNA or suppressing translation (Cai et al., 2009). miRNAs interact with mRNAs in different ways, acting as key molecules responsible for regulating much of the genome. As a result of broad-spectrum gene regulation of miRNAs, they have a regulatory role in cell growth, apoptosis, cellular differentiation, and the performance of various cellular functions (Bushati & Cohen, 2007). Moreover, studies have shown that miRNAs have an important role in autophagy control (Su et al., 2015).

Like lncRNAs, miRNAs can act as tumor suppressors or oncogenic depending on the functions of their target mRNAs (ARMAN et al., 2016). Although it is known that the region selection of miRNAs on the target mRNA is often in favor of the 3'UTR, there are studies showing that they can also bind to regions other than the 3'UTR (Bartel, 2009).

Similar to lncRNAs, miRNAs can be synthesized from intergenic and intronic regions. However, although rarely, miRNAs synthesized from exonic regions are also available. About one-third of miRNAs are synthesized from the intronic region (Olena & Patton, 2010; J. Xu et al., 2012). Most miRNA genes are synthesized by RNA polymerase II in the nucleus, but few miRNAs synthesized by DNA polymerase III have also been identified (Vishnoi & Rani, 2017). Biogenesis of miRNA is a multi-step process. In the first step, the miRNA gene is converted to pri-miRNA by the enzyme RNA polymerase II. Although there is insufficient information about the effects of pri-miRNAs on transcriptional regulation, they are only a few kb in length. pri-miRNAs usually have a 7-methyl guanosine cap at the 5' end and a poly(A) tail at the 3' end and are similar to protein-coding mRNAs. Whether these RNAs contain an ORF (open reading frame) or not, they are spliced and became a loop as the poly(A) tail is attached. After the cleavage of pri-miRNAs is carried out in the nucleus by the Pasha (Drosha/DGCR8) enzyme, the pre-miRNA formed is transferred from the nucleus to the cytoplasm via Exportin-5-Ran-GTP. The loop portion of the pre-miRNA is cleaved by the Dicer/TRBP complex in the cytoplasm. The mature miRNA duplex structure obtained after cutting is transferred to the RISC complex together with Ago2 proteins. In the final step, one of the strands of the RISC complex mature miRNA is selectively digested (Winter et al., 2009).

Autophagy

The dictionary meaning of the word autophagy in the Greek language is self-digestion. The term was coined in 1963 by C. de Duve, who discovered lysosomes in 1955. Then, G. Mortimore revealed the inhibitory effect of amino acids and insulin on autophagy. The relationship between autophagy and insulin have suggested that diabetes may have an effect on autophagy. With the beginning of the 2000s, the molecules involved in the autophagic mechanisms and their roles have begun to be clarified (Ohsumi, 2014). With its current definition, the autophagic process is the directing of damaged proteins and organelles in the cell to the lysosome within the autophagosome vesicles, their destruction by the lysosomal enzymes in the lysosome, and the reuse of the building blocks that emerge after the destruction of the cell. In many studies have shown that autophagy is triggered under cellular stress conditions such as oxygen deficiency, growth factor deficiency and starvation (Klionsky, 2007). As a result of the stimulation of autophagy under cellular stress conditions, organelles and proteins as well as pathogens are destroyed. Building blocks obtained after autophagic destruction play an important role in cell homeostasis by providing nutrients and energy to the cell (Ravikumar et

al., 2010). On the other hand, in cases where apoptosis is not possible, it has also been reported that autophagy leads to cell death, depending on variables such as the type, duration and amount of the stimulator. Therefore, to distinguish autophagic cell death from apoptosis, it is also called type II cell death. Autophagy can also be defined as a mechanism that plays a role in deciding whether the cell will survive or die according to the conditions of the cell (Shintani & Klionsky, 2004; White & DiPaola, 2009).

Anomalies in the autophagy pathway have revealed that autophagy is closely related to cancer, neurodegenerative diseases such as Parkinson's and Huntington's, and infectious diseases. Therefore, it is possible to say that autophagy has an effect on pathophysiological conditions. (Jiang & Mizushima, 2014; Levine & Kroemer, 2008).

Types of Autophagy

There are 4 different types of autophagy in generally: macroautophagy (lysophagy), microautophagy, RN/DNotophagy, and chaperone-mediated autophagy (Yim & Mizushima, 2020). In addition, there are different types of lysosomalphagia named according to the type of digested substrate and digestive vesicle. E.g; the direct digestion of mitochondria by the lysosome is defined by micromitophagy, while autophagosomal digestion is expressed by macromitophagy. The terms lysosomal digestion of the endoplasmic reticulum are reticulophagy, and the terms xenophagy are used for the lysosomal digestion of bacteria and viruses (W. Li et al., 2012).

The process of macroautophagy is one that may also involve digestion of various cytosolic residues and damaged organelles. At the beginning of macroautophagy, the phagophore fuses with the lysosome after maturation to the autophagosome, forming the autolysosome (Yim & Mizushima, 2020). Autophagosome formation is not observed in the microautophagic process. Autophagic material is digested by taking it into the lysosome by forming an inward pocket of the lysosome (W. Li et al., 2012).

In the chaperone-mediated autophagic process, Hsc70 chaperones play an active role in recognizing the substrates to be degraded by their lysine, phenylalanine, glutamic acid, arginine and glutamine sequences and directing them to the lysosome. Substrates transferred to the LMP-2A protein in the lysosomal membrane trigger multimerization of LMP-2A so that the substrate can be translocated across the lysosomal membrane. After translocation, the substrate is digested by lysosomal enzymes (Rios et al., 2021).

In RN/DNautophagy, RNA and DNA bind directly to the receptor on the lysosomal membrane and are transferred by the receptor to the translocon protein. The translocon protein SIDT2 transports nucleic acids directly into the lysosomal lumen and the nucleic acids are digested (Yim & Mizushima, 2020).

Steps of the Autophagic Process

The autophagic process is a multistage and complex set of mechanisms consisting of induction, vesicle nucleation, vesicle elongation, retrieval, and fusion phases (Frankel & Lund, 2012). The first step of this process, the induction step, is the stimulation for the formation of a double-layered membrane structure called the autophagosome. When cells need food or energy, mTORC1, which is active under normal conditions, becomes inactive. Inactive mTORC1 cannot suppress the ULK1/2-ATG13 complex and autophagic stimulation occurs (Mizushima et al., 2002).

Vesicle nucleation, the second step of autophagy, is the nucleation of the membrane structure derived from the membrane of the endoplasmic reticulum, golgi, or mitochondria. This step occurs with the establishment of the PI3KC3 complex. The PI3KC3 complex is formed by the interaction of the proteins PI3KC3, Beclin1, Bcl-2, UVRAG, Atg14, Atg9, Atg2 and Vsp15. Inactivation of mTORC1 as a result of stress conditions such as starvation or hypoxia activates PI3KC3, thereby producing phospholipids required for vesicle nucleation (Y. Yang & Liang, 2015). The Rubicon protein functions as a repressor of the PICKC3 complex (Frankel & Lund, 2012).

In the third step of autophagy, membrane elongation takes place for vesicle formation. In this step, ubiquitin-like conjugation systems take place. In the first of these systems, ATG5 and ATG12 are linked together, via ATG10 and ATG7. Following ATG5 and ATG12 binding, ATG16 binds to this complex. In the second conjugation system, ATG4 cleaves the terminal portion of LC3 to expose the glycine residue. Thus, phosphatidyl ethanolamine can bind to cleaved LC3. The phosphatidylethanolamine binding process to LC3 is activated by the ATG5-ATG12 conjugation system. Added phosphatidyl ethanolamine induces LC3 phagophore formation (Frankel & Lund, 2012; Y. Yang & Liang, 2015).

In the fourth step of autophagy, the ATG9-ATG2-ATG18 complex promotes the expansion of lipids and proteins by incorporating them into the phagophore membrane (Frankel & Lund, 2012).

In the last step of autophagy, the lysosome and autophagosome fuse and the substrates are degraded by lysosomal enzymes and the building blocks are reused by the cell. The fusion of the lysosome and autophagosome is accompanied by the Rab and SNARE proteins (Nakamura & Yoshimori, 2017).

Each step is regulated by many autophagy-related genes and various ncRNAs. This makes the autophagic process very complex and difficult to analyze. However, with increasing studies, new regulatory genes that contribute to the autophagic process are being discovered and their contributions to the process are revealed.

MicroRNAs in Autophagy

ATG6, commonly known as Beclin1, is a member of the ATG family, which are important regulators of the autophagic pathway. Beclin1 plays a scaffold role in the formation and maturation of autophagosome structure (Wirawan et al., 2012). miR-30a (Zhu et al., 2009) and miRNAs such as miR-376b (Korkmaz et al., 2012) and miR-519a (Huang et al., 2012) downregulate autophagy by suppressing the expression of Beclin1. miR-376b, In addition, various modifications of Beclin1 have been associated with various cancers and neurologic diseases such as Alzheimer's and Parkinson's (Wirawan et al., 2012).

ATG5, ATG12 and ATG16 function in triggering autophagic elongation and are promoted by ATG7 and ATG10 (Frankel & Lund, 2012; Noda et al., 2011). miR-519a acts as an inhibitor of autophagic elongation by targeting ATG10 as well as Beclin1 (Huang et al., 2012). miR-199a-5p inhibits autophagosome formation by suppressing ATG7 (N. Xu et al., 2012).

Epidermal Growth Factor Receptor (EGFR) is another protein responsible for the regulation of autophagy. When EGFR is bound by the ligand, autophagic stimulation is inhibited, otherwise autophagic stimulation occurs when the cell is under starvation and stress (Jutten & Rouschop, 2014). miR-7 indirectly contributes to autophagic stimulation by directly targeting EGFR. Upregulation of miR-7 promotes autophagy, whereas inhibition of miR-7 inhibits autophagy (Cao et al., 2019).

LncRNAs in Autophagy

LncRNAs can regulate gene expression of transcripts in many ways. Because of the game-changing role of lncRNAs in gene expression regulation and their effects on genes involved in cellular processes, they are responsible for the development and regulation of various diseases. A large number of lncRNAs have been associated with cancer, various neurologic diseases, autoimmune diseases, muscle diseases, and various physiological conditions (Mathieu et al., 2014). In various cancers, lncRNAs have been identified as tumor suppressor or oncogenic. In addition, some lncRNAs function bifunctionally (Guzel et al., 2020). The diverse nature of lncRNAs makes their interaction with proteins and transcripts in the autophagic pathway inevitable. There are oncogenic and tumor suppressor lncRNAs that induce or inhibit autophagy.

HOTAIR, an oncogenic lincRNA, triggers autophagy by upregulating the autophagy genes ATG3 and ATG7 and promotes cell proliferation in hepatocellular carcinoma (HCC) (L. Yang et al., 2016). Similarly, in HCC, MALAT1 activates autophagy through miR-26b inhibition and promotes multidrug resistance (Yuan et al., 2016). In another study, it was revealed that lincRNA MALAT1 promotes proliferation and metastasis while activating autophagy through LC3 upregulation in pancreatic cancer (L. Li et al., 2016).

HULC associated with autophagy genes activates autophagy in pancreatic cancer and gastric cancer, respectively, by increasing the LC3-II/LC3-I ratio and Sirt1protein levels (Xiong et al., 2017; Zhao et al., 2014). MEG3, a tumor suppressor lncRNA, activates autophagy by upregulating Atg3 in ovarian carcinoma. Upregulation of Atg3 inhibits tumor development in ovarian carcinoma (Xiu et al., 2017). Another study demonstrated that MEG3 suppressed autophagy and cell proliferation (Ying et al., 2013). LncRNA MEG3 exerts a bifunctional effect on autophagy. LncRNA GAS5 suppresses autophagy in non-small cell lung cancer (NSCLC), increases cisplatin drug sensitivity and enhances chemotherapy efficacy (Zhang et al., 2016).

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To Cite This Chapter

Sahin, Y., & Altan, Z. (2021). Non-coding RNAs in autophagy regulation. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.210-222). ISRES Publishing

Plant Tissues

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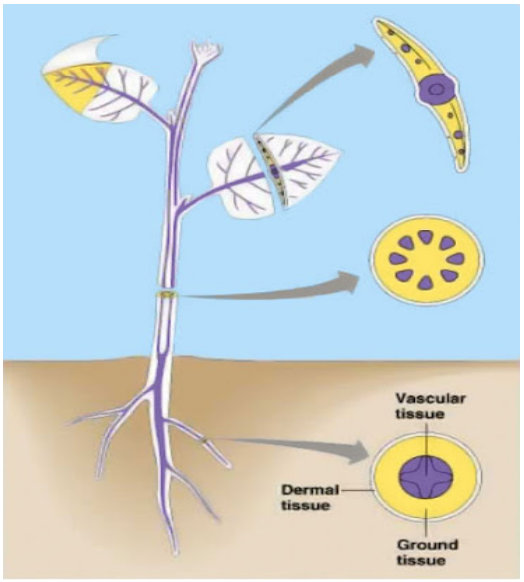
Introduction

Like animals, plant organs also contain tissues. A group of cells that perform a specialized function come together to form tissues. Several types of cells that perform a common task in plants are arranged among themselves to form tissue systems. In other words, a tissue system consists of more than one tissue. Each plant organ (root, stem, leaf) is composed of these tissue systems (ground, vascular, dermal tissue systems). Each tissue system is continuous throughout the entire body of the plant, but is arranged differently in the root, stem, and leaf.



We can generally classify plant tissues under two main headings.

1. Meristematic tissues

2. Permanent tissues

    Dermal tissue

    Ground tissue

    Vascular tissue

    Secretory tissue

Figure 1. Three Tissue System (Campbell and Reece, 2001/2006)

1. Meristematic Tissues

The growth and elongation of the plant occurs by the division and expansion of the cells at the root and shoot tips. This growth is carried out by a tissue called meristem, which consists of cells with a large nucleus, abundant cytoplasm, small and thin walls, and no intercellular spaces. Meristematic cells have the feature of continuous division, thus allowing the plant to grow in length and width. These areas where growth takes place are called growth points. Meristematic tissues are classified according to their location and origin.

A. Meristems by Location

1. Apical (at the tips) meristem: The meristem tissues located at the tips (buds) of the root, stem and their side organs are called apical meristem. It allows the plant to elogation. This elongation, called primary growth, allows the roots to spread in the soil and the shoots to have more contact with light and carbon dioxide. Herbaceous plants only show primary growth. Secondary growth is also seen in woody plants.

2. Intercalary meristem: These are the meristems that remain between the permanent tissues. Leaves, flowers and fruits reproduce their size by division of intercalary meristems. Together with the apical meristem, it ensures the longitudinal growth of the plant.

2. Lateral meristem: It is the meristem tissue that extends along the root and stem and provides the transverse growth of the plant. It is mostly found in plants with secondary growth. Secondary growth in woody plants occurs by the lateral meristem. The cambium on the stem is a good example of lateral meristems. The cambium maintains its effectiveness throughout the life of the plant, it is located between the xylem and the phloem and divides in both directions, allowing the plant to thicken.

B. Meristems by Origin

1. Primary meristem: It is the meristem that does not lose its ability to divide during the life of the plant from the embryo. The apical meristems located at the ends of the roots, stems and lateral branches, called the growth points in plants, produce primary meristem cells. These parts provide both the elongation of the plant and the origin of the tissues that make up the organs. When cross-sections are taken from the growth points, it is observed that there are three layers called dermatogen, periblem and plerome from the outside to the inside. Dermatogen gives rise to epidermal tissue, periblem gives rise to ground tissue and the plerome gives rise to vascular tissue.

2. Secondary meristem: It is formed as a result of the cells in the state of Permanent tissue gaining the ability to divide by the effect of environmental factors or hormones. For example, when a branch of the plant is cut off, some cells begin to divide to close that area and a secondary meristem is formed. Secondary meristem provides transverse thickening in the root and stem parts of the plant that grows longitudinally. Two lateral meristems called cambium and cork cambium are responsible for this transverse thickening.

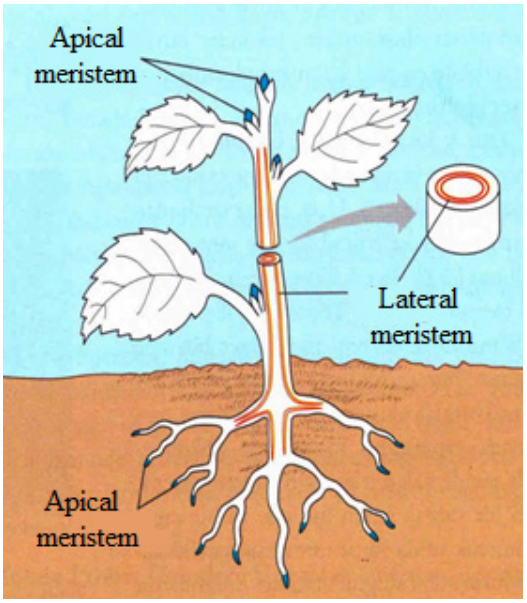


Figure 2. Meristem Regions (Campbell and Reece, 2001/2006)

2. Permanent Tissues

They are tissues that have formed as a result of the development and differentiation of primary and secondary meristem cells and have lost their ability to divide. They can be dead or alive. Their cells have little or no cytoplasm, thick cell walls and wide vacuoles. They have intercellular spaces. With these features, they can be distinguished from meristem cells.

A. Dermal Tissue

It is the tissue that covers the entire surface of the plant and protects the plant organs against water loss, various physical and chemical effects, and disease-causing organisms. Epidermis and Peridermis is dermal tissue.

1. *Epidermis*

Tissue found in young parts of herbaceous and woody plants. It covers organs such as roots, stems and leaves. Its viable, large vacuole, little cytoplasm cells are tightly packed and lack chloroplasts. It is specialized according to the function of the organ it covers. For example, extensions of epidermal cells near the root tip form root hairs, which are important for the plant's water and mineral absorption.

The epidermis of most stems and leaves secretes a waxy and transparent covering called the cuticle. The cuticle prevents excessive water loss in the above-ground parts of the plant. It also provides mechanical support to the plant and protects the plant against microorganisms. The thickness of the cuticle layer varies according to the environment

in which the plant is located. It is thick in arid zone plants and thinner in humid zone plants.

Epidermis cells differentiate and form specialized structures to perform various tasks. These are structures such as.

Stoma (pore): Since the tightly arranged epidermis cells completely cover the outer surface of the plant, stomata have developed to provide gas exchange between the internal and external environment. Stomata are formed by the coming together of two bean-shaped stomatal cells (guard cells) with a stomatal opening (pore) between them. The epidermal cells around the stomatal cells. Stomatal cells are cells with abundant cytoplasm containing chloroplasts. The stoma has the ability to open and close depending on the amount of water the plant receives and the light. Thus, the amount of water vapor given by the plant by transpiration is adjusted and the CO_2 required for photosynthesis is taken from the atmosphere and the excess O_2 and water vapor are removed from the plant.

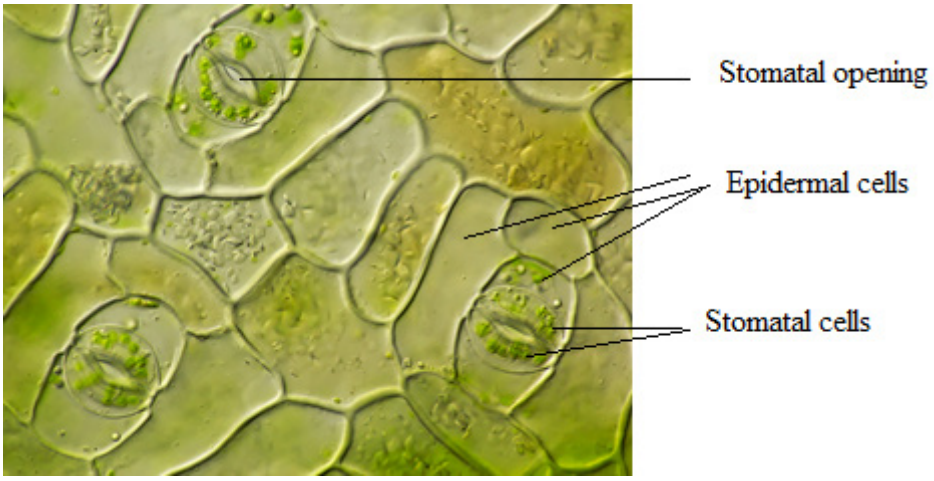


Figure 3. Stomata (https://microscopyofnature.com/stomata)

Hydathode: The openings that throw water out of the plant by dripping (gutation) are called hydathodes. It is found on the edges of the leaves of plants that grow especially in areas with high humidity. It does not have the ability to open and close like stomas. When the air is saturated with moisture, it activates and ensures that the plant takes the water from the soil.

Epidermal Hairs: Epidermis cells sometimes form outward projections to form hairs. Epidermal hairs protect the plant in hot conditions by reducing water loss; especially used as a means of defense against animals; in some climbing plants, it helps the plant to hold on to the support; secretes some substances such as tannin, resin, essential oil out of the plant; It takes part in the absorption process as in root hairs. They can consist of a single cell or multiple cells.

Figure 4. Leaf Hairs in *Solanum quadriloculatum*
(https://www.vcbio.science.ru.nl/en/virtuallessons/leaf/basicanatomy/)

Emergens: Unlike epidermal hairs, they are harder structures that do not only consist of the epidermis, but also form with the participation of the tissues under the epidermis. Emergens have duties such as protection, defense, secretion or attachment. For example, spines found on plants such as rose (Rosa) and blackberry (Rubus) are attachment emerges.

2. *Peridermis*

In plants with secondary growth (perennial), since the plant becomes thicker and the epidermis cannot perform its protective function, a fungal protective tissue formed by the accumulation of suber on its walls develops instead. This tissue is either formed by the accumulation of suberin in the epidermis and the walls of a few cells below it, or the epidermis is fragmented and replaced by the peridermis. Peridermis replaces epidermis in roots and stems and becomes a second protective tissue. It consists of three layers: Phellogen, phelloderm, and phellem.

Phellogen is a secondary meristem called the cork cambium. It occurs when the epidermis or the continuous tissue cells under it gain the ability to divide again. Phellogen cells divide outward to form phellem, and inward divide to form phelloderm.

The phelloderm is the innermost layer of the peridermis. Cell walls are cellulose and not fungal. It can contain chloroplasts, perform photosynthesis and store starch.

The cell walls of this outer layer of the phellem thicken with the accumulation of suberin and form the cork tissue. They do not have intercellular spaces, are tightly arranged, and their cells are dead because their walls are thickened. With these properties, it reduces the permeability of the plant to gases and water. Thus, instead of stomata, openings called lenticels have developed to allow the gas exchange of living cells with the outside environment.

B. Ground Tissue

It is a tissue composed of living and thin-walled cells found in all organs of the plant and responsible for most of the metabolic functions. This tissue forms the basic structure in plants, that is, it fills the parts between the covering and the vascular tissue. Organs have functions such as filling, supporting, photosynthesis and storage. It consists of three cell types as parenchyma, collenchyma, and sclerenchyma.

1. *Parenchyma*

Parenchyma cells are the most abundant cell type in most plants. They are described as a typical plant cell with a living, thin-walled, abundant cytoplasm and large central vacuole. It has several functions, including photosynthesis and storage. Parenchyma cells can divide and transform into other cell types, allowing the damaged parts of the plant to be repaired.

They are divided into four groups according to their duties:

a) Chlorenchyma parenchyma: They are found in the mesophyll layer of the leaves in the plant. They carry chloroplasts and thus synthesize organic matter by photosynthesis. Palisade parenchyma cells perform more photosynthesis in leaf blades that stand perpendicular to sunlight. Palisade parenchyma consists of long cylindrical cells near the upper surface of the leaf and contains abundant chloroplasts. Spongy parenchyma cells in the lower part of the palisade parenchyma also have more intercellular spaces and contain less chloroplasts.

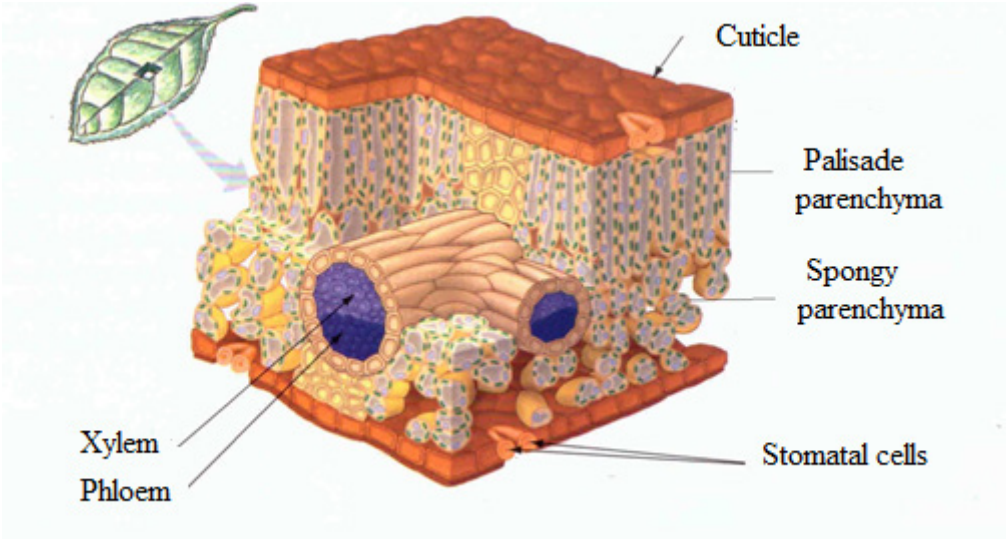


Figure 5. Palisade and Spongy Parenchyma (Modified from Simon, Dickey, Hogan and Reece, 2016/2017)

b) Aerenchyma parenchyma: It has large intercellular spaces. It is the parenchyma tissue that provides the exchange of substances between the cells and the external

environment. Together with stomata, hydatodes and lenticels, it forms the ventilation system of the plant. It is mainly found in marsh and aquatic plants. For example, it is well developed in the aquatic plant Elodea.

c) Vessel parenchyma: It is the parenchyma that provides substance transmission between the vascular tissue and the chlorenchyma parenchyma. They do not have chloroplasts and are thin-walled cells. They are located around the vascular tissue.

d) Storage parenchyma: It is the parenchyma that stores substances such as carbohydrates, fats, proteins and water in plants. It is found in organs such as roots, stems, seeds and fruits of plants. Plants with water-storing parenchyma are called succulent plants (cactus, etc.). Especially in plants living in arid and salty environments, the storage parenchyma is well developed.

2. Collenchyma

It is the tissue that gives plants properties such as bending and stretching and prevents them from breaking. Young stems and petioles often have a cylinder of collenchyma just below the surface. For example, strips of celery stalk. Cells are viable, their walls are thicker than parenchyma cells. Irregular thickenings are seen with the accumulation of cellulose and pectin in their walls. Collenchyma cells are named according to these thickening regions. If the thickening occurs at the corners, it is called the corner collenchyma, and if it is on the tangential walls parallel to the periphery, it is called the plate collenchyma.

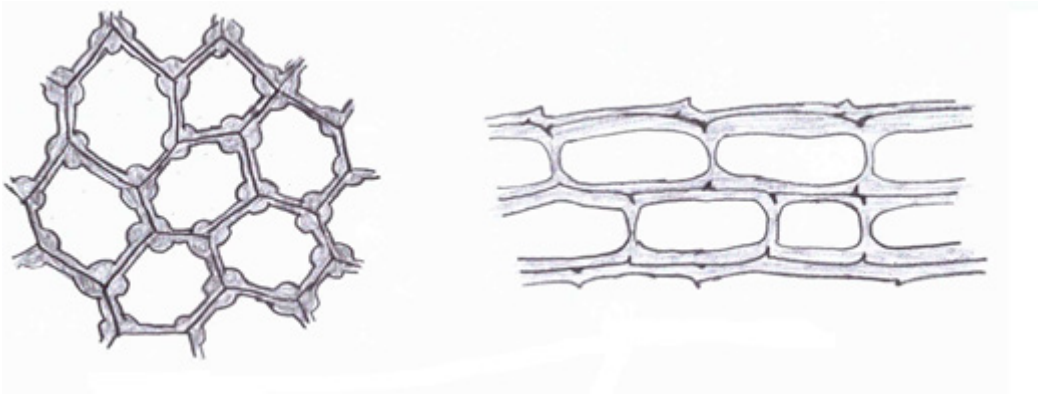


Figure 6. Corner Collenchyma and Plate Collenchyma

3. Sclerenchyma

It is a tissue that gives the plant rigidity and allows the stem to stand upright. Their cells are dead. It is thick and hard as a result of the accumulation of lignin and cellulose in its walls. This tissue consists of two types of cells, sclerenchyma fibers and stone cells.

Sclerenchyma fibers are narrow, long, dead cells with thick walls, pointed ends. Often found in groups. They are tensile resistant and durable fibers. As an example, we can give 20-40 mm long fibers of the Linum (flax) plant. These fibers are used in linen weaving.

Stone cells are spherical, polygonal, cylindrical or randomly protruding dead cells close to their length. For example, the hard particles found in the impact parts of quince and pear fruits are stone cells. It is also found in the shells of plants such as hazelnuts, walnuts, almonds.

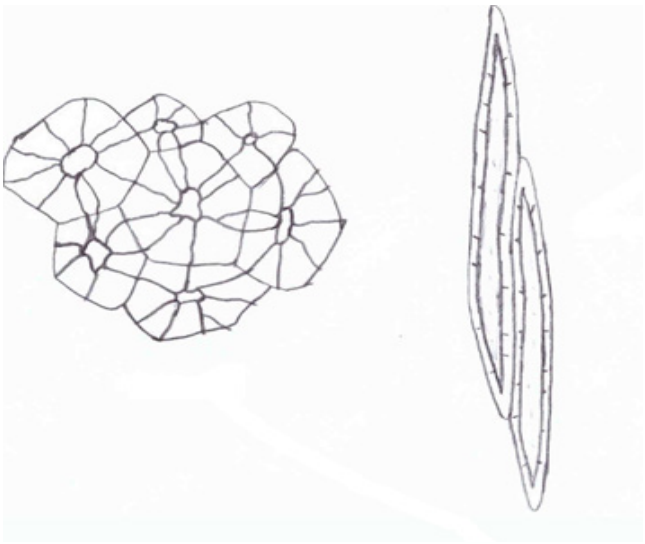


Figure 7. Stone Cells and Sclerenchyma Fibers

C) Vascular Tissue

It is the conduction tissue that provides the transport of substances between the root and the stem and is spread all over the plant body. Conduction tissue carries out the transmission of water and dissolved substances in the soil to organs far from the soil, and the organic matter formed in the assimilation organs to the organs that cannot assimilate for use or storage. For this reason, a transmission occurs from the root to the leaves and from the leaves to the root in a plant. There are two types of vascular tissue: xylem and phloem. In advanced plants, xylem and phloem usually coexist and form vascular bundles. They also provide support to the plant.

1. *Xylem*

The xylem carries water and dissolved minerals from the roots to the stem and leaves. The cell walls are thick, hollow and composed of dead cells. The water-conducting elements of this tissue, which continues uninterrupted from the roots to the leaves, are the trachea and tracheids.

Trachea and tracheids are formed in plant parts where elongation stops. When living cells lined up on top of each other reach functional maturity, they lose their vitality and

form a groove in which water can flow. The walls of these end-to-end cells do not have full thickening, but there are non-thickened areas called passageways. The side walls of the cells also remain intact and take the shape of a regularly elongated wood pipe.

In general, the tracheas are wider, shorter, thinner-walled, and less pointed at the ends than the tracheids.

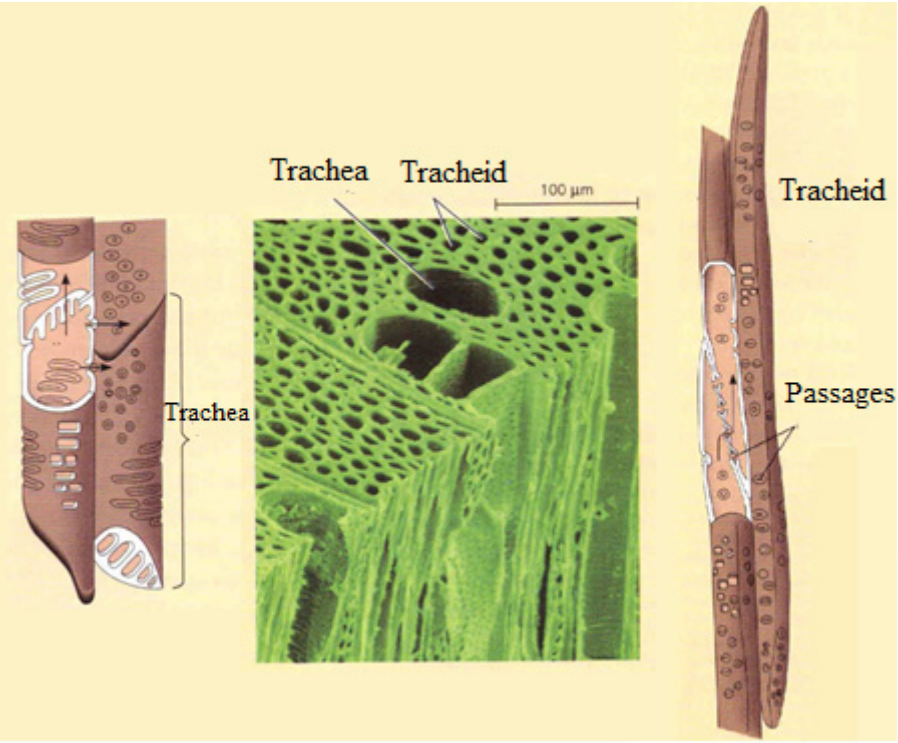


Figure 8. Trachea ve Tracheid (Campbell, Reece, 2001/2006)

2. Phloem

It is the tissue that carries organic substances produced by photosynthesis from leaves to other organs. Phloem tissue consists of two types of cells: sieve tubes and companion cells. In phloem tissue, sieve tubes do the main transport work. Sieve pipes are functionally mature and alive. Each sieve cell is attached end to end to form a column called a sieve tube. Between the sieve cells, a perforated (sieve-shaped) structure is formed by the melting of the end walls from place to place. This surface is called sieve plates. These plaques allow the assimilation products (sucrose, other organic substances, some ions) called phloem sap to pass from one cell to another. Sieve cells lack nuclei, ribosomes, and vacuoles, thus allowing phloem sap to flow easily through sieve tubes.

Next to each sieve cell is a cell called the companion cell, with abundant cytoplasm and large nucleus, which does not function as a communicator. These cells are connected to sieve tubes by channels called plasmodesms. All metabolic tasks of sieve tubes are performed by companion cells. For example, the P-protein secreted by the companion cells is delivered to the sieve cells, and this protein clogs the holes of the injured sieve cells,

preventing the phloem sap from flowing out. Primitive plants (ferns and gymnosperms) do not have companion cells, they are found in angiosperms (angiosperms).

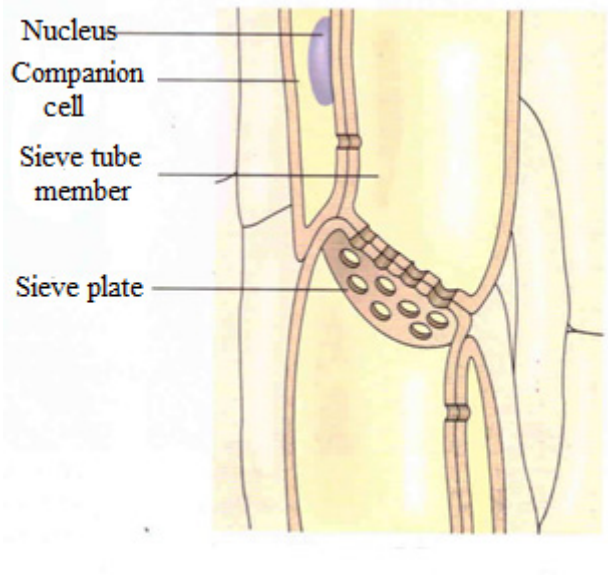


Figure 9. Floem (Campbell, Reece, 2001/2006)

Vascular Bundle: Phloem and xylem are usually found side by side. The entire tissue formed by the phloem and xylem is called the vascular bundle. The vascular bundle consisting of only phloem or only xylem is rarely encountered.

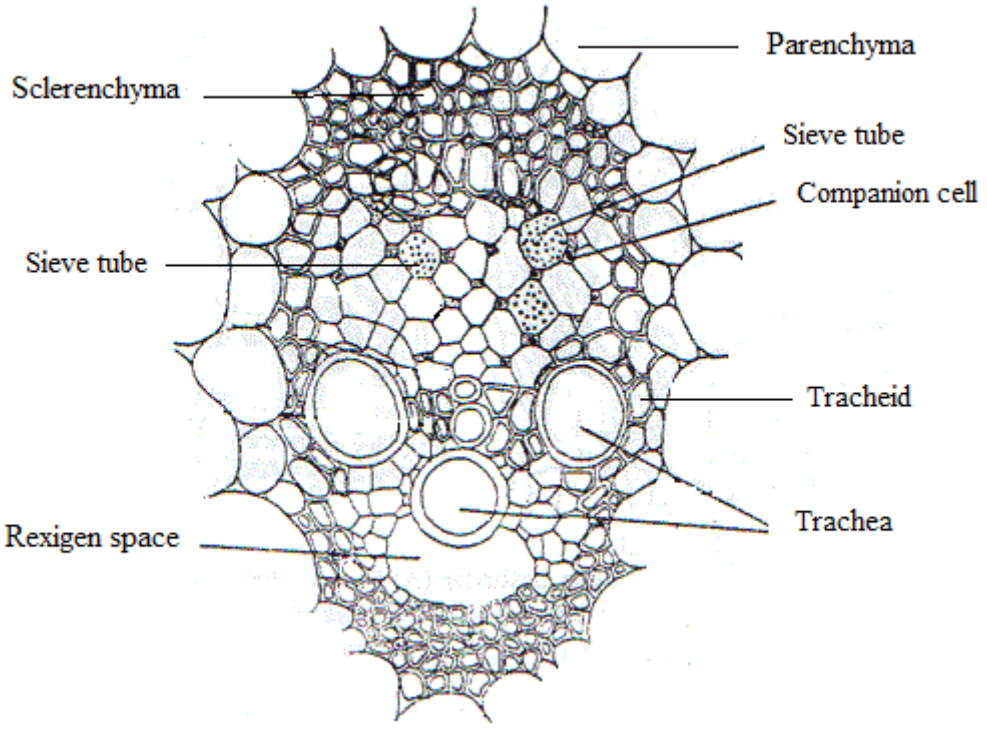


Figure 10. Vascular Bundle (Modified from Kadıoğlu and Kaya, 2001)

D) Secretory Tissue

Cell groups that secrete solid or liquid substances such as water, alkaloid, glycoside, nectar, mucilage, latex, resin, ethereal oil and tannin, which are formed as a result of metabolism in plants, are called secretory tissue. It consists of living cells with abundant cytoplasm and large nuclei. Cells are scattered among other tissues individually or in groups. The secretions they produce play an important role in plant life. For example, antiseptic substances such as tannin and resin protect the plant against rotting, while substances such as alkaloids and glycosides protect the plant against enemies. Substances such as lignin, suberin and cutin also increase the resistance of the cell wall.

Secretory cells are structures that either accumulate their secretions inside the cell or send them out of the cell. Secretory cells that accumulate the secretory substance inside the cell lose their cytoplasm and become dead. For example, etheric fat cells in honeydews are of this type. The secretions in this type of cells are thrown out if the cell is damaged. For example, we see that a yellow or white substance called latex (milk) is flowing from the spurge branch that we take and break.

In cells that release the secretory substance out of the cell, the secretion is either stored in the secretory pockets (intercellular spaces) within the plant or excreted from the plant. The resin secreted by the pine (Pinus) plant or the enzymes secreted by the insect trapping plants (Drosera, Nepenthes and Sarracenia) out of the cell can be given as examples of this type of secretion.

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To Cite This Chapter

Beytur, S.A., & Beytur, C. (2021). Plant tissues. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.223-234). ISRES Publishing

Molecular and Cytogenetical Studies in Iraq

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Introduction

The Iraqi population contain several ethnic groups that need to be genetically characterized and evaluated for possible substructures. Previous studies on the Iraqi population based on Y-STR markers were limited by a restricted number of markers. A larger database for Iraqi Arab population needed to be developed to help study and compare the population with other Middle Eastern populations. Prediction indicated predominance (36.6%) of haplogroup J1 in Iraqi Arabs. The migration rate between other populations and the Iraqis was inferred using coalescence theory in the Migrate-n program. Y-STR data were used to test different out-of-Africa migration models as well as more recent migrations within the Arabian Peninsula. The migration models demonstrated that gene flow to Iraq began from East Africa, with the Levantine corridor the most probable passageway out of Africa (Lazim et al., 2020).

β-thalassemia is a significant problem in the north-eastern part of Iraq, and has imposed a huge burden on the health authorities.

Objective: To identify the molecular characterization and morbidity prevalence in transfusion-dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT) phenotypes in north-eastern Iraq. They conclude that the overall complications rate was 78.9%, with a growing probability of complications with advanced age, with evidently higher rates in patients with $\beta^0\beta^0$ and $\beta^0\beta^+$ genotypes that explain the role of underlying genetic defects in the pathophysiology of disease complications (Amin et al., 2020)

From another genetic aspect common variants among genes coding for enzymes in sex steroid biosynthetic pathways may influence the risk of endometriosis in Iraqi women patients in the last years. Cytochrome P450c17a1 (*CYP17*), a gene that codes for a key enzyme (cytochrome P450c17a1) in a rate-limiting step of estrogen biosynthesis has attracted considerable attention as an important gene for endometriosis. To evaluate the relationship between common genetic variations in *CYP17* and endometriosis risk and determine the main effects of those variations on the gene expression. A women-based case control study of Iraqi women aged range (23–46), the associations between selected single-nucleotide polymorphisms (SNPs) in the *CYP17* gene and endometriosis diagnosis in fifty women and thirty disease-free controls were evaluated. The study found a significant association ($P \leq 0.01$)between endometriosis and selected SNPs

of *CYP17* gene, with the homozygous genotype conferring decreased risk. A highly significant difference ($P \leq 0.01$) in *CYP17* gene expression from women with versus without endometriosis and increased by 1.56-fold in women with endometriosis. These findings suggest that variation in or around *CYP17* may be associated with endometriosis development in the Iraqi women (Al-Rubae'i et al., 2016)

Basrah, the southern most province in Iraq in attempt to investigate the origin of Basrah, two researcher examined the mitochondrial DNA(mt-DNA) variations by hypervariable segment 1(HVS1) Sequencing and determination of specific site haplogroups. The results in Basrah show no significant differences diversity among Iraqis' HVS1 compared with other countries. The values were within the range of gene diversity across the Middle East and exhibited the unimodal pattern of differences in the pairwise sequence. Given the small genetic differences between people living in this area, phylogenetic analysis showed a large variability of the communities of Basrah; they didn't cluster on the phylogenetic tree (Bassim and Adnan 2020). Forty-nine of the 52 autosomal single nucleotide polymorphisms (SNPs) in the SNP for ID 52plex were typed in 101 unrelated Iraqis living in Denmark. No significant deviation from HTHEYwas found in all but one of the 49 SNP systems and no significant pairwise linkage disequilibrium was observed for any SNP pair. When 18 worldwide populations were compared (including populations in Iraq, Turkey, Israel, Pakistan, India, China, Taiwan, Japan, Siberia, Algeria, Somalia, Uganda, Mozambique, Angola, Nigeria, Denmark, Portugal, Spain), a significant global FST value was obtained. All but six FST values were statistically significant when pairwise comparisons were performed between the 18 populations. The Iraqi population did not show significant difference from the population in Turkey and it grouped together with other Middle-Eastern populations when a multidimensional scaling plot was drawn based on the pairwise FST values. The combined mean match probability and the typical paternity index for trios were 8.3 1020 and 259,000, respectively, for the Iraqi population (Carmen et al., 2013). A lot of genetics and molecular data has been reported in the last 10 years and a huge results gained from these observations. One of the most interesting researches field is the researches about relation between molecular and behavioral disorders to assess the prevalence, symptom severity, functional impairment, and treatment of major depressive episode (MDE) in the Iraqi general population. So the Iraq Mental Health Survey is a nationally representative face-to-face survey of 4,332 non-institutionalized adults aged 18+ interviewed in 2006–2007 as part of the WHO World Mental Health Surveys. Prevalence and correlates of DSM-IV MDE were determined with the WHO Composite International Diagnostic Interview (CIDI). Which concludes that MDE is a commonly occurring disorder in the Iraqi general population and is associated with considerable disability and low treatment. Efforts are needed to decrease the barriers to treatment and to educate general medical providers in Iraq about the recognition and treatment of depression (Al-Hamzawi et al., 2015).

Structural variation (CNV) including deletion, duplication, displacement and reflection of chromosomes was identified in some individuals with autism spectrum disorder (ASD), but the full moral role is unknown. This study evaluated the genome extensively for structural abnormalities in 427 unrelated ASD cases through monoclonal monoclonal arrays and a nuclear pattern. With precise matrices, the researchers discovered 277 of unbalanced CNVs in 44% of ASD families not present in 500 controls (and re-examined in 1152 other controls). The nuclear pattern revealed additional balanced changes. Although most variables were inherited, they found a total of 27 cases with de novo modifications, and in three (11%) of these individuals, two or more new variables were observed. De Novo CNVs were found in about 7% and about 2% of idiopathic families had one child, or two or more ASD siblings, respectively. They also discovered 13 sites with repeated / overlapping CNVs in unrelated cases. In these sites, deletions and repetitions affecting the same gene were found in different individuals and sometimes in symptom-free vectors. Despite complications, their results include more SHANK3-NLGN4-NRXN1 involvement in post-clamp density genes as well as new positions in DPP6-DPP10-PCDH9 (compound clamp), ANKRD11, DPYD, PTCHD1, 15q24, among others, for the role In ASD sensitivity. Their most convincing results revealed CNV at 16p11.2 ($p = 0.002$) (with characteristics of genetic disturbance) at a frequency of about 1%. Some areas of ASD were also common in places of mental retardation. Structural variables were found in the high-frequency effect sufficiently ASD suggests that cellular genetic analyses and microarray are considered in the clinical workup routine (Hadi, 2019).

Another study aimed to detect the consistent chromosomal abnormalities of each type of common bone tumours . Thirty bone tumours specimens were processed for direct cytogenetic preparation , only (9 cases) showed success results for chromosomal preparation by banding technique , the results of cytogenetic study were 1- Osteosarcoma (4) cases revealed multiple numerical and structural changes with complex karyotype and pronounced cell to cell variation . chromosome 17 was the most frequent involved in these chromosomal alteration . Also loss or structural changes of chromosome 13 was found in (2) cases of osteosarcoma loss or gain of sex chromosome were detected in these cases , loss of Y chromosome in (2) cases ; loss of X chromosome in (1) case and gain of X chromosome in another case .2- Osteochondroma : revealed the simple numerical change with no structural change in one case . 3- Chondroblastoma : in this tumour structural and numerical abnormalities of chromosome 5 . 4- Chondrosarcoma : showed chromosomal aberration with multiple numerical and structural changes in chromosome (1) was of interest and monosomy 18 was reported in one case . 5- Giant cell tumours : It showed a complex changes and the range of chromosomal number was 50 – 58 with the characteristic telomeric fusion in malignant cases while simple numerical change only in benign giant cell tumour .Conclusion Cytogenetic study of

both benign and malignant bone tumours have revealed abnormalities in the number and / or structures of chromosomes X, Y , 1,5,6,11 , 13,17,18 and complex chromosomal changes in malignant types of bone tumours (Nahi et al., 2017).

Another group of researchers studied thyroid gland that requires a sequence of particular conditions to produce its hormones which are affected by a large number of factors. The disturbances of these factors lead to cause thyroid disorders. The study included 100 samples collected from patients who suffer from thyroid disorders in the Department of Radiation Nuclear Medicine Hospital and Yarmok hospital in Baghdad and 25 sample as quality control during the period from July to October 2009. Ranged in age from patients and healthy individuals (17-79) years. Blood samples were drown from all patients and control in order to be used in hormonal, cytogenetic and molecular studies. The results have showed that the most frequent thyroid disorders among patients are thyroid non-toxic goiter 32% and thyroid toxic goiter 31% while hypothyroidism 20% and thyroid cancer 17%. The results also showed that these disorders distributed highly among the age group 30-50 years old with high prevalence in females. Thyroid hormones (T3, T4 and TSH) levels were determined in all unrelated Iraqi cases by enzyme linked fluorescent assay, a different degree of hormones levels with thyroid disorder groups were shown. TSH level was significantly increased (18.76±6.44 µ IU/ml) in hypothyroidism group. In the thyroid cancer group, TSH and T3 showed to have a low levels (1.49±0.75 µ IU/ml and 1.32±0.13 nmol/L) respectively, combined with a significant increase in T4 level (104.71±9.72 nmol/L). Using new Locked Nucleic Acid primer (LNA) primers - PCR mutations screening technology, DNA from patients and control was screened to detect the existence of 8 TG and TPO selected mutations. Eight mutations were detected in thyroid disorder patients six of TG and two TPO genes mutations. These mutations include g.IVS5+G>A, c.886C >T, c.986A>C, c.2610G>T, g.IVS10-1G>A and g.IVS34-1G>C location in exons 5, 7, 8, 10 and 34 in TG While 1708C>T and 1978C>G location in exons 10 and 11, of TPO mutations, respectively. Also, the results showed a sort of relationship between some of the detected mutations and the level of hormones. The mean values of the hormones levels showed to be slightly varied in terms of age and gender groups. Using new LNA primer- PCR mutations screening technology, DNA from patients and control was screened to detect the existence of 8 TG and TPO selected mutations. Using first designed primers, the results revealed that seventy mutations have been identified to the first time in human TG and TPO genes in thyroid disorders of Iraqi. 53(75.7%) of them were detected in TG gene and 17 (24.3%) in TPO genes. Among 53 TG gene mutations, 26(49.053%) were detected as guanine to adenine transition IVS5 +1 G>A most of them are identified among thyroid toxic goiter and thyroid cancer groups. Other TG mutations such as exon – intron splice mutations and exon mutations were also detected in all tested groups. Seventeen TPO gene mutations including transversion cytosine either by thymine or guanine at the position 1708 of the exon 10

(c.1708C>T) and the position 1978 of the exon 11 (1978C>G) were also detected. Three TG homozygous mutations were detected among thyroid toxic goiter and thyroid cancer which reflect a high DNA instability and 12 compound mutations. Most of the detected mutations in this study were among thyroid toxic goiter (27.38%) and thyroid cancer (21.30%) groups. DNA instability was also identified in Toxic goiter and thyroid cancer groups. The cytogenetic study results indicated that significantly increased BNMN frequency (37.58±3.07) in thyroid cancer group versus other thyroid disorder groups but with significant increase in other thyroid disorder groups compared with healthy control group. On the other hand, NDI of micronucleus was found with a significant decrease (0.009±0.001) in hypothyroidism versus other groups (AL-Faisal et al., 2011).

Congenital adrenal hyperplasia is a group of autosomal recessive disorders. The most frequent one is 21-hydroxylase deficiency. Analyzing CYP21A2 gene mutations was so far not reported in Iraq. This work aims to analyze the spectrum and frequency of CYP21A2 mutations among Iraqi CAH patients. Sixty-two children were recruited from the Pediatric Endocrine Consultation Clinic, Children Welfare Teaching Hospital, Baghdad, Iraq, from September 2014 till June 2015. Their ages ranged between one day and 15 years. They presented with salt wasting, simple virilization, or pseudoprecocious puberty. Cytogenetic study was performed for cases with ambiguous genitalia. Molecular analysis of CYP21A2 gene was done using the CAH StripAssay (ViennaLab Diagnostics) for detection of 11 point mutations and >50% of large gene deletions/conversions. Mutations were found in 42 (67.7%) patients; 31 (50%) patients were homozygotes, 9 (14.5%) were heterozygotes, and 2 (3.2%) were compound heterozygotes with 3 mutations, while 20 (32.3%) patients had none of the tested mutations. The most frequently detected mutations were large gene deletions/conversions found in 12 (19.4%) patients, followed by I2Splice and Q318X in 8 (12.9%) patients each, I172N in 5 (8.1%) patients, and V281L in 4 (6.5%) patients. Del 8 bp, P453S, and R483P were each found in one (1.6%) and complex alleles were found in 2 (3.2%). Four point mutations (P30L, Cluster E6, L307 frameshift, and R356W) were not identified in any patient. In conclusion, gene deletions/conversions and 7 point mutations were recorded in varying proportions, the former being the commonest, generally similar to what was reported in regional countries **(**Ruqayah et al., 2016). Leishmaniasis is a group of parasitic diseases caused by Leishmania spp., an endemic infectious agent in developing countries, including Iraq. Diagnosis of cutaneous lesion by stained smears, serology or histopathology are inaccurate and unable to detect the species of Leishmania. Here, two molecular typing methods were examined to identify the promastigotes of suspected cutaneous leishmaniasis samples, on a species level. The first was species-specific B6-PCR and the second was ITS1-PCR followed by restriction fragment length polymorphism (RFLP) using restriction enzyme HaeIII. DNA was extracted from in vitro promastigote culture followed by amplification of kDNA by B6 or amplification and digestion of LITSR/

L5.8S. PCR produced bands of ~359 bp and ~450 bp for B6 and ITS1, respectively. Digestion of ITS1 by RFLP revealed two distinct bands of ~150 bp and ~300 bp size. The results reviled that the two isolates belong to cutaneous Leishmaniasis, specifically Leishmania tropica. In conclusion, the confirmation of the studied methods will improve rapid and accurate diagnosis of Leishmania species of the most prevalent Iraqi strain of cutaneous leishmaniasis, L. tropica (Bayram & Ali 2021).

In conclusion: each country or geographical zone has its molecular and genetic specifications which may reflects on the prevalence and dominance of some disorders rather than others and that what the previous researches had mention. Iraq is like many other countries that exposed to many pollutants that affects the molecular expression and suppression of some genes and DNA sequences that gave the chance to variable diseases to appear and respond poorly to the well known treatment protocols followed by another countries or another patients which raise the world -nowadays -distributted question of what is the molecular reason behind variable response to the same treatment of the same disease.

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To Cite This Chapter

Almatlob, I.I. (2021). Molecular and cytogenetical studies in Iraq. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.235-241). ISRES Publishing

Personalised Medicine/Drugs

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Introduction

Personalized medicine is a unique approach referring to a tailoring or modifying of medical treatment to the individual features of each patient. Personalized medicine is also known as precision medicine. Every individual has his/her own unique variation in the human genome, due to combination of genetic variations and environment influence. Not all of those genome variations affect their state of health, but could manifest in different individual drug responses during treatment.

In order for physicians to know if a mutation is connected to a certain disease, researchers often do a study called a "genome-wide association study" (GWAS). In genomic medicine, information from genomes and their derivatives (RNA, proteins, and metabolites) is used to guide medical decision making. According to Schilsky (2010), genomic medicine is an important component of personalized medicine, which has been described as a rapidly advancing field of health care based on each person's unique clinical, genetic, genomic, and environmental information.

Along the continuum from health to disease, genome information can provide DNA-based assessment for common complex disease, molecular indication for cancer diagnosis and prognosis, genome-guided therapy, dose selection, and much more for personal health care. This is moving fast in technological development, social and information revolution which will affect the way of thinking in healthcare solutions (Schilsky, 2010). In simple words, genomic medicine is using information from genomes, either human or other organisms, and their derivatives to guide decision making in medicine.

Furthermore, it is now possible to examine a person's entire genome (or a fraction of it as you need) to assess individualized risk prediction and treatment decisions. Many patterns of gene expression across the entire genome are also now readily assayed. Thus, health and disease states can now be characterized by their molecular fingerprints to develop meaningful stratifies for patient populations and to elucidate mechanistic pathways based on genome-wide data.

Personalized medicine is a broad and rapidly advancing field of health care that is informed by each person's unique clinical, genetic, genomic, and environmental information. Health care with personal medicine encircled could integrate and coordinate the evidence-based approach for patient care individually from health to disease.

Personalized medicine needs multidisciplinary health care teams to reach its goal in promoting health and wellness, patients education and satisfaction, also disease prevention, diagnose and treatment. By genomic medicine, personalized medicine could understand molecular pathways of disease, therefore optimal health care strategies could be established in the earliest stage and optimal medical care could be reach for better outcomes for each individual, to include treatments, medication types and dosages, and/or prevention strategies may differ from person to person, resulting in an unprecedented customization of patient care (Schilsky, 2010).

Development of Concept

Diagnostic testing is often employed in personalized medicine for selecting appropriate and optimal therapies based on the context of a patient's genetic content or other molecular or cellular analysis. The use of genetic information has played a major role in certain aspect of personalized medicine (e.g pharmacogenomics), and the term was first coined in the context of genetics, though it has since broadened to encompass all sorts of personalization measures, including the use of proteomics (Priyadharshini et al., 2020) imaging analysis, nanoparticles-based theranostics, among others (Xie et al., 2010).

Background to Personalized Medicine

Every person has a unique variation of the human genome (Dudley & Karczewski, 2014). Although most of the variation between individuals has no effect on health, an individual's health stems from genetic variation with behaviors and influences from the environment (Lu et al., 2014).

Modern advances in personalized medicine rely on technology that confirms a patient's fundamental biology, DNA, RNA, or protein, which ultimately leads to confirming disease. For example, personalized techniques such as genome sequencing can reveal mutations in DNA that influence diseases ranging from cystic fibrosis to cancer. Another method called RNA-seq, can show which RNA molecules are involved with specific diseases. Unlike DNA, levels of RNA can change in response to the environment. Therefore, sequencing RNA can provide a broader understanding of a person's state health. Recent studies have linked genetic differences between individuals to RNA expression (Battle et al., 2014) translation (Cenik et al., 2015) and protein levels (Wu et al., 2013).

The concept of personalized medicine can be applied to new and transformative approaches to health care. Personalized health care is based on the dynamics of systems biology and uses predictive tools to evaluate health risk and to design personalized health plans to help patients mitigate risks, prevent disease and to treat it with precision when it occurs. The concept of personalized health care is receiving increasing acceptance with

veterans' administration committing to personalized, proactive patient driven care of all veterans (Snyderman, 2012).

In some instances personalized health care can be tailored to the markup of the disease-causing agent instead of the patient's genetic markup; examples are drug resistant bacteria or viruses (Altmann et al., 2007).

Genome-Wide Association Study

Genome-wide association study (GWAS) is used by physicians to know if a mutation is connected to a certain disease. In a GWAS study, the researcher will look at one disease, and then sequence the genome of many patients with that particular disease to look for shared mutations in the genome. Mutations that are determined to be related to a disease by a GWAS study can then be used to diagnose that disease in future patients, by looking at their genome sequence to find that same mutation. The first GWAS, conducted in 2005, studied patients with age-related macular degeneration (ARMD). It found two different mutations, each containing only a variation in only one nucleotide (called single nucleotide polymorphisms, or SNPs), which were associated with ARMD. GWAS studies like this have been very successful in identifying common genetic variations associated with diseases. As of early 2014, over 1,300 GWAS studies have been completed.

Disease Risk Assessment

Multiple genes collectively influence the likelihood of developing many common and complex diseases. Personalized medicine can also be used to predict a person's risk for a particular disease, based on one or even several genes. This approach uses the same sequencing technology to focus on the evaluation of disease risk, allowing the physician to initiate preventive treatment before the disease present itself in their patient. For example, if it is found that a DNA mutation increases a person's risk of developing Type 2 Diabetes, this individual can be asked to begin lifestyle changes that will limit the chances of developing Type 2 Diabetes later in life.

Applications of Personalized Medicine

Diagnosis and Intervention

Having the ability to look at a patient on an individual basis will allow for a more accurate diagnosis and specific treatment plan. Genotyping is the process of obtaining an individual's DNA sequence by using biological assays. By having a detailed account of an individual's DNA sequence, their genome can then be compared to a reference genome, like that of the Human Genome Project, to assess the existing genetic variations that can account for possible diseases. A number of private companies, such as 23andMe, Navigenics, and illumine, have created Direct-to-Consumer genome sequencing accessible to the public (Dudley & Karczewski, 2014).

Having this information from individuals can then be applied to effectively treat them. An individual's genetic make-up also plays a large role in how well they respond to a certain treatment, and therefore, knowing their genetic content can change the type of treatment they receive.

An aspect of this is pharmacogenomics, which uses an individual's genome to provide a more informed and tailored drug prescription. Often, drugs are prescribed with the ideas that it will work relatively the same for everyone, but in the application of drugs, there are a number of factors that must be considered.

The detailed account of genetic information from the individual will help prevent adverse events, allow for appropriate dosages, and create maximum efficacy with drug prescriptions. For instance, warfarin is the FDA approved oral anticoagulant commonly prescribed to patients with blood clots. Due to warfarin's significant inter-individual variability in pharmacokinetics and pharmacodynamics, its rate of adverse events is among the highest of all commonly prescribed drugs. However, with the discovery of polymorphic variants in CYP2C9 and VKORC1 genotypes, two genes that encodes the individual anticoagulant response, (Breckenridge, et al., 1974; Rieder et al., 2005). Physicians can use patients' gene profile to prescribe optimum doses of warfarin to prevent side effects such as major bleeding and to allow sooner and better therapeutic efficacy. The pharmacogenomics process for discovery of genetic variants that predict adverse events to a specific drug has been termed toxgnostics (Church et al., 2014).

An aspect of a theranostic platform applied to personalized medicine can be the use of diagnostic test to guide therapy. The test may involve medical imaging such as MRI contrast agents (T1 and T2 agents), fluorescent markers (organic dyes and inorganic quantum dots), and nuclear imaging agents (PET radiotracers or SPECT agents) (Xie, et al., 2010; Kelkar and Reineke, 2011).

In addition to specific treatment, personalized medicine can greatly aid the advancements of preventive care. For instance, many women are already being genotyped for certain mutation in the BRCA1 and BRCA2 gene if they are predisposed because of a family history of breast cancer or ovarian cancer.

As more causes of diseases are mapped out according to mutations that exist within a genome, the easier they can be identified in an individual. Measures can then be taken to prevent a disease from developing. Even if a mutation were found within a genome, having the details of their DNA can reduce the impact or delay the onset of certain diseases. Having the genetic content of an individual will allow better guided decisions and thus treating it or preventing its progression. This will be extremely useful for disease like Alzheimer's or cancers that are thought to be linked to certain mutations in our DNA.

Companion Diagnostics

This is another tool that is being used now to test efficacy and safety of a drug specific to a targeted patient group/subgroup. This technology is an assay that is developed during or after a drug is made available on the market and is helpful in enhancing the therapeutic treatment available based on the individual (Amgen, 2014).

These companion diagnostics have incorporated the pharmacogenomics information related to the drug into their prescription label in an effort to assist in making the most optimal treatment decision possible for the patient (Amgen, 2014).

Drug Developent and Usage

Assessing the genomic information of an individual can be significant in the process of developing drugs as they await approval from the FDA prior to public usage. Today in medicine, physicians commonly employ a trial and error method until they find the most effective treatment therapy for their patient. According to Dudley and Karczeweski (2014), personalized medicine allows these treatments to be more specifically tailored to an individual and hence give insight into how their body will respond to the drug and if that drug will work based on their genome.

The personal genotype can allow physicians to have more detailed information that will guide them in their decision in treatment prescriptions, which will be more cost-effective and accurate. As quoted from the article *Pharmacogenomics*: *The Promise of Personalized Medicine*, "therapy with the right drug at the right dose in the right patient" is a description of how personalized medicine will affect the future of treatment (Mancinelli et al., 2000). For instance, Tamoxifen used to be a drug commonly prescribed for women with ER+ breast cancer, but 65% of women initially taking it developed resistance. After some research work by David Flockhart, it was discovered that women with certain mutation in their CYP2D6 gene, a gene that encodes the metabolizing enzyme, were not able to able to efficiently break down Tamoxifen, making it ineffective treatment for their cancer (Ellsworth et al., 2010). Since then, women are now genotyped for those specific mutations, so that immediately these women can have the most effective treatment therapy.

Screening for these mutations is carried out via high-throughput screening or phenotypic screening. Several drug discovery and pharmaceutical companies are currently utilizing these technologies to not only advance the study of personalized medicine, but also to amplify genetic research; these companies include Alacris Theranostics, Persomics, Flatiron Health, Novartis, among others.

Pharmacy Compounding

Pharmacy compounding is another application of personalized medicine. Though not necessarily utilizing genetic information, the customized production of a drug whose various properties (e.g. dose level, ingredient selection, routes of administration, etc.) are selected and crafted for an individual patient is accepted as an area of personalized medicine.

Theranostics

Theranostics is a personalized approach in treating cancer, using similar molecules for both imaging (diagnosis) and therapy. The word theranostics is derived from the words therapeutics and diagnosis. It is now commonly applied to the field of nuclear medicine where radioactive molecules are attached to gamma or positron emitters for SPECT or PET imaging, and to beta, alpha or Auger electrons for therapy. An earlier use of these methods includes the use of radioactive iodine for treatment patients with thyroid cancer.

Cancer Genomics

The genetic variety of types of cancer has been enumerated in cancer research over the past few decades. There has also been increasing awareness of heterogeneity of tumors and/or genetic diversity within a single tumor. Hence, we consider personalized onco-genomics as the application of personalized medicine to cancer genomics. High throughput sequencing methods are used to characterize genes associated with cancer to better understand disease pathology and improve drug development. Currently, onco-genomics is an emerging field of genomics, particularly because of its implications in drug therapy. An example is tyrosine kinase inhibitors such as imatinib (marketed as Gleeve) have been developed to treat chronic myeloid leukemia (CML), in which the BCR-ABL fusion gene is present in more than 95 per cent of cases and produces hyper activated abl-driven protein signaling. These medications specifically inhibit the Ableson tyrosine kinase (ABL) protein and are thus a prime example of “rational drug design” based on knowledge of disease pathophysiology.

Conclusion

In the fast advancing era of Genomic and Molecular medicine, stakeholders are inevitably inclining to specificity in the practice of medicine. Patient satisfaction on disease management is centered on the demand for drug therapies to be more effective with reduced incident of adverse effects to ensure improved quality of life. Physicians are also welcoming therapies which will result in definite cure and minimize trial-and-error diagnosis and treatment. In addition, medical practice is accepting the molecular and genetic basis of assessing disease risk factors and preventive mechanisms.

Pharmaceutical and biotechnology companies are also advancing in drug development pathways, which are quicker with much predictive outcomes in order to save time and money. Regulatory authorities are also being pressured to approve drug therapies with minimum adverse reactions and increase efficacy. Government agencies and healthcare agencies have also developed an interest in more precise treatments in order to prevent expenditure on ineffective dugs which will lengthen patients' morbidity span and incur more health bills. In conclusion, although conventional medicine cannot be totally ruled out, it is evident that Personalized drugs are shaping the future of medicine and stands a promising chance of overtaking conventional drugs in the future.

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To Cite This Chapter

Laval, R.A. (2021). Personalised medicine/drugs. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.242-249). ISRES Publishing

Biological Fertilization and its Effect on Selected Aromatic Plants

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1. Introduction

Aromatic crops play a pivotal role in mankind daily life as important flavoring agents in foods, beverages (Sarim, 2016) and pharmaceuticals (Bano et al., 2017) and also as ingredients in perfumes and cosmetics (Talal and Feda, 2003). Herbal medicines are currently in demand and their popularity is increasing day by day (Manish et al., 2010).

In general, aromatic crops is showing different promising biological activities. These activities can include protection from and/or alleviation of some ailment, which is supported with different proposed mechanisms of action (Marek et al., 2020). Therefore, quality is one of the most important and critical factors in aromatic crops. In order to reach this high quality, Promotion ecologically sound plant protection measures is highly suggested such as bio-management (Peter, 2006).

Global concerns about degradation of land resources and maintaining natural ecosystems, beside particular attention to the soils which are the bases of agricultural systems, these were clearly expressed in the World Conservation Strategy (IUCN, 1980). Moreover, the most important constraint limiting crop yield in developing nations worldwide, and especially among resource-poor farmers, is soil infertility. Therefore, maintaining soil quality can reduce this problems , utilization of bio-fertilizers is considered as a promising alternative, particularly for these developing countries (Khalid , 2012).

A biological fertilizer (also bio-fertilizer) is a substance which contains living microorganisms, when applied to seed, plant surfaces, or soil colonizes the rhizosphere or the interior of the plant and promotes growth by increasing the supply or availability of primary nutrients to the host plant (Vessey , 2003).

Soil microorganisms represent important component in the evaluation of soil quality used as biological indicator or as sustainability index for production systems. Therefore, emphasis is now laid on the use of bio fertilizers in the crop production like biological nitrogen fixers (*Azotobacter/ Azospirillum /Rhizobium*) and phosphate solubilizing bacteria (PSB). These bio fertilizers improve crop production by supplying nutrients, producing vitamins such as thiamine and riboflavin and plant hormones viz., indole acetic acid (IAA) and gibberellins (GA) (Bao et al., 2015).

However, the current use of microorganisms in agriculture remains at a low level despite

the significant investment in scientific work to understand and use natural microbial resources to improve plant growth and quality. Keeping above facts in view, this chapter will demonstrate the biological potential of selected aromatic plants, discussing the effect of bio-fertilizers on growth, yield and quality of essential oil of these selected plants trying to address its effective implementation on these aspects.

2. Biological Activity of Aromatic Plants

Nowadays because of the emergence of drug resistant strains of pathogens from one side and increasing the prices of medicine due to war and sanctions, people have motivated to use the complementary and alternative therapies, and a strong trend has emerged to study natural sources for biologically active extracts that can be integrated with synthetic drugs in the production of more effective and safer medication, the following will focus on biological activities of some selected aromatic plants for potential use as possible means to treat different disease.

2.1. Davana (Artemisia pallens Wall.)

Davana (*Artemisia pallens* Wall.) is a small herbaceous aromatic plant belonging to *Asteraceae* family, it is native to the southern part of India, Its leaves and flowers are utilized in traditional Ayurveda medicinal preparation (Prasannakumar et al., 2011). The essential oil of davana is obtained by hydro-distillation from newly blossoming flowers (Mallavarapu et al., 1999), and its major constituents are davanone, linalool (Z)- and (E)-methyl cinnamate, (E)-ethyl cinnamate, bicyclogermacrene, davana ether, 2-hydroxyisodavanone, and farnesol (Gopal et al., 1999). Artemisinin is largely obtained from *A. annua* plant, and its main antimalarial compound (Aidah et al., 2018).

Artemisia species are used for the treatment of diseases such as malaria, hepatitis, cancer (Luigi et al., 2015) and its essential oils have been largely employed for their antiseptic properties.

- Antimicrobial Activities

An essential oil sample of davana (*Artemisia pallens* Wall. ex DC.) were investigated by (Stefanie et al., 2008) and it showed antimicrobial activities against *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella enterica* subsp. *enterica* and the yeast *Candida albicans.*

- Antifungal Activities

The anti-fungal constituents from Artemisia species include flavonoids, polyacetylenes, and sesquiterpenes, it have been found to exhibit antifungal activity against plant and human pathogenic fungi (Tan et al.,1998) .

- Anti-malaria Activities

Artemisinin and its derivatives have been highlighted for their potent activity against species of *Plasmodium* genus responsible for malaria, as well as in the treatment of leishmaniasis, schistosomia-sis and trypanomiasis (Antoaneta et al., 2021)

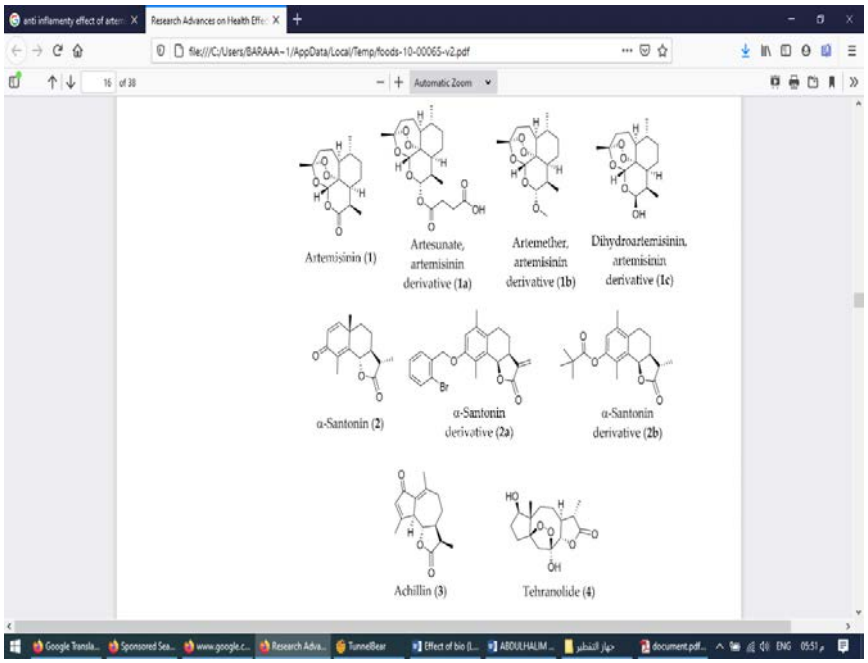

Figure 1. Chemical Structures of Some Sesquiterpene Lactones Constituents of Edible Artemisia sp. and Derivatives with Pharmacological Relevance. (Antoaneta et al., 2021)

2.2. Sweet Flag (Acorus Calamus)

Sweet flag (*Acorus calamus*) is an aromatic plant belonging to *Acoraceae* family, indigenous to Central Asia, Europe and North America, its rhizome is reported to contain active compounds potential therapeutic properties (Wilczewska et al., 2008). The essential oils of Sweet flag is obtained from leaves and rhizomes and have great variation in chemical composition. According to (Rimantas, 2003) β-Asarone and α-asarone were the major constituents in the rhizome oil, while β-asarone and linalool were the major constituents in the leaf oil. In the following some of its biological proprieties:

- Neuro-protective activity

Asarones isolated from Sweet flag have been evaluated for their neuro-protective properties, α and β asarone have been found to inhibit the toxicity induced by the N-Methyl-D-Aspartate in primary cortical cultures through the blockade of NMDA receptor function (Mythili et al., 2013)

- Sedative and hypnotic effect

β.-Asarone compound in volatile oils of Sweet flag showed potentiation of the sedative

activity, the hypnotic potentiating action might be mediated through serotonin and catecholamines (Pulok et al., 2007) .

- Antioxidant activity

α.-Asarone had an effective protective role by normalizing the increased superoxide dismutase (SOD) and lipid peroxidation (LPO), and decreasing catalase (CAT), glutathione peroxidase (GPx) , glutathione (GSH) , vitamins C and E, and protein thiols due to noise exposure. (Manikandan & Devi ,2005).

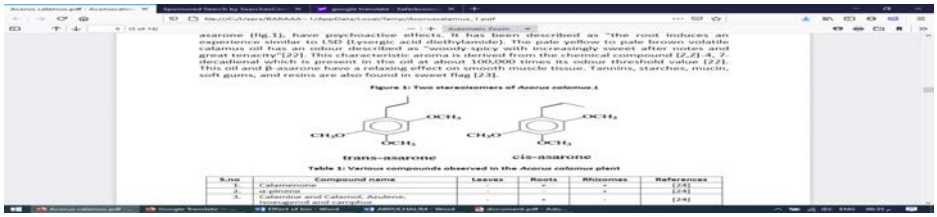

Figure 2. Two Stereoisomers of *Acorus Calamus*.L (Mythili et al., 2013)

2.3. Patchouli (Pogostemon Cablin Benth)

Patchouli (*Pogostemon cablin* Benth) is a perennial herbaceous plant belonging to *Lamiaceae* family, native to Philippines and growing wild in Malaysia, Indonesia, Singapore, China and India has been reputed for it's their sweet smelling leaves (Yogesh & Pawan, 2005). The essential oil of Patchouli is obtained by steam distillation or hydro distillation of the dried leaves. Patchouli alcohol is the major components of the oil, with other components such as Delta-Guaiene , Azulene , Trans Caryophellene , Seychellence (CAS) Nephtalene , Cycloheptane and Caryophyllene (Ermaya et al., 2019). These chemical components possess a wide range of biological activities, in the following some of the therapeutic benefits attributed to its aromatic oil:

- Improving Metabolic Parameters

A study by (Seong et al., 2020) demonstrate that the inhalation of Patchouli essential oil influenced certain markers related to metabolic diseases, may assist in regulating blood pressure.

- Antimicrobial Activities

H. pylori is a Gram-negative bacterial species that colonizes the gut of ~50% of the human population worldwide, Patchouli alcohol is a critical pharmacological agent isolated from patchouli that exhibits antimicrobial activity against H. pylori both in vitro and in vivo (Junren et al., 2021).

- Anti-oxidative Effect

According to (Bhanuz et al., 2017) P. cablin extracts contain antioxidant properties that

should be exploited for possible clinical application. That it showed moderate inhibition of superoxide inhibition (O_2) and nitric oxide (NO) production in concentration-dependent manner

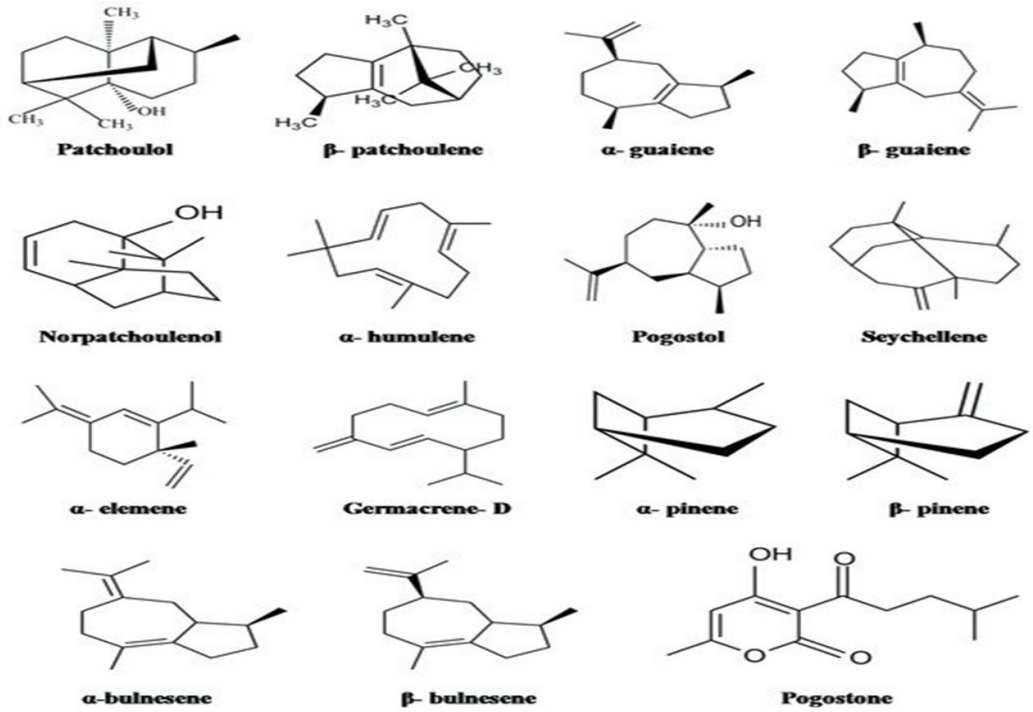

Figure 3. The Structures of Some of the Volatile Chemical Constituents of PO (Mallappa and Uma 2015)

2.4. Lemon Grass (Cymbopogon Citratus)

Lemon grass (*Cymbopogon citratus*) is an aromatic plant belonging to *Gramineae* family the plant is a native herb from India and is cultivated in other tropical and subtropical countries. (Figueirinha et al., 2008). Plants are utilized as therapeutic agents since time immemorial in both organized (Ayurveda, Unani) and unorganized (folk, tribal, native) form (Vanisha, 2012). The essential oil of Lemongrass is obtained by hydro distillation of the dried leaves, geranial (citral-a), neral (citral-b) and myrcene are considered the main components (Mohamed et al., 2012). and here is some studies about health benefits of lemon grass based on its most important chemical components:

- Anti-oxidant properties

Oxidation is a fundamental process in human cells, tissue and systems leading to formation of reactive oxygen species (ROSs). Sharma and Bhat, 2009 identified antioxidant potentials of lemongrass extracts and documented their abilities to reduce ROSs. Such mechanism include inhibition of lipoperoxidation and decolorization of 2, 2-diphenyl-1-picrylhydrazyl (DPPH)

- Anti-inflammatory properties

Oral administration of lemongrass oil showed dose-dependent anti-inflammatory activity. In addition , topical application of oil at doses of 5 and 10mL/ear significantly reduced acute ear edema induced by croton oil in 62.5 and 75% of the mice (Mohamed et al., 2014) .

- Antibacterial properties

According to (Oluwole et al., 2019) α-citral (geranial) and β-citral (neral) are active antibacterial compounds with predominant activities against gram positive and negative bacterial isolates.

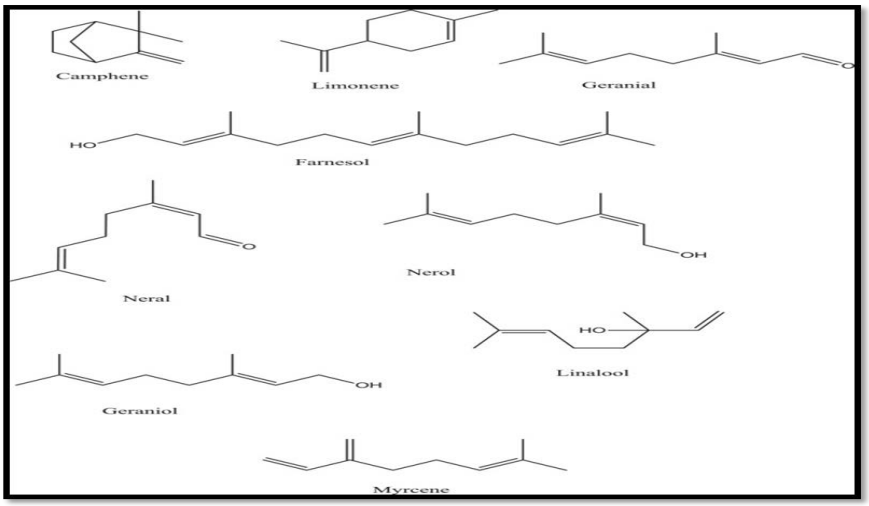

Fig. 4. Chemical Structures of Important Constituents of Lemongrass Essential oil (Oluwole et al., 2019)

2.5. Thyme (Thymus Vulgaris)

Thyme (*Thymus vulgaris*) is an aromatic and culinary herb belonging to *Lamiaceae* family, native to southern Europe from the western Mediterranean to southern Italy. Its aromatic, grey-green leaves have therapeutic characters (Miraj &. Kiani, 2016). The essential oil of thyme is obtained by hydro distillation of the dried leaves, thymol and carvacrol, are considered the main phenolic monoterpenes of it. Also, phenolic acid (rosmarinic acid) and flavonoids (quercetin, eriocitrin, luteolin and apigenin) are proposed to be the polyphenolic compounds responsible for the antioxidant effects of aqueous extracts (Kulisic et al., 2007). Several pharmacological studies have been performed on thyme, and its medicinal functions are attributed to its components, on the following some of them:

- Antimicrobial Activity

Imelouane et al. (2009) evaluated the essential oil of thyme for its antibacterial activities against six Gram-positive and Gram negative pathogenic bacteria:

Staphylococcus aureus, S. epidermidis, Streptococcus sp., Pantoa sp.and *Escherichia coli*, The results obtained in this study showed that the Gram-negative bacteria were more sensitive to the essential oil of thyme.

- Anti-oxidant Activity

Goncalves et al., 2017 showed that the chemical structure of the phenolic compounds of essential oil of thyme allows them to donate hydrogen to free radicals and explains their antioxidant activity.

- Anti-fungal Activity

Essential oils thyme were tested by (Soliman and Badeaa, 2002) for inhibitory activity against Aspergillus flavus, A. parasiticus, A. ochraceus and Fusarium moniliforme. The results also showed that the essential oils of thyme, have effect on fungal development and subsequent mycotoxin production in wheat grains.

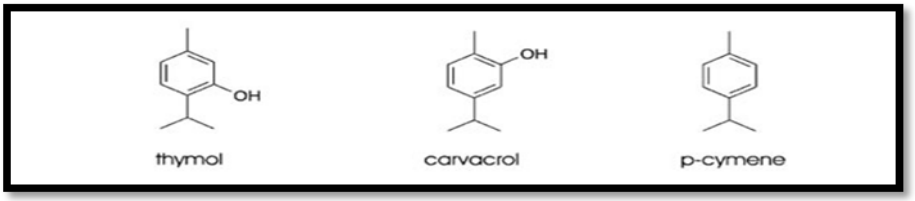

Figure 5. Chemical Structures of Most Important Compounds of Thyme Oil (Taheri et al., 2015)

2.6. Syrian oregano (Origanum syriacum L.)

Syrian oregano (*Origanum syriacum* L.) is perennial aromatic culinary herb belonging to *Lamiaceae* family, mainly native to Syria and Lebanon. Its therapeutic characters related to chemical compounds that found in its leaves (Farhat et al., 2012). The essential oil of Syrian oregano is obtained by hydro distillation of the dried leaves. The two dominant constituents identified in Syrian oregano leaves were carvacrol and thymol (Farhat, et al., 2012). In the following some of its important biological activities:

- Antimicrobial effect :

The main compounds identified in Syrian oregano oil are carvacrol and thymol. These substances are considered as antibacterial agents make the cell membrane permeable due to its impregnation in the hydrophobic domains, this effect is higher against gram positive bacteria (Rodriguez et al., 2016).

- Antioxidant effect :

Luna et al. (2010) evaluated the effects of thymol (150 mg/kg) and its isomer carvacrol (150 mg/kg) on lipid oxidation when supplemented to the feed chickens. Lipid oxidation was determined by the analysis of 2-TBA reactive substances (TBARS). After 5 and 10

days of storage, increasingly higher values of TBARS were detected in thigh samples of the control group in comparison to the supplemented groups. Interestingly, the same lower values of TBARS were detected between those feed-supplemented groups effecting positively on poultry meat quality.

- Anti-inflammatory effect :

The antioxidant activities of oregano due to its main components appear to contribute to its preventive effects against inflammatory diseases, such as stress-induced gastritis and contact hypersensitivity in mice according to (Kyoji et al., 2006).

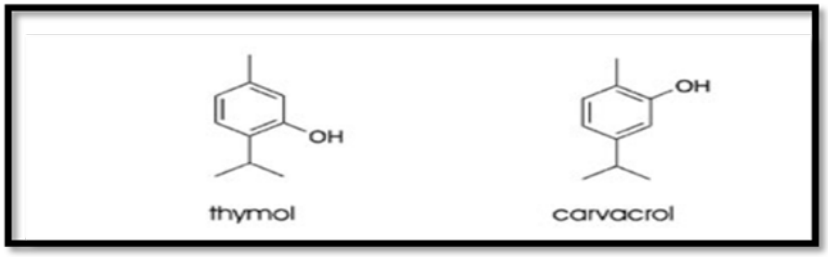

Figure 6. Chemical Structures of Most Important Compounds of Syrian Oregano Oil (Taheri et al., 2015)

2.7. Peppermint (Mentha piperita)

Peppermint (*Mentha piperita*), is perennial aromatic herb belonging to *Lamiaceae* family, growing to throughout Europe and North America. Menthol that presented in its leaves is one of its main phytochemicals that responsible for its traditional uses (Catherine et al., 2007). The essential oil of Peppermint *(Mentha piperita*) is obtained by hydro distillation of the dried leaves, menthol, menthofuran, methone and menthyl acetate are considered the main oil components (Jorge & Pedro, 2002). Peppermint could be used for various commodities of medicinal and pharmacological attributes, in the following some of its therapeutic properties:

- Antimicrobial activities

Mentha piperita L.(Peppermint oil), widely applied for microbial activity against different microbial species; Menthol is bactericidal against *Staphylococcus pyogenes, Staphylococcus aureus, Streptococcus pyogenes, Serratia marcescens, Escherichia coli,* and *Mycobacterium avium*. (Akbari et al., 2015).

- Treatment of Mental Fatigue:

Study by Toyoshi et al. (2001) determined the effects of peppermint oil on behavior in mice. The present study revealed that intraperitoneal administration of natural peppermint oil, which is used for medicinal purposes in aromatherapy, caused a significant dose dependent increase in ambulatory activity. This result demonstrated that

peppermint oil produces an apparent effect on behavior in mice.

- Prevention of chronic degenerative diseases

Sandra et al. (2011) examined the effects of this plant on human biochemical and anthropometric profiles and blood pressure, based on the administration of peppermint juice twice daily for 30 days. Results indicated that 41.5% of the subjects showed a reduction in glycemia, 66.9% in total cholesterol levels, 58.5% in triacylglycerides, 52.3% in LDL-c (low-density lipoproteins) indices, 70% in GOT (glutamic-oxaloacetic transaminase) levels, 74.5% in GPT (glutamic-pyruvic transaminase) levels, and that 52% presented an increase in HDL-c (high-density lipoprotein cholesterol) indices. Also, 52.5% showed a decrease in blood pressure and 48.7% in BMI. According to these results, it could be concluded that peppermint is beneficial in the prevention and treatment of risk factors of chronic degenerative diseases.

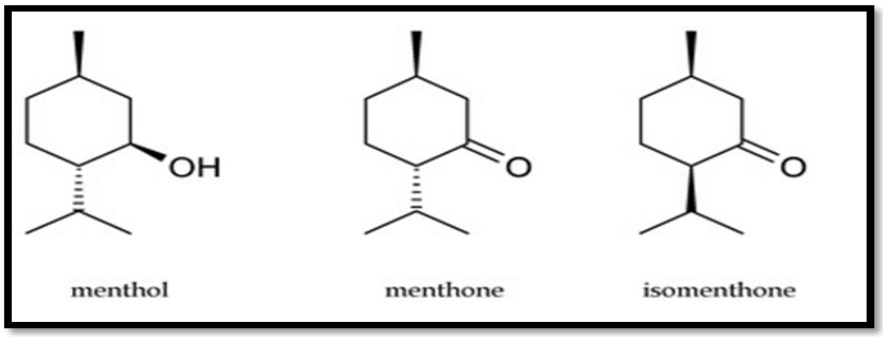

Figure 7. Chemical Structures of Some Important Compounds of Mint Essential Oil (Danuta and Agnieszka, 2020)

2.8. Sage (Salvia Officinalis L.)

Sage (*Salvia Officinalis* L.) an aromatic herb belonging to the *Lamiaceae* family grow in many parts of the world . and it was as discovered by Linneu in 1753, in the East-Mediterranean region its leaves has been used for a long time in traditional medicine to fight disease due particularly to the quantity and quality of the phenolic compounds it contains (Lemle , 2017). The essential oil of *Salvia officinalis* is isolated by hydro-distillation. The main compounds are 1, 8-cineole and camphor (Abu-Darwish et al., 2013). Several medicinal applications for Sage have been identified due to its various biomolecules, in the following some of these biological effects:

- Antibacterial activity

A study conducted on the antibacterial effect of sage against selected food spoiling bacteria in vitro indicates that the sage aqueous extract exerted significant antibacterial activity and it was most effective against *Bacillus mycoides*, *Bacillus subtilis*, *Enterobacter cloacae*, and *Proteus* sp. This has made sage essential oil a

good alternative to the traditional antibiotics as well as food preservatives (Stanojevic et al., 2010).

- Memory improvement

Study was conducted by (Akhondzadeh et al., 2003) to assess the efficacy and safety of *Salvia officinalis* extract using a fixed dose (60 drops/day), in patients with mild to moderate Alzheimer's disease, over a 4-month period. The results of this study indicate the efficacy of *S. officinalis* extract in the management of mild to moderate Alzheimer's disease. That, at 4 months, *S. officinalis* extract produced a significant better outcome on cognitive functions than placebo (ADAS-cog: $F = 4.77$, d.f. = 1, $P = 0.03$) (CDR-SB: $F = 10.84$, d.f. = 1, $P < 0.003$).

- Antioxidant activity

The phenolic compounds can either stimulate endogenous antioxidant defense systems or scavenge reactive species (Mohsen et al., 2011). In a study conducted on the antioxidant activity of many plant extracts, like sage (*S. officinalis*), it was found that the phenolic and flavonoid compounds are mainly responsible for the antioxidant and free radical scavenging effects of these plants (Yadav et al., 2011).

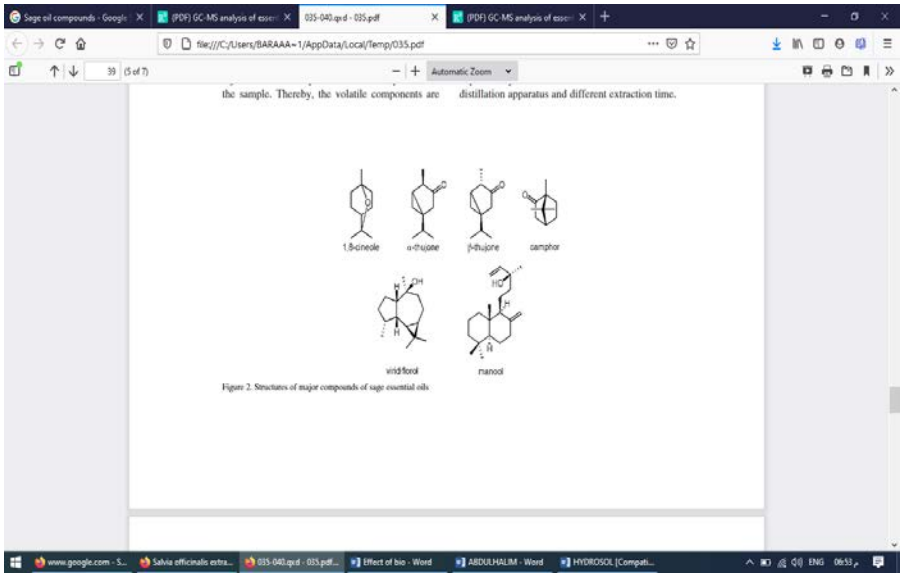

Figure 8. Chemical Structures of Some Important Compounds of Sage Essential Oil (Tomasz et al., 2013)

2.9. Lavender (Lavandula angustifolia L.)

Lavender (*Lavandula angustifolia* L.) is perennial aromatic herb belonging to the *Lamiaceae* family native to the Mediterranean, the Arabian Peninsula, Russia, and Africa. It flowers has been used cosmetically and medicinally through-out history (Ethan et al., 2014). The essential oil Lavender (*Lavandula angustifolia* L.) oil is extracted mostly

from the flowers through steam distillation, and the major constituents are linalool, linalyl acetate, geraniol, β-caryophyllene, lavandulyl acetate, 1,8-cineole, limonene, trans-β-ocimene, cis-β- ocimene, 3-octanone (Krzysztof et al., 2013). Linalool is considered the primary active constituent responsible for the pharmacological effects of lavender, including its supposed calming and sedative activity (Basch et al., 2004) In the following some of Lavender biological proprieties:

- Antiviral effect :

Lavender essential oil is popular as a complementary medicine. According to (Nadjib, 2020) essential oils (EOs) and their chemical constituents are known to be active against a wide range of viruses. Oxygenated monoterpenes and sesquiterpenes present in lavender oil contribute to their antiviral effect.

- Anti-inflammatory activity.

Lavender essential oil presented anti-inflammatory activity. According to (Cardia et al. , 2018) topical application at concentrations of 0.25, 0.5, and 1 mg/ear reduced edema formation, myeloperoxidase (MPO) activity, and nitric oxide (NO) production in croton oil-induced ear edema model. In carrageenan-induced paw edema model, LEO treatment at doses of 75, 100, and 250 mg/kg reduced edema formation, MPO activity, and NO production.

- Controlling Anxiety:

Anxiety is one of the uprising psychiatric disorders of the last decades (Bandelow and Michaelis, 2015), Lavender aromatherapy reduced preoperative anxiety in ambulatory surgery patients (Wotman et al., 2017). *Lavandula angustifolia* hydrosol exhibits also revitalizing and relaxing properties when consumed in the form of an additive to water or food (Rose, 1999)

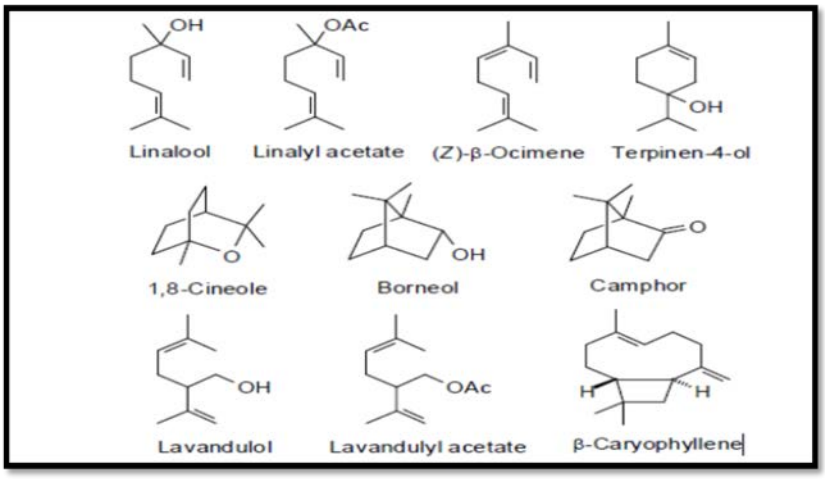

Figure 9. Chemical Structures of Some Important Compounds of Lavender Essential Oil (Cavanagh and Wilkinson 2002)

2.10. Sweet basil (Ocimum basilicum L.)

Sweet basil (*Ocimum basilicum* L.) an aromatic plant belonging to the *Lamiaceae* family, the main centers of diversity in the genus are Africa, America and Asia (Beltrame *et al*., 2014). Since ancient times sweet basil was cultivated as aromatic plant for its medicinal proprieties due to its phenolic acids and aromatic compound (Hussain and Przybylski, 2008). The essential oil of Sweet Basil (*Ocimum basilicum*) is obtained by hydro distillation of the dried and fresh leaves. The high economic value of its oil is due to the presence of phenyl propanoids, like eugenol, chavicol and their derivatives or terpenoids like monoterpen linalool, methyl cinnamate, and limonene (Louie et al., 2007). The following highlight on different implications of sweet basil

- Antioxidant activity

According to (Ademiluyi et al., 2016) the antioxidant and enzyme inhibitory effects of the essential oil could be attributed to the presence of its phytochemicals, which could be the principle responsible for the antidiabetic and antihypertensive properties of the essential oil.

- Anti -inflammatory activity

The anti -inflammatory effect of *Ocimum basilicum* L. and *Ocimum gratissimum* L xylene-induced ear edema as a model of inflammation was studied by (Festus , 2016) At 50 µg/ear OBV, OGV, exhibited significant ($P<0.05$) topical anti-inflammatory effect with edema inhibitions of 50.0, 63.3, 62.7 and 80 % respectively. The effects were comparable ($P<0.05$) with that of 100 µg/ear hydrocortisone (% edema inhibition of 54.8).

- Antifungal activity

The essential oils of different species of *Ocimum* L. (*Lamiaceae*) were studied by (Sethi et al., 2013) for their antifungal activity against a plant pathogenic fungus, *Rhizoctonia solani*. The essential oil of *Ocimum basilicum* L. (Lemon basil) exhibited maximum inhibitory effect with MIC (Minimum inhibitory concentration) of 31. 25 µg/Ml .However, *Ocimum sanctum* L.(Sri tulsi) and *Ocimum gratissimum* L.(Clove basil) exhibited strong inhibitory effects with the MIC of 62.5 µg/mL.

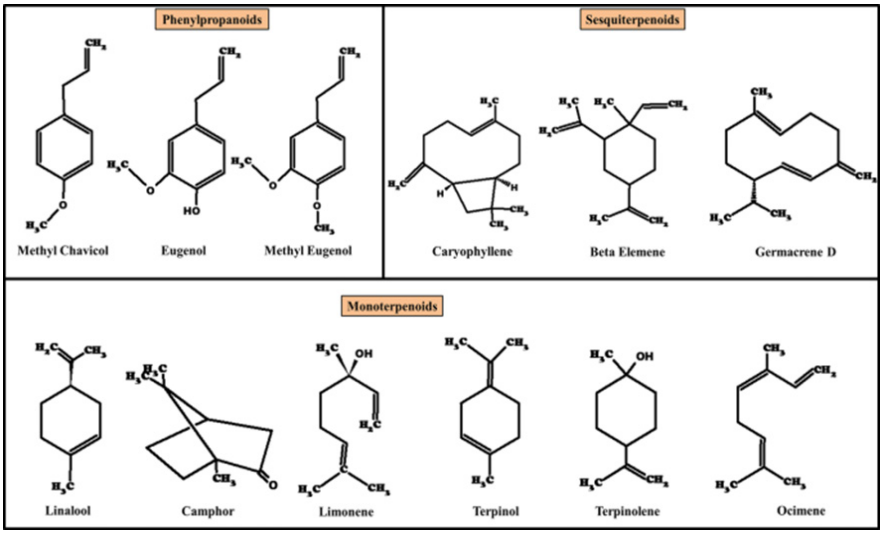

Figure 10. Chemical Structures of Some Important Compounds of Ocimum Species Essential Oil (Maurya, & Sangwan , 2020)

3. Concept of Bio-Fertilizers

The knowledge of applied microbial inoculums is long history which passes from generation to generation of farmers. Bio-fertilizers are rhizosphere colonies including plant root growth promoting bacteria. These bacteria help the plants via supplying nutrients, biological controlling, producing pseudo hormone substances of the plant, and making the plant resistant against different kinds of stress including water and nutrients deficiency and decreasing the contamination effect of plant's heavy metals (Shaharoona et al., 2006). Hence the term bio-fertilizers do not contain any chemicals which are detrimental to the living soil. They are extremely beneficial in enriching the soil with those micro-organisms, which produce organic nutrients for the soil, In large sense, These potential biological fertilizers would play key role in productivity and sustainability of soil and also protect the environment as ecofriendly and cost effective inputs for the farmers. They are cost effective, ecofriendly and renewable source of plant nutrients to supplement chemical fertilizers in sustainable agricultural system. (Khosro, 2012).

Organisms that are commonly used as bio-fertilizers component are nitrogen fixers (N-fixer), solubilizer (K-solubilizer) and phosphorus solubilizer (P- solubilizer), or with the combination of molds or fungi. It cause an increase in nitrogen and phosphorus uptake and consequently the promotion of roots growth of plants according to Violen, 2007.These bacteria may accumulate either in the rhizosphere or even in root or internal cellular space of the plants (Wu et al., 2005).

Azotobacter belongs to family *Azotobacteriaceae*, aerobic, represents the main group of heterotrophic, non-symbiotic free living nitrogen-fixing bacteria principally inhabiting

the neutral or alkaline soils. These bacteria are Gram negative and vary in shape. The first representative of the genus, A. chroococcum was discovered and described in 1901 by the Dutch microbiologist and botanist Martinois Beijerinck. , it is used for studying nitrogen fixation and inoculation of plants due to its rapid growth and high level of nitrogen fixation (Jnawali et al., 2015).

For much of the history of life on Earth, biological nitrogen fixation (BNF) is considered to be an important process which determines nitrogen balance in soil ecosystem (Peter et al., 2015). Occurs naturally in the soil by N fixing bacteria (*Rhizobium* and legumes/ *Azotobacter*). It also occurs naturally in the air by means of lightning. N-fixers contribute to nitrogen accumulation in long term and bring N supply close to the equilibrium (Subba et al., 2017).

Microorganisms are able to solubilize and mineralize P pools in soils and are considered to be vital. Bacteria are among the predominant microorganisms that solubilize mineral P in soils, and most of them live in the plant rhizosphere (Barea and Brown, 2005). Phosphorous Solubilizing Bacteria (PSB) inoculants play an important role in making phosphorus available to crops. The use of phosphate-solubilizing bacteria (PSB) as inoculants simultaneously increases P uptake by the plant and crop yield (Igual et al., 2001)

Therefore, it uses in agricultural practice would not only offset the high cost of manufacturing phosphate fertilizers but would also mobilize insoluble fertilizers to soluble forms in soil (Banerjee et al., 2010).

Growth characters, yield, essential oil and its constituents of aromatic plants were significantly affected by adding the biological fertilizers. The following will concentrates on biological fertilization and its effects on the selected aromatic plants for this chapter.

3.1 Effect of Bio-Fertilizers on Growth and Yield of Selected Aromatic Crops

Kumar *et al*. (2009) observed that application of nitrogen and phosphorus at the rate of 93.75 kg/ ha along with *Azospirillum* gave the highest plant height, number of laterals, fresh and dry weight of shoot, dry matter production, fresh herbage yield and essential oil yield in davana.

Prakash and Karthikeyan (2015) declared that plant growth promoting *rhizobacteria* (PGPR) like *Azotobacter, Bacillus, Pseudomonas* and *Enterobacter* with concentration of 109 CFU/ml improved the plant height (95.05 cm), number of rhizomes per plant (16 rhizomes/plant) , rhizome length (45cm) and rhizome wet and dry weight per plant (75.011 and 37.893 g/plant) respectively in Sweet flag .

A study was conducted by Abdulhalim (2009) to evaluate the effect of enhancing bio-

fertilizer with N-fixer bacteria on patchouli plant. The results showed improvement of leaves and branch growth up to 8% and 5%, respectively compared to original bio-fertilizer.

Ratti *et al*. (2001) investigated the effect of some strains of *arbuscular mycorrhizal fungi* (AMF) e.g. *Glomus mosseae* and *G. fasciculatum* on the yield of *Cymbopogon martini* and concluded that, the biomass yield increased by 3-10% compared to the control condition.

Fatemeh (2014) studied the effect of different types of fertilizers on growth, characteristics of *Thymus vulgaris*. The results indicated that application of nitroxin as liquid culture from each strain at the rate of 5ml/Liter along with compost (25t/ha) recorded highest fresh weight (605g), dry weight (130g) and number of inflorescences (26) followed by the plants treated by NPK chemical fertilizers (100:50:50 kg/ha) that recorded (535g, 116g and 19g) respectively.

Abd El- Wahab (2013) studied the effect of bio-fertilizer and chemical fertilizers on *Origanum syriacum*. Plants received 3/4NPK dose (200:100:50 kg/fed) along with bio-fertilizer as mixture of 5 strains of bacteria namely (*Azotobacter chroococcum, Azospirillum lipoferum, Bacillus polymixa , Bacillus megatherium* and *pseudomonas fluorescence*) at (1X108 / c.f.) gave higher values of vegetative characters as plant height (32 cm), number of branches (21) and fresh weight of herb (80.20g).

Application of combination of FYM at 30 m3 /fed. + phosphorein (4kg/fed) and humic acid (6l/fed) in *Mentha piperita* plants recorded maximum plant hight (93.3cm), number of branches (23.80), herb fresh weight (806.8g) and dry herb weight (88.66g) comparing to control according to Sharaf el-din et al. (2013).

Nadjafi *et al.* (2014) conducted an experiment to study the effect of bio-fertilizers on growth and yield of sage (*Salvia officinalis* L.). Application of nitroxin at 50 ml /liter water recorded maximum plant height (33.08cm), fresh weight (70.43 g) and dry weight (1714.4g) compared to control.

Hadis *et al.* (2014) studied the effect of chemical and biological fertilizers on growth and essential oil content of lavender. Mean comparison showed that flower yield was the highest (3932.5 kg/ha) in application of P at 150 kg/ha along with the triple inoculation of *G. mosseae* + *G. intraradices* + *P. fluorescens*.

Shoae (2013) recorded that inoculation the seed of sweet basil with PGPRs such as *Pseudomonas putida* (1×109 CFU g-1) and *Azospirillum lipoferum* (2×1017) resulted in increase of shoot wet weight (34.9%), shoot dry weight (44.7%), essence yield (47.32%), plant height (15.85%), leaf area (22.04%), chlorophyll a (63.23%), chlorophyll b (61.86%) and chlorophyll a+b (62.96%) relative to control.

3.2 Effect of Bio-Fertilizers on Quality of Selected Aromatic Crops

According to Mohammad et al. (2012) application of biological fertilizers such as Nitroxin [include bacteria which stimulus growth (*Azotobacter* and *Azospirillum*)], Bio-phosphorus [include bacteria which stimulus growth (*Bacillus* and *Pseudomonas*)] lead to increase in active ingredient artemisinin and chlorophyll concentration in Artemisia annua.

According to (Kalyanasundaram et al., 2008) nitrogen fixing bacteria, promoted essential oil yield through the enhancement of yield attribute in sweet flag plant .

Application of 75% NP(100:50 kg/ha) + 100% K (50kg/ha) + *Azotobacter* + *Azospirillum* + VAM in patchouli recorded significantly superior values for Patchouli oil yield (1.231 g/g) which is 155% increase compared to control according to Manjunathatha (2002).

The interaction treatments between of nitrogen and bio-fertilizers led to significant increment for yield of lemon grass essential oil, that is using 150 kg N/fed + 1 kg Microbein/fed gave Maximum content of essential oil (35.62%) While, the maximum content of Citral A was observed in the essential oil of the herb that received 75 kg N/fed with 1 kg Rhizobacteren /fed.

Optimal nutrition along with non-stress conditions has a significant impact on the quantity and quality of thyme essential oil, the interaction between superabsorbent and thiobacillus significantly changed the percentage of thymol, borneol, and caryophyllene. (Pouneh et al., 2018).

According (Emad et al., 2019) to *mycorrhizal* inoculation increased carvacrol and reduced thymol productions in comparison to non-inoculated conditions.

According to (Pourhadi, 2011) the nitroxin and supernitroplus (8 kg/ha) on par with urea fertilizer had the most effect additive on qualitative and quantitative character of peppermint.

Eisa (2004) reported that microbein and nitrobein bio-fertilizers increased the essential oil content per plant and oil yield /ha in *Salvia officinalis*.

Results of (Hadis et al., 2014) indicated that the triple inoculation of *G. mosseae* + *G. intraradices* + *P. fluorescens* gave the best results of Lavender essential oil. The highest flower essential oil yield (114.27 kg/ha) was achieved in application of P (150 kg/ha) along with the double inoculation mycorrhiza fungi.

Nazanin et al. (2014) conducted an experiment with four treatments viz., *Azotobacter chroococcum* (A) *Azospirillum lipoferum* (B) *Bacillus circulans* (C). The maximum

geranial and the minimum caryophyllene in essential oil were obtained by using two biofertilizers (A + C). The highest methyl chavicol was obtained after applying two biofertilizers (B + C).

4. Conclusion

The need for renewable sources of pharm- logical products as well as the need to protect plant biodiversity with trying to reach sustainability, creates an opportunity for farmers to produce aromatic crops. It have a great number of synthetic aromatic compounds have been developed and used in the food, beverage, and pharmaceutical industries, in perfumery and cosmetics industries. Knowing that, quality is one of the most important and critical factors in these crops cultivation, promotion ecologically sound plant protection measures is highly suggested such as bio-fertilizers. However, the current use of microorganisms in agriculture remains at a low level despite the significant investment in scientific work to understand and use natural microbial resources to improve plant growth and health. Keeping the above facts in view, this chapter is highlighting on the bio-fertilizer as an agricultural practice that have positive effect on yield and quality of aromatic crops.

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To Cite This Chapter

Almansour, B. (2021). Biological fertilization and its effect on selected aromatic plants. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.250-275). ISRES Publishing

Covid-19 Variants and Vaccines: An Overview

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Introduction

Coronavirus disease 2019 (COVID-19) is the highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle Eastern Respiratory Syndrome (MERS) appeared in Wuhan, Hubei Province, China, in late December 2019. COVID-19 considered as worldwide pandemic because of their rapid prevalence in whole world and their catastrophic impact on various disciplines such as economy, industry, education, etc. (Marco Cascella, 2021). Moreover, according to World Health Organization (WHO), COVID-19 takes life of more than 4.47 million people and it would destroy the livelihoods people health systems because it is spread through close contact with infected people and could also be transmitted by asymptomatic patients (kern, 2021).

The most characteristics of the COVID-19 are Fever, Dry cough, Fatigue. However, there are other less common symptoms such as Loss of taste or smell, Nasal congestion, Conjunctivitis (also known as red eyes), Sore throat, Headache, Muscle or joint pain, Different types of skin rash, Nausea or vomiting, Diarrhea, Chills or dizziness (Maladie à coronavirus (COVID-19) : Symptômes et traitement, 2021).

Since SARS-CoV-2 affected the Ribonucleic (RNA) and deoxyribonucleic acids (DNA), Reverse Transmission Polymerase Chain Reaction (RT- PCR) was the gold standard method for diagnosing Covid-19 (Alazab, 2020). RT-PCR tests are performed on clinical research samples of nasal secretions by inserting a swab into the nostril and gently moving it into the nasopharynx to collect secretions (Alazab, 2020). Meanwhile, some patients get negative tests even though they had abnormality in their chest radiography.

Chest radiography has great results for important clinical findings such as computed tomography (CT) scans and X-rays images. They frequently used for diagnosing Pneumonia and other chest diseases. Due to their great impact in the medical care worldwide, CT scans and X-rays were highly recommended for the detection of Covid-19 (Jain, 2020).

1. Covid-19 Variants of Concern (VOCs)

As SARS-CoV-2 is RNA virus, it has the ability of genetic evolution with the development of mutations over time, what create new variants with different characteristics. According to WHO, four concern variants (VOC) were discovered (Marco Cascella, 2021):

The first variant of the virus was in December 2020 in United Kingdom (UK) called Alpha (B.1.1.7). In the same period other two variants called Gamma (P.1 lineage) and Delta (B.1.617.2) in Brazil and India respectively. While Beta (B.1.351) variant was discovered South Africa.

1.1 Alpha (B.1.1.7 lineage)

Alpha variant also known as GRY (formerly GR/501Y.V1) is new SARS-CoV-2 variant caused by 17 mutations in the viral genome. Eight mutations (Δ69-70 deletion, Δ144 deletion, N501Y, A570D, P681H, T716I, S982A, D1118H) are in the spike (S) protein. N501Y shows an increased affinity of the spike protein to ACE 2 receptors, enhancing the viral attachment and subsequent entry into host cells. The UK variant was the most contagious one with 43% to 82% times than the original SARS-CoV-2. The clinical study reported that the B.1.1.7 lineage variant had increased severity of disease compared to patients that had other variants of SARS-CoV-2.

A lot of study were done in UK confirmed that the mortality risk of infected patients with this variant was 1.64 (95% confidence interval 1.32 to 2.04, $P<0.0001$) patients with previously circulating strains.

Another study reported that the B 1.1.7 variant was associated with increased mortality compared to other SARS-CoV-2 variants (HR= 1.61, 95% CI 1.42-1.82) (Davies, 2021). The risk of death was reportedly greater (adjusted hazard ratio 1.67, 95% CI 1.34-2.09) among individuals with confirmed B.1.1.7 variant of concern compared with individuals with non-1.1.7 SARS-CoV-2 (Grint, 2021).

1.2 Beta (B.1.351 lineage)

Beta variant also known as GH501Y.V2 is another variant appeared South Africa in October 2020. GH501Y.V2 has nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the spike protein, of which three mutations (K417N, E484K, and N501Y) are located in the RBD and increase the binding (K417N, E484K, and N501Y) are located in the RBD and increase the binding affinity for the ACE receptors.

1.3 Gamma (P.1 lineage)

Gamma variant or GR/501Y.V3 was detected in Brazil in December 2020. The variant has ten mutations in the spike protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y). Three mutations (L18F, K417N, E484K) are located in the RBD, similar to the B.1.351 variant (Faria, 2021).

1.4 Delta (B.1.617.2 lineage)

As December 2020, India identified the B.1.617.2 as new variant of SARS-CoV-2. Also, Delta variant has ten mutations (T19R, (G142D*), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N) in the spike protein. Nowadays, B.1.617.2 variant is the most dominant SARS-CoV-2 strains in the world wide.

2. Covid-19 Variants of Interest (VOIs)

By June 22, 2021, The WHO defines some variants that have remarkable specific genetic which might accelerate the transmission of the virus and even more reduce the natural immune response of the body and decrease in the effectiveness of therapeutics or vaccination. The VOIs declared by WHO are: Epsilon (B.1.427 and B.1.429); Zeta (P.2); Eta (B.1.525); Theta (P.3); Iota (B.1.526); Kappa (B.1.617.1) and Lambda (C.37).

2.1 Epsilon (B.1.427 and B.1.429)

Epsilon (B.1.427 and B.1.429) variants, also called CAL.20C/L452R, emerged in the US around June 2020 and increased from 0% to >50% of sequenced cases from September 1, 2020, to January 29, 2021, exhibiting an 18.6-24% increase in transmissibility relative to wild-type circulating strains. These variants harbor specific mutations (B.1.427: L452R, D614G; B.1.429: S13I, W152C, L452R, D614G) (Zhang, 2021).

2.2 Zeta (P.2)

Zeta (P.2) has key spike mutations (L18F; T20N; P26S; F157L; E484K; D614G; S929I; and V1176F) and was first detected in Brazil in April 2020.This variant classified as a VOI by the WHO and the Centers for Disease Control and Prevention CDC due to its potential reduction in neutralization by antibody treatments and vaccine sera.

2.3 Eta (B.1.525) and Iota (B.1.526)

Eta (B.1.525) and Iota (B.1.526) variants harbor key spike mutations (B.1.525: A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L; B.1.526: (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)) and were first detected in New York in November 2020 and classified as a variant of interest by CDC and the WHO due to their

potential reduction in neutralization by antibody treatments and vaccine sera.

2.4 Theta (P.3)

Theta (P.3) variant, also called GR/1092K.V1 carry key spike mutations (141-143 deletion E484K; N501Y; and P681H) and was first detected in the Philippines and Japan in February 2021 and is classified as a variant of interest by the WHO.

2.5 Kappa (B.1.617.1)

Kappa (B.1.617.1) variant harbor key mutations ((T95I), G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H) and was first detected in India in December 2021 and is classified as a variant of interest by the WHO and the CDC.

2.6 Lambda (C.37)

Lambda (C.37) variant was first detected in Peru and has been designated as a VOI by the WHO in June 2021 due to a heightened presence of this variant in the South American region.

3. Covid-19 Transmission

As SARS-CoV-2 is respiratory virus, it is obvious that the first way of their transmission is the close contact with infected people. Also, contact with surfaces contaminated by the virus, airborne transmission with aerosol-generating procedures and fomite transmission from contamination of inanimate surfaces with SARS-CoV-2 could be source of infection.

Researchers reported that SARS-CoV-2 can be found on plastic and stainless steel for up to 2-3 days, cardboard for up to 1 day, copper for up to 4 hours. Moreover, it seems that contamination was higher in intensive care units (ICUs) than in general wards, and SARS-CoV-2 can be found on floors, computer mice, trash cans, and sickbed handrails as well as in the air up to 4 meters from patients implicating nosocomial transmission as well in addition to fomite transmission (Guo, 2020).

4. The Main Types of Covid-19 Vaccine

Since the declaration of Covid-19 as worldwide pandemic by WHO, experts from various organizations started searching for an accurate vaccine for this pandemic. Till now, various types of vaccine authorized by the WHO: Whole Virus, Protein Subunit, Viral Vector and Nucleic Acid (RNA AND DNA). All vaccines work by exposing the body to molecules from the target pathogen to trigger an immune response with different exposure method.

The main objective of these categories is to get immunity to the virus, and stop the

transmission by smuggling the antigen into the body, or by using the body's own cells to make the viral antigen (Gavi, 2021).

A. Whole Virus

Whole virus vaccines use a weakened (attenuated) or deactivated form of the pathogen that causes a disease to trigger protective immunity to it. There are two types of whole virus vaccines. Live attenuated vaccines use a weakened form of the virus, which can still grow and replicate, but does not cause illness. Inactivated vaccines contain viruses whose genetic material has been destroyed by heat, chemicals or radiation so they cannot infect cells and replicate, but can still trigger an immune response (Gavi W. , 2021).

However, live attenuated ones may risk causing disease in people with weak immune systems and often require careful cold storage, making their use more challenging in low-resource countries (Gavi W. , 2021).

B. Protein Subunit

Subunit vaccines or acellular vaccines is purified pieces of the bacterial pathogen that stimulate immune cells. In general, these specific pieces, called protein, produce a strong and effective immune response which minimize the risk of side effects. However, the subunit vaccines could make immune response weaker because the antigens used to elicit an immune response may lack molecular structures called pathogen-associated molecular patterns which are common to a class of pathogen. These structures can be read by immune cells and recognized as danger signals (Gavi P. , 2021).

C. Nucleic Acid

Nucleic acid vaccines use genetic material (DNA or RNA) from a disease-causing virus or bacterium to stimulate an immune response against it. This genetic material that contains specific nucleotides, linked in a long chain, inserted in the host cells in order to construct the antigens (protein), using protein-making machinery, and trigger an immune response (Gavi N. , 2021).

D. Viral Vector

Unlike other vaccines Viral vector-based vaccines does not have antigens, they use the spike proteins found on the surface of the virus as genetic instructions to produce antigens by delivering these genetic codes into the cell. Ones the cells received these instructions, large amounts of antigens will be produced using cellular machinery of the body and trigger an immune response. This has the advantage of triggering a strong cellular immune response by T cells as well the production of antibodies by B cells. However, since there is a chance that many people may have already been exposed to

the viruses being used as vectors, some may be immune to it, making the vaccine less effective (Gavi V. , 2021).

Meanwhile, National regulatory authorities authorized twenty-two COVID-19 vaccines. Six of those have been approved for emergency or full use by at least one WHO recognized stringent regulatory authority (Oxford–AstraZeneca, Pfizer-BioNTech, Sinopharm-BBIBP, Moderna, Sinovac, and Janssen)

1. Oxford–AstraZeneca

Oxford–AstraZeneca also called Vaxzevria and Covishield is a viral vector vaccine produced by the British University of Oxford, British-Swedish company AstraZeneca, and the Coalition for Epidemic Preparedness Innovations (Wikipedia, 2021).

Oxford–AstraZeneca is an mRNA vaccine that based on the spike proteins of the virus to construct the genetic instructions. After injecting these genetic instructions into cells, the immune system body will be triggered and produce antigens for the virus (Terry, 2021). AstraZeneca vaccine against Covid-19 is given by intramuscular injection in two doses (21 Days between the first and second dose) each dose of 0.5 ml contains: Chimpanzee adenovirus viral particles, GMOs, 2MG of ethanol per dose, 1Mmol of Sodium (Demmer, 2021). The efficacity of vaccine is about 95% and 100% at preventing hospitalization and death. Meanwhile, Lab data suggest “quite effective” against the UK variant as well as the South African and Latin American variants. Also, data suggests it is effective against hospitalization of the Delta variant but more data is needed (Terry, 2021).

2. Pfizer–BioNTech

The Pfizer–BioNTech COVID-19 vaccine, also known as Comirnaty or BNT162b2 is an mRNA vaccine produced by the German company BioNTech and the American company Pfizer. (Wikipedia, 2021) (David Bême, 2021). This vaccine requires 2 doses for maximum protection according to Health Canada at 21-day intervals (Vaccin de Pfizer-BioNTech contre la COVID-19 , 2021). Clinical trials have shown that from one week after the second dose, the Pfizer-BioNTech COVID vaccine was effective at approximately (Vaccin de Pfizer-BioNTech contre la COVID-19 , 2021) 95% to protect trial participants aged 16 and over from COVID-19, 100% to protect participants from 12 to 15 years old.

After a vaccine is given, it is common to have temporary side effects such as Pain, Redness and Swelling in the arm where you got the shot. Also, it might produce other effects like Tiredness, Headache, Muscle pain, Chills, Fever, Nausea. They usually last a few hours or days after vaccination because it is the body’s natural response that

goes together to build immunity against disease (National Center for Immunization and Respiratory Diseases (NCIRD), 2021).

3. Sinopharm-BBIBP

Sinopharm COVID-19 vaccine or BIBP vaccine, is one of two inactivated virus COVID-19 vaccines developed by Sinopharm's Beijing Institute of Biological Products (BBIBP or BIBP). Authorized in 31 December 2020 by China's National Medical Products Administration (Sinopharm, 2021). After injecting the inactivated virus in the body, it triggers the immune response that excites cells T And B to produce antibodies against this inactivated virus what earn the body immune against Covid-19 (Robert Carlson MD, 2021).

Like other vaccines The Sinopharm-BBIBP has some common side effects such as pain, fatigue, headache, lethargy, and tenderness (Robert Carlson MD, 2021). Clinical trials run by the state-owned company Sinopharm showed that it had an efficacy rate of 79% (Corum Jonathan, 2021).

4. Moderna

Like Pfizer-BioNTech vaccine, Moderna vaccine or Spikevax is a messenger RNA vaccine produced by the American company Moderna, the U.S. National Institute of Allergy and Infectious Diseases, the U.S. Biomedical Advanced Research and Development Authority, and the Coalition for Epidemic Preparedness Innovations. The vaccine authorized by the China National Medical Products Administration on December 31, 2020. This ultra-innovative technology consists of injecting strands of genetic instructions (messenger RNA) which will lead our cells to manufacture specific proteins or "antigens" for the coronavirus. These proteins will be identified by the immune system, which will then produce antibodies (Team, 2021). The vaccine requires 2-dose of β-propiolactone-inactivated at 21–28-day intervals. Each dose of 0.5 ml contains: 100 micrograms of messenger RNA (mRNA) encapsulated in the SM-102 lipid nanoparticles and other excipients (Moderna-NIAID, 2021).

AS the most common secondary effects of the vaccine were pain at the injection site, headache, and fatigue. However, other symptoms could be occurred such as nausea and inflammatory demyelination syndrome/acute disseminated encephalomyelitis (vaccines, 2021). The effectiveness of the vaccine against COVID-19 was 94.1% (Team, 2021).

5. Sinovac

CoronaVac, also known as the Sinovac COVID-19 vaccine, is an inactivated virus COVID-19 vaccine developed by the Chinese company Sinovac Biotech. It was Phase III clinical trailed in Brazil, Chile, Indonesia, the Philippines, and Turkey and

relies on traditional technology similar to BBIBP-CorV and Covaxin. In late August 2020, China approved CoronaVac for emergency use to vaccinate high-risk groups such as medical staff. In early February, China approved CoronaVac for general use(CoronaVac, 2021). The Sinovac CoronaVac vaccine does not need to be frozen, and both the vaccine and raw material for formulating vaccine doses could be transported and refrigerated at 2–8 °C (36–46 °F). CoronaVac is a 2-dose β-propiolactone-inactivated, aluminum hydroxide-adjuvanted COVID-19 vaccine administered on a 0/14-28-day schedule to prevent COVID-19 disease. A real-world study of millions of people who received CoronaVac found published by the WHO found the vaccine 67% effective against symptoms, reduced hospitalizations by 85%, intensive care visits by 89%, and deaths by 80% (Robert Carlson MD, CoronaVac COVID-19 Vaccine, 2021). CoronaVac has some side effects included fatigue, diarrhea, and muscle pain. Most of these side effects were mild and lasted only for 2 days (Jeong, 2021).

6. Janssen

The Janssen COVID-19 vaccine is a viral vector vaccine produced by Janssen Pharmaceutica (a subsidiary of Johnson & Johnson) and Beth Israel Deaconess Medical Center. It is also known as Johnson & Johnson COVID-19 Vaccine and as COVID-19 Vaccine Janssen (Wikipedia, 2021). The vaccine consists of a recombinant type 26 adenoviral vector (Ad26.COV2-S) incapable of replicating and expressing the Spike glycoprotein (also called S protein or spike protein) of the SARS-CoV-2 coronavirus (Janssen, 2021).

Unlike the other vaccines require two doses about 28 days apart, the Johnson & Johnson vaccine only requires a single dose. Since COVID-19 Vaccine Janssen has shown effectiveness of 66% in preventing moderate-to-severe COVID-19, 28 days after vaccination and 100% of efficacity ad preventing severe disease after day 49, it has been given conditional marketing authorization throughout the European Union on 11 March 2021, (Terry, 2021). The dose (0.5 mL) of Johnson & Johnson contains: Antigen with at least 8.92 log10 infectious units (I.U.) and genetically modified organisms (GMOs). Also, the product contains some excipients (Janssen, 2021). The most common side effects are pain at the injection site, headache, tiredness, muscle pain and nausea, they just occurred within 1 or 2 days after vaccination (EMA, 2021).

Conclusion

According to the latest development of the virus and the recent variants of this viral illness, several vaccinations were authorized by World Health Organization for emergency and general use. Due to the different categories of the vaccinations, various vaccinations are approved by different countries around world. As a result, the transmission rates and the numbers of new cases have reduced in many countries based on the percentage

of the vaccination. However, the comparison of the effectiveness of these vaccines is not clear because their clinical and preclinical studies were on different population. Moreover, it would be premature to hail the safety and immunogenicity observed in COVID-19 vaccine trials as a real success pandemic vaccine development paradigm (Mangalakumari Jeyanathan, 2020). Also, some variants are having a slight impact on the ability of vaccines to guard against mild disease and infection. Furthermore, vaccines can stop most people from getting sick with COVID-19, but not everyone. Even after someone takes all of the recommended doses and waits a few weeks for immunity to build up, there is still a chance that they can get infected. Vaccines do not provide full (100%) protection, so 'breakthrough infections' – where people get the virus, despite having been fully vaccinated – will occur (WHO, 2021).

Besides the importance of imposing public health and infection control measures to prevent or decrease the transmission of SARS-CoV-2, the most crucial step to contain this global pandemic is by vaccination to prevent SARS-CoV-2 infection in communities across the world. After being vaccinated, individuals should continue taking simple precautions, such as physical distancing, wearing a mask, keeping rooms well ventilated, avoiding crowds, handwashing for a minimum of 20 seconds with soap and water when they come in contact with contaminated surfaces, and coughing into a bent elbow or tissue, call for the emergency service in case of getting infected or sense that you have some symptoms of the virus.

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To Cite This Chapter

Akram, K.M., Sihem, S., & Okba, K. (2021). Covid-19 variants and vaccines: An overview. In M. Ozaslan & Y. Junejo (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2021*(pp.276-288). ISRES Publishing

Current Studies in Basic Sciences, Engineering and Technology 2021 is published annually from the selected papers invited by the editors.

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Current Studies in Basic Sciences, Engineering and Technology 2021 is published by ISRES Publishing.

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