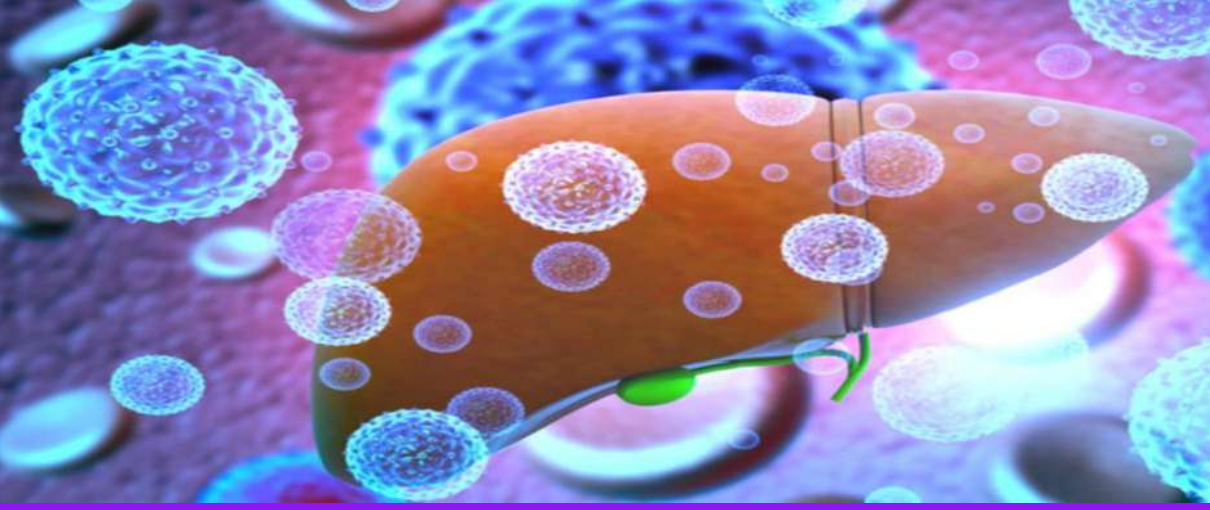

CURRENT APPLICATIONS IN BIOENGINEERING RESEARCH

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PREFACE

The field of bioengineering has been at the forefront of transformative innovations that address some of the most pressing challenges in healthcare, agriculture, and biotechnology. This book serves as a testament to the interdisciplinary nature of bioengineering, bringing together cutting-edge advancements and groundbreaking research in synthetic seed technology, nanotechnology-based drug delivery systems, and artificial intelligence applications in biomedical engineering.

Synthetic seed technology is a cutting-edge approach in plant biotechnology that involves encapsulating somatic embryos, shoot tips, or other plant tissues in a gel-like coating to mimic the function of natural seeds. These synthetic seeds can be directly sown in soil and grown into mature plants under suitable conditions. This characteristic makes them a practical solution for plant propagation. The technology enables the large-scale propagation of genetically identical plants, facilitates the preservation of valuable germplasm, and simplifies the storage and transport of plant material. It holds immense potential in agriculture, horticulture, and forestry by enhancing crop production, conserving endangered species, and supporting sustainable farming practices.

Nanotechnology-based drug delivery systems refer to advanced therapeutic platforms that utilize nanoscale materials, such as nanoparticles, nanocapsules, or liposomes, to transport drugs to specific sites within the body. These systems are designed to enhance drug

efficacy by improving solubility, stability, and bioavailability while minimizing off-target effects and toxicity. By enabling targeted and controlled drug release, nanotechnology-based drug delivery systems offer significant advantages in treating complex diseases, such as cancer and neurological disorders, and play a pivotal role in the development of personalized medicine. The development of biocompatible and biodegradable nanosystems ensures the safety and efficacy of drug delivery, minimizing the risk of side effects and toxicity.

Artificial Intelligence (AI) refers to the simulation of human intelligence in machines that are programmed to think, learn, and make decisions. AI systems use algorithms and data to perform tasks that typically require human intelligence, such as problem-solving, pattern recognition, language understanding, and decision-making. Artificial intelligence is widely used across various fields, including healthcare, finance, transportation, education, and entertainment, to enhance efficiency and innovation. Integrating artificial intelligence into artificial intelligence applications in biomedical engineering offers innovative solutions to complex health problems. Artificial intelligence technologies such as machine learning and deep learning are used in patient monitoring, medical imaging, personalized medicine, etc., facilitating the medical practices of healthcare professionals.

This book offers the target audience a comprehensive overview of the latest advancements in Synthetic Seed Technology, Nanotechnology-Based Drug Delivery Systems for Targeting Tumors and Brain Cancer

Therapy, and Artificial Intelligence Applications in Biomedical Engineering. This collection of cutting-edge research makes it a valuable resource for academics, researchers, and professionals in the field.

Assoc. Prof. Dr. Meltem BAYRAKTAR

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SYNTHETIC SEED TECHNOLOGY

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INTRODUCTION

The seed is the reproductive and propagation organ that forms at the end of fertilization in flowering plants, and contains the embryo, endosperm and shell parts, which can vary in shape, size and color depending on the species, and enables the formation of a new plant (TÜBA Terim, 2023). Seeds are the embryonic stage of the plant life cycle. The part called the embryo is a very small plant containing a root, a stem and one or two leaves. The endosperm is a nutritious tissue that is usually a combination of starch, fat and protein. The seed coat is the protective layer that allows the plant to maintain its vitality for a long time. Seeds can be in many different shapes and sizes. One of the largest seeds, coco de mer, is about 30 cm long and weighs 40 pounds. One of the smallest seeds, epiphytic orchid seeds, are 85 micrometers in size and disperse in the air like dust particles. While some seeds have thorns and hairs that allow them to cling, some have wings that make it easier for them to disperse in the wind (Kelly and Zumajo, 2021).

In nature, seeds overcome three important problems for plants. First, they are the most important method that allows plants to

reproduce. Because a single plant produces many seeds and ensures continuity of life. Second, they ensure that the plant survives for a long time in unsuitable conditions. Because seeds continue to live in the soil when unsuitable conditions occur and have mechanisms that allow them to remain dormant until suitable conditions occur. Third, mature seeds can be transported to very long distances by carriers such as wind, water or birds (Kelly, 2013).

In nature, plants generally reproduce by seeds. However, in some plants, seeds cannot germinate due to various reasons such as seed heterozygosity, small seed size, lack of endosperm and the need for fungal infection for germination. Some plants can be propagated vegetatively. However, classical methods are also time-consuming, expensive and do not allow for large-scale production. At this point, synthetic seeds are a good alternative (Saiprasad, 2001; Nongdam, 2016). Increasing desertification and disappearing forests cause the extinction of many plant species that cannot be propagated or produce low amounts of seeds. Synthetic seeds, in addition to providing *in vitro* protection of endangered species; are also the most effective technique that can be used for the propagation of plant species that have problems in seed propagation and produce non-viable seeds (Ali et al., 2013).

Synthetic seed technology (also called “synseed” or “artificial seed”) used for the protection and reproduction of agricultural plants with high economic value is one of the technologies whose importance is increasing (Mangena, 2021). Synthetic seed technology is one of the most promising tools of plant biotechnology that can be incorporated into horticultural and agricultural improvement studies with special

protocols both today and in the future (Sharma et al., 2021). Synthetic seed is generally defined as a synthetic encapsulation process that allows plant parts such as shoot tip, cell aggregates or somatic embryos to show their potential to develop into a full plant even after long-term storage in *in vitro* or *ex vitro* conditions (Chandra et al., 2018). Synthetic seed production technology is considered as an effective and efficient alternative propagation method for many commercially important agricultural and horticultural species. Synthetic seed stands out as a powerful tool for mass propagation of elite plant species with high commercial value (Saiprasad, 2001).

A mature ovule containing the embryo and the shell is considered as the basic component of a seed. A normal seed contains the components required for the germination process and these components are usually found in the endosperm. Therefore, the endosperm contains various components including proteins, carbohydrates and lipids. In some plants, cotyledons also contain reserve nutrients (Magray et al., 2017). In synthetic seed production, suitable explants are encapsulated in a matrix. This synthetic encapsulation matrix, which is responsible for protecting the embryo within the seed coat, is responsible for providing nutrients, like the endosperm in zygotic seeds (Saxena et al., 2019). Encapsulation technology offers advantages such as protecting the somatic embryo from mechanical damage and providing nutrients for the growing embryo. Therefore, synthetic seeds can be easily used for storage, transportation and planting, like zygotic seeds (Guan et al., 2016). With synthetic seed technology, the use of somatic embryos as seeds with functional capacity provides great advantages in germplasm

conservation and commercial plant production. In addition, synthetic seeds help in understanding the role of endosperm in addition to studying seed coat formation (Shallal et al., 2020).

All explants used in synthetic seed production are propagules produced by micropropagation techniques and clonally propagated. Therefore, meiotic recombination that occurs during crossing over and cross-pollination, known as gametic fusion of two different parental genomes, are not observed in sexual reproduction. Meiotic recombination and gametic fusion can create a new type of heterozygosity in zygotic seeds. Unlike zygotic seeds, a new type of heterozygosity never occurs in synthetic seeds; the heterozygosity already present in the parent plant is transferred to plants derived from the synthetic seed. Completely eliminating the heterozygosity problem and homozygous synthetic seed production is possible by using homozygous double haploid plant species (Haque and Ghosh, 2019).

HISTORICAL BACKGROUND OF SYNTHETIC SEED TECHNOLOGY

In the past, synthetic seeds were economically defined as somatic embryos used only in plant production, in sending plants to the field or greenhouses. Today, they are defined as artificially encapsulated somatic embryos, shoot buds, cell aggregates, tissues that have the ability to develop into a plant under *in vitro* or *ex vitro* conditions and are used for planting and do not lose their ability to develop into a plant after storage (Magray et al., 2017).

The first idea about synthetic seeds was put forward by T. Murashige at the "Symposium on Tissue Culture Applications in Horticultural Plants" held in Ghent, Belgium in 1977. In this speech, the idea that this production method would be an effective seed production method with its features of allowing fast and large number of production in a short time was emphasized (Gantait and Kundu, 2017; Chandra et al., 2018). The first synthetic seed production was carried out by Kitto and Janick in 1982 on carrot somatic embryos. In this study, polyoxyethylene was used as the coating material (Nongdam, 2016). Later, Redenbaugh and his colleagues discovered that hydrogels such as sodium alginate could be used to produce single-embryo synthetic seeds and developed a successful method for the production of synthetic seeds by encapsulating alfalfa somatic embryos in sodium alginate (Qahtan et al., 2019; Sharma et al., 2021). With the development of the synthetic seed concept, synthetic seed technology has been used in many economically important plant species, including fruit and forest trees (Guan et al., 2016).

According to Murashige, who first came up with the idea of synthetic seeds, synthetic seeds are a clonal product that can be used as real seeds for storage, sowing and transportation under *in vitro* or *ex vitro* conditions, encapsulated different somatic embryos. Synthetic seed technology has been accepted as an effective method in the protection and transportation of germplasm, especially in the protection of elite genotypes in recent years. In addition, since they do not involve a genetic recombination process, they can also be used in the determination of polyploidy in plant breeding. Synthetic seed

production through somatic embryos in transgenic plants allows the carriage of a single gene present in the somatic cell and its successful transfer to the offspring (Nandini and Giridhar., 2019). Currently, synthetic seed production systems have advanced significantly, the most advanced of which is seeding under ex vitro or *in vitro*. With this technique, high rates of plant transformation can be achieved (Cartes et al., 2009).

DEFINITION AND IMPORTANCE OF SYNTHETIC SEED

Synthetic seeds are encapsulated plant tissues such as shoot buds, axillary buds, somatic embryos, shoot tips, cell aggregates or other tissues that can be cultured as seeds, can form a complete plant under *in vitro* and ex vitro conditions and have the potential to maintain their viability after cold storage (Qahtan et al., 2019). Increasing desertification and depleted forests are causing the extinction of many plant species that cannot be propagated or produce low amounts of seeds. Synthetic seeds are the most effective technique that can be used for the propagation of plant species that have problems in seed propagation and produce non-viable seeds, as well as providing *in vitro* protection of endangered species (Ali et al., 2013). Synthetic seeds, which have significant advantages in terms of cost due to the reduced area, culture medium and time requirements, are a powerful and low-cost tool for the mass propagation of elite species with high medicinal value and especially rare or endangered plant species (Sharma et al., 2019). Although effective production protocols have been developed in desired plant species with the use of micropropagation techniques,

problems in seed production in some plants have not been solved. In these species where problems have occurred, production has continued with vegetative methods, but since this method is also time-consuming and expensive, alternative techniques have begun to be sought. Therefore, the development of synthetic seed production technology is currently considered an effective and efficient alternative propagation method for many commercially important agricultural and horticultural plants (Saiprasad, 2001).

Seeds are the cornerstone of agriculture. When seeds are planted in the soil and provided with the necessary water and nutrients, plants multiply and produce new plants that can be used for food and feed purposes (Magray et al., 2017). In addition, seeds (zygotic seeds) are tools that provide communication between generations. Plants can continue their genetic structure for generations through seeds. Therefore, it is the most suitable means of propagation, storage and distribution (Ravi and Anad, 2012). Generally, seeds consist of an endopserm, an embryo connected to the endopserm with one or two cotyledons, and a shell called testa covering all of them. The endopserm serves as a reservoir containing the nutrients necessary for the development of the embryo, while the testa protects the embryo from external injuries and harmful effects (Nongdam, 2016).

Synthetic seeds have similar characteristics to zygotic seeds, but they also have some distinct differences. In zygotic seeds, there is fusion of male and female gametes and production occurs sexually. In synthetic seeds, there is no gamete fusion and they are produced asexually. The structure of the zygotic seed includes embryo,

endosperm and seed coat. In synthetic seeds, there is embryo and endosperm but no seed coat (Chandra et al., 2018).

Synthetic seed technology is one of the most influential and promising tools in plant biotechnology (Haque and Ghosh, 2014). Production of synthetic seeds using various plant parts helps to overcome the difficulties encountered in the propagation of economically and medically important plant species using different approaches in plant biotechnology (Faisal and Alatar, 2019). Synthetic seed technology includes various methods for the preparation of seed analogues called synthetic seeds from micropropagules such as somatic embryos. Using somatic embryos as seeds with functional capacity with synthetic seed technology provides great advantages in the preservation of germplasm and commercial plant production. In addition, synthetic seeds help in understanding the role of endosperm in addition to studying seed coat formation (Shallal et al., 2020). Encapsulated propagules provide great advantages in terms of cost in *in vitro* regeneration and mass propagation, as well as great convenience in the transportation of plant materials between national and international laboratories. In addition, this technology has been successfully used for cryopreservation of elite plant species for germplasm storage by encapsulation-dehydration and encapsulation-vitrification (Faisal and Alatar, 2019). Synthetic seeds can eliminate the acclimatization steps required in micropropagation and provide flexibility to plant breeders in this regard (Rihan et al., 2017). This provides great benefits for plant species that are difficult to acclimatize (Sharma et al., 2019).

ADVANTAGES AND DISADVANTAGES OF SYNTHETIC SEEDS

Synthetic seed technology, which combines the advantages of clonal and genetative reproduction, has a wide range of advantages over traditional *in vitro* propagation methods. Synthetic seeds are quite cheap to produce, and they are easy to use, plant and transport (Faisal and Alatar, 2019; Kulus, 2019). Since each bead contains a single explant in a small amount of medium in the encapsulation matrix, the area it occupies is reduced, which reduces the costs of culture media (Sharma et al., 2019). In addition, the fact that synthetic seeds are "genetically identical materials" provides clonal propagation advantages (Nandini and Giridhar, 2019). They offer higher yield and low-cost agricultural opportunities with their features such as being applied in a shorter time and with less labor, being tolerant to drying, and being able to be stored for longer periods thanks to their durable and protective coating. Synthetic seeds, which can be stored for longer periods thanks to the coating material, are also used for germplasm preservation in seed storages. Synthetic seeds also help to study the role of the endosperm (Shallal et al., 2020).

Synthetic seeds provide great advantages in the evaluation of genetic studies to be carried out in plants. The zygotic seed production process takes a long time because of the need for the normal plant reproduction stage and the need to wait for the seed production process to occur. Synthetic seeds can be obtained in a month or less. Normal plants bloom and produce seeds in a certain season, but synthetic seed production is not time-dependent. The presence of long dormancy

periods in some plant species causes significant limitations. With the use of synthetic seeds, these long dormancy periods are reduced and the life cycle of the plant can be shortened (Shallal et al., 2020). In addition to these advantages of synthetic seed applications, other advantages can be listed as follows (Chandra et al., 2018; Yücesan, 2019; Sharma et al., 2021):

- The use of somatic embryos by direct encapsulation reduces the number of subcultures required for plant regeneration.
- It reduces the transfer costs of plants.
- It enables the storage of meiotically unstable-elite genotypes with adjuvants such as plant growth regulators and pesticides.
- It is used in determining the role of endosperm in embryo development and germination.
- They are considered in seed coat formation studies
- Seed production can be carried out with low cost and high efficiency.
- The time required for seed production is extremely short
- Medium-long term or cold storage is possible.
- Seed production can be done in every season and period..
- Dormancy of synthetic seeds can be reduced by shortening the life cycle of the plant.
- It can be used in germplasm preservation.
- Large-scale seed production is possible.
- It allows to obtain information about the developmental periods of the plant and to conduct research on the anatomical characteristics of the endosperm or seed coat.

• Applications are extremely easy and cost-effective.
• Disease eradication is achieved.

Synthetic seed production, in addition to all the conveniences it provides in use, also brings with it various difficulties and limitations. The most important problem encountered can be said to be the optimization of storage conditions in order to prevent dormancy during storage of synthetic seeds. Additionally, somatic embryo synchronization and low plant transformation rate are also frequently encountered problems. Low lignification and weak cuticle formation in plants are among the problems in the germination of synthetic seeds (Chandra et al., 2018). In addition, the rooting needs of non-embryogenic plant parts indicate that more research is needed, especially in woody plants (Qahtan et al., 2019).

The coating material used to prepare synthetic seeds should provide nutrients for germination and growth of seeds. The concentration of these coating materials is a limiting factor in synthetic seed production. In some plant species, somatic embryos do not have the ability to emerge from the coating material; therefore, synthetic seed technology cannot be used for these plant species (Singh, 2022). There are some difficulties during the transfer of synthetic seeds to ex vitro conditions. In addition to the frequently seen oxygen and nutrient deficiencies, pathogens can also cause many limitations such as infection etc. (Khabbazi et al., 2019).

COATING MATERIALS USED IN SYNTHETIC SEED PRODUCTION

The structure of synthetic seeds is similar to that of conventional seeds. While the encapsulated explant mimics the zygotic embryo, the capsule mimics the endosperm tissue. (Rihan et al., 2017). Synthetic seeds have two main components: (1) plant propagules (produced *in vitro*/*in vivo*) and (2) matrix (a gelling material for encapsulating plant propagules) containing nutrients, antibiotics or other essential additives (Sharma et al., 2019). The capsule contains additives such as antibiotics and antifungals, nutrient elements, growth regulators, explants and gelling agents (Rihan et al., 2017). These matrices are considered as synthetic endosperms and play an important role in the storage of synthetic seeds at low temperatures and their regeneration ability after transferring to the germination medium (Qahtan et al., 2019). Synthetic seeds are covered with a coating material that provides protection during storage and transportation and, in some cases, contains various plant nutrients or growth regulators (Sharma et al., 2021). Among many coating materials such as agar, alginate, carboxyl methyl cellulose, sodium pectate, gelrite, guar gum, etc., it has been determined that alginate is the most suitable material for synthetic seed production (Nongdam, 2016; Chandra et al., 2018; Sankari et al., 2020). The encapsulation procedure usually uses suitable gel matrices such as sodium/calcium alginate. This structure is called "synthetic seed coat" and functions like natural seed coats (Kundu et al. 2019). Alginate is a natural polymer obtained from seaweed and gels when treated with Ca^{-2}. It is frequently preferred in synthetic seed production due to its easy

preparation and high protection for plant explants (Karthik, 2023). Calcium alginate is often preferred as it allows the production of durable beads that will protect against mechanical damage. During the coating process, different components such as plant growth regulators, nutrients or antibiotics can be mixed with the coating material to increase germination and support healthy plant formation (Maheshwari and Garg, 2023).

Another coating material widely used in synthetic seed production is chitosan. This biodegradable polymer produced from shellfish provides a coating that is strong enough to withstand mechanical damage and is easily degradable in soil. This feature in particular makes it an environmentally friendly product and increases its preference rate. Another coating material is gelatin. This protein-based product has similar properties to chitosan (Karthik, 2023).

The encapsulation matrix generally protects against desiccation and mechanical damage, but also has other functions. This matrix can contain various antibiotics and antioxidants, as well as fungicides and insecticides. This is particularly beneficial for cryopreservation, as seed removal can lead to wounding stress and superoxide (O^{-2}) burst in cells. As a result of such an oxidative burst, the viability of the tissue decreases or ends. In this context, providing free radical scavenging capacity from outside can help tissue survival during cryopreservation. Adding antioxidant(s) into the encapsulating gel can overcome sources of oxidative explosion and increase survival (Ekinci et al., 2019). Its low viscosity, rapid gelation, low toxicity and explant protection make alginate a preferred coating material.

In the studies, factors such as coating material dose, plant species and explant type as well as mixing time affect the condition of the beads obtained (Qahtan et al., 2019). Redernbagh et al. (1993) stated that alginate hydrogels are the most suitable encapsulation material with their properties such as light viscosity, low toxicity and rapid gelation.

The basic principle in alginate encapsulation is based on the exchange of Na^{+} ions in sodium alginate with Ca^{+2} ions in $CaCl_2.2H_2O$ solution when sodium alginate solution containing plant parts is dropped into $CaCl_2.2H_2O$ solution (Chandra et al., 2018). While irregularly shaped, fragile beads are formed at low doses of sodium alginate and calcium chloride, hard beads that do not allow germination are formed at high concentrations (Saxena et al., 2019).

The coating material should be stable enough to allow the seed to be transported without breaking, and weak enough to allow the bud to freely exit the capsule. The balance between the hardness and softness of the seed can be achieved by encapsulating the explants with sodium alginate hydrogel (Qahtan et al., 2019). Mohanraj et al., (2009) reported that the use of high sodium alginate decreased the germination rate of synthetic seeds. Lulsdorf et al., (1993) determined that the germination rate of seeds stored at 4°C for 4 weeks increased. In another study conducted by Micheli et al. (1998), the germination rate of olive seeds stored at 2°C and 4°C for 23 months was determined to be 61%.

Figure 1. Effect of sodium alginate concentration (in 100 mM calcium chloride) on the size, shape and consistency of beads (Gantait et al., 2015)

In encapsulation, the coating material may contain nutrients, biological fertilizers, pesticides, nitrogen-fixing bacteria, antibiotics or other necessary components (Bapat, 2000). The coating material should not harm the embryo, allow germination, but should be resistant to the difficulties encountered during production, storage, transportation and planting processes, as well as providing nutrients to the embryo for germination (Nongdam, 2016). In a study conducted by Khor and Loh (2005), it was determined that the transformation potential and vitality of synthetic seeds increased in studies where coating material and activated carbon were used together. They attributed this to the fact that the activated carbon broke down the alginate and the embryo in the synthetic seed was more easily aerated in this way (Nongdam, 2016).

The presence of a nutrient source, plant growth regulators, antibiotics and fungicides in the gel matrix increased the regeneration ability of plant species where nutrient availability was low due to the

absence of endosperm in natural seeds (Ahmad and Shahzad, 2019). The most common carbohydrate used as a component of the encapsulation matrix is sucrose (Sharma et al., 2019). Sucrose serves as a carbohydrate that is an energy source in plant tissue culture studies. Its deficiency negatively affects synthetic seed germination (Kulus, 2019). The addition of various plant growth regulators as well as different nutrients into the coating material is one of the important factors affecting germination in synthetic seeds. Because these substances are important factors that increase the viability of synthetic seeds by acting during germination (Qahtan et al., 2019). The addition of growth regulators to the encapsulation matrix has been beneficial in many plant species to improve germination and/or promote rooting (Sharma et al., 2019). Synthetic seeds can show bacterial, fungal and/or microbial infection, especially during *ex vitro* regeneration, even under controlled conditions. The risk of fungal or bacterial infections increases especially when planting synthetic seeds in soil or soilrate (a soil substitute made from processed coconut or husk). Antibiotic and antifungal agents can be added to the gel matrix to control such infections (Sharma et al., 2019). In addition, the coating material containing different plant growth regulators is also effective in ensuring whole plant regeneration from encapsulated propagules in synthetic seeds (Qahtan et al. 2019). In some cases, the addition of plant growth regulators to the regeneration medium increases the germination of synthetic seeds (Sharma et al. 2019). The addition of exogenous auxin enhances rooting because it is related to the endogenous content of the same growth regulator. The accumulation of IBA in the basal region of

vegetative propagules acts as a metabolizing agent and signals to trigger rooting (Micheli et al., 2019).

In most studies on synthetic seeds, a plant propagules are usually encapsulated in a single alginate coating, while different methods such as double-layer encapsulation are also available (Fig 2) (Phanomchai et al., 2022). One of these methods, the single layer encapsulation technique, is an easy-to-apply and frequently preferred hydrogel encapsulation method. In this method, after plant propagules are mixed with a hydrogel agent such as sodium alginate or calcium alginate, they are dropped into $CaCl_2$ or $Ca(NO_3)_2$ solution. Thus, a synthetic surface is formed on the outer surface. In this technique, different propagules such as seeds, somatic embryos, (protocorm-like bodies) PLBs and bulbs are used as explants (Kocak et al., 2019). Double-layer encapsulation can also be done to increase the protection of encapsulated propagules. After producing single-layer seeds, for double-layer encapsulation, the seeds are coated with sodium alginate at the same concentration and then treated with $CaCl_2.2H_2O$ (Khabbazi et al., 2019). In double-layer encapsulation, contamination risks may increase depending on the chemical components of the second layer (Yucesan, 2019).

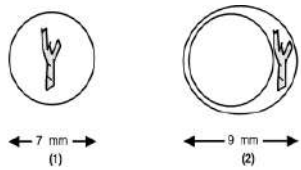

Figure 2. Construction schemes of synthetic seeds: Schematic diagram of (1) single-layered and (2) double-layered synthetic seed (Maruyama et al., 1997)

SYNTHETIC SEED PRODUCTION METHODS

Based on the technology developed so far, two types of synthetic seeds are known (Bhatia et al., 2015). Depending on the many methods used for their production according to the requirements, synthetic seeds are divided into dried and hydrated seeds (Bhatia, 2021).

Dried synthetic seeds are produced by encapsulating multiple somatic embryos together with the drying process (Bhatia, 2021). The drying process ensures complete removal of moisture content in the seeds. Polyoxyethylene (Polyox) is used as an encapsulating material to form a protective coating on somatic embryos or propagules. This material prevents the growth of microorganisms and is not toxic to embryos. The drying process can be done slowly for 1 or 2 weeks in rooms where the relative humidity is gradually reduced, or quickly by leaving the petri dishes on the bench with their lids open for 1 night. However, dried synthetic seeds can only be used for plant species where somatic embryos are tolerant to desiccation (Bhatia et al., 2015). Dried synthetic seeds are naked. In addition to high osmotic pressure, non-lethal stress factors such as nutrient deficiency and low temperature are also used to induce desiccation tolerance in these seeds. Mannitol or sucrose can be used to increase osmotic pressure, or osmotic pressure can be provided with a harder gel (Nongdam, 2016; Chandra et al., 2018). Hydrogel capsules are used to coat plant propagules that are sensitive to drying and have recalcitrant properties (Chandra et al., 2018).

Hydrated synthetic seeds obtained by encapsulating somatic embryos with hydrogel capsules are used for plants that are sensitive to

protection. In particular, synthetic seeds produced by encapsulating somatic embryos are an important research area that increases the success in transferring plants propagated *in vitro* to the field. (Rihan et al., 2017).

Sometimes sodium and chloride ion residues may remain on the surfaces of synthetic seed beads, in such a case, the beads must be washed repeatedly in distilled water to remove excess ions and limit ion toxicity. The washed beads are transferred to blotting paper for drying. Dried synthetic seeds can be stored, transported or transferred to the growing medium again (Saxena et al., 2019). There are three methods used for encapsulation of synthetic seeds: dropping method, molding method and automatic encapsulation method. In the dropping method, sodium alginate solution is prepared and explants are placed in the prepared gel. Then, this sodium alginate gel is placed in the funnel and drops of gel with somatic embryos are dropped from the tip of the funnel into a solution containing calcium chloride or calcium salts at a certain concentration as a complexing agent. The gel containing somatic embryos is kept in the complex solution for 20 minutes. After the gel capsules are formed, they are washed in water for 5 minutes. A simple procedure is followed in the molding method. In this method, temperature-dependent gels (such as agar) are used and the explants are mixed with these gels (Kaur et al., 2021). Agar gel is prepared by adding agar powder to distilled water and heating (0.5%-1%). Then, somatic embryos are placed in the gel and kept for 10-15 minutes to become semi-solid. When the temperature is lowered, the cells are covered with the gel. Then, the gel containing somatic embryos is cut into 1-2 cm

oval or square shapes and removed (Chavan et al., 2021). In the automatic encapsulation method, this method provides rapid encapsulation of synthetic seeds. Coating is provided with a special device designed for this method (Sankari et al., 2020). Based on the technology developed so far, two types of synthetic seeds are known (Bhatia et al., 2015). Depending on the many methods used for their production according to the requirements, synthetic seeds are divided into dried and hydrated seeds (Bhatia, 2021).

Dried synthetic seeds are produced by encapsulating multiple somatic embryos together with the drying process (Bhatia, 2021). The drying process ensures complete removal of moisture content in the seeds. Polyoxyethylene (Polyox) is used as an encapsulating material to form a protective coating on somatic embryos or propagules. This material prevents the growth of microorganisms and is not toxic to embryos. The drying process can be done slowly for 1 or 2 weeks in rooms where the relative humidity is gradually reduced, or quickly by leaving the petri dishes on the bench with their lids open for 1 night. However, dried synthetic seeds can only be used for plant species where somatic embryos are tolerant to desiccation (Bhatia et al., 2015). Dried artificial seeds are naked. In addition to the use of high osmotic potential, non-lethal stress conditions such as nutrient deprivation or low temperature are used to induce desiccation tolerance. High gel strength or osmotic agents such as mannitol or sucrose are used to increase the osmotic potential (Nongdam, 2016; Chandra et al., 2018).

Hydrogel capsules are a method used to encapsulate plant parts that are recalcitrant and sensitive to desiccation (Chandra et al., 2018).

Hydrated synthetic seeds are produced by encapsulating somatic embryos in hydrogel capsules. These seeds are used for plant species that are resistant and sensitive to desiccation. Encapsulation is the best method used for preservation and *in vitro* conversion of micropropagules into synthetic seeds. It is also an important application of micropropagation to improve the success of *in vitro* regenerated plants in the field. However, somatic embryos must be encapsulated in a suitable material that promotes germination (Rihan et al., 2017).

Sometimes sodium and chloride ion residues may remain on the surfaces of synthetic seed beads, in such a case, the beads must be washed repeatedly in distilled water to remove excess ions and inhibit ion toxicity. After the washing process, the beads are placed on blotting paper for drying. Dried synthetic seeds can be stored, transported or transferred to the growing medium again (Saxena et al., 2019). There are three methods used for encapsulation of synthetic seeds: dropping method, molding method and automatic encapsulation method. In the dropping method, sodium alginate solution is prepared and explants are placed in the prepared gel. Then, this sodium alginate gel is placed in the funnel and drops of gel with somatic embryos are dropped from the tip of the funnel into a solution containing calcium chloride or calcium salts at a certain concentration as a complexing agent. The gel containing somatic embryos is kept in the complex solution for 20 minutes. After the gel capsules are formed, they are washed in water for 5 minutes. A simple procedure is followed in the molding method. In this method, temperature-dependent gels (such as agar) are used and the explants are mixed with these gels (Kaur et al., 2021). Agar gel is

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EXPLANT TYPES USED IN SYNTHETIC SEED PRODUCTION

A wide variety of explants can be used in synthetic seed production, and this varies depending on the plant species (Rihan et al., 2017). Potential micropropagules that can be used to create synthetic seeds are plant tissues such as somatic embryos, apical shoot tips, axillary shoot buds, embryogenic calluses and PLBs (Taha et al., 2012). In the first studies on synthetic seeds, somatic embryos were generally used. This is because root and shoot regeneration can be achieved in a single step in somatic embryos. Since there is no differentiation at the callus stage in plants regenerated from somatic embryos, reproduction is achieved by preserving the genetic structure and they can maintain their regeneration potential for a very long time (Chandra et al., 2018; Qahtan et al., 2019). Somatic embryos can be encapsulated by direct encapsulation or by partial drying (Mangena, 2021). Somatic embryos continue to form continuously in cell aggregates, making it possible to produce several thousand embryos per gram in a culture, making somatic embryos a good source (Sharma et al., 2021).

Somatic Embryo:

Somatic embryos are embryos that are asexually formed only by somatic cells without the fusion of gametes (Maheshwari and Garg, 2023). Bipolar structures that include both shoot and root poles are defined as somatic embryos (Qahtan et al., 2019). Somatic embryos have both a shoot and a root axis and also contain a closed vascular system. Due to their bipolar structure, somatic embryos are the most suitable explant type that can be used for encapsulation to produce synthetic seeds. Somatic embryos originating from somatic cells (usually not involved in embryo formation) have the ability to develop into a full plant (Saxena et al., 2019).

Somatic embryos can regenerate from shoots, roots, cotyledon leaves, epicotyls, hypocotyls, embryogenic calli, protocorms or PLBs and can be perceived as clones since they come from a single donor. (Shallal et al., 2020). While indirect somatic embryos regenerate from cultured tissues through an intervening callus phase, direct somatic embryos regenerate directly from cultured cells. Unlike normal embryos, somatic embryos do not experience desiccation or dormancy problems, and they begin to germinate after complete development. With the developments in tissue culture technology, somatic embryo production has been successfully carried out in many plants, and since they are easily available, they have become advantageous for synthetic seed production. If the relative humidity can be kept at 10% through drying, as in conventional seeds, somatic embryos can be preserved viable for a longer period of time (Maheshwari and Garg, 2023). There are many advantages to using somatic embryos in synthetic seed

production. These synthetic seeds allow new plant species produced by biotechnological methods to be planted directly in greenhouses or on the field. In addition, this method will provide clonal reproduction of regenerated plants. Long-term storage can be provided without loss of vitality, transportation is facilitated and mass production of elite plant species can be achieved (Bhatia et al., 2015).

Callus and Embryogenic Masses:

Callus occurs as a result of random cell division and decreased cell specialization, resulting in the formation of irregular structures. The undifferentiated structure and minimal differentiation capacity of callus restrict its use as an explant for synthetic seed production. The use of callus for synthetic seed production was first successfully achieved in *Allium sativum*, and a high regeneration rate from synthetic seeds to plants was achieved (Maheshwari and Garg, 2023). Regenerative embryogenic masses with stable properties are a useful tool for clonal plant production and are frequently used in genetic transformation studies. However, long-term culture of these biomasses in culture vessels and bioreactors requires subculture, which increases both labor and cost. (Magray et al., 2017). The efficiency and regeneration capacity of embryogenic masses may decrease with increasing storage time. However, further studies are needed to determine whether this is also true for synthetic seeds (Maheshwari and Garg, 2023).

Apical Shoot Tips/Shoot Buds and Node Segment:

Among the non-embryogenic explants for synthetic seed production, shoot tip explants have proven to be the most suitable explant source due to their mitotic activity in the meristem. Apical and

axillary shoot buds can easily develop into a full plant as long as there is an abundant nutrient supply and rooting is not a problem. Compared to traditional *in vitro* shoot tip culture, the use of shoot buds in synthetic seed production reduces the space requirement and cost in mass propagation. The amount of space and culture medium required for multiple shoot formation and micropropagation in shoot tip culture is 20 times more than that required for micropropagation with synthetic seed technology. Encapsulation of shoot buds (apical or axillary) allows easy transportation of large numbers of propagule even in limited space (Gantait et al., 2015). Nodal segments containing axillary shoots are frequently used in synthetic seed production. The most important reason for selecting these explants is that they can be produced very easily with micropropagation protocols. In addition, these explants are preferred in germplasm preservation due to their high germination rates and their ability to maintain their viability after long-term storage (Qahtan et al., 2019).

Protocorms and PLBs:

While protocorms are produced by seeds, PLBs arise from explants *in vitro* (Saxena et al., 2019). In the preparation of synthetic seeds from protocorms, making round beads and hardening of encapsulated gel are very important for long-term storage (Pradhan, 2017). Encapsulated protocorms can be stored at low temperature (4 °C) for up to 6 weeks and exhibit 95% regeneration potential after transfer (Qahtan et al., 2019). Asymbiotic germination of synthetic seeds containing protocorms provides a useful means for commercial propagation as well as preservation of germplasm (Pradhan, 2017).

PLBs consist of shoot apical meristem, leaf primordial and constricted basal tissue, and are spherical in the initial stages and transform into a dome shape in advanced stages (Gantait and Mitra, 2019). Synthetic seeds are generally produced using PLBs (Qahtan et al., 2019). For orchids, somatic embryos and PLBs are the same terms, somatic embryos are miniature sphere-like structures and are called protocorms after expansion. The morphology of PLBs differs from typical somatic embryos by the lack of a clear embryonic alignment (Gantait and Mitra, 2019). In some orchid species, PLBs show high regeneration potential in synthetic seed studies (Kocak et al., 2019). PLBs can also be used as explants in cryopreservation studies (Qahtan et al., 2019).

STORAGE OF SYNTHETIC SEEDS

Storage is a critical factor in the transportation and preservation of synthetic seeds (Ikhlaq et al., 2010). Storage conditions and duration are the most critical factors to maintain the viability of the seed during transportation and preservation of synthetic seeds and these help in the successful commercialization of this technique (Qahtan et al., 2019). Synthetic seed storage is carried out in two ways: short/medium term and long-term storage (Yucesan, 2019). In short/medium-term storage, various factors such as appropriate temperature (usually 4°C) and encapsulation material as well as optimum storage conditions (reduced temperature, light, oxygen etc.) are effective. In long-term storage, dehydration and/or cryopreservation methods are used (Rihan et al., 2017).

Short/medium-term storage of plant species is one of the advantages offered by synthetic seed technology. These processes are generally called as slow growth methods. The most important criteria

for the seeds to maintain their viability during transportation and storage are the appropriate storage environment and storage period. The appropriate storage temperature for short/medium-term storage varies depending on the plant species. Synthetic seeds of most plant species are best stored in laboratory freezers at low temperatures of 4°C (Maheshwari and Garg, 2023). In a study conducted on papaya by Castillo et al., in 1998, it was determined that smooth beads were formed at a sodium alginate concentration of less than 2.5%. It was observed that these encapsulated propagules could be stored at 4°C for 4 weeks (Sharma et al., 2021). For long-term storage, alternative methods such as tissue freezing, encapsulation-dehydration or simple drying can be applied depending on the plant species (Yucesan, 2019). In addition to these methods, cryopreservation techniques can also be used for long-term storage of synthetic seeds. Cryopreservation is a method that allows long-term preservation of plant genetic resources by the use of liquid nitrogen (-196°C) (Kaviani, 2011). Under these conditions, heat-catalyzed metabolic reactions either do not occur at all or their rate of occurrence is very low. In this way, long-term viability continues without any genetic changes or other modifications occurring in plant cells. During cryopreservation, all biochemical activities are significantly reduced and biological degradation is stopped. The two main cryopreservation techniques applied to synthetic seeds are encapsulation-dehydration and encapsulation-vitrification. These techniques are quite effective for explants that are sensitive to conventional cryopreservation (Prudente et al., 2019). Cryopreservation protocols are developed experimentally, taking into

account physiological and biophysical factors for specific materials or explants, and aim to minimize stress. The preservation of plant material is ensured by the development of a simple and reliable cryopreservation protocol. Explants with moderate desiccation tolerance can be cryopreserved without complex preconditioning and preculture procedures, while explant materials such as cell suspensions, calli, shoot tips and embryos can be artificially dried (Ekinci et al., 2019).

GERMINATION OF SYNTHETIC SEEDS

Synthetic seeds represent somatic embryos, vegetative buds or seeds encapsulated in alginate. These seeds are germinated after being propagated *in vitro* or *in vivo*. Synthetic seeds are micropropagules that can maintain their regeneration potential after being stored at low temperature (Qahtan et al., 2019).

Seed germination can be defined as the "extrusion of the radicle from the seed coat". There are many different factors that control dormancy and germination. Environmental factors such as light, temperature, soil nutrient content and water potential can be considered as these factors. In addition, internal factors such as the phytohormone content of the seed coat and the genetic status of the plant are effective on dormancy and germination. Seed dormancy is a condition that ensures the survival of the plant under adverse conditions. Seed viability is the germination capacity of the seed under optimum conditions. A non-viable seed cannot germinate under suitable conditions even if it is subjected to the dormancy removal process (Saxena et al., 2019).

Synthetic seed technology is a technique that involves placing a suitable explant in a suitable matrix for successful germination and transformation into a healthy plant. The basis of synthetic seed technology is to mimic natural plant development through seed germination (Saxena et al., 2019). In recent years, interest in the use of synthetic seed applications in plant biotechnology with low seed yield and low germination rate has increased. In addition, the use of this technology has gained importance for plants that depend on mycorrhizal fungus-plant symbiosis for germination (Qahtan et al., 2019). Synthetic seed germination is expressed by the transformation of the encapsulated embryo into a seedling containing a cotyledon and a radicle. Many factors such as appropriate temperature, soil moisture and oxygen level, and light are effective in the germination of zygotic seeds. The term transformation refers to the development of an embryo into a seedling containing true leaves and roots. Lai et al. defined 'germination' as the emergence of a radicle and 'transformation' as the presence of at least one leaf in somatic embryos (Saxena et al., 2019).

Encapsulation method and plant genotype are the determining factors for seed germination rate. In addition, the content of the encapsulation matrix (especially nutrients and growth regulators) also affects the germination and transformation success of the encapsulated explant (Khabbazi et al., 2019). In addition, plant growth regulators, especially gibberellin, and nutrient reserves (stored in cotyledons and endosperm) help seed germination (Saxena et al., 2019). Since the cotyledons and endosperm of synthetic seeds are missing, they must be transferred to the regrowth medium to facilitate germination and ensure

successful transformation. The regrowth medium contains basal salts of nutrient media commonly used as sources of macro and micro nutrients. These include Murashige and Skoog (MS), White and Woody Plant Medium (WPM). Addition of phytohormone to the growth medium increases germination and root development in synthetic seeds (Saxena et al., 2019).

APPLICATION OF SYNTHETIC SEEDS

Synthetic seeds have a wide range of applications in different areas of plant biotechnology for the cultivation of various plant species (Bekele, 2021). Synthetic seed technology is a bioengineering technology that connects agricultural production and genetic improvement and is still developing. With the developing technology, it is inevitable that it will have great application opportunities in many industries such as agriculture and forestry (Lifeasible, 2024). Synthetic seed has a wide range of applications such as micropropagation, germplasm preservation (short/medium or long-term storage), facilitating the transportation of seeds even between countries, as well as the production of species-appropriate, disease-free, haploid/double haploid/triploid, transgenic seeds and seed production for seedless plants (Ghosh and Haque, 2019). Cryopreservation of germplasm is considered to be one of the most important application areas of synthetic seed technology (Qahtan et al., 2019). The synthetic seed process provides great benefit for the vegetative propagation and long-term preservation of superior germplasm of rare and endangered species (Maheshwari and Garg, 2023). Therefore, synthetic seed technique is

an important field of study for the vegetative propagation, preservation and long-term preservation of germplasm of elite plant species (Nandini and Giridhar, 2019).

Currently, synthetic seeds have wide application areas in agriculture due to their long-term storage and direct transfer of seed to the field. In addition, seedless plant species that cannot produce seeds can be propagated through the synthetic seed approach. The development of synthetic seeds for the exchange of elite plant material from private and public laboratories and their aseptic transportation across borders without spreading diseases plays an important role through direct propagation behavior from nursery to field (Nandini and Giridhar, 2019).

Synthetic seed technology allows the ex situ preservation of elite material from a gene bank and enables easy transportation of genetic material between countries. It allows the storage of genetic heterozygous plants or plants with a single superior gene combination that are impossible to maintain using traditional seed production procedures. In addition, mass production of cost-effective hybrid seeds in autogamous species such as barley, wheat and oats may also be possible using synthetic seed propagation (Abbas et al., 2022).

Researchers at the Bioinspired Soft Robotics (BSR) Laboratory coordinated by Barbara Mazzolai at the Italian Institute of Technology (IIT) have developed the first 3D printed seed-robot, I-Seed, in collaboration with the University of Trento. Designed in the shape of a seed, this robotic seed is made of biodegradable materials. The robotic seed, which has the ability to explore the soil according to moisture

changes, can move in the environment without needing an external energy source.

Although research in synthetic seed technology is promising for the propagation of many plant species, there are some basic limitations in the practical application of this technology. Some of these reasons can be listed as follows: limited production of suitable micropropagules in synthetic seed production, inefficient germination and transformation into full plants due to uncontrolled maturation of somatic embryos, dormancy and lack of stress tolerance in somatic embryos that limit the storage of synthetic seeds (Bekele, 2021). Nowadays, the most preferred explants in synthetic seed production are somatic embryos. However, somatic embryos also have important limitations such as asynchrony, loss of embryogenic potential due to culture aging, sensitivity to desiccation and the occurrence of structural anomalies (Qahtan et al., 2019). Non-embryonic meristematic tissues have great potential for synthetic seed production. Therefore, they can be of great benefit for use in cost-effective commercial applications for the storage and transportation of germplasm (Yucesan, 2019). However, unless some important limitations in synthetic seed technology are resolved, the commercialization of this technique cannot be optimized. The cost-effective large-scale production of synthetic seeds with high regeneration capacity is the first step to be achieved to enable the commercialization of this technique (Qahtan et al., 2019). More detailed research is needed to increase the efficiency of synthetic seeds to transform into a full plant (Bekele, 2021). For over 30 years, synthetic seed technology has tried to minimize these limitations

regarding large-scale production and commercialization. Unless certain conditions such as growth medium, storage temperature and duration are optimized, the regeneration efficiency of synthetic seeds will remain low compared to natural seeds (Yucesan, 2019).

CONCLUSION

Synthetic seed is an important technology for plants that cannot produce viable seeds and was first produced by removing water from somatic embryos obtained from tissue culture. Synthetic seed technology has advantages such as easy reproduction, long-term storage, continuation of the species of endangered plants and low-cost production. Due to these features, synthetic seed technology has great potential and has recently emerged as an important biotechnological tool.

Synthetic seed technology has been used for different purposes in the field of plant biotechnology for a long time. Although there are some limitations in the practical application of this technology, it is thought that there are many potential development areas in the future. Despite the significant research investments made in synthetic seed production in recent years, many fundamental problems related to commercialization continue. The important problem that needs to be solved for the implementation of synthetic seed technology is the large-scale production of high-quality micropropagules.

Many methods are used to obtain synthetic seeds with good results. However, there is a need for research on many different topics in the future. In addition to these methods, the effect of using different

plant growth regulators on synthetic seed production can be investigated. Similarly, studies can be conducted on different doses of these plant growth regulators or their use in different environments. The coating materials used are one of the most important elements in obtaining synthetic seeds. Studies can be conducted on the use of different coating materials and the doses of different coating materials used. Research can be conducted on the compounds of the medium used (especially carbohydrate sources, amino acids and vitamins) and more effective synthetic seed production can be achieved. More comprehensive research is needed on the optimum storage conditions of synthetic seeds. In addition, it is recommended to examine the differences between germinating synthetic seeds directly on soil and germinating them in nutrient media. In this way, important data will be obtained to evaluate the performance of commercially important synthetic seeds during the storage and preservation process. In addition, the combined use of synthetic seed technology with artificial intelligence technologies and smart agricultural applications will be promising research topics.

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CHAPTER 2

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR TARGETING TUMORS AND BRAIN CANCER THERAPY

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INTRODUCTION

Cancer is a complex disease that is difficult to understand. Brain cancer poses unique challenges because the brain is vital for survival and well-being. If we consider the statistics of a single year 2023, over 24,810 people were diagnosed with brain tumors. The five-year survival rate for patients with brain tumors is approximately 36%, but this varies based on tumor type and patient age. About 22% of patients survive at least ten years after diagnosis (Hsu et al., 2021). Brain cancer is the most common type of primary tumor in the Central Nervous System (CNS), accounting for 85-90% of cases. The survival rates for brain cancer patients are generally lower than those for other cancers (Mitusova et al., 2022).

Global, deaths from primary brain tumors account for approximately 3% of cancer-related deaths each year. (Ostrom et al., 2019; Višnjić et al., 2020). The most common type of brain tumor is glioma, with more than 100,000 cases of diffuse gliomas reported annually (Table 1) (Brunssen et al., 2020).

Table 1. The survival rates associated with various types of cancer.

Type of cancer	5-year survival rate (%)	10-year survival rate (%)	Studies
Brain tumors	36	31	(Ostrom et al., 2019)
Melanoma	94	90	(Višnjić et al., 2020) (Brunssen et al., 2020)
Colon	54	51	(Zhao et al., 2020)
Breast	77-92	85	(Howlader et al., 2018) (E. H. Park et al., 2017)
Multiple myeloma	54	35	(Hemminki et al., 2021) (Quaresma, et al.,2015)

Conventional cancer treatments, including surgery, pharmacological therapy, and radiation, often have a much lower success rate when dealing with brain tumors compere to other tumors. Nanotechnology has recently emerged as a key component in the field of medicine. Because of this, new approaches have been developed to enhance the precision and efficacy of cancer therapies (Howlader et al., 2018). In this first section, the drug delivery methods that aims to treat brain cancer will be discussed, emphasizing the challenges of localizing and targeting tumors. According to Park et al., (Park et al., 2017), the inability to selectively target cancer cells while not harming healthy ones is a major shortcoming of current cancer therapies. As an example,

chemotherapy medications have the potential to destroy healthy cells throughout the body in addition to causing a host of other undesirable side effects (Park et al., 2017).

1. Nanotechnology

Nanotechnology, a new area where science and technology meet, works with considerably small parts called "nanos". These are usually between 1 to 100 nm in size known as nanoparticles (NPs). At this size, nanomaterials show not seen before features that can be utilized in new ways. The word "nano" meaning one billionth of a meter, is where the term "nanotechnology" comes from (Park et al., 2017). Nanotechnology finds use in many areas, such as biology, chemistry, and physics.

Nanotechnology is of utmost use in healthcare and medicine as it allows the design of safe and effective treatment methods. Nanomedicine, a part of nanotechnology, mainly focuses on ways to diagnose and/or treat diseases using nanosized materials. This also includes tools for taking inside images of the body (Hemminki et al., 2021). NPs could be modified and enhanced to carry drugs or healing substances directly to specific organs and tissues.

This targeting potential aims to lower the chances of inappropriate reactions, raise medicine effectiveness, and decrease treatment time by targeting cancer cells selectively without compromising the integrity of healthy cells (Quaresma et al., 2015).

2. Conventional Cancer Treatment Modalities

Cancer treatments that have been utilized for a long time have been around to fight the disease. Surgery, chemotherapy, and radiation are conventional ways to fight cancer (Shaver et al., 2019). They are often used together to hit different parts of the disease simultaneously. One of the first and easiest ways to deal with cancer is through surgical intervention (Nguyen et al., 2021). Tumors and infected tissue need to be taken out by surgery. Surgery could be considered as a primary treatment option when a tumor is benign and has not moved to other parts of the body. If cancer is found early and removed by surgery, it might be curable. However, unwanted results are always possible because operations can sometimes affect healthy tissue (Nguyen et al., 2021).

Chemotherapy targets rapidly dividing cancer cells to effectively treat via powerful drugs. It is employed because cancer cells grow and multiply much faster than most normal cells, making them more susceptible to the effects of these medications. By disrupting the cell cycle and damaging the DNA of cancer cells, chemotherapy aims to kill these cells or halt their growth, thereby preventing the spread of cancer throughout the body (Saeedi et al., 2019). Since chemotherapy works on both cancer and healthy cells, it can be considerably successful. On the other hand, it may also cause side effects, such as feeling sick, losing hair from the head, and lowering of the ability to fight illnesses. Various chemotherapeutic drugs prove essential in addressing diverse forms of brain tumors during treatment (Figure 1) (Mitusova et al., 2022).

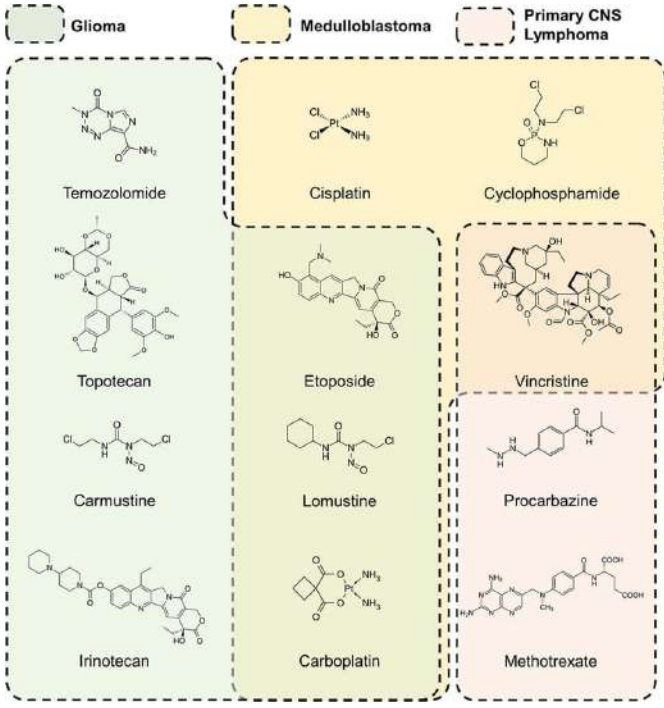

Figure 1. Commercially available drugs designated against different brain tumor types. Color codes: Glioma (green), Medulloblastoma (yellow), and Primary Central Nervous System Lymphoma (PCNSL) (red). The cross-section signifies their application in both cancer treatments (Mitusova et al., 2022).

Radiation therapy is use of intense beams of energy, most often in form of radiation waves to kill cancer cells. Often used to shrink tumors before surgery, cure disease when alternative ways are limited, and help ease symptoms in end-of-life care (Saeedi et al., 2019; Anderson et al., 2021). Even though radiation therapy is precise, it can still harm healthy cells. New kinds of radiation therapy, such as Intensity-Modulated Radiation Therapy (IMRT) and proton treatment,

are made to lessen the unwanted side effects (Saeedi et al., 2019; Anderson et al., 2021; Prabhu et al., 2021).

3. Limitations of Conventional Therapies

Old ways to treat cancer have serious problems. A major one is that how it lacks the capacity to accurately and selectively disseminate medicine, which makes brain tumor treatment especially difficult. One of the biggest obstacle for brain cancer therapy is the Blood Brain Barrier (BBB) which is a selective semi-permeable membrane between the blood vessels and the interstitium of the brain (Sahu et al., 2021). The BBB serves as a natural protective system that prevents many substances from entering the brain. Unfortunately, this also includes certain medications and therapeutic drugs. As a result, these compounds can be blocked from reaching the bloodstream and effectively treating conditions within the brain (Sahu et al., 2021). So, this means that regular chemotherapy proves ineffective. These stoppers not only prevent life-saving drugs from getting to where cancer is located, but also forces patient to take higher doses (Sahu et al., 2021). This could lead to more dangerous side effects and sickness in other parts of the body (Sahu et al., 2021). If this obstacle can be overcome, medicines could reach the tumor spots.

4. Drug Delivery Systems

Drugs for tumor targeting and brain cancer treatment made with nano technology are crucial in this review. Cure medicines, such as ones used to fight cancer tumors, can be taken exactly where they need to go in the body with high accuracy and speed using such systems. They fix

typical medicine-sending issues that have slowed down improvements in cancer treatment, especially for brain tumors.

Nano-carriers, such as NPs, liposomes, and micelles are utilized in drug delivery systems made from nanoscale science. These facilitate more effective drug delivery to the specific targeted locations. Size, surface charge level, and drug delivery patterns are just some traits that can be changed in these carriers. The BBB is a considerably focused membrane that stops most substances, mainly some cancer drugs, from getting through. These nano-carriers can be adjusted to address and overcome this problem and make them instrumental in brain cancer treatment. Since the BBB acts as a shield, it is essential to be able to get healing drugs where brain tumors are.

Also, Medicine drugs can be slowly, and carefully administered through specialized delivery systems. This is crucial in cancer treatment, as maintaining optimal drug concentrations at tumor sites is essential for efficacy (Suri, Wolfram et al., 2015). Controlling how fast a medicine goes into the blood can minimize its potential to harm overall and help cancer treatment work well on cells. It is crucial to do this within safe limits. The literature looks at ways to use nanotechnology so that a drug can be delivered into the brain in such a way that would target cancer cells without causing damage to healthy tissues. Nanotechnology can help in enhancing the treatment effectiveness against brain tumors with reduced side effects on other parts of the body that are healthy and devoid of disease or damage caused by treatments, such as chemotherapy medicines given intravenously directly to the blood.

5. Optimizing Drug Delivery to Brain Tumors: Challenges and Strategies

The tumors developed inside the brain are the primary focus while treating brain cancer. For a cancer drug to be effective, it must be able to penetrate the tumor in sufficient amounts. However, this is a challenge in most systemic solid tumors due to a variety of factors, such as unpredictable levels of oxygen, varying pressures in the tumor, and abnormal blood vessels within the tumor. The situation becomes even more complex in brain cancer because of the presence of the blood-brain barrier and blood-cerebrospinal fluid barrier, which act as physical and physiological barriers to delivering drugs to the central nervous system. There has been significant progress in developing various methods for optimizing the delivery of drugs to brain tumors by manipulating the BBB. These strategies encompass a range of techniques, such as administering high doses of intravenous chemotherapy, utilizing intra-arterial drug delivery, implanting polymers or catheters for localized drug delivery, disrupting the BBB, and biochemically modifying drugs. All of these approaches are currently being actively investigated and the idea of utilizing nanotechnology is also one of them (Suri et al., 2015).

The main purpose of using nanotechnology to treat brain cancer is to inhibit the side effects and enhance drug delivery to show positive results. Researchers try to find and go after chemicals or receptors that are overworked on the outside of cancer cells. Making special medicines that target these signals will help find tumors more

accurately. This makes treatment better by lowering harm to healthy brain tissue. Monoclonal antibodies, small molecule blockers, and gene treatments are all examples of strategies that focus on specific cancer cell features (Sahu et al., 2021). These methods target different parts inside the cells to treat or stop them from growing. One new way to treat brain tumors is using immunotherapy. This uses the natural protective barrier of the body (the immune system) to find and destroy cancer cells in their heads. Studying brain cancer is looking at checkpoint blockers and Chimeric Antigen Receptor Therapy (CAR-T) cell treatment as ways to activate the immune system. They can stop harmful cells while not hurting healthy ones too much (Suri et al.,2007). Nanotechnologies offer unparalleled prospects for creating nano-carriers that effectively deliver drugs to specific locations within the body. Not only do these technologies enable the successful crossing of the blood-brain barrier with specialized nanocarriers, but they also allow for the development of multifunctional nanoplatforms, such as NP-based magnetic resonance imaging, computed tomography, and photoacoustic imaging. Despite being in the preliminary stages, NP-ligand conjugation has demonstrated the most impressive results in facilitating drug transport across the blood-brain barrier and has shown great promise in preclinical studies (Alizadeh-Sani et al., 2018).

6. Revolutionary Cancer Treatment

Nanotechnology can help in fighting cancer because it provides numerous advantages by utilizing nanomaterials and technologies. A novel approach to treating cancer is being aided by nanotechnology. It helps with some major problems that standard ways of treating this

disease have. A big advantage of nanotechnology is that it can send medicine directly to the cancer location with considerably high (Sahu et al., 2021). Small medicine carriers called NPs can be changed and modified in a way so that they effectively strike only the cancer cells located in the brain. In the treatment of cancer, this degree of accuracy is important. It is essential for the removal of harmful cells without affecting healthy ones is of paramount significance when treating individuals afflicted with this disease.

Physical blocks, such as the BBB, might make some cancer cures work less effectively. To treat brain cancer, medicine delivery systems might be made using nanomaterials called nanotechnology. These can go around the problems that other treatments face and reach parts of tumors they could not before (Suri et al., 2015). This skill is new because it lets us fight difficult-to-reach cancers. We can put medicine out one by two in our tumors with the help of small machines. Keeping medicine levels working right over a long time, can make cancer treatments much better. Furthermore, using special traits of small materials can make medicine work better against cancer for a longer time by improving how it is released (Suri et al., 2007).

7. Characteristics and Applications of NP-Based Carrier Systems

NPs are nanoscale small particles that are utilized for various purposes including drug delivery, and medications in health and the environment. Nanotechnology in drug delivery has changed the field of medicine with its adaptable and special properties. Scientists can modify nano-carrier systems to serve specific purposes. The surfaces of these systems are important in determining their effectiveness and

targeting ability. By using functional groups and ligands on the surface, nano-carriers can be made to work against certain cells (Alizadeh-Sani et al., 2018).

The nano-carrier system should be small around 1 nm to 100 nm, optimized, and should reach the target site swiftly. Surface characteristics are essential to determine the activity of nano-carrier systems (Alizadeh-Sani et al., 2018). In addition to the surface modifications, the size of the nanosystem also has a considerable impact on the nano-carrier system (Azevedo et al., 2015). Nano-carrier systems can be hydrophilic, hydrophobic, or amphoteric. The charge on the nanosystem depends on the type of molecules that are used in its synthesis (Huang & Chang, 2009).

8. Nanotechnology: A Versatile and Efficient Approach to Solving Conventional Problems

Nanotechnology is the most diverse and hot spot for advanced solutions to conventional problems. The main advantage of nanotechnology is that it is a swift and quick process without taking much time and easily reaches the target sites. It fits in almost every field of science and daily life. It is cost-effective with least side-effects (Samad et al., 2007). It is bio-compatible and most of the nanosystems including chitosan, liposomes, and polymer-based nanosystems are biodegradable (Caffo et al., 2023). The nano-carrier systems, that are utilized in nanotechnology, are more potent and easily reach the site of action and are easily degraded as they are designed according to the targeted system with high permeability and stability. Zeta potential,

Encapsulation efficiency, and effective dose matter a lot while optimizing the nano-carrier system for drug delivery or other systems. The Figure 2 illustrates the advantage of the nano-carrier system over conventional therapies.

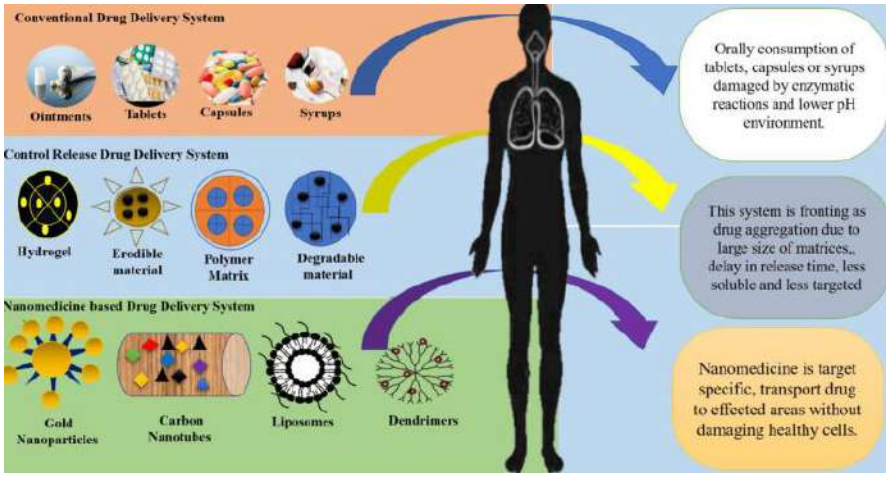

Figure 2. Merits of Nano-carrier Systems (NCS) over conventional therapeutics (Varala et al., 2023).

Apart from being used in the field of medicine, nanotechnology, as a revolutionary discipline, offers promising solutions across various domains due to its unique ability to exploit quantum phenomena and create materials with tailored properties. Scientists can create materials with unique properties by manipulating the size, shape, and makeup of tiny structures called nanostructures. These materials display extraordinary mechanical, thermal, electrical, magnetic, optical, and catalytic qualities. For example, carbon nanotubes are incredibly strong and conductive, while graphene is flexible and transparent. These developments have enabled innovative applications, such as

lightweight yet robust composites for automobiles, and flexible electronics, such as wearable devices (Carmeliet & Jain, 2011).

Nanomaterials, with their unique biocompatibility and extensive surface area, have emerged as promising materials for various biomedical applications. Their exceptional properties make them suitable for use in drug delivery systems, biosensors, imaging agents, and tissue engineering scaffolds (Bailey et al., 2018). Quantum dots, in particular, exhibit remarkable fluorescence characteristics, surpassing traditional dyes in diagnostic tools and cellular imaging techniques. Nanotechnology is crucial for advancing energy storage and conversion technologies, including batteries, supercapacitors, solar cells, and fuel cells. Carbon-based nanomaterials like graphene and carbon nanotubes boost electrochemical performance by accelerating charge transfer rates and delivering higher power densities. Moreover, nanophotonic aids in efficient light management within photovoltaic devices, resulting in improved solar cell performance (Jain, 2011).

Nanotechnology offers a vast range of possibilities to solve global issues and revolutionize existing industries. It has the potential to go beyond what is mentioned in this overview. Nevertheless, it is clear that nanotechnological advancements have the potential to shape our future. However, responsible research and development are crucial to ensure these discoveries are safe and implemented ethically (Carmeliet & Jain, 2011).

9. Emerging Trends in Nanotechnology for Advanced Drug Delivery

Drug delivery is a major point in technology nanotechnology in health and medicines. A drug that must be delivered should be well monitored and trailed for personalized and generalized drug delivery. Surface modifications of nano-carrier systems in terms of size, shape, charge, and encapsulation efficiency are the limiting factors for safe and effective drug delivery. The drug should have proper encapsulation in the nanosystem and enhanced release. Nanomedicines and nanodrugs are quite new. However, has a powerful impact on biological systems (Masood et al., 2023).

Many nanosystems are conjugated with another bio-compatible system for drug delivery. These can be lipid-based nanosystems and could be antibody-labeled nanosystems for direct and targeted delivery of drugs. Many polymeric substances are also there that are conjugated for drug carriers (Bailey et al., 2018). Immunotherapies that are nano-based are now available for the treatment of cancerous cells (Jain, 2011). Bioavailability, encapsulation efficiency, sustained release, and zeta potential have to be considered while designing a nanosystem for controlled drug release (Carmeliet & Jain, 2011).

10. Future Trends of Nanotechnology in Drug Delivery

10.1 Effective Dose for Personalized Treatment

Customized therapy, technology that alters medical practice based on an individual patient's features, including genetics,

metabolism, and illness characteristics, is the goal. Determining the best dose of a medication to provide the best results while minimizing side effects is composed of maximizing therapeutic gain and minimizing side effects. By taking into account numerous factors, including patient demographics, biomarkers, pharmacological drug response, medication impact, and patient allergies, healthcare practitioners may create customized treatment plans that improve patient outcomes while reducing the risk of complications. It makes it easier to offer more reliable and successful treatments (Grothey et al., 2014; Kosorok & Moodie, 2015; Ma et al., 2016).

10.2 Tailoring of a Nano-Based System for Safe Delivery of Drug

One of the essential steps toward customizing a nano-based drug delivery system is to create carriers capable of safely delivering therapeutic chemicals to the desired location in the body. Selecting the best materials, optimizing surface features and particle size, and ensuring controlled release kinetics are all elements of making these carriers tailored to a patient (Badar et al., 2019). By optimizing the nano-carriers' characteristics to optimize security, biocompatibility, and in vivo destination targeting, researchers may make administering chemicals more efficient and less toxic and reduce adverse effects. Personalized nano-based systems might help individuals receive medications more safely and accurately, expanding the horizons of nanomedicine (Hamid & Manzoor, 2021; Vinothini & Rajan, 2019).

10.3 Making Nanosystems Biocompatible and Biodegradable to Avoid the Toxicity of Nanosystems

Biocompatibility and biodegradability must be assured in order to avoid adverse outcomes and toxicity in drug delivery. Such steps will lower the likelihood of immunological reactions due to the selection of biocompatible materials and the use of nanocarriers that disintegrate into comparatively innocuous byproducts (Kunzmann et al., 2011). Furthermore, biodegradable nanosystems improve the safety factor by permitting the controlled release of a drug followed by its eventual expulsion from the body. This is because there is a lower risk of systemic toxicity, and patient safety takes top priority when designing nanosystems in which cells and genes are actively involved (Ambrosio et al., 2022; Shi, 2009).

10.4 Making a Nanosystem with Balanced Encapsulation Efficiency

To attain nanosystems with balanced encapsulation efficiency, the loading capacity of the drug carriers should be adequately optimized while still maintaining the features of stability and controlled release. This may be done via the appropriate alteration of formulation parameters like particle size, surface charge, and drug-polymer interaction without jeopardizing the integrity of the carriers. The desired medication dose reaches the target tissue position when the encapsulation effectiveness is maximized. The total medication consumption is also reduced, resulting in substantial cost savings. Overall, this optimization of nanosystems contributes to the development of dependable drug delivery methods for a variety of

medicinal applications (Correia et al., 2014; Detsi et al., 2020; Di Marco et al., 2010).

10.5 Sustained and Enhanced Drug Release at the Target Area

Sustaining or increasing drug release at the desired site over a period while reducing systemic exposure to ensure that drug levels are therapeutic presents another challenge. Continued release of medicine at particular places in the body is achieved by developing nanocarriers containing controlled release systems, such as stimuli-responsive subsistence or extended-release subcultures. Continuous administration can lead to better treatment results, with several benefits, including reduced dosage frequency, decreased variations in substance concentration, and enhanced therapeutic activity. In a wide range of health situations, medical practitioners may alter medication release kinetics in nanosystems for better therapeutic effects while still promoting compliance (Wang et al., 2019).

10.6 Proper Surface and Charge Modifications for Safe Drug Delivery

Surface and charge modifications are vital for guaranteeing the safety and effectiveness of drug delivery systems. Researchers revolutionize body resilience, cellular retribution, and circulation time by creating nanocarriers with favorable surface attributes, such as targeting ligands or stealth layers. Adjusted charges promote stability, optimize biological tissue communication, and regulate drug release kinetics. Healthcare personnel can increase the accuracy and safety of

medicine delivery using surface properties adjustments. Using biologically changed substances can amplify personalized treatment with reduced adverse effects and superior medical effects (Haddad et al., 2022; Patel et al., 2019; Rana et al., 2011; Sharma & Dang, 2023).

11. Nanotechnology in Brain Cancer Therapy

11.1 Brain Cancer and Challenges

Glioblastomas are the most serious form of brain tumor. NPs selectively target cancerous cells and eliminate them (Ferraris et al., 2020; Masood et al., 2023). The conventional therapeutics not only affected the brain cells but also had less bioavailability to the target sites. Nanomedicines are considerably sensitive and easily cross the BBB and reach the site of administration effectively without damaging the cells of the brain. The physicochemical properties of nano-carriers ensure the characteristic properties of drug carriers, which support the strengthening of the drugs themselves by increasing solubility, degradation, clearance, targeting, theragnostic, and drug combinations. (Meyers et al., 2013).

Nanotechnology is the growing arena for targeted delivery. Malignant cancers of the brain are complex to address through treatment due to BBB (Ahamed et al., 2023). Following the administration of a nano-based drug in brain tumors, the drug concentration peaked at the target site and then went with decreasing intensity away from the site. Nanomaterials are highly reliable tools for the proper localization of brain tumor cells to be well-diagnosed (Barchet & Amiji, 2009).

So far, conventional therapies have somewhat adverse effects on the human system in terms of first-pass metabolism, diffusion, and bioavailability. The US Food and Drug Administration (FDA), concerned with testing the efficacy and safety of food additives drugs regulating their market availability, has examined and verified the use of nanomedicines in the treatment of brain and other types of cancers (Hunt et al., 2005).

In several types of brain diseases that could be a disorder or tumors, the proper functioning of the brain is disturbed. In terms of pharmacological background, the several diseases including brain cancers, Alzheimer's disease, and Parkinson's disease the BBB is affected (Varallyay et al., 2002), as BBB does not allow any pathogen or inducive chemical to pass through it and cause disorder. Because of this, many conventional drugs due to their large size and heavy properties cannot diffuse at the site of action or may leak so that the whole percentage does not reach the site of action (Masood et al., 2023).

No established treatment strategies have been fully able to rectify commonly reported brain cancer types globally and even benchmarked diagnostics, such as Magnetic Resonance Imaging (MRI), use magnetic field matching that of patients due to electrolyte motion in the brain to generate relevant brain image/pattern, have been less effective for identification and characterization of a brain tumor before the metastatic stage, despite much avenues in neuroscience (Varallyay et al., 2002). The current treatment regimens, such as chemotherapy and radiotherapy ensure major side effects to be managed in healthcare setups for comparably long-term periods, of which

leukoencephalopathy is the critical one, often followed by memory and coordination loss, while resection surgeries pose challenges to safely remove brain tumor without causing any damage to nearby nerves/ neuronal microenvironment (Huang et al., 2022). Also, the poor prognosis of brain cancer is an additional challenge in neuro-oncology.

High cost per treatment regimen is an additional challenge in brain cancer treatment, most probably in underdeveloped and developing countries (De Pasquale et al., 2020; Wang et al., 2021).

11.2 Advancements in NP-Based Therapeutics for Brain Tumor Treatment

To date, numerous literatures from the scientific community have emerged that have discussed the engineering of proposing different NPs nano-carriers/nanocomposites/nanosystems to effectively treat brain tumors and recurrence. Earlier studies on effective NPs for brain cancer therapy have revolved mainly around iron NPs (Mo et al., 2019; Wu et al., 2023) and improving them to be employed as a contrast agent in MRI-assisted brain cancer resection therapy perhaps due to their superparamagnetic behaviors. The focus for brain cancer nano-therapy has, however, been shifting steadily towards nanosystems that are organic and biocompatible, owing to the potential cytotoxic effects of iron or other metal-based NPs (Hunt et al., 2005). The nanotherapeutics take advantage of meeting up with considerably small pore size of BBB and their being able to be surface modified.

Recent studies have employed photothermal, as well as reactive oxygen species (ROS) generating nanosystem machinery to

collectively abort glioblastoma progression; a study by Wang et al. 2021 (Wang et al., 2021), engineered chitosan nano gel encapsulating copper NPs and black phosphate nanosheets as a multifunctional nanosystem bandage in post-operative wound stitching; chitosan forms hydrogel upon exposure to >37°C temperature allowing the exchange of encapsulated material to the site of the wound, while copper NP act as a catalyst to generate free radicals from H_2O_2 to selectively eliminate tumor cell and black phosphate nanosheet exhibit potential to generate heat following exposure to Near-Infrared Radiation (NIR), which is believed to inhibit tumor (Wang et al., 2021).

Another study also employed a similar idea, this time surface re-engineering of the black phosphate nanosheet (via its –OH) with L-arginine (via its –COOH) and linking of glucose oxidase enzyme to surface L-arginine; Huang et al. 2022, showed that glucose oxidase would catalyze the deamination of arginine to yield NO, which is a potent free radical generator, while the photothermal property of black phosphate nanosheet simultaneously catalyzes this reaction as well as able to kill cancer cell (Huang et al., 2022).

Studies made in the last decade have also been aimed at finding replacements for NPs/nanocomposites that had been previously proposed for glioblastoma treatment which are now regarded as potentially toxic or non-environment friendly; De Pasquale et al. 2020, proposed boron nitride nanotubes as potential replacement for carbon nanotube for glioblastoma multiforme therapy. The researchers modified the boron nitride nanotubes with a lipid bilayer (or cell membrane) derived from the glioblastoma cell of the patient and

encapsulated with doxorubicin, showing its efficacy to selectively intoxicate glioblastoma cells only and not affecting healthy cells (De Pasquale et al., 2020).

11.3 Multifaceted Applications of NPs in Brain Cancer Treatment

NPs can serve as customizable delivery carriers, providing the ability to control their physical characteristics; size, shape, surface, and targeting elements, such as moieties which play an essential role in improving blood retention bioavailability, and specificity of cancer treatments (Orringer et al., 2009; Sarin et al., 2008). Furthermore, NPs occasionally offer inherent advantages based on their composition. For instance, metallic NPs when exposed to light, radiofrequency, or a magnetic field, can be employed for the thermal ablation of tumors (Jordan et al., 2006; Terentyuk et al., 2010). One other example is magnetic NPs which can be used in Magnetic Resonance Imaging (MRI) and gold NPs (AuNPs) for enhancing contrast in computed tomography imaging (Anderson et al., 2005; Faucher et al., 2011; Hadjipanayis et al., 2010; M. Kumar, Medarova, Pantazopoulos, Dai, & Moore, 2010; Nune et al., 2009; Popovtzer et al., 2008). In the realm of clinical applications for cancer, inorganic NPs have been utilized owning clearance and safety which is always required (Gwinn & Vallyathan, 2006; Orringer et al., 2009). They function as MRI contrast agents exemplified by Fe_3O_4 and gadolinium NPs. Fe_3O_4 NPs, with diameters around 50 nm have displayed relatively favorable tolerability. However, instances of toxicity associated with nephrogenic systemic fibrosis, have been reported for gadolinium NPs (Bernd et al.,

2009; Khurana et al., 2007; Sharma et al., 1999). The selection of the material, its size, and protective coatings assume crucial importance for NPs. Inorganic materials with inherent inertness, such as Au is preferred to be used over materials with inherent side-effects like unchelated quantum dots (Bernd et al., 2009; Gao et al., 2005; Khurana et al., 2007).

The majority of polymer NPs derive advantages from being biodegradable or biocompatible (Zhang et al., 2008). There is a scarcity of data on the toxicity levels they might induce in neuronal cells (Costantino & Boraschi, 2012). Gadolinium and Fe_3O_4 NPs have gained significant attention due to their magnetic properties making them valuable for enhancing contrast in MRI which enhances the accuracy of detecting and monitoring brain tumors specifically in T2-weighted images providing visibility of tissues with high water content, including blood vessels (Hadjipanayis et al., 2010; Muldoon et al., 2005).

QDs demonstrate versatility by allowing fluorescence emission spectra across a broad range from 400 to 2000 nm with optimal in vivo imaging suggested between 700–900 and 1200–1600 nm (Gao et al., 2005). AuNPs are currently under scrutiny for their potential to deliver therapeutics to the brain. The USA National Institute of Standards and Technology has assessed AuNPs as a potential standard for nanosized particle research (Cheng et al., 2011; De Jong et al., 2010; De Jong et al., 2008; Khlebtsov & Dykman, 2011; Lasagna-Reeves et al., 2010; Sonavane et al.,2008; Sousa et al., 2010).

11.4 Diagnostic NPs

Gadolinium chelates presently serve as the prevailing choice for MRI contrast agents due to their significant magnetic moment. It has a size range of 1 to 3 nm which gives it the potential to enter normal tissues, making tumors indistinguishable and complicating MRI-guided resection (Orringer et al., 2009; Park et al., 2009; Veiseh et al., 2009). The Figure 3 illustrates the use of gadolinium NPs for enhancing contrast in rat brain tumors within two hours (Park et al., 2009).

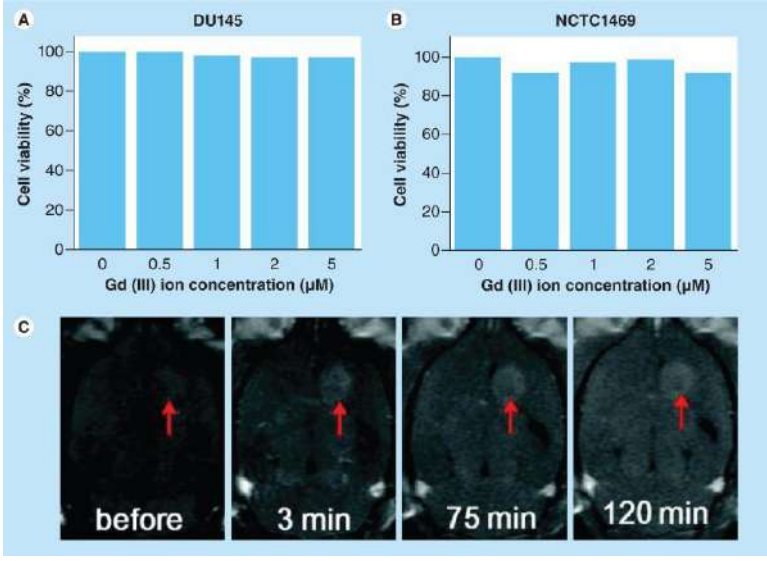

Figure 3. Cytotoxicity examination and showcasing MRI images of a rat brain tumor using gadolinium oxide NPs for improved T1-weighted contrast (Park et al., 2009). Results of in vitro cytotoxicity tests for DU145 (A), NCTC1469 (B) cell lines are presented., and (C) displays in vivo T1-weighted images of a rat brain, highlighting the tumor with arrows before and after the injection of ultrasmall gadolinium oxide NPs.

AuNPs are considered as diagnostic agent for brain cancer. The Figure 4 illustrates the mechanism of delivering gadolinium for MRI preoperative detection and surgical planning.

AuNPs show picomolar-sensitive imaging for tumor margins by using photoacoustic and Raman agents. Also, AuNPs can carry fluorescent imaging agents for diagnostics (Cheng et al., 2011; Kircher et al., 2012).

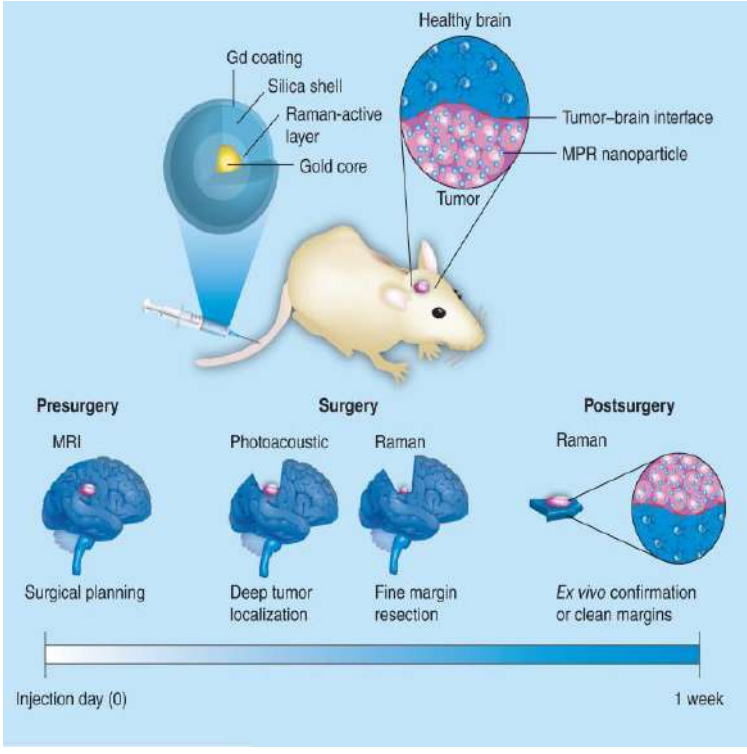

Figure 4. Identifying brain tumor margins and enhancing surgical resection using a gold NP-based system (Kircher et al., 2012).

Organic NPs, such as Liposomes demonstrate success in brain cancer diagnostics, Figure 5 shows their application in noninvasive for the diagnosis of brain tumors by delivering gadolinium through convection-enhanced delivery (Krauze et al., 2005; Mamot et al., 2004; Saito et al., 2006).

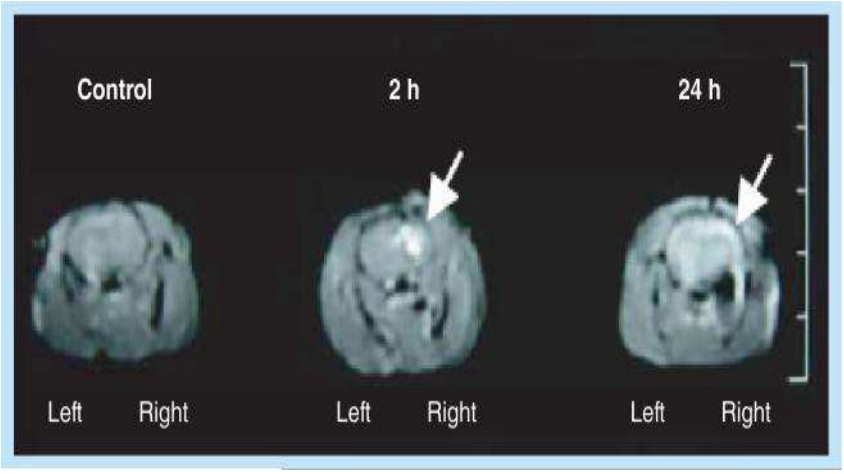

Figure 5. Enhanced MRI contrast via convection gadolinium-loaded liposomes (Mamot et al., 2004).

Dendrimers also proved their ability through scientific experiments to enhance MRI contrast and fluorescent imaging for detecting tumors optically (Sarin et al., 2008; Yan et al., 2011; Yan et al., 2012).

Illustrated in Figure 6, demonstrates the mechanism of targeting tumor vessels first with αvβ3 integrin, then accelerating through LRP receptors for BBTB transversal (Yan et al., 2011; Yan et al., 2012).

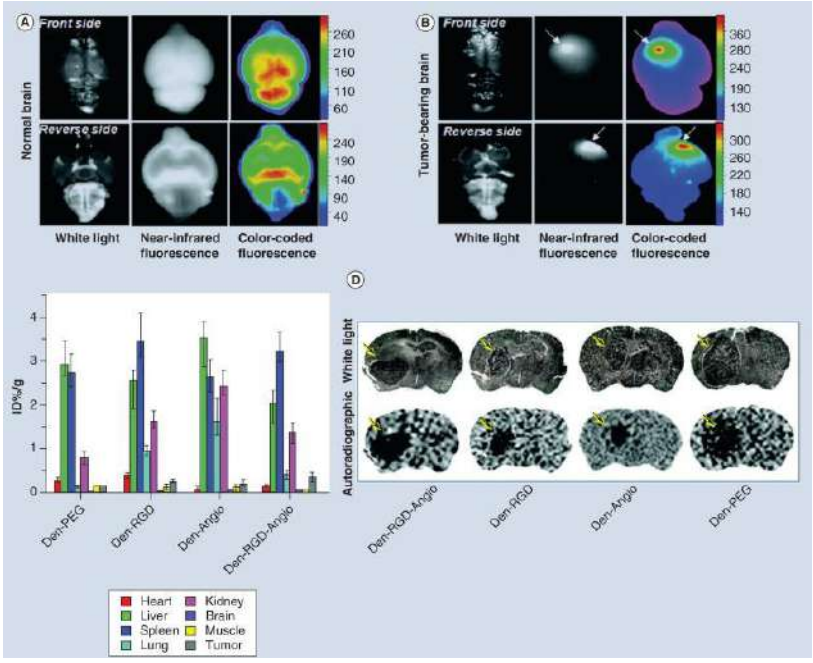

Figure 6. *Ex vivo* brain tumor imaging with optical and paramagnetic dendrimeric NPs targeting tumor vasculature and lipoprotein receptor protein receptors in a mouse brain (Yan et al., 2012). Representative visuals of dissected mouse brains are presented post-injection after 24 hours. Panel (A) exhibits images in white-light white light, near-infrared fluorescence, and color-coded fluorescence for a normal mouse brain, while (B) shows the same for a tumor-bearing mouse brain. Panel (C) illustrates the biodistribution of NPs in tumor-bearing mice (n = 3) after 24 hours, determined through radioactive isotope labeling with 125I. Columns portray mean values, and bars convey the data range. Finally, Panel (D) displays typical white-light microscopic and autoradiographic images of brain sections with tumors at 24 hours post-injection of the radioactive nanoprobe, emphasizing tumor locations with arrows.

12. Blood-Brain Barrier and Brain Cancer

12.1 Structure and Function of the BBB

BBB is the critical structure found at the junction of blood vessels and accessory cells of the CNS (Figure 7), i. e. astrocyte, lining the outer region brain; it is a highly selective permeable region through which only the exchange of gases and nutrients occur without bathing of blood cell into the brain. This is essential to maintain the homeostasis of the brain and protect it from pathogens and even immune system infiltration to avoid damage during immune responses (Hersh et al., 2022).

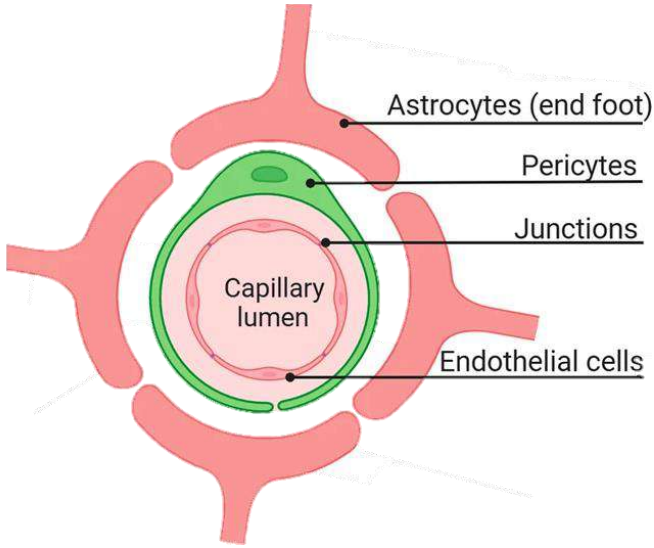

Figure 7. Structure of the BBB (Newton & Kaur, 2019).

The structural hallmark of BBB is the tight junction, found between the endothelial cells lining the blood vessels. This acts as the main barrier against hydrophilic molecule passage and selectively

allows the passage of hydrophobic molecules and proteins only (Ohta et al., 2020). In addition to endothelial cells, the pericytes of mural cells, as well as astrocytes (as discussed already) are also the core part of BBB.

13. Strategies For Overcoming the Blood-Brain Barrier

By employing nano-carriers whose size meets with that of BBB, which is reasonably sizable enough not to be excreted out of the body and easy to be synthesized; neuroscientists agree that a molecule of size less than 200 nm. However, larger than 5 nm or less than 400 Da are somewhere near optimal size that can effectively pass through BBB (Newton & Kaur, 2019), as Glucose Transport Protein (GLUT) is considered a gateway for the entry of components into the brain through Receptor-Mediated Endocytosis (RME) mechanism. The existence of highly concentrated GLUT in brain micro vessels leads to an effective target for drug or nano-carrier delivery. When conjugated with therapeutic molecules, facilitates their penetration through BBB via GLUT receptors as GLUT is overexpressed in tumor cells. Glucose-modified liposomes and peptides have shown enhanced BBB penetration. Various studies demonstrate the efficiency of glucose as a targeting ligand for delivering drugs or nano-carriers to brain tumors, and its potential in improving drug delivery to the brain, (Figure 8) (Mitusova et al., 2022).

By using nano-agents that can trigger the opening of BBB, such as black phosphate nanosheets that can heat the neuronal microenvironment to momentarily permeate BBB (Dadwal et al.,

2018)., such as Levo-Dihydroxyphenylalanine (L-DOPA) a precursor to dopamine. Studies showed that L-DOPA has the potential to cross the BBB due to Large Neutral Amino Acids (LAT1) without causing toxicity. L-DOPA has been reported to be as is a gold standard for dopamine replacement, either alone or in combination with anti-tumor drugs, enhancing their BBB penetration efficiency. Innovative approaches, such as Amphi-DOPA liposomes, demonstrate improved drug delivery directly to glioblastoma. Inorganic nano-carriers modified with L-DOPA exhibit enhanced BBB penetration (Figure 4) (Mitusova et al., 2022).

By surface re-engineering the NPs that target neuronal cells of the brain only, such as Transferrin Receptors (TfRs) (Bastiancich et al., 2019). In addition, Monoclonal Antibodies (MAbs) as an extremely essential agent in enhancing the penetration efficiency of the therapeutic molecules barrier (BBB). Specific MAbs, such as MAb83-7 and MAb83-14 are responsible for targeting human insulin receptors (HIR) provided have shown significant penetration capabilities. Studies showed that therapeutic agents, such as biotinylated Aβ 1–40 conjugated with MAbs demonstrate successful BBB penetration (Figure 4) (Mitusova et al., 2022).

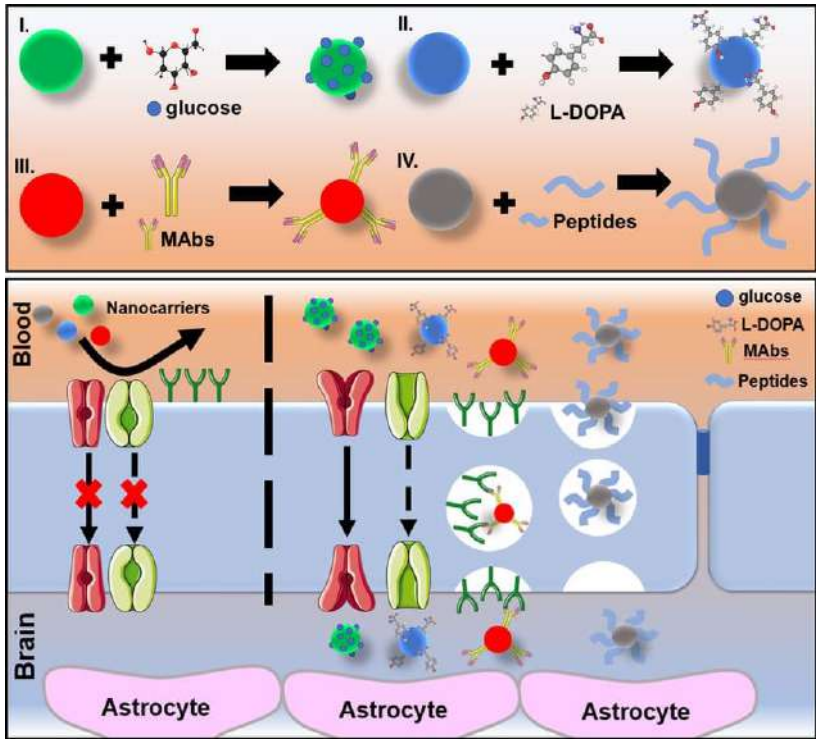

Figure 8. Enhancing nanocarrier surfaces with targeting vectors (Glucose, L-DOPA, and MAbs) illustrating the BBB penetration mechanism (Mitusova et al., 2022).

14. Conclusion

Nanotechnology has revolutionized drug delivery mechanisms, notably in the treatment of brain cancer, to bring new ways of achieving better therapeutic results. The utilization of NPs and nano-carriers, such as liposomes, carbon nanotubes, dendrimers, polymeric micelles, viral-based NPs, and polymeric NPs, has provided a great opportunity to eliminate the challenges associated with traditional brain cancer

treatments. By resolving crucial issues, such as the blood-brain barrier and specific blocking of cancer cells, drugs are more productive and less toxic. For the first time, glioblastoma multiforme and other brain cancers can be treated with medication due to the invaluable instruments that NPs have turned out to be. By-passing the blood-brain barrier and selective bonding to cancer cells maximizes drug accumulation and "working time" in tumors while minimizing the undesirable impact "outside" the focus. The focused nature and efficient mode of deliverance enabled by nanotechnology make it feasible to surmount the downfalls of traditional treatment. Once therapists encapsulate drugs in NPs, they will enhance drug stabilization, controlled release, and bioavailability, eventually achieving spectacular efficacy for brain cancer treatments.

There are many benefits to employing nanotechnology in medication delivery for brain cancer treatment. NPs allow a greater penetration and accumulation of the drug, which leads to higher therapeutic efficacy. The use of nanocarriers, such as liposomes and polymeric micelles makes it feasible for researchers to create drug delivery systems that combine safety and effectiveness and provide therapeutic drugs for target tissues. Nanotechnology has revolutionized cancer therapy by enabling the development of extremely focused medication delivery systems according to the demands of the disease sleeper The use of nano-carrier vehicles or viral-based NPs and dendrimers results in higher focus of the drug distributed to cells or tissues and thus may make the therapy technique simpler and much better. Nanomaterials have the ability to produce novel drug delivery

systems that can provide acceptable transit and control or even improve the release of medication at the site of action in brain cancer sufferers.

In conclusion, the application of nanotechnologies to treat brain cancer has significant potential in promoting personalized medicine and improving patient outcomes in the long term. The development of biocompatible and biodegradable nanosystems ensures the safety and efficacy of drug delivery, minimizing the risk of side effects and toxicity. Increasing encapsulation efficiency and drug release kinetics helps researchers increase the accuracy and efficiency of nanosystems and, as a result, develop more efficient treatments tailored to brain cancer. Nanotechnology has dramatically shifted brain cancer therapy's focus since it provides innovative drug delivery approaches that avoid pitfalls of the traditional treatments. The application of NPs and nano-carries offers outstanding potential for improving therapeutic efficacy, overcoming physiological barriers, such as the blood-brain barrier, and enhancing targeted delivery to cancer cells. Currently, using the unique properties of nanomaterials and personalized drug delivery systems, researchers are advancing the development of safer, more accurate, and more effective brain cancer treatments. Therefore, it is safe to predict that nanotechnology has a promising future in the medical field, and its full potential in oncology, including the treatment and diagnostics of brain cancer, is yet to be tapped.

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CHAPTER 3

ARTIFICIAL INTELLIGENCE APPLICATIONS IN BIOMEDICAL ENGINEERING

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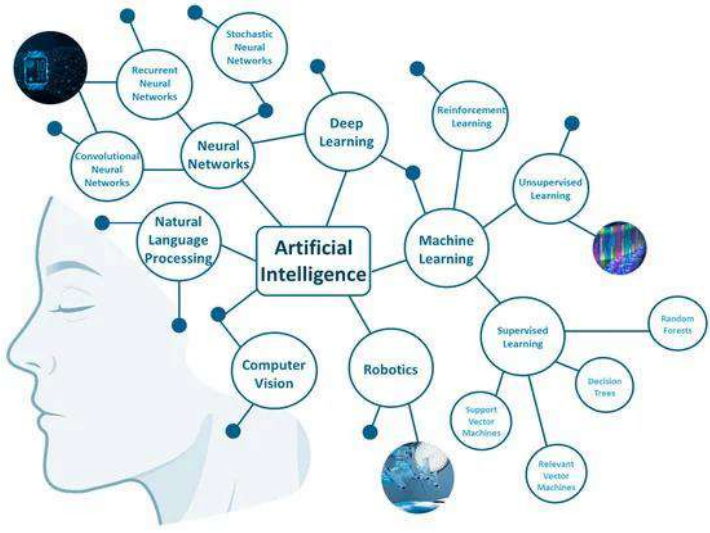
Lect. Dr. Firdevs Banu ÖZDEMİR

INTRODUCTION

Integrating artificial intelligence into artificial intelligence applications in biomedical engineering offers innovative solutions to complex health problems. Artificial intelligence technologies such as machine learning and deep learning are used in patient monitoring, medical imaging, personalized medicine, etc., facilitating the medical practices of healthcare professionals. These advancements are enabling more precise, efficient, and accessible healthcare services. Biomedical engineering has seen significant applications of AI in medical imaging, particularly in radiology and histopathology, where it enhances diagnostic accuracy and reduces human error. AI systems have been pivotal in analyzing large datasets, such as genomic and proteomic data, to support breakthroughs in personalized medicine and predictive modeling. Tools like AlphaFold have advanced the understanding of protein structures, illustrating AI's potential in drug discovery and biological research. With the integration of artificial intelligence and the Internet of Things into remote monitoring systems in the field of health, real-time and continuous patient monitoring and decision-making have been improved. The aim is to provide equality in the field

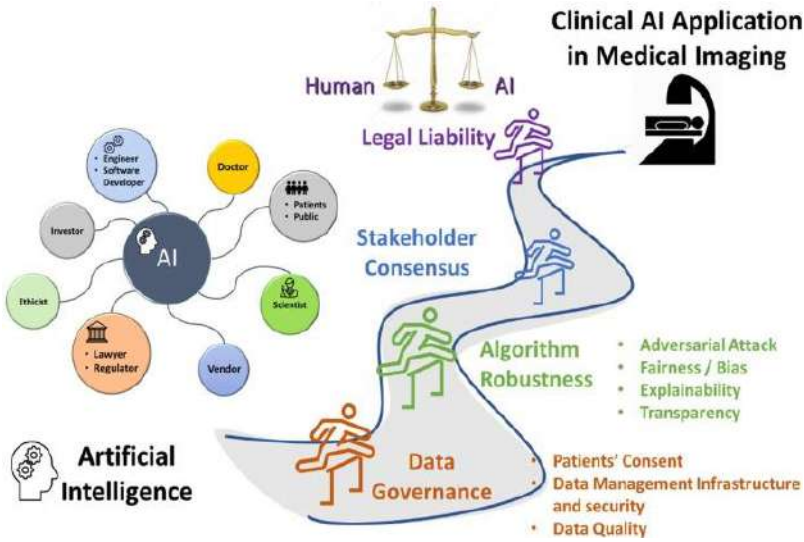
of health by bringing this system to rural areas or regions where health services are inadequate. The role of disease and epidemic detection and surveillance in the field of public health has become much more important during the COVID-19 pandemic. Along with these developments, ethical concerns, critical health scenarios, data privacy issues, and explainability issues of artificial intelligence models are the main problems in the use and design of these systems. A multidisciplinary study is required to understand these problems and to integrate artificial intelligence into health technologies in a safe and effective way. This book chapter examines the areas and depth of artificial intelligence applications in biomedical engineering; examines innovations in this field, current challenges, and describes possible future technologies.



Picture 1. Artıfıcıal Intellıgence Applıcatıons In Bıomedıcal Engıneerıng (Athanasopoulou et.al. 2022)

Chapter 1: Artificial Intelligence in Medical Imaging

Artificial intelligence offers groundbreaking innovations in image acquisition, processing and analysis of the acquired images and has opened up a new field of study in the field of imaging. By using techniques such as machine learning and deep learning, artificial intelligence systems increase diagnostic accuracy and contribute to the speed of physicians' decision-making. Thus, physicians make fewer errors in diagnosis and manage the treatment process more accurately and quickly. In this section, the use of artificial intelligence in medical imaging and its contribution to healthcare will be discussed. At the same time, the challenges associated with the use of artificial intelligence in medical imaging will be discussed.

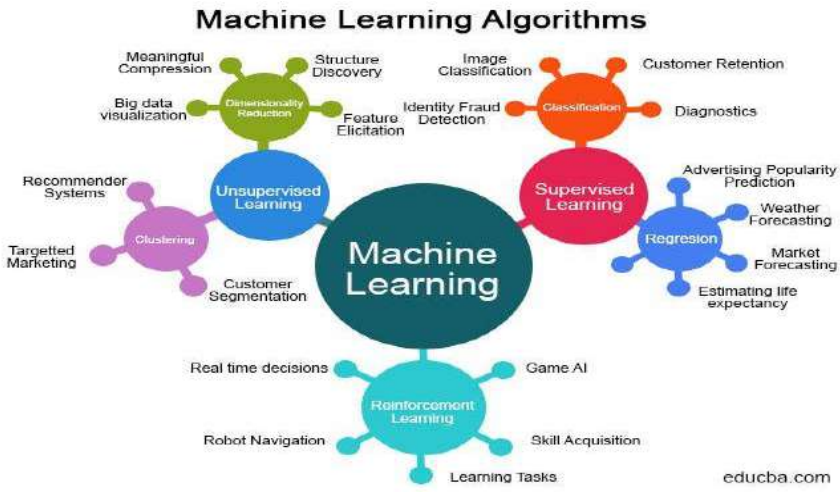


Picture 2. Artificial Intelligence in Medical Imaging (Saw and Ng, 2022)

Chapter 1.1 Applications of AI in Medical Imaging

Chapter 1.1.1 Image Acquisition and Enhancement

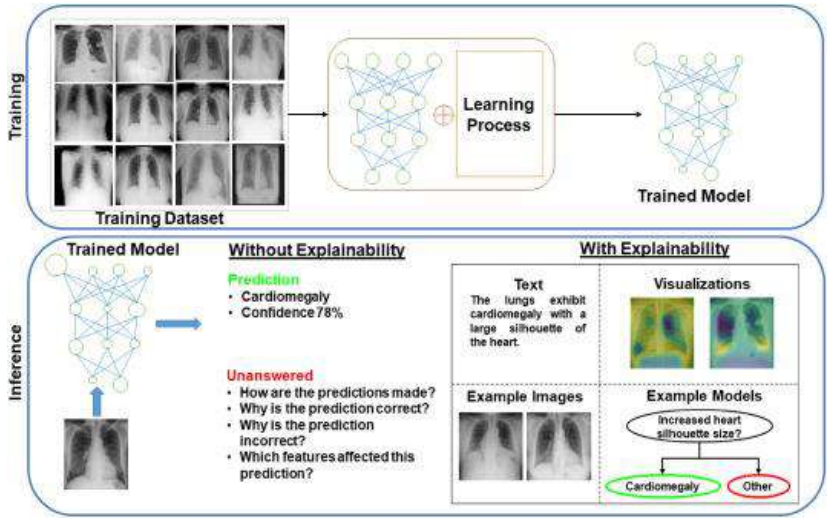
Artificial intelligence algorithms are used to improve image quality and reduce image noise. It is used in the most commonly used medical imaging devices for diagnosis, such as computerized tomography (CT) and magnetic resonance imaging (MRI), as well as other imaging devices such as x-ray, mammography, PET, SPECT and gamma cameras. Improving image quality and reducing noise allow physicians to make faster and more accurate decisions in making diagnoses. These developments are possible with advanced artificial intelligence algorithms, as seen in Figure 3. The field of medical image processing is developing gradually using these algorithms and is significantly helping physicians make diagnoses in the health field (Litjens et al., 2017).



Picture 3. Types of algorithms used in image processing (Aggarwal, 2020)

Chapter 1.1.2 Automated Diagnostics

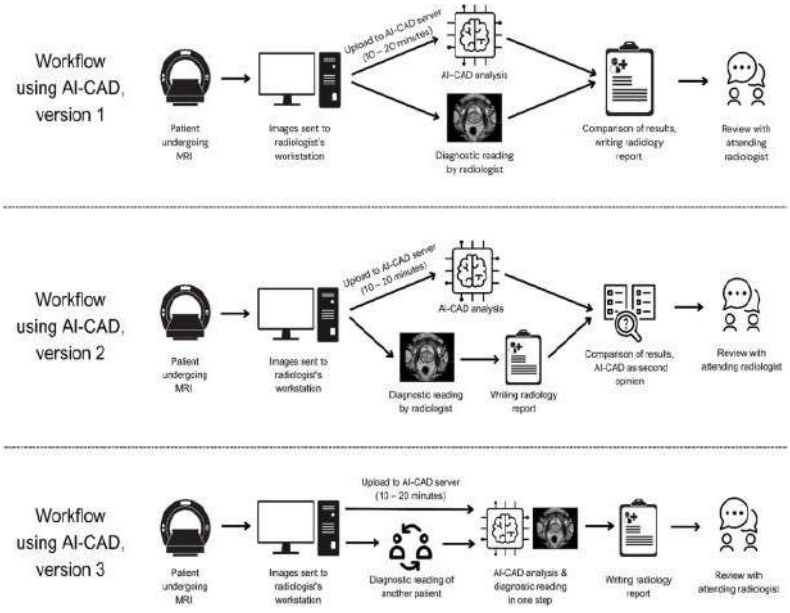
The use of artificial intelligence to detect abnormalities in imaging data is increasing. Convolutional neural networks (CNNs) show high-level performance in detecting and diagnosing medical conditions such as fractures, tumors, and congenital organ abnormalities in radiological images. Recent studies show that they can make diagnoses similar to those of expert radiologists in the detection of lung cancer types, breast cancer, and neurological disorders (Lundervold & Lundervold, 2019). X-ray images are used in the training set and inserted into the CNN, thus creating a training model. The designed system is tested by inserting X-ray images outside the training set into the created training model (picture 4) and the accuracy rate of the system is determined.



Picture 4. Automated Diagnostics in medical ımage with AI (Nazir et al., 2023)

Chapter 1.1.3 Workflow Optimization

The workflow resource is used to change radiological workflows such as automation of repetitive processes, segmentation of organs and organ structures or emergency case classification. Thus, the workload of radiologists is reduced and the reporting order is shortened compared to manual reporting. With these systems, reporting increases and the speed of the final report increases (Hosny ve diğerleri, 2018). Automatic diagnosis system in medical images with workflow optimization using artificial intelligence is shown in Figure 5.



Picture 5. Automated Diagnostics in medical ımage with AI Workflow Optimization (Wenderott et al., 2024)

Chapter 1.1.4 Predictive and Personalized Medicine

Artificial intelligence has been used in recent years to predict patient outcomes and personalize treatment using electronic health records (EHRs). With the development of personalized treatment planning systems, a noticeable decrease in the cost of healthcare services has been observed, along with the personalized and quality of patient care (Esteva et al., 2021).

Chapter 1.2 Challenges in AI Integration

Chapter 1.2.1 Data Quality and Bias

Large datasets are used in artificial intelligence modeling. While big data modules are used in artificial intelligence modules, the appearance of the models varies according to their viewing and protocols. The results of these differences are inequalities in access to health care and the emergence of injustice in access to health care in rural and urban areas of countries.

Chapter 1.2.2 Explainability and Trust

The “Black Box” structure is found in artificial intelligence algorithms. This structure is not fully accepted by clinicians in critical scenarios, trusting artificial intelligence suggestions and transparent decision-making processes. There are prejudices against such applications,

especially among physicians who have been in the profession for over twenty years. (Ardila et al., 2019).

Chapter 1.2.3 Regulatory and Ethical Issues

Applications of artificial intelligence in medical imaging raise issues of medical ethics such as data security, patient safety, and regulatory approval. Legal procedures should be prepared for this and necessary regulations should be made by the ministries of health of the states (Kelly et al., 2019).

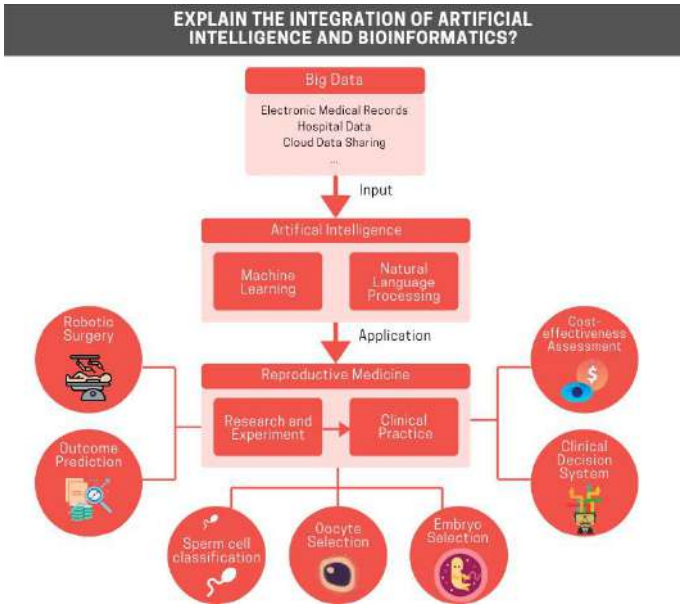
Chapter 1.2.4 Future Directions

Applications of artificial intelligence to medical imaging are summarized in areas such as cancer, internal diseases, heart-lung diseases, orthopedics and nuclear medicine, and within the scope of personalized health services, the diagnosis of specialist physicians is improved in the field of health thanks to more accurate and faster decisions on diagnosis and treatment.

Chapter 2. Artificial Intelligence in Bioinformatics

Bioinformatics is a multidisciplinary field that combines biology, statistics and computer science. In this field, the use of artificial intelligence is done with machine learning and deep learning methods. The analysis of large data sets such as proteomic, genomic and transcriptomic data sets (Figure 6) is evaluated from a biological perspective. This section provides a projection regarding the use of

artificial intelligence in this field along with the progress and recording of bioinformatics supported by artificial intelligence.



Picture 6. Artificial Intelligence in Bioinformatics (Statswork, 2020)

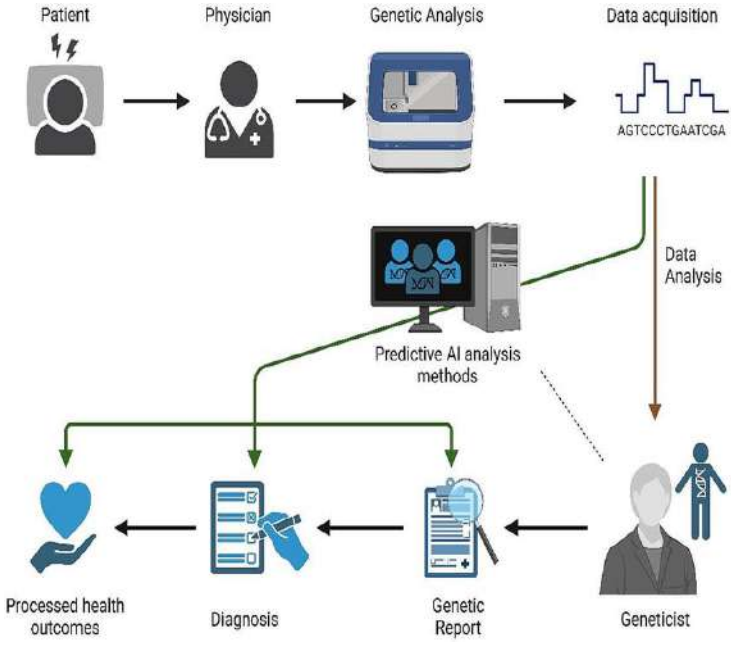
Chapter 2.1 Applications of AI in Bioinformatic

Chapter 2.1.1 Genomic Data Analysis

AI facilitates the annotation, interpretation, and analysis of genomic sequences. Tools powered by AI can predict gene functions, identify regulatory elements, and detect mutations linked to diseases. For example, DeepVariant, an AI-based tool, improves the accuracy of variant calling from sequencing data

Artificial intelligence is frequently used in the fields of annotation, interpretation and analysis of genome sequences. Artificial intelligence algorithms are used to predict gene functions, identify regulatory

elements and detect mutations associated with diseases (Figure 7). DeepVariant is an AI-based tool and is used to increase the accuracy of variant calling from sequencing data (Poplin et al., 2018).



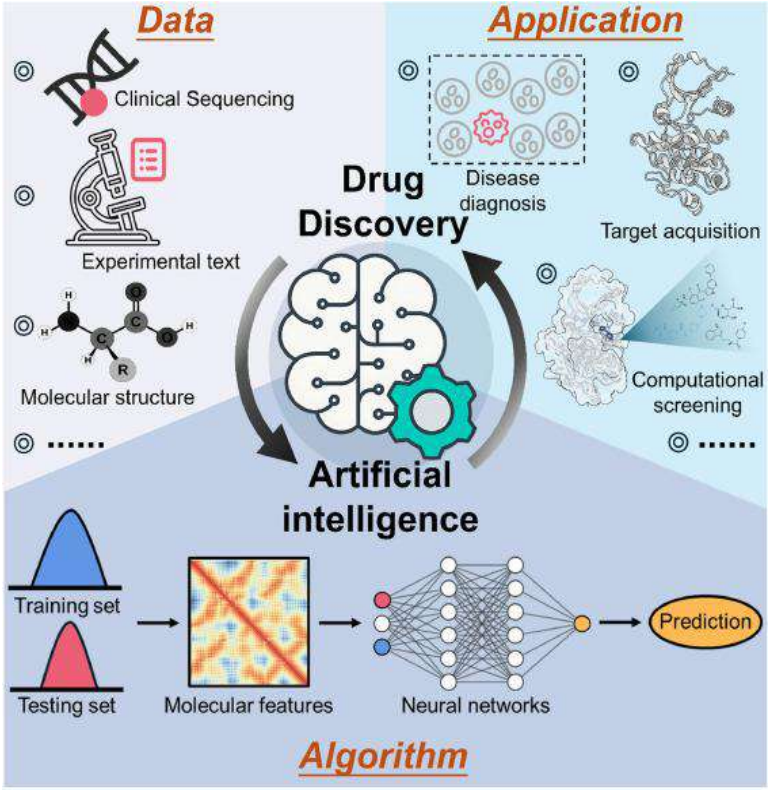
Picture 7. AI applications in functional genomics (Ozcelik, et. al., 2024)

Chapter 2.1.2 Protein Structure Prediction

AlphaFord, a deep learning model developed by DeepMind for protein structure prediction, overcomes this challenge that has been ongoing for years in structural biology by predicting protein folding with unprecedented accuracy (Jumper et al., 2021). This study has accelerated studies in the fields of functional genomics and drug discovery.

Chapter 2.1.3 Drug Discovery and Development

Artificial intelligence is used to integrate bioinformatics data with chemical databases to identify potential drug candidates. Techniques such as de novo drug design and virtual screening are used to predict drug-target interactions and optimize compounds in targeted drug design (Figure 8) (Zhou et al., 2020).



Picture 8. AI applications in Drug Discovery and Development in bioinformatic(Rehman et al., 2024).

Chapter 2.1.4 Transcriptomics and Single-Cell Analysis

Transcriptomics is a technique that uses artificial intelligence models and RNA sequencing to analyze the heterogeneity and gene expression patterns of the captured genomes. Single-cell RNA-seq studies have enabled AI to identify rare records and to understand complex tissues by utilizing clustering of the hosts (Haque et al., 2017).

Chapter 2.1.5 Systems Biology and Network Analysis

Artificial intelligence is also used in modeling complex biological systems and their interactions. Artificial intelligence-based network analysis provides insight into potential therapeutic targets and pathogenesis by identifying genes and pathways that underlie diseases (Chen et al., 2020).

Chapter 2.2. Challenges in AI Integration

Chapter 2.2.1 Data Quality and Standardization

The heterogeneity of biological data originating from different experimental platforms and protocols complicates the generalization of AI models and training. Standardizing metadata and datasets is a key goal

Chapter 2.2.2 Interpretability and Validation

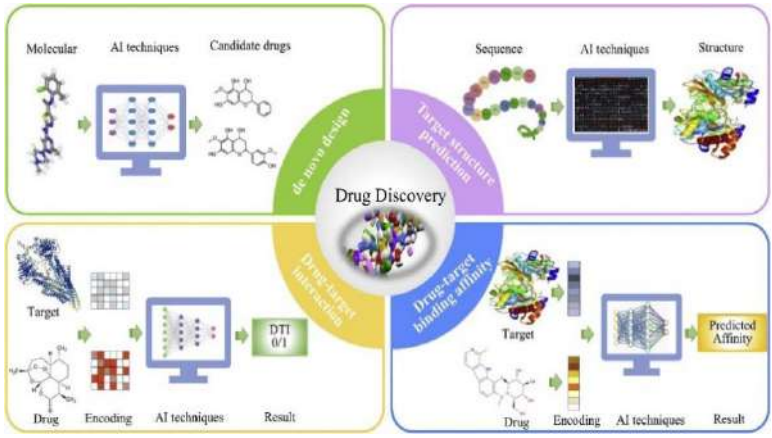
“Black Boxes” often make predictions in AI models difficult to interpret. These models require further work to validate them with experimental data and gain acceptance in clinical and research settings. (Samek et. al., 2017).

Chapter 2.2.3 Ethical and Privacy Concerns

There are concerns among healthcare professionals regarding the use of artificial intelligence in the analysis of sensitive genomic data, ethical issues, and data privacy. In order to solve this problem, data management must be done in a robust manner (Knoppers, 2014).

Chapter 2.3 Future Directions

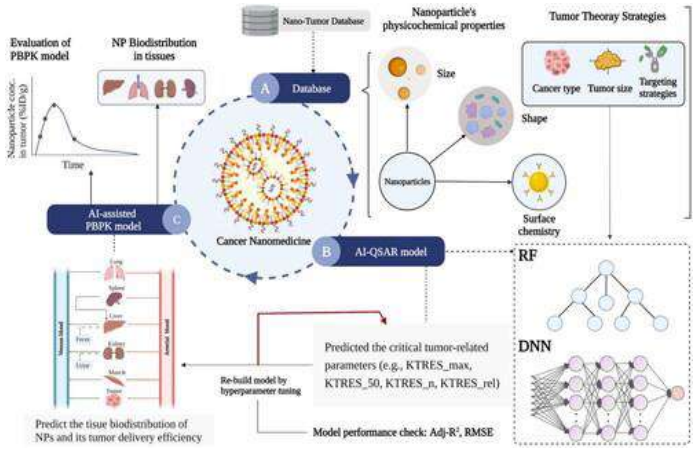
Integration with multi-omics data, including AI applications in proteomics, metabolomics, genomics, and epigenomics, will help understand complex biological systems. Advances in explainable artificial intelligence (XAI) will increase the interpretability of AI models and facilitate their adoption in the fields of bioinformatics and personalized medicine.



Picture 9. AI applications in Drug Discovery and Development in bioinformatic Future Directions (Chan et al., 2023).

Chapter 3 Artificial Intelligence in Bionanotechnology

Bionanotechnology is a multidisciplinary field formed by the combination of nanotechnology, biology and biomedical engineering. Bionanotechnology, which has applications in areas such as biosensors, biomaterial development, diagnostics and smart drug systems, emerges as a transformative and developing field. With the use of artificial intelligence applications in bionanotechnology, the potential, future and application area of the field are increasing exponentially. With the design of devices, production, analysis and optimization of materials at nanoscales, artificial intelligence has accelerated research and development and production and development in this field. This section examines the relationship between AI and bionanotechnology and emphasizes its applications, challenges and expectations.



Picture 10. Artificial Intelligence in Nanotechnology images (Heydari et al., 2024).

Chapter 3.1 Applications of AI in Bionanotechnology

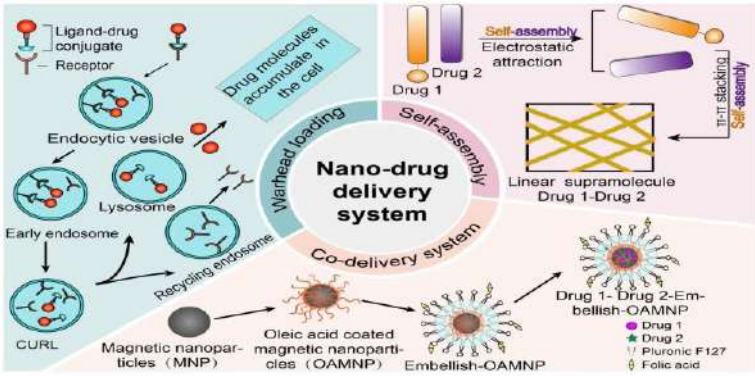
Chapter 3.1.1 Design and Optimization of Nanomaterials

Artificial intelligence is accelerating the process of designing nanomaterials specifically designed for specific biological applications. By predicting the physicochemical properties, functionality, and stability of nanoparticles, machine learning reduces the need for labor-intensive trial-and-error methods. Focused frameworks are used to design nanocarriers used for targeted drug delivery with artificial intelligence (Chan et al., 2020).

Chapter 3.1.2 Nanomedicine and Drug Delivery

Optimizing effective AI such as release kinetics, drug loading and targeting efficiency helps in the development of nanotransports in drug therapy (Figure 11). Deep learning Biology (DL) is used to determine biomarkers obtained by analyzing data sets and to design

nanostructures that can enter into a visually selective interaction and to process therapeutic results (Mousazadeh et al., 2021).



Picture 11. Nanomedicine and Drug Delivery (Chou et al., 2023).

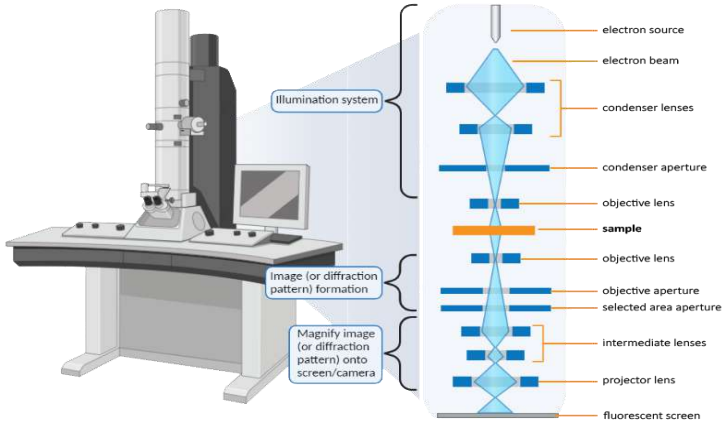
Chapter 3.1.3 Biosensing and Diagnostics

Biosensors made of nanomaterials, AI algorithms that increase their specificity and sensitivity have provided revolutionary developments in the field of biosensors and diagnostics. It paves the way for rapid and accurate disease diagnosis by enabling the interpretation of complex data produced by biosensors. AI-supported plasmonic nanosensors are used in the detection of biomolecules at ultra-low concentrations (Patil et al., 2021).

Chapter 3.1.4 Nano-Scale Imaging and Characterization

Artificial intelligence is used to analyze data obtained from high-end imaging techniques such as transmission electron microscopy (TEM) and atomic force microscopy (AFM). It is used to automate pattern

recognition and image processing, and to understand and improve interactions and properties at the nanometer scale (Su et al., 2020).



Picture 12. Biomedical Nano-Scale Imaging and Characterization (Nanoscience, 2024)

Chapter 3.1.5 Environmental and Sustainability Applications

Nanotechnology applications in environmental science, such as water treatment and pollution monitoring, have been enriched with artificial intelligence algorithms. Using these algorithms, optimization of nanomaterial synthesis, design of sustainable applications and monitoring of interaction with pollutants can be done.

Chapter 3.2 Challenges and Limitations

Chapter 3.2.1 Data Scarcity

The development of robust AI models in bionanotechnology Limited high-quality datasets hinder the generation of robust AI models in bionanotechnology. Integration of diverse computational and

experimental data is critical for the reliability of the models (Rosen et al., 2020).

Chapter 3.2.2 Interpretability

The "black box" nature of many AI algorithms poses challenges in understanding the underlying mechanisms of predictions, particularly for regulatory approval of AI-driven nanotechnologies (Samek et al., 2017).

Chapter 3.2.3 Ethical and Safety Concerns

The combination of nanotechnology and artificial intelligence raises ethical issues such as the responsible use of bionanomaterials designed with artificial intelligence and the potential ecological and human effects of the materials produced. Interdisciplinary studies are needed to address these concerns. (Knoppers, 2014).

Future Directions

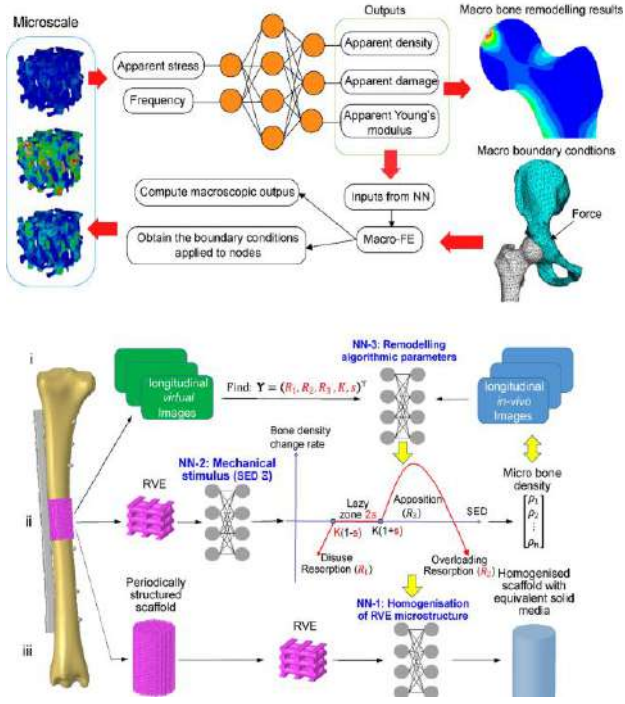
The integration of multi-scale modeling and quantum computing by artificial intelligence is promising for the future of bionanotechnology. Artificial intelligence-based studies in emerging fields such as nanorobotics and synthetic biology will also open up a new field of work for personalized nanomedical and new nanoscale devices.

Chapter 4. Artificial Intelligence in Biomaterials

Designed to interact with biological systems. They have also changed and transformed fields such as drug delivery, tissue engineering, and regenerative medicine. Artificial intelligence is a powerful tool for the

development, characterization (Picture 13), and application generation of biomaterials.

AI is used in predictive modeling, data analysis, biocompatible material design, and optimization. This section will discuss the integration of AI into biomaterial science, as well as the challenges of applications and the future of this topic.



Picture13. Artificial Intelligence in Biomaterials (Wu et al., 2024).

Chapter 4.1. Applications of AI in Biomaterials

Chapter 4.1.2 Predictive Modeling and Material Design

Artificial intelligence techniques, such as machine learning (ML) and deep, have revolutionized the prediction of the properties of biomaterials. Predicting the mechanical, biological and thermal

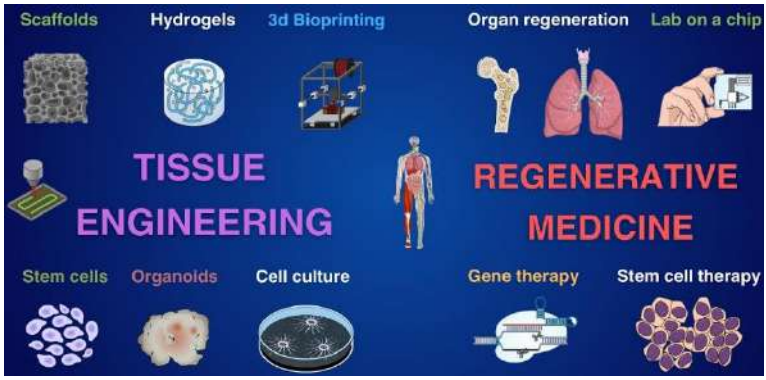
properties of new materials and dependence on costly, time-consuming trial and error methods can be reduced with models trained on experimental data sets. For example, artificial intelligence-driven models are used when the combination of hydrogel-based skeletons is wanted to be optimized for tissue engineering (Li et al., 2024).

Chapter 4.1.3 Drug Delivery Systems

Artificial intelligence facilitates biomaterial design in controlled drug delivery processes. Physiochemical and biological data can be integrated into ML processes to predict drug release profiles. Thus, the properties of nanocarriers can be optimized. Targeted and sustained drug delivery is also used to design therapeutic outcomes and polymer-based systems for diseases (Patra et al., 2020).

Chapter 4.1.3.1 Tissue Engineering and Regenerative Medicine

Artificial intelligence is helping in the selection and optimization of biomaterials for scaffolds in tissue engineering. The models produced can predict how materials interact with tissues and cells, ensuring functionality and compatibility (Picture 14). AI-based approaches are being used to design systems that mimic the extracellular matrix and enhance tissue regeneration. (Cao et al., 2021).



Picture 14. Tissue Engineering and Regenerative Medicine (Bioengineering Hub, 2024)

Chapter 4.1.3.2 Characterization of Biomaterials

Advanced imaging and characterization techniques are producing large datasets that AI can analyze to extract meaningful insights. For example, CNNs have been used to classify and evaluate the surfaces of biomaterials, providing insights into their functional and structural properties. (Park et al., 2019).

Chapter 4.1.3.3 Environmental and Sustainability Considerations

Artificial intelligence is used in the production of biomaterials from renewable resources. Artificial intelligence is effectively used in optimizing the synthesis of these systems and in environmental sustainability. It also contributes to the design of environmentally friendly materials by predicting degradation models and environmental impact. (Bai et al., 2020).

Chapter 4.1.4 Challenges and Limitations

Chapter 4.1.4.1 Data Scarcity

The development of AI models in biomaterial science often presents difficulties in the creation phase of the system to be designed due to

heterogeneous and limited data sets. In order to increase model reliability, data collection and sharing should be increased and certain standards should be determined (Konda et al., 2021).

Integration with Experimental Methods

Rather than replacing experimental methods, artificial intelligence should complement these methods. Ensuring that computational predictions are seamlessly combined with laboratory experiments is a significant source of information and is difficult to obtain (Yang et al., 2020).

Future Directions

Combining multi-omics data, high-throughput experiments, and advanced computational models plays a key role in the future of AI in biomaterials. By leveraging advances in AI, researchers are able to design biomaterials with unprecedented precision and functionality, leading to significant breakthroughs in personalized medicine, regenerative therapies, and environmental sustainability.

Chapter 5: Artificial Intelligence in Biomechanics

Biomechanics, the study of the properties of living organisms and their response to mechanical stress, involves analyzing the movements, forces, and material properties of biological tissues. Artificial intelligence (AI) enables automated data analysis, predictive modeling, and the design of personalized biomechanical interventions. From gait analysis and sports biomechanics to musculoskeletal modeling and rehabilitation, the integration of AI into biomechanics offers profound insights and applications. This chapter examines the role of AI in

advancing biomechanics research and applications, and discusses areas of application, challenges, and future directions.

Chapter 5.1 Applications of AI in Biomechanics

Chapter 5.1.1 Gait Analysis and Human Movement

Artificial intelligence is used effectively in the study of human movement, especially in clinical gait analysis. Artificial intelligence processes motion capture data to classify gait patterns, evaluate the results of treatments, and detect abnormalities. For example, CNNs show high accuracy in diagnosing diseases associated with gait disorders such as cerebral palsy and Parkinson's. (Oh et al., 2021).

Chapter 5.1.2 Musculoskeletal Modeling

AI is improving the efficiency of musculoskeletal simulations by predicting joint torques, muscle activation, and forces. Machine learning (ML) models trained on biomechanical datasets reduce the computational burden of traditional finite element methods. These approaches enable real-time simulations for prosthetic design and surgical planning applications. (Rajagopal et al., 2020).

Chapter 5.1.3 Sports Biomechanics

AI optimizes athlete performance and sports protection strategies through complex biomechanical data analysis. When combined with wearable sensors, AI programs provide real-time feedback on movement patterns. It helps athletes improve their technique. Predictive

models also allow for early intervention when considering risk for injuries (Ghasemzadeh et al., 2015).

Chapter5.1.3 Rehabilitation Engineering

Artificial intelligence-supported devices such as prosthetics and exoskeletons are designed using biomechanical data in anticipation of user needs. Reinforcement learning algorithms enable these devices to learn optimum movement patterns and increase functionality and user comfort (Zhang et al., 2021).

Chapter 5.1.4 Tissue Biomechanics

AI predicts the mechanical properties of synthetic biomaterials and biological tissues in tissue engineering. ML models accelerate the analysis of experimental data to determine material properties and the development of biomimetic structures for regenerative medicine. (Sun et al., 2020).

Chapter 5.2 Challenges and Limitations

Chapter 5.2.1 Data Quality and Variability

Biomechanical data are often incomplete, noisy, and heterogeneous, posing challenges for AI model training. Preprocessing methods and standardized data collection are important for model reliability (Bishop et al., 2022).

Chapter 5.2.1 Computational Complexity

Simulations, especially those involving multi-scale models, require significant computational resources in biomechanics. Balancing model accuracy and efficiency remains a key challenge for AI integration. (Pandy et al., 2017).

Chapter 5.2.1.1 Ethical and Practical Concerns

The deployment of AI in athletic and clinical settings raises ethical concerns regarding bias and data privacy. Ensuring equitable access and widespread adoption of AI-enabled biomechanical solutions is critical (Samek et al., 2017).

Chapter 5.3 Future Directions

The combination of AI with biomechanics, digital twins, and wearables holds great promise for personalized medicine and injury prevention. Advances in explainable artificial intelligence (XAI) will increase model interpretability and facilitate collaboration between engineers, clinicians, and researchers.

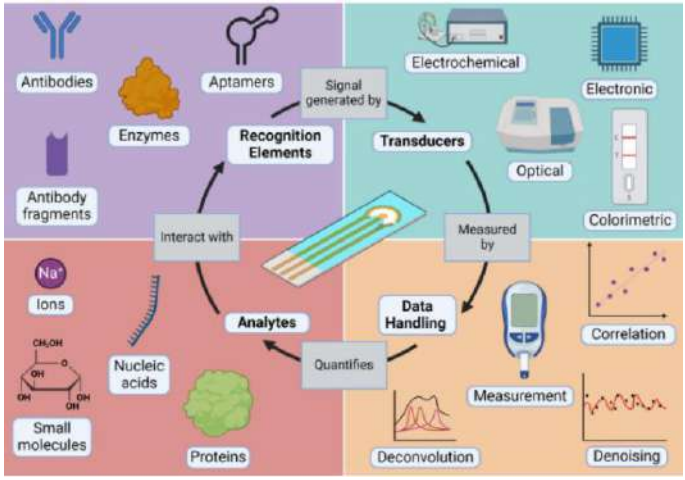
Chapter 6. Applications of AI in Biosensors

Chapter 6.1 Enhancing Sensitivity and Specificity

AI algorithms, particularly machine learning (ML) models, analyze large datasets by identifying subtle changes in sensor outputs and play an important role in improving the performance of biosensors. For example, AI-based models have been used to analyze data obtained from electrochemical biosensors that detect low-concentration glucose and lactate levels (Wang et al., 2021).

Chapter 6.2 Real-Time Data Analysis

Artificial intelligence provides instant feedback for both clinical diagnostics and environmental monitoring by processing data from biosensors in real time. In wearable biosensors, AI-based systems contribute to personalized healthcare by monitoring physiological parameters such as glucose levels and heart rate (Kim et al., 2020).



Picture 15. Applications of AI in Biosensors Real-Time Data Analysis (Flynn and Chang, 2024

Chapter 6.3 Biosensor Optimization

Artificial intelligence plays an important role in the design and optimization of biosensor components, such as electrodes, transducers, and recognition elements. Computational models predict material properties and simulate biosensor performance under different conditions, accelerating development processes (Khan et al., 2021).

Chapter 6.3 Disease Diagnosis

AI-based biosensors have provided major advances in point-of-care diagnostics. For example, Deep Learning (DL) algorithms process data from immunosensors to identify disease-specific biomarkers with high accuracy, reducing the need for laboratory-based techniques (Patel et al., 2022).

Environmental Applications

AI-powered biosensors enhance the capacity to detect pollutants and toxins in air, water, and soil. Machine learning models analyze sensor networks to identify pollutants and provide quick solutions to ecological threats (Singh et al., 2021).

Chapter 6.4 Challenges and Limitations

Chapter 6.4.1 Data Integration and Quality

The integration of AI with biosensors requires large and high-quality datasets for training models. Non-standard or noisy data can degrade the performance of AI models, necessitating robust data preprocessing methods (Mishra et al., 2020).

Chapter 6.4.2 Computational Requirements

AI-powered biosensors often require high levels of computational resources, which may not be feasible for portable or low-power devices. Developing efficient algorithms and hardware solutions to solve these problems is critical (Gautam et al., 2021).

Chapter 6.4.3 Ethical and Privacy Concerns

The use of AI in personalized healthcare with biosensors raises concerns about data privacy and ethical implications. Therefore, implementing secure data handling methods and ensuring compliance with regulatory frameworks is of great importance (Sun et al., 2019).

Chapter 6.4.3 Future Directions

The future of AI-integrated biosensors will be shaped by the development of multimodal systems that combine data from multiple sensor types. Innovations in explainable AI (XAI) and edge computing will make the use of these devices more practical and accessible. Furthermore, the integration of biosensors with Internet of Things (IoT) networks will bring global health monitoring and precision medicine applications to life.

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