

Intelligent Nanocarrier Design and Release Kinetics Prediction: Machine Learning Approaches to Targeted Drug Delivery Optimisation

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1. Introduction to Drug Delivery Systems and the Role of AI

Introduction

Drug delivery systems are a strategic part of modern medical treatments. The ability to reach specific tissues, cells, and even intracellular compartments using tailored delivery vehicles in combination with a multidisciplinary approach allows for the development of safer treatments with minimized side effects. Current advances in the development of multifunctional drug carriers, drug co-formulations, and drug repurposing have led to an explosion of potential therapies for a wide range of diseases, including untreatable ones. A drug delivery system-based approach allows for the combination of such systems in order to form synergistic effects between combined or even sequential treatments, called multimodality, multi-agent, triple, or quadruple therapeutics.

Traditional drug delivery systems are administered to the patient as either once-daily or multiple-daily doses. However, the pharmacokinetics and pharmacology of drugs depend on inter-patient, genetic, or phenotypic variations that form part of both intrinsic and extrinsic variabilities, leading to either no response, a partial response, or even adverse events and the need for strict therapeutic drug monitoring. Personalized medicine, seen for decades as one of the ultimate goals of precise and efficient healthcare therapy, can only be achieved by integrating the personal information of the patients to be treated within the actual therapy, closely analyzing likely therapeutic responses by taking into account diagnostic, therapeutic, lifestyle, and environmental data. In this framework, the use of artificial intelligence (AI)-based solutions seems capable of individually optimizing drug delivery systems or dosages by employing very personal

parameters. AI accomplishes this by developing optimized treatment regimens based on clinical and biological data sets from each patient or even by dynamically adjusting doses in real-time to the individual patient's needs using sophisticated online intelligent systems. In the following, the application of AI has been described to optimize different parameters of the drug delivery system. In section 2, AI is used to adjust doses based on patient data, and in section 3, intelligent systems capable of continuously adding drug until the needed dose is found are described. After the above explanation and definition, the succeeding part develops into typical application examples or case studies that outline what is being performed.

2. Machine Learning Techniques in Drug Delivery Systems

Machine learning techniques can be applied to model diverse systems, including targeted drug delivery, controlled release systems, and several others, to improve drug delivery systems. Both predictive analysis and insights about the current models can be extracted from the results obtained by the use of these techniques. Good state-of-the-art techniques can be used to predict the number of healed patients with different responses, to personalize patient treatment, and can be used to test personalized therapies for novel drugs. Various important biological factors, like biological activity, size, shape, and many other factors, are the important factors that can be determined by using the information present in the data, including only the data of administered dosages and the resulting drug concentration in the body. The efficacy of these techniques lies in the methodology used, such as neural networks, support vector machines, affinity propagation, probabilistic neural networks, and fuzzy clustering, and can also be applied like supervised learning and unsupervised learning techniques.

Some of the supervised learning types, their methodologies, and their applications in the field are also outlined. Some of the popular supervised learning techniques include neural network learning, cascading neural network learning, radial basis function, delayed gain neural network learning, principal component analysis outputs-based clustering, multidimensional or hierarchical clustering, and regression techniques. The predictive analysis done in the field of targeted drug delivery involves the interaction of biological molecules with biological cells. Based on these techniques, one of the most intricate types of drug delivery systems has emerged, called Controlled Release System Techniques. These techniques utilize clustering techniques included in the unsupervised

learning techniques, which are especially helpful in tissue-based and site-integrated therapy, especially peptide, protein, gene delivery, monoclonal antibody application, and many others. At present, many drugs are administered and cared for on the basis of time. Machine learning techniques are widely used in drug delivery systems for developing equipment and systems that would benefit in reducing side effects, drug exposure, and peak levels. The prediction of the number of drug doses as per the ratio of the number of infected individuals to healed individuals in developing a system comprises employing AI-based agent methodology like ANN or neural networks or infusion pumps, which are also known as controlled release systems and TDD. Although time-consuming, these have been considered beneficial, but the major hurdle in technique evolution is the patented drugs.

2.1. Supervised Learning for Targeted Drug Delivery

A popular algorithmic technique for using observational data in targeted therapies is supervised learning. In the context of targeted drug delivery and personalized nanomedicine, this involves training an algorithm to output the best drug carrier, as well as its properties, given a patient's data. This could include, for example, the patient's gene expression signature, phenotypic characteristics of their cells, or their clinical histories. The algorithm can then be used to select optimal nanoparticle designs for each of these patients, with the expectation that these strategies will lead to better treatment outcomes. In the typical setting for a supervised learning algorithm, there are n samples of inputs and labels, with which the algorithm is trained. The algorithm 'learns' to predict the labels by minimizing the difference between its output and the true labels averaged over the training samples. Techniques from supervised learning such as regression and classification have been increasingly applied in recent years to design drug delivery systems. The proposed methods have sought to enhance the outcomes of various therapeutic regimens such as chemotherapy, hyperthermia, immunotherapy, and antibiotic treatment, with a broad range of clinical applications discussed. These studies demonstrated the potential of biomarker-based patient stratification to improve therapeutic tolerance and patient survival. Some remain in preclinical stages, often with experimental proof of concept being conducted in animals. This necessitates large, diverse datasets for efficacy and scalability in order to optimize the resolution of the multi-feature learning approach and the number of biomarker-supported drug dosing strata. Future potential developments in this area may be the move towards patient-

specific treatments that consider the whole spectrum of biological and physiological variables unique to each individual.

2.2. Unsupervised Learning for Controlled Release Systems

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CL-based models, which use data labels, have been previously applied to develop advanced CR systems. However, generating labeled data for AI/ML models can be complex and costly at times. An alternative application of AI/ML is unsupervised learning (UL), which does not require labeled data. Therefore, UL could be used to acknowledge patterns in inherently unlabelable data for the design and optimization of CR systems. Important techniques used in UL, which can be utilized for the design and optimization of CR systems, are clustering and dimensionality reduction.

In some cases, the identification of drug-release patterns from the initial CR prototype formulations could be done using clustering techniques such as K-means, normal distance-based clustering, etc. Later, UL models can potentially help reduce the dimensionality of formulation parameters and demonstrate relationships with different drug release patterns. However, to adequately study UL-derived results, cross-domain collaboration between data scientists and clinicians will become necessary. Studying treatment adherence and therapeutic outcomes can enable model validation as proof of the developed CR system designs. By exploiting these findings, a step toward AI-based development of CR systems is anticipated. Thereafter, combining UL modeling with other AI methods can potentially enhance the CR system research landscape.

Future Research Directions

Extracting hidden formulation-performance relationships from inherently big and complex release profiles while ignoring noise: Learning such complex relationships can facilitate the establishment of next-generation designing paradigms that guarantee the construction of extremely advanced and efficient drug delivery systems. The complexity of the MPS can be overcome using unsupervised model outputs and ultimately employed to model or predict patient therapeutic outcomes. Units will be used to study the health outcomes of patients whose drugs are administered using a healthcare AI model. Furthermore, unsupervised learning models can potentially uncover disease or condition-related health variation in patients due to neglecting their medications, which

are paramount for patient care settings. Integrating unsupervised methodology outputs with supervised predictive models can improve the associated supervised model predictive outcomes. Clustering-based unsupervised models can be helpful in developing unsupervised-based predictive models, which are key to robust and persistent personalized health AI for medication management. Although, until now, unsupervised analytical methodologies have been limited in studying blood pressure and glucose variability profile parameters, this domain has yet to be exploited.

3. Applications of AI in Smart Drug Delivery Technologies

The emergence of AI has broadened the realm of smart drug delivery technologies. Medication error is reduced by embedding AI in the smart drug delivery systems that provide accurate dosage at the right time. Coupling AI with nanotechnology, treatment can be delivered at the cellular, subcellular, or even molecular level inside the human body by actively sensing and monitoring the disease site. AI, in conjunction with IoT in smart drug delivery systems, provides the functionality of remote and real-time monitoring of the inside of the body. AI makes it possible to develop personalized medicine, with dosing and drug release patterns varied according to individual patient responses rather than traditional one-size-fits-all treatment. Currently, many nanotechnology-based active drug delivery systems combined with AI or AI-supported systems are being developed to fight against several chronic diseases, including diabetes, cancer, heart diseases, HIV, and kidney diseases. A number of nano-carrier drug delivery systems embedded with AI have been developed and are commercially available in the drug market. Many AI-empowered wearable devices are in clinical trials for measuring biomarkers in diabetes and electrolytes in heart disease patients. The smart insulin pens, in conjunction with AI, received full commercial approval and were given a positive recommendation in September 2019. Despite significant advancements in exploiting AI in drug delivery-related pharmaceutical technologies, several challenges remain to be addressed before their practical and clinical application.

3.1. Nanotechnology and AI Integration

It is apparent that AI-assisted drug delivery design has promising potential, if combined with nanotechnology, to provide highly improved drugs such as maintaining drug stability, increasing the drug residence time within a target tissue, decreasing unwanted accumulation, controlling drug release at a specific site, minimizing side effects, and

improving therapy efficacy. Nanoformulations created by nanoscaled materials called nanomaterials can realize most of the desired pharmacokinetic and pharmacodynamic goals for a specific drug. Nanomaterials are put into biological systems to deliver drugs efficiently. To date, NPs scaled from 2 to 200 nm are normally composed of a drug, an organic or inorganic carrier, and a lipid, polymeric, or protein surfactant. A diverse range of nanocarriers has been utilized to increase drug delivery efficiencies by improving solubility and stability, prolonging circulation, reducing potential toxicity, and targeting desired tissues, leading to a significant uptake of drugs. Furthermore, smart nanocarriers that respond to environmental changes have been constructed to dynamically modulate release triggering mechanisms. Regenerative medicine and molecular and genetic therapies are also being continuously evaluated for new applications. However, these next-generation medicines are also calling for a new generation of delivery systems that can provide not only targeted transportation but also protection and even assistance in effective cellular and genetic uptake. To achieve this, AI can play a crucial role in the design of drugs and drug vehicles. Moreover, it is expected that personalized treatment will be provided for each unique patient. As it is difficult to demonstrate the successful development of nanomaterials alone at the hospital, in this section, we introduce nanoprodrugs and nanocarriers for successful drug applications in clinical settings. Lastly, we reflect on the positive feedback from patients who have used these drugs, which demonstrates the future prospects for using this method for drug delivery. However, several challenges regarding the use of these nanomaterials remain, such as the prevention of biological barriers and stabilization issues in terms of the nanomaterials themselves. We believe that the future of drug delivery systems will flourish in collaboration with AI and nanotechnology.

3.2. IoT and Wearable Devices for Monitoring and Controlling Drug Release

The control of the release of the drug can be established by using IoT, where by taking the readings of the wearable device, the amount of the drug can be released for the management of diabetes, hypertension, and cancer. Such a system can help doctors in titrating the dose as they have a record of the blood chemistry level of a patient in the usual daily routine. A drug release system for anti-epilepsy is used to reduce the frequency of the drug release and control the epileptic seizure. At any one time, only a certain number of patients are receiving treatment for epilepsy with an antiepilepsy drug. Approximately a portion of these patients are refractory to treatment and continue

to experience seizures. One of the reasons for treatment failure may be in part due to inconsistent circulation or storage of these drugs in patients.

The Internet of Things, wearable, and pleiotropic devices are used in the pharmaceutical field, consisting of drug sensors, image sensors, and real-time communication systems that can respond to nonadherence with feedback control on-dose suggested treatment and dispense it. The system consists of a flexible smart patch with a microelectronic nodule and drug/medicines equipped region. The flexible smart patch for the upper-arm skin is mounted with a temperature sensor and flux to measure physical signals. The vinyl chloride acetate bed is mixed with a heat of reaction and cooled to form a low actuation temperature thermosetting polymer. The wearable sensor patch utilizes a customized dosimeter to deliver the dose into the upper layers of the skin. The drug release of the dosimeter can be controlled to ensure an immediate or controlled release with the collated data transmitted to a mobile phone app and cloud server. Furthermore, a personalized polytherapy regimen that optimally controls the properties in individual cases can be administered by allowing the interactions between the patient's daily routine, health conditions, individual dosimetry needs, and the digital twin using IoT sensors and AI approaches.

4. Challenges and Future Directions in AI-Enhanced Drug Delivery Systems

Despite recent developments in the AI domain, various challenges are being faced in the practical implementation of AI-based drug delivery systems. One of the main issues is the handling of real-time data, which contains multi-level complexities in generating, annotating, and preparing a state-of-the-art infrastructure of quality data. To achieve this, data should be diverse, and as far as possible, real-time, which would be challenging in structured data due to the clinical ethics of privacy. Integrating AI will generate further issues in quality evaluation, as it involves a change in the benchmark illustrative of the gold standard. Moreover, ethical considerations are also a significant hurdle. AI might increase the misuse or mishandling of certain decisions, such as model bias toward the refusal of certain treatments for patients.

Data and ethics aside, the translational potential of AI as a complement to traditional drug delivery methods is up for controversy. Given the broad application of classical strategies, discussing which ones can flourish when combined with AI methods and which ones are simply impractical to succeed is an absolute necessity. Some

conventional methods are just too impractical to improve, given their complexity. A more interdisciplinary approach would be detrimental to the success of these techniques; in the current scenario, pharmacists, AI researchers, dermatologists, biologists, and industry representatives would need to work together. In the near future, we can only hope that a number of advances in AI and IT, along with the development of a regulatory framework, will overcome all these limitations. With newer technology coming up, metamaterial technology is expected to broaden the area of drug delivery, and many researchers are conducting studies to develop AI-based metamaterial design techniques. All we know is that healthcare AI solutions are emerging and have yet to meet their full potential. With constant research and evaluation, we can refine and modify these methods, which shall be useful in enhancing the quality of drug delivery systems.

4.1. Ethical Considerations in AI-Driven Drug Delivery

The introduction of AI in drug delivery offers significant promise. However, there are a variety of ethical concerns to consider with respect to AI. For instance, bias can creep into AI algorithms due to their reliance on outdated, biased, or patterned data. If these biases are not accounted for carefully, they can perpetuate inequalities in access to healthcare. Ethical challenges can also emerge in relation to patient consent and data protection. In order for AI to generate the most valuable insights and solutions, patient data from diverse groups should be used. There are, therefore, questions around transparently sharing the purpose of collecting and analyzing data. Many patients may not fully understand AI, consent to its use, and request to have their data removed from analysis. Similarly, questions around data use and the matter of multi-staged patient consent increase data protection concerns. The problem of ensuring the responsible use of AI in the clinic is another significant ethical issue in AI. There is potential for the automation of medicine and reducing the role of the clinician in decision-making, potentially substituting decisions made based on a doctor-patient relationship for risk stratification from automation.

Additionally, who is accountable if an adverse event occurs due to an error in the AI? In the context of robotic surgery, for example, it is often unclear who holds the legal risk for incidents. Therefore, ensuring how accountability can be split between the developers or users of AI, or the company deploying the tool and managing the algorithm, is

important, and ensuring that there are clear guidelines outlining this is required. In order to ensure that the broadest group of patients benefit from AI-based innovations, and to encourage both health technology and healthcare professionals to act as champions and potential adopters, more work is required to develop solutions to these ethical and data concerns that engage the stakeholders in the field. Clearly legislating the uses and types of uses of patient data and AI may be the purpose of regulators. Finally, engaging AI developers and encouraging ethical discourse can ensure that ethical concerns are built into software and healthcare system development to ensure that true innovation is balanced with responsibility to all. Some potential recommendations for overcoming these ethical concerns are outlined. Some ways to address such challenges and promote an ethical use of innovation include the use of large and diverse datasets, in combination with ongoing engagement and active involvement of both patients and clinicians in the innovation process.

AI has grown rapidly in recent years, and enormous investments have been made in this domain. Although there is still much to learn about how to harness the power of AI, we must ensure that we do so ethically if we are to see more effective treatments reach the patients who need them most.

4.2. Integration of AI with Traditional Drug Delivery Approaches

Integration of state-of-the-art AI methods with traditional drug delivery pathways is much more promising than replacing the latter with artificial intelligence. The philosophy is in favor of the patients, as drug therapy always needs human intervention. Integrating hard medicines with soft care is in line with our views. Existing drug delivery approaches demand a huge infrastructure cost, long training, and the psychology of people. AI can improve them without displacing them. A requirement of AI in nanocarriers is to customize them with other drug delivery organizations so that active and passive targeting is used in tandem. A hybrid system incorporating pegylation of liposomes to enhance the specifically acting effect of NLCs is not unknown. To cater to biological variability in patients, AI-powered hybrid drug delivery systems are likely to emerge in the future. Nevertheless, there are tough challenges facing AI researchers. One is the incompatibility between AI and human behavior. Human clinicians have not been oriented to exploit AI systems together with their clinical judgment and mainly to give them first priority.

Pharmaceutical companies and automation specialists are partnering to develop AI pilot research to uncover frontiers likely to significantly improve patient care. Given this trend, the report calls for the identification of the skills and competencies required to enable drug delivery and manufacturing professionals to interact productively and sustain an AI-powered quality management system. In a decade or so, such thinking and development are likely to shape the work of researchers. The possibility of AI tackling relatively sophisticated issues is likely to persist in the near term. The next section, apart from explaining the integration of AI with the existing drug delivery paradigm, gives an idea of the future direction of drug delivery research. There are certainly some aspects worthy of note that may be the focus for future research. First, the AI-based therapeutic modalities discussed must be aligned with the desired prudent use of AI in health care to not alter the clinical effectiveness and safety of the patient. Also, AI research should not simply confer patient autonomy in the medical process at the cost of proper care of the patient.

5. Conclusion and Potential Impact of AI on Drug Delivery Systems

In this chapter, we have provided a comprehensive review of AI's role in enhancing drug delivery systems. Moving towards the end, it is easier to sum up the discussions and output that the sector carries. Drug delivery systems enhanced by AI technologies can significantly improve the bioavailability of the drug while managing time, cost, and associated toxicity. These capabilities can revolutionize the market by accelerating drug development and regulatory processes. The early-stage preclinical design and development are undergoing substantial changes with AI's integration into drug discovery and dosage optimization. The avenues we discussed indicate the potential of AI applications in the health sector. One of the main advantages of AI is the personalization of treatments. Every individual has different drug responses; what works for one person might not work for another. Some patients are simply 'non-responders' to a particular medication. Through the use of data and machine learning, we can potentially predict the best therapies for individual patients. This is in line with the growing importance of stratified medicine. The fields of AI and health will continue to grow, with impacts not only on current therapeutic areas but also on new drug discovery, development, and treatments for neglected diseases. There are certainly ethical and data protection concerns in these sectors, but we believe that by adhering to stringent regulations and taking extra care, our health and longevity will improve. Time

will tell whether 'AI in Health' is successful in revolutionizing our personal welfare in such a profound manner.