RESEARCH PAPER

Machine Learning Assisted Design and Simulation of Drug Delivery Mechanisms

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ABSTRACT

The integration of machine learning (ML) in the design and/or simulation of drug delivery systems is a rapidly growing area within the pharmaceutical sciences. This review paper discusses how supervised learning, reinforcement learning, and/or neural networks can be used to improve the design of various drug delivery systems including nanoparticles, liposomes, and hydrogels. By using large amounts of data and predictive models, ML can improve our understanding of pharmacokinetics and pharmacodynamics leading to the creation of personalized treatments. Various aspects of ML including feature selection, model training, and model validation are also described. Additionally, a number of innovative applications of ML in real time monitoring and/or control of drug delivery are reviewed, and the importance of experimental validation of computational models is emphasized. Future implications of the combination of ML and drug delivery systems include the potential for fully automated systems that can take into account predictive analytics as well as dynamic biomarker information to improve patient outcomes and reduce toxicity. To achieve these ends, it is clear that there will be a need for a collaborative, interdisciplinary approach to harnessing the capabilities of ML in order to design more efficient drug delivery systems as well as to develop novel therapeutic strategies. In terms of actual drug development, the integration of ML into the drug development process has the potential to improve the speed of the process while ensuring the safety and efficacy of resulting drugs.

Keywords: machine learning, drug delivery, controlled release, nanoparticles, polymeric carriers, PBPK, molecular dynamics, finite element simulation, artificial intelligence, formulation optimization.

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1. Introduction

Advancements in the drug delivery systems have witnessed great transitions in the past few decades. These have transformed the way drugs were initially administered through simple oral consumption and intravenous routes to complex systems such as transdermal and implantable devices[1]. Each form of administration has a different set of goals that include improved bioavailability, and to alter the pharmacokinetic as well as pharmacodynamic properties of drugs, thereby preventing side effects. While traditional methods of administration in drug delivery have had great impacts, they are often insufficient and can fail in certain situations. Therefore, drug delivery systems that can specifically target sites where drug release is required, that can control the release kinetics of drugs, and can improve the drug absorption are necessary.

To increase efficiency and improve the quality of patient treatment, it is required to develop and implement in a clinical environment so called adaptive drug delivery systems, i.e. new drug delivery systems that would enable to treat an individual patient in the best way, i.e. with consideration of specific features of this patient's illness as well as of his or her individual biological features, which may differ significantly from "average human" and are not taken into consideration in case of traditional empirical methods of drug formulation development which are mostly based on so called "one size fits all" approach, i.e. in this approach it is anticipated that one and the same formulation would be effective for treatment of all patients suffering from same illness[2]. As is obvious, such an approach often results in suboptimal results, since individual variations in the pathology of human diseases as well as in human biology can not be ignored. Such variations (which are of great impact on the outcome of a treatment) may relate, for example, to specific features of the genome of a patient, to a specific state of human health of a patient, and to the influence exerted by other medications, which are taken by the

patient at the same time (so called combinatory treatments).

Incorporating machine learning to aid the design and simulation of new delivery systems could provide innovative solutions to many current challenges in drug delivery. New algorithms are being developed which allow the effective processing of large amounts of information from a wide range of biochemical and chemical sources. Using this information to model and predict the behavior of a system under different scenarios has great potential for the rational design of efficient delivery systems that can be customized for individual patients and treatments. The use of to model the behavior of delivery systems prior to clinical testing can also greatly facilitate the screening and optimization of different designs[3].

Simulation of the delivery mechanism by computational models can serve to significantly enhance the design of a system and greatly speed up the development of the system. The more common, traditional methods of testing the effects of delivery of drugs, or assessing the safety of a drug, includes the use of in vivo, i.e. animal studies and clinical (i.e. human) trials. These types of studies, especially clinical trials, are time-consuming and are very expensive. Furthermore, such studies involve considerable risks for test subjects[4]. Therefore, it is very desirable to assess as many characteristics of a system as possible in a computer simulation prior to actual use of the system in vivo. Once a system has been designed on the basis of such in silico data, it is an easy task to test the system in the form of a computer model in order to test the effects of changes made to the system. In other words, by using a computer model it is possible to rapidly test, or design, a system. Thus, by combining design of a delivery system with simulation, the system can be optimized in a fashion that results in the most effective system, for a given intent. Moreover, by using such a strategy, a delivery system can be developed that is of the highest quality in a fraction of the time, and at a fraction of the cost of a system that was developed in the traditional fashion[5].

Another key application for machine learning to enhance the predicted pharmacokinetic and pharmacodynamic profiles, of drugs, to design better drug delivery systems and help in improving therapeutic outcomes for patients. In traditional approaches, predicting the pharmacokinetic and pharmacodynamic profiles, of drugs, are challenging tasks, where several variables need to be considered. Machine learning models can be trained and validated on large datasets, comprising of information from previous clinical studies and biodistribution experiments, which can help in identifying the most critical variables affecting the drug release and absorption[6]. The model thus generated can be used to design and optimize drug delivery systems for specific patient populations and various disease conditions thereby helping in the implementation of personalized medicine.

Monitoring drug release, post administration, in real time, can also be facilitated through the use of smart drug delivery systems incorporating a variety of sensors. These systems could be equipped with sensors that enable the release profile of the active to be continuously monitored. This would then be fed into a machine learning algorithm that enables an assessment of the pharmacokinetics of the drug and the resulting pharmacodynamics to be made. As such, smart systems can facilitate the implementation of adaptive drug release, and thus, of a dosing regimen that takes account of interindividual variability in a variety of patient specific factors, such as blood concentration of the active, and the patient's metabolic rate[7]. This type of dosing is likely to prove highly effective and also to reduce the risk of adverse effects.

The future of the delivery of therapeutic compounds is at the doorstep and the intersection of advanced machine learning methods and sophisticated simulation will result in improved and cost-effective delivery of drugs. This new era of design and improvement of delivery of drugs will have to be understood by individuals involved in drug delivery and will have to understand the complex relationships involved in design of delivery systems, advanced simulation methods and the evolving drug delivery landscape. The end result of the intersection of these powerful tools is the potential to design and develop novel and efficient delivery systems of improved precision for therapeutic compounds to improve human health.

2. Overview of Drug Delivery Mechanisms

With advances in new drugs being developed to combat various diseases, it has become important to look into the delivery of these therapeutics. This overview is designed to explain some of the more common methods of drug delivery and to emphasize their importance in current pharmaceutical research. Conventional delivery systems such as oral, subcutaneous, or intravenous are commonly used to administer drugs, which are then distributed throughout the body by the systemic circulation. Although many drugs have been prescribed for a variety of ailments, there are many problems with conventional systems of drug delivery, for example, short half-lives, variable bioavailability, and failure to act locally at the site of disease[8]. Thus, in order to combat these problems, many advanced methods of drug delivery have been designed and are currently being investigated. Controlled release delivery systems have the potential to enhance therapeutic efficacy and safety by providing constant levels of active moieties for extended periods of time. These delivery systems are often made of biodegradable polymeric materials, which provide advantages over conventional systems by ensuring that the drug is delivered in a controlled

fashion while minimizing the potential for environmental pollution and patient inconvenience[9]. In addition, advanced systems of drug delivery that include targeted, and stimuli-sensitive systems have the potential to greatly enhance therapeutic outcomes and patient safety. To realize these potentials, it is necessary to examine each system in greater detail, as well as to understand the interplay between the various systems that are currently being used. By studying these different methods of delivery and their interplay, it is possible to design an array of delivery systems that are able to take full advantage of newly developed drugs in order to provide optimum therapeutic results for patients.

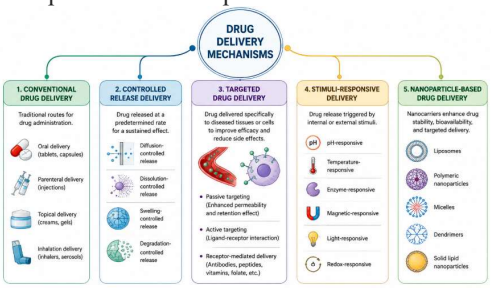

Figure 1. Overview of Major Drug Delivery Mechanisms

Figure.1. illustrates the major drug delivery mechanisms used in pharmaceutical research. It includes conventional, controlled release, targeted, stimuli-responsive, and nanoparticle-based drug delivery systems. These mechanisms help improve drug stability, bioavailability, controlled release, and site-specific therapeutic action. Conventional systems of drug delivery have been the mainstay of most pharmaceutical treatments. Oral, subcutaneous or intravenous administration and reliance on the drugs entering the systemic circulation with subsequent distribution to various sites within the body have been typical features of most conventional systems of drug delivery. The main drawbacks of conventional systems of drug delivery are short half-life of drugs, high first pass metabolism, low and variable bioavailability, unsatisfactory and variable duration of action and inability to provide localized action[10]. These limitations of conventional systems of drug delivery necessitate the development of alternative approaches of drug delivery. Moreover, conventional systems of drug delivery do not allow localized action of drugs and this results in increased exposure of drugs to rest of the body with resultant increase in risk of toxicity at sites away from the site of action (off-target toxicity).

For years conventional systems of drug delivery have been the main method of administering most drugs. The administration of most pharmaceuticals are given via oral, subcutaneous or intravenous routes and depend on the body's circulation to distribute the product throughout the body. Although conventional methods of administration have been proven time and time again to be safe and effective for most diseases, they are not without their limitations[11]. These systems of administration do not allow for adequate localized effect and can result in high levels of systemic exposure thereby causing toxicity to cells and tissues that are not the intended target. Also, most drugs are metabolized rapidly by the body, have a short half-life and have variable bioavailability, all of which affect the duration of action of the pharmaceutical and can cause peaks and troughs in the blood levels of the drug. In addition, many of the most effective drugs for treating chronic diseases, such as diabetes and cancer, require frequent administration, resulting in patient non-compliance and increased cost of treatment.

Another strategy currently used is Targeted delivery. There are many instances within the pharmaceutical market where the effects of a medicine could be amplified if it were distributed to specific areas within the body. The key for the development of Targeted delivery systems is to discover the most appropriate targeted agent. The targeted agent could be a type of molecule (ligand) which binds to specific targets (receptors) found on the surface or within cells and the Targeted delivery system can then be conjugated to this. One of the largest areas for application of Targeted delivery systems is in cancer therapy[12]. Chemotherapeutic agents are currently used to treat all cancers but can also have severe side effects on healthy cells. By linking a chemotherapeutic agent to a molecule that only binds to receptors on the surface of cancer cells, the agent is able to penetrate and act upon only the cancer cells reducing the potential for side effects[13]. Furthermore, there is also great potential for the incorporation of imaging modalities into Targeted delivery systems, allowing the delivery of drugs to be tracked and also monitored for effectiveness in the treatment of disease.

Recent innovations in drug delivery offer stimuli-responsive release systems. These release agents can be designed to respond to various internal (pH dependent, temperature dependent, enzyme sensitive) and external (light, magnetic field) stimuli. In particular release systems offer greater control over the site of action and the amounts of active agents required. Release of pharmaceuticals from nanoparticle systems can be modified to respond to various internal and external triggers within the body thereby improving therapeutic agents and reducing their potential for causing adverse effects[14]. The local release of chemotherapeutic agents from nanoparticles provides an ideal system for tumor-specific release of anticancer drugs within the tumor microenvironment (pH, enzyme profiles). This type of system can allow for greater concentrations of anticancer agents to be delivered to the site of action

thereby increasing the therapeutic ratio for these agents.

Nanoparticles are used for all sorts of applications in drug delivery, because of the flexibility in the surface, size, shape, and composition to achieve the required drug distribution, uptake by cells, and release of drugs. Many nanoparticles can encapsulate drugs, including conventional small molecules, and biologics. Polymeric, liposomal, dendritic, and other classes of nanoparticles are investigated for controlled release and for targeted delivery[15]. As the main drug characteristic is the low water solubility, many drugs are poor water-soluble drugs and require solubilizing tools, like drug delivery systems. The increased bioavailability is of course very attractive, but in particular, modifications on the surface of the nanoparticles to attach targeting moieties enable a very specific recognition of tumor cells, or other cells that are affected by a disease, with therapeutic index.

3. Machine Learning in Drug Delivery Design

Artificial intelligence (AI) and Machine Learning (ML) have recently emerged as innovative tools, which are expected to revolutionize drug delivery in the near future. Indeed, by utilizing "smart computational methods" in the early stages of drug design, it is possible to develop a new system of "intelligent drug delivery" that significantly enhances the efficiency and efficacy of existing delivery systems and greatly reduces the time and financial costs associated with the conventional drug development process. ML has the unique capability of analyzing complex data sets and of "learning" from them to make highly accurate predictions or to develop models that represent the relationships that exist between input data and output variables. Furthermore, once a model has been trained and validated using a "training set" of data, it can be used to make predictions on entirely new data that have not been previously seen. By applying these characteristics to the large amounts of data that are generated during the drug design process, it is possible to uncover hidden patterns and relationships that would otherwise remain "invisible" to the human researcher[16]. In this regard, ML is expected to be one of the most powerful tools in the field of drug design in the future.

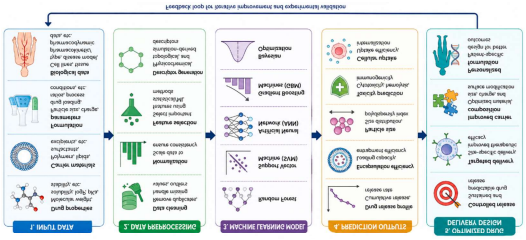

Figure 2. Machine Learning Workflow for Drug Delivery Design

Figure.2. shows the machine learning workflow used for drug delivery design. It begins with input data and preprocessing, followed by ML model training and prediction of drug delivery outcomes. The final stage shows optimized drug delivery design, including controlled release, targeted delivery, improved carrier composition, and personalized formulation. To make the best use of the vast amount of data that is typically generated by drug design processes, ML has the unique capability of enabling the optimization of drug delivery systems, i.e., of drug formulations and the corresponding drug delivery systems. By predicting the pharmacokinetic and pharmacodynamic properties of a drug candidate in advance of clinical trials, ML can support the identification of the most efficient drug candidates and the corresponding formulations[17]. This can also be used to predict the effects of various types of drug delivery systems, such as nanoparticles, liposomes, or hydrogels, on drug stability and on release profiles. Thus, ML supports the development of the most efficient drug delivery systems, i.e., of the most efficient therapeutic effects and the best safety profiles[18].

Machine learning (ML) techniques have been categorized as supervised, unsupervised or even deep learning, based on their individual roles in the process of formulation and design of drug delivery systems. For instance, the ability to utilize large amounts of historical information and thus predict a variety of properties of potential candidates for drug therapy have seen Support Vector Machines (SVMs) and Random Forest Models widely used in a number of drug discovery applications for regression. Cluster analysis has been applied to identify key features of the molecular structures of drugs in order to be able to distinguish between compounds of interest and those that are not. More recently, large datasets from high-throughput screening have been addressed by the growing field of deep learning (DL), often modeled as a sub-space within a very-high-dimensional space in order to simplify the modeling process, identify relationships that would otherwise go undetected and to greatly accelerate the process of drug candidate identification and the associated evaluation.

Data collection is paramount in applying ML to drug delivery design. The more high quality data one can gather, the better ML models will perform. Sources of data for drug delivery system design include: data from experiments conducted in laboratories to design delivery systems, data from completed clinical trials for currently approved drugs, and data from a number of pharmaceutical databases. An important step to ensure that collected data is of maximum use is data preprocessing: this can include data normalization, feature selection, and reduction of dimensionality to name a few[19]. While a significant challenge for those who wish to apply

ML to drug delivery design, the last few years have seen major advances in the field of computing as well as in the open-access publishing of large datasets needed to train robust ML models.

Predicting drug release is one of the most promising applications of ML in the design of delivery systems. By simulating the release of active substances from delivery systems in various environments, and by forecasting release profiles over time in different biological environments, it is possible to optimize a formulation before the start of preclinical trials and reduce the risk of any adverse effects during clinical trials[20]. In this sense, release modeling enables the development of safe delivery systems that can be designed to release their active ingredients in a way and at a time and place in the body that is optimized for therapeutic effects and minimizes any adverse effects.

The author hopes that with Machine Learning Drug Delivery will revolutionize in short time period to design drug with rapid efficient cost effective manner by developing safe and effective formulations using delivery system. Thus, the large collection of sophisticated algorithms of ML can be made useful to design various advanced pharmaceutical formulation using large amount of data, making accurate predictions by establishing correlation of the released drug with its varied applications. The author of this review further states that this formidable task could be possible only with constant growth of new techniques of ML, processing data. Thus, review of current state of affairs reveals, use of intelligent computational tools is now imperative for developing successful formulation in the rapidly advancing Drug Delivery Field to carry safe and effective drugs to the site of action for cure of various disease with improved patient comfort and successful treatment.

4. Simulation Methods for Drug Delivery Systems

Pharmaceutical sciences are significantly impacted by the drug delivery system (DDS) design and optimization by computational modeling. In DDS design and optimization, simulation models such as molecular dynamics simulation (MDS), computational fluid dynamics (CFD), and finite element analysis (FEA) are very powerful. These computational models can describe in detail molecular interaction, fluid behavior, and material structure, which are crucial for design and optimization of DDS. Molecular dynamics simulations have become a very powerful tool for the study of drug-polymer interactions at the atomic or molecular level. The technique allows researchers to study the movement of atoms and molecules over time, enabling the researchers to gather a great deal of information about the molecular system under study. This information can include details on the stability of the system as well as the conformations that the molecules can take. For the design and optimization of drug delivery systems, the study of drug-polymer interactions is critical and the results obtained from MDS can be used to optimize the formulation of nanoparticles and liposomes. For example, it is possible to predict the release of a drug from a delivery system by a simulation of the interaction between the drug and the polymer of the matrix, as well as the effects of environmental conditions, such as temperature and pH, on the stability of the drug. In addition, the results obtained from MDS can be used to determine the critical parameters which control drug release, such as diffusion coefficients and binding affinity. The information thus gained can then be used to design an optimal delivery system for a specific drug.

Computer models that simulate the behavior of liquids and gases are commonly used in pharmaceutical science to study transport phenomena, and in particular, to understand how substances are dispersed and absorbed within a biological system. Such models, developed using computational fluid dynamics (CFD), are particularly useful in predicting how a drug will behave within a drug delivery system and how it will interact with its environment prior to, during and after administration. An example of the use of CFD is in the development of injectable systems, where it is used to model the jet of fluid released from a syringe needle and the subsequent dispersion of the drug in the surrounding tissue. The behavior of the fluid can be affected by a number of factors including the properties of the fluid, the geometry of the system and the form in which the drug is administered. A number of different models can be employed to simulate such behavior, and these can be used in isolation or in combination with each other to understand the effects of different parameters. The results from such models can also be compared with data obtained from in vivo studies to improve the accuracy of the model and to develop a more complete understanding of the factors that affect the distribution of drugs within the body.

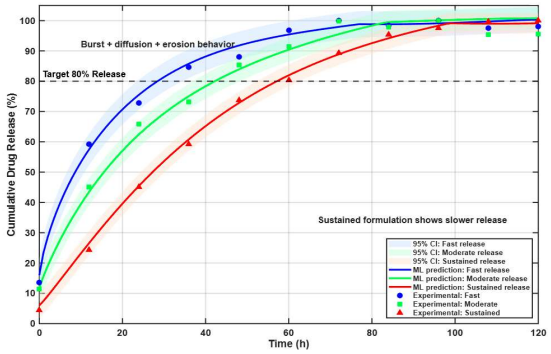

Figure 3. ML-Assisted Simulation of Controlled Drug Release Profiles

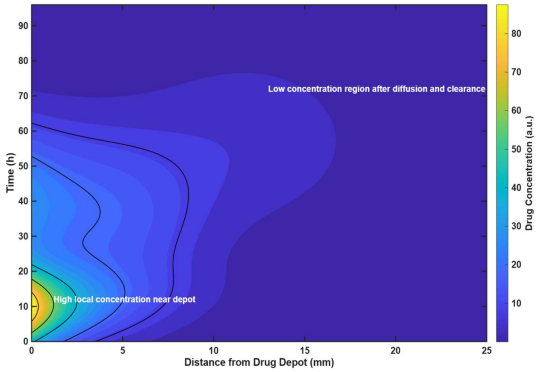

Figure 4. Simulated Spatiotemporal Drug Diffusion in Tissue

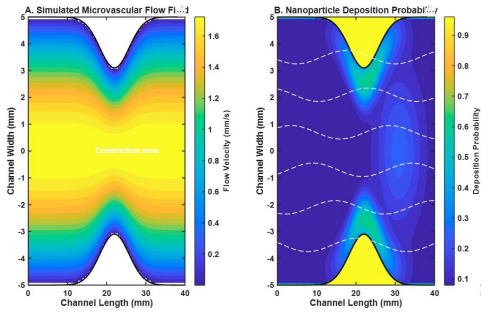

Figure 5. CFD-Inspired Simulation of Nanoparticle Transport and Deposition

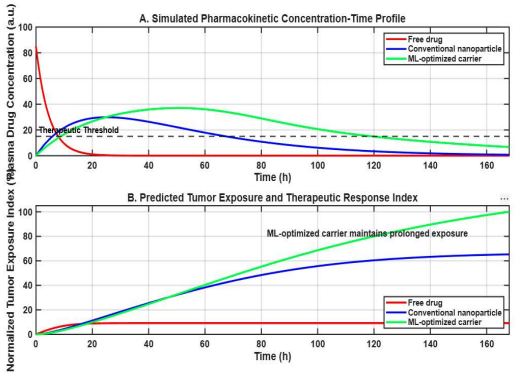

Figure 6. PK/PD Simulation of ML-Optimized Drug Delivery Performance

Figure 3 presents ML-assisted simulated drug release profiles for fast, moderate, and sustained delivery formulations. The figure compares predicted release curves with experimental-like data points and confidence intervals. It shows that the sustained formulation provides slower and more controlled drug release over time. Figure 4 shows simulated spatiotemporal drug diffusion from a drug depot into surrounding tissue. The concentration is highest near the depot and gradually decreases due to diffusion and clearance. Figure 5 illustrates CFD-inspired nanoparticle transport and deposition inside a microvascular channel. Figure 6 compares free drug, conventional nanoparticle, and ML-optimized carrier delivery using PK/PD simulation.

Finite element analysis (FEA) of mechanical behavior and structural integrity of DDS is of growing interest. The majority of DDS components are composed of polymer(s), which are generally subjected to deformation, and in some cases to failure under external load (for example, during administration, handling, or storage) or under influence of environmental conditions (such as storage at elevated temperature). For many biodegradable polymers used in DDS, structural integrity at physiological environments over the period required for drug delivery is a major concern. By performing FEA on geometric models of DDS and on models of individual components, researchers can predict failure, such as tensile or compressive fracture, or material fatigue. In addition, FEA can be used to evaluate the extent of mechanical deformation that a polymer component is likely to undergo under a variety of external conditions, thus optimizing DDS designs to minimize structural failure while maximizing drug delivery efficiency.

Thus, MDS, CFD, and FEA techniques offer an alternative framework of modeling for the DDS design and optimization. These tools give a deep insight to molecular, fluid-dynamic and mechanical processes, which govern DDS behavior. In vitro and in vivo results are integrated into computational models allowing predictive evaluation of DDS performance at the interface between deliverer and biological medium. Therefore, MDS, CFD, and FEA enable a multi-scale approach to DDS development that leads to the new creative solutions to a variety of clinical problems, to enhance therapeutic effects and to design novel drug-delivery systems tailored for individual patients within the scope of personalized medicine. Further improvement of these techniques and their better interaction with experiments will open up new possibilities for the computer-aided designing of new drugs and optimizing existing drug-delivery systems for solving complex medical problems.

5. Machine Learning-Assisted Design Framework

The optimization of drug delivery systems is one of the biggest challenges in pharmaceutical research and development today. The use of machine learning (ML) for improving the efficiency and efficacy of drug delivery systems could play a transformative role. The goal of this paper is to present a structured Machine Learning-Assisted Design Framework for improving drug delivery by optimizing existing systems. The framework consists of a sequence of steps, namely, data preparation, feature selection, and model implementation, which will guide researchers that are interested in improving current drug delivery systems by applying AI tools. The first step of the framework corresponds to the data preparation task. In drug delivery the data is typically derived from in vitro experiments, clinical trials as well as from computational models to simulate several aspects of the drug delivery process. The data should be checked for accuracy

since any inaccuracy could be propagated throughout the rest of the steps in the framework and have a large negative impact on the performance of the resulting model. The data must also be normalized/standardized to all be on the same scale/dimension. There are also missing values in the data which must be imputed or the corresponding samples removed from the analysis. Once the data has been prepared it must be divided into three different datasets which will be used for training the model, validating the model and testing the model to see how it performed on previously unseen data.

The feature selection step is used to choose the most relevant variables that can be used to influence the drug delivery system's efficacy. The number of features that are typically used in drug delivery systems range from the drug's physicochemical properties, the properties of the carrier, to the biological properties found in the therapeutic environment. Techniques, such as univariate analysis, recursive feature elimination, and tree-based methods, can be employed to rank the importance of the features, thus, helping to select the variables that can be used as features to improve the model's performance. By selecting the relevant features, several goals can be achieved: (1) reduce the dimensionality of the data, (2) enhance model interpretability, (3) prevent overfitting, and (4) improve model computational efficiency. Importantly, feature selection should result in a set of features that can collectively describe the mechanisms underlying the drug delivery system while removing any noise and redundancy.

After the design process, the selected models can be implemented. There are several Machine Learning algorithms that can be used for the optimization of drug delivery systems, depending on the type and quality of the available data and the goals of the design process. Most algorithms are supervised, meaning that they can be used for regression (e.g. for predicting the release profile of a drug) or for classification (e.g. for predicting the response of patients to a particular treatment). Commonly used algorithms are regression models (e.g. linear models, Support Vector Machines) and clustering models (e.g. K-Means, Principal Component Analysis). A detailed description of each algorithm and their application is out of the scope of this paper.

The next step in the framework is to train the implemented model to make the best use of the selected features from the prepared data. The process of training the model consists of several parameters called hyperparameters, which need to be tuned in order to get the best results for the model. Usually, a large number of experiments are conducted to test the different combinations of the model's hyperparameters to find the best combination that results in the least error. In addition to this, cross-validation is one of the most common techniques used to evaluate the performance of a model on a given dataset. The advantage of cross-validation is that it tests the model on a number of different data sets, which in turn tests the model's ability to generalize to new, unseen data. It helps us to get a feeling of how well the model will perform on new data that has not yet been used for training. After training the model, it is also important to test the model's performance on new data in order to get a feeling of how well the model will perform on new data, and the performance of the model is usually measured by a set of specific metrics. The most common set of specific metrics used for evaluation of a model's performance include accuracy, F1-score, and the area under the receiver operating characteristic curve (AUC-ROC).

This data needs to be compared against the predicted values made by the model in order to assess the degree to which it accurately predicts the results of drug delivery, and for the identification of improvements that need to be made. These can be measured by the degree of accuracy, the F1-score, and the area under the receiver operating characteristic curve (AUC-ROC) of the results, and by using these measures it can be established whether any changes to the model are having the desired effects. In conclusion, the structured Machine Learning-Assisted Design Framework introduced in this article can be used by researchers for designing and improving drug delivery systems. The framework presented includes steps for data preparation, feature selection and a guide for the implementation of a wide variety of models that can be used for different drug delivery optimization goals. The framework can be used to improve our current drug delivery systems and to design new ones, thus ultimately improving patient treatment.

6. Applications of ML-Assisted Drug Delivery

Artificial intelligence and machine learning (ML) have recently gained immense attention and have brought considerable improvements in the majority of scientific disciplines. In the field of drug delivery systems (DDS), the innovative techniques have been mainly focused on the design and improvement of nanocarriers. Nanocarriers represent a highly efficient and advanced system of drug delivery, which can be divided into several groups including polymeric systems, liposomes, micelles and hydrogels. All of these systems have been exploited for effective drug delivery and have been found to improve the therapeutic effects of drugs and to reduce their side effects by minimizing their toxicity.

A vast library of potential compounds exists within chemical space, yet for the large majority, limited or no information regarding their utility for specific applications exists. Historically, experimental methods were used to determine the behavior of novel compounds within DDS; however, by utilizing historical data to inform the design process

using computational models, such exhaustive searching is avoidable. Many types of machine learning exist for nanocarrier design, for instance, supervised learning can be utilized to predict whether or not a polymer has the necessary properties to serve as a DDS (e.g., biocompatible, biodegradable, drug-encapsulating), by identifying a large dataset that includes the wide variety of physicochemical characteristics that a variety of different polymers have. Using such a large library of potential materials, an ideal candidate for the delivery of a specific drug can be chosen within a relatively short period of time prior to experimental verification, increasing the rate of drug delivery system design.

To better engineer drug delivery systems, researchers have recently leveraged large data sets to identify complex relationships between polymer form and function, thereby selecting the optimal polymeric system for delivery of specific drugs. For example, utilizing vast databases, which are comprised of information pertaining to the diverse array of polymers that have been previously explored for DDS, can be used to facilitate the design of novel, 'smart' polymeric nanocarriers. In addition, the empirical selection of certain polymers can be averted through ML that forecasts the performance of various candidate polymers, prior to experimental verification. Ultimately, by rapidly, and accurately design novel, DDS, that can be tailored for specific applications, and possess improved pharmacokinetics, the therapeutic potential of drugs can be greatly enhanced through the application of ML to polymeric nanocarriers.

Liposomes. Spherical, lipid vesicles are commonly used for the encapsulation of drugs and have seen improvement with the help of machine learning in the design of their shells and the improvement of their efficiency in formulations. Often, liposomes are developed using trial and error methods which are time-consuming and do not deliver optimal results. Therefore, it is of great value to develop models that can predict the behavior of vesicles and improve the interaction of liposomes with drugs. A particularly promising approach is provided by reinforcement learning which supports the development of the optimal formulation of liposomes by iterative testing and learning from the results. This enables the creation of optimal liposomes for specific applications.

Similar approaches have also been recently used to optimize design of micelles. In the case of these amphiphilic surfactants which self-assemble in aqueous solution to form nanoscale aggregates that are able to solubilize drugs and deliver them to the required site, predictive models have been used to take into account parameters that describe their aggregation behavior, for example, the critical micelle concentration (CMC) as well as the hydrophilic-lipophilic balance (HLB) of the molecule. Utilizing these, in conjunction with the properties of the drug of interest, a ML model has been utilized to predict the properties of micellar formulations in terms of maximizing loading and the level of release over a set period of time. Furthermore, ML models have been designed to predict optimum changes to the micelle's composition in order to enhance bioavailability when delivering drugs via the oral route.

Another important system for DDS is hydrogels. Hydrogels are crosslinked networks that have the ability to hold large amounts of water. These systems are attractive for controlled drug release because they are able to swell, which enables them to release a drug in a sustained fashion. By using ML for the synthesis of hydrogels, it is possible to predict how the combination of crosslinking agents and polymers and their ratios will affect the mechanical properties of a hydrogel as well as the drug release. In this way, hydrogels can be 'designer gels' that release their therapeutic payload over extended periods of time at the site of action to maximize the bioactivity of the compound and to minimize any side effects.

7. Challenges and Limitations

By leveraging Machine Learning (ML) in drug delivery design new avenues are opened up for the pharmaceutical market. At the same time, however, several limitations and obstacles have to be removed. The restrictions to current uses of ML in drug delivery design are caused by restrictions to uses of ML in general, and thus restrictions to uses of ML in pharmaceutical research and development. The same four limitations to uses of ML in general, therefore, also apply to uses of ML in drug delivery design: (1) restrictions to data, (2) restrictions to models, (3) restrictions to interpretation, and (4) restrictions to simulation.

Huge difficulties and limitations still exist for all along the entire process of integrating ML into drug delivery design. While sufficient data of very high quality remains the most basic prerequisite for meaningful ML applications, many currently available data in this field consist of large, heterogeneous, non-consistent data sets. They give rise to unstable "learning" with poor generalization ability. During the process of learning from data, it is difficult to account for great numbers of different variables, experimental conditions, and patient's characteristics, such as demographics and different physiological parameters. Also, the large amount of available data is not rich enough. In fact, many of currently available data sets are very sparse. Therefore, it is very difficult to train the model to be able to accurately predict the pharmacokinetics and the pharmacodynamics of the drug delivery system in the whole space of input variables. In addition, there is another very serious problem. The process of adding annotations to the data and of data curation still represents a huge challenge. This challenge will

cause errors in ML model, which will be much amplified by the process of training the model. Such amplified errors will lead to very poor performance of the model. Such a performance will not be able to fulfill any requirements in drug delivery design. When accurate models are generated, they must also be accurate for the specific application. Most ML models are sensitive to the choice of algorithms and features, and simple models cannot capture the non-linearity in biological systems, whereas over-complex models can over-fit the training data and fail to generalise to new, independent data. A number of measures have been used to assess the performance of models, but these are often not sufficient to give confidence that the model will perform well in real-life, clinical situations. Indeed, as new techniques are continuously being developed, models must be validated against a constantly increasing body of data as well as emerging clinical results, which can be time-consuming and require considerable resources.

Lack of interpretability of results is another obstacle preventing the effective use of ML in DDS design. Results of virtually all ML models, especially those highly complex, remain a black box. They do not explain the impact of individual input variables on the respective results. Lack of interpretability of results is a serious problem as biologically meaningful results are required in order to implement results of models in design of DDS in a fully personalized manner. It is well known that results of virtually all ML models remain a black box and as such are not suitable for implementation in health care system. This problem is more pronounced for models that rely on deep learning techniques. Several limitations of ML models need to be addressed by overcoming current constraints of simulation (i.e., computational resources and data) for the translation into real life application. Especially complex biological systems, such as drug delivery systems, are often not able to be simulated sufficient to forecast variations that typically occur in real life situations. The simulations of drug release, of transport through biological barrier systems, as well as of distribution and degradation of drugs in the body and of interaction of drugs with tissues and cells all include stochastic elements. Sufficiently accurate simulation of such complex systems within acceptable computation time is an enormous challenge. Therefore, novel computational methods are needed to efficiently simulate such systems and thereby allow for translation of results into real life situation.

However, while the integration of machine learning in drug delivery design has the potential to revolutionize many therapeutic designs and become a mainstay in future pharmaceutical research and development, there are many challenges exist with current ML and various limitations that must be addressed. These limitations relate primarily to current data quality and lack of model accuracy that in turn are generally related to the model itself. There are also limitations to how the results can be interpreted. The primary challenges to using current models for simulation exist with the translation to real-world delivery systems that require significant resources for complex systems and various biological interactions that are often governed by stochastic processes and the need to simulate these processes with high fidelity. If ML models are to be integrated into drug delivery systems, then they must be able to accurately and predictably model the pharmacokinetics and pharmacodynamics and simulate the various drug delivery systems and interact with biological systems in a manner that effectively predicts clinical performance of a variety of drugs in a variety of different scenarios. Challenges to using ML currently in drug delivery system design exist and need to be addressed with the hope that in the future the integrated use of machine learning and drug delivery will be a mainstay in future pharmaceutical research and development.

8. Conclusion

Integrating machine learning into the design and simulation of drug delivery systems can revolutionize current treatments and maximize therapeutic outcomes by allowing for a design based on complex interaction models. The large number of possible system design variations can be evaluated by using machine learning to model interactions between the system and its environment, enabling for the first time the design of systems to maximize their efficiency and improve pharmacokinetic profiles. Many problems currently facing the use of machine learning to aid in design of drug delivery systems such as those posed by the lack of sufficient data to train or validate a model, and the lack of sufficient interpretation of predictions, can be addressed. Furthermore, rapid advancements in both computational resources and sophisticated methods are underway that are specifically suited for modeling and simulating a wide variety of novel drug delivery systems in detail for the first time. In the future, as a result of continued advancements in computational power and new algorithms that more readily lend themselves to modeling of complex biological systems, simulations can be used to test and aid in the design of individualized systems of delivery for the treatment of patients from around the world. Researchers in all areas will benefit from an increased interaction among computational scientists, pharmacologists and clinicians which will aid in not only refining current models of drug delivery, but also aid in the development of innovative new strategies. Therefore, in the end, machine learning has the potential to transform the field of drug delivery to more readily aid in design of systems of efficient, targeted and patient-specific

treatments with the potential to aid in the treatment of patients from around the world and lead to better health care for all.

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