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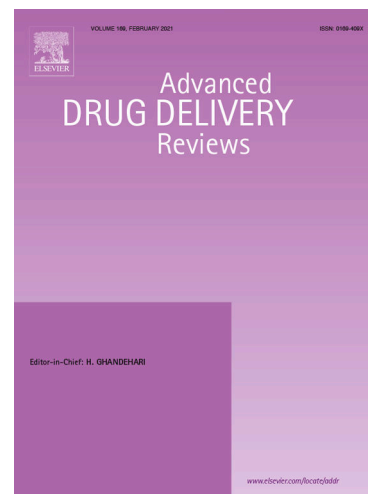
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Advancing pharmacy and healthcare with virtual digital technologies

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Abstract

Digitalisation of the healthcare sector promises to revolutionise patient healthcare globally. From the different technologies, cyber tools including artificial intelligence, blockchain, virtual, and augmented reality, to name but a few, are providing significant benefits to patients and the pharmaceutical sector alike, ranging from improving access to clinicians and medicines, as well as improving real-time diagnoses and treatments. Indeed, it is envisioned that such technologies will communicate together in real-time, as well as with their physical counterparts, to create a large-scale, cyber healthcare system. Despite the significant benefits that cyber-based digital health technologies can bring to patient care, a number of challenges still remain, ranging from data security to acceptance within the healthcare sector. This review provides a timely account of the benefits and challenges of cyber-based health interventions, as well an outlook on how such technologies can be transitioned from research-focused towards real-world healthcare and pharmaceutical applications to transform treatment pathways for patients worldwide.

Keywords: Pharmacy or Pharma 4.0; Cybermedicine; Digitised drug delivery; Industry X.0; Telecommunication; On-demand drug manufacturing; computational drug discovery and development; Precision and personalized medicine; electronic health (e-health); digital and virtual twinning.

1 Introduction

The design, development, and delivery of pharmaceuticals is crossing a new frontier into the digital realm [1]. Next generation digital technologies are being adopted at each stage of a medicine's lifespan, from hit identification to post marketing surveillance and patient delivery. A technological boom over the past few decades has seen the advent of cyber technologies such as artificial intelligence (AI), quantum computing, blockchain, telecommunication, internet of things (IoT), and virtual reality (VR), to name a few [2]. The realisation of these technologies across various sectors of society has led to their incorporation into the pharmaceutical field, transforming and affording significant benefits within numerous processes. For example, AI-guided drug discovery is now employed in many pharmaceutical companies due to its speed, resource-saving potential, and ability to work constantly [3]. Whilst small technology-focused pharmaceutical start-ups have led the way with AI, larger multinational companies are now embracing the tools, and are said to be in the early mature phase of AI utilisation [4]. Common applications of AI within big pharma include disease target identification, *in silico* high throughput screening, formulation development, clinical trial management, and dosage error reduction [5]. Combinatory tools, such as quantum computing, promise to increase the speed at which AI algorithms can be run [6]. Quantum computers may also greatly advance molecular modelling capabilities, allowing inspection of drug-target or drug-formulation interactions at the subatomic scale [7, 8].

Once a medicine has been licensed, delivering it to patients in a safe, secure, and supportive manner is an imperative task. Over 10% of low- and middle-income countries (LMICs) are affected by counterfeit medicines, leading to substandard

treatments, safety concerns, and economic loss to legitimate suppliers [9, 10]. Often, insecure pharmaceutical supply chains can increase the risk of falsified treatments being inadvertently supplied to patients [11]. One solution in securing medicine supply chains is blockchain, a digital ledger which can group information in immutable, chronological blocks [12, 13]. The blockchain network can facilitate reliable tracing of pharmaceuticals at each step of the supply chain, ensuring that only valid products are accepted for patient administration. Due to its compatibility with multiple stakeholders, blockchain can also be used to monitor suppliers' compliance with distribution guidelines, such as management of optimal storage conditions during handling [14]. The technology can even be combined with IoT for direct information capture from devices, such as temperature probes during cold storage [15].

Patient-facing technologies are similarly experiencing substantial innovation. Whereas patients have long been required to visit a pharmacy to collect their prescriptions, rapid delivery of medicines to patients' houses is becoming commonplace [16]. Growing acceptance of virtual medical appointments and advancements in telecommunication also make it more likely for patients to have online consultations with pharmacy professionals than ever before [17]. These strategies have been of paramount importance to maintain patient safety during the COVID-19 pandemic, which forced a move away from face-to-face interactions [18]. From a treatment perspective, technologies such as VR and gamification are leading to more patients being treated with digital interventions [19, 20]. This could lessen the use of drugs in some conditions, especially those that are chronic or difficult to treat pharmacologically [21-24]. Further, patients' adherence to medication regimens can now be supported without direct professional supervision, using technologies such as augmented reality

(AR) [25]. Aside from patient support, VR and AR are also demonstrating potential for the training of students [26] and numerous processes within drug development [27].

Technological advancement is creating great opportunity within the pharmaceutical field, promising to facilitate the development and delivery of medicines in a highly streamlined, efficacious, and innovative manner [28]. Despite the many opportunities that come with emerging technologies, it is wise to introduce them into existing workflows with clear recognition of their challenges. Data security and protection are key considerations during the uptake of most digital technologies, especially those utilising commercially sensitive or patient related data. Moreover, the costs of digital solutions should not impede their adoption, nor should difficulties in integrating with existing regulatory frameworks. This review will provide a timely overview on the most exciting and promising cyber technologies entering the pharmaceutical sector. Topics will include AI, blockchain, interconnected healthcare and virtual/augmented/mixed reality. Whilst references to associated hardware (such as sensors, robotics, and 3D printers) will be made, digital healthcare devices have been reviewed elsewhere in detail [29]. This review will conclude with an appreciation of the most prevalent challenges facing the incorporation of virtual digital technologies, with suggestions of how these may be overcome.

2 Artificial intelligence (AI)

2.1 AI in Pharma: Where Are We At?

AI, also known as machine intelligence, could revolutionise the pharmaceutical sector [30]. It is defined as the ability of computers to examine and interpret complex data, enabling them to perform human-like cognitive actions. In simpler terms, AI is the

ability of a machine to perform processes ordinarily requiring human intelligence. Technologies within AI include predictive algorithms, robotics, natural language processing (NLP), computer vision and smart sensors [31-35]. There are three proposed levels of AI: narrow intelligence, general intelligence, and superintelligence, with each successive level demonstrating superior aptitude (Figure 1A) [36, 37]. At present, no AI software has reached the level of general intelligence, though there are many instances of machines that combine different types of AI to conduct multiple intelligent tasks simultaneously; for example driverless cars can employ computer vision, sensors, robotics, and NLP instantaneously [38]. The recent surge in global AI interest has been triggered by advancements in computer hardware, such as graphical processing units, and ML [39]. The latter is a subset of AI that allows computers to independently learn complex and often hidden patterns within data, facilitating them to execute tasks and make predictions for new, unseen data [40]. An excellent introduction to basic ML methodology, with specific reference to molecular biology, pharmacometrics, and clinical pharmacology, has been published by Badillo et al. [41].

Within healthcare, AI techniques have begun to demonstrate their transformative potential, with at least 29 AI-based medical technologies now approved by the U.S. Food and Drug Administration (FDA) [1, 36, 42, 43]. Approved applications focus mainly on ML-guided diagnosis, such as the detection of stroke from computerised tomography (CT) scans (Figure 1B), breast density via mammography, and fracture diagnosis from X-ray images [43-46]. AI is also facilitating patient monitoring, prognosis prediction, surgery, and public health monitoring [35, 42, 47, 48]. This review is focused on advanced digital technologies within the discovery, development, and management of pharmaceuticals, therefore will not go into detail on AI

applications concerning diagnosis and patient monitoring. However, an excellent overview of medical FDA-approved algorithms has been published by Benjamens et al. [43]. Like the medical field, the pharmaceutical industry is rapidly adopting AI, especially ML, with applications at every stage of drug development from compound discovery to post-marketing surveillance and patient support [3, 49-55]. Since 2001, publications using ML within pharmaceutical research have grown steadily to exceed an exponential rate (Figure 1C). Most of the large, global pharmaceutical companies now use ML as part of their activities, with Novartis and Astra Zeneca leading the way on the number of AI-based projects undertaken from 2014 - 2018 (Figure 1D) [4]. As well as in-house use, it is becoming increasingly common for big pharma to partner with AI-focused healthcare start-ups, of which thousands have been founded in the past 10 years [5]. In fact, there is a wealth of AI-based innovation occurring in pharmaceutical research, with numerous examples discussed in subsequent sections.

One interesting pharmaceutical-focused application of ML is the DreaMed software developed by DreaMed Diabetes and FDA-approved in 2018 [56]. DreaMed is an automated decision support system for the management of patients with type I diabetes mellitus [57, 58]. The proprietary ML algorithm is paired with a cloud server that analyses individuals' capillary glucose concentration, insulin dose history, and carbohydrate intake allowing output of a management report via an app to a healthcare professional who can approve and share personalised insulin dose recommendations with patients (Figure 1E). A 2020 clinical study involving 108 adolescents reported the app to be equally effective at controlling glucose levels as physician advice alone [56]. This non-inferiority could allow healthcare professionals to spend less time analysing

complex insulin pump data, instead working in collaboration with software to approve reliable and safe dosing recommendations.

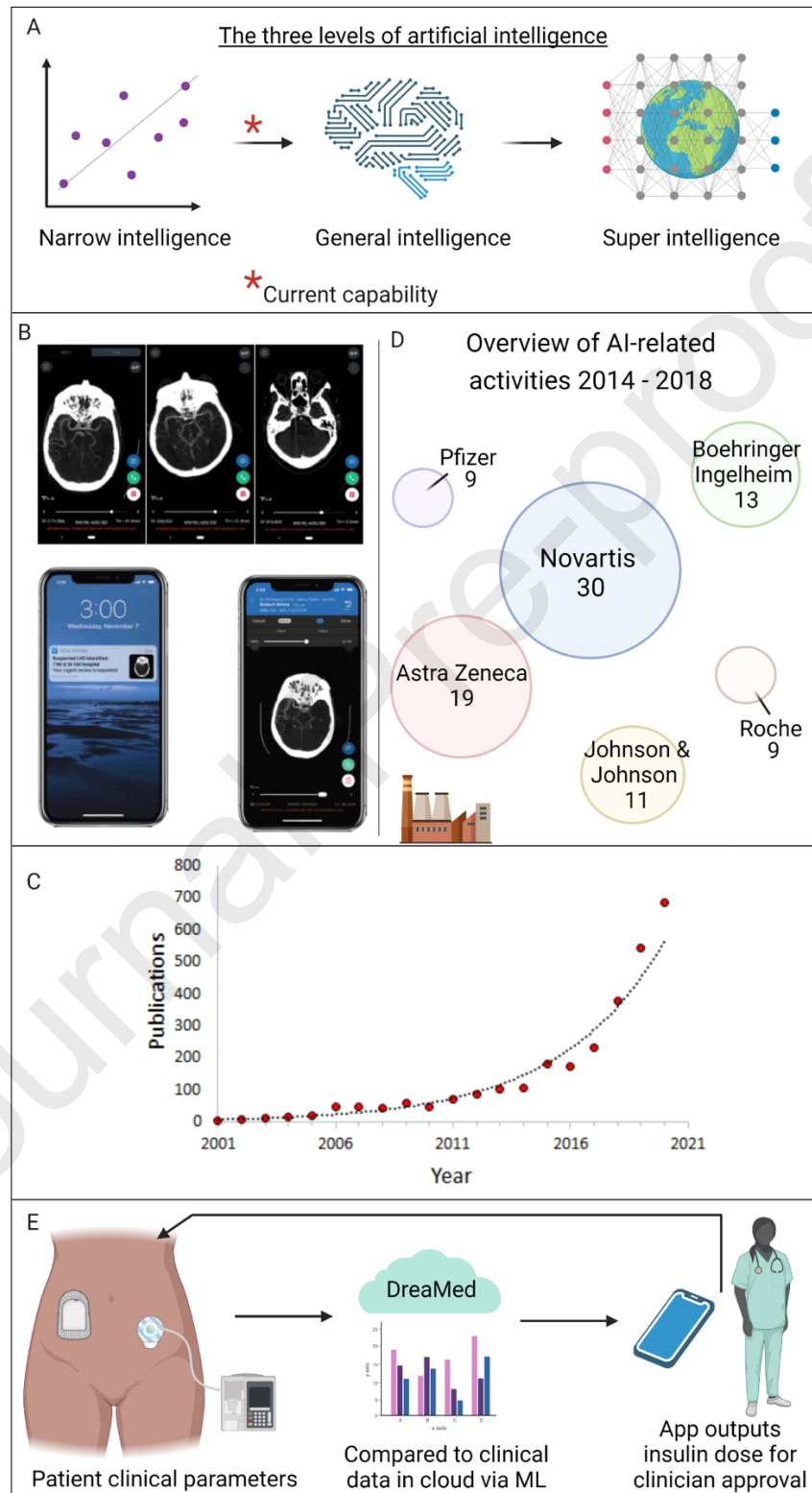


Figure 1. (A) the three levels of artificial intelligence (AI). With narrow intelligence, machines can perform a single task that has been precisely defined by their programmer. With general intelligence, machines would have all the intelligence of a human being, including reasoning, empathy, prediction, and memorisation. At superintelligence, machines could theoretically surpass humanity's cognitive capacity and reach levels of intellect incomprehensible to humans, which is generally regarded as an outcome to avoid [36]. (B) an FDA-approved AI-based software (Viz LVO) for automatic stroke detection and clinician notification (image reproduced with permission) [45]. (C) comparison of a selection of pharmaceutical companies' AI-related activities from 2014 - 2018 [4]. (D) the number of studies from 2001 - 2020 indexed on Scopus under the search term (machine* AND learn* AND pharma*). (E) infographic depicting the DreaMed workflow, a ML-based system for insulin dose management in patients with type I diabetes mellitus. The AI algorithm assesses patient clinical parameters with big data stored in the cloud and outputs personalised insulin dose recommendations for clinician approval [56]. Images were reprinted with permission from their original sources.

2.1 Machine Learning for Drug Discovery

In a seemingly endless chemical space, the pharmaceutical industry is constantly faced with the challenge of identifying new active pharmaceutical ingredients (APIs) for the treatment of a diverse array of diseases. Though the last few decades have achieved great advances in high throughput screening (HTS) of compounds, these methods are resource-intensive, require extensive data analysis, and frequently identify hits that are ultimately unsuitable for progression [59]. Companies are constantly working to reduce the very high failure rate of investigational compounds;

study has shown the successful translation rate of orphan drugs, from phase I clinical trials to market approval, to be just 6.2% [60]. ML techniques offer the ability to circumnavigate manual HTS by instead driving *in silico* HTS [3]. Key advantages of this ML-powered drug discovery include the ability to operate 24/7 at capacities far exceeding manual methods; reducing costs by decreasing the physical number of compounds tested; and identifying negative compound characteristics at an early stage, such as off-target effects, sex-dependent variability, or susceptibility to degradation by gut microbiota [61-63]. ML technologies could facilitate the replacement of lengthier *in silico* predictive tools or manual experimentation in drug discovery pipelines. The speed in which active compounds can be discovered using ML will vary based on the specific drug-target model and ML technology used. An example of the time-saving capability of ML is the DeepBAR algorithm developed by researchers from the Massachusetts Institute of Technology[64]. DeepBAR incorporates deep generative ML to calculate the binding affinities between investigational compounds and therapeutic targets, such as proteins. Importantly, DeepBAR was found to be more efficient, by an order-of-magnitude, than a common existing *in silico* molecular dynamic method (potential of mean force) and provides a much quicker and resource-sparing alternative compared to manual measurement of drug candidates' free binding energies. The DeepBAR technology showcases how ML can be applied to discover novel therapeutics more efficiently than pre-existing tools.

Because of its capabilities in handling large and complex datasets, ML has been extensively demonstrated as a powerful technology for drug discovery [39]. Recognising its capabilities, many drug discovery start-ups are positioning ML at their core, with successful examples including Atomwise, Benevolent AI, and DeepCure

[65-67]. Within ML there are a myriad of techniques suitable for drug discovery, which include traditional supervised and unsupervised methods [68]. Though methodologically heterogeneous, traditional methods typically identify influential chemical attributes within very large libraries of compounds and predict their likelihood of achieving therapeutic activity.

The choice of ML algorithm will depend on the desired output. Traditional regression analysis methods, such as linear regression, neural networks, and support vector machines (SVM), will output numerical values. For instance, Mamoshina et al. [69] obtained the gene expression profiles of skeletal muscle tissue from healthy donors and used several regression techniques (e.g., SVM, random forest, and k-nearest neighbours) to predict the age of the donors based on their tissue's gene expression. The SVM and deep learning models were found to obtain the most accurate predictions, with R^2 values of 0.83 and mean absolute errors of 7.20 and 6.24 years, respectively (Figure 2A). The work allowed the identification of the most important genes for age prediction, which enabled the discovery of potential anti-ageing drug targets. In comparison to regression learning, classification ML offers a way to assign objects to categories based on their features; common techniques include decision trees, neural networks, and SVMs. 13 classification ML techniques have been investigated for their ability to predict the effect of drugs on gut microbiota (Figure 2B) [70]. Models were trained using 18,680 experimentally tested bacteria-drug interactions and 1,613 chemical descriptors per drug. From this, drugs could be categorised as either impairing or having no effect on gut bacterial growth, which could be applied to discover new selective antibiotics. Performance of baseline models was compared, and the three best models were chosen for hyperparameter optimisation,

leading to improvements in predictive capabilities and selection of a final extra trees model with an area under the curve of the receiver operating characteristic (AUROC) score of 0.857 (± 0.014).

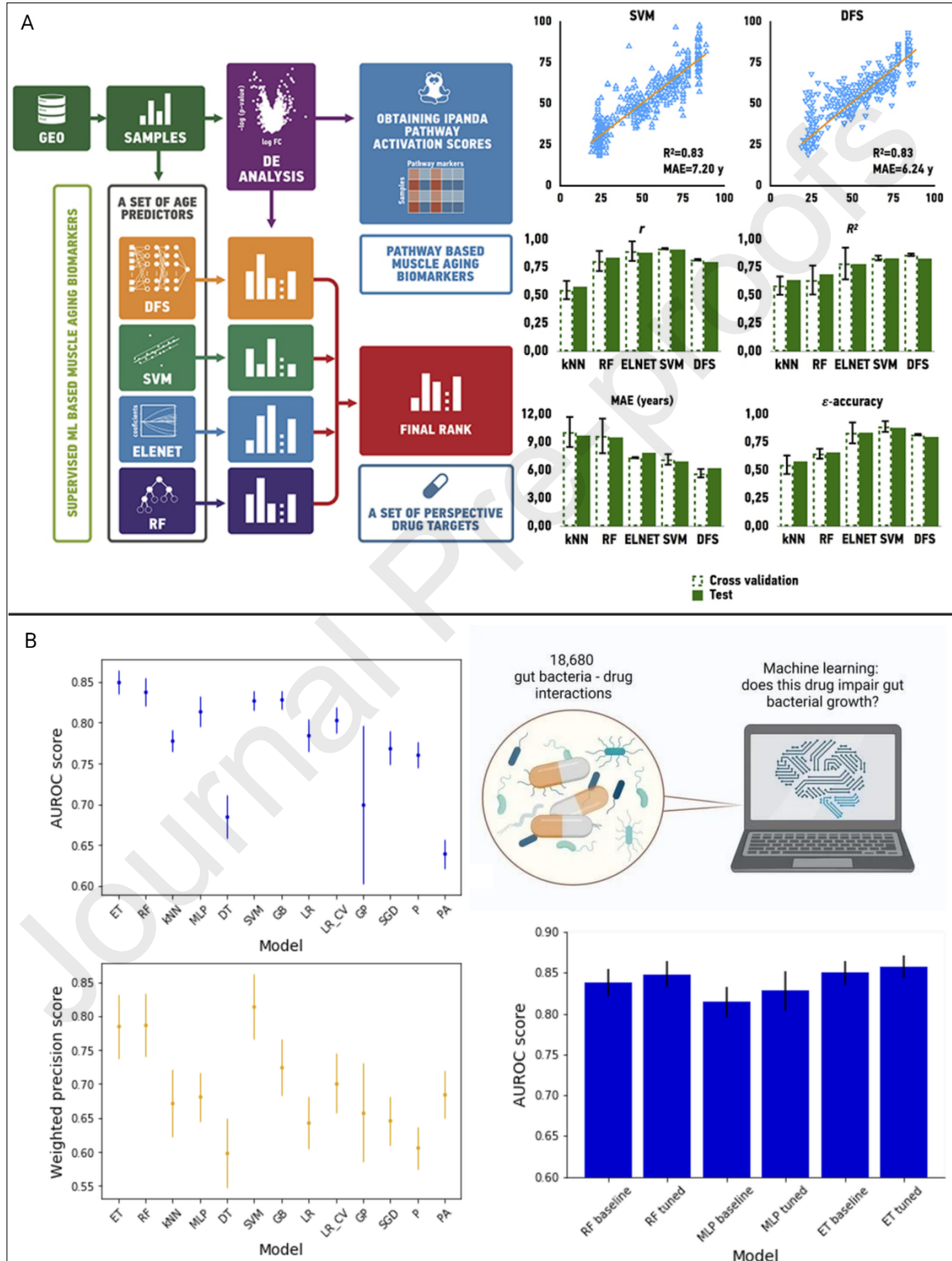


Figure 2. (A) on the left, the workflow for machine learning (ML) prediction of human age based on skeletal muscle gene expression. On the right, comparison of the ML models' performances [69]. (B) the two plots to the left demonstrate the AUROC and weighted precision scores of 13 baseline ML models in predicting drugs' effects on gut bacterial growth. The bottom right plot depicts improvements in the 3 best baseline models' AUROC scores following hyperparameter tuning [70]. *AUROC: area under the curve of the receiver operating characteristic, DFS: Deep Feature Selection, ELNET: ElasticNet, ET: extra trees, GEO: gene expression omnibus, RF: random forest, kNN: k-nearest neighbours, MAE: mean absolute error, MLP: multilayer perceptron, DT: decision trees, SVM: support vector machines, GB: gradient boosting, LR: logistic regression, LR_CV: logistic regression CV, GP: Gaussian process, SGD: stochastic gradient descent, P: perceptron, and PA: passive aggressive classification.* All images have been reproduced under the Creative Commons Licence.

Though powerful tools, potential shortcomings of traditional ML techniques include the requirement for very large, clean datasets and lack of transparency in decision-making. Moreover, algorithms are often 'locked', meaning that they cannot learn new evidence without it being deliberately taught to them [43]. In recognition of the shortcomings of traditional ML techniques, various advanced ML techniques are coming to the fore of drug discovery [3]. These include reinforcement learning, which allows continuous and autonomous update of knowledge; transfer learning, which applies knowledge across different datasets; and active learning, a technique that facilitates accurate predictions from small datasets by requesting human-led experimental feedback [71-73]. Active learning for drug discovery has been reviewed by Reker et al. [74] and typically involves training models on compounds with known

activities, model identification of compounds with unknown activity where results would improve overall model performance, and human testing of these compounds with result feedback to the model (Figure 3A). As laboratories become more and more automated, the sampling process of active ML can become a fully autonomous closed-loop process that operates 24/7 and does not require human intervention [74]. Active learning has been applied to design novel ligands with multiple pharmacological targets, identify structurally diverse molecules with target hits, and predict off-target drug effects on proteins [75-77]. In the latter example, lasso regression paired with multiple approaches to active learning was used to explore the activity of 20,000 compounds on 129 protein targets [77]. It was found that a greedy-uncertainty based sampling approach to active learning was most effective, allowing identification of 60% of all dataset hits with exploration of just 3% of the total chemical space (Figure 3B). This demonstrates how advanced ML techniques can save time and resources during drug discovery.

Deep learning is another advanced ML technique showing good results in drug discovery programmes [78-81]. Deep learning differs from traditional ML techniques in its complexity, wherein it typically describes artificial neural networks (ANNs) (inspired by the structure of the human brain) that are many layers deep. Input features are fed into the model and are subsequently passed through many hidden layers of decision nodes utilising nonlinear transformations, eventually resulting in prediction output via the final layer [39]. Key advantages of deep neural networks are their computational power and flexibility to solve many types of problems. An exciting example of deep ML is AlphaFold's prediction of protein structure (Figure 3C) [82]. Before the algorithm was developed in 2021, just a small fraction of protein structures

was known, despite characterisation of billions of protein sequences. The AlphaFold neural network considers evolutionary, geometric, and physical structural constraints to predict the 3D coordinates of all heavy atoms within a given protein. With only a protein's primary amino acid sequence and aligned sequences of homologues as inputs, AlphaFold demonstrates great accuracy and outperformance of all previous attempts. Its capability to reliably model any protein's structure holds great promise for the discovery of new biologics and analysis of off-target protein binding. Already, AlphaFold has been applied to structurally characterise 98.5% of the human proteome (Figure 3D) [83].

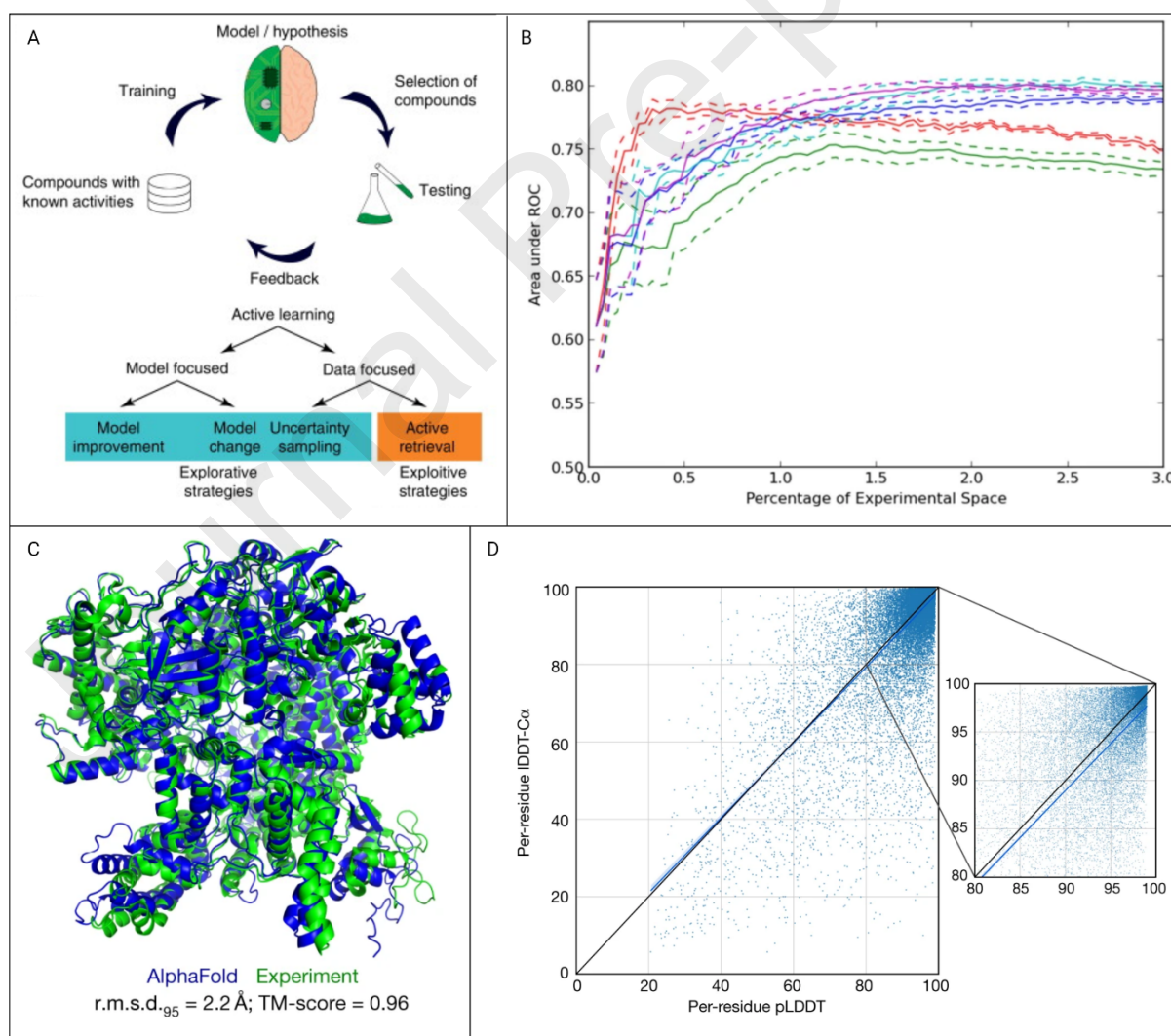


Figure 3. (A) depiction of the active ML workflow [84]. (B) Performance of models built using different approaches to active ML sampling for the prediction of off-target drug effects on proteins [77]. Sampling approaches are shown as random choice (red), greedy combined compound-target (CCT) (green), greedy CCT-uncertainty hybrid (blue), and greedy selection-uncertainty hybrid using memory limits of five (cyan) and ten rounds (magenta). (C) representation of a protein structure (a 2,180-residue single chain) predicted using AlphaFold, overlaid with the experimentally validated structure [82]. (D) correlation between prediction confidence (pLDDT) and agreement with an experimentally validated structure (IDDT-C α) for a subsample of proteins from the human proteome [83]. Images were reprinted with permission from their original sources.

2.2 Machine Learning for Drug Development

As highlighted, the journey of a newly discovered API to market approval is perilous, with only a very slim chance of success [85]. There are thousands of reasons that a novel API may prove unsuccessful, with off-target effects, poor pharmacokinetic profiles, formulation challenges, and lack of superiority over existing treatments being most common. In a typical pharmaceutical pipeline, it takes upwards of 12 years to bring a new API to market [51]. Key stages of the development pathway include lead API optimisation, formulation, pharmacokinetic and toxicology testing, clinical trials, scale-up and manufacturing, and eventually post-marketing surveillance [50, 86]. Understandably, the pharmaceutical industry is constantly assessing ways to reduce risk and speed up processes within the drug development phase, as each day invested in unsuccessful projects accounts for significant direct and indirect wasted costs.

ML has been proposed as an end-to-end enabler for the entire drug development pathway [86]. Numerous studies have demonstrated the utility of ML for guiding rational API formulation strategies [87-89]. Successful applications include prediction of API physicochemical properties; optimisation of controlled release mechanisms; and forecasting biologic stability. Of all ML techniques, ANNs have been most commonly used for the development of solid oral dosage forms, accounting for 67% of publications from 1990 - 2019, as reported by Lou et al. [90]. For example, Li et al. [87] compared traditional design of experiment (DoE) surface response method with an ANN for formulation of controlled release nanoparticles loaded with verapamil hydrochloride. The ANN was proven to be better at predicting nanoparticle size and drug loading based on 3 formulation features (drug to lipid ratio and concentration of Pluronic F68 and Tween 80). Specifically, the ANN was stronger at generalising training data to test data, demonstrated by much smaller distribution of residuals (a marker of predictive power). The ANN was subsequently used to optimise nanoparticle size (predicted: 100.58 nm, experimental: 105.42nm) and drug loading efficiency (predicted: 92.39%, experimental: 92.51%). Elsewhere, several methods of regularised linear regression were used to predict the tensile strength and disintegration time of tablets using 12 material attributes (including bulk density, compressibility, and granule diameter) as inputs [91]. An elastic net model (a hybrid between ridge and least absolute shrinkage and selection operator (LASSO) regression) tablet a was found to hold the highest predictive ability. When accounting for interactions between material attributes, the model was able to predict tensile strength with an R^2 of 0.901 and disintegration time with an R^2 of 0.912.

ML is also facilitating formulation of medicines produced with advanced manufacturing technologies, such as pharmaceutical 3D printing [52, 53, 92-94]. In a recent study, researchers predicted the extrusion temperature, filament mechanical characteristics, printing temperature, printability, and dissolution time of 968 medicines of various geometries manufactured via fused deposition modelling (FDM) [95]. ML techniques employed included random forest, ANNs, logistic regression, support vector machines, and K-nearest neighbours, which were chosen for their distinct learning characteristics. Models were supplied with numerous feature sets on which to learn and make predictions, including shape of printed medicine, formulation components, material chemical structures, and material physical properties. The best ML technique for each output were: ANN (for filament mechanical characteristics, 91% accuracy); ANN (for extrusion temperature, mean absolute error (MAE) of 5.18 °C); ANN (for dissolution time, MAE of ± 24.29 minutes); random forest (for printability, 93% accuracy); and random forest (for printing temperature, MAE of 6.87 °C). These results highlight how ML can take seemingly heterogenous data and provide accurate predictions suitable for the streamlined production of on-demand medicines with personalised qualities.

ML is increasingly being applied to predict pharmacokinetics. For example, AstraZeneca has recently developed a range of ML techniques that could predict several pharmacokinetic parameters (e.g., C_{\max} PO, AUC PO, and volume of distribution) in humans based on drug structure and dose alone [96]. In the future, such models could form the basis for decisions concerning which drugs are suitable for progression from *in vitro* to *in vivo* studies. ML has also been applied to toxicology testing, with multiple ML techniques used to predict compounds' risk of blockading

hERG channels, a key risk factor for adverse cardiovascular effects [97]. Drug-drug interactions have been predicted using ANNs, achieving performances of over 90% during validation [98]. Though not currently a reality, it may be that ML methods come to decrease the requirement for animal models with pharmacokinetic and toxicology studies [50]. Moreover, once thought to be the inactive components of medicine, a growing body of work is highlighting that some excipients have biological activity [99-101]. Reker et al. [102] have used random forest learning to predict the affinity of excipients for two intestinal drug transporters [p-glycoprotein (P-gp) and uridine diphosphate-glucuronosyltransferase-2B7 (UGT2B7)] which are known to alter the pharmacokinetics of 20% of FDA-approved drugs (Figure 4). Through this work, the group was able to identify vitamin A palmitate as an inhibitor of P-gp (IC_{50} of $2.9 \pm 3.6 \mu\text{M}$) and abietic acid as an inhibitor of UGT2B7 (IC_{50} value of $2.2 \pm 0.3 \mu\text{M}$). These excipient-transporter activities could have significant influence on pharmacokinetics. For instance, vitamin A palmitate was demonstrated to significantly increase systemic warfarin exposure in mice after oral administration due to P-gp inhibition. Here, ML has been successfully applied to reveal previously unknown excipient effects which may not have been identified in routine *in vitro* experiments.

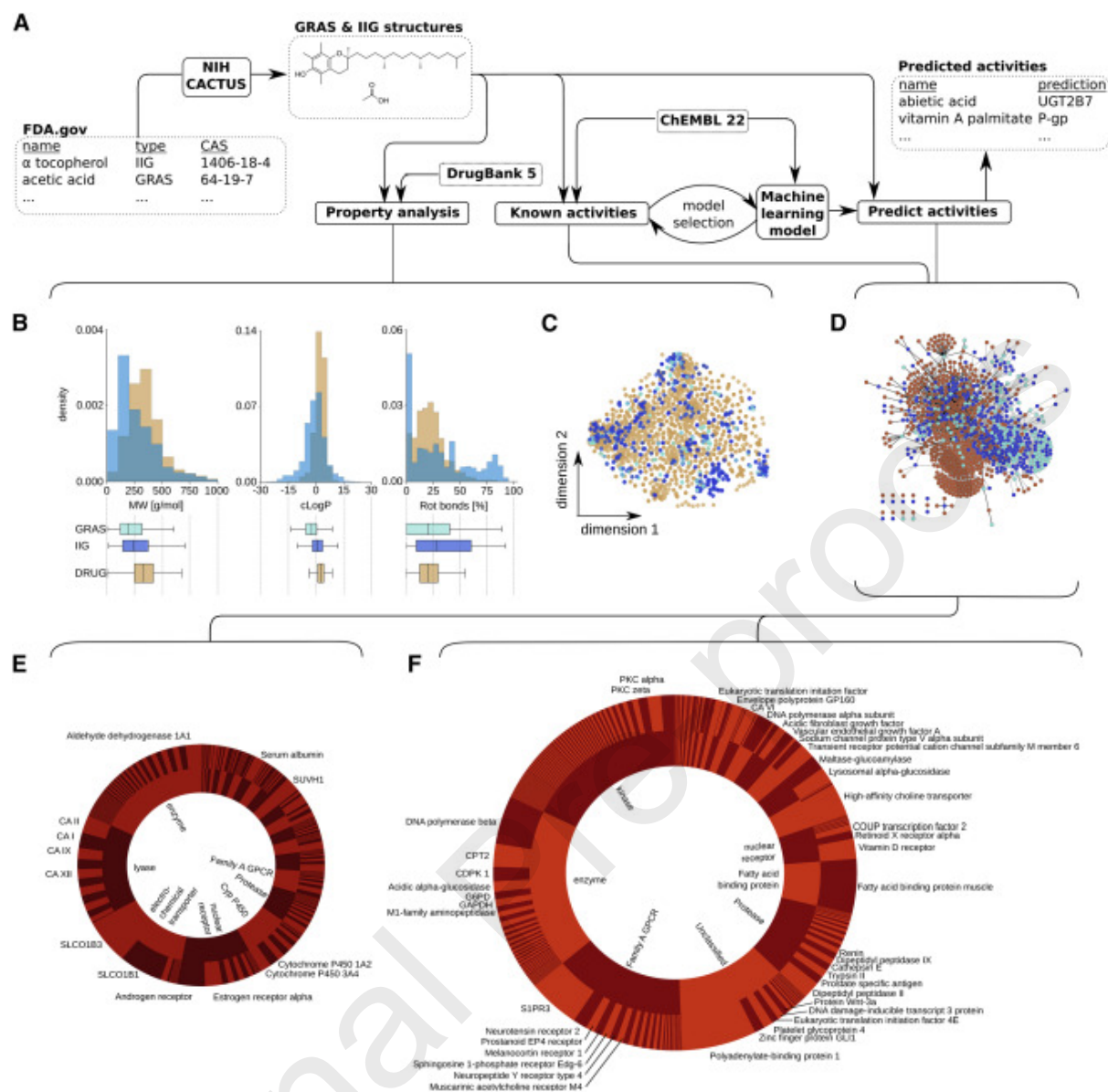


Figure 4. Random forest ML applied to rapidly uncover excipient-drug interactions. (A) the pipeline used by the authors to make predictions. B and C: graphical representations pertaining to the excipient features used as inputs for the model (molecular weight, LogP, and fraction of rotational bonds) (B) and chemical space occupied by excipients (C). D: raw model outputs where connections between light and dark blue nodes represents protein interactions with excipients. E and F: pie charts illustrating previously known (E) and computationally predicted (F) activities on different protein families. Reprinted with permission from [99].

At present the application of other AI technologies outside of ML has yet to be realised in drug discovery and development. If a fully automated laboratory is to be established, then the ability to comprehend text and images will be needed. Fortunately, NLP and computer vision (CV) can be exploited for this task. NLP is a collection of processing techniques capable of interpreting texts. The technology merges computer science and linguistics to help computers comprehend human language, and consequently promote machine-led discovery [103]. For example, NLP was recently used to discover new material through interpreting abstracts of articles [104]. The study demonstrated how NLP can be leveraged to extract information from existing evidence, in this case leading to an undiscovered material with desired functional properties. Moreover, NLP has the potential to streamline ML models by acting as an automated text mining algorithm, which could be applied to the analysis of medical records [105-107]. Considering that the majority of information in science is embedded in texts, NLP will prove to be a potent player in AI, as it can analyse written and spoken word many magnitudes faster than humans NLP, and other ML techniques, have the power to unlock information in big data that could direct pharmaceutical decisions and priorities. For example, ML could be exposed to years of historical experimental data with the aim of improving future processes and informing lead API selection [95].

CV is also capable of enriching the pharmaceutical AI pipeline through its ability to process images. The goal with CV is to replicate human vision behaviour, and in some instances, with enhanced abilities. Similar to NLP, CV encompasses a collection of tools that process images to either facilitate the AI pipeline, or to be used as standalone tools for information extraction. The ability to incorporate sight into machines allows them to operate in areas that would otherwise position humans in

compromising situations. For instance, CV has been used in 3D printing to visualise and analyse processes involving lasers [108, 109]. Aside from this, CV has also been used in 3D printing to automatically self-correct the printer, freeing the printer from human supervision [110]. CV was used to extract images in real-time that were then fed into an ML algorithm to determine whether the printing parameters needed to be adjusted [111]. Other demonstrative applications of CV are also found in biosensors [112-114]. In conclusion, whether integrated into a wider AI ecosystem or used as standalone technologies, pharmaceutical applications stand to benefit from the use of both NLP and CV.

2.3 Redesigning clinical trials

As novel APIs graduate from preclinical development, ML offers great potential to smooth their transition to human studies. For example, ML can facilitate patient recruitment to trials, a key area of risk; phase III trials show a 32% failure rate due to patient recruitment problems [55]. ML techniques can aid with 'clinical trial enrichment', in which patients are screened for recruitment suitability. This could involve helping patients to find clinical trials for which they are eligible, or scouring medical records to identify suitable patients [115]. NLP could become a transformative technology for the identification of eligible patients for trials, as it can be applied to scour medical records at speeds far faster than humans, potentially increasing trial enrolment whilst decreasing human workload [116]. Work by researchers in the Cincinnati Children's Hospital recently demonstrated the promise of NLP for trial recruitment [117]. Here, an NLP package was incorporated in the emergency department's workflow to identify suitable patients for 6 clinical trials using electronic health records. Results at 1 year showed an increase of 14.7% in the number of

patients screened and a reduction of 34% in time required for screening compared to manual screening by staff. This clearly shows how NLP could increase the efficiency of patient identification in other setting with access to medical records. As patients can also be recruited remotely using digital technologies, the burden of trials may be reduced for recruits and their families.

ML can also help reduce the numbers of participants required to ensure statistical significance in a trial. An AI start-up, Unlearn.AI, has created the concept of 'digital twins', which uses ML models to predict how trial participants would respond if they received a placebo [118]. As such, fewer human participants are required to be enrolled, and thus the lengthy recruitment stage of trials is accelerated. Additionally, the number of recruitment dropouts may be lessened, which is one of the leading causes of trial failure [119]. Moreover, the whole study can be carried out remotely (e.g., using wearable devices, ingestible sensors and smartphones [120]), which permits live data collection in a timely manner while reducing costs [121]. As data gathering is not dependent on patients' self-reports, information bias and errors are avoided and more accurate outcomes can be attained [122].

3 Blockchain

Blockchain, a revolutionary technology that is garnering recent interest with the advent of Bitcoin, has received increasing interest across a wide range of industries, ranging from the financial sector to energy suppliers and more recently into the healthcare sector and pharmaceutical industry. Blockchain provides a digital ledger system by grouping records and transactions into chronologically-ordered blocks that are linked using cryptographic hashes, which are immutable and secured [12, 13]. The chain

constantly expands, with new blocks appended to the chain that each contain a reference (a hash value) to information contained in the previous block (Figure 5) [123]. The shareholders in the blockchain are represented as the nodes which are arranged in a peer-to-peer (P2P) network; each node holds both a public key (which encrypts the messages sent to the node) and a private key (decrypts the messages and permits a node to access it). Public key encryption enables the irreversible, non-repudiable and consistent nature of a blockchain [124], with only the correct private key being able to decrypt the messages encrypted with the corresponding public key. It should be noted that a detailed technical explanation of blockchain is outside the scope of this paper, and further details can be found in [124-126].

Favourably, blockchain creates a decentralised and distributed network which reduces the dependence on a single central entity or server to verify integrity of information [127]. This concept empowers collaboration between mutually untrusted stakeholders by providing an immutable and transparent method to record transactions. In pharmaceuticals, the unique features of blockchain holds immense potential for a number of applications, of which end-to-end tracking and data reliability are of prime concern, including (i) prevention of substandard and falsified medicines, (ii) compliance in Pharma supply chains, and (iii) improved transparency and reliability in clinical trials. It should also be acknowledged that academic research could benefit from Blockchain. Such examples include facilitating research workflows and data curation, the peer-review process and conducting computational chemistry on Blockchain environments [128-130].

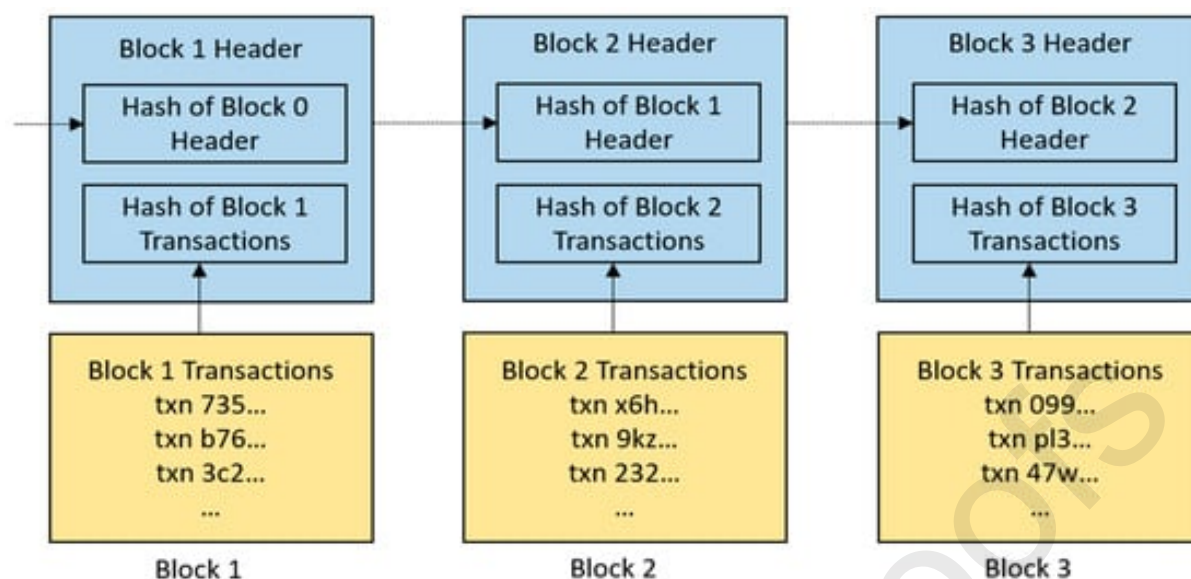


Figure 5. A diagram to depict the way that blocks are linked together to form a blockchain. Every block contains both a header and a number of transactions, with each block transaction being hashed and added to the block header. After the first block is created, every other valid block in sequence must contain the hash output of the previous block header. The hash of the previous block header acts as the chain that links every block to the ones before it. Reprinted with permission from [131].

3.1 Prevention of *substandard or falsified medicines*

Substandard or falsified medicines pose a serious threat to global public health, with over 10% of LMICs being affected by counterfeiting and costing an estimated US\$ 30.5 billion annually [9, 10]. Drugs move across a distribution chain that involves several stakeholders, typically including, but not limited to, a manufacturer, a wholesaler, a distributor and a retailer. Detecting counterfeit drugs is often difficult, because as drug products pass through this long and complicated distribution network, there are numerous opportunities for counterfeits to enter the legitimate supply chain [132]. Indeed, a 2015 study by the British Medical Journal found that over 58% of

counterfeit medicines in Peru were found in legitimate supply chains, suggesting a structural problem in medicine manufacture and supply [11].

Blockchain's advanced features make it capable of providing a basis for complete traceability of drugs, from manufacturer to end consumer, preventing the occurrence of substandard and falsified medicines [14]. Indeed, a number of studies have begun to explore the application of blockchain within pharmaceutical manufacture and supply; one study proposed a new MedLedger framework which successfully stores and records all drug-related activities, events and transactions involving all stakeholders in the blockchain network [133]. Another study proposed a new concept of cryptopharmaceuticals (a blockchain of pharmaceutical dosage units), with each new record containing the unique information of the specific product manufactured along with a cryptographic hash from the previous record, which will chain the records together and make it resistant to modifications [134].

Pharmaceutical companies are also exploring the implementation of blockchain into their processes; Merck, in partnership with Systems, Applications and Products in Data Processing (SAP), developed a series of proof-of-concept apps called the SAP Pharma Blockchain. This Advanced Track and Trace Platform (ATTP) enables a series of unique identifiers are generated for each drug package (e.g., the item number, expiry date, serial number and batch number). Favourably, the distributor can extract the identifiers from the packaging using a mobile scanner app to verify the authenticity of the drug product and verifying the return. The app also has an integrated map to view the real-time location of the medicine, to ensure it is present within its intended geographical region.

25 leading pharmaceutical companies, including Pfizer, Sanofi, Gilead and Novartis, are among the supporters of the blockchain-based MediLedger Network, launched in 2019 by Chronicled [135, 136]. MediLedger has the aim to protect the pharmaceutical supply-chain end-to-end and enable compliance with the FDA Drug Supply Chain Security Act (DSCSA). In 2020, the MediLedger Network authored a Report involving a consortium of pharmaceutical manufacturers, distributors and clinical service providers in order to advise how and why blockchain can meet the 2023 DSCSA requirements for a confidential change of ownership system for the pharmaceutical supply chain [137].

3.2 Compliance in *pharma supply chains*

As medicines are distributed through the pharmaceutical supply chain, companies are required to adhere to guidelines pertaining to drug handling, transport and storage conditions. Indeed, it is now commonplace for operating parameters to be monitored along the supply chain to ensure limits are being met, including temperature, humidity and air quality. However, as every stakeholder in the supply chain maintains their own ledger with regards to monitoring, it can be challenging to track a particular segment of the supply chain readily and to identify the point of failure when issues arise [138].

Blockchain technologies are better able to add compliance and governance to the distributed supply chain because of their inherent transparency and immutable nature [14]. So, for example, if there was a temperature excursion during storage or transportation, the blockchain technology would enable the consumer readily to see at which point the error occurred. To date, several studies have explored the use of

blockchain to for pharmaceutical cold-chain management [139]; One study devised an innovative IoT sensor-based blockchain framework that tracks and traces medicines as they move through the supply chain to monitor the cold-chain for temperature-specific drugs, as well as mitigate the problem of counterfeit medicines [15]. Another study presented an innovative cold-chain system based on Hyperledger Fabric, a private blockchain technology, for the transportation and tracking of blood [140]. The system was able to increase information visibility pertaining to blood supply, including parameters such as blood consumption and disposal to the distributed ledger. Innovations such as these could enable an improved quality assurance of medical products, identify points of failure and enable appropriation mitigation strategic, and reduced wastage across the supply chain.

3.3 Improved *transparency and reliability in clinical trials*

The scientific credibility of data from clinical trials can be undermined by a variety of issues, including data dredging, missing data and endpoint switching. Shockingly, 17% of authors of clinical drug trials reported to be personally aware of intentional fabrication of results [141]. Whilst advances have been made in this area, for example by the World Health Organisation (WHO) requiring all clinical trials to make their methods and results freely available [142], a recent study by the Lancet identified that only 40.9% of clinical trials are compliant with this requirement within the 1 year deadline [143]. To overcome these challenges, and to ensure credibility in scientific findings and to maintain trust and confidence in clinical trial results, blockchain has been explored as a strategy which could be used to readily collect data real-time in a secure and unfalsifiable manner [144, 145]. Indeed, Omar et al. [146] proposed a blockchain-based framework for clinical trial data management using Ethereum Smart

Contracts, generating documents which are unable to be tampered with as they have associated cryptographic hashes.

As well as data credibility, the FDA has also reported that almost 10% of clinical trials feature issues pertaining to informed patient consent collection [147]. Examples include failure to obtain written consent, invalid or unapproved documentation, failure to re-consent upon revisions and missing approvals relating to protocol changes. There have also been reports of fraudulent activities such as issues around backdating consent documents [147]. Using blockchain technologies in clinical trials could instead provide improved transparency and traceability of informed consent. Benchoufi et al. [147] suggest that, in the future, blockchain (Smart Contracts) could be used to track the complex data flow of a clinical trial in a chronological and unfalsifiable manner which, for example, could prevent patients being included in a trial before consent is obtained, as well as store documents in a secure and publicly verifiable way. Further, as noted above, Smart Contracts could be embedded within clinical trial protocols such that if any revisions to protocol were made, the patient would need to provide re-consent before the trial could continue. Albanese et al. [148] present a framework termed SCoDES which is a system based on blockchain technology to enable trusted and transparent consent in clinical trials without the need for a centralised, trusted party.

Several companies are also exploring this area. For example, Exochain (a blockchain Pharma start-up) is working to use blockchain to ensure the secure storage of patient health information [149]. Their blockchain algorithms enable individuals to control how clinical trial researchers may interact with their medical data, potentially leading to an

increased quality and quantity of patient recruitment and giving individuals a greater control over their medical information.

4 Interconnected healthcare

Interconnected healthcare will see digital technologies transforming how healthcare is structured, provided, and reviewed. A key aspect of interconnected healthcare includes telemedicine, which refers to the use of internet services or telecommunication to exchange medical data and provide healthcare services (e.g., medical consultations, education, treatment, monitoring and diagnoses) remotely [150]. This allows healthcare professionals to monitor patients whilst maintaining their lifestyle and at their homes, providing more accurate and real-time measurements, and avoiding external factors that could compromise results. As an example, a patient's vital signs can be continuously monitored, even during sleeping hours, without additional burden to the patient, healthcare professional or even healthcare institute (e.g., hospital, clinic or pharmacy) [151].

The concept of interconnected healthcare is particularly advantageous with the increasing number of ageing populations, which elicits a myriad of financial and socioeconomic challenges [152]. This has led healthcare systems to seek novel healthcare modalities that are flexible and allow for elder patients to receive medical care at the comfort of their homes [152, 153]. In doing so, healthcare services will be accessible by a larger number of patients, especially those who require constant monitoring or suffer from chronic or life-threatening conditions.

To enable the interchange of information, a wide range of wireless devices are used; these span smart watches [e.g., Galaxy Watch (Samsung Electronics Co., Ltd., South Korea) and Apple watch (Apple Inc., United States)], wristband sensors [e.g., Fitbit (Fitbit, United States), smart glasses [e.g., Glass Enterprise Edition (X Development LLC, United States), health monitoring devices and smart scales and pillboxes, as well as medical and health apps installed on smartphones. Data garnered from such devices include heart rate, glucose level, oxygen saturation level, blood pressure, and body temperature, and can be remotely accessed by a healthcare for diagnosis and monitoring purposes.

At the onset of the COVID-19 pandemic, healthcare systems across the world realised that they needed to strengthen their telemedicine infrastructure to meet the needs of their patients [154]. As digital consultations have been adopted out of necessity, many providers and patients are recognising the myriad of advantages to building telemedicine into long term healthcare [18]. Video consultations have been found as more cost-effective than in-person visits, to reduce the consumption of resources, and to obtain high levels of patient and staff satisfaction [155]. A successful example of a telemedicine company is Babylon Health, which provides digital consultations on a global scale [156].

Like telemedicine, telepharmacy is defined as the use of telecommunication by registered pharmacies and pharmacists to provide pharmaceutical healthcare services remotely. Examples of such include the use of e-prescriptions, e-dispensing, electronic health records, virtual consultations, home delivery of medications, and using remotely captured clinical data for pharmaceutical monitoring [17]. This is

particularly useful when pharmacists or patients cannot be physically present in the same place, such as in geographically distant locations [157]. As such, telepharmacy can improve accessibility to healthcare services, enhancing therapeutic outcomes and reducing the need for hospitalisations [158]. The use of e-prescriptions, which refers to the electronic generation of prescriptions, can provide the added benefits of being time- and cost-efficient by directly delivering prescriptions from the point-of-care to the pharmacy, reducing errors relating to unclear handwriting, identification of drug interactions, patient information, and medication dosing [159]. To encourage the home delivery of medications, a new 'Uber of pharmacy', namely Capsule, has been introduced in the United States [160]. This is an app-based pharmacy that delivers medications anywhere and anytime, within two hours. More recently, Amazon has entered the pharmacy sector by launching own digital platform, Amazon Pharmacy [16]. The retail giant has designed a secure pharmacy service that enables patients to upload their insurance data, manage prescriptions, and order medications to their doorstep with one-click ordering.

In the case of developing countries, where the availability of pharmacies may be limited, internet-based systems could be implemented to enable the delivery of medications in a rapid manner [161]. Such systems would be used to locate patients and direct the medicine delivery vehicle to their location by suggesting the best possible route based on traffic and Global Positioning System (GPS) information.

In the future, it is envisioned that a closed-loop electronic healthcare model will be adopted, where AI, smartphones and tablets, mobile sensors and health monitoring devices will enable doctors to remotely manage and adjust therapeutic plans to meet

the individual needs of their patients [162]. E-prescriptions are then sent to a pharmacy or manufacturing site, where personalised therapies are produced using 3D printers that are operated with the help of robots [163]. Once ready, drones then transport the prescription to the patient's doorstep within minutes. Such a system provides a viable example on how pharmaceutical production can be advanced to support the concept of telepharmacy.

Telepharmacy can also be utilised as a novel approach to provide pharmaceutical counselling to patients regarding the proper use of their medications and management of their disease states [164]. Such interventions may decrease hospital or outpatient admissions/appointments, whilst improving adherence to medications and lowering the rates of relapses or preventable complications [159]. Despite their benefits, telemedicine and telepharmacy become less useful when physical interaction or examination are required. Moreover, such technologies remain inaccessible to LMICs, where internet, mobile services and resources may be deficient.

5 Crossing the virtual horizon

5.1 Augmented reality (AR)

AR refers to the integration of artificial information within reality by overlaying digital data onto physical objects or spaces to improve the user experience and enable tasks to be executed more efficiently (Figure 6A) [165-167]. Typically, this involves the use of superimposed imaging, video- or computer-generated simulations, which are projected on a smartphone or tablet. The concept works using four different components [165, 167]: (i) a tracking unit, which involves using a navigation or

geotracking system, i.e., a smartphone's GPS, that determines the exact positioning of a device in a particular location; (ii) an input device, such as a camera or scanner that captures live images; (iii) a computing unit, which compares the captured images with other stored images from web sources using CV and reconstructs 3D virtual objects; and (iv) a display device which overlays 3D data onto the screened object or location, a process termed *registration* [168].

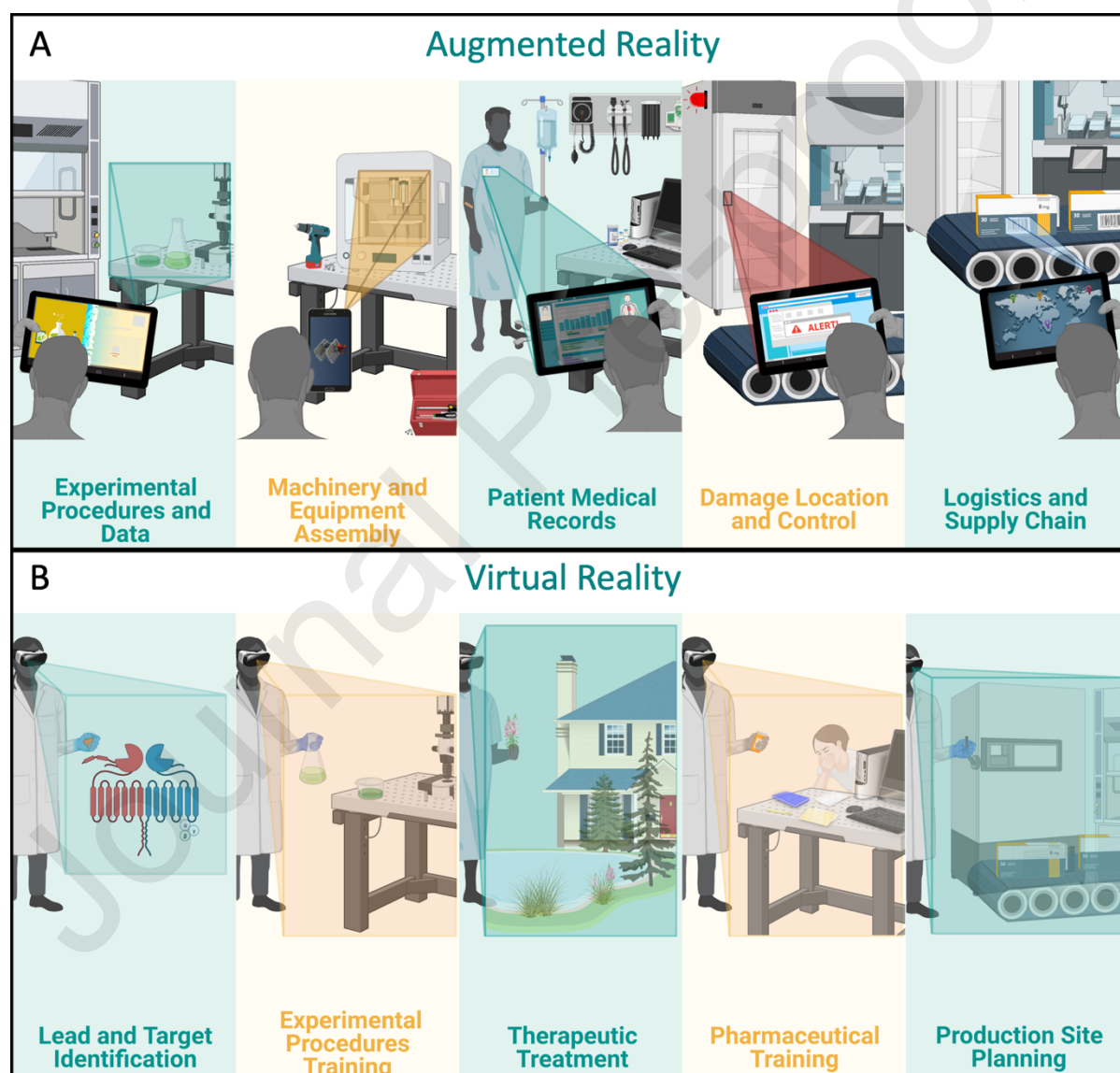


Figure 6. Graphical illustration outlining the differences between (A) augmented and (B) virtual reality, wherein examples of their applications in pharmacy are provided.

The main advantage of AR lies in its ability to simulate procedures prior to their occurrence, enabling the user to visualise, learn and improve them. Because of that, the time needed to perform a task is reduced and errors are kept to a minimum or avoided. In principle, this is achieved by providing virtual images and information which in reality cannot be sensed or perceived by the task performer [169]. Indeed, AR has seen a wide array of applications in the pharmaceutical industry ranging from education, to laboratories and manufacturing facilities all the way through to hospitals and pharmacies [170]. The field has recently benefited from the increase in computational processing capabilities, and, despite being a nascent technology, AR is expected to disrupt both academic and industrial generation and transfer of knowledge significantly. AR is generating new insight to provide alternative means of representing molecules (Figure 7A) [171], where molecular representations are key to developing ML models, and consequently one which the pharmaceuticals field can leverage for when developing ML models. Moreover, by mitigating the need to explain new developments in an 'abstract' manner, AR can facilitate the transition of new medical developments into clinics [172].

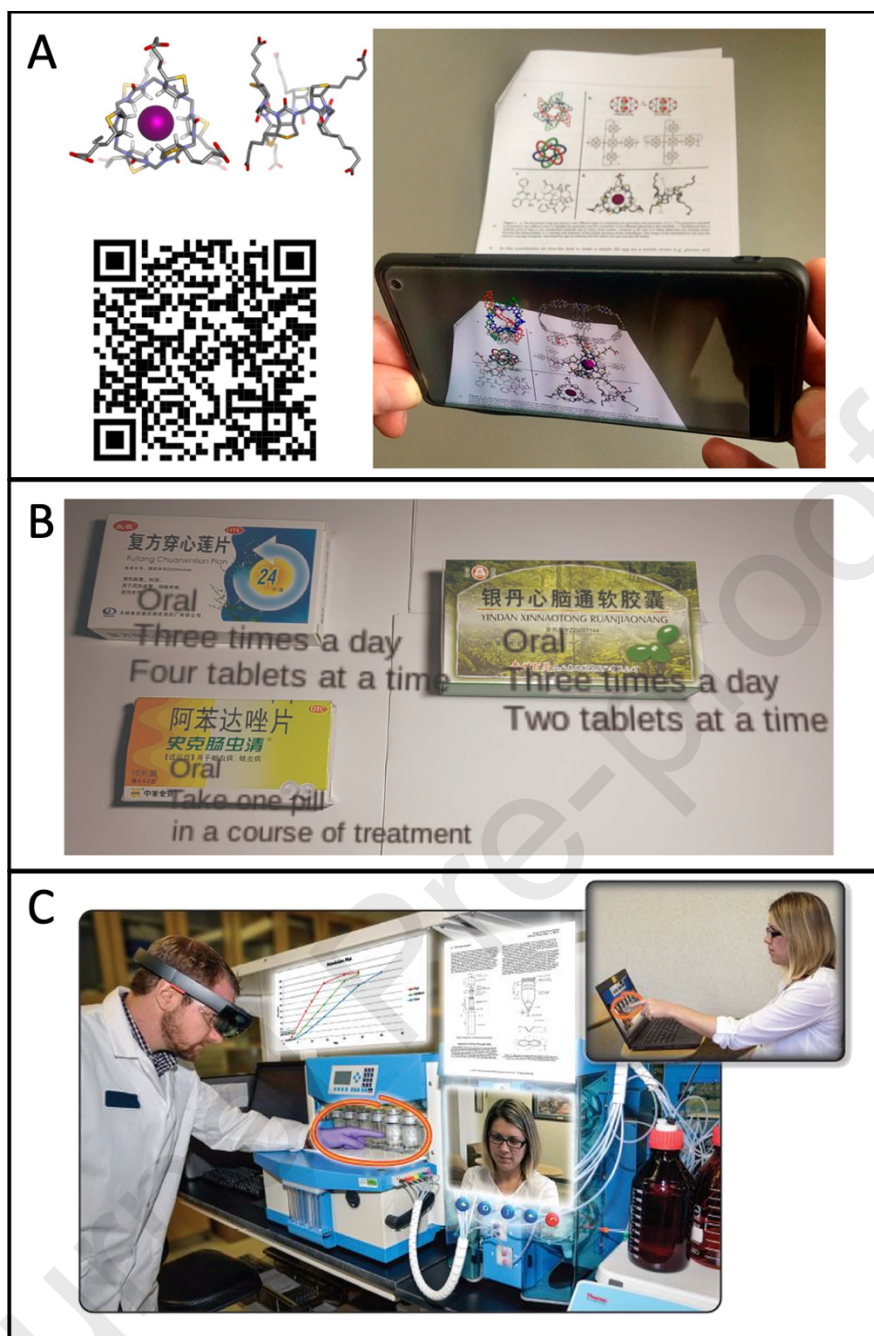


Figure 7. (A) Image showing how AR can aid to represent molecules in 3D to visualise complex compounds [173]. (B) Image showing how AR smartphone app can be used to recognise multiple pill packaging boxes simultaneously, and provide prescription information in the form of virtual words [25]. (C) Theoretical rendering showing the capabilities of a mixed reality headset, HoloLens, which was evaluated for its utility in assisting method transfer [174]. Images were reprinted with permission from their original sources.

AR can also be exploited for aiding patients in handling their medications and improve their adherence to therapy [175]. To do so, a *Medication Coach Intelligent Agent (MCIA)* was developed. This smartphone app provides patients with bespoke medical decisions based on their therapeutic treatment plan, drug restrictions and interactions, patient's own preferences as well as data collected using wireless sensors embedded within the head-mounted display (HMD). The MCIA also sends patients reminders about their medications, ensuring that medicines are taken on time, without any doses being missed. In an alternative approach, AR enhanced medication adherence in elderly patients by displaying augmented images of the corresponding prescriptions onto the surface of pill boxes, avoiding medication errors in patients on a polypharmacy regimen (Figure 7B) [25].

5.2 Virtual reality (VR)

VR refers to the use digital information to create 3D computer-generated environment simulations in which the user can interact (Figure 6B). VR can be generated using different types of tools, such as computers, smartphones, tablets, game consoles or VR rooms equipped with HMDs. In the case of the latter, self-contained spaces are equipped with projectors with embedded 3D visualisation systems that enable the simulation of real or virtual settings [176, 177].

Within digital health, VR has been applied within drug discovery and design, enabling the 3D visualisation of the molecular structures of drugs and their targets [27]. This allows scientists to investigate and identify suitable ligands based on their biochemical characteristics. As an example, eBrain is a VR platform that allows the virtual

simulation of a drug's performance in a patient's brain, enabling the determination of an ideal drug dose and treatment combination [178].

Within laboratories, VR has been applied to help plan experiments [179] or for layout configuration [180], optimising and improving outcomes whilst reducing costs. VR can also be used within pharmaceutical education, for the on-demand training of students on how to handle certain scenarios (e.g., patient counselling or emergencies) [26]. More recently, the concept is being exploited for the 3D visualisation and interaction with scientific data, such as cells, expanding the horizons of scientific knowledge [181].

5.3 Mixed reality (MR)

In mixed reality (MR), elements from both the physical and virtual worlds co-exist, enabling the user to immerse in and navigate through a mixture of superimposed real and digital components using state-of-art sensors and imaging tools. An example of a MR device is Microsoft's HoloLens headset. Within pharmacy, the HoloLens has been investigated as a modern tactic for exchanging experimental procedures across various pharmaceutical domains, ranging from drug synthesis and development, analytical procedures, drug product manufacturing all the way to packaging and shipping (Figure 7C). The use of this hands-free system has been shown to cut down costs and reduce the time needed to complete tasks, improving efficiency and productivity by 10 fold [174].

Although having shown favourable results, some concerns surrounding the use of these interactive technologies still constrain their usage. The relatively high cost of HMDs (e.g., > \$1 million) and absence of insurance coverage could act as the main

barrier to their usage [182]. This is followed by the negative implications of the immersive nature of these technologies on patients' health, which include, but are not limited to, causing motion sickness (known as cybersickness, simulator sickness or sim sickness), vertigo and dizziness, deterioration in eyesight, bacterial infections, risk of falling or injury and exposure to radiation and emissions [183, 184]. The latter is particularly detrimental to patient health and may lead to malignancy. Such harmful outcomes are more pronounced in pregnancy, mental illness, psychiatric disorders or brain injuries. Other factors that limit the use of immersive technologies include subsequent addiction or dependence, isolation from the real-world, absence of anxiety response and issues relating to privacy and data security [185, 186].

6 Challenges and Outlook

Digital transformation is revolutionising the entire pharmaceutical sector by innovating new ways to deliver therapy to patients; from drug discovery and drug development, to medicines supply and logistics, to diagnoses and patient monitoring on the front-line [187]. Furthermore, digital technologies are also being applied for post-marketing surveillance in order to identify rare mild to severe adverse drug reactions enabled for example by access to data from electronic health records, wearables and patient-monitoring devices. By harnessing the emerging power of technological advancement, healthcare professionals can fashion and optimise treatments, including how, when and where they are delivered, based on the individual needs and preferences of their patients [188-190]. To date, the integration of technologies such as AI, machine learning, and big data analytics have already been applied in the fields of drug development and optimisation [52], as well as have applications within point-of-care diagnosis and monitoring for patients [191]. However, legal, institutional, regulatory

and policy support is still required in order to overcome the problems that arise in the process of applying digital transformation to each country.

The investment in digital healthcare technologies has skyrocketed in recent years; in 2019, the global digital healthcare market was worth US\$ 175 billion, which is forecast to almost quadruple to US\$ 660 billion by 2025 [192]. Digital transformation of healthcare has also been listed as a commitment in the UK's National Health Service (NHS) Long Term Plan in order to deliver virtual services, diagnoses and delivery of therapy for patients [193]. Despite this significant investment and commitment by policy makers, the uptake of virtual platforms into the pharmaceutical and healthcare sectors is not being realised as rapidly as in other industries. Indeed, research by McKinsey Global Institute found that the chemical, pharmaceutical and healthcare sectors were some of the poorest digitised industries [194]. There are a number of challenges that still need to overcome in order to expedite the use of novel and revolutionary virtual technologies into these sectors and to translate their theoretical benefits into real-world advantages.

Firstly, there has traditionally been a lack of a clear regulatory framework to guide innovators in strategies for integrating digital technologies into healthcare. Progress has been made in this area in recent years; In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) published guidance to help developers of software and apps to identify if their health apps should be considered as a medical device, and hence be CE marked according to EU regulations [195]. In the U.S., the FDA have recently established the Digital Health Center of Excellence which aims to create a comprehensive approach to digital health technology, and also published a

similar guidance for innovators wishing to develop software healthcare applications [196, 197].

These new initiatives by regulatory agencies will be key in the next few years in facilitating the integration of virtual technologies and digital tools into the healthcare sectors. Despite this, further work is required before meaningful change will occur. Current regulatory guidance is not fit-for-purpose; regulatory agencies must consider developing more transparent regulations and policies particularly around data protection and cybersecurity which presents a major challenge in virtual software integration. Regulatory agencies should also advise how innovators can best demonstrate clinical efficacy for their digital technologies. The most well recognised evidence for medical interventions is the use of randomised controlled trials (RCTs) [198] however, to date, only a limited number of software-based products have been tested in this way [199]. There have been increasing calls for the development of innovative evidence generation approaches that reduce testing time whilst still delivering assurance of clinical benefits and cost effectiveness [200, 201]. Indeed, in the case of VR technologies, there still remain deficiencies in the way studies are designed, with small sample sizes, lack of control groups and lack of side effect reporting being common deficiencies in VR studies [201]. Regulatory agencies must lead the way in advising this to ensure that only those effective technologies that demonstrate real-world benefit are being integrated into pharmaceutical care.

An additional factor that may hinder the uptake of virtual technologies is the inevitable need for these to be used alongside a hardware counterpart. Indeed, hardware systems can be costly to purchase which may be of particular concern for healthcare

services where resources are limited, for example within publicly-funded health services as well as within LMICs. Indeed, a recent survey by Deloitte of over 1,500 healthcare professionals found that the main perceived concern and barrier to digital transformation was the cost of digital technologies (56%) [202]. It is of increasing importance for MedTech companies to develop affordable software and hardware systems to ensure their benefits can be widely available and accessible worldwide.

Another consideration is the usability and complexity of virtual technologies. Whilst some technologies have been developed as a user-friendly software-hardware package (such as in the instance of VR headsets or smartphone applications) where there is little to no requirement for the lay user to need to understand the technical underpinnings and mathematics of the software, others such as AI, ML and FEA technologies may require enhanced knowledge from the end-user. Additionally, it is worth noting that software solutions can often be hindered by hardware; virtual technologies which have highly complex underpinnings will require a more powerful hardware system to function. As such, it is key for developers to strike a balance between 1) Using a simple-enough hardware system that enables appropriate usability for the target audience and 2) Ensuring the software and hardware system runs efficiently, as well as meets the end-users needs (e.g., data outcomes and affordability).

Developing the aforementioned virtual technologies can streamline the consolidation of *digital twinning*; the concept of virtually replicating the entire drug product cycle using data from the physical world [203]. The salient benefit of the all-encompassing technology is that stakeholders can map different scenarios in the virtual domain and

subsequently outline the most suited course of action to pursue, all with minimal wastage of resources. In this regard, AI and finite element analysis (FEA) will be key enabling technologies for developing a pharmaceuticals digital twin, whilst blockchain and quantum-inspired tools will play a supporting role. FEA are digital tools used to solve partial differential equations, with major applications in material properties, fluid dynamics and electric potential. These programs place an emphasis on accurate spatial and temporal equations to map a phenomenon, which in turn provide visual representations and also further insight. In some instances, FEA can perform calculations that otherwise are experimentally infeasible, due to the lack of available technology, such as inaccessible miniature sensors with the desired dimensions. Recent applications of FEA include modelling the mechanical properties of delivery systems, fabrication processes and both *in vitro* and *in vivo*. Overall, FEA have been recognised as indispensable computational modelling techniques with proven cost reduction benefits to R&D in other sectors. Since FEA can computationally mimic challenges frequently encountered in formulation development, such as powder compaction, extrusion, coating; offering a cost-effective approach to improving medicine production, there is potential to transfer the benefits of FEA to the pharmaceuticals sector. Another technology expected to transform technologies are quantum computing and other quantum-inspired tools. While these technologies possess great potential, they are currently computationally demanding. It is worth mentioning however, that the integration of digital twin systems requires constant access to internet connection and high-tech devices, which may be challenging for developing countries to achieve.

To alleviate concerns and to enable digital translation to become a reality requires stakeholders to come together, including academics, big Pharma, small and medium enterprise companies, technology companies, healthcare professionals and patients, to discuss how best to deliver digital tools which have meaningful impact in practice. Senior management teams in pharmaceutical and healthcare organisations should urgently consider their digital readiness and begin developing strategies to enable the best use out of virtual technologies, including liaising with staff to identify areas of critical need for digital transformation. This should include ensuring the organisation has appropriate technical readiness, for example by allocating resource, investing in appropriate infrastructure, ensuring interoperability between technologies, as well as training staff to ensure the best use out of the technology is achieved. Furthermore, in the instance that the technology is integrated into clinical practice, healthcare professionals (including pharmacists, pharmacy technicians, clinicians, nurses and other clinical staff) must be fully competent in the technologies and be comfortable in advising and educating patients on how to use the digital intervention.

Whilst further progress is still required before widespread digital technology uptake and integration will occur, the pharmaceutical and healthcare sectors have made major strides towards enabling a digital healthcare future. The new initiatives, increased investment, and relentless hard work and determination by innovators to create better digitised solutions for across the pharmaceutical sector will continue to make major strides towards this goal, evidenced by the numerous publications and impacts announced daily. These continued collaborative efforts across numerous stakeholders and improved policies and regulatory guidance will in the future enable

virtual technologies to be readily integrated into the pharmaceutical sector, transforming the delivery of services and therapies for patients around the world.

7 Conclusion

Since the emergence of novel technologies, the industrial world has witnessed a major disruptive transformation, marked by the evolution of industry 4.0. Within healthcare, the manifestation of cyber technologies has reshaped treatment approaches. In particular, there has been a noticeable increase in the use of these virtual systems by clinicians, pharmacists and patients. Indeed, the embracement of digital health could accelerate the development of personalised medications with improved efficacy and enable their delivery to remote areas, expediting recovery and reducing hospitalisations. However, this calls for the need for a large sum of medical data and information, which brings about concerns relating to data security and accessibility. With the right regulations in place, the implementation of cyber tools within a digital health model has been projected to effectively reduce burden on healthcare systems by making medical care accessible to everyone, everywhere, all the time.

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Competing Interests

Prof Abdul W. Basit, Prof Simon Gaisford and Dr Alvaro Goyanes are co-founders of FabRx Ltd, Canterbury, UK.

Resources

<https://ec.europa.eu/newsroom/dae/items/709090>

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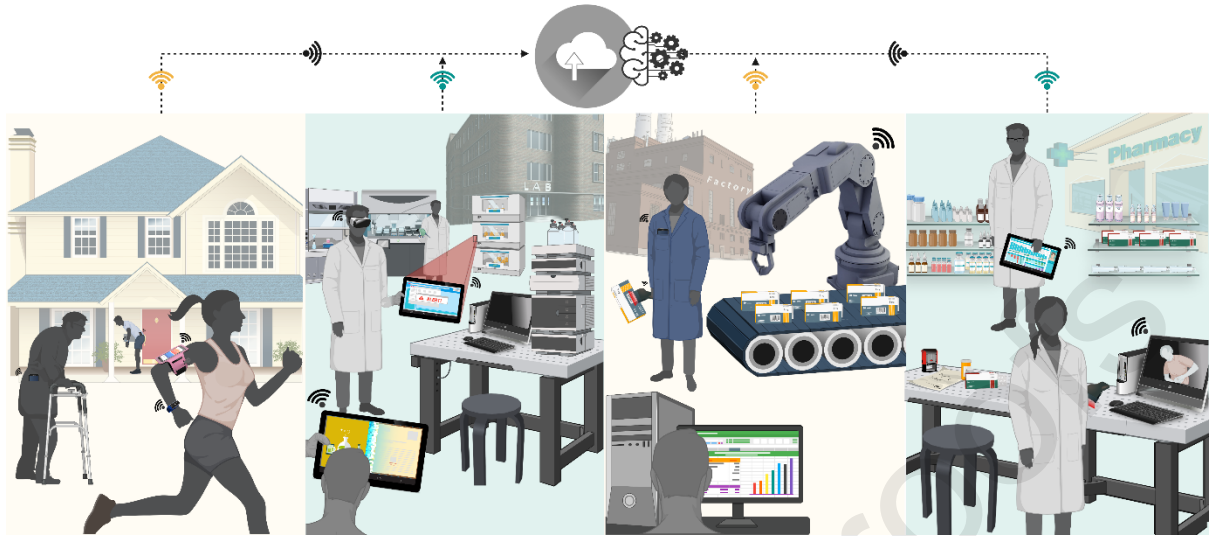
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