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To explore the pharmacological mechanism of action using digital twin

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ABSTRACT

With the advent of medical technology and science, the number of animals used in research has increased. For decades, the use of animals in research and product testing has been a point of conflict. Experts and pharmaceutical manufacturers are harming animals worldwide during laboratory research. Animals have also played a significant role in the advancement of science; animal testing has enabled the discovery of various novel drugs. The misery, suffering, and deaths of animals are not worth the potential human benefits. As a result, animals must not be exploited in research to assess the drug mechanism of action (MOA). Apart from the ethical concern, animal testing has a few more downsides, including the requirement for skilled labor, lengthy processes, and cost. Because it is critical to investigate adverse effects and toxicities in the development of potentially viable drugs. Assessment of each target will consume the range of resources as well as disturb living nature. As the digital twin works in an autonomous virtual world without influencing the physical structure and biological system. Our proposed framework suggests that the digital twin is a great reliable model of the physical system that will be beneficial in assessing the possible MOA prior to time without harming animals. The study describes the creation of a digital twin to combine the information and knowledge obtained by studying the different drug targets and diseases. Mechanism of Action using Digital twin (MOA-DT) will enable the experts to use an innovative approach without physical testing to save animals, time, and resources. DT reflects and simulates the actual drug and its relationships with its target, however presenting a more accurate depiction of the drug, which leads to maximize efficacy and decrease the toxicity of a drug. In conclusion, it has been shown that drug discovery and development can be safe, effective, and economical in no time through the combination of the digital and physical models of a pharmaceutical as compared to experimental animals.

1. Introduction

Using animals for science is widespread all over the world. Rats, mice, hamsters, rabbits, fish, birds, guinea pigs, amphibians primates, dogs, cats, and other animals have long been used in pharmacological science (NRC, 2010). An estimate of 192.1 million animals was used for research purposes in 2015 globally (Taylor and Alvarez, 2019). With the advancement of research and development in medical technology, the number of animals used in research has increased. For a long time, the suffering, misery, and death that animals suffer during laboratory experiments have been a point of contention (Doke and Dhawale, 2015; Festing and Wilkinson, 2007). Therefore, evaluation to identify potentially successful drugs prior to model validation is necessary. The biggest challenge of 21st-century pharmacology, to explain the pathways of a drug to push new methods and creativity. To prescribe the appropriate drug to the right individual it is important to understand their

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mechanism of action (MOA) (De Savi et al., 2020), to predict their usefulness in other diseases that share the same defective pathway. Although there are several natural sources of potential drugs, the detection of their mechanism of action is a challenging issue (Messinis et al., 2021). Furthermore, an awareness of the MOA of a drug before it is evaluated in clinical trials is the rational way to drug development and may increase its chance for success and therefore also approval (Amaral, 2020). The mechanism of action usually includes the reference to specific molecular targets with which the drug binds, such as the enzyme or receptor as shown in Fig. 1. Receptor sites possess particular drug affinities based on the chemical composition of the drug as well as the precise action that is taking place there. Drug design is a groundbreaking approach for finding new drugs based on the knowledge of the molecular target (Sills and Rogawski, 2020). Most universally, drug design includes the design of molecules, which are structurally similar to the Pharmacological target to which they bind.

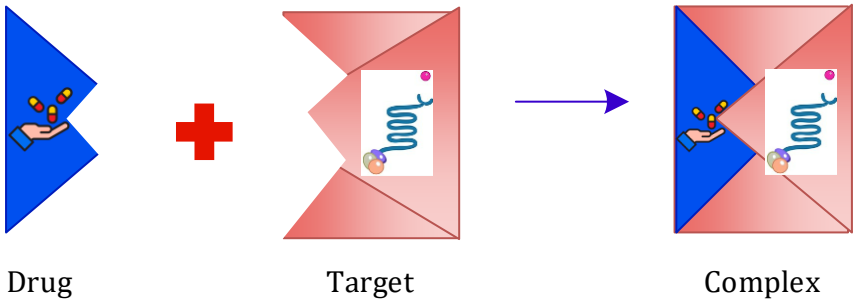

Fig. 1: Mechanism of action

Methods to assess the mechanism are in-silico, in-vivo and in-vitro are reasonably successful but these are time-consuming, expensive well as some mechanisms predict after a clinical trial. The number of patients with ineffective drugs is between 38-75% for various conditions. To investigate the possible mechanisms by which the drugs exert their activity needs the assessment of various drug targets. Assessment of each target will consume a range of resources as well as disturb living nature. As the digital twin works in an autonomous virtual world, it can be studied without impacting the physical structure and biological system. DT, keep the promise to minimize time and cost for the safety and efficacy evaluation of pharmacological drugs, reduce the need for humans and other animals testing, and allow precision medicine (Sinisi et al., 2020). The concept of digital twin (DT) is to create stochastic simulations to produce future "what if" scenarios (Fuller et al., 2020) to improve performance and prevent design flaws. DT innovates the development process and minimizes the risks and costs associated with quality products (Qi and Tao, 2018). Digital twin organizations offer continuous input in order to enhance the quality of life and well-being, to better track, recognize and optimize the roles of all physical entities (El Saddik, 2018). The development of Digital Twin is an attempt to build intelligent adaptive machines through the generation in conjunction with the communication and analysis capabilities of IoT (Boschert and Rosen, 2016; Aberer et al., 2007). Digital couplings are redefined as digital replicates of both non-living and alive entities which make it possible for data to be transferred seamlessly across the physical and virtual worlds originally designed to improve production processes. DT is a digital representation or intangible structure which can be tested, changed, evaluated, and avoids adverse impacts without interacting with the real world. Furthermore, DT is a link between the real and the digital world, made up of three parts: the physical, virtual, and the interaction in the physical and the digital worlds. In the digital world, items are designed in laboratories to predict the item's structure, simulate the behaviors and actions of items, and improve their performance in the real world. In the physical world, objects are detected by the sensors and treated by actuators, their features, performance, and interactions with the users (Rosen et al., 2015) as described in Fig. 2.

Digital twins are described as digital replicas of procedures, structures, or devices that have been created to facilitate broader understanding. Although the definition of digital twins was established in manufacturing but newly developed in pharmacology, it could conceivably reflect the complicated and evolving relationship within biological systems in a digital twin which incorporates data from diverse science and clinical origins. This integrative system could enable a deeper understanding of the pharmacological target and could be used to develop better medicines as a predictive model. The twin duplicates the physical target function, disease development, and treatment results. In conclusion, it has been shown that a method that combines twins with testing steps offers insights into the interaction between drug targets.

DT reflects and simulates the actual drug and its relationships with its target, however presenting a more accurate depiction of the drug which leads to maximize efficacy and decreasing the toxicity of a drug. Since all the information related to drug targets is available before time, we may upgrade our

drugs accordingly to avoid resource wastage and reduce animal suffering. In conclusion, it has been shown that drug development can be enhanced with low risk and cost through the combination of the digital and physical models of a pharmaceutical. The arrangement of the paper includes the

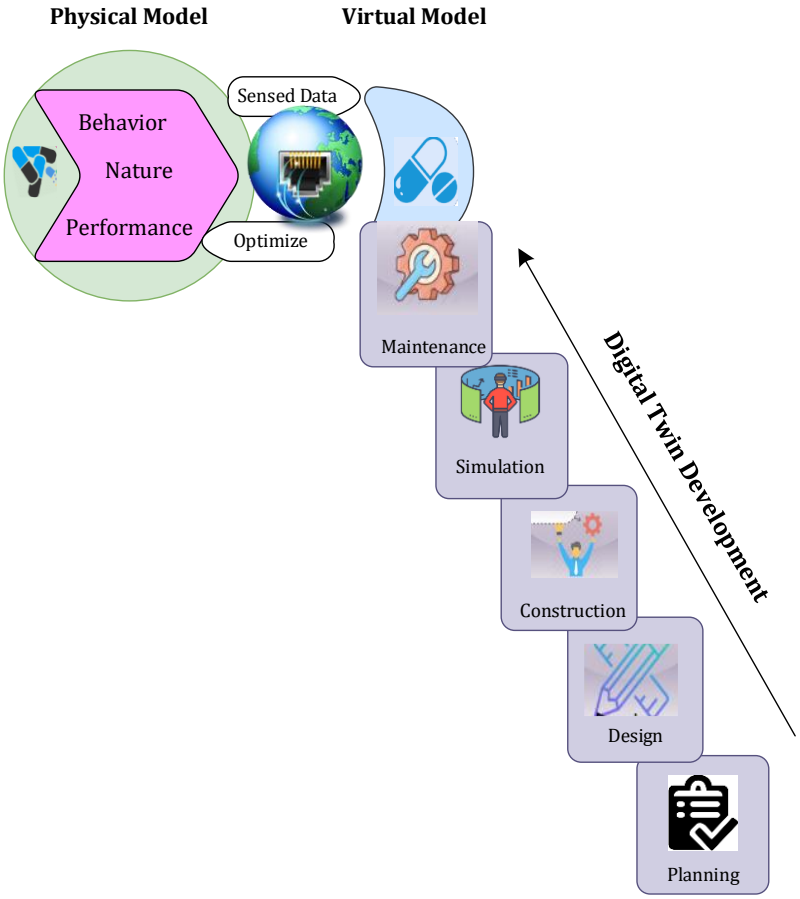

Fig. 2: Overview of digital twin

number of sections to come. Overview of different methods of target identification is presented in Section II, while the proposed Mechanism of Action using Digital twin (MOA-DT) is presented in Section III. Section VI provides a discussion of the impact of the digital twin on the performance of drug discovery. The proposed paper is finally concluded in Section V.

2. Target identification

Target Identification is a process for recognizing a significant molecular target. In pharmaceutical sciences, target recognition is intended to identify the effective target of the medication (Zeng et al., 2020). The approach to identifying active compounds may result in competition between drug development companies. In literature, various certain target identification techniques could be based on one of the two main identification schemes shown in Fig. 3.

The first one is the deconvolution of targets; this paradigm starts with an effective drug that is retroactively established. Target deconvolution is a crucial phase in identifying the compound molecular mechanism and as well as using the recognized targets as resources for further analysis of a given biological function (Saei et al., 2020; Khan et al., 2020). The other one is named target discovery (Paananen and Fortino, 2020), this method operates on the principle that 'if you'd like a new drug you need to find a new target,' and once a target is determined, then searched to find a treatment that binds to the target and causes the desired effect.

2.1. Existing target identification methods

Drug discovery is a revolutionary approach for developing new drugs based on the knowledge of the mechanism of action. In the most basic sense, drug design includes the design of proteins that can bind and charge to the pharmacological target to which they link and thus will stick to it. Various investigations related to identifying successful therapeutics have been presented by researchers in literature as shown in Fig. 4.

2.1.1. In-silico

This approach predicts which cellular pathway and/or protein target is inhibited by select compounds using broad datasets from unrelated cellular and biochemical screens and the guilt-by-association theory (Plouffe et al., 2008). Recent advances in computing tools (e.g. neural network and processing on graphical processing units (GPU))

and in statistical analysis and prediction methods (e.g. artificial intelligence, machine-learning) provide prospects for various fields in data analytics, along with biomedicine.

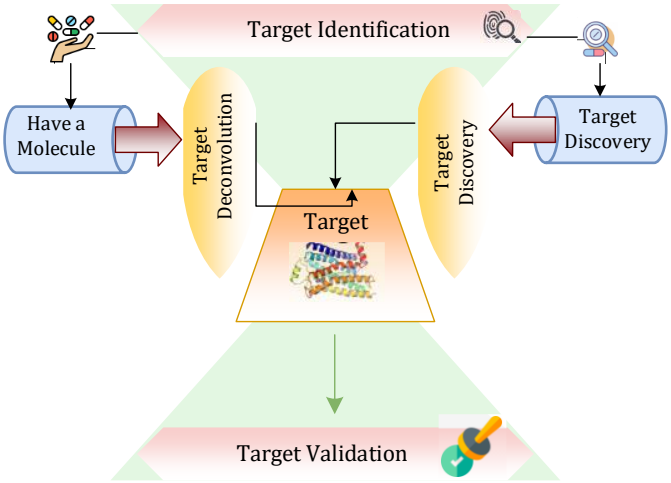

Fig. 3: Target identification

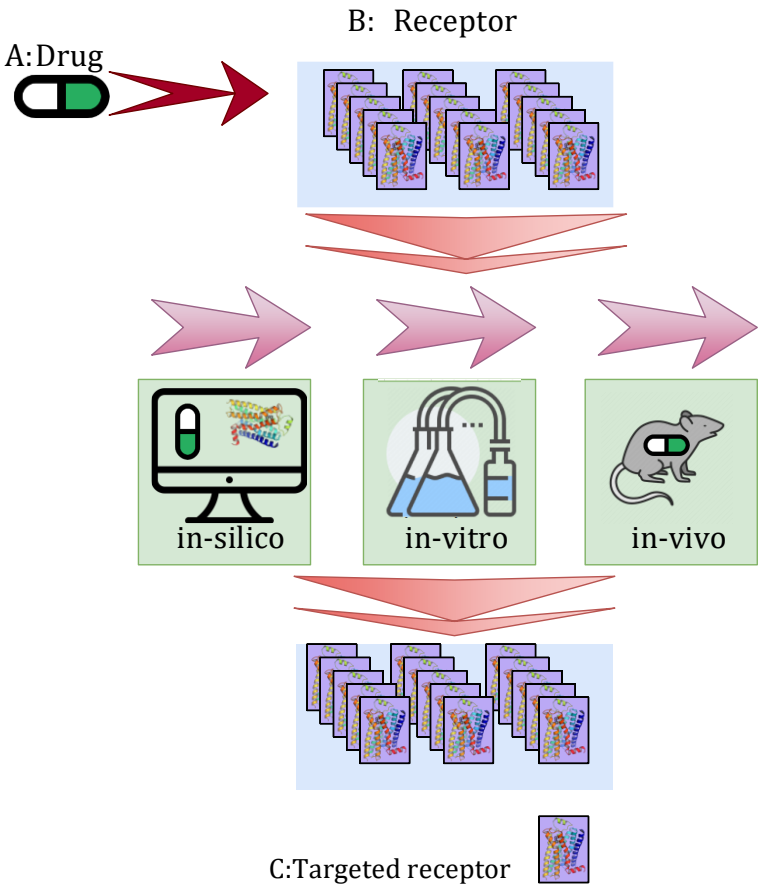

Fig. 4: Existing target identification methods

A computational field known as in-silico research has emerged in the recent century to aid laboratory drug development experiments by statistically predicting unknown bio-interactions among drugs and biological targets (Neto et al., 2020). These approaches use the Physico-chemical and computational characteristics of the materials and target molecules with the experimental and analytical bio-interaction knowledge to produce predictive models. These advances have been implemented in in-silico to improve predictive efficiency (Ibrahim et al., 2020). The author in Ling (2020) presented in silico studies to Figure out exactly traditional Chinese medicine TCM remedial measures that may effectively inhibit the coronavirus COVID-19 replication (Habib et al., 2021). The machine learning method is an effective way for revealing drug mechanisms of action

(MOAs). However, due to the lack of code-free and user friendly applications, it is not easy for pharmacologists to model MOA by this method (Gao et al., 2021; Hamid et al., 2019).

2.1.2. In-vivo

The study of a drug's biological effects in a complex living organism is known as in vivo pharmacology, and it is used to observe the drug's complex physiological effects (Zon and Peterson, 2005). It can help researchers to understand the mechanism of action of drugs (Hunter et al., 2018). The drawback of this is suffering, misery, and death that animals suffer during laboratory experiments has been a point of contention. Aside from the ethical problem, there are a few other drawbacks to animal research, such as the need for professional labor, lengthy procedures, and high costs.

2.1.3. In-vitro

Some studies at the pre-clinical phase are anticipated by drug regulatory authorities. Matter of fact, safety is a critical stage of the pre-clinical development phase. It aims to determine any possible adverse drug effects on the living organism. While in the past, most safety studies of pharmaceuticals were performed on animals, nowadays, safety measures are largely held using in vitro experiments that include individual cell lines and tissues (Charman et al., 2020). Rietdijk et al. (2021) proposed an in vitro assessment of antiviral medications, which provides useful insight into the effect of both infection and medicines on the infected cells. The authors evaluated their proposed technique using a panel of 9 antiviral compounds including recognized and novel molecules on MRC5 human lung fibroblasts contaminated with coronavirus. Modifies that are detectable by microscopy, and that can provide an understanding of the mechanism of action of the Elvitegravir that acts downstream of the NMDA receptor (Merz et al., 2020).

In several cases, however, hybrids of approaches can be needed to fully define on-target and off-target effects and to understand mechanisms of action. Assessment of each target will consume the range of resources as well as disturb living nature. As the digital twin works in an autonomous virtual world, it can be studied without affecting the physical structure and biological system. Our proposed framework suggests that the digital twin is a great reliable model of the physical system that will be beneficial in assessing the possible mechanism of actions prior to time.

3. Proposed framework

The first and only concrete proof is if a medication proves out to be effective and safe in an individual, the main hurdle is that several decades after the time of launch almost all targets face challenges late in the trial. Thus, researchers have to concentrate on the ability to identify potential targets early. By understanding the interaction within a certain site of a drug and some receptors, multiple drugs can be developed in a way that replicates this interaction, thereby achieving the same therapeutic effects. DT reflects and simulates the actual drug and its relationships with its target, however presenting a more accurate depiction of the drug which leads to maximize efficacy and decreasing the toxicity of the drug. Since all the information related to drug targets is available before time, we may upgrade our drugs accordingly to avoid resource wastage and reduce animal suffering. In conclusion, it has been shown that drug development can be enhanced with low risk and cost through the combination of the digital and physical models of a pharmaceutical. With the aid of DT, experts will be able to predict which patients are more likely to respond to treatment as well as allow better dosing because the drug actions on the target pathway can be tracked in the individual. The drug mechanism of action may enable other indications for the drug to be recognized. Our research contribution mainly emphasizes the investigation of the mechanism using digital twin, health care professionals would be able to use a safe, effective and economical drug without physical testing. The proposed study introduces the fundamentals as well as survey the main characteristics of target identification with the mechanism of action using a digital twin. The proposed MOA-DT framework can help identify the drug mechanism of action, potency, and efficacy of a drug, the activity of the compound in different diseases, the safety and toxicity of the drug as well as possible adverse effects frequently in the drug discovery process.

Drug-DT in Fig. 5 represents the drug with an unknown mechanism of action. Then the Drug-DT is directed to Human-DT, the digital twin of patients constructed with an unlimited target. Each target in the twin is computationally treated with Drug-DT. This results in the digital target of COX2 enzyme (green) (Bommu et al., 2019), while the red-colored targets show no interaction of drug. The drug mechanism is identified as Cyclooxygenase COX2 inhibitors, which is an effective analgesic, antipyretic, and anti-inflammatory as well as safe in ulcer patients.

This framework could allow a better understanding of the pharmacological mechanism and could be used to design appropriate drugs as a predictive model. The twin validates the physiological target function and treatment outcomes. It has been shown that a system that combines twins with screening steps provides insights into the relationship between drug targets. DT represents and simulates the real drug and its interactions with its target, however, introduce a more accurate reflection of the drug which contributes to optimize efficacy and reduce the toxicity of a drug. Since all the details regarding drug

targets are known prior to time, we can upgrade our drugs accordingly to avoid wastages and reduce unnecessary suffering.

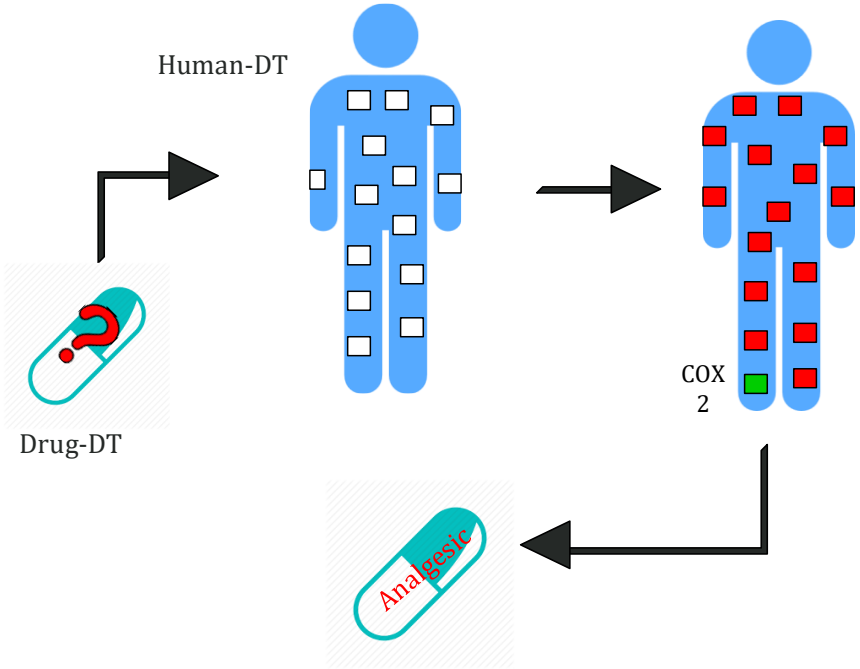

Fig. 5: The digital twin concept for the mechanism of action

In summary, studies show that drug design can be enhanced with minimal risk and cost via the integration of the digital and physical approach of a pharmaceutic as compared (Khan et al., 2018).

4. Discussion

The existing method of the mechanism is relatively effective however, these are tedious, expensive as well as some adverse effect develops after marketing. To evaluate the potential mechanisms through which the drug exerts its action needs the assessment of different drug targets. Evaluation of every target can consume a variety of resources as well as disrupt living organisms.

As the digital twin operates in an autonomous virtual environment, it could be studied without affecting the physical structure and biological system. DT, keep the promise to minimize time and expense for the preclinical and clinical evaluation of pharmacological treatments, lessen the need for living animals testing, and encourage personalized medicine. The proposed work focus on the study of a mechanism using digital twin, Pharmacologists will be able in using safe, effective, and cost-effective medication without physical examination. This study introduces the foundations and evaluates the key features of target recognition with the mechanism of action using a digital twin. MOA-DT concept can be useful in determining the mechanism of action.

5. Conclusion and future work

To determine the potential mechanisms, by which the drug exhibits its impact, facilitates the identification of various drug targets. Assessment of any target will consume a range of resources along with interruption of living organisms. The introduction of digital twins would involve addressing a diverse range of innovative, pharmacological, ethical, and practical challenges. DT may lead not only to greater improvement in pharmacology and understanding of the mechanism of action but also leads to entirely new research directions. Even though all the information about drug targets is specified earlier stage, designers could modify existing drugs accordingly to prevent material waste and decrease unnecessary pain and suffering. In conclusion, studies show that drug design can be enhanced with minimum risk and expense through the combination of the digital and physical framework of pharmaceuticals as compared to Khan et al. (2018).

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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