TOPICAL REVIEW

Recent progress and applications of gold nanotechnology in medical biophysics using artificial intelligence and mathematical modeling

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Abstract

In this topical review, we will explore and challenge how artificial intelligence (AI) and mathematical modeling apply towards the future in medical applications, focusing on their interactions with gold nanotechnology. There have been rapid advancements towards the applications of AI and mathematical modeling in medical biophysics. These specific techniques help to improve studies related to nanoscale technology. Many works have been published in relation to this topic; it is now time to collectively analyze and review them to assess the contributions these applications made within nanotechnology. Through this review, both theoretical and clinical data is examined for a fresh and present-day understanding. Observations of set parameters and defined equations through AI and mathematical modeling are made to help give explanation towards variable interaction. This review focuses on gold nanoparticle synthesis and preparation via the Turkevich and Brust and Schiffrins one-pot method. From this, findings show that gold nanoparticle size, shape, and overall functionality affect its synthetic properties. Depending on the characteristics within the gold nanoparticle, its ability to maximize light absorbency, wavelengths, and optical densities within the particle is limited. Finding an ideal wavelength (dependent on nanoparticle sizing) allows for higher absorbency of light within the nanoparticle itself. Examining the cellular uptake and cytotoxicity within the nanoparticle is done so via transmission electron microscope (TEM) and Fourier transform infrared radiation (FT-IR) spectroscopy. By manipulating AI and stochastic and diagnostic models, nanoparticle efficiency within precision cancer therapy is set to ensure maximal treatment. Set conditions allow ideal tumor treatment planning, where manipulated nano-probes are used in gold nanoparticle-based therapy. Versatility in nanoparticle sensors allow for multimodal imaging and assistance towards further diagnostic and therapeutic imaging practices. Drawn conclusions will help expand further knowledge and growth for future gold nanoparticle technology research in medical biophysics application using AI and mathematical modeling.

1. Introduction

1.1. Nanotechnology

Nanotechnology allows for a unique approach towards biomedical processes from a molecular scale. With the recent progression in both speed and precision, data collection within nanotechnology is a prominent use in biomedical applications \([1]\). Nanomaterials, with a size range from 1 to 1,000 nm in diameter exhibit several unique properties that differ greatly from those observed in fine particles or bulk materials \([2–4]\). Specific applications of therapeutic nanomedicine within medical biophysics allow for the use of nanoscale materials to help diagnose, monitor, and properly prevent further implications from arising. Nanoparticles have the capability of detecting cancer due to the leaky nature of tumor blood vessels, which enables nanoparticles to penetrate and accumulate in the tumor because of their small size \([5–7]\). This nanoparticle-based drug delivery
system is rising in popularity within medical biophysics due to their effective control and release reservoir. This simply means that they can safely deliver therapeutic agents to injury sites or specific cells, in comparison to other drug delivery methods that are more invasive and damaging to the body [8]. The rapid advances within nanotechnology have led to a deeper understanding towards nanomaterials including stem cell therapy applications, tissue engineering, molecular imaging, and drug/gene delivery and signaling [9]. Within these diagnostic and therapeutic purposes, it is important to maintain a stable and non-reactive nanoparticle by encouraging interaction with active elements such as DNA/RNA, peptides, drugs, antibodies, nucleic acids as seen in figure 1 [10].

In this review, we will highlight the recent progress and applications of gold nanotechnology within medical biophysics through AI and mathematical modeling. We will explore past literatures to obtain a general consensus and understanding towards the growth of nanotechnology with a focus on gold nanoparticles in cancer diagnosis and treatment planning.

Common nanomaterials that are applicable in biomedical applications include gold nanoparticles (Au NPs), liposomes, polymeric nanoparticles and quantum dots [11]. Among these, gold nanoparticles have become prevailing contrast agents as they are a very interesting nanomaterial due to their unique biochemical properties. Gold in specific shares a high atomic number (Z = 79), indicating that gold nanoparticles absorb more photons than soft tissue alone [12–14]. The versatility of Au NPs has provided useful materials within biomedical applications [15]. With the use of both DNA and RNA strands, the Au NPs are able to enter into the cell and assist in gene therapy and drug delivery within therapeutic purposes [16]. The reason why Au NPs are the most widespread and preferred metal nanoparticle of choice is due to their strong physicochemical properties. The overall size and shape ensures a stable change in surface plasmon resonance (SPR), conductivity, and redox behaviour, leading to detectable signals [15].

This detectable signals aid in therapeutic cancer treatment, as identifying these signals aids in imaging. As well, Au NPs act as a platform for drugs and targeting agents to enter desired regions. Helpful in cancer imaging, the Au NPs are able to captivate a higher degree of photon beams, inherently limiting the amount exposed to surrounding soft tissues. With their use in drug delivery and cancer imaging, these radio-sensitizers have been used as dose enhancers in nanoparticle radiotherapy through cone-beam computed tomography [17]. Resulting Au NPs share unique properties including high surface area to size ratio as well as easily modified surfaces with ligands to assist in affinity [11].

Many advantages arise from gold nanoparticle use, including their potency to generate contrast, ease of integrating multiple properties, as well as long circulating times with high payloads [18]. Au NPs are said to be biocompatible and nontoxic, with diverse functionality by all kinds of biomolecules [2]. From the high-yielding properties to great reliability, the synthesis of Au NPs results in dynamic versatility within medical applications. Because of this, Au NPs have gained great potential for various biomedical applications, with several publications made elsewhere. They have been potentially applied towards imaging, drug delivery, and tumor therapy to assist in early detection, diagnosis, and treatment of diseases [11].

1.2. Artificial Intelligence and Mathematical Modeling
Artificial intelligence is a branch of computer science that relates to machines that perform tasks requiring ‘human intelligence’ [1]. Specific AI algorithms such as machine learning (ML) allows the ability to compute large datasets while recognizing the complexity within the detailed patterns. When combined with
nanotechnology, they are instrumental in precision cancer treatment. Numerous studies have already demonstrated the potential of AI in revolutionizing the current schemes of image reconstruction and analysis, image guidance, tumor detection and characterization, therapeutic response and toxicity prediction, and treatment decision-making [19, 20]. Prediction of nanoparticle interactions with the target drug, biological media, and cell membranes, in addition to drug encapsulation efficiency and release kinetics can help optimize nanomedicine formulations [1]. Because of these specific capabilities, AI has become ideal in new biophysical applications (including cancer treatment) due to its high complexity and continuous advancement.

In Figure 2, with the use of AI and ML, Pihlajamäki et al [21] shows a dynamic model towards what a 3-Dimensional (3D) model of an Au NP would look like. When observing nanotechnology within AI, these fundamental concepts shape the future of precision cancer medicine and overall treatment planning for patients.

Along with AI, mathematical modeling is being tested to provide a better understanding towards nanoparticle efficiency within precision cancer treatment. Modeling uses mathematical equations to help describe a system and its conditions. They give a fragmented view by breaking down the system to make better predictions and overall test planning. This approach gives mechanical properties and descriptions of tumors and could be seen as a reliable tool for improving cancer diagnosis and treatments [22]. It is essential towards improving our understanding of the physiochemical and physiological underpinnings of nanomaterial behavior in biological systems [23]. Forms within medical applications include derived equations, formulas, flow-charts, graphical software’s, and many more help pave the way in treatment planning. Based on set parameters defined, different forms of mathematical models adhere to certain conditions (see Figure 3). Where typical distinctions within these models are based on model parameters and types, relation to time, and dimensionality factors.

With this, models within deterministic and non-deterministic forms will be further analyzed and reviewed. Computational (numerical) solution based models using either deterministic or stochastic simulation techniques help calculate model variables and are generally used when the model is fairly complicated [25]. Under the stochastic methods, logistic regression models and Monte Carlo methods are just a few forms used within treatment planning. Monte Carlo methods in particular are typically used as they are considered computationally intensive [25]. Many other forms including linear regression and multiple regression methods lie within mathematical modeling as well.

This modeling has provided mechanistic understandings of observations based on physical principles and helped establish important quantitative relationships [22]. From this, mathematical modeling has become an innovative tool within nanomedicine. Some advantages that stem from this modeling include its ability to produce absolute solutions, and is considered rather fast and easy to understand. Models allow the ability to manipulate a complex system and simplify it into a more comprehensible manner. From this, mathematical models help deepen our knowledge and understanding of certain systems and can further advance the research within them. There are, however, drawbacks as well, including its lack of quantifiable knowledge, lack of available data/methods, and inherent stochasticity of biological systems [26]. The complexity of the model increases with complexity of experimental conditions, so more complications may arise. With recent and continuing advances within research however, much improvement is said to be expected.
2. Synthesis and properties

Regulating and controlling the Au NPs size, shape, and functionality can be synthesized through a variety of methods. Synthetic methods of Au NPs include chemical, photochemical, radiation chemical and thermal methods [27]. Of all the available methods, Au NPs are commonly synthesized under the colloidal method. A colloidal system is a system in which one substance is in the form of particles of different size distributed in another [28]. With the use of a metal precursor, a reducing agent, and a stabilizing agent, it allows for the facile tuning of the size, shape, and optical properties of the nanostructures [29]. Colloidal Au NPs from 15 nm to 50 nm in diameter were synthesized using the Turkevich method [30]. Some nanostructures involved in this methodology include nano-cages, nano-rods, and spheres. These specifically synthesized Au NPs exhibited ideal size and shaping distributions. Colloidal solutions are either an intense red colour for smaller Au NP or a dark yellow colour for larger particles [31]. Optical properties of these gold nanoparticles arise from light interaction, where different sizes result in different pigments of colour in the colloidal solution. The principle of the Turkevich method is based on reducing and preparing metal salts to help modify the spherical size and shape of the Au NPs [32]. The synthesis of Au NP under the Turkevich method is easily performed by direct reduction of the AuCl₄⁻ ion from chloroauric acid, HAuCl₄, with reductant chemicals such as citric acid and sodium borohydride [27]. As well, from Brust and Schiffrins one-pot method, they allow for a scalable approach towards synthesizing Au NPs. This occurs when AuCl₄⁻ salts are reduced by NaBH₄ in solution with ligands [33] (figure 4(A)). Computer-assisted (i.e. ML through AI) designs can help accelerate the synthesis process in a more effective way [34]. Through training ML models, they are able to gain experience from previously performed data to help predict future experiences and their outcomes. Figure 4(B) shows a mathematical relationship between dependency of size on overall number of gold nanoparticles per cell present.

These ML model approaches do not need a solid understanding of specific domain covered but rather, they are able to gain knowledge through past experiments and their respective data collected [33]. The Brust and Schiffrins process occurs when nanoparticle formation of the reduced gold atoms diffuse into the solution. This multi-step process begins when high rate reduction occurs, resulting in the first cluster formation being formed [34]. The second step allows for reduction but at a much slower rate, commonly called coalescence. As it continues to grow, metal ions are incorporated and an electric double layer is formed from this process. In the final stage of reduction, consumption of gold salts occurs and metal atoms grow on the nanoparticles [34].

Another harmless strategy developed for the preparation of Au NPs is the photochemical synthesis that uses UV irradiation instead of a chemical reductant [27]. Multiple advantages arise from this reduction including: (i) controlled reduction of metal ions without excess reducing agents; (ii) the radiation is absorbed regardless of light-absorbing solutes, with the reduction reaction arising uniformly; (iii) the photochemical method can be cost-effective and very convenient [36]. This synthesis can be done in aqueous solutions using macromolecular polymers and dendrimers [37, 38]. It is said that as excess salt is added to the aqueous gold solution, the overall surface charge of the Au NPs become neutral, allowing for irradiation to occur [31, 39]. Through the use of polymers and dendrimers, it helps to neutralize agitation within the gold nanoparticle. A polyamidoamine (PAMAM) is the most studied macromolecule dendrimer that possesses remarkable biomedical properties by targeting particular tumor cells [40]. Protein biomarkers and other biomolecules aid in both stabilizing the
nanoparticle and assisting in detection of cancer and other sought diseases [39, 41]. Gold nanoparticle PAMAMS (Au PAMAM) combine to aid as non-viral transfection agents, helping to encourage colloidal stability and transfection efficiency via in vitro [42]. This surface modification helps to diversify the use of gold nanoparticles within many medical biophysical applications. From this, Polte [43] finds that the Au NP growth is due to both agitation and coalescence, where the aggregation affects overall size distribution.

The apparent chemical properties of gold nanoparticles such as surface chemistry, zeta potential and electron positioning make them very versatile in biophysical applications [44]. Physical properties including size and shape affect overall cellular uptake, where spherical nanoparticles are preferred to nano-rods in comparison. The nanospheres are considered much more stimulatory while nano-rods are considered inhibitory [45]. The spherical shape is ideal due to its high surface-to-volume ratios and low toxicity. Under a laser, the use of irradiation helps to reshape nanoparticles into nano-rods. The mathematical modeling produced in figure 5(A) shows uniform distribution of resonance lines within colloids [46]. After irradiation takes place for the colloidal Au NPs, optical density substantially increases due to nanoparticle properties of high light absorbency. The strong light interactions occur from coherent oscillations of electrons when excited by certain wavelengths and frequency levels [47]. This excitation within the nanoparticle is known as SPR which aids in their surface activity. Nano-rod shapes of Au NPs are ideal for SPR observations, as they maximize tumor penetration while minimizing blood loss [45, 47]. The SPR has a high level of absorbance of the incident light and is generally observed through spectrometry and mathematical analysis. Due to SPR oscillations, both light absorbency and oscillation rates increase, where this rate depends on nanoparticle properties including size and shape (figure 5(B)). Depending on the size of the Au NP, they can absorb or scatter incident light at certain wavelengths based on their SPR.

When examining figure 4(B), the total absorbency depends on wavelength within the Au NPs. The collective SPR oscillations explicitly rely on particle size, with increasing size the plasmon absorption maximum is shifted to longer wavelengths [48]. Finding an ideal wavelength (dependent on nanoparticle sizing) allows for higher absorbency of light within the nanoparticle itself. Maximal absorbency values pertain to greater attenuation allowed for photo-thermal therapy. The ratio of scattering rays to absorption shows increasing rates when it comes to larger nanoparticle size (figure 5(B)) [49]. The SPR are also said to improve the Au NPs magnetic field, which aid in surface detection within diagnostic and therapeutic treatment. The SPR helps to improve the Au NPs ability to absorb visible light. The light absorbed can be converted into heat, which makes it suitable for photo-thermal therapy [50]. Along with SPR, the improvement in Au NP intensity allows for easy analysis of surface-enhanced Raman spectroscopy (SERS). SERS is a significantly new technique for molecular detection by analyzing specific vibrations found in molecules. Raman spectroscopy associated with multivariable algorithms could be a valuable tool for developing a comprehensive understanding towards biomolecular changes and antitumor response to drugs [51]. This uses an ultra-sensing and precise detection signals by breaking into the
molecular level to find biomarkers more excessively for biomedical applications [52]. In comparison to other spectroscopic techniques, SERS is especially newer and focuses mainly on molecular absorption with nanostructures. It is a popular technique due to its high sensitivity at nano-molecular levels. Some advantages of SERS over traditional detection technologies, such as fluorescence and chemiluminescence include sensitivity, high levels of multiplexing, robustness, and ability to perform detection in blood [53]. Through this, tumor cell detection via SERS applications assists in further diagnosis. The complex signals produced use multiple mathematical models including linear regression and multivariate data analysis algorithms [54]. This closely studied modeling allows for precise and selective detection of these vibrations. Through the use of AI, individuals are able to automate specific data analysis [54]. The use of SERS is highly critical to magnify the gaps between nanoparticles (∼1 nm apart) since it enhances the electromagnetic field to make detection much easier [50]. The produced SERS signals within the nanoparticle are closely controlled and related to its overall size, shape and agitation state [55]. Specific and large amounts of available atoms on the surface allow larger detection of signals, improving the overall sensitivity and accuracy in the nano-sensor itself [56].

Infrared radiation (IR) is another method within biomedical applications that allows for diagnosis and molecular imaging of cell functionality. Because of its high molecular specificity, wide variety of sampling, rapid measurements, and overall non-invasiveness, it provides a strong approach towards uncovering information on biological material [57]. Within IR, Fourier transform infrared radiation (FT-IR) spectroscopy uses mathematical modeling to translate raw data within light absorbency spectrums [58]. FT-IR instruments are generally much simpler and built smaller, allowing for easier mobility in comparison to more traditional spectrometers. This technique measures each individual wavelength across the spectrum, allowing for multiplex scanning with many scans completed versus more traditional scanning instruments.

3. Cellular uptake of gold nanoparticles and cytotoxicity

As previously mentioned, many physicochemical properties of gold nanoparticles can affect the overall cellular uptake. Properties including size, surface charge, constituent, and coating chemistries could affect the Au NP aggregation and excitation [59]. Due to their nanoscale size, transmission electron microscope (TEM) is commonly used to observe the interacting electrons. TEM is generally used for imaging at high speeds and high resolution, obtaining record of phase contrast, absorption, and contrast images with high frequencies [60]. High vacuums for TEM imaging may lead to complications and encourage Au NP aggregation. Different cellular mechanisms are involved during the cellular uptake including phagocytosis and pinocytosis [61]. The most common analysis of toxicity in gold nanoparticles takes place in vitro [62]. In vitro pertaining to within the cell culture, where those cultured cells exposed to nanoparticles may face cytotoxicity depending on overall dose exposure. Specific complexity of nanoparticle environments contains protein-supplemented and electrolyte rich cell culture mediums [63].
Figure 6 shows three different mediums made up of proteins and biomolecules, including amino acids (blue dots) and ionic salts (red dots). Cell culture mediums maximize extracellular activity by supplying the cells with nutrients to encourage cell survival, growth, and a main source of energy [64]. By placing the Au NPs in the protein and bio molecular mediums, they can either form stabilize dispersions or destabilize spontaneously when combined [59]. This formation or deformation is dependent upon the protein concentration present, size, shape and level of absorbency of the gold nanoparticle. From this, optimal nanoparticle size and surface chemistry affects cellular uptake and is decided by the interaction between receptor diffusion and thermodynamic forces [65, 66]. Smaller Au NPs need to conjugate to generate enough of this force to allow for stable cellular uptake. It is said that knowledge of dose quantity is crucial towards nanoparticle behaviour, where many drugs that are beneficial at low doses are considered toxic to the cell at high dosages [62]. Efficient drug delivery into tumor cells to increase the intercellular drug concentration is a substantial issue in cancer therapy [67]. Specific drug delivery systems (DDS) have been designed to help mediate elicit effects in the body. These nanoscale DDSs help to maximize drug efficiency in within cancer treatment by using nano-carrier systems to aid in drug control and release. Because of their small sizes, (below 4–5 nm) Au NPs have been potentially found to induce toxicity by penetrating the cell nucleus and binding to DNA directly [68].

Predicting cytotoxicity of nanoparticles has been the most common application of data mining and machine learning in research in nano-informatics [69]. Many predictive methods including multiple regression method, logistic regression models and Monte Carlo method are just a few AI techniques to help determine cytotoxicity of Au NPs. In a study done by Winkler et al [70], the Bayesian neural network and multiple linear regression models helped to determine protein binding to the surface of Au NPs. From all of these simulations, multiple interactions between nanoparticles and the direct cells may induce cytotoxicity. Factors including size, shape, dose control, aggregation state, surface charge and chemistry play crucial roles in understanding the root cause of cellular toxicity [71, 72]. From a study done by Lin et al [73], they examine how larger nanoparticles resist random force fluctuations versus smaller particles that were found to move rapidly, causing aggregation in their intensity levels. Smaller Au NPs lead to higher likelihood of toxicity versus larger sized particles due to higher surface areas in respect to their total mass, therefore increasing likelihood of interacting with biomolecules [71]. Along with proteins, the presence of ions may affect the physical and chemical properties within the nanoparticle. The presence of a negative charge on the surface of gold nanoparticles makes them easily modifiable [74]. Au NPs with a cell-surface charge that is positive may induce and encourage toxicity more commonly than negative or neutrally charged particles [74]. Larger surface area of Au NPs leads to higher absorbency capacities, allowing potential effects on optical interference. This cytotoxic effect can encourage a stress response within the cell and indirectly alter gene expression patterns. Mathematical modeling has demonstrated receptor-mediated endocytosis to be optimal when the nanoparticle contains no localized receptor on the cell-surface [75]. From this, we will further investigate reported Au NPs and their effect on DNA damage.
3.1. Plasmid deoxynucleic acids vector (pDNAs) delivery

Use of gold nanoparticles within gene therapy has become a rapidly advanced stream of cancer treatment planning. Gene therapy is a technology that helps to transfer extracellular genes such as plasmid DNAs (pDNA) or small interfering RNA (siRNA) into target cells to treat gene-mediated diseases [76]. Through the use of Au NPs, they have become effective nano-carriers for pDNA, siRNA, and many other peptides and proteins. The tradition approach in gene therapy involves the delivery of a gene (usually pDNA) to the nucleus of a cell, helping to alter the gene expression of the therapeutic protein [77]. Through delivering DNA in vitro to the targeted cells, it allows for an efficient way to deliver dose through the use of nanoparticles. Some obstacles still arise in DNA delivery, such as properly protecting and releasing DNA into the cells as well as obtaining high transfection rates [78]. Because of these challenges, it is difficult to maintain pDNA conformation during the building phase while maintaining the integrity of the pDNAs roles within the cell. When studying polyethylenimine (PEI)/pDNA polyplexes, the nanoparticle size can be influenced by many factors [77]. PEIs are the most effective carriers for pDNA delivery through either branched (BPEI) or linear (LPEI), where LPEI is more commonly used in biomedical applications [77]. In a study done by Reis et al [78], they measured the encapsulation efficiency (EE) of selected nanoparticles to examine how well the prescribed drug was successfully entrapped within the nanoparticle (known as pDNA-NP EE). This was done through equation 1 shown below. From their studies, they detected high EE rates when observing the effectiveness of pDNA within the nanoparticles. Higher EE rates pertain to a high level of drug penetration with the nucleus itself [78].

\[
EE(\%) = \frac{\text{Total amount of pDNA} - \text{free pDNA}}{\text{Total amount of pDNA}} \times 100\%
\]

With the delivery of plasmid DNA, some obstacles that limit gene therapy persist within the therapeutic application itself. One of the larger limitations in controlling the pDNA binding support with polymers. This is a combination of both polymer and DNA, where they are able to deliver viable DNA to cells and their nucleus [79]. A study done by Kim et al [80], prepared α-polysine (APL) and ε-polysine (EPL) to help improve binding affinities with pDNA and their respective polymers. The results conducted from this study showed that smaller and tighter polyplexes delivered a higher concentration of pDNA into the cell and its nucleus in comparison to larger and looser polyplexes [80]. The complexity with these polyplexes lead to more problems depending on their overall sizes. By delivering pDNA into spherical nanoparticles, one can penetrate with high efficiency and relatively low toxicity [81].

For transmission into specific organs/tissues/sites, local administration of vectors is a useful strategy and can be categorized into a vasculature or non-vasculature route [82]. In order for gene therapy to be useful, genetic material can be transferred via a vector that is the ‘vehicle’ used to deliver the desired gene [83]. Expression of the gene to properly be delivered with the vectors allow for reduction in cytotoxicity. Table 1 displays the vasculature routes, including intra-arterial (ia), intra-portal (ip), and retrograde intravenous routes (riv).

In the study conducted by Noh et al [84], they observed the cellular uptake of how combining Au NPs and DNA through gene therapy influenced the plasmid DNA size and shape. With the use of mathematical modeling, multiple ratio factors were taken into account where larger ratios displayed a higher uptake efficiency increase (figure 7). This study found that there was an enhancement in both gene therapy delivery and efficiency of plasmid DNA when using gold nanoparticles, versus other non-viral vectors. A reduction of cytotoxicity was also found post-treatment where Au NP/DNA polyplexes were used [85]. The size of pDNA was both dependent and affected by Au NP/DNA ratios (figure 7). From this, the use of plasmid DNA through gold nanoparticles to help deliver gene therapy within cell nucleus is more effective with larger scaled pDNA values. The increased potency is due to the enhancement of cellular uptake of Au NP values, assisting the pDNA with drug delivery [86]. Plasmid DNA is a useful treatment plan within gene therapy so that efficient dose delivery will be provided, while minimizing risk of cytotoxicity.

| Administration routes | Target organs/tissues | Vectors          |
|-----------------------|-----------------------|------------------|
| ia                    | Liver                 | Naked plasmid DNA|
| ia                    | Pancreas              | Adenoviral vector|
| ia                    | Hind Limb             | Naked plasmid DNA|
| ia                    | Cecum                 | AAV              |
| ia                    | Brain tumour          | Adenoviral vector and lipoplex |
| ip                    | Liver                 | Lipoplex         |
| riv                   | Kidney                | Naked plasmid DNA|

Table 1. Administration route for targeted gene delivery to specific organs and tissues [82]. Vectors including pDNA, adenoviral vectors (AAV) and lipoplexes (liposomal polyplexes). Where lipoplexes are composed of a cationic lipid, a neutral lipid, and plasmid DNA [84].
3.2. Ribonucleic acids (RNAs) delivery

Following DNA nanotechnology, RNA nanotechnology has rapidly evolved at building programmed self-assembly RNA nanoparticles via in vivo and in vitro [87, 88]. Similar to DNA, RNA is a chain-like biopolymer composed of nucleotide subunits joined to phosphodiester bonds [89]. Computational and mathematical modelings of RNA nanoclusters allow for further use in nanomedicine as a whole. Through the use of gold nanoparticles for drug delivery and treatment, nanotechnology systems may be used to target tumor sites and improve overall RNA delivery to select cancer cells [90]. This makes RNA an ideal candidate for nanoparticle drug delivery. One form of RNA includes messenger RNA (mRNA) which assists in copying and carrying genetic information along. Along with pDNA, small interfering (siRNAs) are a useful delivery mechanism for gene therapy treatment with the use of gold nanoparticles. SiRNA is one of the more popular forms of RNA that interacts with the cell and their cytoplasmic proteins. Delivery of small interfering RNA (siRNA) benefits from existing use of pDNA transfer and delivery. SiRNA allows enormous potential as a therapeutic agent with higher specificity, more effectiveness, and less risk of cytotoxicity versus tradition drug delivery [91]. Nanoparticles can be used as a drug delivery transport for the siRNA therapeutics.

Computer-assisted and mathematical modeling can help with the design of nanostructures and RNA nano-designs, where desired shapes guide the choice of specific building blocks [92] (figure 8). Design of these nanoparticles can aid in ensuring molecular interactions and can be predicted through ML and AI simulations. This computer-aided measure ensures a better understanding towards RNA and nanoparticle interactions, leading to higher success rates and efficient nanoparticle use.
Some problems arise with siRNA-based cancer therapeutics in terms of their effective delivery and overall cellular uptake. The small size and anionic nature of siRNA leads to renal excretion, resulting in a decrease in circulating siRNA directed towards target tissue regions [91]. These limitations with siRNA are being solved through theranostic nanotechnology which allows for better integration of siRNA delivery. Gold nanoparticles in specific are advancing in the loading and delivery of siRNA. By coating the Au NPs with polymers, they can successfully deliver siRNA through electrostatic interactions, without losing circulating siRNA [91].

4. Gold nanoparticle-based therapy

As previously mentioned, gold nanoparticles contain many biomedical advantages towards therapy and treatment planning. Through their specific synthesis, properties, and low cytotoxicity found, the possibility to use these nanoparticles within diagnostic and therapeutic methods has expanded. Gold nanoparticles have become advantageous within chemotherapy and radiotherapy treatment planning strategies. Where radiothermal-chemo therapy strategies are used to control the tumor locally and risk of metastasis, multimodal cancer therapy has increased within clinics [35, 93]. Multimodal cancer therapy has benefited from gold nanoparticle-based use. Due to gold nanoparticles abilities to produce cytotoxic reactive oxygen species (ROS), they can also be applied within photo-thermal and sono-dynamic therapy (SDT), respectively [94]. In photothermal therapy, the Au NPs are able to absorb photon energy and convert it into heat upon laser irradiation which aids in tumor-specific thermal therapy [93]. In a study conducted by Advallan et al [94], they used mulberry-mediated gold nanoparticles (MAuNPs) to monitor metabolic changes during streptozotocin-induced diabetic liver tissues using fluorescence spectroscopy (photothermal therapy). They found that with the gold nanoparticle-based assistance, the MAuNPs were said to be more effective in comparison to mulberry leaf extract (MLE) alone. The results of the study show that gold nanoparticle-based therapy in conjunction with fluorescence spectroscopy and statistical analysis help to monitor and predict responses to therapy well [94]. From this Au NPs can be applied towards radiotherapy through allowing higher tumor sensitivity, allowing for smaller amounts of dose to be prescribed. Smaller dosages allow for less possible risk of overexposure and cytotoxicity within healthy cells and tissues nearby.

Use of Au NPs within photothermal therapy have been discovered and applied to assist hyperthermia within cancer therapy. In a study done by Agnass et al [95], they used mathematical modeling to examine the hyperthermic effects for both in vitro and in vivo applications. Through their study, they found that the modeling allowed them to vary irreversible electroporation (IRE), resulting in improvement of the IRE mechanism. By simulating the heat-generating effect and accessing the degree of hyperthermic effects of IRE, researchers were able to contribute hyperthermal effects of IRE to tumor ablation contributions [96]. Where hyperthermia has been found to enhance and improve overall chemo- and radiotherapy uses. This cancer therapy increases temperatures to 40°C and 45°C causing the tumor to be heated and ultimately leading to necrosis and cell death [97]. This happens through radiofrequency (RF) electrical field absorption potentials of Au NPs have improved the therapeutic efficiency of RF hyperthermia [95]. This thermal therapy use of Au NPs allows for their ability to absorb light due to their local surface plasmon resonance (LSPR) [98]. When incorporating nanoparticles within this photothermal therapy, the increase in temperature triggers nanoparticles to absorb the energy of the hyperthermia source to maximize localized heating [95]. The multi-modal therapy comes into effect when radiotherapy is used on the target region, where healthy tissue nearby is spared due to the thermo-responsive nanoparticles [96]. The increased susceptibility of cancerous cells to hyperthermia is a combination of these targeted gold nanoparticles binding and absorbing light to help increase selective killing of cancer cells [99]. Due to gold nanoparticles strong abilities to absorb light (in the form of X-rays), they help to concentrate radiation absorption within the tumor region, thus enhancing radiotherapy dosage prescribed [100].

With the use of pharmacodynamics (PD) mathematical modeling, we can understand nanoparticle based-therapy efficacy and toxicity [27]. Where nanoparticles cellular uptake of cancerous cells helps to increase therapy efficacy. Through gold nanoparticle-based therapy, these multimodal therapies allow for Au NPs to exhibit stronger cytotoxicity to tumors, while requiring smaller dosages for therapy [100]. The use of gold nanoparticles within photothermal therapy allows for many optical forms of treatment via light transmission, commonly in the form of nano-probes.

5. Molecular nano-probes

Molecular nano-probes arise as a type of nanomaterial, commonly used within in vitro and in vivo diagnostics. Through clinical use, the probes are needed to be efficiently produced, highly sensitive, quantitative, rapid, and able to detect and examine micro-molecules, such as DNA, RNA, and proteins, and/or entities including cancer cells, bacteria, and viruses [101]. When applying gold nanoparticles as nano-probes, they aid in their
biocompatibility, use of Raman spectroscopy, SERS, and photothermic effect/therapy allow for diversity in Au NP applications. These nano-probes act as nano-sensors, by monitoring the close interactions and activity within the body during treatment. Through the use detecting these subjects through light sensitivity, they can be programmed and categorized as ‘always-on’ and ‘turn-on’ (smart or activatable) nano-probes [102]. Due to the broad spectrum of cancers, it is hard to develop a generalized nano-probe for all tumor forms. Through the use of passive, active, or TEM targeting helps to accommodate for the broad range of tumors and their specific sensitivities [103]. To make this efficient, mathematical modelling and ML come into use by programming input parameters such as size, concentrations of conjugates, kinetic constants of association and dissociation of receptors and number of receptors affect the model [104]. This applied mathematical modeling produces analytical formulas, allowing for instantaneous data obtained.

Reactive oxygen species (ROS) overproduction can make oxidative stress and overall damage to intercellular DNA, resulting in damage to cellular uptake and increase cellular sensitivity towards further therapeutic agents and treatments [105]. Nano-probes can aid in regulating this overproduction of ROS by monitoring their production and concentration level.

By regulating oxygen levels, these nano-probes can apply their properties within hypoxic conditions. Use of hypoxic treatment within tumors helps reduce DNA damage caused by chemo- and radiotherapy exposure by limiting pO2 levels to cancerous regions. They have recently been developed due to their easy passage into cells, longer blood circulation, protecting ideal binding of bio-macromolecules and more [106]. Targeted tumors possess impaired oxygen and drug delivery from capillaries and help to regulate pO2 towards cancerous regions (figure 9). Hypoxia acts as a propulsive force in tumor reduction by helping to regulate angiogenesis and apoptosis within the cell. As well, these nano-probes help for targeted delivery of imaging agents, drugs, or dyes.

From their long blood circulating times and relatively small size (<100 nm), nano-probes ensure efficiency in neovaculature regions of tumors, allowing for delivery into disease sites [107]. Through the multimodal use of nano-probes in therapy, their optical use can be easily manipulated and practiced with mathematical modeling and ML programming to maximize efficiency in treatment. Acting as vehicles, these nano-probes are able to span larger areas within the body, allowing for various sensing and signal-generating molecules [107]. Versatility in these sensors allows for multimodal imaging and assistance towards further diagnostic and therapeutic imaging practices.

6. Conclusion

Recent advances of nanotechnology have allowed for expansion within medical biophysics. Applications of therapeutic nanomedicine in this field allow for the use of nanoscale materials to help diagnose, monitor, and properly prevent further implications from arising. Artificial intelligence and mathematical modeling techniques can be thoroughly applied to improve studies related to nanoscale technology. With the use of ML and AI, computer-based parameters and algorithms allow the ability to compute large datasets while recognizing complexity within detailed patterns. These trained ML models are able to gain experience from previously performed data to help predict future experiences and their outcomes. This will aid in future nano-technological use within medical biophysical by pre-programming set parameters to minimize risk of error.

Nanoparticles in specific aid in medical biophysics through their interactions with nucleic acids, peptides, receptors, antibodies, and small molecules. Due to their effective release and control mechanisms, nanoparticles

Figure 9. Illustration of nano-probes for imaging and cancer therapy under hypoxic conditions [106]. Oxygen concentration between normoxia (black) and hypoxia tumor regions (red) are located far away from the blood vessels (green) [106]. With the conditions, areas of the tumor become more hypoxic versus surrounding healthy tissues. Reprinted from [106]. Copyright (2011), with permission from Elsevier.
provide much versatility within therapy use. Au NPs in specific have high potential within cancer therapy, drug delivery, therapeutic and diagnostic purposes. Due to their ideal size, shape, and surface area, Au NPs are versatile factors projecting promising results and assistance. Their ideal cellular uptake and preventative cytotoxicity measures ensure for optimal therapy conditions. Au NPs are and will continue to advance in medical biophysics through control with AI and mathematical modeling. With this topical review, expansion for future nanotechnology research in AI and mathematical modeling is key in order to grow through medical biophysics.

Data availability statement
No new data were created or analysed in this study.

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